



## 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)<br>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  $\geq 18$  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  $\geq 9.5$  g/dL and  $< 12.0$  g/dL for females and  $\geq 9.5$  g/dL and  $< 13.0$  g/dL for males (40), as well as serum ferritin levels  $< 30$   $\mu$ g/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  $\geq 4$  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  $\mu$ mol/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:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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  |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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                                                            |
| <b>Arm title</b>             | 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.

|                  |                                                       |
|------------------|-------------------------------------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | 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                                                    |
| Consent withdrawn by subject                        | 1                                                              | 6                                                     |
| Physician decision                                  | 2                                                              | 1                                                     |
| 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:<br>Double-blind phase, 12 week active treatment arm with ST10. |         |
| Reporting group title                                                                       | Placebo |
| Reporting group description:<br>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                                                                                                               | $\pm 1.027$  | $\pm 0.851$ | - |
| Serum Ferritin concentration at baseline                                                                                         |              |             |   |
| Serum Ferritin concentration at baseline of the 12 week double-blind phase                                                       |              |             |   |
| Units: $\mu\text{g/L}$                                                                                                           |              |             |   |
| arithmetic mean                                                                                                                  | 8.6          | 8.2         |   |
| standard deviation                                                                                                               | $\pm 6.8$    | $\pm 6.5$   | - |
| 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                                                                                                               | $\pm 11.7$   | $\pm 7.5$   | - |
| 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                                                                                                               | $\pm 0.942$  | $\pm 1.067$ | - |

## End points

### End points reporting groups

|                                                                                                                                            |                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Reporting group title                                                                                                                      | ST10                                                           |
| Reporting group description:<br>Double-blind phase, 12 week active treatment arm with ST10.                                                |                                                                |
| Reporting group title                                                                                                                      | Placebo                                                        |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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 ( $\pm$ 1.184) | 0.01 ( $\pm$ 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  $\geq 2$  g/dL change from baseline in Hb concentration at Week 12 (Full Analysis Set)**

|                 |                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of subjects that achieved $\geq 2$ 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  $\geq 2$  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  $\geq 2$  g/dL change from baseline in Hb concentration at Week 12 - double-blind phase

| <b>End point values</b>     | 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 $\geq 1$ g/dL change from baseline in Hb concentration at Week 12 (Full Analysis Set)

|                 |                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of subjects that achieved $\geq 1$ 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  $\geq 1$  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  $\geq 1$  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:<br>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:<br>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 ( $\pm$ 0.676) | 0 ( $\pm$ 0.67) |  |  |

**Statistical analyses**

|                                                                                                                                                                                   |                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                 | Change in Hb concentration from Baseline to Week 4 |
| Statistical analysis description:<br>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:<br>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:<br>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:<br>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.   |                                                                                  |

|                                      |                                                                |                                                       |  |  |
|--------------------------------------|----------------------------------------------------------------|-------------------------------------------------------|--|--|
| <b>End point values</b>              | 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:<br>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:<br>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.   |                                                                                  |

|                                      |                                                                |                                                       |  |  |
|--------------------------------------|----------------------------------------------------------------|-------------------------------------------------------|--|--|
| <b>End point values</b>              | 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 ( $\pm$ 1.339)                                            | 2 ( $\pm$ 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.

|                                      |                                                                |                                                       |  |  |
|--------------------------------------|----------------------------------------------------------------|-------------------------------------------------------|--|--|
| <b>End point values</b>              | 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 ( $\pm$ 1.457)                                            | 2.19 ( $\pm$ 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  $\pm$  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  $\pm$  2 days

|                                      |                                                                |                                                       |  |  |
|--------------------------------------|----------------------------------------------------------------|-------------------------------------------------------|--|--|
| <b>End point values</b>              | 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 ( $\pm$ 1.713)                                            | 0.52 ( $\pm$ 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

---

|                             |                                                                |                                                       |  |  |
|-----------------------------|----------------------------------------------------------------|-------------------------------------------------------|--|--|
| <b>End point values</b>     | 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 ( $\pm$ 0.13) | 0.05 ( $\pm$ 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 ( $\pm$ 0.12) | -0.03 ( $\pm$ 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 ( $\pm$ 28.3) | 1.2 ( $\pm$ 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 ( $\pm$ 20.17) | -0.4 ( $\pm$ 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: $\mu\text{g/L}$      |                                                                |                                                       |  |  |

|                                      |                     |                    |  |  |
|--------------------------------------|---------------------|--------------------|--|--|
| arithmetic mean (standard deviation) | 60.4 ( $\pm$ 93.35) | 36.6 ( $\pm$ 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:<br>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:<br>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 ( $\pm$ 12.46)                                            | 17.7 ( $\pm$ 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:<br>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:<br>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          |

|                                                   |                                                               |  |  |
|---------------------------------------------------|---------------------------------------------------------------|--|--|
| <b>Serious adverse events</b>                     | 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          |  |  |
| <b>Infections and infestations</b>              |                |  |  |
| 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          |  |  |
| <b>Peritonitis</b>                              |                |  |  |
| subjects affected / exposed                     | 0 / 47 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Pneumonia</b>                                |                |  |  |
| 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 %

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

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

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

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 64 (4.69%)<br>3 | 0 / 64 (0.00%)<br>0 | 4 / 50 (8.00%)<br>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                   |

|                                                          |                                                                          |  |  |
|----------------------------------------------------------|--------------------------------------------------------------------------|--|--|
| <b>Non-serious adverse events</b>                        | Placebo switch to<br>ST10 treatment-<br>Safety Set, Open-<br>label Phase |  |  |
| Total subjects affected by non-serious<br>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<br>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<br>occurrences (all) | 3 / 47 (6.38%)<br>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 | <p>Global Amendment 1</p> <p>Changes to study endpoints/statistics:</p> <p>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.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 17 January 2012 | <p>Global Amendment 1</p> <p>Changes to inclusion/exclusion criteria:</p> <p>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).</p> <p>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.</p> <p>Other sections within the study protocol that were affected by the change to MCV criteria included: Section 2, Synopsis, Diagnosis/Inclusion Criteria.</p> <p>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.</p> <p>Other sections within the study protocol that were affected by creatinine exclusion changes included: Section 2, Synopsis, Diagnosis/Exclusion Criteria.</p> <p>In summary, these changes were to improve consistency with clinical practice and/or central laboratory results reporting, and to assist with subject recruitment</p> |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 January 2012 | <p>Global Amendment 1</p> <p>Changes to study objectives:</p> <p>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.</p> <p>Section 6.2 Secondary objectives was thus revised to:</p> <p>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.</p> <p>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.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 17 January 2012 | <p>Global Amendment 1</p> <p>Miscellaneous revisions:</p> <ul style="list-style-type: none"> <li>• Minor administrative changes to wording were made throughout the document in order to improve internal consistency and clarity</li> <li>• The number of study centres was increased to 30-40</li> <li>• 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</li> <li>• 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</li> <li>• 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</li> <li>• 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</li> <li>• The safety reporting contact information provided in Section 10.2.5 was updated</li> <li>• 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</li> <li>• In Section 9.2.1, under treatment procedures for the Screening Visit, a sub-bullet was added under instructions for documenting concomitant medications.</li> </ul> |
| 17 January 2012 | <p>Global Amendment 1</p> <p>Changes to study design/visit schedule:</p> <p>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.</p> <p>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.</p> <p>This amendment was not ethically approved in AU; therefore the open-label extension was only available to study subjects in UK, DE and HU.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 January 2012 | <p>Global Amendment 1</p> <p>Changes to prohibited medications:</p> <p>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.</p> <p>Text was added to the instructions on the use of immunosuppressants for clarity.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 17 January 2012 | <p>Global Amendment 1</p> <p>Changes to subject discontinuation criteria:</p> <p>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.</p> <p>Protocol Section 7.4.5 Individual discontinuation criteria was therefore amended as follows:</p> <p>Treatment will be stopped for any of the following reasons: ‘...Hb <math>\leq</math> 9.0 g/dL (5.6 mmol/L)...’</p> <p>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.</p> |
| 19 March 2012   | <p>Global Amendment 2</p> <p>Changes to subject discontinuation criteria Section 7.4.5:</p> <p>The lower limit of Hb concentration for treatment continuation was reduced to reflect the reduction in the lower limit for study inclusion from Hb <math>\geq</math> 10 to Hb <math>\geq</math> 9.5 g/dL (Inclusion criterion 4b). A 1 g/dL difference between the lowest concentration of Hb for study entry (<math>\geq</math> 9.5 g/dL) and mandated study exit (<math>\leq</math> 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.</p>                                                                                                                                                                                                                                                                                                                              |

|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 19 March 2012 | <p>Global Amendment 2</p> <p>Changes to exclusion criteria Section 7.4.2:</p> <p>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.</p> <p>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 &lt;30 µg/mL at screening will exclude subjects with anaemia of chronic disease. Ferritin &lt;30 µg/mL has a positive predictive value for IDA of 92 to 98% (Weiss 2005). As such, this exclusion criterion was removed.</p> <p>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.</p> |
| 19 March 2012 | <p>Global Amendment 2</p> <p>Changes to inclusion criteria Section 7.4.1:</p> <p>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 &lt;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.</p> <p>For randomisation, subjects must have had ferritin &lt; 30 µg/L, a normal serum vitamin B12 level and a normal serum folate level at screening. A serum ferritin &lt;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 &lt; 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 &lt;30 µg/L was determined to be sufficient to define a study population with iron deficiency anaemia.</p>                                                                                                                                                                   |

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 September 2012 | <p>Global Amendment 3</p> <p>Miscellaneous revisions</p> <p>Minor administrative changes to wording were made throughout the document in order to improve internal consistency and clarity.</p> <ul style="list-style-type: none"> <li>• The number of study centres was increased to 30 to 50</li> <li>• Study time periods were clarified with the inclusion of the following definition: For the purposes of this protocol, the following conventions are used: <ul style="list-style-type: none"> <li>o 1 week equals 7 days</li> <li>o 4 weeks equal 28 days</li> <li>o 12 weeks equal 84 days</li> <li>o 52 weeks equal 364 days.</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 27 September 2012 | <p>Global Amendment 3</p> <p>Changes to exclusion criteria Section 7.4.2:</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> |

|              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25 July 2013 | <p data-bbox="416 51 671 80">Global Amendment 5</p> <p data-bbox="416 109 871 138">Changes to the analysis of the study:</p> <p data-bbox="416 168 1426 398">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.</p> <p data-bbox="416 427 1426 689"> <b>Rationale for Change in primary analysis methodology</b><br/>           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.         </p> <p data-bbox="416 719 1426 779">Furthermore, ANCOVA analysis is a more powerful method then the Wilcoxon-Mann Whitney analysis.</p> <p data-bbox="416 808 1426 891">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).</p> |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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>