



Clinical trial results:

TREATMENT OF IRON DEFICIENCY ANAEMIA IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE USING FERROUS SULPHATE OR COSMOFER: TOLERANCE AND EFFECTS ON HAEMOGLOBIN, DISEASE ACTIVITY, MOOD, QUALITY OF LIFE AND AUTONOMIC NERVOUS SYSTEM ACTIVITY. AN OPEN LABEL PHASE IV NON-INFERIORITY STUDY.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-023797-39 |
| Trial protocol | GB |
| Global end of trial date | 20 August 2015 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 26 April 2017 |
| First version publication date | 26 April 2017 |
| Summary attachment (see zip file) | End of Trial report (End of Trial Report DSR 2017.docx) Oral iron treatment response (Final DSR JCC paper Oral Iron Treatment Response.pdf) |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | v.2 21 July 2015 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01991314 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | CSP ref: 40738, EudraCT number: 2010-023797-39, REDA ref: 007495BLT, REC ref: 10/H0504/90 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Barts Health NHS Trust |
| Sponsor organisation address | Joint Research Management Office, QM Innovations Building, 5 Walden Street , London, United Kingdom, E12EF |
| Public contact | Marie-Claire Rickard, Joint Research Management Office, +44 2078827272, m.rickard@qmul.ac.uk |
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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 | 09 June 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 May 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 August 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess these hypotheses:

- [1] there is no difference in the haemoglobin response to oral iron treatment of iron deficiency anaemia (IDA) in adolescent compared to adult IBD patients;
- [2] oral iron does not worsen disease activity in IBD;
- [3] response to oral iron is inversely related to serum hepcidin concentrations at baseline; and
- [4] treatment of anaemia improves QOL, mood and fatigue in adolescent and adult patients with IBD.

Protection of trial subjects:

Patients were fully informed of the aims of the trial verbally and with patient information sheets. Their usual outpatient care was undertaken (including routine blood samples before and after treatment with oral iron), the only extra procedures being collection of two stool samples (for measurement of faecal calprotectin) and completion of psychometric questionnaires. There was no pain or distress involved.

Background therapy:

Patients were on a range of treatments for their inflammatory bowel disease (IBD). These are shown in Table 1 of the attached paper and were, in adolescents and adults respectively, the following: 5 ASA 32 [71%], 17 [40%]; prednisolone/budesonide 7 [16%], 7 [16%]; enteral nutrition 3 [7%], 0 [0%]; thiopurine 23 [51%], 20 [47%]; methotrexate or ciclosporine 2 [4%], 0 [0%]; anti-TNF 2 [4%], 3 [7%]; antidepressants 0 [0%], 3 [7%].

Evidence for comparator:

Iron deficiency anaemia [IDA] is a frequent complication of IBD. In children and adolescents IDA appears to be commoner than in adults and is often undertreated, perhaps reflecting paediatricians' concerns about side effects, including worsening of disease activity, and about young people's medication adherence. Quality of life [QOL] correlates negatively with severity of anaemia in IBD. Prospective studies of oral and intravenous iron in adults with IBD have shown improvements in QOL when the haemoglobin [Hb] is corrected but this effect has not been assessed in young people with IBD. Psychological distress and fatigue are common in people of all ages with IBD but to our knowledge there have been no prospective studies of the effects of oral iron supplementation on these factors in people with IBD.

It is widely stated that the Hb response to oral iron is reduced in patients with active IBD: this has been confirmed in one but not all studies. Such an effect could be explained by involvement of hepcidin, which regulates iron homeostasis by inhibiting its uptake by enterocytes, macrophages and hepatocytes. Serum hepcidin levels are increased by pro-inflammatory cytokines; conversely, in iron deficiency, hepcidin levels fall. Serum hepcidin concentrations at baseline are related inversely to the Hb response to oral iron in patients with rheumatoid arthritis and other diseases, but whether this is true in IBD is unknown.

We therefore undertook a prospective phase IV, open-label, parallel group, 6-week non-inferiority clinical trial using oral ferrous sulphate to assess the hypotheses that: [1] there is no difference in the Hb response to oral iron treatment of IDA in adolescent compared to adult IBD patients; [2] oral iron does not worsen disease activity in IBD; [3] response to oral iron is inversely to serum hepcidin concentrations at baseline; and [4] treatment of anaemia improves QOL, mood and fatigue in these patients

| | |
|---|-----------------|
| Actual start date of recruitment | 04 January 2012 |
| 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: 88 |
| Worldwide total number of subjects | 88 |
| EEA total number of subjects | 88 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 41 |
| Adults (18-64 years) | 46 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Between January 2012 and April 2015, adolescent and adult patients with IBD (ulcerative colitis, Crohn's disease or IBD unclassified) were recruited at Barts and the Royal London Hospitals, Barts Health Trust or at Chelsea and Westminster Hospital, London , UK.

Pre-assignment

Screening details:

Patients who within the next month were due to attend the adult, young people's and paediatric IBD clinics were screened for the result of their haemoglobin concentration at their previous clinic attendance. Those found to be anaemic were sent a letter of explanation about, and invitation to participate in the trial.

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Patients at baseline (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|------------------------------|
| Arm title | Adolescents aged 13-18 years |
|------------------|------------------------------|

Arm description:

Adolescents with IBD and IDA

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ferrous sulphate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200mg twice daily for 6 weeks

| | |
|------------------|------------------------|
| Arm title | Adults aged 19 or more |
|------------------|------------------------|

Arm description:

Adults aged 19 or more with IBD and IDA

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ferrous sulphate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200mg twice daily for 6 weeks

| Number of subjects in period 1 | Adolescents aged 13-18 years | Adults aged 19 or more |
|---------------------------------------|------------------------------|------------------------|
| Started | 45 | 43 |
| Completed | 34 | 32 |
| Not completed | 11 | 11 |
| Adverse event, non-fatal | 5 | 1 |
| Lost to follow-up | 6 | 10 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Adolescents aged 13-18 years |
|-----------------------|------------------------------|

Reporting group description:

Adolescents with IBD and IDA

| | |
|-----------------------|------------------------|
| Reporting group title | Adults aged 19 or more |
|-----------------------|------------------------|

Reporting group description:

Adults aged 19 or more with IBD and IDA

| Reporting group values | Adolescents aged 13-18 years | Adults aged 19 or more | Total |
|------------------------|------------------------------|------------------------|-------|
| Number of subjects | 45 | 43 | 88 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 14.9 | 32.5 | - |
| standard deviation | ± 1.67 | ± 11.4 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 22 | 23 | 45 |
| Male | 23 | 20 | 43 |
| Haemoglobin | | | |
| Units: g/dl | | | |
| arithmetic mean | 10.3 | 10.9 | - |
| standard deviation | ± 1.21 | ± 2.23 | - |
| Serum hepcidin | | | |
| Units: ng/ml | | | |
| arithmetic mean | 31.3 | 28.7 | - |
| standard deviation | ± 26.2 | ± 19 | - |
| transferrin saturation | | | |
| Units: percent weight/weight | | | |
| arithmetic mean | 7 | 7.8 | - |
| standard deviation | ± 2.4 | ± 3.9 | - |
| C-reactive protein | | | |
| Units: mg/l | | | |
| arithmetic mean | 9.9 | 11.4 | - |
| standard deviation | ± 22.8 | ± 19 | - |
| Faecal calprotectin | | | |
| Units: ug/g | | | |
| arithmetic mean | 295 | 299 | - |
| standard deviation | ± 322 | ± 511 | - |
| Shortened IBD Questionnaire | | | |
| Quality of life questionnaire validated for patients with IBD | | | |
| Units: numbers | | | |
| arithmetic mean | 51 | 44 | - |
| standard deviation | ± 12.7 | ± 15.1 | - |

| | | | |
|---|--------|--------|---|
| HADS-A | | | |
| Hospital anxiety and depression score - anxiety | | | |
| Units: numbers | | | |
| arithmetic mean | 7.3 | 8.1 | |
| standard deviation | ± 5.4 | ± 4.6 | - |
| HADS-D | | | |
| HADS-depression | | | |
| Units: numbers | | | |
| arithmetic mean | 4.4 | 6 | |
| standard deviation | ± 4 | ± 3.9 | - |
| Perceived Stress Questionnaire-G | | | |
| Assessment of perceived stress | | | |
| Units: numbers | | | |
| arithmetic mean | 57 | 71 | |
| standard deviation | ± 15.4 | ± 15.7 | - |
| Multidimensional Fatigue Inventory | | | |
| Measure of fatigue | | | |
| Units: numbers | | | |
| arithmetic mean | 58 | 60 | |
| standard deviation | ± 7.5 | ± 7.2 | - |

End points

End points reporting groups

| | |
|---|------------------------------|
| Reporting group title | Adolescents aged 13-18 years |
| Reporting group description: Adolescents with IBD and IDA | |
| Reporting group title | Adults aged 19 or more |
| Reporting group description: Adults aged 19 or more with IBD and IDA | |

Primary: Increase in haemoglobin concentration (1)

| | |
|---|---|
| End point title | Increase in haemoglobin concentration (1) |
| End point description: Intention to treat analysis | |
| End point type | Primary |
| End point timeframe: after 6 weeks on ferrous sulphate | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|---|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 43 | | |
| Units: g/dl | | | | |
| arithmetic mean (confidence interval 95%) | 1.22 (0.79 to 1.64) | 1.3 (0.84 to 1.75) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | ANCOVA |
| Statistical analysis description: To test the hypothesis of non-inferiority with maximal statistical power, ANCOVA was used to compare the change in mean haemoglobin levels between adults and adolescents after accounting for necessary covariates. 95% confidence intervals were established for the treatment effects to determine the status of the primary hypothesis. | |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.8 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.7 |

Primary: Increase in haemoglobin concentration (2)

| | |
|------------------------|---|
| End point title | Increase in haemoglobin concentration (2) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|--------------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 43 | | |
| Units: g/dl | | | | |
| arithmetic mean (standard deviation) | 1.4 (± 1.5) | 1 (± 1.5) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Student's t test (unpaired) |
| Statistical analysis description: | |
| To compare the change in Hb produced by oral iron between the adolescent and adult groups | |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.23 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |

Notes:

[1] - See above. Statistical Package for the Social Sciences [SPSS] [version 16] was used for the statistical analysis.

Primary: Numbers of patients normalising haemoglobin

| | |
|--|---|
| End point title | Numbers of patients normalising haemoglobin |
| End point description: | |
| Using the chi-squared test, we compared the proportions of patients in each group in whom ferrous sulphate produced a normalisation of haemoglobin concentration by WHO criteria | |
| End point type | Primary |

End point timeframe:

6 weeks

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|-----------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 43 | | |
| Units: numbers | | | | |
| number (not applicable) | 13 | 16 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Chi squared test |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5 |
| Method | Chi-squared |

Secondary: Increase in serum hepcidin concentration

| | |
|------------------------|--|
| End point title | Increase in serum hepcidin concentration |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 43 | | |
| Units: ng/ml | | | | |
| arithmetic mean (standard error) | 4.8 (± 2.4) | 6.6 (± 2.6) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Unpaired Student's t test |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.6 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |

Notes:

[2] - This test was to see if there was a difference in hepcidin response to oral iron between the two arms.

Secondary: Increase in transferrin saturation

| | |
|------------------------|------------------------------------|
| End point title | Increase in transferrin saturation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 43 | | |
| Units: percentage | | | | |
| arithmetic mean (standard error) | 10.5 (± 2.3) | 10.7 (± 2.2) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Unpaired Student's t test |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.98 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |

Secondary: Change in C reactive protein

| | |
|------------------------|------------------------------|
| End point title | Change in C reactive protein |
| End point description: | |
| End point type | Secondary |

End point timeframe:

6 weeks

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 32 | | |
| Units: mg/l | | | | |
| arithmetic mean (standard error) | 0.5 (\pm 1.5) | 1.5 (\pm 3.4) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Unpaired Student's t test |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.78 |
| Method | t-test, 2-sided |

Secondary: Change in faecal calprotectin

| | |
|------------------------|-------------------------------|
| End point title | Change in faecal calprotectin |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 32 | | |
| Units: ug/g | | | | |
| arithmetic mean (standard error) | -35 (\pm 38) | -40 (\pm 81) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Unpaired Student's t test |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.96 |
| Method | t-test, 2-sided |

Secondary: Change in SIBDQ

| | |
|------------------------|-----------------|
| End point title | Change in SIBDQ |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 32 | | |
| Units: numbers | | | | |
| arithmetic mean (standard error) | 3.2 (± 2.6) | 5.7 (± 2) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Unpaired Student's t test |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.49 |
| Method | t-test, 2-sided |

Secondary: Change in HADS-A

| | |
|------------------------|------------------|
| End point title | Change in HADS-A |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 32 | | |
| Units: numbers | | | | |
| arithmetic mean (standard error) | -0.7 (\pm 0.5) | -1.1 (\pm 0.7) | | |

Statistical analyses

| Statistical analysis title | Unpaired Student's t test |
|---|---|
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.85 |
| Method | t-test, 2-sided |

Secondary: Change in HADS-D

| | |
|------------------------|------------------|
| End point title | Change in HADS-D |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 32 | | |
| Units: numbers | | | | |
| arithmetic mean (standard error) | -0.5 (\pm 0.5) | -0.9 (\pm 0.7) | | |

Statistical analyses

| Statistical analysis title | Unpaired Student's t test |
|----------------------------|---|
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |

| | |
|---|-----------------|
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.62 |
| Method | t-test, 2-sided |

Secondary: Change in PSQ-G

| | |
|------------------------|-----------------|
| End point title | Change in PSQ-G |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 32 | | |
| Units: numbers | | | | |
| arithmetic mean (standard error) | 4.1 (± 2.5) | -11.8 (± 2.5) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Unpaired Student's t test |
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | t-test, 2-sided |

Secondary: Change in MFI

| | |
|------------------------|---------------|
| End point title | Change in MFI |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 weeks | |

| End point values | Adolescents aged 13-18 years | Adults aged 19 or more | | |
|----------------------------------|------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 32 | | |
| Units: numbers | | | | |
| arithmetic mean (standard error) | 0.9 (\pm 1.4) | 1.9 (\pm 0.7) | | |

Statistical analyses

| Statistical analysis title | Unpaired Student's t test |
|---|---|
| Comparison groups | Adolescents aged 13-18 years v Adults aged 19 or more |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.69 |
| Method | t-test, 2-sided |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 weeks

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-----------|
| Dictionary name | SNOMED CT |
|-----------------|-----------|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Adolescents |
|-----------------------|-------------|

Reporting group description:

Adolescents aged 13-18

| | |
|-----------------------|------------------------|
| Reporting group title | Adults aged 19 or more |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events | Adolescents | Adults aged 19 or more | |
|---|---|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 1 / 43 (2.33%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | Additional description: Also vomiting and constipation | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | Additional description: Relapse of her ulcerative colitis as her steroid dose was reduced | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Adolescents | Adults aged 19 or more | |
|---|-----------------|------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 45 (17.78%) | 7 / 43 (16.28%) | |
| Nervous system disorders | | | |

| | | | |
|--|---------------------------------------|---------------------|--|
| Headache subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 0 / 43 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 4 | 4 / 43 (9.30%) 4 | |
| Nausea | Additional description: with vomiting | | |
| subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 0 / 43 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 3 / 43 (6.98%) 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 24 April 2012 | Because of staffing reductions, we reduced the numbers of investigations (nutritional assessment, exercise tolerance testing and Neuroscope testing) which we had planned in the original version of the Protocol; in addition, we decided that we were no longer able to provide Cosmofer in the necessary time-frame for the patients who proved to be intolerant of oral ferrous sulphate. |
| 14 September 2012 | <ol style="list-style-type: none">1. We requested an increase in the number of patients to be approached for recruitment from 90 to 140, because a higher than expected number of patients had turned out not to meet the inclusion criteria at the time of planned recruitment because their post-consent blood test showed them either to be no longer anaemic by WHO standards, or no longer iron deficient (Fe saturation <18%) (ie, during the time between their previous out-patient appointment and the intended recruitment date, their haemoglobin and iron status had improved).2. Because of Pharmacy staffing shortages, to save time and inconvenience for patients attending afternoon clinics at the Royal London or any clinics at St Bartholomew's Hospital, we arranged for prescriptions for ferrous sulphate to be collected from the Pharmacy at the Royal London by one of the investigators before the potential participants attended the clinic to give their written consent, giving them their tablets if/when this was been obtained. |
| 21 January 2013 | Change of name of sponsor from Barts and the London NHS Trust to Barts Health NHS Trust |
| 24 January 2013 | Because the initial suppliers, Wockhardt Ltd, could no longer make or supply ferrous sulphate tablets, we had to obtain them from an alternative supplier, Teva UK Ltd. |
| 10 October 2013 | <ol style="list-style-type: none">1. Because of staff changes, we altered the arrangements for obtaining and countersigning patients' consent. Consent was taken by suitably trained (including GCP training) medically qualified and delegated staff at each site. At each site the consent form was countersigned by the site PI.2. We changed our protocol to record that we were storing stool and serum samples at -40 rather than -80 degrees C.3. As recruitment was going more slowly than initially hoped, we requested an extension of the duration of the study beyond 31 Dec 2013. |
| 15 July 2015 | <ol style="list-style-type: none">1. We minimally changed the inclusion criteria so that iron deficiency was defined now by a transferrin saturation of <18% rather than <16%. We had noticed at a monitoring visit at Chelsea and Westminster Hospital that they were using a version of the protocol showing 16% rather than 18%.2. The faecal calprotectin assays were to be done in the routine Barts Health NHS Trust immunology laboratory rather than at Kings College Hospital (as originally planned) because the assay had now been established here as a routine clinical test.3. The hepcidin assays were now to be undertaken in the Gastroenterology Laboratory at the University of Birmingham, under the supervision of Dr Tariq Iqbal, rather than here, because the Birmingham assay was well-established and probably the most reliable in the UK.4. The letter to patients' GPs about their recruitment was very minimally modified. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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| For a description of the study's limitations, see the penultimate paragraph of the Discussion in the attached publication in Journal of Crohn's and Colitis, as well as Section 13 of the attached textual End of Trial Report. |
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27932449>