



## Clinical trial results:

### De-Iron: A phase 2 study of the efficacy and safety of Deferasirox administered at early iron loading in patients with transfusion-dependent Myelodysplastic Syndromes

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-004559-38 |
| Trial protocol           | GB             |
| Global end of trial date | 01 May 2017    |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 16 May 2018  |
| First version publication date | 16 May 2018  |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | RG_12-101 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |                                   |
|------------------------------------|-----------------------------------|
| ISRCTN number                      | ISRCTN62162141                    |
| ClinicalTrials.gov id (NCT number) | -                                 |
| WHO universal trial number (UTN)   | -                                 |
| Other trial identifiers            | Sponsors SAF number : ERN_11-0870 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Birmingham  |
| Sponsor organisation address | CR UK Clinical Trials Unit, Birmingham, United Kingdom, B15 2TT                                       |
| Public contact               | Helen Chantal Coulthard, CRCTU, University of Birmingham , +44 01213717865, De-Iron@trials.bham.ac.uk |
| Scientific contact           | Helen Chantal Coulthard, CRCTU, University of Birmingham , +44 01213717865, De-Iron@trials.bham.ac.uk |

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                       | 26 March 2018    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 02 December 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 01 May 2017      |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

The primary aim is to assess the activity of the oral iron chelator, deferasirox, given at early iron overload to patients with transfusion-dependent MDS. The secondary aim is to assess the safety and tolerability of deferasirox.

Protection of trial subjects:

The study protocol involves two additional visits to the hospital than would usually be required, both visits are for blood tests that are extra to what would be performed in standard clinical care. Some patients consent to take part in the Magnetic Resonance Imaging (MRI) scan part of the study, which involves two extra MRI scans. The risks of these extra tests are minimal, and it is possible that early intervention with iron chelating agents may prevent clinically overt or subclinical end organ damage. All patients will benefit from close monitoring during the trial period. As with all medications, treatment with deferasirox has potential side effects, for which all trial staff and patients are full informed. Close monitoring during the treatment period will allow prevention, detection and treatment of these side effects.

Background therapy:

The only treatment provided in the study is deferasirox, however participants are required to have clinical red blood cell transfusion requirements to enter the study. This is defined as transfusion of at least 2 units of red blood cells in the 8 week period preceding registration in the absence of active bleeding.

Evidence for comparator:

N/A

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 19 June 2013 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Worldwide total number of subjects   | 13                 |
| EEA total number of subjects         | 13                 |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|  |    |
|--|----|
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 1  |
| From 65 to 84 years                      | 11 |
| 85 years and over                        | 1  |

## Subject disposition

### Recruitment

Recruitment details:

Trial open to recruitment: 25-Jan-2013, First patient registered: 19-Jun-2013, Last Patient Last Visit: 02-Jun-2016.

### Pre-assignment

Screening details:

Full Blood Count, ALT/AST, Serum Creatinine, EGFR, CRP, Bilirubin and ALP

Serum Creatinine and EGFR

Serum Ferritin

CRP

Transfusion need assessment

Medical history

Bone marrow for IPSS categorisation

Hearing and ocular testing

Please refer to the protocol for eligibility criteria.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Phase I (overall period)    |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

Blinding implementation details:

N/A

### Arms

|           |           |
|-----------|-----------|
| Arm title | Treatment |
|-----------|-----------|

Arm description:

Deferasirox treatment

|  |                |
|--|----------------|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Deferasirox    |
| Investigational medicinal product code |                |
| Other name                             | Exjade         |
| Pharmaceutical forms                   | Soluble tablet |
| Routes of administration               | Oral use       |

Dosage and administration details:

10 mg/kg/day, rounded to the nearest multiple of 125mg. Taken on an empty stomach at least 30 min before food and preferably at the same time each day. The tablets are to be dispersed by stirring in a glass of water or orange/apple juice (100-200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water and swallowed.

| Number of subjects in period 1 | Treatment |
|--------------------------------|-----------|
| Started                        | 13        |
| Completed                      | 6         |
| Not completed                  | 7         |
| Disease progression            | 2         |
| Adverse event, non-fatal       | 2         |

|   |   |
|---|---|
| Toxicity-related treatment modification | 1 |
| Non-trial treatment                     | 1 |
| Consent withdrawn by subject            | 1 |

## Baseline characteristics

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Phase I (overall period) |
|-----------------------|--------------------------|

Reporting group description:

This group contains the full number of patients that took part in the trial.

| Reporting group values  | Phase I (overall period) | Total |  |
|---|--------------------------|-------|--|
| Number of subjects  | 13                       | 13    |  |
| Age categorical   |                          |       |  |
| Units: Subjects   |                          |       |  |
| In utero  | 0                        | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)            | 0                        | 0     |  |
| Newborns (0-27 days)  | 0                        | 0     |  |
| Infants and toddlers (28 days-23 months)                      | 0                        | 0     |  |
| Children (2-11 years)   | 0                        | 0     |  |
| Adolescents (12-17 years)                                     | 0                        | 0     |  |
| Adults (18-64 years)  | 1                        | 1     |  |
| From 65-84 years  | 11                       | 11    |  |
| 85 years and over   | 1                        | 1     |  |
| Age continuous  |                          |       |  |
| Units: years  |                          |       |  |
| median  | 72                       |       |  |
| full range (min-max)  | 61 to 86                 | -     |  |
| Gender categorical  |                          |       |  |
| Units: Subjects   |                          |       |  |
| Female  | 6                        | 6     |  |
| Male  | 7                        | 7     |  |
| Number of blood transfusions in 8 weeks prior to registration |                          |       |  |
| Units: Subjects   |                          |       |  |
| One transfusion   | 0                        | 0     |  |
| Two transfusions  | 5                        | 5     |  |
| Three transfusions  | 4                        | 4     |  |
| Four transfusions   | 3                        | 3     |  |
| Five transfusions   | 1                        | 1     |  |
| Serum Ferritin  |                          |       |  |
| Units: µg/L   |                          |       |  |
| median  | 753                      |       |  |
| full range (min-max)  | 336 to 1336              | -     |  |
| HbA1c   |                          |       |  |
| Units: mmol/mol   |                          |       |  |
| median  | 43.5                     |       |  |
| full range (min-max)  | 25 to 53                 | -     |  |
| Thyroid stimulating hormone                                   |                          |       |  |
| Units: mU/L   |                          |       |  |
| median  | 2.3                      |       |  |

|                              |              |   |  |
|------------------------------|--------------|---|--|
| full range (min-max)         | 0.8 to 7.9   | - |  |
| T4                           |              |   |  |
| Units: pmol/L                |              |   |  |
| median                       | 14.6         |   |  |
| full range (min-max)         | 10.3 to 21.3 | - |  |
| T3                           |              |   |  |
| Units: pmol/L                |              |   |  |
| median                       | 4.5          |   |  |
| full range (min-max)         | 3.6 to 5.0   | - |  |
| FSH                          |              |   |  |
| (females only)               |              |   |  |
| Units: IU/mL                 |              |   |  |
| median                       | 70.7         |   |  |
| full range (min-max)         | 51.6 to 85.9 | - |  |
| LH                           |              |   |  |
| (females only)               |              |   |  |
| Units: IU/mL                 |              |   |  |
| median                       | 24.9         |   |  |
| full range (min-max)         | 19.5 to 36.1 | - |  |
| Cardiac relaxation time      |              |   |  |
| Units: ms                    |              |   |  |
| median                       | 28.0         |   |  |
| full range (min-max)         | 16.2 to 36.0 | - |  |
| Hepatic relaxation time      |              |   |  |
| Units: ms                    |              |   |  |
| median                       | 8.1          |   |  |
| full range (min-max)         | 5.0 to 11.6  | - |  |
| Testosterone                 |              |   |  |
| (males only)                 |              |   |  |
| Units: nmol/L                |              |   |  |
| median                       | 10.6         |   |  |
| full range (min-max)         | 3.2 to 16.4  | - |  |
| Sex hormone binding globulin |              |   |  |
| (males only)                 |              |   |  |
| Units: nmol/L                |              |   |  |
| median                       | 69           |   |  |
| full range (min-max)         | 33 to 84     | - |  |
| Cortisol                     |              |   |  |
| Units: nmol/L                |              |   |  |
| median                       | 337          |   |  |
| full range (min-max)         | 30 to 558    | - |  |

## End points

### End points reporting groups

|   |                          |
|---|--------------------------|
| Reporting group title   | Treatment                |
| Reporting group description:<br>Deferasirox treatment   |                          |
| Subject analysis set title  | Evaluable population set |
| Subject analysis set type   | Safety analysis          |
| Subject analysis set description:<br>The evaluable population set includes all patients who have completed 12 months of treatment and have reached the month 11 assessment of serum ferritin level. |                          |
| Subject analysis set title  | Full population set      |
| Subject analysis set type   | Full analysis            |
| Subject analysis set description:<br>The full population set includes all patients who have taken at least 1 dose of study drug.  |                          |

### Primary: Assessment of Activity

|   |                                       |
|---|---------------------------------------|
| End point title   | Assessment of Activity <sup>[1]</sup> |
| End point description:<br>To assess the activity of the oral iron chelator, deferasirox, given at early iron overload to patients with transfusion-dependent MDS. |                                       |
| End point type  | Primary                               |
| End point timeframe:<br>Within 12 months of deferasirox therapy   |                                       |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis has been carried out on the primary outcome due to small sample size.

| End point values            | Evaluable population set | Full population set  |  |  |
|-----------------------------|--------------------------|----------------------|--|--|
| Subject group type          | Subject analysis set     | Subject analysis set |  |  |
| Number of subjects analysed | 8                        | 13                   |  |  |
| Units: ug/L                 | 3                        | 3                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety and tolerability of deferasirox

|  |  |
|--|--|
| End point title  | Safety and tolerability of deferasirox |
| End point description:<br>Safety and tolerability of deferasirox based on CTCAE criteria version 4.0 |  |
| End point type   | Secondary                              |
| End point timeframe:<br>Within 12 months of deferasirox therapy                                      |  |



| End point values                    | Full population set  |  |  |  |
|-------------------------------------|----------------------|--|--|--|
| Subject group type                  | Subject analysis set |  |  |  |
| Number of subjects analysed         | 13                   |  |  |  |
| Units: Number of participants       |                      |  |  |  |
| Grade 3/4 non-haematological events | 2                    |  |  |  |
| Non-haematological SUSARs           | 0                    |  |  |  |
| Auditory events                     | 0                    |  |  |  |
| Ocular events                       | 0                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean serum ferritin >1500µg/L

|  |                               |
|--|-------------------------------|
| End point title  | Mean serum ferritin >1500µg/L |
| End point description:   |                               |
| Proportion of patients with mean serum ferritin >1500µg/L within 12 months |                               |
| End point type   | Secondary                     |
| End point timeframe:   |                               |
| Within 12 months of deferasirox therapy                                    |                               |

| End point values            | Full population set  |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 13                   |  |  |  |
| Units: ug/L                 |                      |  |  |  |
| Mean SF>1500                | 3                    |  |  |  |
| Mean SF<=1500               | 10                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maintain serum ferritin <1500 µg/L

|   |                                    |
|---|------------------------------------|
| End point title   | Maintain serum ferritin <1500 µg/L |
| End point description:  |                                    |
| Proportion of patients maintaining serum ferritin <1500 µg/L at 12 months |                                    |
| End point type  | Secondary                          |
| End point timeframe:  |                                    |
| Within 12 months of deferasirox therapy                                   |                                    |

| End point values            | Full population set  |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 13                   |  |  |  |
| Units: ug/L                 |                      |  |  |  |
| SF maintained               | 8                    |  |  |  |
| SF not maintained           | 5                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Haematological improvement

|   |                            |
|---|----------------------------|
| End point title   | Haematological improvement |
| End point description:<br>Proportion of patients achieving hematologic improvement (per IWG2006 criteria), time to haematological improvement (per IWG2006 criteria) measured from entry into the trial to first haematological improvement and duration of haematological improvement (per IWG2006 criteria) from first documented improvement to progression/relapse. |                            |
| End point type  | Secondary                  |
| End point timeframe:<br>Within 12 months of deferasirox therapy   |                            |

| End point values                  | Full population set  |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 13                   |  |  |  |
| Units: Haematological improvement | 2                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change in Cardiac iron loading

|  |                                     |
|--|-------------------------------------|
| End point title  | Mean change in Cardiac iron loading |
| End point description:<br>Cardiac iron loading quantified by mean change in relaxation time between pre-treatment (baseline) and post-treatment (at 12 months or when SF >1500 µg/L) assessments measured by MRI R2* and T2* |                                     |
| End point type   | Secondary                           |
| End point timeframe:<br>at 12 months of deferasirox therapy  |                                     |

| End point values                     | Full population set  |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 2                    |  |  |  |
| Units: seconds                       |                      |  |  |  |
| arithmetic mean (standard deviation) | 7.8 ( $\pm$ 12.7)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in hepatic iron loading

|   |                                     |
|---|-------------------------------------|
| End point title   | Mean change in hepatic iron loading |
| End point description:<br>Hepatic iron loading quantified by mean change in relaxation time between pre-treatment (baseline) and post-treatment (at 12 months or when SF >1500 µg/L) assessments measured by MRI R2* and T2*. |                                     |
| End point type  | Secondary                           |
| End point timeframe:<br>at 12 months of deferasirox therapy   |                                     |

| End point values                     | Full population set  |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 2                    |  |  |  |
| Units: seconds                       |                      |  |  |  |
| arithmetic mean (standard deviation) | -1.6 ( $\pm$ 0.6)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in endocrine function

|  |                                   |
|--|-----------------------------------|
| End point title  | Mean change in endocrine function |
| End point description:<br>Endocrine function defined as the mean change from baseline at 6 and 12 months in the following parameters: HbA1c (glycated haemoglobin), Thyroid function (as measured by TSH, free T4, and T3 if indicated), FSH and LH (women only), Testosterone and Sex hormone binding globulin (men only), Cortisol |                                   |
| End point type   | Secondary                         |
| End point timeframe:<br>Within 12 months of deferasirox therapy  |                                   |

| End point values                     | Full population set  |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 13                   |  |  |  |
| Units: Endocrine function            |                      |  |  |  |
| arithmetic mean (standard deviation) |                      |  |  |  |
| Diabetes                             | -2.4 ( $\pm$ 3.5)    |  |  |  |
| Thyroid                              | 0 ( $\pm$ 0.7)       |  |  |  |
| FSH                                  | 2.5 ( $\pm$ 3.3)     |  |  |  |
| LH                                   | -0.5 ( $\pm$ 5.6)    |  |  |  |
| Cortisol 30                          | 0 ( $\pm$ 0)         |  |  |  |
| Cortisol 60                          | 0 ( $\pm$ 0)         |  |  |  |
| Testosterone                         | -2.9 ( $\pm$ 4.7)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in biochemical iron parameters

|  |  |
|--|--|
| End point title  | Mean change in biochemical iron parameters |
| End point description:   |  |
| Mean change from baseline at 6 and 12 months in the following biochemical iron parameters: Transferrin saturation, Hepcidin, Non-transferrin bound iron, GDF15 |  |
| End point type   | Secondary                                  |
| End point timeframe:   |  |
| Within 12 months of deferasirox therapy  |  |

| End point values                     | Full population set     |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Subject analysis set    |  |  |  |
| Number of subjects analysed          | 13                      |  |  |  |
| Units: Biochemical iron parameters   |                         |  |  |  |
| arithmetic mean (standard deviation) |                         |  |  |  |
| Transferrin saturation 6 months      | 5.36 ( $\pm$ 23.41)     |  |  |  |
| Transferrin saturation 12 months     | 6.11 ( $\pm$ 30.52)     |  |  |  |
| Hepcidin 6 months                    | 3.01 ( $\pm$ 25.7)      |  |  |  |
| Hepcidin 12 months                   | 4.38 ( $\pm$ 33.78)     |  |  |  |
| Non-transferrin bound iron 6 months  | 0.26 ( $\pm$ 1.83)      |  |  |  |
| Non-transferrin bound iron 12 months | 0.52 ( $\pm$ 1.51)      |  |  |  |
| GDF15 6 months                       | 682.38 ( $\pm$ 5691.45) |  |  |  |
| GDF15 12 months                      | 1439.26 ( $\pm$ 5898.6) |  |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Date of commencement of protocol-defined treatment(e.g. first date of taking deferasirox) until 30 days after the administration of the last trial treatment

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events                            | All patients   |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 4 / 13 (30.77%)  |  |  |
| number of deaths (all causes)                     | 2  |  |  |
| number of deaths resulting from adverse events    | 0  |  |  |
| Surgical and medical procedures                   |  |  |  |
| Incarcerated hernia                               |  |  |  |
| subjects affected / exposed                       | 1 / 13 (7.69%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Blood and lymphatic system disorders              |  |  |  |
| Febrile neutropenia                               |  |  |  |
| subjects affected / exposed                       | 1 / 13 (7.69%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Gastrointestinal disorders                        |  |  |  |
| Abdominal pain                                    |  |  |  |
| subjects affected / exposed                       | 1 / 13 (7.69%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Infections and infestations                       |  |  |  |
| Urinary tract infection                           | Additional description: Chronic kidney disease. Fever. |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 13 (7.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Device related infection                        |                |  |  |
| subjects affected / exposed                     | 1 / 13 (7.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                                   | All patients      |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events               |                   |  |  |
| subjects affected / exposed   | 13 / 13 (100.00%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Cyst  |                   |  |  |
| subjects affected / exposed   | 1 / 13 (7.69%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Benign prostatic hyperplasia  |                   |  |  |
| subjects affected / exposed   | 1 / 13 (7.69%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Basal cell carcinoma  |                   |  |  |
| subjects affected / exposed   | 1 / 13 (7.69%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Surgical and medical procedures                                     |                   |  |  |
| Incarcerated inguinal hernia  |                   |  |  |
| subjects affected / exposed   | 1 / 13 (7.69%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| General disorders and administration site conditions                |                   |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed   | 5 / 13 (38.46%)   |  |  |
| occurrences (all)   | 6                 |  |  |
| Fever   |                   |  |  |
| subjects affected / exposed   | 1 / 13 (7.69%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Flu like symptoms   |                   |  |  |

|   |  |  |  |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leg oedema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>1</p>                                 |  |  |
| <p>Reproductive system and breast disorders</p> <p>Vaginal haemorrhage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 13 (7.69%)</p> <p>1</p>   |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sore throat</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 13 (23.08%)</p> <p>3</p> <p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>1</p> |  |  |
| <p>Psychiatric disorders</p> <p>Confusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>1</p>  |  |  |
| <p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>4 / 13 (30.77%)</p> <p>6</p>  |  |  |



|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| Alkaline Phosphatase increased       |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 3               |  |  |
| Aspartate aminotransferase increased |                 |  |  |
| subjects affected / exposed          | 5 / 13 (38.46%) |  |  |
| occurrences (all)                    | 3               |  |  |
| Blood bilirubin increased            |                 |  |  |
| subjects affected / exposed          | 3 / 13 (23.08%) |  |  |
| occurrences (all)                    | 4               |  |  |
| Cholesterol high                     |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Creatinine increased                 |                 |  |  |
| subjects affected / exposed          | 7 / 13 (53.85%) |  |  |
| occurrences (all)                    | 18              |  |  |
| Raised white cell count              |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Raised platelets                     |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 3               |  |  |
| Haematocrit decreased                |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Testosterone reduced                 |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Urea reduced                         |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| C-reactive protein increased         |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Serum ferritin decreased             |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                    | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Lymphocyte count decreased                     |                 |  |  |
| subjects affected / exposed                    | 3 / 13 (23.08%) |  |  |
| occurrences (all)                              | 11              |  |  |
| Neutrophil count decreased                     |                 |  |  |
| subjects affected / exposed                    | 4 / 13 (30.77%) |  |  |
| occurrences (all)                              | 13              |  |  |
| Platelet count decreased                       |                 |  |  |
| subjects affected / exposed                    | 4 / 13 (30.77%) |  |  |
| occurrences (all)                              | 27              |  |  |
| White blood cell count decreased               |                 |  |  |
| subjects affected / exposed                    | 4 / 13 (30.77%) |  |  |
| occurrences (all)                              | 11              |  |  |
| Injury, poisoning and procedural complications |                 |  |  |
| Bruising                                       |                 |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Cardiac disorders                              |                 |  |  |
| Mitral valve disease                           |                 |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Palpitations                                   |                 |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Sinus bradycardia                              |                 |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Nervous system disorders                       |                 |  |  |
| Dizziness                                      |                 |  |  |
| subjects affected / exposed                    | 4 / 13 (30.77%) |  |  |
| occurrences (all)                              | 4               |  |  |
| Dysgeusia                                      |                 |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Headache                                       |                 |  |  |

|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed          | 2 / 13 (15.38%) |  |  |
| occurrences (all)                    | 2               |  |  |
| Lethargy                             |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Cold feet                            |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Numbness-calves (hypoesthesia)       |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Paresthesia                          |                 |  |  |
| subjects affected / exposed          | 3 / 13 (23.08%) |  |  |
| occurrences (all)                    | 3               |  |  |
| Peripheral motor neuropathy          |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Blood and lymphatic system disorders |                 |  |  |
| Anaemia                              |                 |  |  |
| subjects affected / exposed          | 7 / 13 (53.85%) |  |  |
| occurrences (all)                    | 48              |  |  |
| Febrile neutropenia                  |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Ear and labyrinth disorders          |                 |  |  |
| Blocked ears                         |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Ear pain                             |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Vertigo                              |                 |  |  |
| subjects affected / exposed          | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Eye disorders                        |                 |  |  |

|                                 |                 |  |  |
|---------------------------------|-----------------|--|--|
| Gritty eyes                     |                 |  |  |
| subjects affected / exposed     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Puffiness around eyes           |                 |  |  |
| subjects affected / exposed     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Puffy eyes                      |                 |  |  |
| subjects affected / exposed     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Gastrointestinal disorders      |                 |  |  |
| Abdominal distension            |                 |  |  |
| subjects affected / exposed     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)               | 2               |  |  |
| Abdominal pain                  |                 |  |  |
| subjects affected / exposed     | 3 / 13 (23.08%) |  |  |
| occurrences (all)               | 4               |  |  |
| Bloating                        |                 |  |  |
| subjects affected / exposed     | 2 / 13 (15.38%) |  |  |
| occurrences (all)               | 2               |  |  |
| Constipation                    |                 |  |  |
| subjects affected / exposed     | 4 / 13 (30.77%) |  |  |
| occurrences (all)               | 5               |  |  |
| Diarrhoea                       |                 |  |  |
| subjects affected / exposed     | 3 / 13 (23.08%) |  |  |
| occurrences (all)               | 6               |  |  |
| Dry mouth                       |                 |  |  |
| subjects affected / exposed     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Dyspepsia                       |                 |  |  |
| subjects affected / exposed     | 2 / 13 (15.38%) |  |  |
| occurrences (all)               | 3               |  |  |
| Faecal incontinence             |                 |  |  |
| subjects affected / exposed     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)               | 1               |  |  |
| Gastroesophageal reflux disease |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Small bowel obstruction                |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Loss of appetite                       |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Mucositis oral                         |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Nausea                                 |                 |  |  |
| subjects affected / exposed            | 3 / 13 (23.08%) |  |  |
| occurrences (all)                      | 5               |  |  |
| Rectal haemorrhage                     |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Stomach pain                           |                 |  |  |
| subjects affected / exposed            | 2 / 13 (15.38%) |  |  |
| occurrences (all)                      | 2               |  |  |
| Vomiting                               |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Skin and subcutaneous tissue disorders |                 |  |  |
| Alopecia                               |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Pruritis                               |                 |  |  |
| subjects affected / exposed            | 2 / 13 (15.38%) |  |  |
| occurrences (all)                      | 2               |  |  |
| Rash maculo-papular                    |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Night sweats                           |                 |  |  |
| subjects affected / exposed            | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                      | 1               |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 3 / 13 (23.08%)<br>3 |  |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)           | 1 / 13 (7.69%)<br>5  |  |  |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)                                       | 4 / 13 (30.77%)<br>7 |  |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| Nocturia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| Urea raised<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>2  |  |  |
| Urinary frequency<br>subjects affected / exposed<br>occurrences (all)  | 2 / 13 (15.38%)<br>2 |  |  |
| Endocrine disorders<br>Hypoparathyroidism<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 13 (7.69%)<br>1  |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthritis<br>subjects affected / exposed<br>occurrences (all) | 1 / 13 (7.69%)<br>1  |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)  | 3 / 13 (23.08%)<br>3 |  |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| Cramp - legs/feet           |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Shoulder pain               |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Achey legs                  |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pain - shoulders and back   |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Cramps                      |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Myalgia                     |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Neck pain                   |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Infections and infestations |                |  |  |
| Bronchial infection         |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Device related infection    |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Cold                        |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Cold sore - nose            |                |  |  |
| subjects affected / exposed | 1 / 13 (7.69%) |  |  |
| occurrences (all)           | 1              |  |  |
| Unknown source              |                |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Lung infection                     |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Rhinitis infective                 |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Skin infection                     |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Upper respiratory infection        |                 |  |  |
| subjects affected / exposed        | 3 / 13 (23.08%) |  |  |
| occurrences (all)                  | 3               |  |  |
| Urinary tract infection            |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Metabolism and nutrition disorders |                 |  |  |
| Anorexia                           |                 |  |  |
| subjects affected / exposed        | 2 / 13 (15.38%) |  |  |
| occurrences (all)                  | 2               |  |  |
| Hypercalcaemia                     |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Hyperkalaemia                      |                 |  |  |
| subjects affected / exposed        | 2 / 13 (15.38%) |  |  |
| occurrences (all)                  | 3               |  |  |
| Hypoalbuminaemia                   |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Hypocalcaemia                      |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Hypophosphataemia                  |                 |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                  | 1               |  |  |



|   |                     |  |  |
|---|---------------------|--|--|
| Iron overload<br>subjects affected / exposed<br>occurrences (all) | 1 / 13 (7.69%)<br>1 |  |  |
|---|---------------------|--|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 31 August 2012    | <ul style="list-style-type: none"> <li>• Change in exclusion criteria from &gt;40ml/min creatinine clearance to &gt;60ml/min creatinine clearance</li> </ul>  |
| 20 November 2012  | <ul style="list-style-type: none"> <li>• Addition of 2 secondary endpoints: (time to Haematological response and duration of response)</li> <li>• Reduction of Iron parameter sampling from 8 to 4 time points</li> <li>• Clarifications of dose modifications and discontinuation</li> <li>• Minor typing errors</li> </ul>  |
| 28 December 2012  | <ul style="list-style-type: none"> <li>• The addition of four sites: <ul style="list-style-type: none"> <li>- University Hospital Southampton NHS Foundation Trust</li> <li>- University Hospital of Leicester NHS Trust</li> <li>- East Cheshire NHS Trust</li> <li>- Sherwood Forest NHS Foundation Trust</li> </ul> </li> </ul>  |
| 25 April 2013     | <ul style="list-style-type: none"> <li>• The addition of two sites: <ul style="list-style-type: none"> <li>The Royal Wolverhampton Hospitals NHS Trust</li> <li>Epsom and St Helier University Hospitals NHS Trust</li> </ul> </li> <li>• Change of Trust name of Oxford Radcliff Hospitals NHS Trust to the Oxford University Hospitals NHS Trust.</li> </ul>  |
| 17 May 2013       | Addition of three sites: <ul style="list-style-type: none"> <li>• Northampton General Hospital NHS Trust</li> <li>• North West London Hospitals NHS Trust</li> <li>• North Bristol NHS Trust</li> </ul>   |
| 05 September 2013 | <ul style="list-style-type: none"> <li>• Change of Eligibility criteria - inclusion criteria updated to prevent patients entering the De-Iron study with platelets &lt;30 x10<sup>9</sup>/L and/or Neutrophils ≤0.5 x10<sup>9</sup>/L</li> <li>• Addition of Trial Management staff and contact numbers</li> <li>• Clarification of MRI endpoint analysis</li> <li>• Correction of the schedule of events</li> <li>• Advice for missed doses and clarification of patient follow up and treatment discontinuation</li> <li>• Change to the IMP Label wording</li> <li>• Updates to Patient Information Sheet/Informed Consent Form - correction of the version of the Patient Information Sheet referenced in the Informed Consent Form, addition to clarify that patients may have to have a bone marrow biopsy, if they had not had one in the 6 months prior to entering the trial, and further information about the procedure</li> </ul> |
| 20 September 2013 | <ul style="list-style-type: none"> <li>• Addition of 1 site <ul style="list-style-type: none"> <li>- East Sussex Healthcare NHS Trust</li> </ul> </li> </ul>  |
| 18 October 2013   | <ul style="list-style-type: none"> <li>• Addition of 1 site: <ul style="list-style-type: none"> <li>- Royal Cornwall Hospitals NHS Trust</li> </ul> </li> </ul>   |
| 02 December 2013  | <ul style="list-style-type: none"> <li>• Update to the Reference Safety Information (RSI) to reflect new information provided in the SPC (aggravated anaemia added as a new expected side effect)</li> <li>• Update to the Patient Information Sheet/Informed Consent Form to reflect the above change</li> </ul>   |
| 06 March 2014     | <ul style="list-style-type: none"> <li>• Modification of serum ferritin inclusion criteria to extend range from &lt;1000µg/l to &lt;1200µg/l</li> <li>• Minor typing errors</li> <li>• Changes to trials office contact details</li> </ul>  |

|                   |  |
|-------------------|--|
| 21 March 2014     | <ul style="list-style-type: none"> <li>• Addition of 1 site</li> <li>- Shrewsbury and Telford Hospitals NHS Trust</li> </ul>   |
| 28 May 2014       | <ul style="list-style-type: none"> <li>• Reordering of secondary endpoints</li> <li>• Changes to the definition of transfusion dependence - patients now able to start screening as soon as they start transfusions, rather than waiting 12 weeks before starting screening</li> <li>• Update to the schedule of assessments for clarity</li> <li>• Rewording of dose escalation for clarity</li> <li>• Updates and rewording of dose modification regarding Steven Johnsons Syndrome and pancreatitis</li> <li>• Update to the Patient Information Sheet to include Steven Johnsons Syndrome as a potential adverse event of unknown frequency and has added pancreatitis as a potential complication of gallstones that can develop from Deferasirox treatment</li> </ul>  |
| 22 September 2014 | Update to the Reference Safety Information (RSI) to include Stevens-Johnson Syndrome and Pancreatitis added as new expected side effects of unknown frequency  |
| 21 October 2014   | <ul style="list-style-type: none"> <li>• Addition of 1 site:</li> <li>- Taunton &amp; Somerset NHS Foundation Trust</li> </ul>   |
| 11 May 2015       | <ul style="list-style-type: none"> <li>• Change of Principal Investigator at St James' Hospital, Leeds</li> </ul>  |
| 15 July 2015      | <ul style="list-style-type: none"> <li>• Addition of 1 site:</li> <li>- South Tees Hospitals NHS Foundation Trust</li> </ul>   |
| 02 September 2015 | <ul style="list-style-type: none"> <li>• An extension of the recruitment period due to poor recruitment</li> <li>• A reduction in the recruitment target due to poor recruitment</li> <li>• Changes in the statistical considerations due to the updated recruitment target</li> <li>• An update of the eligibility criteria to include patients receiving erythropoietin</li> <li>• Changes in exclusion criteria to reduce use of prior investigational agents from 6 to 4 weeks, and clarification of active infection to <math>\geq</math> grade 3 according to CTCAE v4</li> <li>• Clarification of outcome measures to ensure appropriate statistical analysis</li> <li>• Clarifications to the trial assessments schedule to remove some inconsistencies observed by sites</li> <li>• Clarifications to the dose escalation section to include CRP <math>&lt;3 \times</math> ULN and EGFR <math>\geq 60</math> ml/min and change of serum ferritin from <math>1500\mu\text{g/L}</math> to <math>1350\mu\text{g/L}</math></li> <li>• Update to the dose modification section to include changes in the Deferasirox SPC</li> <li>• Clarifications to the discontinuation and follow-up procedures</li> <li>• Changes to adverse event reporting to exclude reporting of abnormal laboratory findings unless the abnormal laboratory finding results in early discontinuation, requires drug modification or interruption, requires therapeutic intervention or is of significant clinical importance</li> <li>• Inclusion of travel expenses to patients</li> <li>• Update to the Patient Information Sheet/Informed Consent Form to include updated information on dose modifications, travel expenses, Deferasirox information and side effects and to include the update that samples are not sent to Kings College, London.</li> <li>• Update to the GP letter to reflect updates to trial objectives, prescription of medication affecting hepatic and/or renal function or known to trigger skin reactions and care of patients who develop diarrhoea or vomiting.</li> <li>• Updates to the patient diary</li> </ul> |
| 29 October 2015   | <ul style="list-style-type: none"> <li>• Change of Principal Investigator at Royal Cornwall Hospitals NHS Trust</li> </ul>   |

|                   |   |
|-------------------|---|
| 19 September 2016 | <ul style="list-style-type: none"> <li>• Update to the Reference Safety Information (RSI) to reflect new information provided in the SPC in the reporting year: <ul style="list-style-type: none"> <li>- minor changes to the wording of the summary of the safety profile including the description of reduced creatinine cases in patients with beta thalassemia and iron overload</li> <li>- small changes to the terminology in the list of adverse reactions</li> <li>- Toxic Epidermal Necrolysis (TEN) has been added as a "not known" frequency side effect under Skin and subcutaneous tissue disorders</li> <li>- Acute pancreatitis has been added as a "not known" frequency side effect within gastrointestinal disorders</li> <li>- An additional paragraph added concerning creatinine clearance cases as identified in a retrospective meta-analysis</li> </ul> </li> </ul> |
| 21 March 2017     | <ul style="list-style-type: none"> <li>• Change of Principal Investigator at Conquest Hospital, East Sussex</li> </ul>  |

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.

Due to poor recruitment, the initial recruitment target of 54 was reduced and a total of 13 patients were recruited into the trial.

Notes: