# Clinical trial results:
# PhaseOut DMD: A Phase 2 Clinical Study to Assess the Activity and Safety of Utrophin Modulation with SMT C1100 in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy (C11005)

## Summary

| | |
|---|---|
| EudraCT number | 2015-004333-27 |
| Trial protocol | GB |
| Global end of trial date | 11 September 2018 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 13 June 2019 |
| First version publication date | 25 October 2018 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | SMT C11005 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02858362 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Summit (Oxford) Limited |
| Sponsor organisation address | 136a Eastern Avenue, Milton Park, Abingdon, United Kingdom, |
| Public contact | Clinical Trial Information, Summit (Oxford) Limited, clinicaltrials@summitplc.com |
| Scientific contact | Clinical Trial Information, Summit (Oxford) Limited, clinicaltrials@summitplc.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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 11 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 April 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 September 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To investigate changes in leg magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) in paediatric patients with Duchenne Muscular Dystrophy (DMD), following treatment with SMT C1100 (Cohorts 1 and 2).
To investigate the relationships between changes in leg MRI/MRS with plasma concentrations of SMT C1100 and its metabolites in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2).
To assess the safety and tolerability of SMT C1100 and its metabolites in paediatric patients with DMD.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, The International Council on Harmonisation of technical requirements for pharmaceuticals for human use (ICH) harmonized tripartite guideline regarding Good Clinical Practice (ICH-GCP E6 (R2) Consolidated Guidance, November 2016), all applicable subject privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013). This includes but is not limited to: Independent IRB/EC review and approval of study protocol and any subsequent amendments, subject informed consent, and investigator reporting requirements.

Prior to initiation of a study site, the Sponsor obtained approval from the appropriate regulatory agency to conduct the study in accordance with the ICH GCP and applicable country specific regulatory requirements.

The study was conducted in accordance with all applicable regulatory requirements.

The Investigator was to ensure that this protocol was conducted in full conformance with these principles or with the laws and regulations of the locality in which the research was conducted, whichever afforded the greater protection of the individual.

Written informed consent and assent was obtained from each patient (and their parents/guardian) prior to participation in the study. Written informed consent was collected following a review of the patient information leaflet by the potential patient and their parents/guardian and a discussion between the subject and their parents/guardian and the Investigator or suitably qualified designee.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 16 June 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Ethical reason |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 21 |
| Country: Number of subjects enrolled | United States: 22 |
| Worldwide total number of subjects | 43 |
| EEA total number of subjects | 21 |

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) | 41 |
| Adolescents (12-17 years) | 2 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Cohort 1 was conducted in the United Kingdom (UK) and the United States (US). Cohort 2 was conducted in the US. Cohort 3 was conducted in the UK.

### Pre-assignment

Screening details:

40 male patients aged between 5 and 10 years, with a diagnosis of Duchenne Muscular Dystrophy (confirmed by phenotypic and genetic evidence) were enrolled in either Cohort 1 or Cohort 2. An additional 3 patients were enrolled to Cohort 3 who had previously received SMT C1100 in other studies, but were not eligible for Cohorts 1 or 2 in this study.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1: Microfluidised Oral Suspension F3 |

Arm description:

Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous oral suspension formulation (F3) twice-daily (BID) for at least 48 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | SMT C1100 |
| Investigational medicinal product code | Ezutromid |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous suspension formulation (F3) BID for at least 48 weeks.

| | |
|---|---|
| **Arm title** | Cohort 2: Powder for Oral Suspension F6 |

Arm description:

Patients were to receive 1 g of SMT C1100 as a powder for oral suspension (F6) BID for at least 48 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | SMT C1100 |
| Investigational medicinal product code | Ezutromid |
| Other name | |
| Pharmaceutical forms | Powder for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive 1 g of SMT C1100 as a powder for oral suspension (F6) BID for at least 48 weeks.

| | |
|---|---|
| **Arm title** | Cohort 3: Microfluidised Oral Suspension F3 |

Arm description:

Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous oral suspension formulation (F3) twice-daily (BID) for at least 48 weeks. All 3 patients in Cohort 3 discontinued from the study prior to Week 24 due to premature study termination.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | SMT C1100 |
| Investigational medicinal product code | Ezutromid |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous suspension formulation (F3) BID for at least 48 weeks.

| **Number of subjects in period 1** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | Cohort 3: Microfluidised Oral Suspension F3 |
|---|---|---|---|
| Started | 30 | 10 | 3 |
| Completed | 29 | 9 | 0 |
| Not completed | 1 | 1 | 3 |
| Consent withdrawn by subject | 1 | - | - |
| Discontinued due to study termination | - | - | 3 |
| Protocol deviation | - | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1: Microfluidised Oral Suspension F3 |
| Reporting group description: | |
| Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous oral suspension formulation (F3) twice-daily (BID) for at least 48 weeks. | |
| Reporting group title | Cohort 2: Powder for Oral Suspension F6 |
| Reporting group description: | |
| Patients were to receive 1 g of SMT C1100 as a powder for oral suspension (F6) BID for at least 48 weeks. | |
| Reporting group title | Cohort 3: Microfluidised Oral Suspension F3 |
| Reporting group description: | |
| Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous oral suspension formulation (F3) twice-daily (BID) for at least 48 weeks. All 3 patients in Cohort 3 discontinued from the study prior to Week 24 due to premature study termination. | |

| Reporting group values | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | Cohort 3: Microfluidised Oral Suspension F3 |
|---|---|---|---|
| Number of subjects | 30 | 10 | 3 |
| Age categorical<br>Units: Subjects | | | |
| Children (2-11 years) | 30 | 10 | 1 |
| Adolescents (12-17 years) | 0 | 0 | 2 |
| Age continuous<br>Units: years | | | |
| median | 8.820 | 8.835 | 12.21 |
| full range (min-max) | 5.22 to 10.02 | 6.82 to 10.10 | 11.27 to 12.56 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 30 | 10 | 3 |
| Race<br>Units: Subjects | | | |
| White | 26 | 9 | 3 |
| Asian | 1 | 1 | 0 |
| Other | 3 | 0 | 0 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 2 | 0 |
| Not Hispanic or Latino | 29 | 8 | 3 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 43 | | |
| Age categorical<br>Units: Subjects | | | |
| Children (2-11 years) | 41 | | |
| Adolescents (12-17 years) | 2 | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>median<br>full range (min-max) | -<br> | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 0<br>43 | | |
| Race<br>Units: Subjects | | | |
| White<br>Asian<br>Other | 38<br>2<br>3 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino<br>Not Hispanic or Latino | 3<br>40 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1: Microfluidised Oral Suspension F3 |
| Reporting group description: | |
| Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous oral suspension formulation (F3) twice-daily (BID) for at least 48 weeks. | |
| Reporting group title | Cohort 2: Powder for Oral Suspension F6 |
| Reporting group description: | |
| Patients were to receive 1 g of SMT C1100 as a powder for oral suspension (F6) BID for at least 48 weeks. | |
| Reporting group title | Cohort 3: Microfluidised Oral Suspension F3 |
| Reporting group description: | |
| Patients were to receive 2.5 g of SMT C1100 microfluidised aqueous oral suspension formulation (F3) twice-daily (BID) for at least 48 weeks. All 3 patients in Cohort 3 discontinued from the study prior to Week 24 due to premature study termination. | |
| Subject analysis set title | All Patients |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1, Cohort 2 and Cohort 3. | |
| Subject analysis set title | Baseline (MRS FF Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Baseline for MRS FF vastus lateralis leg muscle parameter. | |
| Subject analysis set title | Week 12 Change from Baseline (MRS FF Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for MRS FF vastus lateralis leg muscle parameter. | |
| Subject analysis set title | Week 24 Change from Baseline (MRS FF Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for MRS FF vastus lateralis leg muscle parameter. | |
| Subject analysis set title | Week 36 Change from Baseline (MRS FF Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for MRS FF vastus lateralis leg muscle parameter. | |
| Subject analysis set title | Week 48 Change from Baseline (MRS FF Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for MRS FF vastus lateralis leg muscle parameter. | |
| Subject analysis set title | Baseline (MRS FF Soleus) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Baseline for MRS FF soleus leg muscle parameter. | |
| Subject analysis set title | Week 12 Change from Baseline (MRS FF Soleus) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for MRS FF soleus leg muscle parameter. | |

| | |
|---|---|
| Subject analysis set title | Week 24 Change from Baseline (MRS FF Soleus) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for MRS FF soleus leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 36 Change from Baseline (MRS FF Soleus) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for MRS FF soleus leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 48 Change from Baseline (MRS FF Soleus) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for MRS FF soleus leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Baseline (MRS WTRT Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for MRS WTRT vastus lateralis leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 12 Change from Baseline (MRS WTRT Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for MRS WTRT vastus lateralis leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 24 Change from Baseline (MRS WTRT Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to week 24 for MRS WTRT vastus lateralis leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 36 Change from Baseline (MRS WTRT Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for MRS WTRT vastus lateralis leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 48 Change from Baseline (MRS WTRT Vastus Lateralis) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for MRS WTRT vastus lateralis leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Baseline (MRS WTRT Soleus) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for MRS WTRT soleus leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 12 Change from Baseline (MRS WTRT Soleus) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for MRS WTRT soleus leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 24 Change from Baseline (MRS WTRT Soleus) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for MRS WTRT soleus leg muscle parameter.

| | |
|---|---|
| Subject analysis set title | Week 36 Change from Baseline (MRS WTRT Soleus) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for MRS WTRT soleus leg muscle parameter.

| Subject analysis set title | Week 48 Change from Baseline (MRS WTRT Soleus) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for MRS WTRT soleus leg muscle parameter.

| Subject analysis set title | Week 24 Baseline (Utrophin Intensity) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for Week 24 utrophin intensity. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 24 Observed Values (Utrophin Intensity) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Observed values for subjects at Week 24 visit. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 48 Baseline (Utrophin Intensity) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for Week 48 utrophin intensity. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 48 Observed Values (Utrophin Intensity) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Observed values for subjects at Week 48 visit. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 24 Baseline (Percentage Developmental Myosin) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for Week 24 percentage developmental myosin. Data from Week 24 and Week 48 are from different subjects.

| Subject analysis set title | Week 24 Observed Values (Percentage Developmental Myosin) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Observed values for subjects at Week 24 visit. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 48 Baseline (Percentage Developmental Myosin) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for Week 48 percentage developmental myosin. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 48 Observed Values (Percentage Developmental Myosin) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Observed values for subjects at Week 48 visit. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 24 Baseline (Fibre Diameter) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for Week 24 fibre diameter. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 24 Observed Value (Fibre Diameter) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Observed values for subjects at Week 24 visit. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 48 Baseline (Fibre Diameter) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for Week 48 fibre diameter. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Week 48 Observed Values (Fibre Diameter) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Observed values for subjects at Week 48 visit. Data from Week 24 and Week 48 are from different patients.

| Subject analysis set title | Baseline (Forced Expiratory Volume in 1 Second [FEV1]) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for FEV1.

| Subject analysis set title | Week 12 Change from Baseline (FEV1) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for FEV1.

| Subject analysis set title | Week 24 Change from Baseline (FEV1) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for FEV1.

| Subject analysis set title | Week 36 Change from Baseline (FEV1) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for FEV1.

| Subject analysis set title | Week 48 Change from Baseline (FEV1) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for FEV1.

| Subject analysis set title | Baseline (Forced Vital Capacity [FVC]) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Baseline for FVC.

| Subject analysis set title | Week 12 Change from Baseline (FVC) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for FVC.

| Subject analysis set title | Week 24 Change from Baseline (FVC) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for FVC.

| Subject analysis set title | Week 36 Change from Baseline (FVC) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for FVC.

| Subject analysis set title | Week 48 Change from Baseline (FVC) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for FVC.

| | |
|---|---|
| Subject analysis set title | Baseline (Maximum Inspiratory Pressure [MIP]) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Baseline for MIP. | |
| Subject analysis set title | Week 12 Change from Baseline (MIP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for MIP. | |
| Subject analysis set title | Week 24 Change from Baseline (MIP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for MIP. | |
| Subject analysis set title | Week 36 Change from Baseline (MIP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for MIP. | |
| Subject analysis set title | Week 48 Change from Baseline (MIP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for MIP. | |
| Subject analysis set title | Baseline (Maximum Expiratory Pressure [MEP]) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Baseline for MEP. | |
| Subject analysis set title | Week 12 Change from Baseline (MEP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for MEP. | |
| Subject analysis set title | Week 24 Change from Baseline (MEP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for MEP. | |
| Subject analysis set title | Week 36 Change from Baseline (MEP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for MEP. | |
| Subject analysis set title | Week 48 Change from Baseline (MEP) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for MEP. | |
| Subject analysis set title | Baseline (Peak Expiratory Flow [PEF]) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Baseline for PEF. | |
| Subject analysis set title | Week 12 Change from Baseline (PEF) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 12 for PEF. | |
| Subject analysis set title | Week 24 Change from Baseline (PEF) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 24 for PEF. | |

| | |
|---|---|
| Subject analysis set title | Week 36 Change from Baseline (PEF) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 36 for PEF. | |
| Subject analysis set title | Week 48 Change from Baseline (PEF) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. Change from baseline to Week 48 for PEF. | |
| Subject analysis set title | Cohort 1 and Cohort 2 Total |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclusive of Cohort 1 and Cohort 2. | |

## Primary: MRS Fat Fraction (FF) Vastus Lateralis Leg Muscle Parameter

| | |
|---|---|
| End point title | MRS Fat Fraction (FF) Vastus Lateralis Leg Muscle Parameter[1] |
| End point description: | |
| Value of 99999 has been used as there is no confidence interval data for baseline measure. The standard deviation for the baseline measure is 13.3788. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 12, Week 24, Week 36, Week 48 | |

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: Descriptive statistics are presented for this endpoint, which include the 95% confidence interval for the mean changes from baseline.

| **End point values** | Baseline (MRS FF Vastus Lateralis) | Week 12 Change from Baseline (MRS FF Vastus Lateralis) | Week 24 Change from Baseline (MRS FF Vastus Lateralis) | Week 36 Change from Baseline (MRS FF Vastus Lateralis) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39 | 39 | 36 | 37 |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | 14.954 (-99999 to 99999) | 1.779 (0.939 to 2.620) | 3.914 (2.695 to 5.132) | 5.238 (3.563 to 6.913) |

| **End point values** | Week 48 Change from Baseline (MRS FF Vastus Lateralis) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 36 | | | |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | 7.142 (4.866 to 9.417) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: MRS FF Soleus Leg Muscle Parameter

| End point title | MRS FF Soleus Leg Muscle Parameter[2] |
|---|---|

End point description:

Value of 99999 has been used as there is no confidence interval data for baseline measure. The standard deviation for baseline measure is 8.6310.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint, which include the 95% confidence interval for the mean changes from baseline.

| **End point values** | Baseline (MRS FF Soleus) | Week 12 Change from Baseline (MRS FF Soleus) | Week 24 Change from Baseline (MRS FF Soleus) | Week 36 Change from Baseline (MRS FF Soleus) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 40 | 40 | 38 | 38 |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | 9.123 (-99999 to 99999) | 0.615 (0.068 to 1.162) | 1.108 (0.350 to 1.865) | 2.384 (1.287 to 3.481) |

| **End point values** | Week 48 Change from Baseline (MRS FF Soleus) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | 2.584 (1.258 to 3.909) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: MRS Water Transverse Relaxation Time (WTRT) Vastus Lateralis Leg Muscle Parameter

| End point title | MRS Water Transverse Relaxation Time (WTRT) Vastus Lateralis Leg Muscle Parameter[3] |
|---|---|

End point description:

Value of 99999 has been used as there is no confidence interval data for baseline measure. The standard deviation for the baseline measure is 1.9954.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint, which include the 95% confidence interval for the mean changes from baseline.

| **End point values** | Baseline (MRS WTRT Vastus Lateralis) | Week 12 Change from Baseline (MRS WTRT Vastus Lateralis) | Week 24 Change from Baseline (MRS WTRT Vastus Lateralis) | Week 36 Change from Baseline (MRS WTRT Vastus Lateralis) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39 | 39 | 36 | 37 |
| Units: milliseconds | | | | |
| arithmetic mean (confidence interval 95%) | 32.226 (-99999 to 99999) | -0.559 (-1.190 to 0.072) | -0.486 (-1.193 to 0.221) | -0.849 (-1.454 to -0.244) |

| **End point values** | Week 48 Change from Baseline (MRS WTRT Vastus Lateralis) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 36 | | | |
| Units: milliseconds | | | | |
| arithmetic mean (confidence interval 95%) | -0.822 (-1.673 to 0.028) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: MRS WTRT Soleus Leg Muscle Parameter

| End point title | MRS WTRT Soleus Leg Muscle Parameter[4] |
|---|---|

End point description:

Value of 99999 has been used as there is no confidence interval data for baseline measure. The standard deviation for baseline measure is 1.9235.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint, which include the 95% confidence interval for the mean changes from baseline.

| End point values | Baseline (MRS WTRT Soleus) | Week 12 Change from Baseline (MRS WTRT Soleus) | Week 24 Change from Baseline (MRS WTRT Soleus) | Week 36 Change from Baseline (MRS WTRT Soleus) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 40 | 40 | 38 | 38 |
| Units: milliseconds | | | | |
| arithmetic mean (confidence interval 95%) | 31.878 (-99999 to 99999) | -0.655 (-1.209 to -0.101) | -0.861 (-1.440 to -0.281) | -0.447 (-1.085 to 0.190) |

| End point values | Week 48 Change from Baseline (MRS WTRT Soleus) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: milliseconds | | | | |
| arithmetic mean (confidence interval 95%) | -0.119 (-0.747 to 0.509) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Trough Concentration (Ctrough) Steady State Plasma Pharmacokinetic Parameter

| End point title | Trough Concentration (Ctrough) Steady State Plasma Pharmacokinetic Parameter[5][6] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point values | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |

| | | | | |
|---|---|---|---|---|
| geometric mean (geometric coefficient of variation) | 17 (± 140) | 80 (± 83.1) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Simulated Maximum Concentration (Cmax) Steady State Plasma Pharmacokinetic Parameter

| End point title | Simulated Maximum Concentration (Cmax) Steady State Plasma Pharmacokinetic Parameter[7][8] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | 135 (97 to 185) | 415 (303 to 640) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Simulated Average Concentration (Cav) Steady State Plasma Pharmacokinetic Parameter

| End point title | Simulated Average Concentration (Cav) Steady State Plasma Pharmacokinetic Parameter[9][10] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | 54 (37 to 82) | 163 (114 to 272) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Ctrough Steady State Plasma Pharmacokinetic Parameter for Dihydrodiol I (DHD I)

| End point title | Ctrough Steady State Plasma Pharmacokinetic Parameter for Dihydrodiol I (DHD I)[11][12] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient | 155 (± 61) | 365 (± 55) | | |

| of variation) |
|---|

## Statistical analyses

No statistical analyses for this end point

## Primary: Simulated Cmax Steady State Plasma Pharmacokinetic Parameter for DHD I

| End point title | Simulated Cmax Steady State Plasma Pharmacokinetic Parameter for DHD I[13][14] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | 1897 (1690 to 2158) | 2829 (2597 to 3072) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Simulated Cav Steady State Plasma Pharmacokinetic Parameter for DHD I

| End point title | Simulated Cav Steady State Plasma Pharmacokinetic Parameter for DHD I[15][16] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | 742 (685 to 836) | 1109 (1028 to 1217) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Ctrough Steady State Plasma Pharmacokinetic Parameter for Dihydrodiol III (DHD III)

| End point title | Ctrough Steady State Plasma Pharmacokinetic Parameter for Dihydrodiol III (DHD III)[17][18] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient | 484 (± 67) | 1206 (± 68) | | |

| of variation) |
|---|

## Statistical analyses

No statistical analyses for this end point

## Primary: Simulated Cmax Steady State Plasma Pharmacokinetic Parameter for DHD III

| End point title | Simulated Cmax Steady State Plasma Pharmacokinetic Parameter for DHD III[19][20] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | 3162 (2392 to 4053) | 4652 (3802 to 6116) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Simulated Cav Steady State Plasma Pharmacokinetic Parameter for DHD III

| End point title | Simulated Cav Steady State Plasma Pharmacokinetic Parameter for DHD III[21][22] |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| End point type | Primary |
|---|---|

End point timeframe:

Week 1 to Week 48

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented for this endpoint.

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary includes data from Cohorts 1 and 2. Cohort 3 participants were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded.

| **End point values** | Cohort 1: Microfluidised Oral Suspension F3 | Cohort 2: Powder for Oral Suspension F6 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | 1359 (972 to 1790) | 2211 (1707 to 3066) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Patients Reporting One or More Treatment-Emergent Adverse Events (TEAEs)

| End point title | Number of Patients Reporting One or More Treatment-Emergent Adverse Events (TEAEs)[23] |
|---|---|

End point description:

Data provided includes up to the end of the study.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline to end of study

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis associated with this endpoint, as this is a count of participants who experienced TEAEs.

| **End point values** | All Patients | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 43 | | | |
| Units: Participants | 43 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Utrophin Intensity by Time Point

| End point title | Utrophin Intensity by Time Point |
|---|---|

End point description:

Data entered for Weeks 24 and Week 48 are for different subjects.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 24 Baseline, Week 24, Week 48 Baseline, Week 48

| End point values | Week 24 Baseline (Utrophin Intensity) | Week 24 Observed Values (Utrophin Intensity) | Week 48 Baseline (Utrophin Intensity) | Week 48 Observed Values (Utrophin Intensity) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 15 | 15 |
| Units: Arbitrary Units | | | | |
| arithmetic mean (standard deviation) | 0.3686 (± 0.0553) | 0.3918 (± 0.0536) | 0.3520 (± 0.0357) | 0.3634 (± 0.0572) |

### Statistical analyses

| Statistical analysis title | Week 24 Change from Baseline |
|---|---|

Statistical analysis description:

The number of subjects included in this statistical analysis was 23 and not 44. 22 subjects had evaluable data at both baseline and Week 24, and 1 subject only had evaluable data at baseline.

The analysis used a mixed effect model.

| Comparison groups | Week 24 Observed Values (Utrophin Intensity) v Week 24 Baseline (Utrophin Intensity) |
|---|---|
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Least Square Mean |
| Point estimate | 0.023 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.002 |
| upper limit | 0.048 |

| Statistical analysis title | Week 48 Change from Baseline |
|---|---|

Statistical analysis description:

The number of subjects included in this statistical analysis was 16 and not 30. 15 subjects had evaluable data at both baseline and Week 48, and 1 subject only had evaluable data at baseline.

The analysis used a mixed effect model.

| Comparison groups | Week 48 Baseline (Utrophin Intensity) v Week 48 Observed |
|---|---|

| | Values (Utrophin Intensity) |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Least Square Mean |
| Point estimate | 0.006 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.042 |

## Secondary: Developmental Myosin by Time Point

| End point title | Developmental Myosin by Time Point |
|---|---|
| End point description: | |
| Data entered for Weeks 24 and Week 48 are for different subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 24 Baseline, Week 24, Week 48 Baseline, Week 48 | |

| **End point values** | Week 24 Baseline (Percentage Developmental Myosin) | Week 24 Observed Values (Percentage Developmental Myosin) | Week 48 Baseline (Percentage Developmental Myosin) | Week 48 Observed Values (Percentage Developmental Myosin) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 16 | 16 |
| Units: Percent (%) | | | | |
| arithmetic mean (standard deviation) | 11.1392 (± 3.3915) | 8.8226 (± 3.1082) | 12.7340 (± 3.9410) | 13.9588 (± 5.8819) |

## Statistical analyses

| **Statistical analysis title** | Week 24 Change from Baseline |
|---|---|

Statistical analysis description:

The number of subjects included in this statistical analysis was 24 and not 44. 22 subjects had evaluable data at both baseline and Week 24, 1 subject only had evaluable data at baseline, and 1 subject only had evaluable data at Week 24.

The analysis used a mixed effect model.

| Comparison groups | Week 24 Observed Values (Percentage Developmental Myosin) v Week 24 Baseline (Percentage Developmental Myosin) |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Least Square Mean |
| Point estimate | -2.611 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.324 |
| upper limit | -0.898 |

| **Statistical analysis title** | Week 48 Change from Baseline |
|---|---|

Statistical analysis description:

The number of subjects included in this statistical analysis was 16 and not 32. 16 subjects had evaluable data at both baseline and Week 48.

The analysis used a mixed effect model.

| | |
|---|---|
| Comparison groups | Week 48 Baseline (Percentage Developmental Myosin) v Week 48 Observed Values (Percentage Developmental Myosin) |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Least Square Mean |
| Point estimate | 1.166 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.103 |
| upper limit | 3.435 |

## Secondary: Fibre Diameter by Time Point

| | |
|---|---|
| End point title | Fibre Diameter by Time Point |

End point description:

Data for Week 24 and Week 48 are from different subjects.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 24 Baseline, Week 24, Week 48 Baseline, Week 48

| **End point values** | Week 24 Baseline (Fibre Diameter) | Week 24 Observed Value (Fibre Diameter) | Week 48 Baseline (Fibre Diameter) | Week 48 Observed Values (Fibre Diameter) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 16 | 16 |
| Units: Micrometers (µm) | | | | |
| arithmetic mean (standard deviation) | 42.2288 (± | 40.3083 (± | 44.7365 (± | 46.8001 (± |

| | | | |
|---|---|---|---|
| 6.0723) | 6.9697) | 4.7681) | 5.1765) |

**Statistical analyses**

| **Statistical analysis title** | Week 48 Change from Baseline |
|---|---|

Statistical analysis description:

The number of subjects included in this statistical analysis was 16 and not 32. 16 subjects had evaluable data at both baseline and Week 48.

The analysis used a mixed effect model.

| | |
|---|---|
| Comparison groups | Week 48 Baseline (Fibre Diameter) v Week 48 Observed Values (Fibre Diameter) |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Least Square Mean |
| Point estimate | 2.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.096 |
| upper limit | 4.324 |

| **Statistical analysis title** | Week 24 Change from Baseline |
|---|---|

Statistical analysis description:

The number of subjects included in this statistical analysis was 24 and not 44. 22 subjects had evaluable data at both baseline and Week 24, 1 subject only had evaluable data at baseline, and 1 subject only had evaluable data at Week 24.

The analysis used a mixed effect model.

| | |
|---|---|
| Comparison groups | Week 24 Observed Value (Fibre Diameter) v Week 24 Baseline (Fibre Diameter) |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Least Square Mean |
| Point estimate | -1.837 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.989 |
| upper limit | 0.315 |

**Secondary: Forced Expiratory Volume (FEV) in 1 Second by Time Point**

| End point title | Forced Expiratory Volume (FEV) in 1 Second by Time Point |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. No data was available for Cohort 3 from Weeks 12 to 48.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48

| **End point values** | Baseline (Forced Expiratory Volume in 1 Second [FEV1]) | Week 12 Change from Baseline (FEV1) | Week 24 Change from Baseline (FEV1) | Week 36 Change from Baseline (FEV1) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 38 | 38 | 37 | 36 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 95.0 (± 23.18) | -3.4 (± 20.86) | -2.5 (± 24.88) | -7.3 (± 24.26) |

| **End point values** | Week 48 Change from Baseline (FEV1) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 2.0 (± 18.31) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Forced Vital Capacity (FVC) by Time Point

| End point title | Forced Vital Capacity (FVC) by Time Point |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. No data was available for Cohort 3 from Weeks 12 to 48.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48

| End point values | Baseline (Forced Vital Capacity [FVC]) | Week 12 Change from Baseline (FVC) | Week 24 Change from Baseline (FVC) | Week 36 Change from Baseline (FVC) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39 | 39 | 38 | 37 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 94.3 (± 19.52) | -4.0 (± 16.31) | 1.1 (± 16.75) | -3.4 (± 18.39) |

| End point values | Week 48 Change from Baseline (FVC) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 35 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 1.1 (± 16.29) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Inspiratory Pressure (MIP) by Time Point

| End point title | Maximum Inspiratory Pressure (MIP) by Time Point |
|---|---|
| End point description: | |
| Summary includes data from Cohorts 1 and 2. No data was available for Cohort 3 from Weeks 12 to 48. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12, Week 24, Week 36, Week 48 | |

| End point values | Baseline (Maximum Inspiratory Pressure [MIP]) | Week 12 Change from Baseline (MIP) | Week 24 Change from Baseline (MIP) | Week 36 Change from Baseline (MIP) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 | 36 | 35 | 31 |
| Units: cm H2O | | | | |
| arithmetic mean (standard deviation) | 45.0 (± 20.23) | 3.6 (± 32.68) | 3.0 (± 25.00) | 9.0 (± 18.40) |

| End point values | Week 48 Change from Baseline (MIP) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 32 | | | |

| | | | | |
|---|---|---|---|---|
| Units: cm H2O | | | | |
| arithmetic mean (standard deviation) | 8.7 (± 20.30) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Peak Expiratory Flow (PEF) by Time Point

| End point title | Peak Expiratory Flow (PEF) by Time Point |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. No data was available for Cohort 3 from Weeks 12 to 48.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48

| End point values | Baseline (Peak Expiratory Flow [PEF]) | Week 12 Change from Baseline (PEF) | Week 24 Change from Baseline (PEF) | Week 36 Change from Baseline (PEF) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 35 | 32 | 34 | 32 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 82.5 (± 29.64) | 0.5 (± 20.65) | -0.1 (± 23.86) | -0.4 (± 23.46) |

| End point values | Week 48 Change from Baseline (PEF) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 32 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 9.6 (± 30.09) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Patients Meeting Specific Changes From Baseline with Vital Sign Parameters

| End point title | Number of Patients Meeting Specific Changes From Baseline with Vital Sign Parameters |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded. Two

Cohort 3 patients had post-baseline measurements recorded, and all were within 20% of their baseline value except 1 pulse measurement.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to Week 48

| **End point values** | Cohort 1 and Cohort 2 Total | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Participants | | | | |
| Systolic Blood Pressure (SBP): < 20% Change | 28 | | | |
| SBP: >= 20% Reduction and < 20% Increase | 2 | | | |
| SBP: >= 20% Increase and < 20% Reduction | 10 | | | |
| SBP: >= 20% Reduction and >= 20% Increase | 0 | | | |
| Diastolic Blood Pressure (DBP): < 20% Change | 19 | | | |
| DBP: >= 20% Reduction and < 20% Increase | 11 | | | |
| DBP: >= 20% Increase and < 20% Reduction | 10 | | | |
| DBP: >= 20% Reduction and >= 20% Increase | 0 | | | |
| Pulse: < 20% Change | 21 | | | |
| Pulse: >= 20% Reduction and < 20% Increase | 6 | | | |
| Pulse: >= 20% Increase and < 20% Reduction | 13 | | | |
| Pulse: >= 20% Reduction and >= 20% Increase | 0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Patients with Abnormal Echocardiogram Measurements

| End point title | Number of Patients with Abnormal Echocardiogram Measurements |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. Data was not collected for Cohort 3.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 24, Week 48

| End point values | Cohort 1 and Cohort 2 Total | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Participants | | | | |
| Baseline: Normal | 38 | | | |
| Baseline: Abnormal, Not Clinically Significant | 2 | | | |
| Baseline: Abnormal, Clinically Significant | 0 | | | |
| Week 24: Normal | 33 | | | |
| Week 24: Abnormal, Not Clinically Significant | 5 | | | |
| Week 24: Abnormal, Clinically Significant | 0 | | | |
| Week 24: Missing the Visit | 2 | | | |
| Week 48: Normal | 33 | | | |
| Week 48: Abnormal, Not Clinically Significant | 2 | | | |
| Week 48: Abnormal, Clinically Significant | 1 | | | |
| Week 48: Missing the Visit | 4 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Patients with Liver Function Test Results of Potential Clinical Concern

| End point title | Number of Patients with Liver Function Test Results of Potential Clinical Concern |
|---|---|
| End point description: | |
| Laboratory measurements for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), alkaline phosphatase (ALP), and glutamate dehydrogenase (GLDH). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to End of Study | |

| End point values | All Patients | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: Participants | | | | |
| ALT >= ULN (Upper Limit of Normal) | 43 | | | |
| ALT >= 2*ULN | 43 | | | |
| ALT >= 3*ULN | 42 | | | |
| AST >= ULN | 43 | | | |
| AST >= 2*ULN | 42 | | | |
| AST >= 3*ULN | 42 | | | |
| TB >= ULN | 0 | | | |
| ALP >= 1.5*ULN | 0 | | | |

| | | | | |
|---|---|---|---|---|
| GLDH >= ULN Excluding Hemolysed Samples | 28 | | | |
| GLDH >= ULN Including Hemolysed Samples | 31 | | | |
| GLDH >= 2.5*ULN Excluding Hemolysed Samples | 1 | | | |
| GLDH >= 2.5*ULN Including Hemolysed Samples | 1 | | | |
| GLDH >= 3*ULN Excluding Hemolysed Samples | 3 | | | |
| GLDH >= 3*ULN Including Hemolysed Samples | 3 | | | |
| Patients Meeting Hy's Law | 0 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Patients Meeting Specific Levels of Changes from Baseline for Electrocardiogram (ECG) Parameters

| End point title | Number of Patients Meeting Specific Levels of Changes from Baseline for Electrocardiogram (ECG) Parameters |
|---|---|

End point description:

Summary includes data from Cohorts 1 and 2. ECG results included PR interval (PR), heart rate (HR), and heart rate corrected QT interval using Fridericia's formula (QTcF). Cohort 3 patients were a different study population (i.e. different eligibility criteria), and as only limited data was available, their data has been excluded. All three Cohort 3 patients had post-baseline measurements recorded, of which 1 had an increase in HR ≥20% recorded and another had both an increase and decrease in HR ≥20% recorded (means of replicates were all <20% different to baseline).

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to Week 48

| End point values | Cohort 1 and Cohort 2 Total | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Participants | | | | |
| PR: < 170 ms | 37 | | | |
| PR: >= 170 ms | 3 | | | |
| PR: < 20% Change | 35 | | | |
| PR: >= 20% Reduction and < 20% Increase | 2 | | | |
| PR: >= Increase and < 20% Reduction | 3 | | | |
| PR: >= 20% Reduction and >= 20% Increase | 0 | | | |
| HR: < 20% Change | 7 | | | |
| HR: >= 20% Reduction and < 20% Increase | 6 | | | |
| HR: >= 20% Increase and < 20% Reduction | 22 | | | |

| | | | | |
|---|---|---|---|---|
| HR: >= 20% Reduction and >= 20% Increase | 5 | | | |
| Maximum QTcF: < 450 ms | 40 | | | |
| Maximum QTcF: >= 450 ms | 0 | | | |
| Maximum Increase from Baseline in QTcF: < 30 ms | 32 | | | |
| Maximum Increase from Baseline in QTcF: 30 - 59 ms | 8 | | | |
| Maximum Increase from Baseline in QTcF: >= 60 ms | 0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The condition of each patient was monitored throughout the study. All TEAEs to the end of the study are presented. Treatment related events are those considered as at least possibly related to study treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### 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 / 43 (9.30%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral swelling | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Chromaturia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tonsillitis bacterial | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis viral | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| 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 %

| **Non-serious adverse events** | All Patients | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 43 / 43 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Eye haemangioma | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Skin papilloma | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Pallor | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| Eyeglasses therapy | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Catheter site bruise | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Facial pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| occurrences (all) | 5 | | |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | |
| occurrences (all) | 12 | | |
| Thirst | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Unevaluable event | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Vessel puncture site pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Multiple allergies | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 12 / 43 (27.91%) | | |
| occurrences (all) | 15 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 5 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 10 / 43 (23.26%) | | |
| occurrences (all) | 10 | | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Sinus congestion | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 4 | | |
| Throat irritation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Anger | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 3 | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Asocial behaviour | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Belligerence | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Enuresis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Irritability | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Initial insomnia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Mood altered | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Glutamate dehydrogenase increased | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | |
| occurrences (all) | 4 | | |
| Protein urine present | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Thyroxine increased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 5 | | |

| | | | | |
|---|---|---|---|---|
| Ear injury | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Fall | | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | | |
| occurrences (all) | 16 | | | |
| Foot fracture | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Head injury | | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | | |
| occurrences (all) | 2 | | | |
| Limb injury | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Ligament sprain | | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | | |
| occurrences (all) | 2 | | | |
| Joint injury | | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | | |
| occurrences (all) | 2 | | | |
| Post procedural contusion | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Procedural nausea | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Procedural pain | | | | |
| subjects affected / exposed | 7 / 43 (16.28%) | | | |
| occurrences (all) | 7 | | | |
| Skin abrasion | | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | | |
| occurrences (all) | 2 | | | |

| | | | |
|---|---|---|---|
| Spinal fracture<br>subjects affected / exposed<br>occurrences (all) | 2 / 43 (4.65%)<br>2 | | |
| Torus fracture<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Spinal compression fracture<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Scratch<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Thermal burn<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Congenital, familial and genetic disorders<br>Cryptorchism<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Nervous system disorders<br>Disturbance in attention<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Dizziness<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Headache<br>subjects affected / exposed<br>occurrences (all) | 11 / 43 (25.58%)<br>27 | | |
| Lethargy<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Sensory processing disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|---|---|
| Ear pain | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Excessive cerumen production | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Motion sickness | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Astigmatism | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Chalazion | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Erythema of eyelid | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Eye inflammation | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Eye pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Hypermetropia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Scleral disorder | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 4 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 12 / 43 (27.91%) | | |
| occurrences (all) | 24 | | |
| Constipation | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | |
| occurrences (all) | 4 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 18 / 43 (41.86%) | | |
| occurrences (all) | 21 | | |
| Dental plaque | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | |
| occurrences (all) | 4 | | |
| Faeces discoloured | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |

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|---|---|---|---|---|
| Faeces pale | | | | |
| subjects affected / exposed | 24 / 43 (55.81%) | | | |
| occurrences (all) | 29 | | | |
| Gastritis | | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | | |
| occurrences (all) | 2 | | | |
| Frequent bowel movements | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Gingival recession | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Haemorrhoids | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 2 | | | |
| Lip swelling | | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | | |
| occurrences (all) | 4 | | | |
| Nausea | | | | |
| subjects affected / exposed | 7 / 43 (16.28%) | | | |
| occurrences (all) | 13 | | | |
| Oral mucosal eruption | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 2 | | | |
| Rectal haemorrhage | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Rectal prolapse | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 2 | | | |
| Toothache | | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | | |
| occurrences (all) | 3 | | | |
| Abdominal pain | | | | |
| subjects affected / exposed | 7 / 43 (16.28%) | | | |
| occurrences (all) | 11 | | | |

| | | | |
|---|---|---|---|
| Vomiting | | | |
| subjects affected / exposed | 23 / 43 (53.49%) | | |
| occurrences (all) | 79 | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Gastric hypomotility | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Erythema | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Rash | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| occurrences (all) | 17 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Skin discolouration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Swelling face | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Chromaturia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Growth hormone deficiency | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| occurrences (all) | 5 | | |
| Back pain | | | |
| subjects affected / exposed | 10 / 43 (23.26%) | | |
| occurrences (all) | 14 | | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Neck pain | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | |
| occurrences (all) | 12 | | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |

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|---|---|---|---|---|
| Ear infection | | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | | |
| occurrences (all) | 3 | | | |
| Eye infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 2 | | | |
| Gingival abscess | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 2 | | | |
| Gastrointestinal viral infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | | |
| occurrences (all) | 3 | | | |
| Impetigo | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Localised infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Molluscum contagiosum | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Nail infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Nasopharyngitis | | | | |
| subjects affected / exposed | 11 / 43 (25.58%) | | | |
| occurrences (all) | 14 | | | |
| Otitis media | | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | | |
| occurrences (all) | 3 | | | |

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|---|---|---|---|---|
| Paronychia | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 2 | | | |
| Pharyngitis | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Pharyngitis streptococcal | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Post procedural infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Rhinitis | | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | | |
| occurrences (all) | 6 | | | |
| Sinusitis | | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | | |
| occurrences (all) | 2 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | | |
| occurrences (all) | 6 | | | |
| Viral upper respiratory tract infection | | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | | |
| occurrences (all) | 2 | | | |
| Gastroenteritis viral | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Conjunctivitis | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |
| Adenovirus infection | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences (all) | 1 | | | |

| | | | |
|---|---|---|---|
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1 | | |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)<br>Increased appetite<br>subjects affected / exposed<br>occurrences (all)<br>Overweight<br>subjects affected / exposed<br>occurrences (all)<br>Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all) | <br><br>3 / 43 (6.98%)<br>3<br><br>2 / 43 (4.65%)<br>3<br><br>1 / 43 (2.33%)<br>1<br><br>2 / 43 (4.65%)<br>2 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 08 December 2015 | Amendment 1 (dated 08 December 2015) added additional information on potential interactions of ezutromid with the Cytochrome P-450 pathway, particularly CYP2B6, and introduced the prohibition of taking medications known to be Cytochrome P450 inhibitors, inducers, and substrates during the study. |
| 24 February 2016 | Amendment 2 (dated 24 February 2016) resolved minor administrative issues identified after the finalization of the protocol. These issues did not impact the conduct of the study. |
| 07 October 2016 | Amendment 3 (dated 07 October 2016) added Cohort 2 (10 subjects) to study a microfluidized aqueous oral suspension at a dose of 1000 mg twice daily. Cohort 2 subjects were only enrolled at US sites. The number of subjects in the original cohort was correspondingly reduced from 40 to 30. The amendment also provided additional information on Summit Study ezutromid, in which the suspension formulation was previously tested, and made various minor administrative changes. |
| 24 February 2017 | Amendment 4 (24 February 2017) added Cohort 3 (15 subjects), which consisted of patients who had previously received ezutromid and were not eligible for Cohorts 1 or 2. These patients entered a safety arm and underwent additional cardiac MRI scans and pulmonary function tests. Cohort 3 patients were only enrolled at UK sites. The amendment also added the Extension Phase into the study design. All patients were eligible to continue into the Extension Phase. The amendment also made various minor administrative changes. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported