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 Units: Subjects			
Children (2-11 years)	30	10	1
Adolescents (12-17 years)	0	0	2
Age continuous 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 Units: Subjects			
Female	0	0	0
Male	30	10	3
Race Units: Subjects			
White	26	9	3
Asian	1	1	0
Other	3	0	0
Ethnicity 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 Units: Subjects			
Children (2-11 years)	41		
Adolescents (12-17 years)	2		

Age continuous Units: years median full range (min-max)	- 		
Gender categorical Units: Subjects			
Female Male	0 43		
Race Units: Subjects			
White Asian Other	38 2 3		
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino	3 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 subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Torus fracture subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Spinal compression fracture subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Scratch subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Thermal burn subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Congenital, familial and genetic disorders Cryptorchism subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Dizziness subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Headache subjects affected / exposed occurrences (all)	11 / 43 (25.58%) 27		
Lethargy subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Sensory processing disorder subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 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		

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		

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			

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 subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Increased appetite subjects affected / exposed occurrences (all) Overweight subjects affected / exposed occurrences (all) Vitamin D deficiency subjects affected / exposed occurrences (all)	 3 / 43 (6.98%) 3 2 / 43 (4.65%) 3 1 / 43 (2.33%) 1 2 / 43 (4.65%) 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