EU Clinical Trials Register

Clinical trial results:
A Two-Part Study to Assess the Safety and Tolerability, Pharmacokinetics, and Effects on Histology and Different Clinical Parameters of Givinostat in Ambulant Children with Duchenne Muscular Dystrophy

Summary

EudraCT number	2012-002566-12
Trial protocol	IT
Global end of trial date	17 November 2017

Results information

Result version number	v1 (current)
This version publication date	08 May 2020
First version publication date	08 May 2020

Trial information

Trial identification

Sponsor protocol code	DSC/11/2357/43

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01761292
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ITALFARMACO S.p.A.
Sponsor organisation address	Via dei Lavoratori, 54, Cinisello Balsamo (MI), Italy, 20092
Public contact	Clinical R&D Department, Italfarmaco, +39 02 64431, s.cazzaniga@italfarmaco.com
Scientific contact	Clinical R&D Department, Italfarmaco, +39 02 64431, s.cazzaniga@italfarmaco.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2017
Global end of trial reached?	Yes
Global end of trial date	17 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the histologic effects of Givinostat administered chronically at the selected daily dose

Protection of trial subjects:

The study was performed in accordance with local national laws (as applicable), the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and the guidelines of the Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and amended by subsequent assemblies in Tokyo, Japan in 1975; Venice, Italy in 1983; Hong Kong in 1989; Somerset West, South Africa in 1996, and in Edinburgh, Scotland in October 2000.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1 pt discontinued due to an AE during Part 1; all other pts completed the study. Another pt was enrolled in Part 1 but started the treatment in Part 2. Hence, 19 pts completed Part 2. These 19 pts continued to Extension 1. 1 pt withdrew consent & discontinued at the beginning of Extension 2. The remaining 18 completed Extensions 2 and 3.

Pre-assignment

Screening details:

Twenty-one patients were screened in this study: 1 patient failed the screening, 20 were enrolled in Part 1 but only 19 were treated in Part 1; 1 was discontinued in Part 1; 19 were treated in Part 2 (18 who have completed Part 1 + 1 enrolled in Part 1 but not treated in Part 1).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	25 mg BID

Arm description:

Out of the 20 enrolled children, the first 4 were treated at a low dose of givinostat (25 mg BID). None of the stopping criteria were met after 2 weeks at the low dose, an intermediate dose was used for the treatment of an additional 8 children. The 4 children previously treated at the low dose were also switched to the intermediate dose (50 mg BID).

Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	ITF2357
Other name	
Pharmaceutical forms	Capsule, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Givinostat oral suspension 10 mg/mL or oral capsules 50 mg, administered orally under fed conditions at the dose of 25 mg BID, 37.5 mg BID, and 50 mg BID during Part 1 and 25 mg BID and 37.5 mg BID during Part 2. Givinostat, oral suspension 10 mg/mL, administered orally under fed conditions at the dose of 25 mg BID or 37.5 mg BID during Extension 1, and modified as per patient's weight during Extensions 2 and 3. Study drug safety and tolerability continued to be measured in patients during Extension 3.

Arm title	50 mg BID

Arm description:

The second tested dose was 50 mg BID. 8 children were treated at this dose for at least 2 weeks. A stopping criteria was met, the dose was considered not tolerated and all subjects discontinued the treatment.

Arm type	Experimental

Investigational medicinal product name	Givinostat
Investigational medicinal product code	ITF2357
Other name	
Pharmaceutical forms	Capsule, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Givinostat oral suspension 10 mg/mL or oral capsules 50 mg, administered orally under fed conditions at the dose of 25 mg BID, 37.5 mg BID, and 50 mg BID during Part 1 and 25 mg BID and 37.5 mg BID during Part 2. Givinostat, oral suspension 10 mg/mL, administered orally under fed conditions at the dose of 25 mg BID or 37.5 mg BID during Extension 1, and modified as per patient's weight during Extensions 2 and 3. Study drug safety and tolerability continued to be measured in patients during Extension 3.

Arm title	37.5 mg BID

Arm description:

Out of the 20 enrolled children, the first 4 were treated at a low dose of givinostat (25 mg BID).
The second dose i.e. 50 mg BID was not considered tolerated, a stopping criteria was met, therefore an intermediate dose was tested.
7 out of 8 children were treated at 37.5 mg BID for at least 2 weeks and none of the stopping criteria were met.
Once all 20 children enrolled during Part 1 had been treated for at least 2 weeks, the recommended dose (RD) i.e. 37.5 mg BID to be used in Part 2 was determined.
All the children enrolled were switched to the RD level (37.5 mg BID), which was administered for the subsequent 12 months (Part 2). During the Part 2 the dose was reduced for safety in 12 children (i.e. treated at 25 mg BID).
At the end of Part 2, patients continued to receive givinostat at the dose ongoing at 12 months and were treated for additional 40 months (Extensions 1, 2, and 3 up to month 52). Due to patients growth the dose was adjusted by patient's weight.

Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	ITF2357
Other name	
Pharmaceutical forms	Capsule, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Givinostat oral suspension 10 mg/mL or oral capsules 50 mg, administered orally under fed conditions at the dose of 25 mg BID, 37.5 mg BID, and 50 mg BID during Part 1 and 25 mg BID and 37.5 mg BID during Part 2. Givinostat, oral suspension 10 mg/mL, administered orally under fed conditions at the dose of 25 mg BID or 37.5 mg BID during Extension 1, and modified as per patient's weight during Extensions 2 and 3. Study drug safety and tolerability continued to be measured in patients during Extension 3.

Number of subjects in period 1	25 mg BID	50 mg BID	37.5 mg BID
Started	4	8	8
Completed	4	7	7
Not completed	0	1	1
Adverse event, non-fatal	-	1	-
Was not treated in Part 1	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	25 mg BID

Reporting group description:

Out of the 20 enrolled children, the first 4 were treated at a low dose of givinostat (25 mg BID). None of the stopping criteria were met after 2 weeks at the low dose, an intermediate dose was used for the treatment of an additional 8 children. The 4 children previously treated at the low dose were also switched to the intermediate dose (50 mg BID).

Reporting group title	50 mg BID

Reporting group description:

The second tested dose was 50 mg BID. 8 children were treated at this dose for at least 2 weeks. A stopping criteria was met, the dose was considered not tolerated and all subjects discontinued the treatment.

Reporting group title	37.5 mg BID

Reporting group description:

Out of the 20 enrolled children, the first 4 were treated at a low dose of givinostat (25 mg BID). The second dose i.e. 50 mg BID was not considered tolerated, a stopping criteria was met, therefore an intermediate dose was tested.

7 out of 8 children were treated at 37.5 mg BID for at least 2 weeks and none of the stopping criteria were met.

Once all 20 children enrolled during Part 1 had been treated for at least 2 weeks, the recommended dose (RD) i.e. 37.5 mg BID to be used in Part 2 was determined.

All the children enrolled were switched to the RD level (37.5 mg BID), which was administered for the subsequent 12 months (Part 2). During the Part 2 the dose was reduced for safety in 12 children (i.e. treated at 25 mg BID).

At the end of Part 2, patients continued to receive givinostat at the dose ongoing at 12 months and were treated for additional 40 months (Extensions 1, 2, and 3 up to month 52). Due to patients growth the dose was adjusted by patient's weight.

Reporting group values	25 mg BID	50 mg BID	37.5 mg BID
Number of subjects	4	8	8
Age categorical			
Units: Subjects			
Children (2-11 years)	4	8	8
Age continuous			
Units: years			
arithmetic mean	7.8	8.8	7.9
standard deviation	± 0.96	± 1.16	± 1.13
Gender categorical			
Units: Subjects			
Male	4	8	8

Reporting group values	Total		
Number of subjects	20		
Age categorical			
Units: Subjects			
Children (2-11 years)	20		

Age continuous
Units: years
    arithmetic mean
    standard deviation
	-		

Gender categorical Units: Subjects			
Male	20		

Subject analysis sets

Subject analysis set title	Overall - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all children who were enrolled in the Part 1 portion or entered the Part 2 portion of the study. Patients were analyzed according to the dose level to which they were allocated. ITT analysis population was set up to 19 patients during Extension 1.

Subject analysis set title	Overall - Evaluable population
Subject analysis set type	Full analysis

Subject analysis set description:

The evaluable population included all patients who were in Part 2 of the study, received givinostat of at least 80% dose in Part 2, had at least 1 baseline and 1 postbaseline assessment of biopsies, and had no major protocol violations.

Subject analysis set title	Overall - Baseline - Evaluable
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The evaluable population included all patients who were in Part 2 of the study, received givinostat of at least 80% dose in Part 2, had at least 1 baseline and 1 postbaseline assessment of biopsies, and had no major protocol violations.

Subject analysis set title	Overall - Baseline - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all children who were enrolled in the Part 1 portion or entered the Part 2 portion of the study. Patients were analyzed according to the dose level to which they were allocated. Twenty patients were included in the ITT population.

Subject analysis set title	Overall - Part 2/EoT - Evaluable
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The evaluable population included all patients who were in Part 2 of the study, received givinostat of at least 80% dose in Part 2, had at least 1 baseline and 1 postbaseline assessment of biopsies, and had no major protocol violations.

Subject analysis set title	Overall - Part 2/EoT - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all children who were enrolled in the Part 1 portion or entered the Part 2 portion of the study. Patients were analyzed according to the dose level to which they were allocated. Twenty patients were included in the ITT population.

Subject analysis set title	Overall - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all children who received any investigational product. The dose level under which the patient was analyzed was the dose of investigational product that was actually received; 19 patients were included in the safety population of Part 1 and 19 patients were included in the safety population of Part 2.
In all Extensions, the Safety Analysis Population was set up to 20 patients (100%), including all patients who received any investigational product.

Reporting group values	Overall - ITT population	Overall - Evaluable population	Overall - Baseline - Evaluable
Number of subjects	19	18	18
Age categorical Units: Subjects			
Children (2-11 years)	20	18	18
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Male	20	18	18

Reporting group values	Overall - Baseline - ITT	Overall - Part 2/EoT - Evaluable	Overall - Part 2/EoT - ITT
Number of subjects	19	18	19
Age categorical Units: Subjects			
Children (2-11 years)	19	18	19
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Male	19	18	19

Reporting group values	Overall - Safety population		
Number of subjects	20		
Age categorical Units: Subjects			
Children (2-11 years)	20		
Age continuous Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Male	20		

End points

End points reporting groups

Reporting group title	25 mg BID

Reporting group description:

Out of the 20 enrolled children, the first 4 were treated at a low dose of givinostat (25 mg BID).
None of the stopping criteria were met after 2 weeks at the low dose, an intermediate dose was used for the treatment of an additional 8 children. The 4 children previously treated at the low dose were also switched to the intermediate dose (50 mg BID).

Reporting group title	50 mg BID

Reporting group description:

The second tested dose was 50 mg BID. 8 children were treated at this dose for at least 2 weeks.
A stopping criteria was met, the dose was considered not tolerated and all subjects discontinued the treatment.

Reporting group title	37.5 mg BID

Reporting group description:

Out of the 20 enrolled children, the first 4 were treated at a low dose of givinostat (25 mg BID).
The second dose i.e. 50 mg BID was not considered tolerated, a stopping criteria was met, therefore an intermediate dose was tested.
7 out of 8 children were treated at 37.5 mg BID for at least 2 weeks and none of the stopping criteria were met.
Once all 20 children enrolled during Part 1 had been treated for at least 2 weeks, the recommended dose (RD) i.e. 37.5 mg BID to be used in Part 2 was determined.
All the children enrolled were switched to the RD level (37.5 mg BID), which was administered for the subsequent 12 months (Part 2). During the Part 2 the dose was reduced for safety in 12 children (i.e. treated at 25 mg BID).
At the end of Part 2, patients continued to receive givinostat at the dose ongoing at 12 months and were treated for additional 40 months (Extensions 1, 2, and 3 up to month 52). Due to patients growth the dose was adjusted by patient's weight.

Subject analysis set title	Overall - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all children who were enrolled in the Part 1 portion or entered the Part 2 portion of the study. Patients were analyzed according to the dose level to which they were allocated.
ITT analysis population was set up to 19 patients during Extension 1.

Subject analysis set title	Overall - Evaluable population
Subject analysis set type	Full analysis

Subject analysis set description:

The evaluable population included all patients who were in Part 2 of the study, received givinostat of at least 80% dose in Part 2, had at least 1 baseline and 1 postbaseline assessment of biopsies, and had no major protocol violations.

Subject analysis set title	Overall - Baseline - Evaluable
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The evaluable population included all patients who were in Part 2 of the study, received givinostat of at least 80% dose in Part 2, had at least 1 baseline and 1 postbaseline assessment of biopsies, and had no major protocol violations.

Subject analysis set title	Overall - Baseline - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all children who were enrolled in the Part 1 portion or entered the Part 2 portion of the study. Patients were analyzed according to the dose level to which they were allocated.
Twenty patients were included in the ITT population.

Subject analysis set title	Overall - Part 2/EoT - Evaluable
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The evaluable population included all patients who were in Part 2 of the study, received givinostat of at least 80% dose in Part 2, had at least 1 baseline and 1 postbaseline assessment of biopsies, and had no major protocol violations.

Subject analysis set title	Overall - Part 2/EoT - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all children who were enrolled in the Part 1 portion or entered the Part 2 portion of the study. Patients were analyzed according to the dose level to which they were allocated. Twenty patients were included in the ITT population.

Subject analysis set title	Overall - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all children who received any investigational product. The dose level under which the patient was analyzed was the dose of investigational product that was actually received; 19 patients were included in the safety population of Part 1 and 19 patients were included in the safety population of Part 2.
In all Extensions, the Safety Analysis Population was set up to 20 patients (100%), including all patients who received any investigational product.

Primary: Change From Baseline to Part 2 in the Value of Muscle Fiber Area % (MFA%) Comparing the Histology Biopsies Before and After 12 Months of Treatment With Givinostat

End point title	Change From Baseline to Part 2 in the Value of Muscle Fiber Area % (MFA%) Comparing the Histology Biopsies Before and After 12 Months of Treatment With Givinostat

End point description:

The primary endpoint was the change in histology comparing the brachial biceps biopsies before and after ≥12 months of treatment with Givinostat.
Muscle biopsies: A first brachial biceps biopsy (baseline) was taken prior to the first dose of study drug. A second brachial biceps biopsy was taken at Visit 10 (12 months) from the opposite arm.
The muscle biopsy samples from the biceps muscle were collected by open biopsy. The minimum amount of muscle tissue required was a piece of muscle of at least 0.5 × 0.5 × 0.5 cm.

End point type	Primary

End point timeframe:

After12 months of treatment

End point values	Overall - Baseline - Evaluable	Overall - Part 2/EoT - Evaluable		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: percentage change				
arithmetic mean (standard deviation)	51.003 (± 9.6138)	64.909 (± 8.3469)		

Statistical analyses

Statistical analysis title	Overall - Part2/EoT vs Baseline
Comparison groups	Overall - Baseline - Evaluable v Overall - Part 2/EoT - Evaluable

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001 [2]
Method	t-test, 2-sided
Parameter estimate	absolute mean change
Point estimate	13.906
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.5657
upper limit	16.2466

Notes:

[1] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

[2] - The paired t-test or non-parametric signed rank test for 2 means (paired observations) (as is appropriate) was applied for testing the statistical significance of the Change From Baseline to End of Study. MFA% P < 0.05 was set as significant.

Secondary: Change from baseline to end of study in cross sectional area (CSA)

End point title	Change from baseline to end of study in cross sectional area (CSA)

End point description:

This histological parameter was evaluated on the brachial biceps biopsies taken prior to the first dose of study drug and after 12 months of treatment with givinostat.

End point type	Secondary

End point timeframe:

At 12 months

End point values	Overall - Baseline - ITT	Overall - Part 2/EoT - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: µm2				
arithmetic mean (standard deviation)	1191.087 (± 400.9813)	2056.356 (± 781.3925)		

Statistical analyses

Statistical analysis title	Overall - Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	t-test, 2-sided

Notes:

[3] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Secondary: Change from baseline to end of study in fibrosis, necrosis, fatty replacement

End point title	Change from baseline to end of study in fibrosis, necrosis, fatty replacement
End point description:	
These histological parameters were evaluated on the brachial biceps biopsies taken prior to the first dose of study drug and after 12 months of treatment with givinostat.	
End point type	Secondary
End point timeframe:	
After 12 months	

End point values	Overall - Baseline - ITT	Overall - Part 2/EoT - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: percentage of total area				
arithmetic mean (standard deviation)				
Total fibrosis	46.128 (± 9.6129)	33.488 (± 8.2430)		
Perimysial fibrosis	23.469 (± 8.6600)	15.884 (± 5.5629)		
Endomysial fibrosis	22.660 (± 6.5066)	17.604 (± 3.7859)		
Fatty replacement	0.886 (± 0.6970)	0.584 (± 0.6000)		
Necrosis	1.983 (± 0.7311)	1.019 (± 0.3172)		

Statistical analyses

Statistical analysis title	Total fibrosis - Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Absolute mean change
Point estimate	-12.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.953
upper limit	-10.328

Variability estimate	Standard deviation
Dispersion value	4.6493

Notes:

[4] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Statistical analysis title	Perimysial fibrosis - Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0001
Method	t-test, 2-sided
Parameter estimate	Absolute mean change
Point estimate	-7.585
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8062
upper limit	-4.3634
Variability estimate	Standard deviation
Dispersion value	6.4779

Notes:

[5] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Statistical analysis title	Endomysial fibrosis - Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0032
Method	t-test, 2-sided
Parameter estimate	Absolute mean change
Point estimate	-5.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1653
upper limit	-1.9461
Variability estimate	Standard deviation
Dispersion value	6.2531

Notes:

[6] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Statistical analysis title	Fatty replacement - Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0002
Method	t-test, 2-sided
Parameter estimate	Absolute mean change
Point estimate	-0.302
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4391
upper limit	-0.165
Variability estimate	Standard deviation
Dispersion value	0.2756

Notes:

[7] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Statistical analysis title	Necrosis - Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Absolute mean change
Point estimate	-0.964
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.275
upper limit	-0.6524
Variability estimate	Standard deviation
Dispersion value	0.626

Notes:

[8] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Secondary: Change From Baseline to End of Study in Number of Hypercontracted Fibers

End point title	Change From Baseline to End of Study in Number of Hypercontracted Fibers

End point description:

This histological parameter was evaluated on the brachial biceps biopsies taken prior to the first dose of study drug and after 12 months of treatment with givinostat. The number of fibers is calculated per microscopic field (20x).

End point type	Secondary

End point timeframe:

At 12 months

End point values	Overall - Baseline - ITT	Overall - Part 2/EoT - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: number of fibers				
arithmetic mean (standard deviation)	1.977 (± 0.7139)	0.773 (± 0.5429)		

Statistical analyses

Statistical analysis title	Part 2/EoT vs Baseline
Comparison groups	Overall - Part 2/EoT - ITT v Overall - Baseline - ITT
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Absolute mean change
Point estimate	-1.204
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5334
upper limit	-0.8749
Variability estimate	Standard deviation
Dispersion value	0.6621

Notes:

[9] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Secondary: Change from Baseline in muscular function after 12 months of treatment with Givinostat at the selected daily dose based on the 6-Minute Walk Test

End point title	Change from Baseline in muscular function after 12 months of treatment with Givinostat at the selected daily dose based on the 6-Minute Walk Test

End point description:

This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes.
The 6-Minute Walk Test is a useful measure of functional capacity targeted at people with at least moderately severe impairment.
The longer the walked distance the better the outcome.

End point type	Secondary

End point timeframe:

At 12 months

End point values	Overall - Baseline - ITT	Overall - Part 2/EoT - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: meters				
arithmetic mean (standard deviation)	453.0 (± 62.23)	432.2 (± 63.60)		

Statistical analyses

Statistical analysis title	Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Mean difference (final values)
Point estimate	-24.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.53
upper limit	-6.61
Variability estimate	Standard deviation
Dispersion value	36.11

Notes:

[10] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Secondary: Change from Baseline in muscular function after 12 months of treatment with Givinostat at the selected daily dose based on the North Star Ambulatory Assessment (NSAA)

End point title	Change from Baseline in muscular function after 12 months of treatment with Givinostat at the selected daily dose based on the North Star Ambulatory Assessment (NSAA)

End point description:

The NSAA was graded using the standard scorecard with each assessment rated as 0 – unable to achieve independently, 1 – modified method but achieves goal independent of physical assistance from another, or 2 – normal with no obvious modification of activity. The higher the score, the better the outcome.

End point type	Secondary

End point timeframe:

At 12 months

End point values	Overall - Baseline - ITT	Overall - Part 2/EoT - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: score on a scale				
arithmetic mean (standard deviation)	28.1 (± 5.13)	25.2 (± 7.39)		

Statistical analyses

Statistical analysis title	Part 2/EoT vs Baseline
Comparison groups	Overall - Baseline - ITT v Overall - Part 2/EoT - ITT
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Median difference (final values)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.36
upper limit	-1.32
Variability estimate	Standard deviation
Dispersion value	3.15

Notes:

[11] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Secondary: Change from baseline in muscular function after 12 months of treatment with Givinostat at the selected daily dose based on the performance of upper limb (PUL)

End point title	Change from baseline in muscular function after 12 months of treatment with Givinostat at the selected daily dose based on the performance of upper limb (PUL)

End point description:

The PUL was devised to assess motor performance in the upper limb for patients with Becker and Duchenne muscular dystrophy. The purpose is to assess change that occurs in motor performance of the upper limb over time from when a child is still ambulant until he loses all arm function when non-ambulant. The PUL will be administered according to the guidelines developed by the Physiotherapy Working Group.
The revised version (1.2) of the PUL included 22 items taking into account the rescoring and additional items to reduce the floor effect. These include one entry item to define the starting functional level, and 21 items subdivided into shoulder level (score range: 0-16), elbow level (score range 0-34) and distal level (score range: 0-24) dimension. The total score being the sum of all scores of the subscales (score range: 0-74).
For all items, the higher the score, the better the outcome.

End point type	Secondary

End point timeframe:

At 12 months

End point values	Overall - Baseline - ITT	Overall - Part 2/EoT - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: score on a scale				
arithmetic mean (standard deviation)	71.7 (± 2.40)	71.6 (± 2.81)		

Statistical analyses

Statistical analysis title	Part 2/EoT vs Baseline
Comparison groups	Overall - Part 2/EoT - ITT v Overall - Baseline - ITT
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	1.14
Variability estimate	Standard deviation
Dispersion value	2.69

Notes:

[12] - The system inappropriately adds up the number of patients in each arm. Since it is a crossover study,
the subjects in the two groups are the same and therefore the comparison is intra-group.

Secondary: Change From Baseline in Muscular Function After 24 (Extension 1), 36 (Extension 2), and 52 Months (Extension 3) of Treatment With Givinostat at the Selected Daily Dose Based on the 6-Minute Walk Test

End point title	Change From Baseline in Muscular Function After 24 (Extension 1), 36 (Extension 2), and 52 Months (Extension 3) of Treatment With Givinostat at the Selected Daily Dose Based on the 6-Minute Walk Test

End point description:

This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes.
The 6-Minute Walk Test is a useful measure of functional capacity targeted at people with at least moderately severe impairment.
The longer the walked distance the better the outcome.

End point type	Secondary

End point timeframe:

At 24, 36, and 52 months

End point values	Overall - ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	19[13]			
Units: meters				
arithmetic mean (standard deviation)				
Extension 1	-80.0 (± 110.69)			
Extension 2	-127.0 (± 110.40)			
Extension 3	-287.8 (± 159.47)			

Notes:

[13] - n=18 at month 36 (Extension 2) and month 52 (Extension 3).

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Muscular Function After 24 (Extension 1), 36 (Extension 2), and 52 Months (Extension 3) of Treatment With Givinostat at the Selected Daily Dose Based on the North Star Ambulatory Assessment (NSAA)

End point title	Change From Baseline in Muscular Function After 24 (Extension 1), 36 (Extension 2), and 52 Months (Extension 3) of Treatment With Givinostat at the Selected Daily Dose Based on the North Star Ambulatory Assessment (NSAA)

End point description:

The NSAA was graded using the standard scorecard with each assessment rated as 0 – unable to achieve independently, 1 – modified method but achieves goal independent of physical assistance from another, or 2 – normal with no obvious modification of activity.

End point type	Secondary

End point timeframe:

At 24, 36, and 52 months

End point values	Overall - ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: score on a scale				
arithmetic mean (standard deviation)				
Extension 1	-5.2 (± 5.06)			
Extension 2	-7.4 (± 5.90)			
Extension 3	-15.2 (± 7.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in muscular function after 24 (Extension 1), 36

(Extension 2), and 52 months (Extension 3) of treatment with Givinostat at the selected daily dose based on the performance of upper limb (PUL)

End point title	Change from baseline in muscular function after 24 (Extension 1), 36 (Extension 2), and 52 months (Extension 3) of treatment with Givinostat at the selected daily dose based on the performance of upper limb (PUL)

End point description:

The PUL was devised to assess motor performance in the upper limb for patients with Becker and Duchenne muscular dystrophy. The purpose is to assess the change that occurs in motor performance of the upper limb over time from when a child is still ambulant until he loses all arm function when non-ambulant. The PUL will be administered according to the guidelines developed by the Physiotherapy Working Group.

The revised version of the PUL included 22 items taking into account the rescoring and additional items to reduce the floor effect. These include one entry item to define the starting functional level, and 21 items subdivided into shoulder level, elbow level, and distal level dimension. For weaker patients, a low score on the entry item (modified Brooke) means high-level items do not need to be performed. Scoring options varied across the scale between 0–1 and 0–6, according to performance.
The higher the score the better the outcome.

End point type	Secondary

End point timeframe:

At 24, 36, and 52 months

End point values	Overall - ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: score on a scale				
arithmetic mean (standard deviation)				
Extension 1	-0.2 (± 2.71)			
Extension 2	-0.2 (± 2.75)			
Extension 3	-4.4 (± 6.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of children experiencing treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and type and severity of TEAEs

End point title	Number of children experiencing treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and type and severity of TEAEs

End point description:

Summary of Treatment-emergent Adverse Events (TEAE) Reporting from Baseline to the End of Extension 3 (Month 52). In the analysis were included: Any TEAE, Any treatment-related TEAE, Any mild or moderate or severe TEAE, Any life-threatening or disabling TEAE, Any TEAE resulting in death, any serious adverse event, and Any TEAE resulting in study discontinuation.

End point type	Secondary

End point timeframe:

Part 1, Part 2, and Extensions 1, 2, and 3

End point values	Overall - Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: participants				
TEAEs	20			
Any treatment-related TEAE	20			
Any mild TEAE	20			
Any moderate TEAE	16			
Any severe TEAE	9			
Any life-threatening or disabling TEAE	1			
Any TEAE resulting in death	0			
Any SAE	8			
Any TEAE resulting in study discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed throughout the study: in Part 1, Part 2, Extension 1, Extension 2, Extension 3. Extensions 1, 2 and 3 together represent Part 3 of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety population included all children who received any investigational product. The dose level under which the patient was analyzed was the dose of investigational product that was actually received.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Gait disturbance			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	20		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	12		
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		

Laryngeal inflammation				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nasal congestion				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Oropharyngeal pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Pharyngeal erythema				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Investigations				
Blood bilirubin increased				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Intraocular pressure increased				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Neutrophil count decreased				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	4			
Platelet count decreased				
subjects affected / exposed	13 / 20 (65.00%)			
occurrences (all)	39			
White blood cell count decreased				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	7			
Injury, poisoning and procedural complications				
Contusion				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Fall				
subjects affected / exposed	8 / 20 (40.00%)			
occurrences (all)	9			
Femur fracture				

subjects affected / exposed	2 / 20 (10.00%)
occurrences (all)	2
Foot fracture	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Head injury	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Joint injury	
subjects affected / exposed	2 / 20 (10.00%)
occurrences (all)	2
Laceration	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Ligament injury	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Ligament sprain	
subjects affected / exposed	5 / 20 (25.00%)
occurrences (all)	7
Limb injury	
subjects affected / exposed	3 / 20 (15.00%)
occurrences (all)	3
Lower limb fracture	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Muscle strain	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Spinal compression fracture	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Spinal cord injury sacral	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Tendon injury	

subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Tibia fracture				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Congenital, familial and genetic disorders				
Gilbert's syndrome				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Cardiac disorders				
Cardiac discomfort				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Extrasystoles				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Left ventricular dilatation				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Left ventricular dysfunction				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Palpitations				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Sinus tachycardia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Tachycardia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Ventricular extrasystoles				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nervous system disorders				

Dizziness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Lens discoloration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Lenticular opacities			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 20 (55.00%)		
occurrences (all)	19		
Cholitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	15 / 20 (75.00%)		
occurrences (all)	66		
Faeces soft			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		

Frequent bowel movements			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Haemorrhoids			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Dermatosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ecchymosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Erythema annulare			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Intertrigo			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nail dystrophy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Seborrhoeic dermatitis			

subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Skin lesion				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Solar dermatitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Autoimmune thyroiditis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Delayed puberty				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Hypothyroidism				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Secondary adrenocortical insufficiency				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Back pain				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Fracture pain				

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	5		
Osteopenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Tendinous contracture			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Tendon pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tendonitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Gastroenteritis			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		

Gastrointestinal viral infection	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Influenza	
subjects affected / exposed	9 / 20 (45.00%)
occurrences (all)	14
Molluscum contagiosum	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Nasopharyngitis	
subjects affected / exposed	3 / 20 (15.00%)
occurrences (all)	3
Paronychia	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Pharyngitis	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Respiratory tract infection	
subjects affected / exposed	2 / 20 (10.00%)
occurrences (all)	2
Rhinitis	
subjects affected / exposed	2 / 20 (10.00%)
occurrences (all)	2
Tooth infection	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1
Upper respiratory tract infection	
subjects affected / exposed	2 / 20 (10.00%)
occurrences (all)	3
Urinary tract infection	
subjects affected / exposed	2 / 20 (10.00%)
occurrences (all)	2
Varicella	
subjects affected / exposed	1 / 20 (5.00%)
occurrences (all)	1

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	8		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2012	• Added MRI of muscle on the upper limb, if possible and if the child was compliant. • Better described the muscles to be observed during the MRI, inserting "muscle of lower limb" instead of "quadriceps femoris" and "muscle of upper limb" instead of "brachial biceps." • Clarified the timing around the collection of PK blood samples.
25 March 2013	• Added the 25-mg hard gelatin capsule. • Changed oral suspension accountability to counting the bottles of suspension (used, empty, partially used, and unused) rather than measuring the amount of residual volume of suspension in the bottles by means of a calibrated glass cylinder.
23 October 2013	• Noted that the RD was determined to be 37.5 mg BID. • Since in some children, platelet counts below the normal range ($\leq 150 \times 10^9$/L) might be observed at the RD, the platelet counts were assessed at least every 2 weeks in the first 2 months of therapy at 37.5 mg BID and the dose was lowered to 25 mg BID if persistent platelet counts $\leq 150 \times 10^9$/L were observed. • Assessments were added to explore the acceptability/palatability of the oral suspension.
17 April 2014	• Updated the study to allow the patients to continue the treatment with givinostat at least until the final analysis was performed (at 12 months following start of treatment), and in case the results were positive, to continue the study drug treatment for an additional 12 months (Extension study treatment). • Asked patients to share information regarding the type of mutation they carried in DMD. • Added PK blood samples at 12 months of treatment. • Added Peak Expiratory Flow to the assessments. • Discontinued the collection of samples to study the effect of study drug on cytokines.
16 March 2015	• Updated the study to allow patients with positive results from the first extension of the study (Extension 1) to continue study treatment for an additional 12 months in a second extension of the study (Extension 2). During Extension 2, the dose of givinostat was to be adjusted based on the weight of the children. • Asked patients to share information related to 2 biomarkers: latent TGFβ binding protein 4 (LTBP4) and osteopontin genotype.
21 January 2016	• Updated the study to allow patients on treatment in the second extension of the study to continue for an additional 12 months in a third extension (Extension 3). During Extension 3, the dose of givinostat was to be adjusted based on the weight of the children.
11 April 2017	• Updated the study to allow patients on treatment in the third extension of the study to continue for additional 4 months until the activation of the Long Term Safety study (Study N. DSC/14/2357/51 - EUDRACT: 2017-000397-10) that was submitted to the Ethic Committees and already obtained the approval in October 2017. In this way the patients who accepted to be included in the Long Term Safety study would continue the treatment with givinostat, without any interruptions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial?   No

Limitations and caveats

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

Because of the small sample size and of the lack of a control group, no efficacy considerations can be made regarding the effects of givinostat on muscle function.

Notes: