EU Clinical Trials Register

Clinical trial results:
Randomised, double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy.

Summary

EudraCT number	2016-000401-36
Trial protocol	GB BE DE NL IT ES FR
Global end of trial date	22 February 2022

Results information

Result version number	v1 (current)
This version publication date	07 January 2023
First version publication date	07 January 2023

Trial information

Trial identification

Sponsor protocol code	DSC/14/2357/48 (EDYPIS)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03373968
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 126598

Notes:

Sponsors

Sponsor organisation name	ITALFARMACO S.p.A.
Sponsor organisation address	Via dei Lavoratori 54, Cinisello Balsamo , Italy, 20092
Public contact	Clinical Trial Transparency Manager, Italfarmaco S.p.A., +39 02 66041503, info@italfarmaco.com
Scientific contact	Clinical Trial Transparency Manager, Italfarmaco S.p.A., +39 02 66041503, info@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	10 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2022
Global end of trial reached?	Yes
Global end of trial date	22 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant DMD subjects

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Italy: 37
Worldwide total number of subjects	179
EEA total number of subjects	106

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	155
Adolescents (12-17 years)	24
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were randomised in 2:1 ratio of givinostat versus placebo. 118 subjects were enrolled in the givinostat group, and
61 subjects were enrolled in the placebo group.

Pre-assignment

Screening details:

A total of 359 subjects were screened. 36 subjects passed screening but were not randomised. 144 failed screening. 179 subjects were randomized with a 2:1 ratio: 118 subjects in the givinostat group, and 61 in the placebo group.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Subjects receiving givinostat or placebo received medication indistinguishable in appearance. Personnel involved in the study
(Investigators, nurses, all other site personnel, clinical research associates (CRAs), Medical Monitors, project managers, and personnel involved in data management) remained blinded at all times, unless under exceptional circumstances when knowledge of the study drug was essential for treating the subject, such as in case of an AE.

Arms

Are arms mutually exclusive?	Yes
Arm title	Givinostat

Arm description:

Givinostat oral suspension (10 mg/mL) twice daily (bid).

Arm type	Active comparator
Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	TF2357
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The oral suspension of givinostat (10 mg/mL) was to be dosed in fed condition as described below:
Givinostat or placebo starting dose > or =10 and < 12.5 kg of weight: 13.3 mg bid = 1.3 ml oral suspension bid > or =12.5 and < 20 kg: 16.7 mg bid =1.7 ml oral suspension bid > or = 20 and < 25 kg: 20 mg bid = 2.0 ml oral suspension bid > or = 25 and < 30 kg: 23.3 mg bid = 2.3 ml oral suspension bid > or = 30 and < 40 kg:
26.7 mg bid = 2.7 ml oral suspension bid > or = 40 and < 50 kg: 33.3 mg bid = 3.3 ml oral suspension bid > > or = 50 and < 60 kg: 36.7 mg bid = 3.7 ml oral suspension bid > or = 60 and < 70 kg: 40 mg bid = 4 ml oral suspension bid > or = 70 kg: 46.7 mg bid = 4.7 ml oral suspension bid

Arm title	Placebo

Arm description:

Placebo oral suspension (10 mg/mL) twice daily (bid).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The oral suspension of placebo, manufactured to mimic givinostat, was to be dosed in fed condition as described for givinostat.

Number of subjects in period 1	Givinostat	Placebo
Started	118	61
Completed	111	59
Not completed	7	2
Consent withdrawn by subject	4	2
Adverse event, non-fatal	3	-

Baseline characteristics

Reporting groups

Reporting group title	Givinostat
Reporting group description:	
Givinostat oral suspension (10 mg/mL) twice daily (bid).	
Reporting group title	Placebo
Reporting group description:	
Placebo oral suspension (10 mg/mL) twice daily (bid).	

Reporting group values	Givinostat	Placebo	Total
Number of subjects	118	61	179
Age categorical			
Units: Subjects			
Children (2-11 years)	100	49	149
Adolescents (12-17 years)	18	12	30
Age continuous			
Units: years			
arithmetic mean	9.78	9.97	
standard deviation	± 2.022	± 2.082	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	118	61	179

Subject analysis sets

Subject analysis set title	Givinostat ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Givinostat oral suspension (10 mg/mL) twice daily
givinostat: The oral suspension of givinostat (10 mg/mL) was to be dosed in fed condition as described below:
Givinostat or placebo starting dose
• > or =10 and < 12.5 kg of weight: 13.3 mg bid = 1.3 ml oral suspension bid
• > or =12.5 and < 20 kg: 16.7 mg bid =1.7 ml oral suspension bid
• > or = 20 and < 25 kg: 20 mg bid = 2.0 ml oral suspension bid
• > or = 25 and < 30 kg: 23.3 mg bid = 2.3 ml oral suspension bid
• > or = 30 and < 40 kg: 26.7 mg bid = 2.7 ml oral suspension bid
• > or = 40 and < 50 kg: 33.3 mg bid = 3.3 ml oral suspension bid
• > or = 50 and < 60 kg: 36.7 mg bid = 3.7 ml oral suspension bid
• > or = 60 and < 70 kg: 40 mg bid = 4 ml oral suspension bid
• > or = 70 kg: 46.7 mg bid = 4.7 ml oral suspension bid

Subject analysis set title	Placebo ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo oral suspension (10 mg/mL) twice daily
placebo: the oral suspension of placebo, manufactured to mimic givinostat, was to be dosed in fed condition as
described for givinostat.

Reporting group values	Givinostat ITT	Placebo ITT	
Number of subjects	118	61	
Age categorical Units: Subjects			
Children (2-11 years)	100	49	
Adolescents (12-17 years)	18	12	
Age continuous Units: years			
arithmetic mean	9.78	9.97	
standard deviation	± 2.022	± 2.082	
Gender categorical Units: Subjects			
Female	0	0	
Male	118	61	

End points

End points reporting groups

Reporting group title	Givinostat
Reporting group description:	
Givinostat oral suspension (10 mg/mL) twice daily (bid).	
Reporting group title	Placebo
Reporting group description:	
Placebo oral suspension (10 mg/mL) twice daily (bid).	
Subject analysis set title	Givinostat ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Givinostat oral suspension (10 mg/mL) twice daily
givinostat: The oral suspension of givinostat (10 mg/mL) was to be dosed in fed condition as described below:
Givinostat or placebo starting dose
- \> or =10 and < 12.5 kg of weight: 13.3 mg bid = 1.3 ml oral suspension bid
- \> or =12.5 and < 20 kg: 16.7 mg bid =1.7 ml oral suspension bid
- \> or = 20 and < 25 kg: 20 mg bid = 2.0 ml oral suspension bid
- \> or = 25 and < 30 kg: 23.3 mg bid = 2.3 ml oral suspension bid
- \> or = 30 and < 40 kg: 26.7 mg bid = 2.7 ml oral suspension bid
- \> or = 40 and < 50 kg: 33.3 mg bid = 3.3 ml oral suspension bid
- \> or = 50 and < 60 kg: 36.7 mg bid = 3.7 ml oral suspension bid
- \> or = 60 and < 70 kg: 40 mg bid = 4 ml oral suspension bid
- \> or = 70 kg: 46.7 mg bid = 4.7 ml oral suspension bid

Subject analysis set title	Placebo ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo oral suspension (10 mg/mL) twice daily
placebo: the oral suspension of placebo, manufactured to mimic givinostat, was to be dosed in fed condition as
described for givinostat.

Primary: Mean Change From Baseline in 4 Standard Stairs (4SC) Climb After 18 Months of Treatment

End point title	Mean Change From Baseline in 4 Standard Stairs (4SC) Climb After 18 Months of Treatment
End point description:	

The time (in seconds) to climb 4 standard-sized stairs is a TFT that represents stair-climbing ability. The test was evaluated by qualified functional evaluators (ie, physiotherapists) who were different from the site personnel who reviewed subjects' safety results. The test was performed in a standardized manner described in a specific site manual.
Baseline 4SC was the measurement taken at the randomization assessment, unless this was missing, in which case baseline was taken as the last non missing value recorded prior to or on the date of first study treatment. The shorter the time, the better the outcome.

End point type	Primary
End point timeframe:	
18 months	

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	39		
Units: seconds				
least squares mean (standard error)	1.27 (± 0.040)	1.48 (± 0.058)		

Statistical analyses

Statistical analysis title	Givinostat vs Placebo
Statistical analysis description:	
Log transformation applied	
Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0345 [2]
Method	ANCOVA
Parameter estimate	generalised least square mean ratio
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.745
upper limit	0.989

Notes:

[1] - LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA) model on change from baseline in 4SC at Month 18 with baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.

[2] - LS Means, CIs, and p-values are obtained from ANCOVA model on change from baseline in 4SC at Month 18 with baseline values for the above-mentioned parameters as covariates, with steroid use and treatment group as independent classification factors.

Secondary: Mean Change From Baseline in Time to Rise From Floor After 18 Months of Treatment

End point title	Mean Change From Baseline in Time to Rise From Floor After 18 Months of Treatment
End point description:	
An analysis of time (in seconds) to rise from the floor by change from baseline at 18 months is presented for the Target Population in the ITT analysis set. The shorter the time, the better the outcome	
End point type	Secondary
End point timeframe:	
18 months	

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	39		
Units: second				
least squares mean (confidence interval 95%)	9.33 (5.821 to 12.838)	12.61 (7.491 to 17.724)		

Statistical analyses

Statistical analysis title	Givinostat vs Placebo
Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.3044
Method	ANCOVA
Parameter estimate	difference in least square means
Point estimate	-3.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.573
upper limit	3.018

Notes:

[3] - LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA) model on change from baseline in time to rise from the Floor at Month 18 with baseline values for: 4SC, time to rise from floor, time to run/walk 10 m, distance walked in 6 minutes and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.

Secondary: Mean Change From Baseline in the Six-minute Walking Test (6MWT) After 18 Months of Treatment

End point title	Mean Change From Baseline in the Six-minute Walking Test (6MWT) After 18 Months of Treatment

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.
A modified version of the 6MWT recommended by American Thoracic Society (2002) for use in adults was performed.
The longer the walked distance the better the outcome.

End point type	Secondary

End point timeframe:

18 months

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	39		
Units: Meters				
least squares mean (confidence interval 95%)	-38.43 (-50.704 to -26.153)	-48.38 (-66.288 to -30.482)		

Statistical analyses

Statistical analysis title	Givinostat vs Placebo
Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.3723 [5]
Method	ANCOVA
Parameter estimate	difference in least square means
Point estimate	9.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.071
upper limit	31.983

Notes:

[4] - LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA)
model on change from baseline in distance walked at the end of the 6-minute walking test (6MWT) at Month 18 with baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification actors.

[5] - LS means, CIs, p-values were obtained from analysis of covariance model on change from baseline in distance walked at the end of the 6MWT at Month18.

Secondary: Mean Change From Baseline in Total North Star Ambulatory Assessment (NSAA) Score After 18 Months of Treatment

End point title	Mean Change From Baseline in Total North Star Ambulatory Assessment (NSAA) Score After 18 Months of Treatment

End point description:

The total North Star Ambulatory Assessment (NSAA) is a 17-item rating scale that is used to measure functional motor abilities in ambulant children with Duchenne Muscular Dystrophy (DMD). It is usually used to monitor the progression of the disease and treatment effects. The 17 items of the NSAA, ranging from standing to running 10 meters, were graded using the standard score card 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. This scale is ordinal with 0 as the minimum score (indicating full dysfunctionality, i.e. the worst outcome) and with 34 as the maximum score indicating fully-independent function (the best outcome).

End point type	Secondary

End point timeframe:

18 months

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	39		
Units: score on a scale				
least squares mean (confidence interval 95%)	-2.66 (-3.563 to -1.759)	-4.58 (-5.891 to -3.260)		

Statistical analyses

Statistical analysis title	Givinostat vs Placebo
Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0209
Method	ANCOVA
Parameter estimate	difference in least square means
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.295
upper limit	3.533

Notes:

[6] - LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA) model on change from baseline in total NSAA score at Month 18 with baseline values for: total NSAA score, 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.

Secondary: Cumulative Loss of Function on the NSAA

End point title	Cumulative Loss of Function on the NSAA

End point description:

Analysis of cumulative loss of function on the NSAA over 18 months of treatment is presented for the Target Population in the ITT analysis set. It has been expressed as estimated cumulative failures.

End point type	Secondary

End point timeframe:

over 18 months

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	39		
Units: estimated cumulative failures				
number (confidence interval 95%)	3.42 (2.692 to 4.334)	5.56 (4.002 to 7.715)		

Statistical analyses

Statistical analysis title	Givinostat vs Placebo
Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0202 [8]
Method	negative binomial regression model
Parameter estimate	Ratio of cumulative failures]
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.408
upper limit	0.927

Notes:

[7] - Estimated cumulative failures, ratio of cumulative failures, CIs, and p-values are obtained from a negative binomial regression on the subject cumulative number of failures across all post-baseline visits. Total failed items at baseline, baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose were included as independent covariates, with treatment group and steroid use included as indep classification factors.

[8] - Estimated cumulative failures, their ratio were obtained from a negative binomial regression on the cumulative N of failures across all visits.

Secondary: Mean Change From Baseline of Muscle Strength Normalized Overtime

End point title	Mean Change From Baseline of Muscle Strength Normalized Overtime

End point description:

The mean change of muscle strength normalized was evaluated by knee extension and elbow flexion normalized by subject weight, both measured by hand-held myometry (HHM).

End point type	Secondary

End point timeframe:

over 18 months

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	39		
Units: N/kg normalized				
least squares mean (confidence interval 95%)				
Overall knee extension	-0.32 (-0.441 to -0.197)	-0.50 (-0.681 to -0.328)		
Overall elbow flexion	-0.10 (-0.174 to -0.031)	-0.19 (-0.292 to -0.085)		

Statistical analyses

Statistical analysis title	Givinostat vs Placebo

Statistical analysis description:

Overall knee extension

Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0902
Method	ANCOVA
Parameter estimate	Difference in least square means]
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.401

Notes:

[9] - LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA) model on change from baseline in normalized muscle strength at Month 18 with baseline normalised muscle strength and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.

Statistical analysis title	Givinostat vs Placebo

Statistical analysis description:

Overall elbow flexion

Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.1818
Method	ANCOVA
Parameter estimate	difference in least square means
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.213

Notes:

[10] - LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA) model on change from baseline in normalised muscle strength at Month 18 with baseline normalized muscle strength and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.

Secondary: Mean Change From Baseline in Vastus Lateralis Muscle Fat Fraction (VL MFF) at 18 Months

End point title	Mean Change From Baseline in Vastus Lateralis Muscle Fat Fraction (VL MFF) at 18 Months

End point description:

Vastus lateralis muscle fat fraction (VL MFF) was expressed as fat infiltration in this muscle. Fat infiltration was assessed by Magnetic Resonance (MRS).

End point type	Secondary

End point timeframe:

at 18 months

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	37		
Units: percentage of fat				
least squares mean (confidence interval 95%)	7.63 (6.098 to 9.172)	10.56 (8.331 to 12.783)		

Statistical analyses

Statistical analysis title	Givinostat vs Placebo
Comparison groups	Givinostat ITT v Placebo ITT
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0354
Method	ANCOVA
Parameter estimate	difference in least square means
Point estimate	-2.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.641
upper limit	-0.204

Notes:

[11] - LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA) model on change from baseline in VL MFF at Month 18 with baseline VL MFF and rederived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.

Secondary: Number of Subjects Experiencing Treatment-emergent AEs (TEAEs), Serious AEs (SAEs), Mild TEAE Moderate TEAE, Severe TEAE

End point title	Number of Subjects Experiencing Treatment-emergent AEs (TEAEs), Serious AEs (SAEs), Mild TEAE Moderate TEAE, Severe TEAE

End point description:

Adverse Events are unfavorable changes in health, including abnormal laboratory findings, that occur in trial participants during the clinical trial or within a specified period following the trial.
Serious Adverse Events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned.

End point type	Secondary

End point timeframe:

Baseline through end of study, that is the end of 18° month

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	61		
Units: Count of Participants				
Subjects with TEAE	112	57		
Subjects with serious AE	8	2		
Subjects with mild AE	69	39		
Subjects with moderate AE	38	17		
Subjects with severe AE	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Acceptability/Palatability of the Oral Suspension

End point title	Evaluation of Acceptability/Palatability of the Oral Suspension

End point description:

Acceptability and palatability of the oral suspension over time are presented. More in details, child perception of the medicine at the three timepoints hereunder specified; parent perception of the medicine based on the child's reaction at the same three timepoints; and parent problems administering the medication at the same timepoints are reported.

End point type	Secondary

End point timeframe:

Week 4, EOS, early withdrawal

End point values	Givinostat ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	61		
Units: Count of Participants				
Child perception - week 4 - dislike very much	31	11		
Child perception - week 4 - dislike a little	21	17		
Child perception - week 4 - not sure	30	16		
Child perception - week 4 - like a little	19	12		
Child perception - week 4 - like very much	11	3		
Child perception - EOS - dislike very much	21	7		
Child perception - EOS - dislike a little	24	13		
Child perception - EOS - not sure	34	16		
Child perception - EOS - like a little	19	10		
Child perception - EOS - like very much	7	9		
Child perception - early withdrawal - dislike very	1	0		
Child perception - early withdrawal - dislike a li	1	0		
Child perception - early withdrawal - not sure	2	0		

Child perception - early withdrawal - like a littl	1	0
Child perception - early withdrawal - like very mu	0	0
Parent perception - week 4 - unpleasant	50	31
Parent perception - week 4 - not sure	28	10
Parent perception - week 4 - pleasant	35	18
Parent perception - EOS - unpleasant	42	14
Parent perception - EOS - not sure	40	22
Parent perception - EOS - pleasant	26	19
Parent perception - early withdrawal - unpleasant	1	0
Parent perception - early withdrawal - not sure	3	0
Parent perception - early withdrawal - pleasant	1	0
Parent admin problems - week 4 - yes	6	1
Parent admin problems - week 4 - no	107	58
Parent admin problems - EOS - yes	5	0
Parent admin problems - EOS - no	102	55
Parent admin - early withdrawal - yes	0	0
Parent admin - early withdrawal - no	5	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study, Visits 4 and 7 (month 1), at Visit 9 (month 2), at Visit 10 (month 3), at Visit 11 (month 6), at Visit 12 (month 9), at Visit 13 (month 12), at Visit 14 (month 15), at Visit 15 (EOS, month 18) and at the FUV (ie, 4 weeks ± 7 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Givinostat SAF

Reporting group description:

Givinostat oral suspension (10 mg/mL) twice daily.
The Safety set (SAF) consisted of all randomized subjects who received at least one dose of the IMP. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.

Reporting group title	Placebo SAF

Reporting group description:

Placebo oral suspension (10 mg/mL) twice daily.
The Safety set (SAF) consisted of all randomized subjects who received at least one dose of the IMP. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.

Serious adverse events	Givinostat SAF	Placebo SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 118 (6.78%)	2 / 61 (3.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Gastrointestinal disorders

Abdominal pain

subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Vomiting

subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Skin and subcutaneous tissue disorders

Rash

subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Infections and infestations

Gastroenteritis

subjects affected / exposed	1 / 118 (0.85%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Gastroenteritis viral

subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Influenza

subjects affected / exposed	1 / 118 (0.85%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Givinostat SAF	Placebo SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 118 (88.14%)	55 / 61 (90.16%)	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	6 / 118 (5.08%)	0 / 61 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 118 (7.63%)	0 / 61 (0.00%)	
occurrences (all)	10	0	
Pyrexia			
subjects affected / exposed	15 / 118 (12.71%)	5 / 61 (8.20%)	
occurrences (all)	18	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 118 (11.02%)	9 / 61 (14.75%)	
occurrences (all)	13	9	
Epistaxis			
subjects affected / exposed	8 / 118 (6.78%)	5 / 61 (8.20%)	
occurrences (all)	21	9	
Oropharyngeal pain			
subjects affected / exposed	7 / 118 (5.93%)	1 / 61 (1.64%)	
occurrences (all)	8	1	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	11 / 118 (9.32%)	4 / 61 (6.56%)	
occurrences (all)	14	4	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	14 / 118 (11.86%)	3 / 61 (4.92%)	
occurrences (all)	19	6	
Platelet count decreased			
subjects affected / exposed	21 / 118 (17.80%)	0 / 61 (0.00%)	
occurrences (all)	26	0	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	11 / 118 (9.32%)	3 / 61 (4.92%)	
occurrences (all)	32	6	
Fall			
subjects affected / exposed	15 / 118 (12.71%)	13 / 61 (21.31%)	
occurrences (all)	24	18	
Ligament sprain			
subjects affected / exposed	8 / 118 (6.78%)	3 / 61 (4.92%)	
occurrences (all)	9	4	
Limb Injury			
subjects affected / exposed	6 / 118 (5.08%)	2 / 61 (3.28%)	
occurrences (all)	8	2	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	8 / 118 (6.78%)	1 / 61 (1.64%)	
occurrences (all)	12	2	
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 118 (23.73%)	14 / 61 (22.95%)	
occurrences (all)	41	30	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	19 / 118 (16.10%)	0 / 61 (0.00%)	
occurrences (all)	27	0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	6 / 118 (5.08%)	3 / 61 (4.92%)	
occurrences (all)	11	4	
Eye disorders			
Eye disorders			
subjects affected / exposed	5 / 118 (4.24%)	4 / 61 (6.56%)	
occurrences (all)	8	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	25 / 118 (21.19%)	9 / 61 (14.75%)	
occurrences (all)	52	16	
Abdominal pain upper			

subjects affected / exposed	17 / 118 (14.41%)	7 / 61 (11.48%)
occurrences (all)	21	9

Constipation
subjects affected / exposed	8 / 118 (6.78%)	1 / 61 (1.64%)
occurrences (all)	9	1

Diarrhoea
subjects affected / exposed	43 / 118 (36.44%)	11 / 61 (18.03%)
occurrences (all)	117	16

Dyspepsia
subjects affected / exposed	2 / 118 (1.69%)	4 / 61 (6.56%)
occurrences (all)	3	4

Nausea
subjects affected / exposed	8 / 118 (6.78%)	4 / 61 (6.56%)
occurrences (all)	9	6

Vomiting
subjects affected / exposed	34 / 118 (28.81%)	8 / 61 (13.11%)
occurrences (all)	64	12

Skin and subcutaneous tissue disorders
Rash
subjects affected / exposed	11 / 118 (9.32%)	1 / 61 (1.64%)
occurrences (all)	18	1

Musculoskeletal and connective tissue disorders
Back pain
subjects affected / exposed	6 / 118 (5.08%)	8 / 61 (13.11%)
occurrences (all)	9	8

Myalgia
subjects affected / exposed	11 / 118 (9.32%)	2 / 61 (3.28%)
occurrences (all)	18	2

Pain in extremity
subjects affected / exposed	8 / 118 (6.78%)	7 / 61 (11.48%)
occurrences (all)	14	10

Infections and infestations
Ear infection
subjects affected / exposed	3 / 118 (2.54%)	4 / 61 (6.56%)
occurrences (all)	5	4

Gastroenteritis

subjects affected / exposed	9 / 118 (7.63%)	3 / 61 (4.92%)
occurrences (all)	12	3
Influenza		
subjects affected / exposed	3 / 118 (2.54%)	4 / 61 (6.56%)
occurrences (all)	3	4
Nasopharyngitis		
subjects affected / exposed	31 / 118 (26.27%)	19 / 61 (31.15%)
occurrences (all)	50	27
Rhinitis		
subjects affected / exposed	6 / 118 (5.08%)	7 / 61 (11.48%)
occurrences (all)	11	8
Upper respiratory tract infection		
subjects affected / exposed	7 / 118 (5.93%)	8 / 61 (13.11%)
occurrences (all)	9	9
Metabolism and nutrition disorders		
Decreased appetite		
subjects affected / exposed	8 / 118 (6.78%)	0 / 61 (0.00%)
occurrences (all)	10	0
Hypertriglyceridaemia		
subjects affected / exposed	14 / 118 (11.86%)	1 / 61 (1.64%)
occurrences (all)	22	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2016	Final Protocol Version 1.0 dated 07 MAY 2016 was amended for the following reasons: • To amend the wording of an inclusion criterium to limit the exclusion of patient due to operator error of stopwatch. • To amend the stratification process at randomization, including 2 additional strata based on type of steroids because new data suggest that Deflazacort use is associated with more prolonged time to loss of ambulation and increased frequency of side effects. • To change the MRI cohort in MR cohort because the magnetic resonance spectroscopy (MRS) exam was added at the same time points of MRI test. The reason of the inclusion of MRS is explained in the next bullet point. • To change the Key secondary endpoints in the MR cohort related to imaging data using the data from MRS instead of MRI data by 3 point-Dixon technique. Both teniques are responsive to disease progression, but MRS is considered the gold standard for quantification of drug effects in vivo, and Fat Fraction measures from single-voxel spectroscopy have been shown to be associated with function in DMD. Moreover, MRS is the most direct and sensitive approach to discriminate water and fat proton component signals in MR. • To amend the wording of an exclusion criterium related to MR cohort in order to include also MRS exam. • To specify the type of Raven progressive matrices to be used for assessing the cognitive function. • To better clarify the pharmacokinetics procedures, by limiting the decision of site personnel to collect the PK samples • To allow personnel authorized by the Investigator to perform blood collection during visits 5, 6 and 8 in order to facilitate the management of these visits. • to correct some typographic mistakes existing in the final protocol version 1.0 (dated 07 MAY 2016).
05 September 2016	Final Protocol Version 2.0 dated 13 JUL 2016 was amended for the following reasons: · To address relevant GNAs regarding to the VHP procedure VHP934 (VHP2016102); · To add the acceptability/palatability test as suggested by PDCO during the PIP discussion; · To better clarify the pharmacokinetics sampling and procedures; · To better clarify the time window of the Visits; · To update the functional algorithm after an additional discussion was performed with the statistician to include also 6MWT in the algorithm; · To specify the videos procedures which will be followed to ensure and maintain during the study, quality standard of functional evaluators; · To add "age" as covariate in the statistical analysis as discussed with the PDCO during the PIP discussion. . to correct some misleading or unclear sentences existing in the final protocol version 2.0 (dated 13 JUL 2016).

12 July 2017	Final Protocol Version 3.0 dated 05 SEP 2016 (For European sites) and Final Protocol Version 3.1 dated 04 OCT 2016 were amended for the main following reasons: · To address relevant FDA comments regarding to the 'May Proceed Letter' (dated 18Oct2016); · To modify the exclusion criterion n.1 related to the exposure to another investigational drug (only for the European sites because for the US and Canada sites the criterion was already amended); · To modify the exclusion criterion n. 6 related to the ankle joint contractures to render it more applicable to the target population and to permit the recruitment of a wider number of children affected by Duchenne Muscular Dystrophy; · To better clarify the pharmacokinetics sampling and procedures; · To better clarify the time window of some assessments; · To add a blood sample for the evaluation of serum biomarkers related to DMD and to insert them as exploratory assessments and endpoints; · To add in the schedule of Assessment the possibility to perform the genetic test to confirm the diagnosis of DMD, as requested in the relevant inclusion criterion. . to correct some misleading or unclear sentences existing in the final protocol versions 3.0 and 3.1 (dated 05 SEP 2016 and 04 OCT 2016).
19 October 2018	Final Protocol Version 4.0 dated 12 Jul 2017 is amended for the main following reasons: 1. To address safety issue. 2. To safeguard subject safety, a new exclusion criterion is added to the protocol excluding subjects with triglycerides > 300 mg/dL (3.42 mmol/L). 4. To increase the frequency of thyroid function monitoring (TSH, fT3 and fT4 assessments) to ensure patient safety. 5. To address the IDMC recommendation a complete blood count (CBC) test assessment has to be performed weekly for 8 consecutive weeks if the dose is reduced due to platelet count ≤150 x 109/L and/or white blood cell <3.0 x 109/L and/or hemoglobin <10.0 mg/dL for safety reasons. 6. To guarantee a right safety evaluation, spirometry should be repeated if the test does not meet ATS/ERS criteria and/or the evaluator deems that a valid attempt to perform a correct maneuver has not been made by the subject. 7. To update the Inclusion criterion #6 from "Have time to rise from floor of < 10 seconds at screening" to "Have time to rise from floor ≥ 3 seconds and < 10 seconds at screening". The "time to rise" lower boundary is selected to avoid subjects who will not have enough function decline in 18 months if on placebo. 8. To update the Inclusion criterion #7 from "Have manual muscle testing (MMT) of quadriceps at screening ≥ Grade 3" to "Have manual muscle testing (MMT) of quadriceps at screening ≥ Grade – 3", to permit recruiting of a wider no. of subjects. 9. To remove the Inclusion criterion (Criterion #8) 10. To update the Inclusion criterion #9 (#8 in the amended protocol). 11. 11. To update the Exclusion criterion #4
29 August 2019	Final Protocol Version 6.0 dated 19 October 2018 is amended for the main following reasons: 1. In the original protocol sample size was calculated using publicly available standard deviation (SD), in particular from DMD Phase 3 study data on ataluren and drisapersen, where subjects have specific DMD genetic mutations (ie. Skippable 51 mutations or non-sense mutations). Since in the current protocol, inclusion of subjects is not depending on type of DMD genetic mutation, in case the Standard Deviation (SD) in the current study population will be lower than the estimated SD stated in the protocol, the sponsor believes appropriate to reduce the sample size of the study. Due to this, statistiscal analysis section is updated accordingly. 2. To update the background of givinostat regarding non clinical studies and clinical experience on risks and benefits section according to the new Investigator Brochure version 20 - July 2019. 3. To correct some typographic mistakes and/or clarify some paragraphs of Protocol version 6.0 (dated 19 Oct 2018) that could be unclear.

08 April 2020	1. To amend the protocol based on the results of the pre-planned futility interim analysis as described in protocol version 7.0, performed in January 2020: it was concluded that futility on VLFF was not met and the trial should continue. 2. To amend the effect size, in 4SC 18 month change from baseline, from 3 seconds to 2 seconds. The Sponsor considers more appropriate 2 seconds based on the recent analyses performed by C-Tap (Wong B, et al. Action Duchenne International Conference, November 9–11, 2018, Birmingham, UK), where the minimally clinically important difference (MCID) for timed function tests (TFTs) in DMD was estimated at ~1.0 to 1.6 seconds. 3. Update the no. of subjects to be included in the MR cohort following the blinded sample size re-estimation done during the interim analysis in January 2020. 4. To cancel the second interim analysis following the recommendation made by FDA during the Type C meeting in October 2019. Since the second interim analysis has been deleted, the imaging endpoint has been moved to Key efficacy Endpoint. 5. To include an additional analytic method for the NSAA assessment. 6. To update the "Background on DMD" paragraph following the recent NDA approval received by Sarepta for the treatment of DMD boys. 7. To correct some typographic mistakes and/or clarify some paragraphs of Protocol version 7.0 that could be unclear.

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.

No limitations and caveats are applicable to this summary of results.

Notes: