Clinical trial results:

A randomised, double-blind, placebo-controlled study to evaluate the micro-macroscopic effects on muscles, the safety and tolerability, and the efficacy of givinostat in patients with Becker Muscular Dystrophy.

Summary

EudraCT number	2017-001629-41
Trial protocol	NL IT
Global end of trial date	19 March 2021

Results information

Result version number	v1 (current)
This version publication date	27 May 2022
First version publication date	27 May 2022

Trial information

Trial identification

Sponsor protocol code	DSC/15/2357/53

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03238235
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ITALFARMACO S.p.A.
Sponsor organisation address	Viale dei Lavoratori, 54, Cinisello Balsamo, MIlano, Italy, 20092
Public contact	Clinical Trial Transparency Manager, Italfarmaco SpA, ITALFARMACO S.p.A., +39 0264431, info@italfarmaco.com
Scientific contact	Clinical Trial Transparency Manager, Italfarmaco SpA, ITALFARMACO S.p.A., +39 0264431, 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	19 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2021
Global end of trial reached?	Yes
Global end of trial date	19 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:	
To establish the histological effects of givinostat versus placebo administered over 12 months.	
Protection of trial subjects:	
This study was conducted in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, International Conference of Harmonization – Good Clinical Practice Guidelines (ICH GCP E6 (R2)) and all applicable national laws and regulations.	
Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	08 January 2018
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	Netherlands: 6
Country: Number of subjects enrolled	Italy: 45
Worldwide total number of subjects	51
EEA total number of subjects	51

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	51
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients were randomized in a 2:1 ratio to receive givinostat or placebo for 12 months. Randomization was stratified by concomitant steroid use at baseline (yes or no).

Pre-assignment

Screening details:

70 ambulant patients had provided written informed consent to participate in this study. They underwent a 4-week screening period to determine their study eligibility. 51 patients (72.86%) completed screening successfully and were randomized as follow: 34 patients (66.67%) were assigned to the givinostat group and 17 (33.33%) to 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, Carer, Assessor

Blinding implementation details:

This was a double-blind, placebo-controlled study. Placebo was indistinguishable from the active product in color, appearance, smell and taste. Personnel involved in the study (Investigators, nurses, all other site personnel, clinical research associates [CRA], medical monitors, project managers, data managers and statisticians) were blinded at all times unless knowledge of the study treatment was necessary for the patient's safety.

Arms

Are arms mutually exclusive?	Yes
Arm title	Givinostat - ITT

Arm description:

Givinostat (ITF2357) oral suspension (10 mg/mL) was initially administered as 2 daily doses of 40-70 mg according to body weight after a meal (high dose). With amendment 2 of the protocol, a lower starting dose was implemented to address cases of thrombocytopenia reported following the treatment of the first 21 patients. The investigational study drug was administered for 12 months.

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

Dosage and administration details:

Givinostat (ITF2357) oral suspension (10 mg/mL) was initially administered as 2 daily doses of 40-70 mg according to body weight after a meal (high dose) and more precisely in the morning after breakfast and in the evening after dinner using a graduated dosing syringe. With amendment 2 of the protocol, a lower starting dose was implemented to address cases of thrombocytopenia reported following the treatment of the first 21 patients and corresponded to the reduced dose of the original protocol (i.e., 26.7-46.7 mg b.i.d according to body weight, i.e., low dose).

Arm title	Placebo - ITT

Arm description:

Matching placebo was administered in the same formulation, same times and same way of givinostat. This means that placebo was administered as oral suspension bid after meals.

Arm type	Placebo

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

Dosage and administration details:

Matching placebo was administered in the same formulation, same times and same way of givinostat. This means that placebo was administered as oral suspension bid after a meal (i.e., in the morning after breakfast and in the evening after dinner) using a graduated dosing syringe.

Number of subjects in period 1	Givinostat - ITT	Placebo - ITT
Started	34	17
Completed	30	17
Not completed	4	0
Adverse event, non-fatal	2	-
unable to travel to the site due to pandemic	2	-

Baseline characteristics

Reporting groups

Reporting group title	Givinostat - ITT
Reporting group description:	

Givinostat (ITF2357) oral suspension (10 mg/mL) was initially administered as 2 daily doses of 40-70 mg according to body weight after a meal (high dose). With amendment 2 of the protocol, a lower starting dose was implemented to address cases of thrombocytopenia reported following the treatment of the first 21 patients. The investigational study drug was administered for 12 months.

Reporting group title	Placebo - ITT
Reporting group description:	

Matching placebo was administered in the same formulation, same times and same way of givinostat. This means that placebo was administered as oral suspension bid after meals.

Reporting group values	Givinostat - ITT	Placebo - ITT	Total
Number of subjects	34	17	51
Age categorical			
Units: Subjects			
18-65	34	17	51
Age continuous			
Units: years			
arithmetic mean	36.5	39.2	
standard deviation	± 11.56	± 9.84	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	34	17	51

End points

End points reporting groups

Reporting group title	Givinostat - ITT
Reporting group description:	
Givinostat (ITF2357) oral suspension (10 mg/mL) was initially administered as 2 daily doses of 40-70 mg according to body weight after a meal (high dose). With amendment 2 of the protocol, a lower starting dose was implemented to address cases of thrombocytopenia reported following the treatment of the first 21 patients. The investigational study drug was administered for 12 months.	
Reporting group title	Placebo - ITT
Reporting group description:	
Matching placebo was administered in the same formulation, same times and same way of givinostat. This means that placebo was administered as oral suspension bid after meals.	

Primary: Mean change from baseline in total fibrosis comparing the histology of muscle biopsies after 12 months of treatment

End point title	Mean change from baseline in total fibrosis comparing the histology of muscle biopsies after 12 months of treatment
End point description:	
Mean change from baseline in total fibrosis was calculated both on log scale in the ITT and back-transformed on the original scale in ITT. Here only log scale values are reported for the primary endpoint.	
End point type	Primary
End point timeframe:	
At baseline and at visit 11 (i.e. after 12 months of treatment)	

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	15		
Units: percentage				
geometric mean (standard deviation)	0.14 (± 0.437)	-0.06 (± 0.625)		

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8282
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.38

Notes:

[1] - ANCOVA model was performed considering the difference between log of total fibrosis at Visit 11 and log baseline values as the dependent variable; log baseline value was included as covariate, treatment and concomitant steroid use at baseline as independent class variables.

Secondary: Mean change from baseline in fat fraction of the vastus lateralis after 12 months of treatment (MRS)

End point title	Mean change from baseline in fat fraction of the vastus lateralis after 12 months of treatment (MRS)

End point description:

Evaluations were performed comparing Magnetic Resonance Spectroscopy (MRS) at baseline and after 12 months of treatment with givinostat versus placebo. Mean absolute change from baseline in fat fraction was reported both for vastus lateralis and soleus.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	17		
Units: percentage				
arithmetic mean (standard deviation)				
Fat fraction in vastus lateralis	1.06 (± 6.17)	3.82 (± 5.69)		

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.1991
Method	ANCOVA
Parameter estimate	log difference of the least square means
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.03

Notes:

[2] - ANCOVA model was performed considering baseline fat fraction of vastus lateralis or fat fraction in the soleus value as covariate and treatment and concomitant steroid use at baseline as independent class variables.

Secondary: Mean change from baseline of fat fraction of lower limb muscles, thigh and pelvic girdle after 12 months of treatment (Dixon MRI)

End point title	Mean change from baseline of fat fraction of lower limb muscles, thigh and pelvic girdle after 12 months of treatment (Dixon MRI)

End point description:

Mean change of fat fraction of lower limb muscles (quadriceps,hamstrings,triceps sure), tigh (whole and medial) and pelvic girdle was measured using Dixon Magnetic Resonance Imaging (MRI) technique. Previous studies have shown that MRI can visualize structural alterations of muscle in muscular dystrophies and that fat fraction measured by MRI or magnetic resonance spectroscopy (MRS) highly correlates with lower limb function. Although longitudinal data on MRI/MRS particularly from randomised clinical trials are still limited, fatty degeneration of the muscle, in particular Muscle Fat Fraction (MFF) evaluated by MRI Dixon technique of the thigh muscles showed excellent correlation with clinical function in BMD patients, and might be a promising surrogate outcome marker in clinical trials. For the reason described above, MFF evaluated by MRI with Dixon technique as well as MRS are secondary endpoints of the study.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[3]	17[4]		
Units: percentage				
arithmetic mean (standard deviation)				
whole tigh	0.70 (± 1.684)	1.98 (± 1.761)		
quadriceps	0.38 (± 1.991)	2.25 (± 1.945)		
medial tigh	0.24 (± 2.139)	1.71 (± 2.913)		
hamstrings	1.50 (± 2.839)	1.97 (± 2.460)		
triceps surae	1.37 (± 2.672)	3.13 (± 1.999)		
pelvis girdle	0.32 (± 2.193)	1.69 (± 1.776)		

Notes:

[3] - n=22 and not 33 only for fat fraction in triceps surae

[4] - n=11 and not 17 only in fat fraction of triceps surae

Statistical analyses

Statistical analysis title	Givinostat vs placebo for whole thigh

Statistical analysis description:

Estimated between-group difference for the whole thigh

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0149
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-1.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.43
upper limit	-0.28

Notes:

[5] - ANCOVA model was performed considering baseline Fat Fraction of lower limb muscles value as covariate and treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	Givinostat vs placebo for quadriceps

Statistical analysis description:

Estimated between-group difference for quadriceps

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0022
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.18
upper limit	-0.75

Notes:

[6] - ANCOVA model was performed considering baseline Fat Fraction of lower limb muscles value as covariate and treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	Givinostat vs placebo for medial thigh

Statistical analysis description:

Estimated between-group difference for medial thigh

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1165
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.01

Notes:

[7] - ANCOVA model was performed considering baseline Fat Fraction of lower limb muscles value as covariate and treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	Givinostat vs placebo for hamstrings

Statistical analysis description:

Estimated between-group difference for hamstrings

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.4869
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	1.08

Notes:

[8] - ANCOVA model was performed considering baseline Fat Fraction of lower limb muscles value as covariate and treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	Givinostat vs placebo for triceps surae

Statistical analysis description:

Estimated between-group difference for triceps surae. Please note that since for triceps sure analysis n=22 for givinostat and n= 11 for placebo, the number of subjects involved in this particular analysis is 33 and not 50 as indicated below.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0939
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	0.29

Notes:

[9] - ANCOVA model was performed considering baseline Fat Fraction of lower limb muscles value as covariate and treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	Givinostat vs placebo for pelvis girdle

Statistical analysis description:

Estimated between-group difference for pelvis girdle

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.1579
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	0.36

Notes:

[10] - ANCOVA model was performed considering baseline Fat Fraction of lower limb muscles value as covariate and treatment and
concomitant steroid use at baseline as independent class variables.

Secondary: Mean change from baseline in cross-sectional area (CSA) of lower limb muscles and pelvic girdle after 12 months of treatment (Dixon MRI)

End point title	Mean change from baseline in cross-sectional area (CSA) of lower limb muscles and pelvic girdle after 12 months of treatment (Dixon MRI)

End point description:

Mean change of CSA of lower limb muscles and pelvic girdle was measured using Dixon Magnetic Resonance Imaging (MRI) technique.
Previous studies have shown that MRI can visualize structural alterations of muscle in muscular dystrophies and that fat fraction measured by MRI or magnetic resonance spectroscopy (MRS) highly correlates with lower limb function. Although longitudinal data on MRI/MRS particularly from randomised clinical trials are still limited, fatty degeneration of the muscle, in particular Muscle Fat Fraction (MFF) evaluated by MRI Dixon technique of the thigh muscles showed excellent correlation with clinical function in BMD patients, and might be a promising surrogate outcome marker in clinical trials. For the reason described above, MFF evaluated by MRI with Dixon technique as well as MRS are secondary endpoints of the study.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[11]	17[12]		
Units: area in cm2				
arithmetic mean (standard deviation)				
Whole thigh	2.55 (± 4.514)	2.14 (± 4.906)		
Quadriceps	0.94 (± 1.950)	1.04 (± 2.244)		
Medial Thigh	0.76 (± 2.081)	0.42 (± 1.871)		
Hamstrings	0.85 (± 1.780)	0.68 (± 1.767)		
Triceps surae	0.65 (± 3.037)	0.63 (± 3.114)		
Pelvis girdle	1.21 (± 2.962)	0.88 (± 3.421)		

Notes:

[11] - n=22 and not 33 only for triceps surae

[12] - n=11 and not 17 only for triceps surae

Statistical analyses

Statistical analysis title	Givinostat vs placebo for the whole thigh
Statistical analysis description:	
This analysis regards the whole thigh	
Comparison groups	Givinostat - ITT v Placebo - ITT

Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	superiority[13]
P-value	= 0.777
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.45
upper limit	3.26

Notes:

[13] - ANCOVA model was performed considering baseline CSA as covariate, treatment and concomitant steroid use at baseline as
independent class variables

Statistical analysis title	Givinostat vs placebo in quadriceps
Statistical analysis description:	
This analysis regards quadriceps	
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.8926
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	1.18

Notes:

[14] - ANCOVA model was performed considering baseline CSA as covariate, treatment and concomitant steroid use at baseline as
independent class variables

Statistical analysis title	Givinostat vs placebo in medial thigh
Statistical analysis description:	
This analysis regards medial thigh	
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.572
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	1.58

Notes:

[15] - ANCOVA model was performed considering baseline CSA as covariate, treatment and concomitant steroid use at baseline as
independent class variables

Statistical analysis title	Givinostat vs placebo in hamstrings

Statistical analysis description:

This analysis regards in hamstrings

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.8386
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	1.18

Notes:

[16] - ANCOVA model was performed considering baseline CSA as covariate, treatment and concomitant steroid use at baseline as
independent class variables

Statistical analysis title	Givinostat vs placebo in triceps surae

Statistical analysis description:

This analysis regards in triceps surae. Please note that in this particular analysis the number of subjects is 33 and not 50 as reported hereunder, since n=22 in givinostat group and n=11 in the placebo group, for a total of 33.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.8591
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	2.25

Notes:

[17] - ANCOVA model was performed considering baseline CSA as covariate, treatment and concomitant steroid use at baseline as
independent class variables

Statistical analysis title	Givinostat vs placebo in pelvis girdle

Statistical analysis description:

This analysis regards pelvis girdle.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.7392
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2.24

Notes:

[18] - ANCOVA model was performed considering baseline CSA as covariate, treatment and concomitant steroid use at baseline as
independent class variables

Secondary: Mean change from baseline in biopsy histological parameters (muscle fiber area [MFA], mean adipose tissue, other histological structures etc.) after 12 months of treatment - slide 1

End point title	Mean change from baseline in biopsy histological parameters (muscle fiber area [MFA], mean adipose tissue, other histological structures etc.) after 12 months of treatment - slide 1

End point description:

Biopsy histological parameters (slide 1) analysed were: muscle fiber area fraction (MFA), adipose tissue, other histological structures, Mean value of fibers with nuclear centralization and Mean value of total number of fibers. This latter is calculated as the sum of the number of fibers of available fields analyzed on Slide I for each patient.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. 12 months after the treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	15		
Units: percentage				
arithmetic mean (standard deviation)				
MFA	-4.53 (± 12.892)	0.01 (± 21.768)		
Adipose tissue	-0.07 (± 1.896)	-0.29 (± 3.639)		
Other histological structures	0.39 (± 1.464)	0.83 (± 2.359)		
Fiber with nuclear centralizations	0.80 (± 9.525)	1.20 (± 14.950)		
Total number of fibers Slide 1	-7.10 (± 32.145)	-2.67 (± 51.854)		

Statistical analyses

Statistical analysis title	givinostat vs placebo
Statistical analysis description:	
this analysis regards the MFA (%) at visit 11	
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.634
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.87
upper limit	12.77
Variability estimate	Standard error of the mean
Dispersion value	5.256

Notes:

[19] - ANCOVA model was performed considering baseline Biopsy histological parameters (Slide I) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	givinostat vs placebo
Statistical analysis description:	
This analysis regards the adipose tissue (%) at visit 11. For this comparison, log difference of the least square means and Log SE are reported.	
Comparison groups	Placebo - ITT v Givinostat - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.4893
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.224

Notes:

[20] - ANCOVA model was performed considering baseline Biopsy histological parameters (Slide I) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards the other histological structures (%) at visit 11. For this comparison, log difference of the least square means and Log SE are reported.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.1498
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.13

Notes:

[21] - ANCOVA model was performed considering baseline Biopsy histological parameters (Slide I) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards fiber with nuclear centralizations (%) at visit 11. For this comparison, log difference of the least square means and Log SE are reported.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.1055
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.06

Notes:

[22] - ANCOVA model was performed considering baseline Biopsy histological parameters (Slide I) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards total number of fibers (%) at visit 11. For this comparison, log difference of the least square means and Log SE are reported.

Comparison groups	Givinostat - ITT v Placebo - ITT

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.6265
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.26

Notes:

[23] - ANCOVA model was performed considering baseline Biopsy histological parameters (Slide I) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables.

Secondary: Mean change from baseline in Motor function Measurement (MFM) score after 12 months of treatment

End point title	Mean change from baseline in Motor function Measurement (MFM) score after 12 months of treatment

End point description:

Motor function measurement (MFM) scores assessed were: Standing and transfers (D1) score, Axial and proximal motor function (D2) score, Mean distal motor function (D3) score and mean total score, using the Motor Function Measurement scale with givinostat versus placebo.

End point type	Secondary

End point timeframe:

At baseline, and at visit 11 (ie. after 12 months of tretament)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: score				
arithmetic mean (standard deviation)				
Standing and transfers (D1)	-1.28 (± 4.900)	-3.92 (± 4.166)		
Axial and proximal motor function (D2)	-0.16 (± 1.667)	-0.16 (± 2.077)		
Mean distal motor function (D3)	0.00 (± 2.345)	0.28 (± 2.042)		
Mean total score	-0.58 (± 2.435)	-1.59 (± 1.652)		

Statistical analyses

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards standing and transfers (D1) at visit 11. For this comparison, log difference of the least square means is reported.

Comparison groups	Givinostat - ITT v Placebo - ITT

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.0602
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.13

Notes:

[24] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards axial and proximal motor function (D2) at visit 11. For this comparison, log difference of the least square means is reported.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.5906
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.01

Notes:

[25] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards in Distal motor function (D3) at visit 11. For this comparison, log difference of the least square means is reported.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.7799
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.01

Notes:

[26] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards the total score at visit 11. For this comparison, log difference of the least square means is reported.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.1116
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.03

Notes:

[27] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Secondary: Mean change from baseline in the Time Function Test (TFT) "Time to climb 4 standard steps" after 12 months of treatment

End point title	Mean change from baseline in the Time Function Test (TFT) "Time to climb 4 standard steps" after 12 months of treatment

End point description:

Overall, the time function tests (TFT) accomplished in this study are the following: Time to climb 4 standard steps, Time to walk/run 10 meters, Time to rise from the floor. Herunder the Time to climb 4 standard steps is reported.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	15		
Units: seconds				
arithmetic mean (standard deviation)	3.09 (± 31.929)	-2.21 (± 10.439)		

Statistical analyses

Statistical analysis title	givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.8914
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.28

Notes:

[28] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate

Secondary: Mean change from baseline in 6 Minute Walking Test (6MWT) after 12 months of treatment

End point title	Mean change from baseline in 6 Minute Walking Test (6MWT) after 12 months of treatment

End point description:

The 6 Minute Walk Test is a sub-maximal exercise test used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes is used as the outcome by which to compare changes in performance capacity. The 6MWT was performed indoors on a flat, smooth path, at least 30 m long and 3 m wide, with a cone at each end around which the patient had to walk. Six progressively numbered markers were used to mark the distance travelled at each minute. Five progressively lettered markers were used to indicate any falls. Here, the maximum distance walked after 6 minutes is reported.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. 12 month of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: metre				
arithmetic mean (standard deviation)	-9.07 (± 45.850)	-13.21 (± 24.236)		

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.8106
Method	ANCOVA
Parameter estimate	Log difference of least square means
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.08

Notes:

[29] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Secondary: Proportion of patients with < 10% worsening in 6MWT after 12 months of treatment

End point title	Proportion of patients with < 10% worsening in 6MWT after 12 months of treatment
End point description:	
Percentage of patients who lost less than 10% in the 6MWT	
End point type	Secondary
End point timeframe:	
At visit 11 (i.e. 12 month of treatment)	

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: percent				
number (not applicable)	20.59	5.88		

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.1626
Method	Mantel-Haenszel
Parameter estimate	difference of proportion
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.7

Notes:

[30] - The proportion of patients with < 10% worsening after 12 months of therapy was compared between arms using a stratified Cochran Mantel-Haenszel (CMH) chi square test with a two-sided α=0. 05 level. The proportion, along with its exact two-sided 95% CI, was computed within each treatment group. A two-sided 95% CI for difference of proportion between the treatment groups was also computed.

Secondary: Proportion of patients who lose the ability to rise from floor till the end of the study

End point title	Proportion of patients who lose the ability to rise from floor till the end of the study
End point description:	
Proportion of patients who lost the ability to rise from floor during the rise from the floor test	
End point type	Secondary
End point timeframe:	
From baseline to the end of study (EOS)	

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: percent				
number (not applicable)	0	5.88		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients who lose ambulation till the end of the study

End point title	Proportion of patients who lose ambulation till the end of the study

End point description:

percentage of patients who lose ambulation during the study (6MWT not done) was assessed. Here the data at visit 11 are reported.

End point type	Secondary

End point timeframe:

Throughout the study till EOS (i.e. 12 month of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: percent				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in muscle strength evaluated by knee extension, elbow flexion, as measured by Hand Held Myometry (HHM)

End point title	Mean change from baseline in muscle strength evaluated by knee extension, elbow flexion, as measured by Hand Held Myometry (HHM)

End point description:

Muscle strength (knee extension and elbow flexion) was tested on all four limbs using a MICROFET myometer held perpendicularly to the direction of the force of the muscle groups being tested and at a set distance from the joint.
A "make test" was adopted with the patient holding an isometric contraction for 3-5 seconds. Three measurements were taken and recorded for each limb. The highest values of muscle strength at the knee and elbow (three attempts) were considered for the analysis. A summary of muscle strength was assessed by hand-held myometry considering the following parameters: mean left knee extension, mean right knee extension, mean left elbow flexion, mean right elbow flexion.

End point type	Secondary

End point timeframe:

at visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[31]	16[32]		
Units: newton				
arithmetic mean (standard deviation)				
mean left knee extension	-2.51 (± 19.011)	-4.79 (± 10.519)		
mean right knee extension	-1.32 (± 12.397)	-1.82 (± 6.501)		
mean left elbow flexion	4.19 (± 27.317)	-0.07 (± 7.353)		
mean right elbow flexion	4.55 (± 31.556)	-1.07 (± 12.098)		

Notes:

[31] - LKE n=32 , LEF,REF n=31

[32] - n=14 (LKE,LEF); n=15 (REF)

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Statistical analysis description:	
This Analisys regards LKE, this group involved 46 patients and not 49	
Comparison groups	Placebo - ITT v Givinostat - ITT
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.5099
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	3.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.27
upper limit	14.41

Notes:

[33] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Statistical analysis title	Givinostat vs placebo
Statistical analysis description:	
This Analisys regards RKE	
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.7355
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	1.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.73
upper limit	8.06

Notes:

[34] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Statistical analysis title	Givinostat vs placebo

Statistical analysis description:

This Analisys regards LEF this group involved 45 patients and not 49

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.6037
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	3.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.22
upper limit	19.06

Notes:

[35] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Statistical analysis title	Givinostat vs placebo

Statistical analysis description:

This Analisys regards REF this group involved 46 patients and not 49

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.6178
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.35
upper limit	20.55

Notes:

[36] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Secondary: Mean changes from baseline in quality of life (QoL) after 12 months of

treatment

End point title	Mean changes from baseline in quality of life (QoL) after 12 months of treatment

End point description:

QoL is assessed by the 36-item Short Form survey [SF36]). The SF-36 is a set of generic, coherent, and easily administered patient reported outcomes that is widely utilized by managed care organizations for routine monitoring and assessment of care outcomes in adult patients. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score, the greater the disability.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical Functioning	-1.03 (± 16.274)	-5.00 (± 11.989)		
Role-Physical	-2.21 (± 19.697)	0.37 (± 16.006)		
Bodily Pain	5.12 (± 19.384)	2.12 (± 15.227)		
General Health	0.82 (± 14.532)	1.47 (± 13.267)		
Vitality	0.55 (± 11.654)	3.68 (± 12.705)		
Social Functioning	2.94 (± 22.415)	8.82 (± 20.139)		
Role-Emotional	0.00 (± 20.205)	4.90 (± 15.607)		
Mental Health	4.12 (± 15.977)	4.41 (± 13.793)		
Physical Component Summary	-0.17 (± 5.633)	-1.20 (± 5.535)		
Mental Component Summary	1.41 (± 7.345)	3.70 (± 7.177)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in fat fraction of the soleus after 12 months of treatment (MRS)

End point title	Mean change from baseline in fat fraction of the soleus after 12 months of treatment (MRS)

End point description:

Evaluations were performed comparing Magnetic Resonance Spectroscopy (MRS) at baseline and after 12 months of treatment with givinostat versus placebo. Mean absolute change from baseline in fat fraction was reported both for vastus lateralis and soleus

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	14		
Units: percentage				
arithmetic mean (standard deviation)	-1.07 (± 4.187)	0.43 (± 3.322)		

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.7849
Method	ANCOVA
Parameter estimate	difference of the least share means
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	1.69

Notes:

[37] - ANCOVA model was performed considering baseline fat fraction of vastus lateralis or fat fraction in the soleus value as covariate and treatment and concomitant steroid use at baseline as independent class variables.

Secondary: Mean change from baseline in contractile area of lower limb muscles (MRI) after 12 months of treatment

End point title	Mean change from baseline in contractile area of lower limb muscles (MRI) after 12 months of treatment

End point description:

Contractile area evaluations were performed (in the
whole thigh, quadriceps, medial thigh, pelvic girdle, hamstring and
triceps surae comparing Magnetic Resonance Images (MRI) at baseline and after 12 months of
treatment with givinostat versus placebo.

End point type	Secondary

End point timeframe:

at visit 11 (i.e after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[38]	17[39]		
Units: area in cm2				
arithmetic mean (standard deviation)				
Whole thigh	0.49 (± 2.164)	-0.94 (± 1.783)		
Quadriceps	0.22 (± 1.052)	-0.31 (± 1.059)		
Medial thigh	0.40 (± 1.094)	-0.14 (± 0.843)		
Hamstrings	-0.13 (± 0.971)	-0.49 (± 0.951)		
Triceps surae	-0.59 (± 2.615)	-1.58 (± 2.649)		
Pelvis girdle	0.31 (± 1.433)	-0.49 (± 0.957)		

Notes:

[38] - n=22 only in the triceps surae, instead of being 33

[39] - n=11 only in triceps surae, instead of being 17

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Statistical analysis description:	
This comparison regards Contractile Area in Whole Thigh at Visit 11	
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.0375
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	2.65
Variability estimate	Standard error of the mean
Dispersion value	0.577

Notes:

[40] - ANCOVA model was performed considering baseline Contractile Area value as covariate, treatment and concomitant steroid use
at baseline as independent class variables

Statistical analysis title	Givinostat vs placebo
Statistical analysis description:	
This comparison regards Contractile Area in quadriceps at Visit 11	
Comparison groups	Placebo - ITT v Givinostat - ITT

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.0528
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	1.27
Variability estimate	Standard error of the mean
Dispersion value	0.296

Notes:

[41] - ANCOVA model was performed considering baseline Contractile Area value as covariate, treatment and concomitant steroid use
at baseline as independent class variables

Statistical analysis title	Givinostat vs placebo

Statistical analysis description:

This comparison regards Contractile Area in medial thigh at Visit 11

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.2012
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.91
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[42] - ANCOVA model was performed considering baseline Contractile Area value as covariate, treatment and concomitant steroid use
at baseline as independent class variables

Statistical analysis title	Givinostat vs placebo

Statistical analysis description:

This comparison regards Contractile Area in hamstrings at Visit 11. In this area values are provided as Log Difference of Least Square Means (95% CI), and Log SE

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.1939
Method	ANCOVA
Parameter estimate	Log difference of least square means
Point estimate	0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.033

Notes:

[43] - ANCOVA model was performed considering baseline Contractile Area value as covariate, treatment and concomitant steroid use
at baseline as independent class variables

Statistical analysis title	Givinostat vs placebo

Statistical analysis description:

This comparison regards Contractile Area itriceps surae at Visit 11. Please note that the number of subjects involved in this analysis is 33 (22 for givinostat and 11 for placebo) and not 50 as reported below

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.4676
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	2.83
Variability estimate	Standard error of the mean
Dispersion value	1.494

Notes:

[44] - ANCOVA model was performed considering baseline Contractile Area value as covariate, treatment and concomitant steroid use
at baseline as independent class variables

Statistical analysis title	Givinostat vs placebo

Statistical analysis description:

This comparison regards Contractile Area pelvis girdle at Visit 11.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.1549
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	1.3

Variability estimate	Standard error of the mean
Dispersion value	0.336

Notes:

[45] - ANCOVA model was performed considering baseline Contractile Area value as covariate, treatment and concomitant steroid use
at baseline as independent class variables

Secondary: Mean change from baseline in biopsy histological parameters after 12 months of treatment - slide 2

End point title	Mean change from baseline in biopsy histological parameters after 12 months of treatment - slide 2

End point description:

Biopsy histological parameters (slide 2) analysed were: regenerative fibers and Mean value of total number of fibers. This latter is calculated as the sum of the number of fibers of available fields analyzed on Slide II for each patient.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	15		
Units: percentage				
arithmetic mean (standard deviation)				
regenerative fibers	-0.40 (± 8.426)	0.82 (± 4.092)		
total number of fibers slide II	-39.24 (± 100.834)	-7.67 (± 82.690)		

Statistical analyses

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards the regenerative fibers (%). For this comparison, log difference of the least square means and Log SE are reported.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.1562
Method	ANCOVA
Parameter estimate	Log difference of least square means
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	0.17

Variability estimate	Standard error of the mean
Dispersion value	0.345

Notes:

[46] - ANCOVA model was performed considering baseline biopsy histological parameters (Slide II) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables.

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards the regenerative fibers (%).

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.8846
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.05
upper limit	28.59
Variability estimate	Standard error of the mean
Dispersion value	17.099

Notes:

[47] - ANCOVA model was performed considering baseline biopsy histological parameters (Slide II) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables.

Secondary: Mean change from baseline in biopsy histological parameters after 12 months of treatment - slide 3

End point title	Mean change from baseline in biopsy histological parameters after 12 months of treatment - slide 3

End point description:

Biopsy histological parameters (slide 2) analysed were: CSA Type I (µm2), CSA Type II (µm2), total CSA (µm2), total number of fibers slide III. This latter is calculated as the sum of the number of fibers of available fields analyzed on Slide III for each patient.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	15		
Units: area in µm2				
arithmetic mean (standard deviation)				
CSA Type I	-62.01 (± 2316.099)	243.82 (± 4017.531)		
CSA Type II	-669.06 (± 2361.490)	412.22 (± 2637.085)		

Total CSA	-307.57 (± 1946.462)	558.15 (± 2027.072)		
Total number of fibers slide III	-4.83 (± 30.236)	-17.80 (± 29.121)		

Statistical analyses

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards the CSA Type I at visit 11. For this comparison, log difference of the least square means and Log SE are reported.

Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.9493
Method	ANCOVA
Parameter estimate	Log difference of least square means
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[48] - ANCOVA model was performed considering baseline biopsy histological parameters (Slide III) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables

Statistical analysis title	givinostat vs placebo

Statistical analysis description:

This analysis regards the CSA Type II at visit 11.

Comparison groups	Placebo - ITT v Givinostat - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.324
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-619.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1872.37
upper limit	633.98

Notes:

[49] - ANCOVA model was performed considering baseline biopsy histological parameters (Slide III) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables

Statistical analysis title	givinostat vs placebo
Statistical analysis description:	
This analysis regards the total CSA at visit 11.	
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.307
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	-572.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1690.73
upper limit	545.64

Notes:

[50] - ANCOVA model was performed considering baseline biopsy histological parameters (Slide III) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables

Statistical analysis title	givinostat vs placebo
Statistical analysis description:	
This analysis regards the total number of fibers at visit 11.	
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.4054
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	4.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.62
upper limit	16.06

Notes:

[51] - ANCOVA model was performed considering baseline biopsy histological parameters (Slide III) value as covariate, treatment and
concomitant steroid use at baseline as independent class variables

Secondary: Mean change from baseline in the Time Function Test (TFT) "Time to walk/run 10 meters" after 12 months of treatment

End point title	Mean change from baseline in the Time Function Test (TFT) "Time to walk/run 10 meters" after 12 months of treatment
End point description:	
Overall, the time function tests (TFT) accomplished in this study are the following: Time to climb 4 standard steps, Time to walk/run 10 meters, Time to rise from the floor. Herunder the Time to walk/run 10 meters is reported	
End point type	Secondary
End point timeframe:	
At visit 11 (i.e. after 12 months of treatment)	

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: seconds				
arithmetic mean (standard deviation)	0.25 (± 7.114)	0.26 (± 1.089)		

Statistical analyses

Statistical analysis title	givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.4346
Method	ANCOVA
Parameter estimate	log difference of least square means
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.1

Notes:

[52] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate

Secondary: Mean change from baseline in the Time Function Test (TFT) "Time to rise from floor" after 12 months of treatment

End point title	Mean change from baseline in the Time Function Test (TFT) "Time to rise from floor" after 12 months of treatment

End point description:

Overall, the time function tests (TFT) accomplished in this study are the following: Time to climb 4 standard steps, Time to walk/run 10 meters, Time to rise from the floor. Herunder the Time to rise from the floor is reported.

End point type	Secondary

End point timeframe:

At visit 11 (i.e. after 12 months of treatment)

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	10		
Units: seconds				
arithmetic mean (standard deviation)	2.08 (± 6.204)	1.69 (± 4.417)		

Statistical analyses

Statistical analysis title	Givinostat vs placebo
Comparison groups	Givinostat - ITT v Placebo - ITT
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.7629
Method	ANCOVA
Parameter estimate	difference of least square means
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	4.75

Notes:

[53] - Least squares mean is obtained from the mixed effects model for repeated measures with treatment, visit, visit by treatment
interaction and concomitant steroid use at baseline as fixed effect; baseline value is included as a covariate.

Secondary: Number of patients experiencing treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) throughout the study (EOS)

End point title	Number of patients experiencing treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) throughout the study (EOS)

End point description:

All treatment emergent adverse events (TEAEs) and the serious adverse events (SAEs) were collected with their relationship to the study drug

End point type	Secondary

End point timeframe:

From baseline through the end of the study

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: number				
number (not applicable)				
TEAE	30	9		
SAE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Type, incidence, and severity of TEAEs and SAEs throughout the study

End point title	Type, incidence, and severity of TEAEs and SAEs throughout the study

End point description:

Treatment-emergent AEs (TEAEs): events with an onset date after study treatment initiation. Deaths, SAEs and AEs leading to withdrawal of study treatment are also listed.

End point type	Secondary

End point timeframe:

 From baseline to EOS

End point values	Givinostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: number				
number (not applicable)				
fatal TEAE	0	0		
mild TEAE	30	9		
moderate TEAE	12	1		
severe TEAE	5	0		
SAE	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were assessed throughout the study: from visit 1 and V2 (screening) up to visit 11 (week 48, month 12 which corresponds to EOS) and visit 12 (FUV=follow up visit 4 weeks after the last dose of study treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Givinostat - safety
Reporting group description: -	
Reporting group title	Placebo - safety

Reporting group description: -

Serious adverse events	Givinostat - safety	Placebo - safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)	0 / 17 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Givinostat - safety	Placebo - safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 34 (88.24%)	12 / 17 (70.59%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Tooth repair			
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

Umbilical hernia repair			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 34 (5.88%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Hyperpyrexia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	2 / 34 (5.88%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Edema peripheral			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 34 (8.82%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Nasal congestion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Restrictive pulmonary disease			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Sleep apnea syndrome			

subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Oropharyngeal pain		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1

Psychiatric disorders

Insomnia		
subjects affected / exposed	2 / 34 (5.88%)	0 / 17 (0.00%)
occurrences (all)	2	0

Investigations

Alanine aminotransferase increased		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Aspartate aminotransferase increased		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Blood bilirubin increased		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Blood glucose increased		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood phosphorus increased		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood potassium increased		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood sodium increased		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood triglycerides increased		
subjects affected / exposed	4 / 34 (11.76%)	1 / 17 (5.88%)
occurrences (all)	8	2
C-reactive protein increased		

subjects affected / exposed	1 / 34 (2.94%)	1 / 17 (5.88%)
occurrences (all)	1	1
Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 34 (2.94%)	1 / 17 (5.88%)
occurrences (all)	1	1
Heart rate increased		
subjects affected / exposed	2 / 34 (5.88%)	0 / 17 (0.00%)
occurrences (all)	2	0
N-terminal prohormone brain natriuretic peptide increased		
subjects affected / exposed	2 / 34 (5.88%)	0 / 17 (0.00%)
occurrences (all)	2	0
Platelet count decreased		
subjects affected / exposed	20 / 34 (58.82%)	0 / 17 (0.00%)
occurrences (all)	40	0
Weight increased		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
White blood cell count decreased		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Lymphocyte count increased		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Injury, poisoning and procedural complications		
Chest injury		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Contusion		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Face injury		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Fall		

subjects affected / exposed	2 / 34 (5.88%)	3 / 17 (17.65%)	
occurrences (all)	2	5	
Head injury			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	4 / 34 (11.76%)	1 / 17 (5.88%)	
occurrences (all)	5	1	
Rib fracture			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Tooth injury			
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Post procedural haematoma			
subjects affected / exposed	3 / 34 (8.82%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Procedural pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			

subjects affected / exposed	1 / 34 (2.94%)	1 / 17 (5.88%)
occurrences (all)	1	1
Hand-arm vibration syndrome		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	2
Headache		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Paresthesia		
subjects affected / exposed	2 / 34 (5.88%)	2 / 17 (11.76%)
occurrences (all)	2	1
Blood and lymphatic system disorders		
Lymphocytosis		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Gastrointestinal disorders		
Abdominal pain		
subjects affected / exposed	2 / 34 (5.88%)	0 / 17 (0.00%)
occurrences (all)	3	0
Abdominal pain upper		
subjects affected / exposed	4 / 34 (11.76%)	1 / 17 (5.88%)
occurrences (all)	7	2
Diarrhoea		
subjects affected / exposed	16 / 34 (47.06%)	0 / 17 (0.00%)
occurrences (all)	95	0
Dyspepsia		
subjects affected / exposed	3 / 34 (8.82%)	1 / 17 (5.88%)
occurrences (all)	6	1
Gastrointestinal disorder		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Vomiting		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Skin and subcutaneous tissue disorders		

Dermal cyst		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Rash erythematous		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	2	0
Dyshidrotic eczema		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Musculoskeletal and connective tissue disorders		
Back pain		
subjects affected / exposed	2 / 34 (5.88%)	0 / 17 (0.00%)
occurrences (all)	2	0
Intervertebral disc protrusion		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Joint swelling		
subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)
occurrences (all)	1	0
Muscle hypertrophy		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Muscle spasms		
subjects affected / exposed	2 / 34 (5.88%)	0 / 17 (0.00%)
occurrences (all)	2	0
Muscular weakness		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	2
Myalgia		
subjects affected / exposed	2 / 34 (5.88%)	0 / 17 (0.00%)
occurrences (all)	2	0
Neck pain		
subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Periarthritis		

subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Infections and infestations

COVID-19

subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Cystitis

subjects affected / exposed	0 / 34 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	

Gastroenteritis viral

subjects affected / exposed	1 / 34 (2.94%)	1 / 17 (5.88%)	
occurrences (all)	1	1	

Influenza

subjects affected / exposed	2 / 34 (5.88%)	1 / 17 (5.88%)	
occurrences (all)	3	1	

Nasopharyngitis

subjects affected / exposed	1 / 34 (2.94%)	1 / 17 (5.88%)	
occurrences (all)	1	4	

Rhinitis

subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Tonsillitis

subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Urinary tract infection

subjects affected / exposed	1 / 34 (2.94%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Metabolism and nutrition disorders

Hypertriglyceridaemia

subjects affected / exposed	10 / 34 (29.41%)	1 / 17 (5.88%)	
occurrences (all)	25	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2018	The main purposes of protocol amendment 1 are: 1. To specify that the fat fraction and cross section evaluations by means of Dixon MRI will involve muscles of the lower leg, as well as those of the thigh and pelvic girdle as originally planned. 2. To modify the age limit stated in Inclusion Criterion 1. Age has been raised from 60 to 65 years after Investigators advised of the presence of potential patients over the age of 60 who otherwise meet all eligibility criteria. 3. To delete the repetition of the functional tests (i.e. time to climb 4 standard steps, time to rise from floor, time to walk 10 meters, motor function measure and muscle strength) at the randomization visit, since noteworthy changes are not expected in these patients within 1 month of screening. Only 6MWT will be performed and the average of the scores at screening and randomization will be used as baseline value. 4. To correct the information related to the evaluation of serum circulating proteins as potential biomarkers for BMD. These analyses will not be carried out through SomaScan® technique because the central laboratory originally chosen for this study no longer provides this service. Biomarker evaluation will be performed by a different provider using an ELISA-based system. 5. To increase the frequency of thyroid function monitoring to ensure patient safety. Monitoring will now be carried out monthly until the third month and then every 3 months until the end of the study. 6. To include information on the backup system for randomization and treatment assignment. The Interactive Voice Response System (IVRS) will be used in the unlikely case of Web Response System (IWRS) unavailability. 7. To correct the information on the urine analysis, which will be done by dipstick on site and not by the central lab. 8. To include minor changes to increase clarity and correct typographic errors.
31 July 2018	The main purpose of Amendment 2 is to address safety issue, namely thrombocytopenia arising following the treatment of the first 21 patients enrolled in the present study. More precisely, preliminary blinded results therefore suggests that the starting dose of the current protocol would be difficult to manage outside of a clinical trial environment, and since the current dose reduction rule is adequate in keeping an acceptable level of platelets, a new starting dose corresponding to the reduced dose of the original protocol (i.e. 26.7-46.7 mg b.i.d according to body weight) is now proposed by the Sponsor and Investigator. In addition, new safety rules are applied, allowing the study drug to be reduced by 20% from the new starting dose if the patient meets stopping criteria. Furthermore, to provide the highest degree of safety, the study protocol has been amended to intensify patient monitoring (i.e. Additional unscheduled visits with a cardiologist at the discretion of study clinicians; Additional safety assessments (blood tests) at the discretion of study clinicians). Other minor changes have been made to the protocol.

13 December 2019	The main purposes of amendment 3 are as follows: 1. The protocol has been integrated with pertinent information added to the latest version of the Investigator's Brochure (Version 20.0). Section 4.2.2 – Clinical Experience with Givinostat Including Risks and Benefits – has been updated with new information concerning hemorrhagic drug-related AEs. Section 8.7.2 – Prior and concomitant medications – now includes P-glycoproteins (P-gp) as medications whose use requires caution. The study drug is a P-glycoprotein and breast cancer resistance protein (BCRP) substrate and therefore co-administration of P-gp inhibitors may result in increased plasma concentrations of givinostat. Increased oral absorption is usually of limited clinical concern except for drugs that have a narrow therapeutic index, which is not the case of givinostat. Nevertheless, Pgp inhibitors should be properly managed in clinical studies and a new appendix listing P-gp inhibitors has been added to the protocol. 2. Section 9.1.10 – End of Study Visit – and Table 5 – Schedule of Assessments – now indicate that MRI/MRS and biopsy evaluations scheduled for the end of study visit may be performed on different days and that treatment is to continue up to the last assessment. 3. Section 13.10 - Interim Analyses – besides the interim analysis foreseen to check the sample size assumption, it was decided to plan an additional interim analysis to obtain a preliminary overview of the baseline patient characteristics after study enrollment is completed. 4. The Interim analysis section of the synopsis has been updated according to the protocol changes described in item 3.
17 June 2020	1.The main purposes of amendment 4 is to amend the primary endpoint. More precisely, the change of total fibrosis is considered a more indicative outcome measure of the possible effect of givinostat relative to the assessment of CSA and, hence, it is to be evaluated as the primary endpoint for the trial. 2. Sections "Sample size determination" (13.1) and "Statistical Analysis" (13) were revised according to the change of the primary endpoint described above. With a reasonable allowance of 5% of patients with unevaluable biopsies at the end of study, the total number ofpatients to be randomized is 51. Moreover, in the context of the new primary endpoint (it is expected that total fibrosis (%) will increase less in the givinostat group than in the placebo group) a LOCF analysis is considered not appropriate because any missing follow-up value will be replaced by that subject's previously observed value (i.e. the baseline value) and this approach can be questionable and not conservative, for this reason a multiple imputation method will be used to handle missing data. 3. Sections "Study Design" (6.1 and 6.2) and "Interim Analysis" (13) were updated including a description of conclusions on the first blinded interim analysis performed on the first 20 baseline biopsies which led the protocol amendment n. 4. as described above. The details about methodology and the results are reported in the specific SAP and Statistical Report available as stand-alone documents. 4. Section "Biomarker" (11.3) was modified to indicate that patients who have already concluded the study may be asked to return to the center for a blood sample collection necessary for LTBP4 and Osteopontin genotyping if the sample was not already collected.

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 or caveats are applicable to this summary of results.

Notes: