Clinical trial results:
A multicenter, randomized, double-blind, placebo-controlled, multiple-dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RO6885247 following 12 weeks of treatment in adult and pediatric patients with spinal muscular atrophy (MOONFISH).

Summary

EudraCT number	2014-002246-41
Trial protocol	IT ES
Global end of trial date	23 July 2015

Results information

Result version number	v1 (current)
This version publication date	24 June 2017
First version publication date	24 June 2017

Trial information

Trial identification

Sponsor protocol code	BP29420

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02240355
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	F. Hoffmann-La Roche AG,, F. Hoffmann-La Roche AG,, +41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG,, F. Hoffmann-La Roche AG,, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and tolerability of 12 weeks of treatment with RO6885247 in adult and pediatric subjects with Spinal Muscular Atrophy (SMA)

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	16
EEA total number of subjects	10

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)	7
Adults (18-64 years)	9
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 3 sites/centers in Switzerland, United Kingdom, and Italy.

Pre-assignment

Screening details:

A total 16 subjects were enrolled in Part 1 (13 subjects in Cohort 1a and 3 subjects in Cohort 1b). Parts 2 and 3 were not conducted as the study was terminated early by the Sponsor.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	RO6885247 10 mg

Arm description:

Subjects with Spinal Muscular Atrophy received RO6885247 10 milligrams (mg) once daily (QD)

Arm type	Experimental
Investigational medicinal product name	RO6885247
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received 10 mg once daily (QD) of oral solution of either RO6885247.

Arm title	RO6885247 20 mg

Arm description:

Subjects with Spinal Muscular Atrophy recieved RO6885247 20 mg once daily (QD).

Arm type	Experimental
Investigational medicinal product name	RO6885247
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received 20 mg QD of oral solution of RO6885247.

Arm title	Placebo

Arm description:

Subjects with Spinal Muscular Atrophy received a matching placebo to RO6885247 dose once daily (QD)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:
Subjects received an oral solution of matching Placebo to RO6885247 QD.

Number of subjects in period 1	RO6885247 10 mg	RO6885247 20 mg	Placebo
Started	9	2	5
Completed	9	0	4
Not completed	0	2	1
Study put on hold by sponsor	-	2	1

Baseline characteristics

Reporting groups	
Reporting group title	RO6885247 10 mg
Reporting group description:	
Subjects with Spinal Muscular Atrophy received RO6885247 10 milligrams (mg) once daily (QD)	
Reporting group title	RO6885247 20 mg
Reporting group description:	
Subjects with Spinal Muscular Atrophy recieved RO6885247 20 mg once daily (QD).	
Reporting group title	Placebo
Reporting group description:	
Subjects with Spinal Muscular Atrophy received a matching placebo to RO6885247 dose once daily (QD)	

Reporting group values	RO6885247 10 mg	RO6885247 20 mg	Placebo
Number of subjects	9	2	5
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 26.7 ± 14.2	 20 ± 4.2	 31.8 ± 15.6
Gender Categorical Units: Subjects			
Female	4	1	1
Male	5	1	4

Reporting group values	Total		
Number of subjects	16		
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender Categorical Units: Subjects			
Female	6		
Male	10		

End points

End points reporting groups

Reporting group title	RO6885247 10 mg
Reporting group description:	
Subjects with Spinal Muscular Atrophy received RO6885247 10 milligrams (mg) once daily (QD)	
Reporting group title	RO6885247 20 mg
Reporting group description:	
Subjects with Spinal Muscular Atrophy recieved RO6885247 20 mg once daily (QD).	
Reporting group title	Placebo
Reporting group description:	
Subjects with Spinal Muscular Atrophy received a matching placebo to RO6885247 dose once daily (QD)	

Primary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)[1]
End point description:	
An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study and laboratory or clinical tests that resulted in a change in treatment or discontinuation from study drug were reported as adverse events. Safety population included all subjects who had received at least 1 dose of study medication assigned to treatment arms.	
End point type	Primary
End point timeframe:	
Up to 8 months approximately	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported.

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: subjects				
number (not applicable)	9	1	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) at Day 1 and Day 28

End point title	Maximum Plasma Concentration (Cmax) at Day 1 and Day 28[2]
End point description:	
To evaluate the maximum plasma concentration (Cmax) in treated subjects blood. The pharmacokinetic (PK) analysis population included all subjects who received at least one dose of the study medication.	
End point type	Secondary
End point timeframe:	
2, 4, 6, 8, 24 h Day 1, pre-dose, 2, 4, 6, 8 h Day28	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Day 1	7.75 (± 2.87)			
Day 28	59.6 (± 21.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Curve (AUC) Over the 24-hour Dosing Interval at Day 1 and Day 8

End point title	Area Under Curve (AUC) Over the 24-hour Dosing Interval at Day 1 and Day 8[3]

End point description:

AUC is a measure of the plasma concentration of a drug over time. The PK analysis population included all subjects who received at least one dose of the study medication.

End point type	Secondary

End point timeframe:

2, 4, 6, 8, 24h Day1, pre-dose, 2, 4, 6, 8h Day 28

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hour*nanograms per milliliters (h*ng/mL)				
arithmetic mean (standard deviation)				
Day 1	147 (± 54.6)			
Day 28	1300 (± 478)			

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Concentration at the End of a Dosing Interval (Ctrough) at Day 28

End point title	Steady-State Concentration at the End of a Dosing Interval (Ctrough) at Day 28[4]

End point description:

To evaluate steady-state concentration of drug in blood at the end of dosing interval. The PK analysis population included all subjects who received at least one dose of the study medication.

End point type	Secondary

End point timeframe:

pre-dose, 2, 4, 6, 8 h Day 28

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng/mL				
arithmetic mean (standard deviation)	50.9 (± 17.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Plasma Concentration (Tmax) at Day 1 and Day 28

End point title	Time to Maximum Observed Plasma Concentration (Tmax) at Day 1 and Day 28[5]

End point description:

To evaluate the time to maximum observed plasma concentration. All treated subjects were analyzed for this endpoint.

End point type	Secondary

End point timeframe:

2, 4, 6, 8, 24 h Day 1; pre-dose, 2, 4, 6, 8 h Day 28

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hours (h)				
median (full range (min-max))				
Day 1 Day 28	8 (6 to 24) 6 (4.38 to 8.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio (Racc) at Day 28

End point title	Accumulation Ratio (Racc) at Day 28[6]

End point description:

To evaluate the relationship between the dosing interval and the elimination rate constant. The PK analysis population included all subjects who received at least one dose of the study medication.

End point type	Secondary

End point timeframe:

pre-dose, 2, 4, 6, 8 h Day 28

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: unitless				
arithmetic mean (standard deviation)	9.08 (± 2.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax Under Fasted and Fed Conditions

End point title	Tmax Under Fasted and Fed Conditions[7]

End point description:

To evaluate the time to maximum observed plasma concentration in subjects in fed and fasted states. The PK analysis population included all subjects who received at least one dose of the study medication.

End point type	Secondary

End point timeframe:

12h Day 14, pre-dose, 2, 4, 6, 8, 12, 24h Day 15

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hour (h)				
median (full range (min-max))				
Fasted	6.02 (3.92 to 12)			
Fed	6 (2 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax Under Fasted and Fed Conditions

End point title	Cmax Under Fasted and Fed Conditions[8]

End point description:

To evaluate the maximum plasma concentration in treated subjects blood under both fed and fasted conditions.The PK analysis population included all subjects who received at least one dose of the study medication.

End point type	Secondary

End point timeframe:

12h Day 14, pre-dose, 2, 4, 6, 8,12, 24 h Day 15

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng/mL				
arithmetic mean (standard deviation)				
Fasted	55.1 (± 12.2)			
Fed	52.9 (± 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau Under Fasted and Fed Conditions

End point title	AUCtau Under Fasted and Fed Conditions[9]

End point description:

To evaluate drug concentration in subjects blood plasma over time under both fed and fasted states. The PK analysis population included all subjects who received at least one dose of the study medication.

End point type	Secondary

End point timeframe:

12h Day 14, pre-dose, 2, 4, 6, 8, 12, 24h Day 15

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Fasted	1140 (± 248)			
Fed	1100 (± 308)			

Statistical analyses

No statistical analyses for this end point

Secondary: Survival of Motor Neuron (SMN) Protein Levels in Blood

End point title	Survival of Motor Neuron (SMN) Protein Levels in Blood

End point description:

To evaluate SMN protein levels in subjects blood. All enrolled subjects. Here, n signifies the number of subjects who evaluable at each time point. Here, 9999 indicates arithmetic mean and standard deviation for time points where number of subjects evaluable is 0.

End point type	Secondary

End point timeframe:

Day -1, 28, 84, 114, 144, Early withdrawal

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: picogram per millilitre (pg/mL)				
arithmetic mean (standard deviation)				
Day -1 (n= 9, 2, 50)	4693.62 (± 2747.54)	2878 (± 578.98)	3762.48 (± 1295.09)	
Day 28 (n= 6, 0, 3)	6980.87 (± 3975.76)	99999 (± 99999)	4458.87 (± 1776.89)	
Day 84 (n= 9, 0, 40)	5984.89 (± 903.76)	99999 (± 99999)	3935.8 (± 1135.86)	
Day 114 (n= 8, 2, 5)	3647.15 (± 1121.68)	3122.2 (± 1357.65)	3033.26 (± 1025.76)	
Day 144 (n= 9, 2, 5)	3425.41 (± 1050.39)	3301.9 (± 662.84)	2929.08 (± 1022.03)	
Early Withdrawal (n= 0, 2, 1)	99999 (± 99999)	3345.8 (± 1504.44)	2343.4 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Compound Muscle Action Potential (CMAP)

Parameter; Temperature	
End point title	Change From Baseline in Compound Muscle Action Potential (CMAP) Parameter; Temperature

End point description:

CMAP was assessed by evaluating change from baseline in the following parameter- temperature. All enrolled subjects. Here, n indicates number of subjects evaluable at specified time points. Here, 99999 indicates mean and standard deviation at early withdrawal.

End point type	Secondary

End point timeframe:

Baseline (Day-1), early withdrawal

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: degree celsius (C)				
arithmetic mean (standard deviation)				
Change at Day-1 (n=9,9,5)	32.41 (± 2.56)	33 (± 1.41)	32.78 (± 1.68)	
Change at Early Withdrawal (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	0 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of RO6885247 on Electrical Impedance Myography	
End point title	Effect of RO6885247 on Electrical Impedance Myography[10]

End point description:

Data for this endpoint was not collected during the study.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report the values for reporting group (RO6885247 10 mg).

End point values	RO6885247 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: hertz (Hz)				
number (not applicable)				

Notes:

[11] - No data for this endpoint are included as assessment was not performed in any of the subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: In Vivo Splicing Modification of Survival of Motor Neuron 2 (SMN2) Messenger Ribonucleic Acid(mRNA) in Blood

End point title	In Vivo Splicing Modification of Survival of Motor Neuron 2 (SMN2) Messenger Ribonucleic Acid(mRNA) in Blood

End point description:

To evaluate subjects SMN2 mRNA blood levels over time. All enrolled subjects. Here, n signifies the number of subjects who were evaluable at specified time points. Here, 99999 indicates arithmetic mean and standard deviation for the reporting groups where no subject was analysed.

End point type	Secondary

End point timeframe:

Day -1, 1, 28, 56, 84, 114, 144, Early Withdrawal

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: Unitless				
arithmetic mean (standard deviation)				
SMN2: Day -1 (n= 9, 2, 5)	25.45 (± 3.57)	24.46 (± 0.57)	24.19 (± 0.16)	
SMN2: Day 1 (n= 9, 1, 5)	23.93 (± 0.62)	23.98 (± 99999)	23.15 (± 0.3)	
SMN2: Day 28 (n= 9, 0, 4)	23.81 (± 0.67)	99999 (± 99999)	23.62 (± 0.87)	
SMN2: Day 56 (n= 9, 0, 4)	24.57 (± 1.32)	99999 (± 99999)	24.3 (± 0.56)	
SMN2: Day 84 (n= 9, 0, 4)	24.7 (± 0.65)	99999 (± 99999)	24.43 (± 1.56)	
SMN2: Day 114 (n= 9, 2, 5)	24.72 (± 0.85)	24.17 (± 0.79)	24.88 (± 0.69)	
SMN2: Day 144 (n= 9, 2, 5)	24.68 (± 0.63)	24.49 (± 0.88)	24.71 (± 0.77)	
SMN2: Early Withdrawal (n= 0, 2, 5)	99999 (± 99999)	24.78 (± 0.58)	24.17 (± 0)	
SMNd7: Day-1 (n= 9, 2, 5)	25.31 (± 3.15)	24.33 (± 0.67)	24.14 (± 0.56)	
SMNd7: Day 1 (n= 9, 1, 5)	24.19 (± 0.61)	24.34 (± 99999)	23.25 (± 0.28)	
SMNd7: Day 28 (n= 9, 0, 4)	24.72 (± 0.76)	99999 (± 99999)	23.55 (± 0.74)	
SMNd7: Day 56 (n= 9, 0, 4)	25.36 (± 1.11)	99999 (± 99999)	24.22 (± 0.55)	
SMNd7: Day 84 (n= 9, 0, 4)	25.5 (± 0.71)	99999 (± 99999)	24.26 (± 1.36)	
SMNd7: Day 114 (n= 9, 2, 5)	24.67 (± 0.82)	24.73 (± 0.45)	24.62 (± 0.59)	
SMNd7: Day 144 (n= 9, 2, 5)	24.6 (± 0.56)	24.57 (± 0.54)	24.2 (± 1.13)	
SMNd7: Early Withdrawal (n= 0, 2, 1)	99999 (± 99999)	24.66 (± 0.67)	24.07 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CMAP Parameter; Distance

End point title	Change From Baseline in CMAP Parameter; Distance

End point description:

CMAP was assessed by evaluating change from baseline in the following parameter- distance. All enrolled subjects. Here, n indicates number of subjects evaluable at specified time points. Here, 99999 indicates mean and standard deviation at early withdrawal.

End point type	Secondary

End point timeframe:

Baseline (Day-1), Early withdrawal

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: millimetre (mm)				
arithmetic mean (standard deviation)				
Change at Day -1 (n=9,9, 5))	71.7 (± 8.3)	87.5 (± 10.6)	69 (± 12.4)	
Change at Early Withdrawal (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	0 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CMAP Parameter; Distal Motor Latency

End point title	Change From Baseline in CMAP Parameter; Distal Motor Latency

End point description:

CMAP was assessed by evaluating change from baseline in the following parameter- distal motor latency. All enrolled subjects. Here, n indicates number of subjects evaluable at specified time points. Here, 99999 indicates mean and standard deviation at early withdrawal.

End point type	Secondary

End point timeframe:

Baseline (Day-1), Early Withdrawal

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: milliseconds (msecs)				
arithmetic mean (standard deviation)				
Change at Day-1 (n= 8,2,5)	3.2 (± 0.97)	2.85 (± 0.07)	3.06 (± 0.27)	
Change at Early Withdrawal (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	0 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CMAP Paramter; Amplitude

End point title	Change From Baseline in CMAP Paramter; Amplitude

End point description:

CMAP was assessed by evaluating change from baseline in the following parameter- Amplitude. All enrolled subjects. Here, n indicates number of subjects evaluable at specified time points. Here, 99999 indicates mean and standard deviation at early withdrawal.

End point type	Secondary

End point timeframe:

Baseline (Day-1), Early Withdrawal

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: millivolt (mV)				
arithmetic mean (standard deviation)				
Change at Day-1 (n=8,2,5)	3.28 (± 4.43)	5.8 (± 4.24)	6.3 (± 3.63)	
Change at Early Withdrawal (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	0.3 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CMAP; Area

End point title	Change From Baseline in CMAP; Area

End point description:

CMAP was assessed by evaluating change from baseline in the following parameter- Area. All enrolled subjects. Here, n indicates number of subjects evaluable at specified time points. Here, 99999 indicates mean and standard deviation at early withdrawal.

End point type	Secondary

End point timeframe:

Baseline (Day-1), Early Withdrawal

End point values	RO6885247 10 mg	RO6885247 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	2	5	
Units: millivolt milliseconds (mVmsecs)				
arithmetic mean (standard deviation)				
Change at Day-1 (n=8,2,5)	10.95 (± 13.77)	18.95 (± 17.47)	19.42 (± 12.54)	
Change at Early Withdrawal (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	-6 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 8 months approximately	
Adverse event reporting additional description:	
The safety analysis population included all subjects who had received at least one dose of the study medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	RO6885247 10 mg
Reporting group description:	
Subjects received a 10 mg dose of RO6885247 once daily (QD).	
Reporting group title	RO6885247 20 mg
Reporting group description:	
Subjects received a 20 mg dose of RO6885247 once daily (QD).	
Reporting group title	Placebo
Reporting group description:	
Subjects received a placebo dose once daily (QD)	

Serious adverse events	RO6885247 10 mg	RO6885247 20 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	RO6885247 10 mg	RO6885247 20 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	1 / 2 (50.00%)	5 / 5 (100.00%)
General disorders and administration site conditions			
Application Site Erosion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pyrexia			

subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Eye disorders			
Corneal Disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye Irritation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lacrimation Increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Vision Blurred			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Abdominal Pain Upper			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	2 / 9 (22.22%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Dry Mouth			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Sounds Abnormal			

subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Mouth Ulceration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2014	Two exclusion criteria for females of child-bearing potential and hypersensitivity to RO6885247 or to the constituents of its formulation were updated, as a request from MHRA during review of original protocol (v1).
24 December 2014	1. Addition of a cohort of infant subjects with Spinal Muscular Atrophy Type 1, 2. Clarification on the food effect assessment in Cohort 1a, 3. Addition of staggered enrollment in Cohorts 1b and 2a; 4. Changes to the criteria for treatment discontinuation for skin AEs, to the AE reporting period, study medication intake on the days of site visits, SMN2 mRNA and SMN protein time points (Parts 1 and 2), and follow up calls of the first 4 weeks of the study.

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.

The study was put on hold by the sponsor as it did not reveal any notable safety issues.

Notes: