EU Clinical Trials Register

Clinical trial results:
The effects of RNS60 on ALS biomarkers

Summary

EudraCT number	2016-002382-62
Trial protocol	IT
Global end of trial date	23 November 2020

Results information

Result version number	v1 (current)
This version publication date	14 October 2022
First version publication date	14 October 2022

Trial information

Trial identification

Sponsor protocol code	RNS60-ALS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03456882
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IRCCS Istituto di Ricerche Farmacologiche "Mario Negri"
Sponsor organisation address	Via Mario Negri 2, Milano, Italy, 20156
Public contact	Laboratorio di malattie neurologich, IRCCS Istituto di Ricerche Farmacologiche "Mario Negri", Milano, 0039 0239014605, rns60@marionegri.it
Scientific contact	Laboratorio di malattie neurologich, IRCCS Istituto di Ricerche Farmacologiche "Mario Negri", Milano, 0039 0239014605, rns60@marionegri.it

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	18 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2020
Global end of trial reached?	Yes
Global end of trial date	23 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To measure the effect of RNS60 treatment on selected pharmacodynamic biomarkers in ALS patients concurrently treated with riluzole. Candidate markers include:
1. T-reg (measured via FOXP3 and CD25 mRNA);
2. Cyp-A;
3. 3-NT;
4. Actin-NT;
5. MCP-1;
6. IL-17.

Protection of trial subjects:

Eligible patients can be included in the study only after proving written the IRB/IEC/REB -approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. The physician will obtain a signed informed consent form (ICF) from the subject prior to any procedures. The signed and completed ICF will be accessible in the patient's records on site. A copy of the signed ICF will be given to each subject. The process of obtaining informed consent should be documented in the patient source documents.
Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. All AEs and SAEs will be recorded. Subject diaries about AEs and/or concomitant medication will not be copied but will be considered source documents. AE documentation by the investigator will include the date of onset and duration of the AE, as well as the severity and causality of each AE, and the actions taken, including the discontinuation of the experimental drug, where required.

Background therapy:

Patients were treated wit 50mg riluzole twice in a day while concomitantly taking active or placebo

Evidence for comparator: -

Actual start date of recruitment	03 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 147
Worldwide total number of subjects	147
EEA total number of subjects	147

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)	101
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial participants were enrolled at 22 Italian Expert ALS Centers from May 2017 to January 2020. The trial enrolled adults (age: 18-80) with a diagnosis of definite, probable or probable lab-supported ALS according to the revised El Escorial criteria whose symptom onset had occurred 6 to 24 months prior to enrollment.

Pre-assignment

Screening details:

not applicable

Period 1

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

Blinding implementation details:

This is a randomized, double-blind, placebo-controlled trial. Both subject and physician will be blinded to the treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	active

Arm description:

Patients randomly assigned to receive RNS60 administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period

Arm type	Experimental
Investigational medicinal product name	RNS60
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Inhalation solution
Routes of administration	Enteral use , Inhalation use

Dosage and administration details:

intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks

Arm title	PLACEBO

Arm description:

Patients randomly assigned to receive placebo administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Inhalation solution
Routes of administration	Enteral use , Inhalation use

Dosage and administration details:

intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks

Number of subjects in period 1	active	PLACEBO
Started	74	73
Completed	60	50
Not completed	14	23
Adverse event, serious fatal	7	6
Consent withdrawn by subject	5	6
covid-19 infection	-	2
Adverse event, non-fatal	2	3
started prhibited therapy	-	1
disease progression	-	2
Protocol deviation	-	3

Baseline characteristics

Reporting groups

Reporting group title	active
Reporting group description:	
Patients randomly assigned to receive RNS60 administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period	
Reporting group title	PLACEBO
Reporting group description:	
Patients randomly assigned to receive placebo administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period	

Reporting group values	active	PLACEBO	Total
Number of subjects	74	73	147
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	59.3	56.0	
standard deviation	± 10.4	± 10.0	-
Gender categorical			
Units: Subjects			
Female	22	26	48
Male	52	47	99
Onset type			
Site of onset of the disease			
Units: Subjects			
Bulbar	11	9	20
Spinal	63	63	126
Missing	0	1	1
El Escorial category			
ALS diagnostic category			
Units: Subjects			
Definite ALS	21	20	41
Probable ALS	46	43	89
Probable laboratory supported ALS	7	10	17

Disease duration			
Time between the date of ALS diagnosis and the date of inclusion into the study			
Units: Months			
arithmetic mean	15.5	14.3	
standard deviation	± 5.8	± 5.8	-
Diagnostic delay			
Time between the date of onset of ALS symptoms and the date of ALS diagnosis			
Units: Months			
arithmetic mean	9.8	8.8	
standard deviation	± 5.1	± 4.9	-
BMI			
Body mass index			
Units: Units			
arithmetic mean	25.0	24.8	
standard deviation	± 3.3	± 4.1	-
FVC%			
Forced Vital Capacity percent value			
Units: Percent of predicted			
arithmetic mean	102.7	103.3	
standard deviation	± 18.2	± 16.1	-
ALSFRS-R			
ALS functional rating scale - min score 0 corresponding to maximum functional impairment - max score 48 corresponding to no functional impairment			
Units: Points			
arithmetic mean	41.6	41.4	
standard deviation	± 3.2	± 3.6	-
ALSAQ-40 - physical mobility domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the physical mobility domain addresses problems of mobility, for example, falling and difficulties in walking, standing up and going up and down the stairs (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	32.1	33.2	
standard deviation	± 21.3	± 23.1	-
ALSAQ-40 - ADL and independence domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the ADL (activities of daily living) and independence domain addresses a variety of limitations in ADL, for example, difficulties in washing/dressing oneself, doing tasks around the house, as well as difficulty writing (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	36.8	32.9	
standard deviation	± 27.8	± 26.1	-
ALSAQ-40 - eating and drinking domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the eating and drinking domain adresses problems eating solid foods, swallowing and drinking liquids (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	14.5	13.5	
standard deviation	± 23.9	± 23.9	-
ALSAQ-40 - communication domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the communication domain addresses a variety of problems in communicating with others, for example difficulties with speech such as talking slowly, stuttering whilst			

speaking and feeling self-conscious about speech (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)

Units: Points			
arithmetic mean	19.3	18.6	
standard deviation	± 25.5	± 28.6	-

ALSAQ-40 - emotional reactions domain			

ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the emotional reactions domain addresses various emotional problems, for example, feeling lonely, bored, depressed, feeling embarrassed in social situations and feeling worried about future disease progression (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)

Units: Points			
arithmetic mean	33.6	33.1	
standard deviation	± 18.5	± 22.2	-

Subject analysis sets

Subject analysis set title	Intention to Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized participants

Subject analysis set title	Per Protocol - active group
Subject analysis set type	Per protocol

Subject analysis set description:

Participants randomized to active arm and completing the study without significant protocol deviations

Subject analysis set title	Per Protocol - placebo group
Subject analysis set type	Per protocol

Subject analysis set description:

Participants randomized to placebo arm and completing the study without significant protocol deviations

Subject analysis set title	Completers and compliers - active group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants randomized to active arm, completing the 24 weeks of treatment and 24 weeks of follow-up, for a total of 48 weeks in the study, and taking at least 75% of the assigned study medication

Subject analysis set title	Completers and compliers - placebo group
Subject analysis set type	Per protocol

Subject analysis set description:

Participants randomized to active arm, completing the 24 weeks of treatment and 24 weeks of follow-up, for a total of 48 weeks in the study, and taking at least 75% of the assigned study medication

Reporting group values	Intention to Treat	Per Protocol - active group	Per Protocol - placebo group
Number of subjects	147	25	22
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			

85 years and over			

Age continuous			
Units: years			
arithmetic mean	57.7		
standard deviation	± 10.3	±	±
Gender categorical			
Units: Subjects			
Female	48		
Male	99		
Onset type			
Site of onset of the disease			
Units: Subjects			
Bulbar	20		
Spinal	63		
Missing			
El Escorial category			
ALS diagnostic category			
Units: Subjects			
Definite ALS	41		
Probable ALS	89		
Probable laboratory supported ALS	17		
Disease duration			
Time between the date of ALS diagnosis and the date of inclusion into the study			
Units: Months			
arithmetic mean	14.9		
standard deviation	± 10.3	±	±
Diagnostic delay			
Time between the date of onset of ALS symptoms and the date of ALS diagnosis			
Units: Months			
arithmetic mean	9.3		
standard deviation	± 5.0	±	±
BMI			
Body mass index			
Units: Units			
arithmetic mean	24.9		
standard deviation	± 3.7	±	±
FVC%			
Forced Vital Capacity percent value			
Units: Percent of predicted			
arithmetic mean	103.1		
standard deviation	± 17.1	±	±
ALSFRS-R			
ALS functional rating scale - min score 0 corresponding to maximum functional impairment - max score 48 corresponding to no functional impairment			
Units: Points			
arithmetic mean	41.5		
standard deviation	± 3.4	±	±
ALSAQ-40 - physical mobility domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the physical mobility domain addresses problems of mobility, for			

example, falling and difficulties in walking, standing up and going up and down the stairs (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	32.7		
standard deviation	± 22.1	±	±
ALSAQ-40 - ADL and independence domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the ADL (activities of daily living) and independence domain addresses a variety of limitations in ADL, for example, difficulties in washing/dressing oneself, doing tasks around the house, as well as difficulty writing (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	34.9		
standard deviation	± 26.9	±	±
ALSAQ-40 - eating and drinking domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the eating and drinking domain adresses problems eating solid foods, swallowing and drinking liquids (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	14.0		
standard deviation	± 23.8	±	±
ALSAQ-40 - communication domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the communication domain addresses a variety of problems in communicating with others, for example difficulties with speech such as talking slowly, stuttering whilst speaking and feeling self-conscious about speech (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	19.0		
standard deviation	± 27.0	±	±
ALSAQ-40 - emotional reactions domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the emotional reactions domain addresses various emotional problems, for example, feeling lonely, bored, depressed, feeling embarrassed in social situations and feeling worried about future disease progression (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean	33.4		
standard deviation	± 20.3	±	±

Reporting group values	Completers and compliers - active group	Completers and compliers - placebo group	
Number of subjects	60	50	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			

85 years and over			

Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical Units: Subjects			
Female			
Male			
Onset type			
Site of onset of the disease			
Units: Subjects			
Bulbar			
Spinal			
Missing			
El Escorial category			
ALS diagnostic category			
Units: Subjects			
Definite ALS			
Probable ALS			
Probable laboratory supported ALS			
Disease duration			
Time between the date of ALS diagnosis and the date of inclusion into the study			
Units: Months			
arithmetic mean			
standard deviation	±	±	
Diagnostic delay			
Time between the date of onset of ALS symptoms and the date of ALS diagnosis			
Units: Months			
arithmetic mean			
standard deviation	±	±	
BMI			
Body mass index			
Units: Units			
arithmetic mean			
standard deviation	±	±	
FVC%			
Forced Vital Capacity percent value			
Units: Percent of predicted			
arithmetic mean			
standard deviation	±	±	
ALSFRS-R			
ALS functional rating scale - min score 0 corresponding to maximum functional impairment - max score 48 corresponding to no functional impairment			
Units: Points			
arithmetic mean			
standard deviation	±	±	
ALSAQ-40 - physical mobility domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the physical mobility domain addresses problems of mobility, for			

example, falling and difficulties in walking, standing up and going up and down the stairs (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean			
standard deviation	±	±	
ALSAQ-40 - ADL and independence domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the ADL (activities of daily living) and independence domain addresses a variety of limitations in ADL, for example, difficulties in washing/dressing oneself, doing tasks around the house, as well as difficulty writing (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean			
standard deviation	±	±	
ALSAQ-40 - eating and drinking domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the eating and drinking domain adresses problems eating solid foods, swallowing and drinking liquids (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean			
standard deviation	±	±	
ALSAQ-40 - communication domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the communication domain addresses a variety of problems in communicating with others, for example difficulties with speech such as talking slowly, stuttering whilst speaking and feeling self-conscious about speech (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean			
standard deviation	±	±	
ALSAQ-40 - emotional reactions domain			
ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the emotional reactions domain addresses various emotional problems, for example, feeling lonely, bored, depressed, feeling embarrassed in social situations and feeling worried about future disease progression (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition)			
Units: Points			
arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	active
Reporting group description:	
Patients randomly assigned to receive RNS60 administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period	
Reporting group title	PLACEBO
Reporting group description:	
Patients randomly assigned to receive placebo administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period	
Subject analysis set title	Intention to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized participants	
Subject analysis set title	Per Protocol - active group
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants randomized to active arm and completing the study without significant protocol deviations	
Subject analysis set title	Per Protocol - placebo group
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants randomized to placebo arm and completing the study without significant protocol deviations	
Subject analysis set title	Completers and compliers - active group
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants randomized to active arm, completing the 24 weeks of treatment and 24 weeks of follow-up, for a total of 48 weeks in the study, and taking at least 75% of the assigned study medication	
Subject analysis set title	Completers and compliers - placebo group
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants randomized to active arm, completing the 24 weeks of treatment and 24 weeks of follow-up, for a total of 48 weeks in the study, and taking at least 75% of the assigned study medication	

Primary: MCP-1 on-treatment period variation

End point title	MCP-1 on-treatment period variation
End point description:	
Mean change of plasma levels of Monocyte Chemoattractant Protein-1 (MCP-1) during the on-treatment period (from baseline to week 24). Measured at weeks 0, 4, 12, 24.	
End point type	Primary
End point timeframe:	
24 weeks (week 0 - week 24)	

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: pg/ml				
least squares mean (standard error)	4.6 (± 1.8)	2.2 (± 1.9)	6.0 (± 2.8)	1.2 (± 3.0)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: pg/ml				
least squares mean (standard error)	5.0 (± 2.1)	3.3 (± 2.4)		

Statistical analyses

Statistical analysis title	MCP-1 contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups.
Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3585 [1]
Method	Repeated measures ANOVA with unstructure

Notes:

[1] - Global test of treatment*time interaction effect p=0.6346. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	MCP-1 contrast week 24 (end of treatment) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - placebo group v Per Protocol - active group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2508 [2]
Method	Repeated measures ANOVA with unstructure
Confidence interval	
sides	2-sided

Notes:

[2] - Global test of treatment*time interaction effect p=0.6272. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	MCP-1 contrast week 24 (end of treatment) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5977 [3]
Method	Repeated measures ANOVA with unstructure

Notes:

[3] - Global test of treatment*time interaction effect p=0.8018. Null hypothesis: the change over time is not different between groups.

Primary: Cyp-A on-treatment period variation

End point title	Cyp-A on-treatment period variation

End point description:

Mean change of blood levels of Cyclophilin A (Cyp-A) during the on-treatment period (from baseline to week 24). Measured at weeks 0, 4, 12, 24.

End point type	Primary

End point timeframe:

24 weeks (week 0 - week 24)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Arbitrary units				
least squares mean (standard error)	6.6 (± 14.3)	6.9 (± 14.4)	18.8 (± 25.8)	-8.1 (± 28.3)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Arbitrary units				
least squares mean (standard error)	9.0 (± 15.7)	7.7 (± 17.1)		

Statistical analyses

Statistical analysis title	Cyp-A contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9887 [4]
Method	Repeated measures ANOVA with unstructure

Notes:

[4] - Global test of treatment*time interaction effect p=0.4388. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Cyp-A contrast week 24 (end of treatment) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4862 [5]
Method	Repeated measures ANOVA with unstructure

Notes:

[5] - Global test of treatment*time interaction effect p=0.0.0362. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Cyp-A contrast week 24 (end of treatment) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.956 [6]
Method	Repeated measures ANOVA with unstructure

Notes:

[6] - Global test of treatment*time interaction effect p=0.3873. Null hypothesis: the change over time is not different between groups.

Primary: Actin-NT on-treatment period variation

End point title	Actin-NT on-treatment period variation

End point description:

End point type	Primary

End point timeframe:

24 weeks (week 0 - week 24)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Arbitrary units				
least squares mean (standard error)	9.4 (± 10.0)	2.9 (± 10.2)	29.5 (± 17.1)	14.4 (± 19.2)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Arbitrary units				
least squares mean (standard error)	9.8 (± 11.1)	8.1 (± 12.2)		

Statistical analyses

Statistical analysis title	Actin-NT contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6533 [7]
Method	Repeated measures ANOVA with unstructure

Notes:

[7] - Global test of treatment*time interaction effect p=0.9622. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Actin-NT contrast week 24 (end of treatment) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5529 [8]
Method	Repeated measures ANOVA with unstructure

Notes:

[8] - Global test of treatment*time interaction effect p=0.7100. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Actin-NT contrast week 24 (end of treatment) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not

different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9178 [9]
Method	Repeated measures ANOVA with unstructure

Notes:

[9] - Global test of treatment*time interaction effect p=0.7873. Null hypothesis: the change over time is not different between groups.

Primary: 3-NT on-treatment period variation

End point title	3-NT on-treatment period variation

End point description:

Mean change of blood levels of 3-nitrotyrosine (3-NT) during the on-treatment period (from baseline to week 24). Measured at weeks 0, 4, 12, 24.

End point type	Primary

End point timeframe:

24 weeks (week 0 - week 24)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Arbitrary units				
least squares mean (standard error)	14.3 (± 13.8)	-2.4 (± 14.1)	41.3 (± 19.6)	13.2 (± 23.4)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Arbitrary units				
least squares mean (standard error)	18.9 (± 13.9)	14.2 (± 15.4)		

Statistical analyses

Statistical analysis title	3-NT contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3985 [10]
Method	Repeated measures ANOVA with unstructure

Notes:

[10] - Global test of treatment*time interaction effect p=0.9137. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	3-NT contrast week 24 (end of treatment) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3638 [11]
Method	Repeated measures ANOVA with unstructure

Notes:

[11] - Global test of treatment*time interaction effect p=0.4919. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	3-NT contrast week 24 (end of treatment) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8194 [12]
Method	Repeated measures ANOVA with unstructure

Notes:

[12] - Global test of treatment*time interaction effect p=0.5052. Null hypothesis: the change over time is not different between groups.

Primary: IL-17 on-treatment period variation

End point title	IL-17 on-treatment period variation

End point description:

Mean change of plasma levels of Interleukin-17 (IL-17) during the on-treatment period (from baseline to week 24). Measured at weeks 0, 4, 12, 24.

End point type	Primary

End point timeframe:

24 weeks (week 0 - week 24)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: log(pg/ml*10^5)				
least squares mean (standard error)	0.12 (± 0.15)	0.39 (± 0.15)	0.04 (± 0.18)	0.50 (± 0.19)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: log(pg/ml*10^5)				
least squares mean (standard error)	0.09 (± 0.17)	0.56 (± 0.19)		

Statistical analyses

Statistical analysis title	IL-17 contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2209 [13]
Method	Repeated measures ANOVA with unstructure

Notes:

[13] - Global test of treatment*time interaction effect p=0.2543. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	IL-17 contrast week 24 (end of treatment) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0839 [14]
Method	Repeated measures ANOVA with unstructure

Notes:

[14] - Global test of treatment*time interaction effect p=0.1072. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	IL-17 contrast week 24 (end of treatment) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not

different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0701 [15]
Method	Repeated measures ANOVA with unstructure

Notes:

[15] - Global test of treatment*time interaction effect p=0.0653. Null hypothesis: the change over time is not different between groups.

Primary: Nfl on-treatment period variation

End point title	Nfl on-treatment period variation

End point description:

Mean change of plasma levels of Neurofilament Light chain (NfL) during the on-treatment period (from baseline to week 24). Measured at weeks 0, 4, 24.

End point type	Primary

End point timeframe:

24 weeks (week 0 - week 24)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: pg/ml				
least squares mean (standard error)	2.7 (± 2.6)	5.6 (± 2.7)	3.6 (± 3.2)	2.0 (± 3.5)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: pg/ml				
least squares mean (standard error)	5.1 (± 2.5)	6.4 (± 2.7)		

Statistical analyses

Statistical analysis title	Nfl contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4239 [16]
Method	Repeated measures ANOVA with unstructure

Notes:

[16] - Global test of treatment*time interaction effect p=0.2738. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Nfl contrast week 24 (end of treatment) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7357 [17]
Method	Repeated measures ANOVA with unstructure

Notes:

[17] - Global test of treatment*time interaction effect p=0.2388. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Nfl contrast week 24 (end of treatment) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.719 [18]
Method	Repeated measures ANOVA with unstructure

Notes:

[18] - Global test of treatment*time interaction effect p=0.2880. Null hypothesis: the change over time is not different between groups.

Primary: FOXP3 mRNA on-treatment period variation

End point title	FOXP3 mRNA on-treatment period variation

End point description:

Mean change of quantity of regulatory T cells (measured via FOXP3 mRNA) during the on-treatment period (from baseline to week 24). Measured at weeks 0, 4, 12, 24.

End point type	Primary

End point timeframe:

24 weeks (week 0 - week 24)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: (Fold change 2ΔCT)*10^3				
least squares mean (standard error)	-0.14 (± 0.18)	-0.20 (± 0.18)	-0.21 (± 0.27)	0.15 (± 0.28)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: (Fold change 2ΔCT)*10^3				
least squares mean (standard error)	-0.11 (± 0.21)	-0.17 (± 0.22)		

Statistical analyses

Statistical analysis title	FOXP3 mRNA contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8133 [19]
Method	Repeated measures ANOVA with unstructure

Notes:

[19] - Global test of treatment*time interaction effect p=0.1707. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	FOXP3 mRNA contrast week 24 (end of treat) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3558 [20]
Method	Repeated measures ANOVA with unstructure

Notes:

[20] - Global test of treatment*time interaction effect p=0.8414. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	FOXP3 mRNA contrast week 24 (end of treat) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not

different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8508 [21]
Method	Repeated measures ANOVA with unstructure

Notes:

[21] - Global test of treatment*time interaction effect p=0.3676. Null hypothesis: the change over time is not different between groups.

Primary: CD25 mRNA on-treatment period variation

End point title	CD25 mRNA on-treatment period variation

End point description:

Mean change of quantity of regulatory T cells (measured via CD25 mRNA) during the on-treatment period (from baseline to week 24). Measured at weeks 0, 4, 12, 24.

End point type	Primary

End point timeframe:

24 weeks (week 0 - week 24)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: log((Fold change 2ΔCT)*10^3)				
least squares mean (standard error)	-0.01 (± 0.08)	-0.10 (± 0.09)	-0.02 (± 0.18)	0.03 (± 0.19)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: log((Fold change 2ΔCT)*10^3)				
least squares mean (standard error)	-0.01 (± 0.09)	-0.02 (± 0.10)		

Statistical analyses

Statistical analysis title	CD25 mRNA contrast week 24 (end of treatment)

Statistical analysis description:

Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4401 [22]
Method	Repeated measures ANOVA with unstructure

Notes:

[22] - Global test of treatment*time interaction effect p=0.5239. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	CD25 mRNA contrast week 24 (end of treat) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8409 [23]
Method	Repeated measures ANOVA with unstructure

Notes:

[23] - Global test of treatment*time interaction effect p=0.9882. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	CD25 mRNA contrast week 24 (end of treat) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 24 - baseline) within treatment groups. Null hypothesis: the change from baseline to week 24 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9319 [24]
Method	Repeated measures ANOVA with unstructure

Notes:

[24] - Global test of treatment*time interaction effect p=0.6591. Null hypothesis: the change over time is not different between groups.

Secondary: MCP-1 off-treatment period variation

End point title	MCP-1 off-treatment period variation

End point description:

Mean change of plasma levels of Monocyte Chemoattractant Protein-1 (MCP-1) during the off-treatment follow-up period (from week 24 to week 48)

End point type	Secondary

End point timeframe:

24 weeks (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: pg/ml				
least squares mean (standard error)	1.1 (± 2.6)	-0.2 (± 3.8)	0.4 (± 3.8)	7.3 (± 4.0)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: pg/ml				
least squares mean (standard error)	0.8 (± 2.8)	0.7 (± 3.0)		

Statistical analyses

Statistical analysis title	MCP-1 contrast week 48 (end of study)

Statistical analysis description:

Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9563 [25]
Method	Repeated measures ANOVA with unstructure

Notes:

[25] - Global test of treatment*time interaction effect p=0.6346. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	MCP-1 contrast week 48 (end of study) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2124 [26]
Method	Repeated measures ANOVA with unstructure
Confidence interval	
sides	2-sided

Notes:

[26] - Global test of treatment*time interaction effect p=0.6272. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	MCP-1 contrast week 48 (end of study) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9767 [27]
Method	Repeated measures ANOVA with unstructure

Notes:

[27] - Global test of treatment*time interaction effect p=0.8018. Null hypothesis: the change over time is not different between groups.

Secondary: Cyp-A off-treatment period variation

End point title	Cyp-A off-treatment period variation

End point description:

Mean change of blood levels of Cyclophilin A (Cyp-A) during the off-treatment follow-up period (from week 24 to week 48)

End point type	Secondary

End point timeframe:

24 weeks (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Arbitrary units				
least squares mean (standard error)	16.0 (± 16.4)	-12.5 (± 16.7)	36.0 (± 24.8)	-22.9 (± 26.7)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Arbitrary units				
least squares mean (standard error)	17.1 (± 16.6)	-16.8 (± 17.4)		

Statistical analyses

Statistical analysis title	Cyp-A contrast week 48 (end of study)

Statistical analysis description:

Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	PLACEBO v active
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2253 [28]
Method	Repeated measures ANOVA with unstructure

Notes:

[28] - Global test of treatment*time interaction effect p=0.4388. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Cyp-A contrast week 48 (end of study) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1127 [29]
Method	Repeated measures ANOVA with unstructure

Notes:

[29] - Global test of treatment*time interaction effect p=0.0362. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Cyp-A contrast week 48 (end of study) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1612 [30]
Method	Repeated measures ANOVA with unstructure

Notes:

[30] - Global test of treatment*time interaction effect p=0.3873. Null hypothesis: the change over time is not different between groups.

Secondary: Actin-NT off-treatment period variation

End point title	Actin-NT off-treatment period variation

End point description:

Mean change of blood levels of Tyrosine Nitrated-Actin (Actin-NT) during the off-treatment follow-up period (from week 24 to week 48)

End point type	Secondary

End point timeframe:

24 weeks (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Arbitrary units				
least squares mean (standard error)	-4.8 (± 11.0)	2.9 (± 11.2)	-0.6 (± 17.5)	-6.7 (± 18.5)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Arbitrary units				
least squares mean (standard error)	-6.7 (± 11.4)	-0.2 (± 12.2)		

Statistical analyses

Statistical analysis title	Actin-NT contrast week 48 (end of study)

Statistical analysis description:

Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6263 [31]
Method	Repeated measures ANOVA with unstructure

Notes:

[31] - Global test of treatment*time interaction effect p=0.9622. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Actin-NT contrast week 48 (end of study) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8134 [32]
Method	Repeated measures ANOVA with unstructure

Notes:

[32] - Global test of treatment*time interaction effect p=0.7100. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	Actin-NT contrast week 48 (end of study) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not

different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6985 [33]
Method	Repeated measures ANOVA with unstructure

Notes:

[33] - Global test of treatment*time interaction effect p=0.7873. Null hypothesis: the change over time is not different between groups.

Secondary: 3-NT off-treatment period variation

End point title	3-NT off-treatment period variation

End point description:

Mean change of blood levels of 3-nitrotyrosine (3-NT) during the off-treatment follow-up period (from week 24 to week 48)

End point type	Secondary

End point timeframe:

24 weeks (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Arbitrary units				
least squares mean (standard error)	-26.3 (± 14.6)	-7.3 (± 15.1)	-30.9 (± 25.9)	-18.7 (± 29.3)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Arbitrary units				
least squares mean (standard error)	-29.4 (± 15.6)	-17.7 (± 17.1)		

Statistical analyses

Statistical analysis title	3-NT contrast week 48 (end of study)

Statistical analysis description:

Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3671 [34]
Method	Repeated measures ANOVA with unstructure

Notes:

[34] - Global test of treatment*time interaction effect p=0.9137. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	3-NT contrast week 48 (end of study) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7573 [35]
Method	Repeated measures ANOVA with unstructure

Notes:

[35] - Global test of treatment*time interaction effect p=0.4919. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	3-NT contrast week 48 (end of study) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.613 [36]
Method	Repeated measures ANOVA with unstructure
Confidence interval	
sides	2-sided

Notes:

[36] - Global test of treatment*time interaction effect p=0.5052. Null hypothesis: the change over time is not different between groups.

Secondary: IL-17 off-treatment period variation

End point title	IL-17 off-treatment period variation

End point description:

Mean change of plasma levels of Interleukin-17 (IL-17) during the off-treatment follow-up period (from week 24 to week 48)

End point type	Secondary

End point timeframe:

24 weeks (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: log(pg/ml*10^5)				
least squares mean (standard error)	-0.15 (± 0.15)	-0.11 (± 0.16)	-0.22 (± 0.28)	0.004 (± 0.31)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: log(pg/ml*10^5)				
least squares mean (standard error)	-0.16 (± 0.15)	-0.10 (± 0.17)		

Statistical analyses

Statistical analysis title	IL-17 contrast week 48 (end of study)

Statistical analysis description:

Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.854 [37]
Method	Repeated measures ANOVA with unstructure

Notes:

[37] - Global test of treatment*time interaction effect p=0.2543. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	IL-17 contrast week 48 (end of study) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5921 [38]
Method	Repeated measures ANOVA with unstructure

Notes:

[38] - Global test of treatment*time interaction effect p=0.1072. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	IL-17 contrast week 48 (end of study) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not

different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8215 [39]
Method	Repeated measures ANOVA with unstructure

Notes:

[39] - Global test of treatment*time interaction effect p=0.0701. Null hypothesis: the change over time is not different between groups.

Secondary: FOXP3 mRNA off-treatment period variation

End point title	FOXP3 mRNA off-treatment period variation

End point description:

Mean change of quantity of regulatory T cells (measured via FOXP3 mRNA) during the off-treatment follow-up period (from week 24 to week 48)

End point type	Secondary

End point timeframe:

24 weeks (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: (Fold change 2ΔCT)*10^3				
least squares mean (standard error)	-0.55 (± 0.22)	-0.15 (± 0.23)	-0.53 (± 0.35)	-0.64 (± 0.36)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: (Fold change 2ΔCT)*10^3				
least squares mean (standard error)	-0.49 (± 0.24)	-0.16 (± 0.25)		

Statistical analyses

Statistical analysis title	FOXP3 mRNA contrast week 48 (end of study)

Statistical analysis description:

Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2161 [40]
Method	Repeated measures ANOVA with unstructure

Notes:

[40] - Global test of treatment*time interaction effect p=0.1708. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	FOXP3 mRNA contrast week 48 (end of study) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8327 [41]
Method	Repeated measures ANOVA with unstructure

Notes:

[41] - Global test of treatment*time interaction effect p=0.8414. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	FOXP3 mRNA contrast week 48 (end of study) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3478 [42]
Method	Repeated measures ANOVA with unstructure
Confidence interval	
sides	2-sided
Variability estimate	Standard error of the mean
Dispersion value	0.35

Notes:

[42] - Global test of treatment*time interaction effect p=0.3676. Null hypothesis: the change over time is not different between groups.

Secondary: CD25 mRNA off-treatment period variation

End point title	CD25 mRNA off-treatment period variation

End point description:

Mean change of quantity of regulatory T cells (measured via CD25 mRNA) during the off-treatment follow-up period (from week 24 to week 48)

End point type	Secondary

End point timeframe:

24 weeks (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: log((Fold change 2ΔCT)*10^3)				
least squares mean (standard error)	0.21 (± 0.11)	0.11 (± 0.11)	0.13 (± 0.18)	-0.01 (± 0.19)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: log((Fold change 2ΔCT)*10^3)				
least squares mean (standard error)	0.20 (± 0.12)	0.08 (± 0.12)		

Statistical analyses

Statistical analysis title	CD25 mRNA contrast week 48 (end of study)

Statistical analysis description:

Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4962 [43]
Method	Repeated measures ANOVA with unstructure

Notes:

[43] - Global test of treatment*time interaction effect p=0.5239. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	CD25 mRNA contrast week 48 (end of study) - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6115 [44]
Method	Repeated measures ANOVA with unstructure

Notes:

[44] - Global test of treatment*time interaction effect p=0.9882. Null hypothesis: the change over time is not different between groups.

Statistical analysis title	CD25 mRNA contrast week 48 (end of study) - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast between treatment groups of the differences (week 48 - week 24) within treatment groups. Null hypothesis: the change from week 24 to week 48 is not different between treatment groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49 [45]
Method	Repeated measures ANOVA with unstructure

Notes:

[45] - Global test of treatment*time interaction effect p=0.6591. Null hypothesis: the change over time is not different between groups.

Secondary: FVC% on-treatment and off-treatment variation

End point title	FVC% on-treatment and off-treatment variation

End point description:

The mean change of Forced Vital Capacity percent value (FVC%) over the on-treatment period and the off-treatment follow-up period. Measured at weeks 0, 4, 12, 24, 36, 48.

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Percentage of predicted				
least squares mean (standard error)				
Slope on-treatment period (change per week from ba	-0.46 (± 0.11)	-0.87 (± 0.10)	-0.27 (± 0.1)	-0.38 (± 0.1)
Slope off-treatment follow-up period (change per w	-0.45 (± 0.11)	-0.54 (± 0.13)	-0.44 (± 0.2)	-0.45 (± 0.2)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Percentage of predicted				
least squares mean (standard error)				
Slope on-treatment period (change per week from ba	-0.36 (± 0.1)	-0.53 (± 0.1)		
Slope off-treatment follow-up period (change per w	-0.47 (± 0.1)	-0.52 (± 0.1)		

Statistical analyses

Statistical analysis title	FVC% slope week 0 week 24

Statistical analysis description:

Contrast of the slopes during the on-treatment period (change per week, from baseline to week 24) between treatment groups. Null hypothesis: the rate of change from baseline to week 24 is not different between groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0101
Method	Mixed models analysis

Statistical analysis title	FVC% slope week 24 week 48

Statistical analysis description:

Contrast of the slopes during the off-treatment follow-up period (change per week, from week 24 to week 48) between treatment groups. Null hypothesis: the rate of change from week 24 to week 48 is not different between groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5924
Method	Mixed models analysis

Statistical analysis title	FVC% slope week 0 week 24 - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast of the slopes during the on-treatment period (change per week, from baseline to week 24) between treatment groups. Null hypothesis: the rate of change from baseline to week 24 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5153
Method	Mixed models analysis

Statistical analysis title	FVC% slope week 24 week 48 - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast of the slopes during the off-treatment follow-up period (change per week, from week 24 to week 48) between treatment groups. Null hypothesis: the rate of change from week 24 to week 48 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9536
Method	Mixed models analysis

Statistical analysis title	FVC% slope week 0 week 24 - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast of the slopes during the on-treatment period (change per week, from baseline to week 24) between treatment groups. Null hypothesis: the rate of change from baseline to week 24 is not different between groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2522
Method	Mixed models analysis

Statistical analysis title	FVC% slope week 24 week 48 - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast of the slopes during the off-treatment follow-up period (change per week, from week 24 to week 48) between treatment groups. Null hypothesis: the rate of change from week 24 to week 48 is not different between groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8008
Method	Mixed models analysis

Secondary: ALSFRS-R on-treatment and off-treatment variation

End point title	ALSFRS-R on-treatment and off-treatment variation

End point description:

The mean change of ALS functional rating scale (min score 0 corresponding to maximum functional impairment - max score 48 corresponding to no functional impairment) over the on-treatment period and the off-treatment follow-up period. Measured at weeks 0, 4, 12, 24, 36, 48.

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Points				
least squares mean (standard error)				
Slope on-treatment period (change per week from ba	-0.26 (± 0.03)	-0.28 (± 0.03)	-0.17 (± 0.03)	-0.17 (± 0.04)
Slope off-treatment follow-up period (change per w	-0.26 (± 0.03)	-0.24 (± 0.03)	-0.21 (± 0.03)	-0.19 (± 0.03)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Points				
least squares mean (standard error)				
Slope on-treatment period (change per week from ba	-0.21 (± 0.03)	-0.19 (± 0.03)		
Slope off-treatment follow-up period (change per w	-0.24 (± 0.03)	-0.21 (± 0.03)		

Statistical analyses

Statistical analysis title	ALSFRS-R slope week 0 week 24

Statistical analysis description:

Contrast of the slopes during the on-treatment period (change per week, from baseline to week 24) between treatment groups. Null hypothesis: the rate of change from baseline to week 24 is not different between groups.

Comparison groups	PLACEBO v active
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5725
Method	Mixed models analysis

Statistical analysis title	ALSFRS-R slope week 24 week 48

Statistical analysis description:

Contrast of the slopes during the off-treatment follow-up period (change per week, from week 24 to week 48) between treatment groups. Null hypothesis: the rate of change from week 24 to week 48 is not different between groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5728
Method	Mixed models analysis

Statistical analysis title	ALSFRS-R slope week 0 week 24 - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast of the slopes during the on-treatment period (change per week, from baseline to week 24) between treatment groups. Null hypothesis: the rate of change from baseline to week 24 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9439
Method	Mixed models analysis

Statistical analysis title	ALSFRS-R slope week 24 week 48 - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast of the slopes during the off-treatment follow-up period (change per week, from week 24 to week 48) between treatment groups. Null hypothesis: the rate of change from week 24 to week 48 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6729
Method	Mixed models analysis

Statistical analysis title	ALSFRS-R slope week 0 week 24 - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast of the slopes during the on-treatment period (change per week, from baseline to week 24) between treatment groups. Null hypothesis: the rate of change from baseline to week 24 is not different between groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5952
Method	Mixed models analysis

Statistical analysis title	ALSFRS-R slope week 24 week 48 - CC
Statistical analysis description:	

Completers and compliers (CC) population. Contrast of the slopes during the off-treatment follow-up period (change per week, from week 24 to week 48) between treatment groups. Null hypothesis: the rate of change from week 24 to week 48 is not different between groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4275
Method	Mixed models analysis

Secondary: ALSAQ-40 - physical mobility domain

End point title	ALSAQ-40 - physical mobility domain
End point description:	

The mean change of ALSAQ-40 physical mobility domain over the on-treatment period and the off-treatment follow-up period. Measured at weeks 0, 24, 48. The ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the physical mobility domain addresses problems of mobility, for example, falling and difficulties in walking, standing up and going up and down the stairs (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition).

End point type	Secondary
End point timeframe:	

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.45 (± 0.10)	0.58 (± 0.10)	0.35 (± 0.1)	0.51 (± 0.1)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.40 (± 0.1)	0.53 (± 0.1)		

Statistical analyses

Statistical analysis title	ALSAQ-40 physical mobility slopes
Statistical analysis description:	

Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1503
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 physical mobility slopes - PP
Statistical analysis description:	

Per Protocol (PP) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2351
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 physical mobility slopes - CC
Statistical analysis description:	

Completers and compliers (CC) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1638
Method	Mixed models analysis

Secondary: ALSAQ-40 - ADL and independence domain

End point title	ALSAQ-40 - ADL and independence domain

End point description:

The mean change of ALSAQ-40 ADL and independence domain over the on-treatment period and the off-treatment follow-up period. Measured at weeks 0, 24, 48. ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the ADL (activities of daily living) and independence domain addresses a variety of limitations in ADL, for example, difficulties in washing/dressing oneself, doing tasks around the house, as well as difficulty writing (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition).

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.47 (± 0.06)	0.59 (± 0.10)	0.33 (± 0.1)	0.56 (± 0.1)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.44 (± 0.1)	0.51 (± 0.1)		

Statistical analyses

Statistical analysis title	ALSAQ-40 ADL and independence slopes

Statistical analysis description:

Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1556
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 ADL and independence slopes - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0755
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 ADL and independence slopes - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4045
Method	Mixed models analysis

Secondary: ALSAQ-40 - eating and drinking domain

End point title	ALSAQ-40 - eating and drinking domain

End point description:

The mean change of ALSAQ-40 eating and drinking over the on-treatment period and the off-treatment follow-up period. Measured at weeks 0, 24, 48. ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the eating and drinking domain adresses problems eating solid foods, swallowing and drinking liquids (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition).

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.19 (± 0.10)	0.38 (± 0.10)	0.07 (± 0.1)	0.36 (± 0.1)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.13 (± 0.1)	0.32 (± 0.1)		

Statistical analyses

Statistical analysis title	ALSAQ-40 eating and drinking slopes

Statistical analysis description:

Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0319
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 eating and drinking slopes - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.016
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 eating and drinking slopes - CC
Statistical analysis description:	
Completers and compliers (CC) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.	
Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0315
Method	Mixed models analysis

Secondary: ALSAQ-40 - communication domain

End point title	ALSAQ-40 - communication domain

End point description:

The mean change of ALSAQ-40 communication domain over the on-treatment period and the off-treatment follow-up period. Measured at weeks 0, 24, 48. ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the communication domain addresses a variety of problems in communicating with others, for example difficulties with speech such as talking slowly, stuttering whilst speaking and feeling self-conscious about speech (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition).

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.29 (± 0.10)	0.33 (± 0.10)	0.22 (± 0.1)	0.26 (± 0.1)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.23 (± 0.1)	0.22 (± 0.1)		

Statistical analyses

Statistical analysis title	ALSAQ-40 communication slopes
Statistical analysis description:	

Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6419
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 communication slopes - PP
Statistical analysis description:	

Per Protocol (PP) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7173
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 communication slopes - CC
Statistical analysis description:	

Completers and compliers (CC) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.977
Method	Mixed models analysis

Secondary: ALSAQ-40 - emotional reactions domain

End point title	ALSAQ-40 - emotional reactions domain

End point description:

The mean change of ALSAQ-40 emotional reactions domain over the on-treatment period and the off-treatment follow-up period. Measured at weeks 0, 24, 48. ALS Assessment Questionnaire, a 40-item questionnaire measuring health status and health related quality of life in ALS patients - the emotional reactions domain addresses various emotional problems, for example, feeling lonely, bored, depressed, feeling embarrassed in social situations and feeling worried about future disease progression (min score =0 corresponding to the better condition - max score =100 corresponding to the worse condition).

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.18 (± 0.10)	0.25 (± 0.10)	0.10 (± 0.1)	0.37 (± 0.1)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Points				
least squares mean (standard error)				
Slope (change per week from baseline to week 48)	0.14 (± 0.1)	0.19 (± 0.1)		

Statistical analyses

Statistical analysis title	ALSAQ-40 emotional reactions slopes

Statistical analysis description:

Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3951
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 emotional reactions slopes - PP

Statistical analysis description:

Per Protocol (PP) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0353
Method	Mixed models analysis

Statistical analysis title	ALSAQ-40 emotional reactions slopes - CC

Statistical analysis description:

Completers and compliers (CC) population. Contrast of the slopes during the on-treatment and off-treatment follow-up period (change per week, from baseline to week 48) between treatment groups. Null hypothesis: the rate of change from baseline to week 48 is not different between groups.

Comparison groups	Completers and compliers - active group v Completers and compliers - placebo group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.482
Method	Mixed models analysis

Secondary: Self-sufficiency

End point title	Self-sufficiency

End point description:

The cumulative number of participants losing self-sufficiency at 4, 12, 24, 36 and 48 weeks in the two treatment arms. Self-sufficiency was defined as a score of 3 or higher in the 3 items ALSFRS-R: swallowing, cutting food and handling utensils, walking. ALSFRS-R is the ALS functional rating scale (min score 0 corresponding to maximum functional impairment - max score 48 corresponding to no functional impairment). This scale is made of 12 items, each with scores ranging from 0 to 4.

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	73[46]	71[47]	25	22
Units: Participants				
Week 4	28	27	9	10
Week 12	51	44	16	14
Week 24	61	55	20	15
Week 36	64	60	23	18
Weekk 48	66	65	24	19

Notes:

[46] - 1 participant excluded because not self-sufficient at baseline

[47] - 2 participants excluded because not self-sufficient at baseline

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Participants				
Week 4	21	17		
Week 12	39	28		
Week 24	49	36		
Week 36	52	41		
Weekk 48	54	45		

Statistical analyses

Statistical analysis title	Self-sufficiency Kaplan-Meier
Statistical analysis description:	

Kaplan-Meier curves for the probability of remaining self-sufficient at 4, 12, 24, 36 and 48 weeks in the two treatment arms. Null hypothesis: the survival curves describing the probability of remaining self-suffucent over the on-treatment and the off-treatment follow-up period are not different between groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4527
Method	Logrank

Statistical analysis title	Self-sufficiency Kaplan-Meier - PP
Statistical analysis description:	

Per Protocol (PP) population. Kaplan-Meier curves for the probability of remaining self-sufficient at 4, 12, 24, 36 and 48 weeks in the two treatment arms. Null hypothesis: the survival curves describing the probability of remaining self-suffucent over the on-treatment and the off-treatment follow-up period are not different between groups.

Comparison groups	Per Protocol - active group v Per Protocol - placebo group

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5554
Method	Logrank

Statistical analysis title	Self-sufficiency Kaplan-Meier - CC

Statistical analysis description:

Completers and compliers (CC) population. Kaplan-Meier curves for the probability of remaining self-sufficient at 4, 12, 24, 36 and 48 weeks in the two treatment arms. Null hypothesis: the survival curves describing the probability of remaining self-suffcent over the on-treatment and the off-treatment follow-up period are not different between groups.

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3791
Method	Logrank

Secondary: Survival

End point title	Survival

End point description:

The cumulative number of deaths at 4, 12, 24, 36 and 48 weeks in the two treatment arms.

End point type	Secondary

End point timeframe:

24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Participants				
Week 4	0	0	0	0
Week 12	0	1	0	0
Week 24	0	1	0	0
Week 36	3	1	0	0
Week 48	7	6	0	0

End point values	Completers and compliers - active group	Completers and compliers - placebo group		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Participants				
Week 4	0	0		
Week 12	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		

Statistical analyses

Statistical analysis title	Survival Kaplan-Meier analysis

Statistical analysis description:

The cumulative survival probability at 4, 12, 24, 36 and 48 weeks in the two treatment arms. Null hypothesis: the survival curves over the on-treatment and the off-treatment follow-up period are not different between groups.

Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9212
Method	Logrank

Secondary: AE leading to treatment discontinuation

End point title	AE leading to treatment discontinuation

End point description:

The total number of subjects in the two treatment arms experiencing at least one adverse event (AE) leading to treatment discontinuation at 4, 12 and 24 weeks

End point type	Secondary

End point timeframe:

24 weeks on-treatment period

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Participants				
Week 4	0	0	0	0
Week 12	0	1	0	0
Week 24	0	3	0	0

End point values	Completers and compliers -	Completers and compliers -		

	active group	placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Participants				
Week 4	0	0		
Week 12	0	0		
Week 24	0	0		

Statistical analyses

Statistical analysis title	AE treatment discontinuation 4 weeks
Statistical analysis description:	
Null hypothesis: the percentage of patients experiencing at least one adverse event leading to treatment discontinuation within 4 weeks is not different between groups	
Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9598
Method	Fisher exact

Statistical analysis title	AE treatment discontinuation 12 weeks
Statistical analysis description:	
Null hypothesis: the percentage of patients experiencing at least one adverse event leading to treatment discontinuation within 12 weeks is not different between groups	
Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.939
Method	Fisher exact

Statistical analysis title	AE treatment discontinuation 24 weeks
Statistical analysis description:	
Null hypothesis: the percentage of patients experiencing at least one adverse event leading to treatment discontinuation within 24 weeks is not different between groups	
Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3442
Method	Wilcoxon (Mann-Whitney)

Secondary: Mean number of AE

End point title	Mean number of AE
End point description:	
The mean number of AEs per treatment arm at 4, 12, 24 and 48 weeks	
End point type	Secondary
End point timeframe:	
24 weeks on-treatment period (week 0 - week 24) + 24 weeks off-treatment follow-up period (week 24 - week 48)	

End point values	active	PLACEBO	Per Protocol - active group	Per Protocol - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	73	25	22
Units: Number of AE				
arithmetic mean (standard deviation)				
Week 4	0.4 (± 0.8)	0.5 (± 1.1)	0.5 (± 0.8)	0.4 (± 0.7)
Week 12	1.0 (± 1.6)	1.2 (± 2.4)	1.0 (± 1.1)	0.9 (± 1.3)
Week 24	1.7 (± 2.6)	2.0 (± 3.6)	1.9 (± 2.1)	1.5 (± 1.7)
Week 48	1.9 (± 2.8)	2.1 (± 3.6)	2.2 (± 2.8)	1.8 (± 2.0)

End point values	Completers and compliers - active group	Completers and compliers - placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	50		
Units: Number of AE				
arithmetic mean (standard deviation)				
Week 4	0.5 (± 0.8)	0.4 (± 1.0)		
Week 12	1.0 (± 1.3)	0.9 (± 1.4)		
Week 24	1.6 (± 2.0)	1.6 (± 2.4)		
Week 48	1.8 (± 2.4)	1.8 (± 2.5)		

Statistical analyses

Statistical analysis title	Mean AE treatment discontinuation 4 weeks
Statistical analysis description:	
Null hypothesis: the number of adverse events occurred within 4 weeks is not different between groups	
Comparison groups	active v PLACEBO

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8738
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 12 weeks
Statistical analysis description:	
Null hypothesis: the number of adverse events occurred within 12 weeks is not different between groups	
Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7556
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 24 weeks
Statistical analysis description:	
Null hypothesis: the number of adverse events occurred within 24 weeks is not different between groups	
Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6477
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 48 weeks
Statistical analysis description:	
Null hypothesis: the number of adverse events occurred within 48 weeks is not different between groups	
Comparison groups	active v PLACEBO
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6048
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 4 weeks - PP
Statistical analysis description:	
Per Protocol (PP) population. Null hypothesis: the number of adverse events occurred within 4 weeks is not different between groups	
Comparison groups	Per Protocol - active group v Per Protocol - placebo group

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3744
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 12 weeks - PP
Statistical analysis description:	

Per Protocol (PP) population. Null hypothesis: the number of adverse events occurred within 12 weeks is not different between groups

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.572
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 24 weeks - PP
Statistical analysis description:	

Per Protocol (PP) population. Null hypothesis: the number of adverse events occurred within 24 weeks is not different between groups

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9477
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 48 weeks - PP
Statistical analysis description:	

Per Protocol (PP) population. Null hypothesis: the number of adverse events occurred within 48 weeks is not different between groups

Comparison groups	Per Protocol - active group v Per Protocol - placebo group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9652
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 4 weeks - CC
Statistical analysis description:	

Per Protocol (PP) population. Null hypothesis: the number of adverse events occurred within 4 weeks is

not different between groups

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5933
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 12 weeks - CC

Statistical analysis description:

Completers and compliers (CC) population. Null hypothesis: the number of adverse events occurred within 12 weeks is not different between groups

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7438
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 24 weeks - CC

Statistical analysis description:

Completers and compliers (CC) population. Null hypothesis: the number of adverse events occurred within 24 weeks is not different between groups

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9132
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mean AE treatment discontinuation 48 weeks - CC

Statistical analysis description:

Completers and compliers (CC) population. Null hypothesis: the number of adverse events occurred within 48 weeks is not different between groups

Comparison groups	Completers and compliers - placebo group v Completers and compliers - active group
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7659
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
24 weeks on-treatment period + 24 weeks off-treatment follow-up period	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	active

Reporting group description:

Patients randomly assigned to receive RNS60 administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period

Reporting group title	PLACEBO

Reporting group description:

Patients randomly assigned to receive placebo administered intravenously (375ml) once a week and inhaled via nebulization (4ml/day) on non-infusion days for 24 weeks, and then followed by a 24-week off-treatment observation period

Serious adverse events	active	PLACEBO	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 74 (6.76%)	5 / 73 (6.85%)	
number of deaths (all causes)	7	6	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
HEART ATTACK			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	active	PLACEBO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 74 (59.46%)	48 / 73 (65.75%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 74 (6.76%)	4 / 73 (5.48%)	
occurrences (all)	6	5	
Fracture			
subjects affected / exposed	2 / 74 (2.70%)	5 / 73 (6.85%)	
occurrences (all)	2	6	
Haematoma			
subjects affected / exposed	3 / 74 (4.05%)	1 / 73 (1.37%)	
occurrences (all)	4	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 74 (4.05%)	4 / 73 (5.48%)	
occurrences (all)	4	4	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 74 (9.46%)	7 / 73 (9.59%)	
occurrences (all)	7	11	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 74 (5.41%)	1 / 73 (1.37%)	
occurrences (all)	4	1	
Flu			
subjects affected / exposed	8 / 74 (10.81%)	6 / 73 (8.22%)	
occurrences (all)	11	11	
Malaise			

subjects affected / exposed	3 / 74 (4.05%)	2 / 73 (2.74%)	
occurrences (all)	6	4	
Temperature			
subjects affected / exposed	3 / 74 (4.05%)	6 / 73 (8.22%)	
occurrences (all)	4	7	
Gastrointestinal disorders			
Abdominal colic			
subjects affected / exposed	1 / 74 (1.35%)	2 / 73 (2.74%)	
occurrences (all)	8	2	
Achalasia event			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences (all)	5	0	
Diarrhoea			
subjects affected / exposed	2 / 74 (2.70%)	1 / 73 (1.37%)	
occurrences (all)	4	1	
Nausea			
subjects affected / exposed	1 / 74 (1.35%)	2 / 73 (2.74%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	3 / 74 (4.05%)	0 / 73 (0.00%)	
occurrences (all)	4	0	
Nasal congestion			
subjects affected / exposed	2 / 74 (2.70%)	3 / 73 (4.11%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	4 / 74 (5.41%)	3 / 73 (4.11%)	
occurrences (all)	8	4	
Musculoskeletal and connective tissue disorders			
Joint pain			
subjects affected / exposed	6 / 74 (8.11%)	1 / 73 (1.37%)	
occurrences (all)	7	1	
Lumbosciatalgia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 73 (2.74%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported