Clinical trial results:
Study NOG112264, a Phase II Study of Ozanezumab (GSK1223249) versus Placebo in the Treatment of Amyotrophic Lateral Sclerosis

Summary

EudraCT number	2012-003349-13
Trial protocol	BE NL IT DE GB FR
Global end of trial date	22 January 2015

Results information

Result version number	v1 (current)
This version publication date	22 May 2016
First version publication date	22 May 2016

Trial information

Trial identification

Sponsor protocol code	NOG112264

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	22 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of ozanezumab on the physical function and survival of Amyotrophic Lateral Sclerosis (ALS) subjects over a treatment period of 48 weeks. Function will be measured using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R).

Protection of trial subjects:

The study was split into Part A (intensive safety monitoring for an initial subset of participants during the first four infusions of study drug) and Part B; recruitment was halted until an Independent Data Monitoring Committee (IDMC) reviewed Part A data. On the IDMC's recommendation, recruitment into Part B commenced (less intensive safety monitoring required). The IDMC was deployed for the duration of the study to review unblinded safety and selected efficacy data at regular intervals throughout the study period. For participants randomized in Part A, the investigator sought agreement from the GSK study medical monitor prior to administering the next dose (until IDMC recommendation to start Part B). A GSK safety review team comprising the Safety Physician, Safety Scientist, Medical Monitor, and Statistician met at regular intervals throughout the study to review blinded safety information. The study was designed to allow for participants to provide key efficacy and safety data over the telephone should they not be able to attend clinic (with medical monitor approval).

Background therapy:

Participants were permitted to continue their standard of care management as per protocol.

Evidence for comparator: -

Actual start date of recruitment	20 December 2012
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	Australia: 14
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 67
Country: Number of subjects enrolled	Italy: 20
Worldwide total number of subjects	303
EEA total number of subjects	182

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)	235
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 304 participants were randomized (151 to placebo; 153 to ozanezumab 15 milligrams [mg]/kilogram [kg]), and 303 participants (151 placebo; 152 ozanezumab 15 mg /kg) received at least one dose of investigational product (one of the participants randomized to ozanezumab was re-

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo once every 2 weeks by intravenous infusion up to Week 46.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Normal saline (0.9% sodium chloride) administered by intravenous infusion every 2 weeks up to Week 46 (last dose)

Arm title	Ozanezumab 15 mg/kg

Arm description:

Participants received ozanezumab 15 milligrams per kilogram (mg/kg) once every 2 weeks by intravenous infusion up to Week 46.

Arm type	Experimental
Investigational medicinal product name	Ozanezumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ozanezumab 200 milligrams per milliliter (mg/mL) solution diluted at a dose of 15 milligrams per kilogram (mg/kg) and administered by intravenous infusion every 2 weeks up to Week 46 (last dose)

Number of subjects in period 1	Placebo	Ozanezumab 15 mg/kg
Started	151	152
Completed	110	106
Not completed	41	46
Physician decision	4	2
Consent withdrawn by subject	14	24
Reached Protocol-defined Stopping Criteria	1	-
Adverse event, non-fatal	17	18
Lost to follow-up	2	1
Lack of efficacy	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo once every 2 weeks by intravenous infusion up to Week 46.	
Reporting group title	Ozanezumab 15 mg/kg
Reporting group description:	
Participants received ozanezumab 15 milligrams per kilogram (mg/kg) once every 2 weeks by intravenous infusion up to Week 46.	

Reporting group values	Placebo	Ozanezumab 15 mg/kg	Total
Number of subjects	151	152	303
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	55.5	55.7	
standard deviation	± 11.04	± 10.4	-
Gender categorical			
Units: Subjects			
Female	54	49	103
Male	97	103	200
Race, Customized			
Units: Subjects			
African American/African Heritage	1	2	3
Asian - Central/South Asian Heritage	2	3	5
Asian - East Asian Heritage	3	8	11
Asian - Japanese Heritage	5	10	15
Asian - South East Asian Heritage	13	5	18
White - Arabic/North African Heritage	3	2	5
White - White/Caucasian/European Heritage	124	121	245
Mixed Race	0	1	1

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo once every 2 weeks by intravenous infusion up to Week 46.	
Reporting group title	Ozanezumab 15 mg/kg
Reporting group description:	
Participants received ozanezumab 15 milligrams per kilogram (mg/kg) once every 2 weeks by intravenous infusion up to Week 46.	

Primary: Joint rank scores for combined analysis of function (amyotrophic lateral sclerosis functional rating scale revised [ALSFRS-R] score) and 48 week overall survival

End point title	Joint rank scores for combined analysis of function (amyotrophic lateral sclerosis functional rating scale revised [ALSFRS-R] score) and 48 week overall survival

End point description:

The joint rank score is a combined assessment of function and survival, whereby function is assessed using change from Baseline in the ALSFRS-R total score. To calculate the joint rank scores, every participant was compared with all other participants in a pair wise manner and assigned a score of -1, 0 or 1 based on their relative outcomes. The joint rank score for a subject is then the sum of their scores across the pair wise comparisons. Outcomes are considered in a hierarchical manner with death considered a worse outcome than functional decline, and a large functional decline considered a worse outcome than a small/no functional decline. See the description of the subsequent outcome measure for information regarding the ALSFRS-R questionnaire. The Intent-to-Treat (ITT) population was comprised of all randomized participants who received at least one dose of investigational product.

End point type	Primary

End point timeframe:

Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[1]	152[2]		
Units: Scores on a scale				
least squares mean (standard error)	15 (± 13.58)	-14.9 (± 13.54)		

Notes:

[1] - ITT population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

[2] - ITT population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg

Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-30
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.9
upper limit	7.9

Secondary: Change from Baseline in the ALSFRS-R total score at Week 48

End point title	Change from Baseline in the ALSFRS-R total score at Week 48

End point description:

The ALSFRS-R is a questionnaire-based rating scale that assesses the functioning of ALS participants across four domains: gross motor activity, fine motor activity, bulbar function, and respiratory function. The ALSFRS-R consists of 12 questions, each of which is scored on a 5-point scale from 0 to 4, where 4 is the best possible outcome and 0 is the worst. The total score is calculated by summing the responses to each of the 12 individual questions. The maximum total score is therefore 48; lower scores indicate worse functioning. If there were any missing responses to questions, the total score was set to missing. The Week 0 (Visit 2) value was considered to be the Baseline value. Change from Baseline was calculated by subtracting the derived Baseline value from the post-Baseline value. A mixed-model repeated measures adjusted for treatment, visit, treatment by visit, Baseline ALSFRS-R, Baseline ALSFRS-R by visit, riluzole use, and country group was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104[3]	101[4]		
Units: Scores on a scale				
least squares mean (standard error)	-9.1 (± 0.64)	-10.4 (± 0.64)		

Notes:

[3] - ITT Population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

[4] - ITT Population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0.4

Secondary: Rate of decline over Week 48 in the ALSFRS-R total score

End point title	Rate of decline over Week 48 in the ALSFRS-R total score

End point description:

The rate of decline was estimated by the change from Baseline in ALSFRS-R. The monthly slope for the ALSFRS-R score (i.e., the monthly rate of decline) was calculated as change from Baseline in the ALSFRS-R score at the last visit for that treatment period divided by the study day at the last visit for that treatment period /30.4. The Week 0 (Visit 2) value was considered to be the Baseline value. Change from Baseline was calculated by subtracting the derived Baseline value from the post-Baseline value. A random coefficients model with treatment, time, treatment by time, Baseline ALSFRS-R, Baseline ALSFRS-R by time, riluzole use, and country group in the model as fixed effects was used for the analysis. Time and intercept were included in the model as random effects.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149[5]	150[6]		
Units: monthly rate of change in ALSFRS-R				
least squares mean (standard error)	-0.84 (± 0.063)	-0.96 (± 0.062)		

Notes:

[5] - ITT Population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

[6] - ITT Population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg

Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173
Method	Random coefficients analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.05

Secondary: Change from Baseline in slow vital capacity (SVC) at Week 48

End point title	Change from Baseline in slow vital capacity (SVC) at Week 48

End point description:

SVC was measured by using a validated spirometer. Three SVC measurements were performed for each participant at each assessment provided the difference from the second trial (if arranged by the numerical value) was not greater than 10%. If the difference between the best and the next best (based on the largest numerical value) SVC value from the first three trials was greater than 10%, additional trials (up to 5 in total) could have been performed. The Week 0 (visit 2) value was considered to be the Baseline value. Change from Baseline was calculated by subtracting the derived Baseline value from the post-Baseline value. A mixed-model repeated measures (MMRM) adjusted for treatment, visit, treatment by visit, Baseline SVC, Baseline SVC by visit, riluzole use. and country group was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96[7]	98[8]		
Units: Liters (L)				
least squares mean (standard error)	-0.899 (± 0.0804)	-1.026 (± 0.0804)		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.265
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.351
upper limit	0.097

Secondary: Change from Baseline in muscle strength as measured by Hand Held Dynamometry (HHD) score at Week 48

End point title	Change from Baseline in muscle strength as measured by Hand Held Dynamometry (HHD) score at Week 48

End point description:

The HHD is a device placed between the hand of the practitioner and the tested body part and provides a quantified measurement of muscle strength. Each muscle was tested twice, and both values were recorded. Additionally, a third trial could have been performed if the variability between the first two trials was greater than 15 % or if the rater thought that one of the first two trials was not valid. The Week 0 (Visit 2) value was considered to be the Baseline value. Percent change from Baseline for each muscle group was calculated as 100*(HHD score minus the Baseline score) divided by the Baseline score. The average percent change was the mean percent change across the muscle groups that were non-missing/non-zero at Baseline. MMRM adjusted for treatment, visit, treatment by visit, number of non-missing/non-zero muscle groups at Baseline, number of non-missing/non-zero muscle groups at Baseline by Visit, riluzole use, and country group was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[9]	95[10]		
Units: Percent change				
least squares mean (standard error)	-34.7 (± 3.77)	-42.9 (± 3.75)		

Notes:

[9] - ITT Population

[10] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7
upper limit	2.3

Secondary: Number of clinical global impression-improvement scale (CGI-I) responders at Week 48

End point title	Number of clinical global impression-improvement scale (CGI-I) responders at Week 48

End point description:

The CGI-I scale is a single observer-rated item measuring global improvement relative to Baseline. The CGI-I score is rated on a 7-point scale, from 1 (very much improved) to 7 (very much worse). Participant status at Baseline was assessed using the Clinical Global Impression Severity scale (CGI-S), which is a 7-point scale (1: normal, not at all ill; 7: most extremely ill) used to rate the severity of the participant's illness. Participants achieving a score of 1-4 in the CGI-I at Week 48 were considered to be responders. A a logistic regression adjusted for CGI-S at Baseline, riluzole use, and world region was used for the analysis.

End point type	Secondary

End point timeframe:

Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101[11]	97[12]		
Units: Participants				
number (not applicable)	23	18		

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.49

Secondary: Overall survival at Week 48 and Week 60

End point title	Overall survival at Week 48 and Week 60

End point description:

Overall survival is defined as the time from randomization to death or censoring at the time point of analysis, whichever comes first. Kaplan Meier estimates at Week 48 were evaluated at Day 344. A participant was considered to have completed if he/she was censored at Day 344. Kaplan Meier estimates at Week 60 were evaluated at Day 428. A participant was considered to have completed if he/she was censored at Day 428. Confidence intervals were estimated using the Brookmeyer Crowley method. Results are shown as the estimated percentage of participants alive at Weeks 48 and 60. Week 48: Only on-treatment data (data within 21 days of the last dose) were analyzed. Week 60: Including off treatment data (data after 21 days after the last dose) were analyzed.

End point type	Secondary

End point timeframe:

Week 48 and Week 60

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[13]	152[14]		
Units: Percentage of participants surviving				
number (confidence interval 95%)				
Week 48	95.5 (92 to 99)	94.3 (90.4 to 98.1)		
Week 60	87.4 (81.5 to 93.3)	85.4 (79.4 to 91.3)		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 48

Comparison groups	Placebo v Ozanezumab 15 mg/kg

Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.986
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	2.89

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Week 60	
Comparison groups	Placebo v Ozanezumab 15 mg/kg
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.923
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.01

Secondary: Progression-free survival at Week 48

End point title	Progression-free survival at Week 48

End point description:

Progression-free survival at Week 48 is defined as the time from randomization to progression (decline of at least six points on the ALSFRS-R from Baseline) or death or censored at Week 48, whichever comes first. Kaplan Meier estimates at Week 48 were evaluated at Day 344. A participant was considered to have completed if he/she was censored at Day 344. Confidence intervals were estimated using the Brookmeyer Crowley method. Results are shown as the estimated percentage of participants alive and without disease progression at Week 48.

End point type	Secondary

End point timeframe:

Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[15]	152[16]		
Units: Percent participants without progression				
number (confidence interval 95%)	30.8 (23 to 38.6)	28.5 (21.1 to 35.9)		

Notes:

[15] - ITT Population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

[16] - ITT Population. Only on-treatment data (data within 21 days of the last dose) were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.642
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.42

Secondary: Change from Baseline in the EuroQol 5 dimensions-5 level short form (EQ-5D-5L) utility score at Week 48

End point title	Change from Baseline in the EuroQol 5 dimensions-5 level short form (EQ-5D-5L) utility score at Week 48

End point description:

The EQ-5D is a standardized measure of health status developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L QoI comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each of these dimensions, the participant self assigned a score: 1 (no problems); 2 (slight problems); 3 (moderate problems); 4 (severe problems); 5 (extreme problems). A utility score for each participant was calculated based on the value set for England. The Week 0 (Visit 2) value was considered to be the Baseline value. Change from Baseline was calculated by subtracting the derived Baseline value from the post-Baseline value. A mixed-model repeated measures adjusted for treatment, visit, treatment by visit, Baseline EQ5D, Baseline EQ5D by visit, riluzole use, and country group was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[17]	102[18]		
Units: Scores on a scale				
least squares mean (standard error)	-0.234 (± 0.0207)	-0.238 (± 0.0207)		

Notes:

[17] - ITT Population

[18] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Ozanezumab 15 mg/kg v Placebo
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.062
upper limit	0.053

Secondary: Change from Baseline in the amyotrophic lateral sclerosis assessment questionnaire-40 (ALSAQ-40) total score at Week 48

End point title	Change from Baseline in the amyotrophic lateral sclerosis assessment questionnaire-40 (ALSAQ-40) total score at Week 48

End point description:

The ALSAQ-40 is a disease specific health status assessment for individuals with ALS/motor neurone disease. The ALSAQ-40 is comprised of 40 questions measuring 5discrete dimensions of health status that are affected by the disease: physical mobility (10 items); activities of daily living and independence (10 items); eating and drinking (3 items); communication (7 items); emotional reactions (10 items). Participants were asked to indicate the frequency of each event by selecting one of five options (Likert scale: 0-4): never/rarely/sometimes/often/ always or cannot do at all. The total score (maximum possible score=160) was calculated by adding the five domain scores. A low score indicates a better health state. Change from Baseline was calculated by subtracting the derived Baseline value from the post-Baseline value. A mixed-model repeated measures adjusted for treatment, Visit, Treatment by Visit, and Baseline ALSAQ-40 total score was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo	Ozanezumab 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[19]	96[20]		
Units: Scores on a scale				
least squares mean (standard error)	19.2 (± 1.47)	20.6 (± 1.49)		

Notes:

[19] - ITT Population

[20] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Ozanezumab 15 mg/kg
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	5.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAE) and non-serious AEs were collected from the date of the first dose of study medication up to 21 days after the last dose of investigational product.

Adverse event reporting additional description:

AEs and SAEs were collected in members of the Safety Population, comprised of all participants in the treatment cohort who gave informed consent, were randomized, and received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo once every 2 weeks by intravenous infusion up to Week 46.

Reporting group title	Ozanezumab 15 mg/kg

Reporting group description:

Participants received ozanezumab 15 mg/kg once every 2 weeks by intravenous infusion up to Week 46.

Serious adverse events	Placebo	Ozanezumab 15 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 151 (30.46%)	47 / 152 (30.92%)	
number of deaths (all causes)	16	20	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Prostate cancer			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 151 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 151 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Euthanasia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	7 / 151 (4.64%)	12 / 152 (7.89%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 5	0 / 10	
Pneumonia aspiration			
subjects affected / exposed	4 / 151 (2.65%)	4 / 152 (2.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea			
subjects affected / exposed	3 / 151 (1.99%)	4 / 152 (2.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 151 (1.99%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 151 (0.66%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercapnia			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Respiratory distress			
subjects affected / exposed	2 / 151 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	2 / 151 (1.32%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Head injury			
subjects affected / exposed	2 / 151 (1.32%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Humerus fracture			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye penetration			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			

subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site pain			

subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	3 / 151 (1.99%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (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			
Amyotrophic lateral sclerosis			
subjects affected / exposed	2 / 151 (1.32%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cerebral haemorrhage			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Dyskinesia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor neurone disease			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parosmia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo positional			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 151 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral disorder			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary hypersecretion			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subileus			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 151 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 151 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 151 (1.32%)	4 / 152 (2.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lower respiratory tract infection			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Appendicitis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lobar pneumonia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Ozanezumab 15 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 151 (78.81%)	120 / 152 (78.95%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	68 / 151 (45.03%)	56 / 152 (36.84%)	
occurrences (all)	211	139	
Contusion			
subjects affected / exposed	18 / 151 (11.92%)	11 / 152 (7.24%)	
occurrences (all)	33	17	

Vascular disorders			
Haematoma			
subjects affected / exposed	10 / 151 (6.62%)	5 / 152 (3.29%)	
occurrences (all)	12	7	
Hypertension			
subjects affected / exposed	8 / 151 (5.30%)	4 / 152 (2.63%)	
occurrences (all)	8	4	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 151 (17.22%)	29 / 152 (19.08%)	
occurrences (all)	61	74	
Dizziness			
subjects affected / exposed	14 / 151 (9.27%)	16 / 152 (10.53%)	
occurrences (all)	17	16	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 151 (8.61%)	11 / 152 (7.24%)	
occurrences (all)	28	12	
Oedema peripheral			
subjects affected / exposed	12 / 151 (7.95%)	12 / 152 (7.89%)	
occurrences (all)	12	15	
Peripheral swelling			
subjects affected / exposed	7 / 151 (4.64%)	8 / 152 (5.26%)	
occurrences (all)	7	11	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 151 (7.95%)	25 / 152 (16.45%)	
occurrences (all)	13	31	
Constipation			
subjects affected / exposed	12 / 151 (7.95%)	23 / 152 (15.13%)	
occurrences (all)	14	26	
Nausea			
subjects affected / exposed	11 / 151 (7.28%)	14 / 152 (9.21%)	
occurrences (all)	14	18	
Dyspepsia			

subjects affected / exposed	4 / 151 (2.65%)	10 / 152 (6.58%)	
occurrences (all)	4	11	
Vomiting			
subjects affected / exposed	8 / 151 (5.30%)	5 / 152 (3.29%)	
occurrences (all)	10	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 151 (13.25%)	17 / 152 (11.18%)	
occurrences (all)	23	18	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 151 (3.31%)	8 / 152 (5.26%)	
occurrences (all)	5	12	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 151 (5.96%)	7 / 152 (4.61%)	
occurrences (all)	9	7	
Depression			
subjects affected / exposed	5 / 151 (3.31%)	11 / 152 (7.24%)	
occurrences (all)	5	11	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 151 (5.30%)	13 / 152 (8.55%)	
occurrences (all)	10	13	
Arthralgia			
subjects affected / exposed	9 / 151 (5.96%)	11 / 152 (7.24%)	
occurrences (all)	12	11	
Pain in extremity			
subjects affected / exposed	7 / 151 (4.64%)	13 / 152 (8.55%)	
occurrences (all)	10	15	
Musculoskeletal pain			
subjects affected / exposed	6 / 151 (3.97%)	11 / 152 (7.24%)	
occurrences (all)	6	12	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	32 / 151 (21.19%)	35 / 152 (23.03%)	
occurrences (all)	37	42	
Urinary tract infection			
subjects affected / exposed	10 / 151 (6.62%)	5 / 152 (3.29%)	
occurrences (all)	12	9	
Bronchitis			
subjects affected / exposed	8 / 151 (5.30%)	6 / 152 (3.95%)	
occurrences (all)	10	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2013	• Changes have been made to the statistical section to reflect the refinements made to the simulations used to calculate the power of the study. • An additional secondary analysis using the ALSFRS-R data has been added for consistency with other studies. • Secondary medical monitor details have been added, and the author list has been updated. • Text has been added to provide sites with some flexibility regarding duration of post-dose clinical monitoring once a patient has passed Week 24 (to alleviate patient burden). • Typographical error corrections and changes to text have been made to ensure clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 January 2013	Planned halt to recruitment following completion of recruitment of Part A participants. Recruitment commenced into Part B once confirmation was obtained from the IDMC.	13 May 2013

Notes:

Limitations and caveats

None reported