Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Efficacy and Safety of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravis

Summary

EudraCT number	2019-000968-18
Trial protocol	DK GB PL DE HU CZ BE ES IT
Global end of trial date	26 October 2021

Results information

Result version number	v1 (current)
This version publication date	06 November 2022
First version publication date	06 November 2022

Trial information

Trial identification

Sponsor protocol code	MG0003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03971422
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma SRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 1070
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2021
Global end of trial reached?	Yes
Global end of trial date	26 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate the clinical efficacy of rozanolixizumab in participants with generalized myasthenia gravis (MG)

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable

Actual start date of recruitment	03 June 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Georgia: 13
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	200
EEA total number of subjects	84

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)	151
From 65 to 84 years	47
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study started to enroll study participants in Jun 2019 and concluded in Oct 2021. Two participants randomized to RLZ ~7mg/kg, were administered RLZ ~10mg/kg at baseline visit. So, these two participants were included in RLZ ~7 mg/kg group in randomized set, but in RLZ ~10 mg/kg group in safety set.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set which consisted of all study participants who were randomized and analyzed according to the treatment assigned instead of the actual treatment received.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).

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

Dosage and administration details:

Participants received placebo at pre-specified time points.

Arm title	Rozanolixizumab ~7 mg/kg

Arm description:

Participants received rozanolixizumab (RLZ) equivalent to approximately 7 milligrams/kilogram (mg/kg) subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).

Arm type	Experimental
Investigational medicinal product name	Rozanolixizumab
Investigational medicinal product code	UCB7665
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received rozanolixizumab equivalent to approximately 7 mg at pre-specified time points.

Arm title	Rozanolixizumab ~10 mg/kg

Arm description:

Participants received rozanolixizumab equivalent to approximately 10 mg/kg subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).

Arm type	Experimental

Investigational medicinal product name	Rozanolixizumab
Investigational medicinal product code	UCB7665
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received rozanolixizumab equivalent to approximately 10 mg at pre-specified time points.

Number of subjects in period 1	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg
Started	67	66	67
Completed	42	43	43
Not completed	25	23	24
Worsening of MG Symptoms	1	4	2
Adverse event, not fatal	2	2	5
Roll over to MG0007 (NCT04650854)	10	6	9
Roll over to MG0004 (NCT04124965)	7	8	6
Lost to follow-up	-	1	-
Due to COVID-19 pandemic	-	1	1
Lack of efficacy	5	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).	
Reporting group title	Rozanolixizumab ~7 mg/kg
Reporting group description:	
Participants received rozanolixizumab (RLZ) equivalent to approximately 7 milligrams/kilogram (mg/kg) subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).	
Reporting group title	Rozanolixizumab ~10 mg/kg
Reporting group description:	
Participants received rozanolixizumab equivalent to approximately 10 mg/kg subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).	

Reporting group values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg
Number of subjects	67	66	67
Age Categorical Units: participants			
<=18 years	1	0	0
Between 18 and 65 years	50	49	51
>=65 years	16	17	16
Age Continuous Units: years			
arithmetic mean	50.4	53.2	51.9
standard deviation	± 17.7	± 14.7	± 16.5
Sex: Female, Male Units: participants			
Female	47	39	35
Male	20	27	32

Reporting group values	Total		
Number of subjects	200		
Age Categorical Units: participants			
<=18 years	1		
Between 18 and 65 years	150		
>=65 years	49		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: participants			
Female	121		
Male	79		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).	
Reporting group title	Rozanolixizumab ~7 mg/kg
Reporting group description:	
Participants received rozanolixizumab (RLZ) equivalent to approximately 7 milligrams/kilogram (mg/kg) subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).	
Reporting group title	Rozanolixizumab ~10 mg/kg
Reporting group description:	
Participants received rozanolixizumab equivalent to approximately 10 mg/kg subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).	
Subject analysis set title	Rozanolixizumab ~10 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received rozanolixizumab equivalent to approximately 10 mg/kg subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).	

Primary: Change from Baseline to Day 43 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) score

End point title	Change from Baseline to Day 43 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) score
End point description:	
The Myasthenia Gravis Activities of Daily Living (MG-ADL) is an 8-item patient-reported outcome (PRO) instrument developed on the basis of the Quantitative Myasthenia Gravis (QMG). The MG-ADL targeted symptoms and disability across ocular, bulbar, respiratory, and axial symptoms. The total MG-ADL score was obtained by summing the responses to each individual item (8 items; Grades: 0, 1, 2, 3), where 0 represents no symptoms or impaired performance and 3 represents the most severe symptoms or impaired performance. The total score ranges from 0 to 24, with a higher score indicating more disability. A positive change in the score indicates worsening and a negative change indicates improvement. The Randomized Set consisted of all study participants who were randomized and analyzed according to the treatment assigned instead of the actual treatment received.	
End point type	Primary
End point timeframe:	
Baseline and Day 43	

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	66	67	
Units: units on a scale				
least squares mean (standard error)	-0.784 (± 0.488)	-3.370 (± 0.486)	-3.403 (± 0.494)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~7 mg/kg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-2.586
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.091
upper limit	-1.249

Notes:

[1] - Mixed model repeated measure (MMRM) analysis of covariance (ANCOVA) model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[2] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~10 mg/kg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-2.619
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.994
upper limit	-1.163

Notes:

[3] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[4] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Secondary: Percentage of participants achieving Myasthenia Gravis-Activities of Daily Living (MG-ADL) response at Day 43

End point title	Percentage of participants achieving Myasthenia Gravis-Activities of Daily Living (MG-ADL) response at Day 43

End point description:

The MG-ADL is an 8-item PRO instrument developed on the basis of the QMG. The MG-ADL targeted

symptoms and disability across ocular, bulbar, respiratory, and axial symptoms. The total MG-ADL score was obtained by summing the responses to each individual item (8 items; Grades: 0, 1, 2, 3), where 0 represents no symptoms or impaired performance and 3 represents the most severe symptoms or impaired performance. The total score ranges from 0 to 24, with a higher score indicating more disability. A positive change in the score indicates worsening and a negative change indicates improvement. Study participants were classified as responders at Day 43 if the value was at least a 2-point improvement (decrease) from Baseline at Day 43. The Randomized Set consisted of all study participants who were randomized and analyzed according to the treatment assigned instead of the actual treatment received.

End point type	Secondary

End point timeframe:

Day 43

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	66	67	
Units: percentage of participants				
number (not applicable)	28.4	68.2	61.2	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Rozanolixizumab ~10 mg/kg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	Wald test
Parameter estimate	Odds ratio (OR)
Point estimate	4.273
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.653
upper limit	11.791

Notes:

[5] - The OR of responder rates is estimated and tested between treatment groups using logistic regression model with treatment group, Baseline MG-ADL score and stratification factor (MuSK+ or AChR+). An OR > 1 favours rozanolixizumab.

[6] - p-value is nominal. Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Rozanolixizumab ~7 mg/kg

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	Wald test
Parameter estimate	Odds ratio (OR)
Point estimate	5.765
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	14.882

Notes:

[7] - The OR of responder rates is estimated and tested between treatment groups using logistic regression model with treatment group, Baseline MG-ADL score and stratification factor (MuSK+ or AChR+). An OR > 1 favours rozanolixizumab.

[8] - p-value is nominal. Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Secondary: Change from Baseline to Day 43 in Myasthenia Gravis-Composite (MG-C) total score

End point title	Change from Baseline to Day 43 in Myasthenia Gravis-Composite (MG-C) total score

End point description:

MG-C scale is a validated assessment and scale tests 10 items with individual item being weighted differently. The items included ptosis/upward gaze (range: 0 [>45 second] - 3 [Immediate]), double vision on lateral gaze (range: 0 [>45 second] - 4 [Immediate]), eye closure (range: 0 [Normal] - 2 [severe weakness]), talking (range: 0 [Normal] - 6 [difficult to understand speech]), chewing (range: 0 [Normal] - 6 [gastric tube]), swallowing (range: 0 [Normal] - 6 [gastric tube]), breathing (range: 0 [Normal] - 9 [ventilator dependence]), neck flexion (range: 0 [Normal] - 4 [severe weakness]), shoulder abduction (range: 0 [Normal] - 5 [severe weakness]) and hip flexion (range: 0 [Normal] - 5 [severe weakness]), lower scores= lower disease activity. Total MG-C score was obtained by summing responses to each individual item and score ranges from 0 to 50, with lower scores indicating lower disease activity. A positive change indicates worsening and a negative change indicates improvement.

End point type	Secondary

End point timeframe:

Baseline and Day 43

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	66	67	
Units: units on a scale				
least squares mean (standard error)	-2.029 (± 0.917)	-5.930 (± 0.916)	-7.554 (± 0.934)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~10 mg/kg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001 [10]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-5.525
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.303
upper limit	-2.968

Notes:

[9] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[10] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~7 mg/kg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-3.901
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.634
upper limit	-1.245

Notes:

[11] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[12] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Secondary: Change from Baseline to Day 43 in Quantitative Myasthenia Gravis (QMG) total score

End point title	Change from Baseline to Day 43 in Quantitative Myasthenia Gravis (QMG) total score

End point description:

The QMG is a validated assessment and the scale tested 13 items, including ocular and facial involvement, swallowing, speech, limb strength, and forced vital capacity. The total QMG score was obtained by summing the responses to each individual item (13 items; Responses: None=0, Mild=1, Moderate=2, Severe=3) and the score ranges from 0 to 39, with lower scores indicating lower disease activity. A positive change in the score indicates worsening and a negative change indicates improvement. The Randomized Set consisted of all study participants who were randomized and analyzed according to the treatment assigned instead of the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline and Day 43

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	66	67	
Units: units on a scale				
least squares mean (standard error)	-1.915 (± 0.682)	-5.398 (± 0.679)	-6.672 (± 0.692)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~7 mg/kg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001 [14]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-3.483
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.614
upper limit	-1.584

Notes:

[13] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.

[14] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~10 mg/kg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001 [16]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-4.756

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.821
upper limit	-2.859

Notes:

[15] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.

[16] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Secondary: Change from Baseline to Day 43 in the Myasthenia Gravis (MG) Symptoms Patient Reported Outcome (PRO) 'Muscle Weakness Fatigability' score

End point title	Change from Baseline to Day 43 in the Myasthenia Gravis (MG) Symptoms Patient Reported Outcome (PRO) 'Muscle Weakness Fatigability' score

End point description:

MG symptoms PRO instrument consisted of 42 items across 5 scales: ocular muscle weakness (items 1-5); bulbar muscle weakness (items 6-15); respiratory muscle weakness (items 16-18); physical fatigue (items 19-33) and muscle weakness fatigability (items 34-42). Participants were asked to choose response option that how frequently they experienced muscle weakness fatigability (items 34-42) over past 7 days using a 5-point Likert scale (1="none of the time" to 5="all of the time") for each item. Sum of each item score is linearly transformed to have all domain scores ranging from 0 to 100. Total score is calculated as: (sum of item scores within the scale)/(raw score range) x (total number of items in the scale)/(number of non-missing items in the scale) x100 and ranged from 0 to 100, where higher scores indicated severe symptoms. Randomized Set consisted of all study participants who were randomized and analyzed according to the treatment assigned instead of actual treatment received.

End point type	Secondary

End point timeframe:

Baseline and Day 43

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	66	67	
Units: units on a scale				
least squares mean (standard error)	-10.588 (± 3.034)	-23.029 (± 3.034)	-25.751 (± 3.095)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~7 mg/kg

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001 [18]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-12.441
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.804
upper limit	-4.089

Notes:

[17] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[18] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~10 mg/kg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.001 [20]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-15.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.596
upper limit	-6.45

Notes:

[19] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[20] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Secondary: Change from Baseline to Day 43 in the Myasthenia Gravis (MG) Symptoms Patient Reported Outcome (PRO) 'Physical Fatigue' score

End point title	Change from Baseline to Day 43 in the Myasthenia Gravis (MG) Symptoms Patient Reported Outcome (PRO) 'Physical Fatigue' score

End point description:

MG symptoms PRO instrument consisted of 42 items across 5 scales: ocular muscle weakness (items 1-5); bulbar muscle weakness (items 6-15); respiratory muscle weakness (items 16-18); physical fatigue (items 19-33) and muscle weakness fatigability (items 34-42). Study participants were asked to choose the response option that how frequently they experienced physical fatigue (items 19-33) over the past 7 days using a 5-point Likert scale (1="none of the time" to 5="all of the time") for each item. Sum of each item score is linearly transformed to have all domain scores ranging from 0 to 100. Total score is calculated as: (sum of item scores within the scale)/(raw score range) x (total number of items in the scale)/(number of non-missing items in the scale) x100 and ranged from 0 to 100, where higher scores

indicated severe symptoms. Randomized Set consisted of all study participants who were randomized and analyzed according to treatment assigned instead of actual treatment received.

End point type	Secondary

End point timeframe:

Baseline and Day 43

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	66	67	
Units: units on a scale				
least squares mean (standard error)	-10.637 (± 3.051)	-19.287 (± 3.046)	-25.459 (± 3.107)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~10 mg/kg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.001 [22]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-14.822
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.759
upper limit	-5.936

Notes:

[21] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.

[22] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~7 mg/kg

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.012 [24]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-8.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.058
upper limit	-0.134

Notes:

[23] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.

[24] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Secondary: Change from Baseline to Day 43 in the Myasthenia Gravis (MG) Symptoms Patient Reported Outcome (PRO) 'Bulbar Symptoms' score

End point title	Change from Baseline to Day 43 in the Myasthenia Gravis (MG) Symptoms Patient Reported Outcome (PRO) 'Bulbar Symptoms' score

End point description:

The MG symptoms PRO instrument consisted of 42 items across 5 scales: ocular muscle weakness (items 1-5); bulbar muscle weakness (items 6-15); respiratory muscle weakness (items 16-18); physical fatigue (items 19-33) and muscle weakness fatigability (items 34-42). Study participants were asked to choose response option that best described severity of bulbar muscle weakness (items 6-15) symptoms over past 7 days using a 4-point Likert scale (1="none" to 4="severe") for each item. Sum of each item score is linearly transformed to have all domain scores ranging from 0 to 100. Total score is calculated as: (sum of item scores within the scale)/(raw score range) x (total number of items in the scale)/(number of non-missing items in the scale) x100 and ranged from 0 to 100, where higher scores indicated severe symptoms. The Randomized Set consisted of all study participants who were randomized and analyzed according to the treatment assigned instead of the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Day 43

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	66	67	
Units: units on a scale				
least squares mean (standard error)	-3.519 (± 2.397)	-14.839 (± 2.406)	-14.224 (± 2.464)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated

Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~7 mg/kg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.001 [26]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-11.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.958
upper limit	-4.998

Notes:

[25] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[26] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A sequential testing procedure was used. The parallel gatekeeping testing procedure with a truncated Hochberg test was used to control the familywise type I error rate at a 2-sided alpha level of 0.05.

Comparison groups	Placebo v Rozanolixizumab ~10 mg/kg
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.001 [28]
Method	Lehmacher and Wassmer method
Parameter estimate	LS Mean Difference
Point estimate	-10.705
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.787
upper limit	-3.998

Notes:

[27] - MMRM ANCOVA model included treatment group, Baseline score, region, stratification factor (MuSK+ or AChR+) and treatment group by day (interaction term) as fixed factors and participant as a random effect.
[28] - Confidence intervals and p-values are based on stage-wise inverse normal combination using the Lehmacher and Wassmer method.

Secondary: Number of Participants With treatment-emergent adverse events (TEAEs)

End point title	Number of Participants With treatment-emergent adverse events (TEAEs)[29]

End point description:

A TEAE is defined as an AE starting on or after the time of first administration of investigational medicinal product (IMP) up to and including 8 weeks after the last dose. The Safety Set consisted of all randomized study participants who received at least one dose of IMP and analyzed according to the actual treatment the participants received. Two participants randomized to RLZ ~7mg/kg, were administered RLZ ~10mg/kg at baseline visit. So, these two participants were included in RLZ ~7 mg/kg group in randomized set, but in RLZ ~10 mg/kg group in safety set.

End point type	Secondary

End point timeframe:

From Baseline until End of Study Visit (up to Week 14)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	67	64	69	
Units: participants	45	52	57	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With treatment-emergent adverse events (TEAEs) leading to withdrawal of investigational medicinal product (IMP)

End point title	Number of Participants With treatment-emergent adverse events (TEAEs) leading to withdrawal of investigational medicinal product (IMP)[30]

End point description:

A TEAE is defined as an AE starting on or after the time of first administration of IMP up to and including 8 weeks after the last dose. The Safety Set consisted of all randomized study participants who received at least one dose of IMP and analyzed according to the actual treatment the participants received. Two participants randomized to RLZ ~7mg/kg, were administered RLZ ~10mg/kg at baseline visit. So, these two participants were included in RLZ ~7 mg/kg group in randomized set, but in RLZ ~10 mg/kg group in safety set.

End point type	Secondary

End point timeframe:

From Baseline until End of Study Visit (up to Week 14)

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Placebo	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	67	64	69	
Units: participants	2	2	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until End of Study Visit (up to Week 14)

Adverse event reporting additional description:

Safety Set was analyzed for TEAEs. Two participants randomized to RLZ ~7mg/kg, were administered RLZ ~10mg/kg at baseline visit. So, these two participants were included in RLZ ~7 mg/kg group in randomized set, but in RLZ ~10 mg/kg group in safety set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).

Reporting group title	Rozanolixizumab ~10 mg/kg

Reporting group description:

Participants received rozanolixizumab equivalent to approximately 10 mg/kg subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).

Reporting group title	Rozanolixizumab ~7 mg/kg

Reporting group description:

Participants received rozanolixizumab equivalent to approximately 7 mg/kg, subcutaneously on a weekly basis over a 6-week Treatment Period. After 6-week Treatment Period, participants were followed for up to 8 weeks (up to Week 14).

Serious adverse events	Placebo	Rozanolixizumab ~10 mg/kg	Rozanolixizumab ~7 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 67 (8.96%)	7 / 69 (10.14%)	5 / 64 (7.81%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Thoracic vertebral fracture			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis			
subjects affected / exposed	1 / 67 (1.49%)	2 / 69 (2.90%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis crisis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Rozanolixizumab ~10 mg/kg	Rozanolixizumab ~7 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 67 (38.81%)	42 / 69 (60.87%)	40 / 64 (62.50%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	5 / 64 (7.81%)
occurrences (all)	0	0	5
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 67 (19.40%)	26 / 69 (37.68%)	29 / 64 (45.31%)
occurrences (all)	31	51	54
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 67 (1.49%)	14 / 69 (20.29%)	8 / 64 (12.50%)
occurrences (all)	1	25	10
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 67 (13.43%)	11 / 69 (15.94%)	16 / 64 (25.00%)
occurrences (all)	14	18	18
Nausea			
subjects affected / exposed	5 / 67 (7.46%)	8 / 69 (11.59%)	5 / 64 (7.81%)
occurrences (all)	12	8	7
Vomiting			
subjects affected / exposed	1 / 67 (1.49%)	4 / 69 (5.80%)	1 / 64 (1.56%)
occurrences (all)	4	4	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 67 (2.99%)	5 / 69 (7.25%)	3 / 64 (4.69%)
occurrences (all)	2	5	4
Myalgia			

subjects affected / exposed	1 / 67 (1.49%)	4 / 69 (5.80%)	2 / 64 (3.13%)
occurrences (all)	1	4	9
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 67 (4.48%)	5 / 69 (7.25%)	1 / 64 (1.56%)
occurrences (all)	4	5	1
Urinary tract infection			
subjects affected / exposed	4 / 67 (5.97%)	2 / 69 (2.90%)	2 / 64 (3.13%)
occurrences (all)	4	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2019	Protocol Amendment 1 (dated 30 Oct 2019) was implemented to add an additional "other" efficacy endpoint (time to first rescue therapy), an additional exploratory objective and endpoint (tetanus IgG antibodies), amend 2 secondary endpoints (both patient-reported outcomes [PROs] with text added to include muscle/limb weakness in the score), and remove 2 "other" efficacy endpoints at each scheduled assessment during the Treatment and Observation Periods as follows: 1) value and change from Baseline in the MG Symptoms PRO multi-component total score and 2) value and change from Baseline in the enhanced MG Symptoms PRO total score.
04 March 2020	Protocol Amendment 2 (dated 04 Mar 2020) was implemented to incorporate the harmonization of inclusion criteria with studies performed across the rozanolixizumab development program, and include a new section to include temporary discontinuation of IMP in case of low IgG levels observed in study participants. Furthermore, additional blood and PK samples, as well details pertaining to a substudy were incorporated to provide the opportunity to increase confidence in the PK exposure from the selected doses and help clinically validate the ADA assay's drug tolerance through analysis of a drug onboard postdose sample as opposed to the predose samples that were likely to be below the limit of quantification (BLQ). Protocol Amendment 2 was an internally approved document, which was not implemented at the study sites or submitted to the regulatory authorities. Protocol Amendment 3 included changes related to the coronavirus disease 2019 (COVID-19) pandemic and incorporated the changes made in Protocol Amendment 2.
29 July 2020	Protocol Amendment 3 (dated 29 Jul 2020) was implemented to introduce the MG0007 study as the OLE study to MG0003 and closure of the MG0004 study once the MG0007 study was available, decrease the complexity of assessments to be performed (including revising the MG Impairment Index [MGII] from mandatory to optional), to clarify some operational aspects of the study, and to include the management of study participant treatment during the COVID-19 pandemic, including contingency measures.
23 February 2021	Protocol Amendment 4 (dated 23 Feb 2021) included the following changes: • Updated the requirement for study participants who received rescue therapy to be followed up through to the end of the Observation Period • Updated the criteria for discontinuation due to other adverse events (AEs) or medical conditions • Remove the participant exit interview. • Additional updates have been incorporated to provide further clarity on the protocol and/or to correct errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	Due to Covid pandemic	29 May 2020

Notes:

Limitations and caveats

None reported