Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study

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Summary

Background Generalised myasthenia gravis is a chronic, unpredictable, and debilitating autoimmune disease. New treatments for this disease are needed because conventional therapies have limitations, such as side-effects (eg, increased infection risk) or inadequate control of symptoms. Rozanolixizumab is a neonatal Fc receptor blocker that might provide a novel therapeutic option for myasthenia gravis. We aimed to assess the safety and efficacy of rozanolixizumab for generalised myasthenia gravis.

Methods MycarinG is a randomised, double-blind, placebo-controlled, adaptive phase 3 study done at 81 outpatient centres and hospitals in Asia, Europe, and North America. We enrolled patients (aged ≥18 years) with acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) autoantibody-positive generalised myasthenia gravis (Myasthenia Gravis Foundation of America class II–IVa), a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 3 (non-ocular symptoms), and a quantitative myasthenia gravis score of at least 11. Patients were randomly assigned (1:1:1) to receive subcutaneous infusions once a week for 6 weeks of either rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, or placebo. Randomisation was stratified by AChR and MuSK autoantibody status. Investigators, patients, and people assessing outcomes were masked to random assignments. The primary efficacy endpoint was change from baseline to day 43 in MG-ADL score, assessed in the intention-to-treat population. Treatment-emergent adverse events (TEAEs) were assessed in all randomly assigned patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov (NCT03971422) and EudraCT (2019-000968-18); an open-label extension study has been completed (NCT04124965; EudraCT 2019-000969-21) and another is underway (NCT04650854; EudraCT 2020-003230-20).

Findings Between June 3, 2019, and June 30, 2021, 300 patients were assessed for eligibility, of whom 200 were enrolled. 66 (33%) were randomly assigned to rozanolixizumab 7 mg/kg, 67 (34%) to rozanolixizumab 10 mg/kg, and 67 (34%) to placebo. Reductions in MG-ADL score from baseline to day 43 were greater in the rozanolixizumab 7 mg/kg group (least-squares mean change –3·37 [SE 0·49]) and in the rozanolixizumab 10 mg/kg group (–3·40 [0·49]) than with placebo (–0·78 [0·49]; for 7 mg/kg, least-squares mean difference –2·59 [95% CI –4·09 to –1·25], p<0·0001; for 10 mg/kg, –2·62 [–3·99 to –1·16], p<0·0001). TEAEs were experienced by 52 (81%) of 64 patients treated with rozanolixizumab 7 mg/kg, 57 (83%) of 69 treated with rozanolixizumab 10 mg/kg, and 45 (67%) of 67 treated with placebo. The most frequent TEAEs were headache (29 [45%] patients in the rozanolixizumab 7 mg/kg group, 26 [38%] in the rozanolixizumab 10 mg/kg group, and 13 [19%] in the placebo group), diarrhoea (16 [25%], 11 [16%], and nine [13%]), and pyrexia (eight [13%], 14 [20%], and one [1%]). Five (8%) patients in the rozanolixizumab 7 mg/kg group, seven (10%) in the rozanolixizumab 10 mg/kg group, and six (9%) in the placebo group had a serious TEAE. No deaths occurred.

Interpretation Rozanolixizumab showed clinically meaningful improvements in patient-reported and investigator-assessed outcomes in patients with generalised myasthenia gravis, for both 7 mg/kg and 10 mg/kg doses. Both doses were generally well tolerated. These findings support the mechanism of action of neonatal Fc receptor inhibition in generalised myasthenia gravis. Rozanolixizumab represents a potential additional treatment option for patients with generalised myasthenia gravis.

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Introduction

Generalised myasthenia gravis is a rare, chronic, autoimmune neuromuscular disease, which is characterised by fluctuating muscle weakness and fatigue.[1] Exacerbations are unpredictable and are characterised by potentially severe symptoms affecting activities of daily living.[2] Myasthenic crises—during which symptoms worsen rapidly—can be life-threatening, and affect one in

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Research in context

Evidence before this study

We searched PubMed up to June 3, 2019, for relevant clinical studies in generalised myasthenia gravis, with no language restrictions. Key search terms included "FcRn inhibitor" and the article type selected was "randomised controlled trial". There remains a need for targeted treatments for generalised myasthenia gravis that do not have the limitations of conventional treatments, such as corticosteroids and immunosuppressants. These treatments can be limited by inadequate control of patients' symptoms, which can interfere with their daily activities and quality of life, comorbidities such as diabetes, osteoporosis, and hypertension, and side-effects such as increased infection risk. Neonatal Fc receptor (FcRn) blockade might provide an effective therapeutic option for myasthenia gravis and other IgG autoantibody-mediated autoimmune disorders by reducing the concentration of circulating IgG, including pathogenic autoantibodies. In most patients with myasthenia gravis, pathogenic IgG autoantibodies disrupt neuromuscular transmission by binding to either acetylcholine receptors (AChRs) or muscle-specific kinase (MuSK). When MycarinG was designed, no phase 3 study results had been published for FcRn inhibitors in myasthenia gravis. MycarinG was designed after a phase 2a study of rozanolixizumab in patients with moderate-to-severe myasthenia gravis. Although the primary efficacy endpoint of the phase 2 study was not met (no significant difference *vs* placebo), when considering all the prespecified efficacy measures, the results suggested that rozanolixizumab might provide clinical benefit in generalised myasthenia gravis, and the phase 3 MycarinG study was initiated. Rozanolixizumab was also under investigation in phase 2 studies in patients with chronic inflammatory demyelinating polyradiculoneuropathy and immune thrombocytopenia. Finally, an exploratory phase 2 trial of another FcRn inhibitor, efgartigimod, in patients with AChR autoantibody-positive generalised myasthenia gravis, was published in May, 2019, with a primary endpoint of safety and tolerability.

Added value of this study

MycarinG is a phase 3, randomised, placebo-controlled study of the FcRn inhibitor rozanolixizumab, which is subcutaneously administered once a week, in contrast to efgartigimod (intravenously administered). The study included patients with generalised myasthenia gravis who were either AChR or MuSK autoantibody positive, with a specific inclusion criterion of patients with MuSK-positive disease representing a novel aspect compared with the efgartigimod trial. Additionally, the study included several established myasthenia gravis-specific outcomes and the novel Myasthenia Gravis Symptoms Patient-Reported Outcomes scales, which provide more detailed assessment of some myasthenia gravis symptoms than existing measures.

Implications of all the available evidence

In the MycarinG study, compared with placebo, treatment with rozanolixizumab at doses of 7 mg/kg and 10 mg/kg once a week for 6 weeks was well tolerated and resulted in statistically significant and clinically meaningful improvements from baseline in the Myasthenia Gravis Activities of Daily Living score and other disease-related endpoints. These findings show that subcutaneous treatment with rozanolixizumab is efficacious in patients with both AChR-positive and MuSK-positive generalised myasthenia gravis. Together with data from the phase 3 trial of the FcRn inhibitor efgartigimod, these results support inhibition of FcRn as a treatment approach for generalised myasthenia gravis.

five patients.[3,4] The disease also negatively affects employment and social acceptance.[5] Myasthenia gravis costs almost US$100 000 per myasthenia gravis-related hospital admission, resulting in an overall cost of more than $500 million per year for all myasthenia gravis-related hospital admissions in the USA in 2013; in Europe, the total cost was more than €450 million per year in 2010.[6,7]

Conventional treatment for both acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) autoantibody-positive myasthenia gravis includes acetylcholinesterase inhibitors, corticosteroids, and non-steroidal immunosuppressant therapy, but these treatments do not completely alleviate symptoms or function loss in all patients, with symptoms remaining inadequately controlled in about 15% of people with myasthenia gravis.[8] Moreover, conventional treatments are burdensome, negatively affecting quality of life.[4,9] Corticosteroids and non-steroidal immunosuppressants, although effective for some, have many adverse effects, including diabetes and hypertension.[4,10] Intravenous immunoglobulin and plasma exchange are used as short-term treatments during both AChR and MuSK autoantibody-positive myasthenia gravis exacerbations or crisis, when a rapid response is needed, or less frequently as maintenance treatment if patients do not respond to immunotherapy.[4,10,11] Intravenous immunoglobulin and plasma exchange are time-consuming treatments, which can take place over several days and require specialised centres, which are not uniformly available.[10–12] Supply of intravenous immunoglobulin is inconsistent, limiting its availability, and plasma exchange is invasive.[10,11]

Muscle weakness in patients with MuSK autoantibody-positive generalised myasthenia gravis can be particularly severe, is more likely to affect swallowing and speech than the AChR autoantibody-positive subtype, and can be resistant to existing treatments, such as intravenous immunoglobulin.[13,14] MuSK autoantibody-positive generalised myasthenia gravis can respond well to plasma exchange, but this treatment has limitations.[12,15] Rituximab can be considered in patients with MuSK autoantibody-positive generalised myasthenia gravis who have an unsatisfactory response to initial immunotherapy,

although this treatment is not approved for this indication.[15,16]

In AChR autoantibody-positive generalised myasthenia gravis, IgG1 and IgG3 autoantibodies bind to AChRs, disrupting neuromuscular transmission via activation of the classic complement pathway, crosslinking between AChRs, and blocking acetylcholine binding to AChRs.[17,18] In MuSK autoantibody-positive generalised myasthenia gravis, IgG4 autoantibodies bind MuSK, disrupting neuromuscular transmission.[13,18] Reduction of IgG autoantibodies is therefore a possible therapeutic target for the treatment of generalised myasthenia gravis. The neonatal Fc receptor (FcRn) is a salvage and recycling mechanism that prolongs the half-life of serum IgG (including pathogenic IgG autoantibodies) by preventing lysosomal IgG degradation.[19] Rozanolixizumab is a humanised IgG4 monoclonal antibody targeting the IgG binding region of FcRn, reversibly inhibiting IgG salvage and recycling, accelerating IgG catabolism by the lysosomal degradation pathway, thus reducing IgG concentrations.[19]

In a phase 2 study, rozanolixizumab reduced total IgG and AChR antibody concentrations in patients with generalised myasthenia gravis.[20] Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Composite (MGC), and Myasthenia Gravis Activities of Daily Living (MG-ADL) scores improved in that study with rozanolixizumab, compared with placebo, although the change in QMG (primary outcome) did not differ significantly from placebo.[20] In the phase 3 MycarinG study, we aimed to study the safety and efficacy of rozanolixizumab in adults with AChR or MuSK autoantibody-positive generalised myasthenia gravis.

Methods

Study design and patients

MycarinG is a randomised, double-blind, placebo-controlled, parallel-group, two-stage adaptive, phase 3 study. The study followed a two-stage confirmatory adaptive design, with a formal interim analysis after stage 1 to assess futility, confirm rozanolixizumab doses to enter stage 2, and re-estimate the sample size to ensure adequate power.

Participants were recruited from 81 outpatient centres and hospitals in Asia, Europe, and North America (appendix pp 2–9). We enrolled patients (aged ≥18 years) with a diagnosis of generalised myasthenia gravis (Myasthenia Gravis Foundation of America class II–IVa disease) and presence of AChR or MuSK autoantibodies. Patients were eligible for the study if they had an MG-ADL score of at least 3 (for non-ocular symptoms) and a QMG score of at least 11, had been considered for treatment with additional therapy such as intravenous immunoglobulin or plasma exchange, and had a bodyweight of at least 35 kg. Key exclusion criteria were severe oropharyngeal or respiratory weakness, clinically relevant active infection or recent serious infection, a total IgG concentration of no more than 5·5 g/L, hypersensitivity to any components of the study medication, and pregnancy or breastfeeding. Permitted concomitant medications were cholinesterase inhibitors (stable dose not required), oral corticosteroids (stable for 4 weeks before baseline), azathioprine, ciclosporin, methotrexate, mycophenolate mofetil, and tacrolimus (all received for the previous 6 months and on a stable dose 2 months before baseline). Prohibited concomitant medications were intravenous immunoglobulin or plasma exchange (other than when used as rescue therapy), biological agents (including rituximab and eculizumab), cyclophosphamide, pimecrolimus, immunoadsorption, and vinca alkaloids. A complete list of eligibility criteria is provided in the appendix (pp 11–14).

A national, regional, or independent ethics committee or institutional review board (depending on site) approved the protocol (see appendix). All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1) to either rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, or placebo. Randomisation was stratified by presence of AChR or MuSK autoantibodies. After investigators had enrolled patients, interactive response technology (IRT) was used for central randomisation on the basis of a predetermined block randomisation schedule (block size of six) produced by the IRT vendor within each stratum. Investigators, patients, and those assessing outcomes were masked to treatment allocation and block size; study site pharmacists who prepared treatments had access to treatment allocations for individual patients. Masking was achieved by means of stickers to cover the syringes and adding saline solution to the 7 mg/kg dose to ensure the same volume between doses.

Procedures

Rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, or placebo were administered once a week for 6 weeks via subcutaneous infusion, with the dose adjusted for patient bodyweight (appendix p 10). Infusion volume was adjusted downwards for absolute (actual) dose (range 3–8 mL) by discarding excess medicinal product. Study drug was administered by health-care professionals via an infusion pump. The treatment period was 6 weeks' duration, followed by 8 weeks of observation. Patients who had disease worsening could be considered for rescue therapy (intravenous immunoglobulin or plasma exchange) at the investigator's discretion. Patients who received rescue therapy during the treatment period completed their remaining weekly visits in the treatment period (without receiving further study drug) before moving to the observation period. Patients who completed the observation period or whose disease severity worsened (investigator judgment) during the observation period could roll over from this trial to one of two open-label extension (OLE) trials (the MG0004 trial [completed; NCT04124965; EudraCT 2019-000969-21] or the MG0007 trial [ongoing; NCT04650854; EudraCT

See Online for appendix

2020-003230-20]). Patients who received rescue therapy during the observation period discontinued the trial and were not eligible for the OLE trials.

Outcomes

The primary efficacy outcome was change from baseline to day 43 in MG-ADL. Secondary efficacy outcomes were change from baseline to day 43 in MGC, QMG, and Myasthenia Gravis Symptoms Patient-Reported Outcome (PRO) scales (Muscle Weakness Fatigability, Physical Fatigue, and Bulbar Muscle Weakness), and MG-ADL response (based on the established clinically meaningful improvement on an individual patient level of ≥2 points)[21] at day 43. Other efficacy outcomes were MGC and QMG responses (based on the clinically meaningful improvement of ≥3 points)[22,23] at day 43, changes in MG-ADL, MGC, and QMG each week, changes in MG-ADL, MGC, and QMG excluding ocular items each week, changes in Myasthenia Gravis Symptoms PRO scales (Muscle Weakness Fatigability, Physical Fatigue, and Bulbar Muscle Weakness) each week, the proportion of patients with MG-ADL, MGC, and QMG response each week, time to MG-ADL response, minimal symptom expression (MG-ADL score of 0 or 1), change in Myasthenia Gravis Impairment Index (MGII) score, change in MGII ocular and generalised domain subscores, Patient Global Impression of Severity, Patient Global Impression of Change, change in Myasthenia Gravis Quality of Life 15-item scale revised score, European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L), use of rescue therapy, and time to rescue therapy.

Safety outcomes were treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation. Other safety outcomes were adverse events of special monitoring (severe headache, severe vomiting, severe diarrhoea, severe abdominal pain, or opportunistic infection), change from baseline in vital signs, electrocardiogram, laboratory values, and suicidality (Columbia Suicide Severity Rating Scale). Pharmacokinetic and pharmacodynamic outcomes were rozanolixizumab concentrations and change from baseline in myasthenia gravis-specific autoantibody and total and subclass IgG concentrations. Other outcomes were complement, cytokine, other immunoglobulin classes, anti-tetanus toxoid, anti-drug antibody, protein, and metabolite concentrations (appendix pp 15–17).

Statistical analysis

On the basis of historical data,[20,24–26] the sample size was selected to provide adequate power, assuming a mean change from baseline in MG-ADL between rozanolixizumab and placebo was in the range of 1·5–2·0, with an SD of between 3·5 and 4·0. A mean difference of more than 1·5 between treatment groups was judged to be clinically meaningful.[20,24] An interim analysis was done at the end of stage 1 after approximately 90 patients (n=30 per group) were evaluable for the primary endpoint (appendix pp 43–50). At the end of stage 1, a non-binding

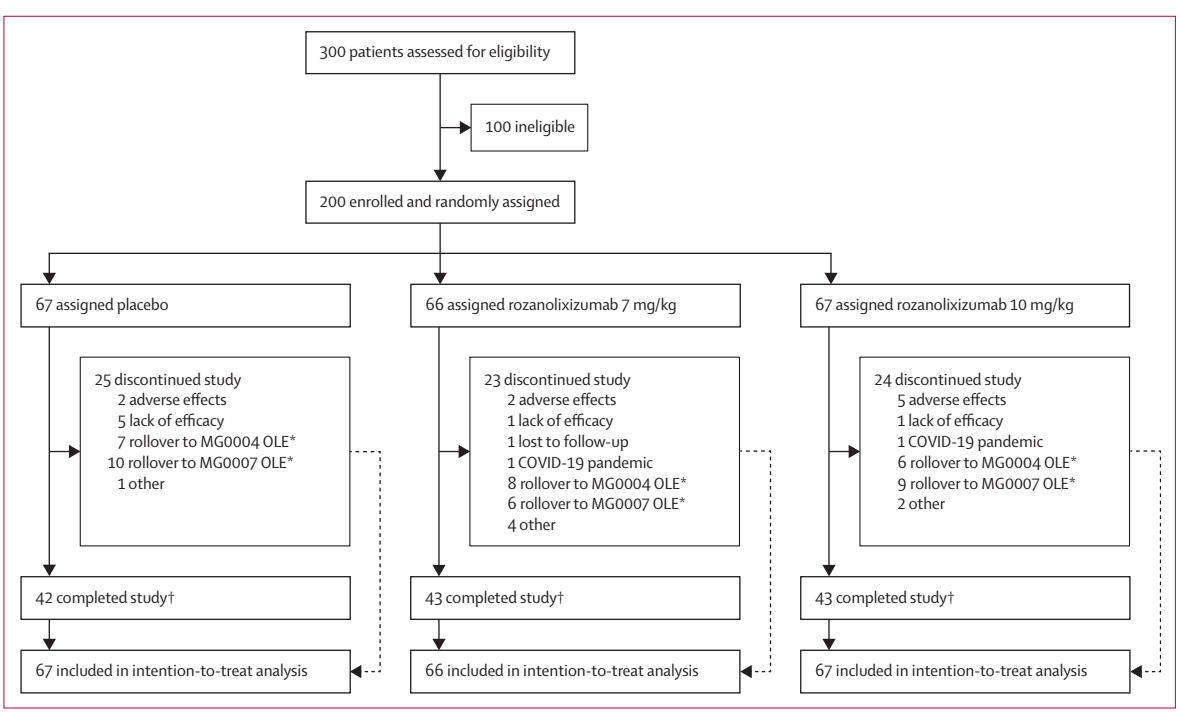

Figure 1: **Trial profile**

OLE=open-label extension. *Disease worsened (investigator judgment) during the observation period. †Completed both the treatment and observation periods. 64 patients completed the treatment period in each of the placebo and rozanolixizumab 7 mg/kg groups and 62 patients completed the treatment period in the rozanolixizumab 10 mg/kg group.

futility rule meant that the study could be stopped if the observed effect in both rozanolixizumab groups was inferior to placebo (ie, the nominal stage 1 p value of each dose >0·5 [one-sided]). If both rozanolixizumab groups were better than placebo, but the difference in mean MG-ADL score between groups was greater than one point, the group with the lowest response could be stopped. Early stopping for a positive treatment effect was not considered. If the study was not stopped for futility, the sample size could be increased, subject to a maximum cap, to provide an overall conditional power target of 90% based on the observed effect size in stage 1.[27] Depending on the selection of one, or two, of the rozanolixizumab doses after stage 1, a further 60 eligible study patients (up to a maximum of 150) were to be randomly assigned in stage 2 of the study. Thus, the total sample size of the study could range between 150 and 240 patients if the study was not considered futile at stage 1. Following the planned interim analysis of the first 92 patients who were evaluable for the primary endpoint after stage 1, both planned doses of rozanolixizumab were continued into the next stage with no increase from the planned additional 30 patients per group required (ie, a target sample size of 182 patients).

Patients in stage 1 represent those enrolled up to the formal interim analysis, and patients in stage 2 represent those included after the interim analysis. A patient was included only once in analyses, either in stage 1 or stage 2 as appropriate. At the interim analysis, a p value from the mixed model for repeated measures was computed for each pairwise comparison of rozanolixizumab versus placebo. As the trial was not stopped for futility, at the end of the trial, the p values computed at stage 1 and stage 2 were combined by means of the inverse-normal method of combination test[28] on the basis of the inverse-normal method of combination independent stagewise p values[29] to derive the combined p value for evaluation of the primary efficacy endpoint assuming equal weighting of each stage, with weights equal to $1/\sqrt{2}$. The least- squares mean (LSM) for each treatment group, and the stagewise combined LSM differences between each rozanolixizumab dose group and placebo, were reported for day 43, along with multiplicity-adjusted two-sided 95% CIs and combined p values.

The primary efficacy endpoint was analysed in all randomly assigned patients, by means of the treatment assigned for analysis (intention-to-treat). Safety outcomes were analysed in all randomly assigned patients who received at least one dose of treatment according to treatment actually received (safety set). The primary outcome was analysed with a stage-wise mixed model for repeated measures by means of an unstructured covariance pattern for the residual errors. The model included treatment group, baseline MG-ADL score, region, stratification factors MuSK and AChR auto-antibody status, and treatment group by day (interaction term) as fixed factors, and study patient was a random effect.

The primary endpoint was analysed with a hypothetical strategy for patients who had the intercurrent event of rescue therapy use, for which data at the time of and after the intercurrent event were set to missing. For patients having an intercurrent event of treatment discontinuation due to TEAEs, permanent discontinuation, or discontinuation because of COVID-19, a treatment policy strategy was used in which all available data were used. Missing MG-ADL scores (including missing data after intercurrent events) were handled on the basis of the maximum likelihood estimation method under the missing-at-random assumption. Change from baseline in MGC, QMG, and Myasthenia Gravis Symptoms PRO scale was analysed by means of the same two-stage approach as for the primary endpoint.

Statistical analysis accounted for multiplicity and controlled for the familywise type I error rate at a two-sided α level of 0·05 by means of a parallel gatekeeping testing procedure with a truncated Hochberg test for each of the six type-I error families (corresponding to the primary endpoint and five secondary endpoints). For the primary endpoint comparisons of each dose versus

	Placebo group (n=67)	Rozanolixizumab 7 mg/kg group (n=66)	Rozanolixizumab 10 mg/kg group (n=67)	All participants (n=200)
Age, years	50·4 (17·7)	53·2 (14·7)	51·9 (16·5)	51·8 (16·3)
Age category				
≤18 years	1 (1%)	0	0	1 (1%)
19 to <65 years	50 (75%)	49 (74%)	51 (76%)	150 (75%)
≥65 years	16 (24%)	17 (26%)	16 (24%)	49 (25%)
Female	47 (70%)	39 (59%)	35 (52%)	121 (61%)
Male	20 (30%)	27 (41%)	32 (48%)	79 (40%)
Bodyweight				
<50 kg	4 (6%)	7 (11%)	1 (1%)	12 (6%)
50 to <70 kg	16 (24%)	19 (29%)	26 (39%)	61 (31%)
70 to <100 kg	35 (52%)	26 (39%)	22 (33%)	83 (42%)
≥100 kg	12 (18%)	14 (21%)	18 (27%)	44 (22%)
Geographical region				
Europe	41 (61%)	36 (55%)	43 (64%)	120 (60%)
North America	21 (31%)	21 (32%)	18 (27%)	60 (30%)
Japan	4 (6%)	5 (8%)	4 (6%)	13 (7%)
Asia excluding Japan	1 (1%)	4 (6%)	2 (3%)	7 (4%)
Race				
White	46 (69%)	41 (62%)	49 (73%)	136 (68%)
Asian	5 (7%)	9 (14%)	7 (10%)	21 (11%)
Black	1 (1%)	0	4 (6%)	5 (3%)
Native Hawaiian or other Pacific Islander	1 (1%)	0	0	1 (1%)
American Indian or Alaska native	0	0	0	0
Missing*	14 (21%)	16 (24%)	7 (10%)	37 (19%)

(Table continues on next page)

	Placebo group (n=67)	Rozanolixizumab 7 mg/kg group (n=66)	Rozanolixizumab 10 mg/kg group (n=67)	All participants (n=200)
(Contined from previous page)				
Age at initial myasthenia gravis diagnosis, years	41·4 (19·1)	46·6 (16·0)	42·6 (19·1)	43·5 (18·2)
Duration of disease, years	6·8 (2·6–13·4)	5·3 (2·1–8·3)	5·7 (2·7–14·3)	5·8 (2·5–10·6)
Myasthenia Gravis Foundation of America disease class				
Class IIa	11 (16%)	13 (20%)	13 (19%)	37 (19%)
Class IIb	12 (18%)	16 (24%)	13 (19%)	41 (21%)
Class IIIa	28 (42%)	21 (32%)	26 (39%)	75 (38%)
Class IIIb	13 (19%)	13 (20%)	13 (19%)	39 (20%)
Class IVa	2 (3%)	3 (5%)	2 (3%)	7 (4%)
Class IVb	1 (1%)†	0	0	1 (1%)†
Medications				
Corticosteroids for systemic use	38 (57%)	43 (65%)	48 (72%)	129 (65%)
Immunosuppressants	33 (49%)	32 (48%)	38 (57%)	103 (52%)
Parasympathomimetics‡	60 (90%)	55 (83%)	57 (85%)	172 (86%)
Thymectomy	31 (46%)	32 (48%)	20 (30%)	83 (42%)
Myasthenia Gravis Activities of Daily Living score	8·4 (3·4)	8·4 (3·8)	8·1 (2·9)	8·3 (3·4)
Quantitative Myasthenia Gravis score	15·8 (3·5)	15·4 (3·7)	15·6 (3·7)	15·6 (3·6)
Total IgG, g/L	10·2 (2·6)	10·2 (3·2)	9·7 (2·6)	10·0 (2·8)
MuSK autoantibody-positive	8 (12%)§	5 (8%)	8 (12%)§	21 (11%)
AChR autoantibody-positive	59 (88%)¶	60 (91%)¶	60 (90%)	179 (90%)

Data are mean (SD), n (%), or median (IQR). AChR=acetylcholine receptor. MuSK=muscle-specific kinase. *Data on race were not permitted to be collected in certain countries. †Patient was classified as Myasthenia Gravis Foundation of America class III at screening, but class IVb at baseline. ‡Includes cholinesterase inhibitors. §Includes one patient who had positive AChR and MuSK autoantibody status. ¶Includes one patient who had unknown AChR and MuSK autoantibody status.

Table 1: **Baseline characteristics**

placebo (family 1), the Hochberg truncation parameter was set to 0, equivalent to use of a Bonferroni adjustment, for which each rozanolixizumab dose level was tested at a two-sided α level of 0·025. For families 2–5, the Hochberg truncation parameter was set to 0·2 each, and for the final family, the truncation parameter was 1.

The primary and secondary efficacy outcomes were evaluated for prespecified subgroups of interest, including sex (male or female) and autoantibody status (AChR or MuSK). Subgroup analyses were not part of the parallel gatekeeping testing procedure and, therefore, stricter 97·5% CIs were provided in keeping with the Bonferroni adjustment for the primary endpoint. Sensitivity analyses were done on the primary endpoint by means of a hypothetical and treatment policy strategy checking the robustness of the missing-at-random assumption by means of a jump-to-reference approach for missing data via multiple imputation, as well as a trimmed mean approach whereby missing data were imputed with a worst score, and an analysis that excluded patients with confirmed COVID-19.

Analyses were done with SAS version 9.3 or later. An independent data monitoring committee reviewed safety, efficacy, and interim analysis data.

This trial is registered with ClinicalTrials.gov (NCT03971422) and EudraCT (2019-000968-18).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report and manuscript, and the decision to submit for publication.

Results

Between June 3, 2019, and June 30, 2021, 300 patients were assessed for eligibility. Of these, 200 were randomly assigned to receive either rozanolixizumab 7 mg/kg (n=66 [33%]), rozanolixizumab 10 mg/kg (n=67 [34%]), or placebo (n=67 [34%]; figure 1). Baseline characteristics were generally similar between groups, with a slightly higher proportion of female patients in the placebo group than the rozanolixizumab groups and a slightly shorter duration of disease in the rozanolixizumab 7 mg/kg group than in the other groups (table 1). 179 (90%) patients were AChR autoantibody positive and 21 (11%) were MuSK autoantibody positive.

Greater reductions from baseline in MG-ADL were observed at day 43 (primary efficacy endpoint) for both rozanolixizumab 7 mg/kg (least-squares mean –3·37 [SE 0·49]) and rozanolixizumab 10 mg/kg (–3·40 [0·49]) groups than for the placebo group (–0·78 [0·49]), with least-squares mean differences from placebo of –2·59 (95% CI –4·09 to –1·25, p<0·0001) for rozanolixizumab 7 mg/kg and –2·62 (–3·99 to –1·16, p<0·0001) for rozanolixizumab 10 mg/kg (table 2). Sensitivity analyses were consistent with the primary analysis (appendix pp 35–42).

Reductions from baseline to day 43 in MG-ADL scores were observed in patients with AChR autoantibody-positive generalised myasthenia gravis (rozanolixizumab 7 mg/kg least-squares mean –3·03 [SE 0·89]; rozanolixizumab 10 mg/kg –3·36 [0·87]; placebo –1·10 [0·87]; least-squares mean difference from placebo –1·94 [97·5% CI –3·06 to –0·81] and –2·26 [–3·39 to –1·13] in the rozanolixizumab 7 mg/kg and 10 mg/kg groups, respectively). For patients with MuSK autoantibody-positive gMG, least-squares mean reductions were –7·28 [SE 1·94] in the rozanolixizumab 7 mg/kg group, –4·16 [1·78] in the rozanolixizumab 10 mg/kg group, and 2·28 [1·95] in the placebo group (least-squares mean difference from placebo for rozanolixizumab 7 mg/kg –9·56 [97·5% CI –15·25 to –3·87]; –6·45 [–11·03 to –1·86] for the rozanolixizumab 10 mg/kg group). Reductions were consistent across males (rozanolixizumab 7 mg/kg least-squares mean –3·12 [SE 0·91]; rozanolixizumab 10 mg/kg –2·85 [0·98]; placebo –0·50 [1·04]; least-squares mean reduction –2·62 [97·5% CI –4·88 to –0·35] in the rozanolixizumab 7 mg/kg group;

	Placebo (n=67)	Rozanolixizumab 7 mg/kg (n=66)			Rozanolixizumab 10 mg/kg (n=67)		
	Measure	Measure	Difference *vs* placebo	p value for difference	Measure	Difference *vs* placebo	p value for difference
MG-ADL score*	−0·78	−3·37	−2·59 (−4·09 to −1·25)	<0·0001	−3·40	−2·62 (−3·99 to −1·16)	<0·0001
MGC score	−2·03	−5·93	−3·90 (−6·63 to −1·25)	0·0004	−7·55	−5·53 (−8·30 to −2·97)	<0·0001
QMG score	−1·92	−5·40	−3·48 (−5·61 to −1·58)	<0·0001	−6·67	−4·76 (−6·82 to −2·86)	<0·0001
MG Symptoms PRO: Muscle Weakness Fatigability	−10·59	−23·03	−12·44 (−21·80 to −4·09)	0·0003	−25·75	−15·16 (−23·60 to −6·45)	<0·0001
MG Symptoms PRO: Physical Fatigue	−10·64	−19·29	−8·65 (−18·06 to −0·13)	0·0120	−25·46	−14·82 (−23·76 to −5·94)	0·0002
MG Symptoms PRO: Bulbar Muscle Weakness	−3·52	−14·84	−11·32 (−18·96 to −5·00)	0·0001	−14·22	−10·71 (−17·79 to −4·00)	0·0001
MG-ADL responders†	20/64 (31%)	46/64 (72%)	..	..	43/62 (69%)	..	..

Data are least-squares mean (95% CI) or n/N (%). MG-ADL=Myasthenia Gravis Activities of Daily Living. MGC=Myasthenia Gravis Composite. QMG=Quantitative Myasthenia Gravis. MG Symptoms PRO= Myasthenia Gravis Symptoms Patient-Reported Outcome. *Primary outcome. †Observed values; this outcome was not included in the hierarchical testing procedure.

Table 2: **Change from baseline to day 43 in primary and secondary efficacy outcomes**

−2·35 [−4·54 to −0·16] in the rozanolixizumab 10 mg/kg group) and females (rozanolixizumab 7 mg/kg least-squares mean −3·61 [SE 0·59]; rozanolixizumab 10 mg/kg −4·02 [0·59]; placebo −0·89 [0·55]; least-squares mean difference from placebo −2·71 [97·5% CI −4·20 to −1·22] in the rozanolixizumab 7 mg/kg group; −3·13 [−4·66 to −1·61] in the rozanolixizumab 10 mg/kg group).

Both rozanolixizumab groups showed statistically significant improvements compared with placebo for change from baseline to day 43 in MGC and QMG scores (table 2). Myasthenia Gravis Symptoms PRO scales were also significantly improved. Improvements from baseline in MG-ADL, MGC, QMG, and Myasthenia Gravis Symptoms PRO scores were seen as early as day 8 and throughout the treatment period, before returning towards baseline levels by day 99 (figure 2, appendix pp 18–19).

A greater proportion of patients in the rozanolixizumab groups than in the placebo group were MG-ADL responders (improvement of ≥2 points), MGC responders (≥3 points), and QMG responders (≥3 points) at day 43 (appendix pp 25–27). All five (100%) MuSK autoantibody-positive patients in the rozanolixizumab 7 mg/kg group with data available, and all seven (100%) patients in the rozanolixizumab 10 mg/kg group, were MG-ADL responders compared with one (14%) of seven in the placebo group. More patients achieved minimal symptom expression in both rozanolixizumab groups (17 [26%] patients in the rozanolixizumab 7 mg/kg group and 19 [28%] patients in the rozanolixizumab 10 mg/kg group) than in the placebo group (two [3%] patients; appendix p 19). No patients in the rozanolixizumab groups received rescue therapy during the treatment period (appendix p 19). Rapid reductions in total IgG were observed as early as day 8, with levels gradually increasing to approach baseline by day 99 (appendix p 23). Findings for other prespecified efficacy outcomes were supportive of the primary outcome (pp 18–19, 24, 28–31). Complete data can be made available on request as explained in the data sharing section.

The proportion of patients having any TEAEs and treatment-related TEAEs was similar between both rozanolixizumab groups and higher than the placebo group (table 3). Most TEAEs were mild to moderate. The most frequently reported TEAEs were headache, diarrhoea, pyrexia, and nausea. More headaches were reported in the rozanolixizumab groups than in the placebo group, occurring most frequently after the first infusion (data not shown). Of the patients who had headache in the rozanolixizumab 7 mg/kg group, the maximum intensity was mild in 17 (59%) of 29 patients, moderate in 11 (38%) of 29 patients, and severe in one (3%) of 29 patients. In the rozanolixizumab 10 mg/kg group, maximum headache intensity was mild in nine (35%) of 26 patients, moderate in 11 (42%) of 26 patients, and severe in six (23%) of 26 patients. In the placebo group, maximum headache intensity was mild in ten (77%) of 13 patients and moderate in three (23%) of 13 patients; no patients reported a severe headache. Generally, severe headache was well managed with non-opioid analgesics, and all patients recovered fully with no sequelae; no patients had severe headache recurrence. One (2%) patient in the rozanolixizumab 7 mg/kg group discontinued owing to a severe headache. One (1%) patient in the rozanolixizumab 10 mg/kg group had a severe headache classified as serious, which did not lead to treatment interruption, dose change, or discontinuation.

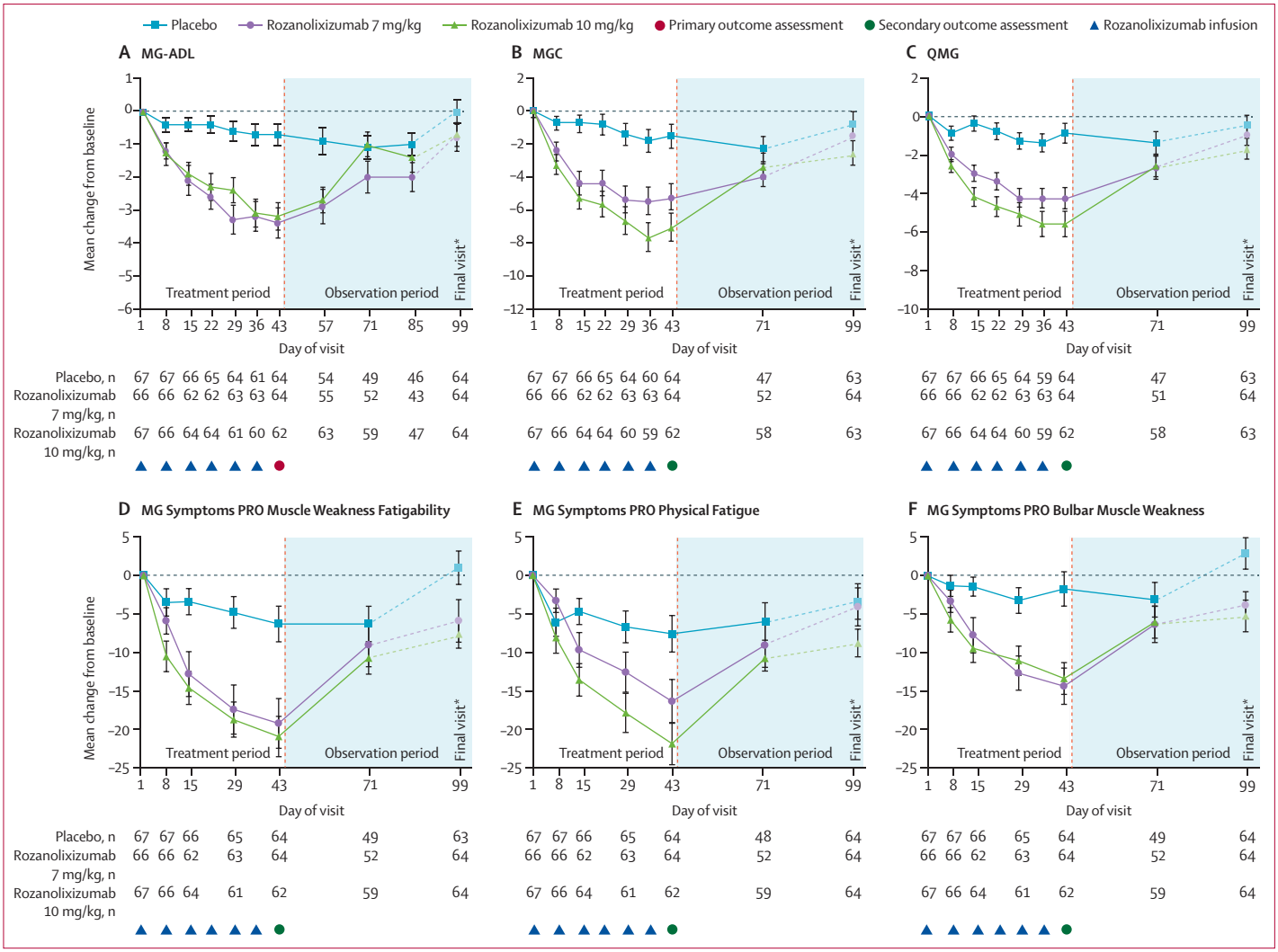

Figure 2: **Change from baseline to day 43 in primary and secondary endpoints**

Plots show change from baseline to day 43 in observed scores for MG-ADL (A), MGC (B), QMG (C), and MG Symptoms PRO Muscle Weakness Fatigability (D), Physical Fatigue (E), and Bulbar Muscle Weakness (F). Datapoints are observed mean change from baseline, and error bars show SEs. MG-ADL=Myasthenia Gravis Activities of Daily Living. MGC=Myasthenia Gravis Composite. MG Symptoms PRO=Myasthenia Gravis Symptoms Patient-Reported Outcomes. QMG=Quantitative Myasthenia Gravis. *Final visit could occur on any day up to day 99; investigators attempted to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

The rate of infections was similar between the rozanolixizumab 7 mg/kg (ten [16%]) and placebo (13 [19%]) groups, but higher in the rozanolixizumab 10 mg/kg group (21 [30%]). No severe or serious infections occurred in either rozanolixizumab group, with one (2%) serious infection (COVID-19 pneumonia) occurring in the placebo group. The most frequently reported infections (at least two patients in any group and more frequent in patients receiving rozanolixizumab than placebo) were nasopharyngitis (rozanolixizumab 7 mg/kg, one [2%]; rozanolixizumab 10 mg/kg, five [7%]; placebo, three [4%]), oral herpes (three [4%] in the rozanolixizumab 10 mg/kg group), and upper respiratory tract infection (two [3%], one [1%], and one [1%], respectively). No opportunistic infections occurred. Severe vomiting was reported in one (2%) patient in the rozanolixizumab 7 mg/kg group and severe diarrhoea was reported in two (3%) patients in the rozanolixizumab 10 mg/kg group; no patients in the placebo group reported severe vomiting or diarrhoea. Adverse events of special monitoring are reported in the appendix (p 34).

The proportion of patients with serious TEAEs was small and similar between both rozanolixizumab groups and the placebo group (table 3). All serious TEAEs reported in more than one patient in each treatment group were reported for the disease under investigation. A serious TEAE of myasthenia gravis worsening requiring admission to hospital occurred in one (2%) patient in the rozanolixizumab 7 mg/kg group during the treatment period and two (3%) patients in the rozanolixizumab 10 mg/kg group during the observation period. No myasthenia gravis crises occurred in the

rozanolixizumab groups, compared with two (3%) patients in the placebo group. The proportion of patients with severe TEAEs was similar in the rozanolixizumab 7 mg/kg and placebo groups, but higher in the rozanolixizumab 10 mg/kg group. The proportion of TEAEs leading to discontinuation was also similar in the rozanolixizumab 7 mg/kg (arthralgia and headache) and placebo (myasthenia gravis and myasthenia gravis crisis) groups, but higher in the rozanolixizumab 10 mg/kg group (diarrhoea, upper abdominal pain, vomiting, oral herpes, metastatic squamous cell carcinoma, pruritus, and deep vein thrombosis; some patients reported more than one of these events). No deaths occurred in the study.

No serious hypersensitivity or anaphylactic reactions occurred. Subcutaneous infusions were well tolerated, with no serious injection-site reactions. The frequency of injection-site reactions was low (four [6%] in the rozanolixizumab 7 mg/kg group, four [6%] in the rozanolixizumab 10 mg/kg group, and two [3%] in the placebo group). No injection-site reaction TEAEs occurred in more than one patient, except for injection-site rash, which was reported in two (3%) patients in the rozanolixizumab 7 mg/kg group (one treatment related) and no patients in the rozanolixizumab 10 mg/kg or placebo groups.

Vital signs measurements, electrocardiogram, haematology, clinical chemistry, and urinalysis laboratory results remained stable over time. No patients had active suicidal ideation during the study.

	Placebo (n=67)	Rozanolixizumab 7 mg/kg (n=64)*	Rozanolixizumab 10 mg/kg (n=69)*
Any TEAE†	45 (67%)	52 (81%)	57 (83%)
Headache	13 (19%)	29 (45%)	26 (38%)
Diarrhoea	9 (13%)	16 (25%)	11 (16%)
Pyrexia	1 (1%)	8 (13%)	14 (20%)
Nausea	5 (7%)	5 (8%)	8 (12%)
Arthralgia	2 (3%)	4 (6%)	5 (7%)
Nasopharyngitis	3 (4%)	1 (2%)	5 (7%)
Myalgia	1 (1%)	2 (3%)	4 (6%)
Vomiting	1 (1%)	2 (3%)	4 (6%)
Hypertension	0	5 (8%)	0
Urinary tract infection	4 (6%)	2 (3%)	2 (3%)
Any serious TEAE‡	6 (9%)	5 (8%)	7 (10%)
Myasthenia gravis	1 (1%)	1 (2%)	2 (3%)
Myasthenia gravis crisis	2 (3%)	0	0
Treatment discontinuation due to TEAE	2 (3%)	2 (3%)	4 (6%)
Treatment-related TEAEs	22 (33%)	32 (50%)	39 (57%)
Severe TEAEs	3 (4%)	3 (5%)	13 (19%)
Deaths	0	0	0

Data are n (%). TEAE=treatment-emergent adverse event. *Two patients in the 7 mg/kg group who incorrectly received 10 mg/kg were analysed in the 10 mg/kg group for pharmacokinetic–pharmacodynamic and safety analyses. †Specific TEAEs listed are those occurring in ≥5% of patients in any treatment arm. ‡Occurring in more than one patient in any treatment group.

Table 3: **Adverse events**

Discussion

The findings of the phase 3 MycarinG study showed that the FcRn inhibitor rozanolixizumab, at doses of 7 mg/kg and 10 mg/kg, had consistent and clinically meaningful efficacy across patient-reported and clinician-reported outcomes in patients with generalised myasthenia gravis, with both doses generally well tolerated. More patients receiving rozanolixizumab reached the established clinically meaningful improvement of at least 2 points for MG-ADL and at least 3 points for QMG and MGC,[21–23] and over a quarter of patients in the rozanolixizumab groups achieved minimal symptom expression (an MG-ADL score of 0 or 1), improving from a baseline mean MG-ADL score of 8·3. Baseline demographics were similar to other phase 3 studies of targeted therapies for myasthenia gravis, and the proportion of patients who were AChR and MuSK autoantibody positive was similar to the overall myasthenia gravis population.[18,24,30,31] 21 patients had MuSK autoantibody-positive generalised myasthenia gravis, and these patients had greater score reductions than did the overall population, with all MuSK autoantibody-positive patients who received rozanolixizumab and for whom data were available at day 43 achieving an MG-ADL response. As expected for an FcRn inhibitor, rozanolixizumab led to rapid reductions in IgG concentrations as early as day 8, which were associated with improvements in efficacy endpoints.

MycarinG included a novel PRO, the Myasthenia Gravis Symptoms PRO.[32] This measure contains more detailed assessments of muscle weakness and fatigability than existing PRO measures and includes assessment of physical fatigue, which is absent from other myasthenia gravis clinical outcome assessments.[33] Rozanolixizumab showed statistically significant improvements over placebo in all three prespecified domains: Muscle Weakness Fatigability, Physical Fatigue, and Bulbar Muscle Weakness. Clinically meaningful between-group differences and within-patient change are in the process of being defined.[34]

Response to rozanolixizumab was rapid, with improvements versus placebo seen as early as day 8, the first timepoint at which efficacy was assessed. Speed of onset appears similar to that of approved myasthenia gravis treatments such as the FcRn inhibitor efgartigimod and the complement inhibitors eculizumab and ravulizumab.[17,31,35]

In a previous phase 2 study of rozanolixizumab in patients with generalised myasthenia gravis, no significant difference between rozanolixizumab and placebo was observed for the primary endpoint of QMG.[20] In the phase 2 study, patients received three once-weekly infusions of rozanolixizumab 4 mg/kg or 7 mg/kg, with the primary endpoint measured 2 weeks after the final

dose. Taking into account the observation that better responses were achieved in the phase 2 trial when three additional weekly doses were administered and when efficacy was assessed 1 week after the last dose, we administered six once-weekly infusions of study medication and assessed efficacy 1 week after the last dose in MycarinG. In this phase 3 trial, both 7 mg/kg and 10 mg/kg doses of rozanolixizumab showed statistically significant differences versus placebo for the primary and all key secondary endpoints, including QMG. Improvements with 10 mg/kg appear greater than with 7 mg/kg for several secondary efficacy endpoints, suggesting a possible dose response; however, the study was not powered for comparison of doses.

Broad-spectrum immunosuppressants and corticosteroids typically used to treat myasthenia gravis are associated with side-effects that can be burdensome and, in many instances, the time until treatment effect is long.[4,10] Rozanolixizumab was generally well tolerated at both 7 mg/kg and 10 mg/kg doses. The most frequent adverse event was headache; the protocol did not require analgesic pretreatment and, consistent with previous studies, most headaches were mild to moderate, with severe headaches generally well managed with non-opioid analgesics.[20] As the IgG reduction associated with FcRn inhibition could lead to increased susceptibility to infections, infections were monitored. No severe, serious, or opportunistic infections were reported with rozanolixizumab. The rate of infections was similar between the placebo and rozanolixizumab 7 mg/kg groups, and higher with the rozanolixizumab 10 mg/kg group. In addition to its effect on IgG recycling, FcRn also helps prevent albumin degradation,[19] so albumin concentrations were monitored. However, rozanolixizumab binds FcRn remotely from the albumin binding site,[19] and no clinically meaningful decreases in mean albumin concentrations over time were observed, indicating that albumin salvage remains intact. The long-term safety of rozanolixizumab is being assessed from the completed OLE study MG0004 (NCT04124965) and the ongoing OLE study MG0007 (NCT04650854).

To our knowledge, MycarinG is the largest clinical trial in myasthenia gravis. [24,31] A strength of the trial includes the use of PROs, which are important in showing that treatment translates into clinically meaningful benefits. MG-ADL (a PRO) was the primary endpoint, complemented by the secondary outcomes of QMG, which is a clinician-reported outcome, and MGC, which is a composite outcome of both clinician-reported and patient-reported items. Although MG-ADL is widely used in myasthenia gravis trials and management, some aspects of patient experience are not reflected by this score, such as fatigue.[32,33] The Myasthenia Gravis Symptoms PRO measure was included as a secondary endpoint in the hierarchical testing procedure, which provides thorough assessment of symptom severity and effect of myasthenia gravis on patients' lives, including aspects such as fatigue, thereby complementing existing assessments.[32,33]

As frequently seen, the demographics of our study did not fully represent the demographics of the countries where the study was done (particularly the USA), with a lower proportion of Black patients recruited than in the general population.[36] This proportion is similar to other myasthenia gravis studies.[24,31] The population was relatively old, with a quarter of patients aged 65 years and older. This study only investigated one 6-week cycle of rozanolixizumab therapy; the safety and efficacy of repeated 6 weekly cyclic treatment is being investigated in the ongoing OLE study MG0007 to provide data on the safety and efficacy of rozanolixizumab over repeated treatment cycles. 95% of patients completed the treatment period of the MycarinG study, and around two-thirds of patients completed the observation period without rolling over into an OLE study. Around a quarter of patients rolled over into an OLE study after disease worsening during the observation period.

These results lend further support to the mechanism of action of FcRn inhibition in generalised myasthenia gravis. Rozanolixizumab and other new targeted therapies will provide more options and will prompt discussion around which treatments are most appropriate for which patients. Convenience and patient preferences will affect treatment decisions, because treatments with different modes of administration and dosing schedules will become available. Extension studies and real-world use will be needed to show long-term safety and effectiveness of rozanolixizumab.

MG0003 study investigators

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Contributors

MB, AB, MG, BG, FW, and VB designed the study. VB, AD, JG, AAH, RM, SS, KU, JV, TV, and HJK enrolled patients. FW did the statistical analysis. MB, AB, MG, FW, and VB developed the clinical study report. All authors accessed, verified, and interpreted the data. VB and FW have directly assessed and verified the underlying data reported in the manuscript. Ogilvy Health, a medical writing company, produced the

first draft of the paper on the basis of input and direction from all authors. All authors had full access to study data, reviewed, edited, and provided final approval of the manuscript content, and had final responsibility for the decision to submit for publication.

Declaration of interests

VB is a consultant for Grifols, CSL, UCB, argenx, Takeda, Alnylam, Octapharma, Pfizer, Powell Mansfield, Akcea, Ionis, Immunovant, Sanofi, Momenta (now J&J), Roche, Janssen, Alexion, and NovoNordisk. She has received research support from Alexion, Grifols, CSL, UCB, argenx, Takeda, Octapharma, Akcea, Momenta, Immunovant, Ionis, and Viela Bio (now Horizon). JG has served as a consultant for Biogen, Alexion, and UCB, and his institution has received research support from the Boris Canessa Foundation. AAH has received research support from argenx, Alexion, Cabaletta Bio, Viela Bio, UCB Pharma, Genentech, Regeneron, Sanofi, and Immunovant. He has received consulting fees or honoraria from argenx, Alexion, Immunovant, Regeneron, and UCB Pharma. RM has received funding for travel and meeting attendance or advisory board participation from Alexion, argenx, Biomarin, Catalyst, Sanofi, Regeneron, and UCB. KU has served as a paid Consultant for UCB Pharma, argenx, Janssen Pharma, Viela Bio, Chugai Pharma, Hanall BioPharma, and Mitsubishi Tanabe Pharma, and has received speaker honoraria from argenx, Alexion Pharmaceuticals, and the Japan Blood Products Organization. JV has been a consultant on advisory boards for Sanofi Genzyme, Sarepta Therapeutics, Viela Bio, Novartis Pharma, Fulcrum Therapeutics, Stealth Biotherapeutics, Roche, Biogen, Lupin, Genethon, Amicus Therapeutics, Zogenix, Regeneron, UCB Biopharma, Arvinas, ML Biopharma, Horizon Therapeutics, Pfizer, and Lundbeck Pharma; has received research, travel support, or speaker honoraria from Sanofi Genzyme, argenx, Alexion Pharmaceuticals, Biogen, Lupin, Stealth Biotherapeutics, Edgewise Therapeutics, Fulcrum Therapeutics, and UCB Biopharma, and is a principal investigator in clinical trials for Sanofi Genzyme, Roche, Horizon Therapeutics, argenx, Novartis Pharma, Alexion Pharmaceuticals, Stealth Biotherapeutics, Spark Pharmaceuticals, UCB Biopharma, Genethon, ML Biopharma, Reneo Pharma, Pharnext, Janssen Pharmaceuticals, Khondrion, Regeneron, Atamyo therapeutics, and Dynacure. TV is the USF site principal investigator for MG clinical trials sponsored by Alexion, argenx, Ra–UCB, Horizon–Viela Bio, Janssen–Momenta, Sanofi, Regeneron, and Cartesian Therapeutics, and receives speaking and consulting honoraria from Alexion, argenx, and UCB. HJK is a consultant for Roche, Cabeletta Bio, Lincoln Therapeutics, Takeda, and UCB Pharmaceuticals, and is CEO and CMO of ARC Biotechnology on the basis of US Patent 8,961,98; he is principal investigator of the Rare Disease Network for Myasthenia Gravis, National Institute of Neurological Disorders & Stroke, U54 NS115054, and Targeted Therapy for Myasthenia Gravis; and has received R41 NS110331-01 to ARC Biotechnology. MB, MG, BG, and FW are employees and shareholders of UCB Pharma. AB was an employee and shareholder of UCB Pharma during the conduct of the study, but is currently employed at Otsuka Pharmaceutical Commercialization and Development. AD and SS have nothing to disclose.

Data sharing

Data from this trial can be requested by qualified researchers 6 months after product approval in the USA or Europe, or global development is discontinued, and 18 months after trial completion. Investigators can request access to anonymised individual patient-level data and redacted trial documents, which might include analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Before use of the data, proposals need to be approved by an independent review panel and a signed data-sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal. This plan might change if the risk of re-identifying trial participants is established to be too high after the trial is completed. In this case, and to protect participants, individual patient-level data would not be made available.

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