

CADTH Horizon Scan

Emerging Drugs for Generalized Myasthenia Gravis

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Key Messages

- Horizon Scan reports provide brief summaries of information regarding new and emerging health technologies. These technologies are identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada. This Horizon Scan summarizes the available information regarding emerging targeted therapies for the treatment of generalized myasthenia gravis (MG).
- MG is a rare and chronic autoimmune disease in which autoantibodies attack specific proteins in the neuromuscular junction, resulting in muscle weakness. Many patients develop generalized MG resulting in severe fatigable muscle weakness with difficulties in facial expression, speech, swallowing, and mobility.
- Current treatments for MG include anticholinesterase inhibitors, systemic corticosteroids, and nonsteroidal immunosuppressive drugs. IV immunoglobulins or therapeutic plasma exchange are the current treatment options for patients with severe or acutely worsening generalized MG. Thymectomy is also considered a treatment option for patients with generalized MG who fail to respond to immunotherapy or have intolerable side effects.
- In this scan, we have reviewed 6 new treatment strategies that target specific areas of the immune system involved in the pathogenesis of MG: efgartigimod, rozanolixizumab, zilucoplan, ravulizumab, batoclimab, and nipocalimab. Phase II and III clinical trials have shown that these drugs may potentially benefit patients with generalized MG based on improvements in measures of disease severity and functional disability.
- The information presented is limited in that most of the available evidence comes from phase II trials that were designed to primarily investigate safety and tolerability based on small sample sizes, short trial duration, and narrow inclusion criteria. Therefore, findings do not reflect current standard of practice for maintenance therapy for generalized MG in the real-world setting.
- Considerations for future use include identifying the population that will most likely benefit from therapy and evaluating these drugs for rare and serious adverse events. Factors such as ease of administration, dosing schedule, and cost are all important factors that will help determine uptake and place in therapy for these emerging targeted therapies.

Methods

These bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a particular technology.

Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were efgartigimod, rozanolixizumab, zilucoplan,

batoclimab, and nipocalimab. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents but not limited by publication year.

Regular alerts updated the search until project completion; only citations retrieved before January 10, 2022 were incorporated into the analysis.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was an emerging drug under investigation for the treatment of MG with results (published or preliminary) from phase II or III clinical trials. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

Peer Review

A draft version of this bulletin was reviewed by 1 clinical expert. The manufacturers were also given the opportunity to comment on an earlier draft.

Background

Myasthenia gravis (MG) is a rare and chronic autoimmune disease in which immunoglobulin G (IgG) autoantibodies attack specific proteins in the neuromuscular junction, disrupting signal transmission.^{1,2} In approximately 85% of MG patients, these antibodies are targeted against acetylcholine receptors (AChR).³ Some patients have antibodies targeted against muscle-specific kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4), although as many as 15% of patients with MG are seronegative with no detectable autoantibodies in the blood.^{3,4} The thymus is thought to be involved in the production of anti-AChR antibodies.⁵ The age of onset follows a bimodal distribution, peaking at 30 and 50 years of age.⁶ Estimates of the incidence of MG range from 0.3 to 2.8 per 100,000 worldwide, and the median global estimated prevalence is 10 per 100,000.⁷ In Canada, the incidence has been stable over the last few decades and is estimated at 23 per 1 million person-years, with a prevalence of 263 per 1 million population.^{8,9}

Symptoms of MG include muscle weakness that often begins in the eyes and eyelids (ocular MG) affecting vision.² Many patients eventually develop generalized MG characterized by weakness in other areas of the body, including the head, neck, trunk, limbs, and chest. Patients with generalized MG experience fatigable muscle weakness with difficulties in facial expression, speech, swallowing, and mobility. Severity of the disease can vary for each individual patient due to periods of relapse and periods of remission. In extreme cases, MG can affect the muscles involved in breathing and could be life-threatening (known as myasthenic crisis). Currently, the frequency of mortality from the disease is estimated to be between 5% and 9%.¹⁰

Current treatments options for MG, including corticosteroids and nonsteroidal immunosuppressive therapies, broadly suppress the immune system and do not selectively target the autoantibodies that play a role in generalized MG pathophysiology.⁷ Long-term use of these conventional immunotherapies may be associated with the risk of intolerance and systemic toxicity.¹¹ Moreover, at least 15% of patients do not respond to these treatments.^{12,13}

In recent years, promising new treatment strategies that target specific areas of the immune system involved in the pathogenesis of MG have been explored and several clinical trials have recently been completed or are in progress.¹⁴ These new drugs aim to provide improved efficacy, less toxicity, a quicker onset of action, and better maintenance of disease remission compared to conventional immunotherapies for MG. Eculizumab (Soliris, Alexion Pharma Canada Corp.), the first of these new targeted therapies, was approved by Health Canada in 2018 for adult patients with refractory generalized MG.¹⁵ A CADTH Canadian Drug Expert Committee (CDEC) recommendation is available for the use of Soliris in this patient population.¹⁶ Rituximab, a monoclonal antibody directed against the CD-20 receptor on B-lymphocytes, is increasingly used in treating generalized MG. It has not been approved for this indication by Health Canada and as such is currently used off-label.

The Technologies

There are several emerging immunotherapies for the treatment of generalized MG (Table 1). These drugs have been developed to mitigate the effects of the autoantibodies involved in the pathogenesis of MG, resulting in an improvement in signal transmission at the neuromuscular junction.

Zilucoplan and ravulizumab work by blocking the C5 protein in the terminal complement cascade (a pathway in the immune system).¹⁷ Blocking the C5 protein reduces the over-activation of the complement cascade which occurs when pathogenic autoantibodies attack structures in the neuromuscular junction. Efgartigimod, rozanolixizumab, batoclimab, and nipocalimab all target the IgG binding site on the endogenous neonatal Fc receptor (FcRn).¹⁴ The FcRn plays a central role in rescuing IgG antibodies from degradation.¹⁸ IgG that is not bound to FcRn cannot be recycled and thus undergoes lysosomal degradation. These FcRn antagonists are expected to reduce serum levels of total IgG and pathogenic IgG autoantibodies involved in the pathogenesis of MG.

Regulatory Status

Efgartigimod (Vyvgart, Argenx US Inc.) was approved by the US FDA on December 17, 2021 for use in adults with generalized myasthenia gravis who test positive for the anti-acetylcholine receptor (AChR) antibody.²⁷ Zilucoplan has been granted orphan drug designation by the FDA for the treatment of MG.²⁸ Ravulizumab is approved by the Health Canada for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).²⁹

Cost

Cost information is not currently available given that these drugs are all still in clinical development and have not been approved for use in Canada or the US.

Target Population

These emerging targeted therapies are anticipated to be used for patients with severe refractory generalized MG as an adjunct to standard-of-care immunotherapies.

Current Practice

Treatment for MG is individualized and dependent on the rate of progression of symptoms, the presence of respiratory and bulbar involvement, the age of the patient, and the presence of anti-AchR or anti-MuSK antibodies.^{30,31} The main goal of treatment is to achieve long-term remission and improve functional ability and quality of life by reducing the severity of MG to mild or minimal symptoms. Treatment approaches include increasing the amount of acetylcholine available to bind with receptors and to decrease the binding of antibodies to AchR through immunosuppression.³⁰

The current mainstays of MG treatment include anticholinesterase inhibitors (e.g., pyridostigmine), systemic corticosteroids (e.g., prednisone), and nonsteroidal immunosuppressive agents (e.g., azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus).³⁰ It can take weeks to several months for these treatments to have a beneficial effect.³² Rapid immunomodulatory drugs (such as IV immunoglobulins or therapeutic plasma exchange) are the current treatment options for patients with severe or acutely

Table 1: Characteristics of Emerging Immunotherapies for the Treatment of Generalized MG

Generic name (development/brand name)	Manufacturer	Route of administration ^a
C5 complement inhibitors		
Zilucoplan ¹⁹ (RA101495)	UCB SA	Subcutaneous injection daily (self-administered at home)
Ravulizumab ²⁰ (ALXN-1210/Ultomiris)	Alexion AstraZeneca Rare Disease	IV infusion every 8 weeks
FcRn inhibitors		
Efgartigimod ²¹ (ARGX-113/Vyvgart)	Argenx	IV infusion once a week
Rozanolixizumab ²² (UCB7665)	UCB SA	Subcutaneous infusion once a week
Batoclimab ^{b23,24} (HBM9161/IMVT-1401/RVT-1401)	Harbour BioMed Immunovant	Subcutaneous injection every one or two weeks
Nipocalimab ²⁵ (M281)	Janssen Research and Development	IV infusion every two or four weeks

^aInvestigated in phase II or III clinical trials.

^bBatoclimab is being developed by Harbour Biomed and Immunovant for commercialization in Greater China (Hong Kong, Macau, and Taiwan) and North America (US and Canada), respectively.²⁶

worsening generalized MG. However, these therapies can be associated with high treatment burden (requiring IV preparations and long administration times), high cost and potential adverse effects.³³ Based on the results of an international randomized controlled trial,³⁴ guidelines were recently updated to recommend the consideration of thymectomy (surgical removal of the thymus gland) early in therapy to improve clinical outcomes in patients with generalized MG who are positive for anti-AchR antibodies and have no evidence of a thymoma (Thymoma, a tumour originating from cells in the thymus, is found in about 20% of patients, and is treated by thymectomy and sometimes radiotherapy).³⁰ Thymectomy is also considered a treatment option for patients with generalized MG who fail to respond to immunotherapy or have intolerable side effects, regardless if they are positive for anti-AchR antibodies. The guidelines also recommend that rituximab and eculizumab be considered for patients with disease refractory to conventional treatment.³⁰

Summary of Evidence

This section summarizes the available evidence of efficacy and safety for efgartigimod, rozanolixizumab, zilucoplan, ravulizumab, batoclimab, and nipocalimab in the treatment of generalized MG. The Myasthenia Gravis Foundation of America (MGFA) clinical classification was used in the trials to define disease severity (Appendix 1, Table 3).³⁵ Efficacy outcome measures included changes in the MG Activity of Daily Living (MG-ADL) scale and the Quantitative Myasthenia Gravis (QMG) scale (Appendix 1, Table 3).³⁶ The MG-ADL scale is a patient-reported outcome measure that assesses day-to-day functional disability while the QMG scale is an objective measure of disease severity based on clinical evaluation.³⁶

Efgartigimod

The characteristics of the published and ongoing trials investigating efgartigimod for generalized MG are depicted in Appendix 1, Table 4. One phase II trial³⁷ and 1 phase III trial (ADAPT)³⁸ evaluating the safety and efficacy of IV efgartigimod in adult patients with generalized MG have been published. The safety and efficacy of a subcutaneous (SC) formulation of efgartigimod is being studied in a phase III trial.³⁹ The long-term safety of the IV and SC formulations of efgartigimod is being evaluated in 2 single-arm, open-label extension studies.^{40,41} A phase III open-label study⁴² is investigating the efficacy and safety of a continuous IV regimen of efgartigimod compared with a cyclic IV regimen. In addition, an ongoing phase II/III trial⁴³ is assessing the safety and efficacy of IV efgartigimod in children and adolescents with generalized MG aged between 2 and 18 years.

Phase II Efficacy Results

In a double-blind phase II trial, 24 participants were randomized 1:1 to receive 4 weekly doses over a 3-week period of either 10 mg/kg IV efgartigimod or matched placebo in combination with stable standard-of-care MG treatment.³⁷ This treatment period was followed by an observation period with no infusions up to day 78. The clinical efficacy analysis was performed on the full analysis set which consisted of all randomized patients with 1 or more evaluable efficacy end points (including changes in the MG-ADL and QMG scores). More efgartigimod-treated patients (75%) showed a 2-point or greater improvement in the change from baseline in MG-ADL score for a period of at least 6 consecutive weeks compared to placebo-treated patients (25%). The difference in proportions was 50.34% (95% confidence interval [CI], 15.93 to 84.74; P = 0.0391).

Phase II Safety Results

The safety analysis consisted of data of all randomized patients who received at least 1 full or partial infusion of efgartigimod or placebo.³⁷ There were no deaths, serious adverse events (SAEs), severe treatment-emergent adverse events (TEAEs), or TEAEs that led to discontinuation during the study. One patient discontinued efgartigimod treatment because they received rescue therapy due to lack of efficacy. TEAEs occurred with equal frequency in each treatment group (83.3%; 10 of 12 for both groups). The majority of TEAEs were mild. A moderately severe headache was reported by 1 patient in the placebo group and a moderately severe episode of shingles on the arm preceded by infusion site pain was reported by 1 patient in the efgartigimod group who was also on prednisone and mycophenolate mofetil. The most frequently reported TEAE (any grade) in patients who received efgartigimod were headache (33.3%; 4 of 12 in efgartigimod group versus 25.0%; 3 of 12 in placebo group). Abnormal differential white blood cell counts were observed in 3 patients, 2 of which were on chronic cortisone and azathioprine and all cases were mild and asymptomatic.

ADAPT Trial Efficacy Results

ADAPT was a randomized, double-blind phase III trial evaluating the safety and efficacy of efgartigimod in 167 adult patients with generalized MG who were on a stable dose of at least 1 treatment for generalized MG.³⁸ Although patients were enrolled regardless of AchR-antibody status, the primary efficacy analysis was conducted on 129 patients positive for anti-AchR antibodies. Patients were randomly assigned 1:1 to efgartigimod 10 mg/kg IV or matching placebo, administered as 4 infusions per cycle (one infusion per week), repeated as needed depending on clinical response but no sooner than 8 weeks after initiation of the previous cycle. Of interest, although patients were required to be on a stable dose of at least 1 treatment for generalized MG, approximately 30% had never been treated with nonsteroidal immunosuppressants.

Results showed that more anti-AchR-antibody positive patients were responders following treatment with efgartigimod (67.7%; 44 of 65) than placebo (29.7%; 19 of 64) during the first treatment cycle (odds ratio [OR] 4.95; 95% CI, 2.21 to 11.53; $P < 0.001$). Responders were defined as having at least a 2-point improvement sustained for 4 or more consecutive weeks on the MG-ADL score. Additionally, the improvement in MG-ADL score was seen in the majority (84.1%; 37 of 44) of responders within the first 2 weeks of treatment. A subgroup analysis for patients who were anti-AchR-antibody negative showed that patients randomized to efgartigimod were only slightly more likely to respond based on the MG-ADL score (68.4%; 13 of 19 versus 63.3%; 12 of 19).

The percentage of QMG responders (patients with ≥ 3 -point improvement for at least 4 consecutive weeks with the first reduction in score occurring no later than 1 week after the last infusion) was greater in AChR-Ab seropositive patients treated with efgartigimod (63.1%; 41 of 65) than in AChR-Ab seropositive patients treated with placebo (14.1%; 9 of 64) during cycle 1 (OR 10.84; 95% CI, 4.18 to 31.20; $P < 0.0001$).

ADAPT Trial Safety Results

The safety analysis included all participants who received at least 1 full or partial dose of efgartigimod or placebo.³⁸ No deaths were reported and most TEAEs were mild or moderate in severity. SAEs were reported in 4.8% (4 of 84) of patients randomized to efgartigimod and in 8.4% (7 of 83) of those randomized to placebo. SAEs reported in the efgartigimod treatment group included thrombocytosis, renal adenocarcinoma, MG worsening (each leading to discontinuation) and depression. SAEs reported in the placebo group, included 1

case each of myocardial ischemia, atrial fibrillation, and spinal ligament ossification, which all led to treatment discontinuation. The remaining SAEs reported in the placebo group were upper respiratory infection, spinal compression fracture, MG worsening, and MG crisis.

The percentage of TEAEs reported in the efgartigimod group was 77.4% (65 of 84) compared to 84.3% (70 of 83) in the placebo group. The most common TEAEs were headache, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, and urinary tract infection. Of these, infections were more common in the efgartigimod group compared to the placebo group (46.4%; 39 of 84 versus 37.3%; 31 of 83). However, the infections were mild-to-moderate except for 3 severe events, which were influenza and pharyngitis in efgartigimod-treated patients and upper respiratory tract infections in the placebo group. Three patients in each treatment group (4%) discontinued treatment during the study.

Rozanolixizumab

The characteristics of the published, completed, and ongoing trials investigating SC rozanolixizumab for generalized MG are depicted in Appendix 1, Table 5. One phase II trial evaluating the clinical efficacy of rozanolixizumab as a chronic-intermittent treatment for generalized MG has been published.⁴⁴ A phase III randomized controlled trial (RCT) is further evaluating the efficacy and safety of rozanolixizumab in patients with generalized MG.⁴⁵ Two phase III single-group, open-label extension studies are evaluating the long-term safety of additional treatment cycles with rozanolixizumab.^{46,47}

Phase II Efficacy Results

The phase II double-blind trial consisted of 2 treatment periods followed by an observation period.⁴⁴ In period 1 (days 1 to 29), 43 adults with generalized MG were randomized 1:1 to receive 3 once-weekly SC infusions of rozanolixizumab 7 mg/kg or matched placebo. A treatment-free period of 2 weeks occurred between the last dose of period 1 (day 15) and initiation of period 2 (day 29). In period 2 (days 29 to 43) participants were re-randomized to 3 once-weekly SC infusions of rozanolixizumab 7 mg/kg or 4 mg/kg. This was followed by an observation period from days 44 to 99. Improvements from baseline to day 29 in QMG score was obtained for rozanolixizumab compared with placebo (least squares [LS] mean -1.8 versus -1.2 ; difference -0.7 ; 95% upper confidence limit [UCL] 0.8 ; $P = 0.221$). Improvements from baseline to day 29 in MG-ADL was observed following treatment with rozanolixizumab compared with placebo (LS mean -1.8 versus -0.4 ; difference -1.4 ; 95% UCL -0.4). Day 29 responder rates (with at least a 3-point improvement from baseline) were higher in patients receiving rozanolixizumab 7 mg/kg versus placebo for QMG (38% versus 23%) and MG-ADL (48% versus 14%). Efficacy measures continued to improve for patients during period 2 but were greater in patients receiving the 7 mg/kg dose.

Phase II Safety Results

No deaths were reported during the trial.⁴⁴ During period 1, SAEs were not reported in any patients receiving rozanolixizumab 7 mg/kg compared with 9% (2 of 22) of patients receiving placebo. By the end of the observation period (day 99), 5 of 43 (12%) reported 1 or more SAE. Headache was the most common TEAE which was reported in 38% (8 of 21) patients receiving rozanolixizumab 7 mg/kg and 9% (2 of 22) of patients receiving placebo. Overall, 4 rozanolixizumab-treated patients withdrew from the trial, 1 due to MG crisis (considered a SAE) and 3 due to headache (2 due to the pre-specified protocol withdrawal criteria of severe headache [1 of which was considered a SAE] and 1 moderately severe headache). Infusion site reactions occurred in 1 patient in each of the following groups:

placebo (4.5%, period 1), placebo/rozanolixizumab 4 mg/kg (9.1%, period 2), rozanolixizumab 7 mg/kg/ rozanolixizumab 7 mg/kg (10%, period 2). The incidence of infections between rozanolixizumab and placebo groups were similar.

Zilucoplan

The characteristics of the published and ongoing trials investigating SC zilucoplan for generalized MG are depicted in Appendix 1, Table 6. A phase II trial evaluating the safety and efficacy of 2 different doses of zilucoplan in patients with generalized MG has been published.⁴⁸ An ongoing phase III trial is further investigating the efficacy and safety of zilucoplan in patients with generalized MG who are on stable therapy.⁴⁹ An open-label extension study is evaluating the long-term efficacy and safety of zilucoplan in patients with generalized MG.⁵⁰

Phase II Efficacy Results

In a phase II double-blind trial, 44 patients were randomized 1:1:1 to receive once daily zilucoplan 0.3 mg/kg SC, zilucoplan 0.1 mg/kg SC, or matched placebo SC.⁴⁸ Study drug or placebo were self-administered at home. Treatment with zilucoplan 0.3 mg/kg resulted in improvements compared with placebo in QMG score at 12 weeks (LS mean [SEM] difference -2.8 [1.7]; $P = 0.05$) and MG-ADL score (-2.3 [1.3]; $P = 0.04$). A total of 10 patients (71.4%) in the zilucoplan 0.3 mg/kg group achieved an improvement in QMG score (at least a 3-point decrease) when compared with the placebo group (53.3%; 8 of 15) ($P = 0.27$). The zilucoplan 0.1 mg/kg group showed a delayed and less pronounced response than the 0.3 mg/kg group versus placebo at week 12 for the MG-ADL score (SEM difference -2.2 [1.3]; $P = 0.05$).

Phase II Safety Results

No deaths or life-threatening events were reported.⁴⁸ A total of 8 SAEs were reported, 5 (35.8%) with the higher dose of zilucoplan and 3 (20.0%) for the placebo group. The highest number of TEAEs occurred in the zilucoplan 0.1 mg/kg group (53.3%; 8/15) followed by the zilucoplan 0.3 mg/kg and placebo groups (21.4%; 3/14 and 20.0%; 3/15, respectively). The most common TEAE was headache which occurred more frequently in the zilucoplan groups (26.7%; 4 of 15 for 0.1 mg/kg and 14.3%; 2/14 for 0.3 mg/kg) compared with the placebo group (6.7%; 1 of 15). Injection-site reactions occurred in 3 (21.4%) of 14, 4 (26.7%) of 15, and 2 (13.3%) of 15 patients who received zilucoplan 0.3 mg/kg, zilucoplan 0.1 mg/kg, and placebo, respectively. All injection-site reactions in zilucoplan-treated patients were mild. All patients were vaccinated against *Neisseria meningitidis*, and no meningococcal infections were reported. Two patients discontinued the study before week 12 (1 placebo-treated patient owing to worsening MG and 1 patient receiving 0.3mg/kg zilucoplan due to a prolonged hospital admission for an exacerbation of preexisting diverticulitis with paracolic abscess).

Ravulizumab

The characteristics of 1 ongoing phase III trial⁵¹ investigating IV ravulizumab for generalized MG with preliminary results is depicted in Appendix 1, Table 7. Currently, there are no published or other ongoing trials.

Phase III Efficacy Results

In a phase III double-blind trial, 175 patients were randomized 1:1 to receive ravulizumab 10 mg/mL IV or matched placebo for a total of 26 weeks.⁵¹ Patients received a loading dose on day 1, followed by maintenance doses every 8 weeks beginning on day 15. Results from

a press release showed that the study met its primary end point, with a change in MG-ADL score from baseline through week 26 for patients receiving ravulizumab compared to those receiving placebo (ravulizumab -3.1 versus placebo -1.4; treatment difference -1.6; $P < 0.001$).⁵² A total of 30% of patients receiving ravulizumab experienced an improvement of at least 5 points in their QMG score compared to 11.3% of patients receiving placebo (P value not reported). The improvements in MG-ADL and QMG scores were observed by week 1 and were sustained through to week 26.

Phase III Safety Results

No deaths were reported in the preliminary results. Adverse events (AEs) were comparable between the ravulizumab and placebo groups. The most frequently observed SAEs were MG crisis (ravulizumab 1.2%) and MG worsening (placebo 3.4%). The most frequently observed AEs were headache (ravulizumab 18.6% versus placebo 25.8%), diarrhea (ravulizumab 15.1% versus placebo 12.4%) and nausea (ravulizumab 10.5% versus placebo 10.1%).

Patients who completed the randomized controlled period were eligible to continue into an ongoing open-label extension study evaluating the long-term safety of ravulizumab for up to 2 years. At the time of the preliminary analysis, 75 patients had completed 26 weeks of treatment in the extension study for a total of 52 weeks of treatment. Over 52 weeks, there were 4 deaths in the ravulizumab group (three due to COVID-19). No cases of meningococcal infection were observed during the 52-week period.

Batoclimab

The characteristics of the completed and ongoing trials investigating SC batoclimab for generalized MG are depicted in Appendix 1, Table 8. One phase II trial in patients with generalized MG has been completed with preliminary results.⁵³ An ongoing phase III is further evaluating the safety and efficacy of batoclimab in patients with generalized MG.

Phase II Efficacy Results

The phase II double-blind trial randomized 30 adult patients with generalized MG 1:1:1 to receive batoclimab 340 mg SC, batoclimab 680 mg SC or matching placebo once weekly for 6 weeks.⁵³ The treatment period was followed by an open-label extension study evaluating batoclimab 340 mg SC every other week for a further 6 weeks. Results obtained from a press release and abstract show that the batoclimab treatment groups demonstrated MG-ADL score improvement on day 43, by -4.7 (standard error [SE] 0.6) for the 340 mg group and -4.4 (SE 1.0) for the 680 mg group, respectively, compared with -2.2 (SE 0.9) for the placebo group ($P = 0.043$).^{54,55} A greater proportion of batoclimab-treated patients showed improvements in 2 weeks after first dose in the MG-ADL scale (defined as a score drop of at least 2 points) (57% versus 33% for placebo) and in the QMG scale (defined as a decline in score of 3 or more points) (76% versus 11% for placebo).

Phase II Safety Results

In preliminary results from the phase II trial, batoclimab treatment had an incidence of AEs comparable to placebo, with most AEs characterized as mild. No deaths, SAEs and no discontinuation due to AEs were reported.⁵⁴ Of note, clinical dosing in all clinical trials for batoclimab was voluntarily paused in February 2021 due to elevated low-density lipoprotein cholesterol levels (associated with an increased risk for heart disease) in an ongoing trial for thyroid eye disease.⁵⁶ Following a review of data from multiple clinical trials, it was determined that the increase was dose-dependent, reversible, and tied to a decrease in albumin (a protein

that helps regulate the transport of cholesterol). Clinical testing of batoclimab for generalized MG has since been resumed.

Nipocalimab

The characteristics of the completed and ongoing trials investigating IV nipocalimab for generalized MG are depicted in Appendix 1, Table 9. One phase II trial (Vivacity-MG) has been completed with preliminary results.⁵⁷ An open-label extension study of the Vivacity-MG trial originally intended to assess the long-term safety and tolerability of nipocalimab in generalized MG was halted due to the COVID-19 pandemic and later terminated.⁵⁸ An ongoing phase III double-blind, placebo-controlled RCT is investigating the efficacy and safety of nipocalimab in adult patients with generalized MG.⁵⁹ This study will consist of a screening phase (up to 4 weeks), treatment phase (a 24-week double-blind placebo-controlled phase) followed by an open-label extension phase of up to 2 years and a follow-up safety visit (up to 8 weeks after last infusion of study intervention). The overall duration of study will be up to 4 years and 8 months.

Vivacity-MG Efficacy Results

Vivacity-MG was a phase II double-blind, placebo-controlled RCT that evaluated the safety, tolerability, and efficacy of nipocalimab in 68 adults with generalized MG who did not have a sufficient clinical response to ongoing standard-of-care therapy.⁵⁷ Patients with anti-AChR or anti-MuSK antibodies were randomized to nipocalimab treatment groups at various doses or a placebo group. All patients received an IV infusion (either nipocalimab or placebo) every other week for a total of 5 infusions during the 8-week treatment period. Preliminary results obtained from a conference abstract show that treatment with nipocalimab resulted in greater mean improvement from baseline in MG-ADL scores across nipocalimab dosing arms compared with placebo at the end of the treatment period (day 57). A greater proportion of patients treated with nipocalimab showed improvement within 2 weeks of treatment in MG-ADL across all 4 dosing arms compared to placebo. A total of 51.9% of patients who received nipocalimab (all doses) were MG-ADL responders (defined as an MG-ADL improvement of 2 points or greater from baseline for at least 4 consecutive weeks during the first 8 weeks of treatment) versus 15.4% of those who received placebo (P = 0.017).

Vivacity-MG Safety Results

No deaths have been reported.⁵⁷ One SAE was reported in the nipocalimab group (shoulder pain) and 2 SAEs were reported in the placebo group (one case of ischemic stroke and 1 case of MG worsening). There were no discontinuations due to TEAEs in the nipocalimab group. The frequency of infections was higher in the nipocalimab combined dose group compared with the placebo group (33.3% versus 21.4%, respectively), but there were no severe or serious infections. The frequency of headaches in the nipocalimab groups were comparable to placebo.

Trial Limitations

- Most of the available evidence comes from phase II trials that were designed to primarily investigate safety and tolerability based on limited sample sizes, short trial duration, and narrow inclusion criteria. Therefore, findings do not reflect current standard of practice for maintenance therapy for generalized MG in the real-world setting.

- Most of the patients in the published clinical trials were White, middle aged individuals with MGFA class II or III disease severity. The generalizability of findings to older patients, other ethnic groups, and those with more severe disease is limited.
- Many trials did not evaluate safety and efficacy in certain subpopulations with MG including patients who were positive for anti-LRP4 or anti-MuSK antibodies, were seronegative for autoantibodies, were under the age of 18, were women who were pregnant or breastfeeding, or had comorbid conditions including other autoimmune disorders. Consequently, the utility of these drugs in these populations is not known.
- None of the published trials required patients to be refractory to standard-of-care MG treatment or have long-standing disease duration. Furthermore, some of the trials required patients to be on a stable treatment or excluded patients who had recently received rescue therapy for severe or acutely worsening generalized MG.
- Due to the short-term treatment period of most trials (up to 26 weeks), there is very limited long-term safety data for rare and serious adverse events (SAEs), given that these drugs are intended for a chronic disease. Long-term safety and efficacy will need to be confirmed in open-label extension trials.
- Some of the evidence presented for efficacy and safety was obtained from limited preliminary or unpublished results. Findings will need to be confirmed from peer-reviewed published results.

Concurrent Developments

Several other emerging therapies in phase II or III clinical development for generalized MG are awaiting published results (Appendix 1, Table 10). These include additional FcRn and C5 complement inhibitors, and therapies that target different areas of the immune pathway including B-cells (preventing the development of pathogenic autoantibodies that may be involved in the disease process of MG) and interleukin 6 (a cytokine that promotes the inflammatory response in autoimmune conditions).¹⁴ Of note, belimumab (Benlysta, GSK) and iscalimab (Novartis) were 2 other investigational B-cell inhibitors that failed to show benefit in phase II trials and are no longer in development for generalized MG.^{60,61}

Efgartigimod, rozanolixizumab, zilucoplan, batoclimab, and nipocalimab are also being evaluated for the treatment of patients with several other autoimmune or immune-related conditions (Appendix 1, Table 11).

Considerations for Future Uptake

The following are all factors to consider for the place in therapy and future uptake of emerging targeted therapies for generalized MG into clinical practice.

Target Population

There are many subgroups of interest for which there is no data or very limited data. This includes patients who are elderly, have severe or acutely worsening disease, are positive for anti-LRP4 or anti-MuSK antibodies, are seronegative, are people who identify as other than

White, are under the age of 18, are pregnant or breastfeeding women, or have a comorbid condition including another autoimmune disorder. Furthermore, a few trials excluded patients who had undergone thymectomy within a year of trial initiation. This is problematic given that current guidelines recommend considering thymectomy early in therapy to improve clinical outcomes in patients with generalized MG who are positive for anti-AchR antibodies or in those who fail to respond to immunotherapy or have intolerable side effects, regardless if they are positive for anti-AchR antibodies.³⁰ None of the published trials required patients to be refractory to standard-of-care MG treatment or have long-standing disease duration. Furthermore, some of the trials required patients to be on a stable treatment or excluded those who received rescue therapy for severe or acutely worsening MG. This does not reflect current standard of practice for maintenance therapy in the real-world setting.

Long-Term Safety

There is very limited long-term safety data for rare and SAEs, given that it is anticipated that these drugs are intended for a chronic disease. C5 complement inhibitors are known to increase the risk of meningococcal infections.¹⁷ For this reason, patients treated with C5 complement inhibitors need to be vaccinated against *Neisseria meningitidis* at least 2 weeks before treatment initiation and vaccination should be repeated after 2 years. There appears to be a signal for severe headache following treatment with rozanolixizumab. In addition, there is a signal for a higher frequency of infections with efgartigimod. Long-term safety and efficacy will need to be confirmed in open-label extension trials.

Optimal Use of Drugs

Given that generalized MG symptoms fluctuate, the need for initiation of therapy, discontinuation, and retreatment will require further investigation.³³ At present, there is no suggestion that the underlying generation of pathogenic autoantibodies is altered by targeted therapies.⁶² Therefore, discontinuation of therapy would be expected to lead to a return of muscle weakness. In addition, how to optimize use of targeted therapies in combination with conventional immunosuppressive therapies remains unknown.

Some of the emerging drugs for generalized MG have certain advantages in terms of dosing schedule and ease of administration. Those that have been formulated for SC injection (including rozanolixizumab, batoclimab, and zilucoplan) have the potential to be self-administered at home. These drugs may provide a more feasible option for some patients due to a lower treatment burden and decrease the use of health care resources required for IV infusion. Ravulizumab is being investigated for IV infusion every 8 weeks, which is currently the longest interval between treatments.

Cost

In Canada, the estimated annual cost for treatment with eculizumab for refractory generalized MG is over \$700,000.^{16,61} Cost-effectiveness studies will be required to help health care plans assess the value of new targeted therapies over current standard of care to determine place in generalized MG treatment.

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Appendix 1: Additional Information and Characteristics of Trials

Note that this appendix has not been copy-edited.

Table 2: Myasthenia Gravis Foundation of America Clinical Classification

Class ³⁵	Symptoms
Class I	Ocular muscle weakness only
Class II	Ocular and mild systemic weakness
Class III	Ocular and moderate systemic weakness
Class IV	Ocular and severe systemic weakness
Class V	Myasthenic crisis with respiratory failure requiring intubation
Subtypes ^a	<ul style="list-style-type: none"> • Predominately affecting limb and/or axial muscles (oropharyngeal muscles may be affected to lesser extent). • Predominantly affecting oropharyngeal and/or respiratory muscles (limb and/or axial muscles may be affected to lesser extent).

^aApplies to classes II to IV.

Table 3: Description of Key Outcome Measures

Key features	MG-ADL ⁶³⁻⁶⁵	QMG ^{65,66}
Instrument items	An 8-item patient-reported outcome measure assessing functional disability based on the following symptoms: <ul style="list-style-type: none"> • Ocular (2 items) • Bulbar (3 items) • Respiratory (1 item) • Limb (2 items) 	A 13-item physician evaluation that quantifies disease severity based on impairments documented using a spirometer and dynamometer: <ul style="list-style-type: none"> • Ocular (2 items) • Facial (1 item) • Bulbar (2 items) • Gross motor (6 items) • Axial (1 item) • Respiratory (1 item)
Score range ^a	0 to 24	0 to 39
Minimally important difference	2 points	Mild-to-moderate MG (baseline QMG score \leq 16): 2 points Severe MG (baseline QMG score \geq 16): 3 points

^aHigher score indicates greater severity of symptoms and functional disability.

MG-ADL = myasthenia gravis; MG-ADL = Myasthenia Gravis-specific Activities of Daily Living; QMG = Quantitative Myasthenia Gravis.

Table 4: Characteristics of Efgartigimod Trials

Author, year; Study name; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Published trials				
Howard et al., 2019 ³⁷ ARGX-113 to 1602 (NCT02965573) Argenx	Phase II, double-blind, RCT 78 days N = 24	Age ≥ 18 years MGFA class II to IVa AChR-antibody positive MG-ADL score ≥ 5 (≥ 50% total score attributable to nonocular symptoms) Stable dose of standard-of-care MG treatment	Intervention: Efgartigimod 10 mg/kg IV (n = 12) Comparator: Placebo IV (n = 12) Both given QW for 4 doses, followed by an 8-week observation period	Safety and tolerability
Howard et al., 2021 ³⁸ ADAPT (NCT03669588) Argenx	Phase III, double-blind, RCT 26 weeks N = 167 ^a	Age ≥ 18 years MGFA class II to IV AChR-antibody positive or negative MG-ADL score ≥ 5 (≥ 50% total score attributable to nonocular symptoms) Minimum 1 stable gMG therapy (acetylcholinesterase inhibitor, steroid, and/or nonsteroidal immunosuppressive drug)	Initial treatment cycle Intervention: Efgartigimod 10 mg/kg IV (n = 84) Comparator: Placebo IV (n = 83) Both given QW for 4 weeks, followed by 4 weeks with no infusions Subsequent treatment cycles The time between each treatment was individualized based on the duration of the patient’s clinically meaningful response as measured by the MG-ADL scale (maximum 3 treatment cycles in 26 weeks). Patients were eligible for retreatment if they met the following criteria: <ul style="list-style-type: none"> • ≥ 8 weeks since initiation of previous treatment cycle • Total MG-ADL score ≥ 5 points with at least 50% of the total score due to nonocular symptoms • Treatment cycle can be completed within the time frame of the trial (26 weeks) • For MG-ADL responders, no clinically meaningful improvement in MG-ADL (i.e., < 2-point reduction compared to the start of the cycle). 	Proportion of AChR-antibody positive patients with at least 2-point reduction in MG-ADL score for at least 4 consecutive weeks in the initial treatment cycle (8 weeks).

Author, year; Study name; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Ongoing trials				
ADAPT+ ⁴⁰ (NCT03770403) Argenx Completion: June 2023	Phase III, single-arm, open-label, extension study Up to 3 years N = 151	Age ≥ 18 years Participated in ADAPT trial and are eligible for roll over	Intervention: Efgartigimod IV (dosing and schedule not specified) Comparator: N/A	Incidence of treatment-emergent (serious) adverse events in AchR-positive population.
ADAPTSC ³⁹ (NCT04735432) Argenx Completion: November 2021	Phase III, open-label, RCT 12 weeks N = 111	Age ≥ 18 years MGFA class II to IV	Intervention: Efgartigimod PH20 SC (dosing and schedule not specified) Comparator: Efgartigimod IV (dosing and schedule not specified)	Percent change from baseline in total IgG levels at day 29.
ADAPTSC+ ⁴¹ (NCT04818671) Argenx Completion December 2021	Phase III, open-label, single-arm, extension study Up to 2 years N = 201	Age ≥ 18 years Previously enrolled in ADAPT or ADAPT+ and are eligible for rollover	Intervention: Efgartigimod PH20 1000 mg SC 3-week treatment periods, repeated as needed with at least 28 days in between treatment periods Comparator: N/A	Incidence and severity of adverse events, SAEs, and adverse events of special interest.
ADAPT NXT ⁴² (NCT04980495) Argenx Completion: October 2023	Phase III, open-label, RCT 128 weeks Part A: Regimen comparison period – 21 weeks. Part B: Extension period – up to 105 weeks. N = 72	Age ≥ 18 years MGFA class II to IV AChR-antibody positive MG-ADL score ≥ 5 (≤ 50% score due to nonocular symptoms) Stable dose of MG treatment (steroids or nonsteroidal immunosuppressive drugs)	Interventions Continuous regimen: Efgartigimod 10 mg/kg IV Q2W Cyclic regimen: Efgartigimod 10 mg/kg IV QW for 4 infusions per treatment period for 2 treatment periods with a fixed 4-week interval between each treatment period Comparator: N/A	Change in mean MG-ADL score from baseline at 21 weeks.

Author, year; Study name; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
ARGX-113 to 200643 (NCT04833894) Argenx Completion: December 2022	Phase II/III, open-label, single-arm 28 weeks Part A: Treatment duration for dose confirmation – 8 weeks. Part B: Treatment response period – 18 weeks N = 12	Children ≥ 2 and ≤ 18 years MGFA class II, III, and IVa AChR-antibody positive Unsatisfactory response to stable therapy of immunosuppressants, steroids, or acetylcholinesterase inhibitor	Intervention: Efgartigimod IV (dosing and schedule not specified) Comparator: N/A	Serum efgartigimod concentrations, total IgG levels, AChR-antibodies.

*Primary efficacy analysis was conducted on 129 adults with gMG positive for anti-AChR antibodies.

AChR = acetylcholine receptor; gMG = generalized myasthenia gravis; IgG = immunoglobulin G; MG = myasthenia gravis; MG-ADL = myasthenia gravis activities of daily living; MGFA = Myasthenia Gravis Foundation of America; PH20 = recombinant human hyaluronidase; QW = every week; Q2W = every two weeks; RCT = randomized controlled trial; SAE = serious adverse events; SC = subcutaneous.

Table 5: Characteristics of Rozanolixizumab Trials

Author, year: Name of study; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Published trials				
Bril et al., 2020 ⁴⁴ MG0002 (NCT03052751) UCB Biopharma SRL	Phase II, double blind, RCT Treatment period 1: Days 1 to 29 Treatment period 2: Days 29 to 43 Observation period: Days 44 to 99 N = 43	Age ≥ 18 years Positive for anti-AchR or anti-MuSK antibodies QMG score ≥ 11 at baseline Total serum IgG concentration > 6 g/L at screening Currently considered for IVIg or PLEX treatment	Treatment period 1 Intervention: Rozanolixizumab 7 mg/kg SC (n = 21) Comparator: Placebo SC (n = 22) Both given as 3 once-weekly infusions. Treatment period 2 Intervention: Rozanolixizumab 4 mg/kg SC (n = 21) Comparator: Rozanolixizumab 7 mg/kg SC (n = 21) Both given as 3 once-weekly infusions.	Change from baseline in QMG score at day 29.

Author, year: Name of study; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Completed trials (unpublished)				
MG0004 ⁴⁷ (NCT04124965) UCB Biopharma SRL Completion: September 2021	Phase III, open-label, single-group, extension study 60 weeks N = 71	Age ≥ 18 years Eligible for MG0003 or MGC003 trials at the time of enrolment Completed the observation periods of MG0003 or MGC003 or required rescue therapy during the observation period	Interventions: Rozanolixizumab regimen 1 SC or Rozanolixizumab regimen 2 SC (dosing and schedule not specified) Study participants will receive dosage originally assigned for initial cycle. Dosage regimen may be switched before the start of each subsequent treatment cycle based on investigator discretion. Comparator: N/A	Percentage of participants with TEAEs or TEAEs leading to withdrawal of investigational drug at 60 weeks.
Ongoing trials				
MG0003 ⁴⁵ (NCT03971422) UCB Biopharma SRL Completion: October 2021	Phase III, double-blind, RCT screening period: days 1 to 28 treatment period: 6 weeks observation period: 8 weeks N = 200	Age ≥ 18 years MGFA class II to IVa Positive for anti-AchR or anti-MuSK antibodies MG-ADL score ≥ 3 (with ≥ 3 points from nonocular symptoms) QMG score ≥ 11 Currently considered for IVIg or PLEX treatment	Interventions: Rozanolixizumab regimen 1 SC or Rozanolixizumab regimen 2 SC Comparator: Placebo SC (dosing and schedule not specified)	Change from baseline in MG-ADL score at day 43.
MG0007 ⁴⁶ (NCT04650854) UCB Biopharma SRL Completion: August 2023	Phase III, open-label, single-group, extension study 20 months N = 200	Age ≥ 18 years Completed MG0003, required rescue therapy during the observation period in MG0003, or completed at least 6 visits in MG0004	Interventions: Rozanolixizumab regimen 1 SC or Rozanolixizumab regimen 2 SC (dosing and schedule not specified) Study participants will receive dosage originally assigned for initial cycle. Dosage regimen may be switched before the start of each subsequent treatment cycle based on investigator discretion. Comparator: N/A	Percentage of participants with TEAEs Percentage of participants with TEAEs leading to withdrawal of investigational drug at 20 months.

AchR = acetylcholine receptor; IVIg = IV immunoglobulin; MG-ADL = myasthenia gravis activities of daily living; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle-specific kinase; PLEX = plasma exchange; QMG = quantitative myasthenia gravis; RCT = randomized controlled trial; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Table 6: Characteristics of Zilucoplan Trials

Author, year; Name of study; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Published trials				
Howard et al., 2020 ⁴⁸ (NCT03315130) Ra Pharmaceuticals	Phase II, double-blind, RCT 12 weeks N = 44	Age 18 to 85 years MGFA class II to IVa Positive for anti-AchR antibodies QMG score \geq 12 (with a score of \geq 2 on at least 4 items) No change in corticosteroid dose or immunosuppressive therapy for 30 days before baseline and during trial treatment period	Interventions: Zilucoplan 0.1 mg/kg SC daily (n = 15) Zilucoplan 0.3 mg/kg SC daily (n = 15) Comparator: Placebo SC daily (n = 15)	Change from baseline in QMG score at 12 weeks.
Ongoing trials				
RAISE ⁴⁹ (NCT04115293) Ra Pharmaceuticals Completion: December 2021	Phase III, double-blind, RCT 12 weeks N = 174	Age \geq 18 years MGFA class II to IV Positive for anti-AchR antibodies MG-ADL score \geq 6 QMG score \geq 12 No change in corticosteroid dose or immunosuppressive therapy for 30 days before baseline and during trial treatment period	Intervention: Zilucoplan 0.3 mg/kg SC daily Comparator: Placebo SC daily	Change from baseline in MG-ADL score at 12 weeks.
RAISE-XT ⁵⁰ (NCT04225871) Ra Pharmaceuticals Completion: December 2023	Phase III, open-label, single-arm, extension study 36 months N = 200	Age \geq 18 years Completion of a qualifying Ra Pharmaceuticals sponsored zilucoplan study	Interventions: Zilucoplan 0.3 mg/kg SC daily Comparator: N/A	Incidence of TEAEs during follow-up of up to 36 months.

AchR = acetylcholine receptor; MG = myasthenia gravis; MG-ADL = myasthenia gravis activities of daily living; MGFA = Myasthenia Gravis Foundation of America; QMG = quantitative myasthenia gravis; RCT = randomized controlled trial; SC = subcutaneous; TEAEs = treatment-emergent adverse events.

Table 7: Characteristics of Ravulizumab Trials

Author, year; Name of study; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Ongoing trials				
ALXN1210-MG-306 ⁵¹ (NCT03920293) Alexion Pharmaceuticals Completion: December 2021	Phase III, double-blind, RCT 26 weeks N = 175	Age ≥ 18 years MG diagnosis at least 6 months before screening MGFA class II to IV MG-ADL score ≥ 6 Vaccinated against meningococcal infections within 3 years before, or at the time of initiating trial	Intervention: Ravulizumab 10 mg/mL IV Comparator: Placebo IV Both given as a single weight-based loading dose on day 1, followed by regular weigh-based maintenance dosing beginning day 15 every 8 weeks.	Change from baseline in MG-ADL score at 26 weeks.

IgG = immunoglobulin G; MG-ADL = myasthenia gravis activities of daily living; MGFA = Myasthenia Gravis Foundation of America; RCT = randomized controlled trial.

Table 8: Characteristics of Batoclimab Trials

Author, year; Name of study; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Completed trials (unpublished)				
NCT04346888 ⁵³ Harbour BioMed	Phase II, double-blind, RCT Double-blind period: 6 weeks Open-label Extension period: 6 weeks N = 30	Age 18 to 99 years Moderate to severe gMG Positive for anti-AChR or anti-MuSK antibodies	Double-Blind Period Interventions: Batoclimab 340 mg SC QW (n = 10) Batoclimab 680 mg SC QW (n = 11) Comparator: Placebo SC QW (n = 9) Open-label Extension Period Batoclimab 340 mg SC Q2W	MG-ADL score at day 43 compared to baseline.
Ongoing trials				
NCT05039190 ⁶⁷ Harbour BioMed Completion: March 2023	Phase II/III, double-blind, RCT Double-blind period: 6 weeks Open-label Extension period: 6 weeks followed by 4-week observation period N = 144	Age 18 to 99 years MGFA class IIa to IVa Positive (n = 120) or negative (n = 24) for anti-AChR or anti-MuSK antibodies	Double-Blind Period Interventions: Batoclimab 680 mg SC QW Comparator: Placebo SC QW Open-label Extension Period^a Batoclimab 680 mg SC QW	Percentage of patients positive for anti-AChR or anti-MuSK antibodies with MG-ADL score reduction ≥ 3 points from baseline that persists for at least 64 days.

^aParticipants who completed the double-blind period started the open-label extension if they met dosing criteria at week 9.

AChR = acetylcholine receptor; MG-ADL = myasthenia gravis activities of daily living; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle-specific kinase; QW = every week Q2W = every 2 weeks; RCT = randomized controlled trial; SC = subcutaneous.

Table 9: Characteristics of Nipocalimab Trials

Author, year; Name of study; (NCT number); Funding	Design, Duration, Sample size	Population	Intervention (s), Comparator(s)	Primary outcome
Completed trials (unpublished)				
Antozzi et al., 2021 ⁵⁷ (conference abstract) Vivacity-MG (NCT03772587) Momenta Pharmaceuticals, Inc.	Phase II, double-blind, RCT 8 weeks N = 68	Age ≥ 18 years Moderate to severe gMG Positive for anti-AChR or anti-MuSK antibodies	Interventions: Nipocalimab 5 mg/kg IV Q4W Nipocalimab 30 mg/kg IV Q4W Nipocalimab 60 mg/kg IV Q2W Nipocalimab 60 mg/kg IV single dose Comparator: Placebo IV Q2W	Number of participants with adverse events (up to day 113) Change in MG-ADL score from baseline to day 57.
Ongoing trials				
CR109046 ⁵⁹ (NCT04951622) Janssen Research and Development, LLC Completion: February 2024	Phase III, double-blind, RCT Double-blind phase: 24 weeks Open-label extension: Up to 2 years N = 180	Age ≥ 18 years MGFA class II to IV MG-ADL score ≥ 6	Double-blind phase: Intervention: Nipocalimab IV Q2W (dose not specified) Comparator: Placebo IV Q2W Open-label extension: Intervention: Nipocalimab IV Q2W (dose not specified) (participants who are stable on Q2W dosing regimen may be transitioned to dosing Q4W) Comparator: N/A	Average change from baseline in MG-ADL score over weeks 22, 23 and 24.

AChR = acetylcholine receptor; gMG = generalized myasthenia gravis; MG = myasthenia gravis; MG-ADL = myasthenia gravis activities of daily living; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle-specific kinase; Q2W = every two weeks; Q4W = every four weeks; RCT = randomized controlled trial.

Table 10: Immunotherapies in Clinical Development for Generalized Myasthenia Gravis

Generic name (development or brand name), Manufacturer	Clinical development phase	Population	Trial completion	Regulatory status
FcRn inhibitors				
Orilanolimab ^{20,68} (ALXN1830) Alexion AstraZeneca Rare Disease	Phase II	Adults with generalized myasthenia gravis with who are positive for anti-AChR antibodies	January 2023	NR
Complement C5 inhibitors				
Pozelimab (REGN3918) plus emdisiran (CALN-CC5) ^{69,70} Regeneron	Phase III	Adults with generalized myasthenia gravis who are positive for anti-AchR or anti-LRP4 antibodies	February 2024	NR

Generic name (development or brand name), Manufacturer	Clinical development phase	Population	Trial completion	Regulatory status
B-cell inhibitors				
Mezagitamab ^{71,72} (TAK-079) Takeda	Phase II	Adults with generalized myasthenia gravis who are positive for anti-AChR or anti-MuSK antibodies	April 2022	NR
Inebilizumab-cdon ^{73,74} (MEDI-551) Horizon Therapeutics	Phase III	Adult with generalized myasthenia gravis who are positive for anti-AChR or anti-MuSK antibodies	June 2023	Approved by the US FDA for the treatment of adults with NMOSD. ⁷⁴
Descartes-08 ^{75,76} Cartesian Therapeutics	Phase I/II	Adults with generalized myasthenia gravis	November 2021	NR
RC18 ^{77,78} (Telitacicept) RemeGen	Phase II	Adults with generalized myasthenia gravis who are positive for anti-AChR or anti-MuSK antibodies	December 2021	Approved in China for patients with SLE. ⁷⁸
IL-6 inhibitors				
Tocilizumab ^{79,80} (Actemra) Hoffmann-La Roche	Phase II	Adult with generalized myasthenia gravis who are positive for anti-AChR antibodies	March 2024	Approved by Health Canada for the treatment of adult patients with moderately to severe active rheumatoid arthritis, adults with giant cell arteritis, children older than 2 years with certain types of arthritis, and patients with CAR T-cell induced cytokine release syndrome. ³⁴
Satralizumab ^{68,81} (Enspryng) Hoffmann-La Roche	Phase III	Patients over the age of 12 with generalized myasthenia gravis who are positive for anti-AChR, anti-MuSK, or anti-LRP4 antibodies	July 2023	Approved by Health Canada for the treatment of patients over the age of 12 with NMOSD. ⁸¹

AChR = acetylcholine receptor; CAR = chimeric antigen receptor; IL-6 = interleukin 6; LRP = lipoprotein receptor-related protein 4; NMOSD = neuromyelitis optica spectrum disorder; NR = not reported; MuSK = muscle-specific kinase; SLE = systemic lupus erythematosus.

Table 11: Developmental Phase for Additional Indications

Indication	Efgartigimod ²¹	Rozanolixizumab ²²	Zilucoplan ¹⁹	Ravulizumab ²⁰	Batoclimab ^{23,24}	Nipocalimab ²⁵
Primary immune thrombocytopenia	Phase III	Phase III	NR	NR	Phase II/III	NR
Warm autoimmune hemolytic anemia	NR	NR	NR	NR	Phase II	Phase II/III
Hemolytic disease of the fetus and newborn	NR	NR	NR	NR	NR	Phase II
Pemphigus vulgaris and Foliaceus	Phase III	NR	NR	NR	NR	NR
Chronic inflammatory demyelinating polyneuropathy	Phase II	Phase II	NR	NR	NR	NR
LGI1 autoimmune encephalitis	NR	Phase II	NR	NR	NR	NR
PNH	NR	NR	Phase II	Phase III	NR	NR
ALS	NR	NR	Phase II/III	Phase III	NR	NR
COVID-19	NR	NR	Phase III	Phase III	NR	NR
Graves' ophthalmopathy	NR	NR	NR	NR	Phase II/III	NR
NMOSD	NR	NR	NR	Phase III	Phase I	NR
Rheumatoid arthritis	NR	NR	NR	NR	NR	Phase II
Sjogren syndrome	NR	NR	NR	NR	NR	Phase II
SLE	NR	NR	NR	NR	NR	Phase II
Lupus nephritis	NR	NR	NR	Phase II	NR	Phase II
IgA nephropathy	NR	NR	NR	Phase II	NR	NR
Dermatomyositis	NR	NR	NR	Phase II/III	NR	NR
Atypical hemolytic uremic syndrome	NR	NR	NR	Phase III	NR	NR

Indication	Efgartigimod ²¹	Rozanolixizumab ²²	Zilucoplan ¹⁹	Ravulizumab ²⁰	Batoclimab ^{23,24}	Nipocalimab ²⁵
Thrombotic microangiopathy following HSCT	NR	NR	NR	Phase III	NR	NR

ALS = amyotrophic lateral sclerosis HSCT = hematopoietic stem cell transplantation; IgA = immunoglobulin A; LGI1 = leucine-rich glioma inactivated 1; NMOSD = neuromyelitis optica spectrum disorder; NR = not reported; PNH = paroxysmal nocturnal hemoglobinuria; SLE = systemic lupus erythematosus.