

Sustained Safety and Efficacy Profile of Active C1s Inhibitor Claseprubart in Patients with Generalized Myasthenia Gravis

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MAIN FINDINGS

- Long-term treatment with claseprubart in the open-label extension demonstrated a sustained efficacy profile over 65 weeks with no new safety findings.

- Patients switching from placebo to claseprubart in the extension showed rapid and robust improvements in efficacy endpoints during 52 weeks of treatment.

- Subcutaneous claseprubart 300mg Q2W and Q4W is being further evaluated in the ongoing phase 3 EMERGE trial in patients with gMG.

INTRODUCTION

- Generalized myasthenia gravis (gMG) is a chronic autoimmune disease caused by immunoglobulin G (IgG) autoantibodies targeting the acetylcholine receptor (AChR), leading to activation of the classical complement pathway and damage to the neuromuscular junction.¹
- Although currently approved C5 complement inhibitors can be effective for many patients, these therapies either require intravenous (IV) infusions or daily injections.^{2–4} Additionally, by targeting C5, these therapies block all three complement pathways and potentially increase the risk of acquiring life-threatening encapsulated bacterial infections.⁵
- Claseprubart (DNTH103) is an investigational monoclonal antibody that specifically inhibits the classical complement pathway upstream by selectively binding active C1s.
- Unlike currently approved complement inhibitors, claseprubart offers a more focused treatment approach in gMG by only blocking the classical pathway and leaving the lectin and alternative pathways intact (**Figure 1**).
- In the MaGic phase 2 study, subcutaneous (SC) Q2W claseprubart treatment was well-tolerated and resulted in clinically meaningful and statistically significant efficacy improvements compared to placebo in patients with AChR antibody-positive (Ab+) gMG.⁶
- Here, we report results from the ongoing MaGic study open-label extension.

- OLE-eligible patients must have completed the RCT without missing >1 dose. All patients entering the OLE received claseprubart 600mg Q2W for varying periods of time before the OLE dose was unified to 300mg Q2W following RCT analysis. Patients were assessed for safety and efficacy for up to 52 weeks. Patients who declined participation in the OLE were monitored for 40 weeks after the last study dose.

Study Population

- Adults aged 18–75 years (inclusive) with a diagnosis of AChR Ab+ gMG, Myasthenia Gravis Foundation of America (MGFA) Class II–IVa at screening and randomization, and Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥6 at screening and randomization.
- Individuals with current or prior use of a complement inhibitor, use of an anti-neonatal Fc receptor agent within 90 days of randomization, use of rituximab within 6 months, or IV immunoglobulin/plasma exchange within 4 weeks of randomization were not permitted to participate in the study.

Assessments in the OLE

- The primary assessment of the OLE is to evaluate the safety and tolerability of claseprubart.
- Efficacy assessments include change in MG-ADL, Quantitative Myasthenia Gravis (QMG) score, and Myasthenia Gravis Composite (MGC) score.
- Since benefit/risk of 300mg and 600mg were similar in the RCT portion of the study, safety and efficacy data in the OLE are presented as pooled analyses.

RESULTS

Safety Assessments

- Sixty-three patients completed the 13-week RCT and 60 enrolled in the OLE (**Table 1**). The median time between first and last/latest dose in the OLE is 50 weeks.
- Safety and tolerability of claseprubart in the OLE was consistent with the RCT, including no meningococcal infections.

Table 1. Disposition and Safety of Patients in the OLE.

Adverse event (AE)	13-week RCT period, n (%)		52-week OLE, n (%)
	Placebo (n=22)	Pooled SC claseprubart* (n=43)	All SC claseprubart (n=60)
Clinical AEs	11 (50.0)	28 (65.1)	45 (75.0)
Related serious AEs	1 (4.5)	0 (0.0)	1 (1.7) ^a
Discontinuation due to related AE	0 (0)	0 (0)	1 (1.7) ^b
Infections	10 (45.5)	11 (25.6)	28 (46.7)
Related serious infections	1 (4.5)	0 (0)	1 (1.7) ^a
Injection site reaction	0 (0)	4 (9.3)	1 (1.7)
Arthralgia	1 (4.5)	1 (1.7)	4 (6.7)
Myasthenia gravis exacerbation ^c	2 (9.1)	4 (9.3)	7 (11.7)

^aPatient with influenza who recovered and restarted claseprubart treatment (not considered related by sponsor). ^bPatient with arthritis. ^cDefined as worsening of disease regardless of receiving rescue treatment. No patients required respiratory intervention. During the RCT period two claseprubart patients received rescue treatment for the exacerbation and one patient had MG worsening attributed to missed pyridostigmine doses on the first day of claseprubart dosing (Day 1). During the OLE six patients received rescue therapy for the exacerbation. *Includes 21 patients who received claseprubart 300mg Q2W and 22 patients who received 600mg Q2W. Clinical AEs exclude events in the investigations System Organ Class (MedDRA). There was one death from a cardiovascular event deemed unrelated to claseprubart during the safety follow-up period in a 71-year-old male subject with a history of preexisting diabetes mellitus, hypertension, smoking, dyslipidemia and chronic obstructive pulmonary disease.

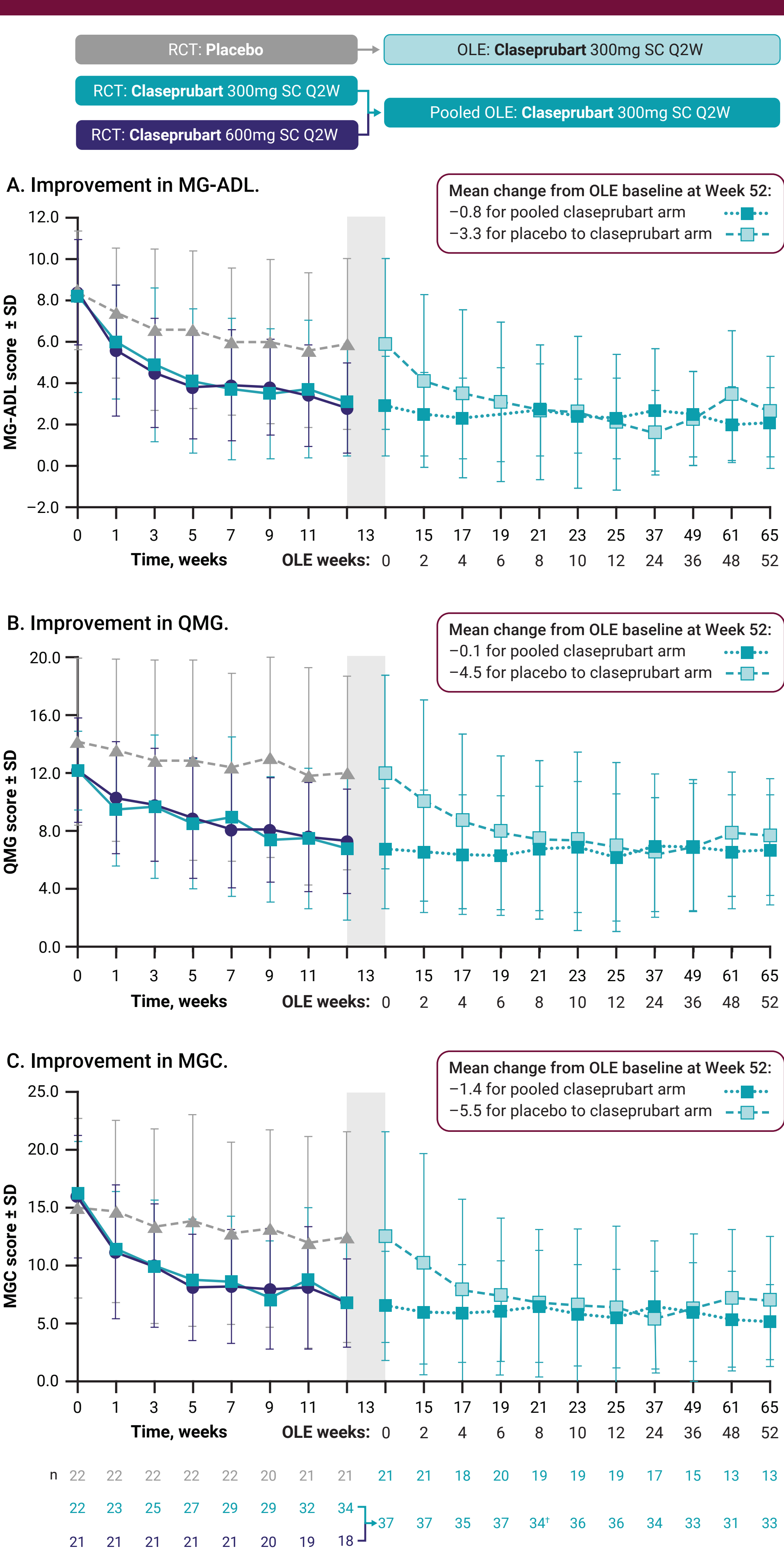
MedDRA; Medical Dictionary for Regulatory Activities; MG, myasthenia gravis; OLE, open-label extension; SC, subcutaneous; RCT, randomized controlled trial.

Efficacy Assessments

- Claseprubart patients who continued with Q2W claseprubart in the OLE demonstrated sustained improvement in MG-ADL (**Figure 3A**), QMG (**Figure 3B**), and MGC (**Figure 3C**) at OLE Week 52 compared to the end of RCT (65 total weeks on treatment).

- Rapid improvements in MG-ADL (**Figure 3A**), QMG (**Figure 3B**), MGC (**Figure 3C**) were observed as early as OLE Week 2 after switching from placebo to Q2W claseprubart. Consistent with the continuous claseprubart arm, robust improvements in efficacy endpoints were observed during 52 weeks of claseprubart treatment.

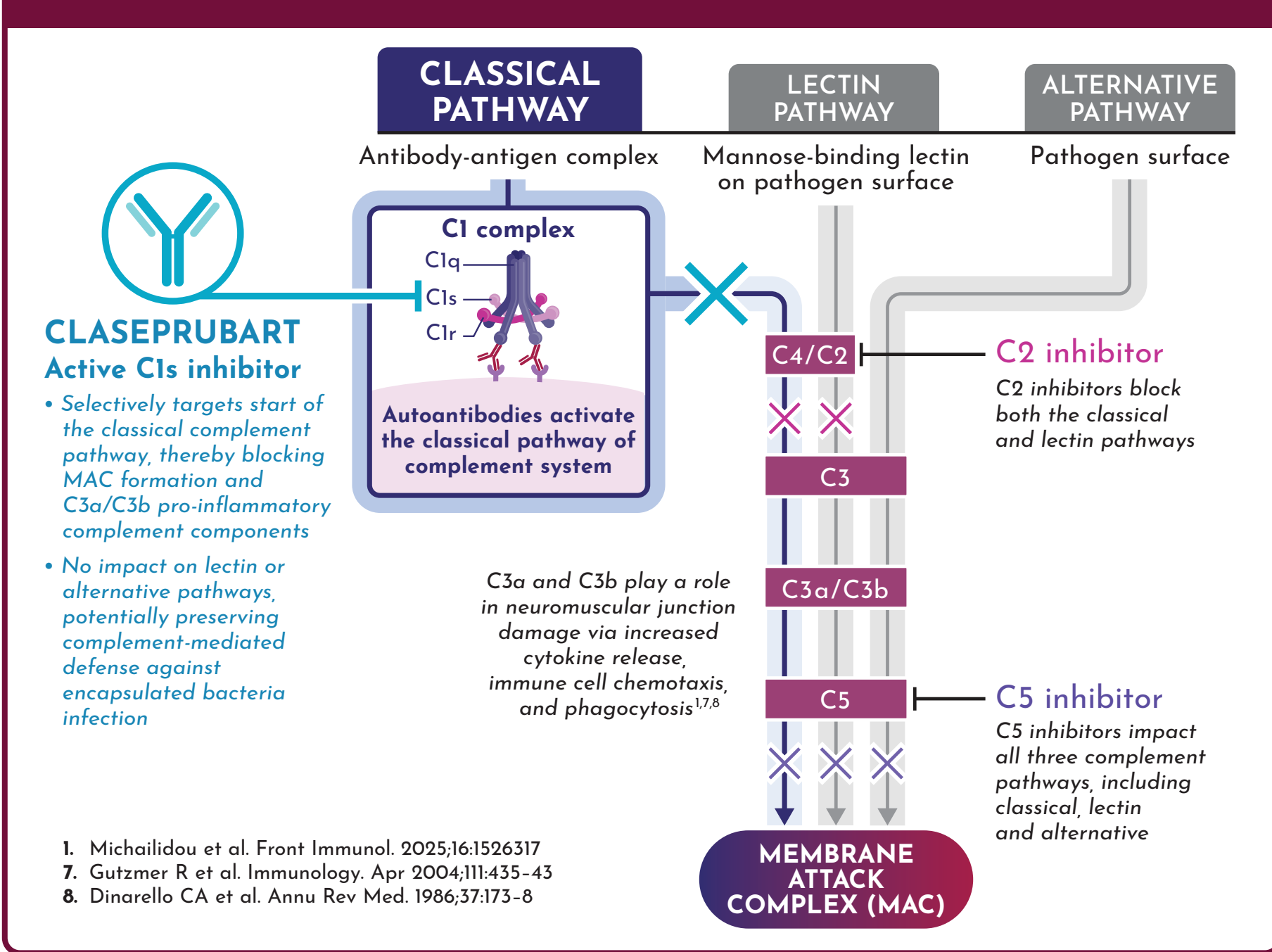
Figure 3. Efficacy of Claseprubart After at Least 52 Weeks of Treatment.



All patients entering the OLE received claseprubart 600mg Q2W for varying periods of time before the OLE dose was unified to 300mg Q2W following RCT analysis. OLE data for 300mg and 600mg claseprubart arms in the RCT were pooled. MG-ADL, Myasthenia Gravis Activities of Daily Living score; MGC, Myasthenia Gravis Composite score; OLE, open-label extension; Q2W, once every 2 weeks; QMG, Quantitative Myasthenia Gravis score; RCT, randomized controlled trial; SC, subcutaneous; SD, standard deviation.

^an=35 for MG-ADL

Figure 1. Claseprubart Mechanism of Action.



OBJECTIVE

- To assess the safety and efficacy of long-term claseprubart treatment in the MaGic open-label extension

METHODS

Study Design and Dosing

- MaGic is a global, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of SC claseprubart (NCT06282159).
- Patients with AChR Ab+ gMG were enrolled and randomized 1:1:1 to receive claseprubart 300mg (Q2W), claseprubart 600mg (Q2W), or placebo for 13 weeks, followed by an ongoing 52-week open-label extension (OLE) (**Figure 2**).

Figure 2. MaGic Phase 2 Study Design.

