Myasthenia Gravis: An Update on Key Selected Pipeline Developments and Clinical Trials

IQVIA Pipeline Link/Trial Link

ANKITHA R, Insights Associate, IQVIA Pipeline Link/Trial Link
SWATI S KUMAR, Senior Insights Associate, IQVIA Pipeline Link/Trial Link

Myasthenia gravis is a rare neuromuscular disorder characterized by muscle weakness stemming from an autoimmune response, in which the body's immune system erroneously targets and gradually damages certain receptors within muscles that receive nerve signals. Patients with myasthenia gravis mainly exhibit autoantibodies against acetylcholine receptors (AChRs) which disrupt the transmission of signals between nerve endings and muscle fibers by inducing downregulation, destruction, functional blocking of AChRs, or interfering with the clustering of AChRs in the postsynaptic membrane.[1]

Common symptoms associated with myasthenia gravis include weakness in the muscles of the eyes, resulting in eyelid drooping, double vision or blurred vision, as well as weakness in the muscles of the face, neck, arms, legs and throat. The condition most commonly affects young adult women aged below 40 years and older men aged 60 years and above.[2] According to the Myasthenia Gravis Foundation of America, the prevalence of myasthenia gravis in the USA is estimated at 14 to 20 per 100,000 population.[3]

This article provides an update on current treatment options for myasthenia gravis and outlines the latest development activities including ongoing clinical trials of key experimental drugs with data sourced from IQVIA Pipeline Link and the newly launched IQVIA Trial Link.

In recent years, new types of myasthenia gravis therapeutics have emerged, altering significantly the traditional therapeutic approaches for managing myasthenia gravis. Over the last six years, a total of five novel agents were approved in the USA to treat generalized myasthenia gravis (gMG).

Treatment options for Myasthenia Gravis

Myasthenia gravis is a chronic medical condition that requires lifelong attention. Early diagnosis and treatment are essential for effective disease control. Standard treatments for myasthenia gravis include two main classes of therapeutics: cholinesterase inhibitors and immunosuppressants. Cholinesterase inhibition increases the amount of available acetylcholine by preventing its breakdown, triggering muscle activation and contraction. Immunosuppressants, such as corticosteroids, attack the disease at its source.[4]

In recent years, new types of myasthenia gravis therapeutics have emerged, altering significantly the traditional therapeutic approaches for managing myasthenia gravis. Over the last six years, a total of five novel agents were approved in the USA to treat generalized myasthenia gravis (gMG). These include three complement C5 inhibitors: Alexion's eculizumab (SOLIRIS), AstraZeneca's ravulizumab (ULTOMIRIS), and UCB's zilucoplan (ZILBRYSQ) and two Fc gamma receptor and transporter protein antagonists (FCGRT; also called neonatal fragment crystallizable receptor (FCRN)): Argenx's efgartigimod alfa (VYVGART, HYTRULO) and UCB's rozanolixizumab (RYSTIGGO). Complement C5 inhibitors target and block the activity of the component protein C5, preventing the formation of the membrane attack complex and the destruction of the neuromuscular junction, which consequently leads to muscle weakness. FCGRT inhibitors block IgG from binding to FCGRT leading to the breakdown of IgG, which in turn lowers the overall levels of IgG and reduces the level of circulating pathogenic autoantibody.[5,6,7]

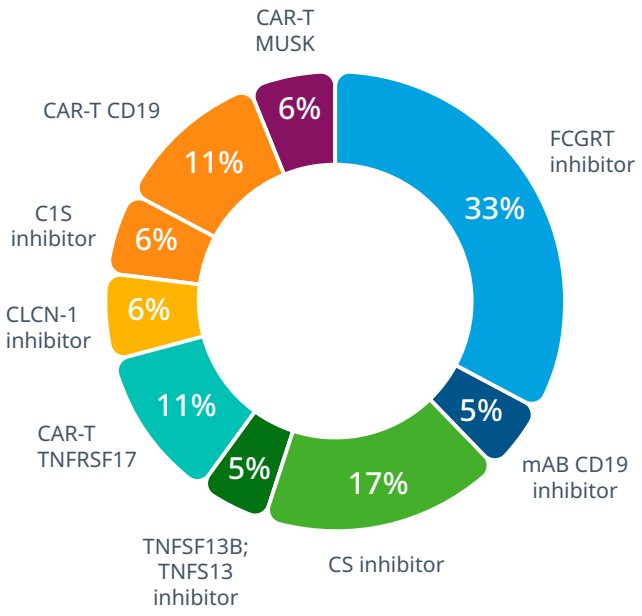
UCB emerged as the first to secure marketing authorization for a treatment targeting both AChR and anti-muscle-specific MUSK antibody-positive myasthenia gravis following rozanolixizumab's approval by the US FDA in June 2023.[8] The approval was based on data from the MycarinG pivotal Phase 3 trial (NCT03971422), which demonstrated that rozanolixizumab achieved a mean improvement in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score of 2.586 and 2.619 at 7 and 10 mg/kg doses, respectively, when compared with placebo by Day 43 (both doses at p less than 0.001).[9] Rozanolixizumab was approved by the EMA in January 2024.[10]

Following closely, UCB's zilucoplan, a C5 inhibitor, received approval from the US FDA in October 2023 and was approved by the EMA in December 2023 for treating gMG in adult patients who are AChR antibody positive.[11,12] The Phase 3 RAISE trial (NCT04115293) met its primary endpoint: zilucoplan (0.3 mg/kg daily) demonstrated a mean improvement of 2.12 points in the MG-ADL score at week 12 when compared with placebo (p less than 0.001).[9]

Novel therapies in development for Myasthenia Gravis

Research on developing treatment options for myasthenia gravis is rapidly evolving, with notable developments for patients with moderate to severe AChR-positive gMG. As of June 2024, IQVIA's Pipeline and Trial Link listed 18 programs in development with various mechanisms of action.

Figure 1: The mechanism of action of therapies in active development for myasthenia gravis



Source: IQVIA Pipeline Link/Trial Link

The most advanced program, Harbour BioMed's batoclimab (HBM9161), a fully human anti-FCGRT monoclonal antibody (mAb), is pending approval in China with a BLA accepted for review by the National Medical Products Administration (NMPA) of China in June 2023.[13] According to Pipeline Link, this program is expected to launch in Q1 2025. The submission was based on data from a Phase 3 trial (NCT05039190) that recruited 132 patients in China, which demonstrated a significantly greater reduction in MG-ADL scores on Day 43 (final dose) in patients receiving batoclimab compared to those receiving placebo, with a mean difference of -1.9 (p less than 0.001).[14] Another Phase 3 trial of batoclimab (NCT05403541) is ongoing at 78 trial sites across 12 countries, including the USA, Canada, Japan, South Korea and Europe. This trial is expected to be completed in April 2025.

According to Pipeline Link, following batoclimab, the next Phase 3 programs expected to reach the market are Johnson & Johnson's nipocalimab, an FCGRT antagonist and Amgen's inebilizumab, an anti-CD19 mAb, both in fourth quarter 2025, and Regeneron's pozelimab (VEOPOZ), a C5 inhibitor studied in combination with cemdisiran for adults with symptomatic gMG, in second quarter 2027.

Although the myasthenia gravis programs currently in the pipeline are still dominated by complement inhibitors and FCGRT inhibitors, new mechanisms of action are also being investigated, including CAR-T cell therapies. CAR-T cell therapies involve genetically modifying a patient's T cells to express chimeric antigen receptors that target specific proteins in the autoimmune response. The modified CAR-T cells are then reintroduced into the patient to eliminate autoreactive B cells that produce antibodies against AChRs. This aims to reduce the autoimmune attack on neuromuscular junctions, alleviating myasthenia gravis symptoms more effectively than traditional treatments.[15,16] Cartesian Therapeutics' Descartes-08, an IV autologous mRNA CAR-T cell therapy directed against TNF Receptor Superfamily Member 17 (TNFRSF17; also known as B-cell maturation antigen (BCMA)), is currently undergoing a Phase 2b trial (NCT04146051) as a single agent, which is expected to complete in March 2026.

Other novel targets include TNF Superfamily Member 13b (TNFSF13B; also called B-lymphocyte stimulator (BLyS)), TNF Superfamily Member 13 (TNFSF13; also called proliferation-inducing ligand (APRIL)), CD19, and the CLCN-1 chloride channel. These targets are crucial in regulating B cell activity and survival, which are central to the autoimmune response in myasthenia gravis. Remegen's Phase 3 program telitacicept (RC18), a TNFSF13B and TNFSF13 inhibitor, works by reducing the maturation and survival of B cells, decreasing the production of autoantibodies. Amgen's Phase 3 program inebilizumab (UPLIZNA), an anti-CD19 mAb, aims to deplete pathogenic B cells, while NMD Pharma's Phase 2 program NMD670, a CLCN-1 chloride channel inhibitor, is involved in muscle function and its modulation can help improve muscle strength. Together, these therapies offer a multifaceted approach to managing and potentially alleviating the symptoms of myasthenia gravis.[17, 18]

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Myasthenia Gravis clinical trial landscape

As of June 2024, Trial Link listed 17 ongoing clinical trials, including 11 trials in Phase 2/3 and Phase 3 development, as listed in the table below.

Table 1: Ongoing clinical trials, including 11 trials in Phase 2/3 and Phase 3 development

TRIAL ID	PROGRAM STUDIED	COMPANY	PHASE	STATUS	TARGET	NUMBER OF SITES (COUNTRIES)	PRIMARY OUTCOME MEASURES	START DATE	ESTIMATED PRIMARY COMPLETION DATE
NCT 05332210	BATOCLIMAB (HBM9161)	Harbour Biomed	Phase 3	Recruiting	FCGRT	1 (China)	Adverse events (safety)	Jun-2022	Sep-2023
NCT 04951622 (VIVACITY)	NIPOCALIMAB (JNJ-80202135)	Johnson & Johnson, Momenta	Phase 3	Recruiting	FCGRT	111 (USA+16)	MG-ADL total score (efficacy)	Jul-2021	Nov-2023
NCT 05403541	BATOCLIMAB (HBM9161)	Harbour Biomed, Roivant	Phase 3	Recruiting	FCGRT	78 (USA+11)	MG-ADL total score (efficacy)	Jun-2022	Apr-2024
NCT 04524273 (MINT)	INEBILIZUMAB (UPLIZNA)	Amgen, Mitsubishi Tanabe Pharma	Phase 3	Active, not recruiting	CD19	103 (USA+18)	MG-ADL total score (efficacy)	Aug-2020	May-2024
NCT 04833894	EFGARTIGIMOD ALFA (VYVGART)*	Argenx	Phase 3	Recruiting	FCGRT	24 (USA+11)	Clearance (pharmaco-kinetic), ACHR-AB (efficacy), +2	Oct-2021	Aug-2024
NCT 05265273	NIPOCALIMAB (JNJ-80202135)	Johnson & Johnson	Phase 2/3	Recruiting	FCGRT	18 (USA+3)	Total IGG levels (efficacy), AUCSS (pharmaco-kinetic), +8	Jul-2022	Mar-2025
NCT 05070858 (NIMBLE)	POZELIMAB (in combination with CEMDISIRAN)	Alnylam, Regeneron	Phase 3	Recruiting	C5	116 (USA+19)	MG-ADL total score (efficacy)	Dec-2021	Aug-2025
NCT 05556096	GEFURULIMAB (ALXN1720)	Alexion, Astrazeneca	Phase 3	Recruiting	C5	163 (USA+21)	MG-ADL total score (efficacy)	Nov-2022	Aug-2025
NCT 05644561	RAVULIZUMAB (ULTOMIRIS)*	Alexion	Phase 2/3	Recruiting	C5	18 (USA+8)	Plasma concentration, (pharmaco-kinetic), Serum free C5 concentration (efficacy)	Jun-2023	Jul-2026
NCT 05737160	TELITACICEPT (RC18)	Remegen	Phase 3	Recruiting	TNFS 13B; TNFS 13	51 (China)	MG-ADL total score (efficacy)	Mar-2023	Dec-2026
NCT 05374590 (ADAPT JR +)	EFGARTIGIMOD ALFA (VYVGART)*	Argenx	Phase 2/3	Recruiting	FCGRT	8 (USA+4)	Adverse events (safety), Body weight (efficacy), +3	Aug-2022	Sep-2028

Source: IQVIA Trial Link

* denotes products that are already available in the market fot this indication

Insights on early-stage agents for Myasthenia Gravis

In recent years, advancements in understanding the mechanisms of myasthenia gravis have broadened treatment options. Ongoing research efforts have focused on identifying novel molecules for drug development, aiming to create pharmacological treatments that offer enhanced efficacy and precision.

CABA-201, MUSK-CAART

Cabaletta Bio is developing 2 CAR-T cell therapies for autoimmunity (CARTA) for the treatment of multiple autoimmune diseases, including myasthenia gravis. The RESET-MG Phase 1/2 trial (NCT06359041) evaluating CABA-201, a fully human CD19 CAR-T cell therapy containing a TNFRSF9 co-stimulatory domain, was initiated in June 2024 for the treatment of gMG. This trial has an estimated primary completion date of September 2029. The company also initiated a Phase 1 trial (NCT05451212) evaluating MUSK-CAART in patients with anti-MUSK-antibody-positive myasthenia gravis in November 2022. The trial has an estimated primary completion date of October 2028.

NMD670

NMD Pharma's NMD670, is a small molecule oral inhibitor of CLCN-1, currently in a Phase 2b trial (NCT06414954) for gMG. Top-line data from a Phase 1/2a clinical trial of NMD670 showed notable improvements in the Quantitative Myasthenia Gravis Score, with approximately 50% of patients meeting responder criteria after receiving single doses indicating that blocking CLCN-1 can enhance neuromuscular transmission and restore muscle function.[19]

DNTH103

Dianthus' DNTH103, a mAb that selectively targets the active form of the complement component 1S (C1S) protein, is being evaluated in the MAGIC Phase 2 trial (NCT06282159) in adults with AChR-positive+ gMG. This trial is anticipated to be completed by December 2025. Initial top-line data from this trial are expected in the second half of 2025.[20]

Summary

Encouraging progress in the treatment of myasthenia gravis has been observed in recent years. The approvals of complement inhibitors and FCGRT antagonists have considerably improved the management of symptoms for many patients, enabling them to lead more active lives. The treatment landscape for myasthenia gravis is undergoing significant change, with promising outcomes from several products in advanced developmental stages. Immunosuppressants are emerging as the primary focus for managing and preventing this disease. Recent advancements in this disease area include CAR-T cell therapies, which effectively locate and eliminate aberrant plasma cells responsible for pathogenic antibody production in myasthenia gravis. Additionally, TNFSF13B and TNFSF13 inhibitors, and anti-CD19 antibodies are being explored to suppress harmful B cell activity, while CLCN-1 inhibitors aim to enhance muscle strength. These approaches represent a multifaceted strategy towards managing and potentially alleviating symptoms of the condition.

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Authors

ANKITHA R
Insights Associate,
IQVIA Pipeline Link/Trial Link

Ankitha R is an Insights Associate within IQVIA and has close to 4 years of experience in market and secondary research, data analysis, scientific writing, and syndicated analytics. She holds a master's degree in biotechnology and has been associated with the team for 4 years.

SWATI S KUMAR
Senior Insights Associate,
IQVIA Pipeline Link/Trial Link

Swati S Kumar is a Senior Insights Associate in IQVIA. She holds a bachelor's degree in biotechnology and has close to 5 years of experience in syndicated analytics, market research and scientific writing.

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