A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study With an Open-label Extension Period to Evaluate the Efficacy and Safety of Telitacicept in Patients With Generalized Myasthenia Gravis (UPSTREAM MG)

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*At the time of the study.

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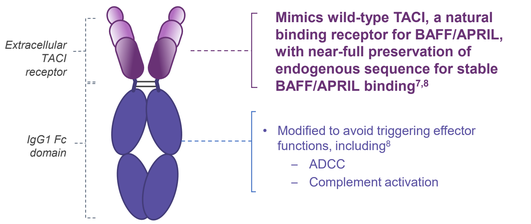
BACKGROUND

- Myasthenia gravis is an autoimmune neuromuscular disease in which autoreactive B cells target the postsynaptic membrane of the neuromuscular junction[1]
- The predominant manifestation is fatigable weakness, which affects limb, respiratory, bulbar, and ocular muscles[2]
- Current therapies treat the symptoms of generalized myasthenia gravis (gMG), induce nonspecific immunosuppression, remove pathogenic antibodies, or block postsynaptic membrane damage caused by complement activation[1,3,4]
- Telitacicept is a novel, fully human TACI-Fc fusion protein that targets B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) modulating B-cell development and survival, resulting in pathogenic autoantibody reduction[5]
- By modulating B cells both upstream and downstream in their development, BAFF/APRIL inhibition has potential as a therapy in multiple autoimmune diseases, including gMG (**Figure 1**)[6,7]

Figure 1. Telitacicept Is a Fusion Protein Based on the Human TACI Receptor Designed to Target BAFF and APRIL



ADCC, antibody-dependent cellular cytotoxicity; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; Fc, fragment crystallizable; IgG, immunoglobulin G; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor.

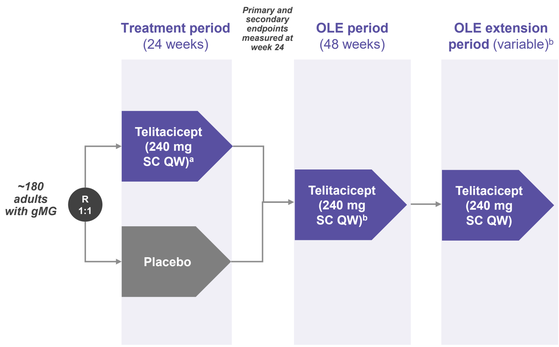
- Data from phase 2 (NCT04302103) and phase 3 (NCT05737160) studies of telitacicept conducted in China showed efficacy and safety in adults with acetylcholine receptor (AChR) autoantibody-positive gMG[9-13]
- In a phase 3 trial from China, telitacicept showed sustained efficacy and was well tolerated in patients with gMG[12,13]
  - The primary endpoint of change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score at week 24 was met with a change of -5.74 in the telitacicept 240 mg group and -0.91 in the placebo group (P<0.001)[12]
  - The secondary endpoint of change from baseline in Quantitative Myasthenia Gravis (QMG) score at week 24 was met with a change of -8.66 in the telitacicept 240 mg group and -2.27 in the placebo group (P<0.001)[12]
  - Telitacicept was generally well tolerated with most adverse events being mild to moderate in severity[12,13]
- Here, we present the study design of an ongoing, global, phase 3, double-blind, placebo-controlled study (NCT06456580) in adults with gMG in order to understand the effect of BAFF/APRIL inhibition by telitacicept in a heterogeneous international population[14]

METHODS

Study Design

- UPSTREAM MG will randomize ~180 patients with gMG 1:1 to receive either placebo or telitacicept subcutaneously weekly (**Figure 2**)
- UPSTREAM MG will consist of a screening period of ≤4 weeks; a 24-week, double-blind, placebo-controlled phase; and a 48-week open-label extension (OLE)
  - This is followed by an extended OLE period, which has a variable duration, defined as after the OLE period until telitacicept is available or the further development in the indication is concluded (**Figure 2**)

Figure 2. Study Design



EOS, end of study; EOT, end of treatment; gMG, generalized myasthenia gravis; OLE, open-label extension; QW, once weekly; R, randomized; SC, subcutaneous. [a]For patients who discontinue treatment before the OLE period, EOT and EOS time points are at 24 and 32 weeks, respectively. For those not continuing with the OLE, EOT and EOS time points are at 72 and 80 weeks, respectively. [b]Patients who complete week 72 of the ongoing OLE and who, in the opinion of the investigator, continue to benefit from treatment and meet all eligibility criteria may enter the extended OLE and continue receiving open-label telitacicept. The duration of the extended OLE is of variable duration, defined as after the OLE period until telitacicept is approved for myasthenia gravis in the country or the further development in the indication is concluded. This will allow ongoing dosing of patients upon completion of the OLE.

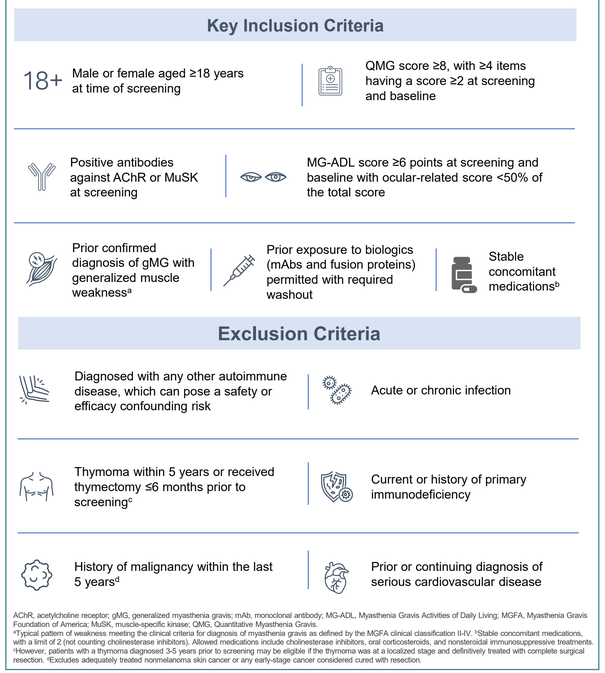
Endpoints

- The primary endpoint is the change from baseline in MG-ADL score at week 24
- Secondary efficacy endpoints include
  - Change from baseline in QMG score at week 24
  - Change from baseline in MG Quality of Life 15-item Revised scale (MG-QOL15r) at week 24
  - Proportion of patients with a ≥2-point decrease in MG-ADL score at week 24
  - Proportion of patients with a ≥3-point decrease in QMG score at week 24
  - Proportion of patients who achieved minimal symptom expression (MSE; defined as having an MG-ADL score of 0 or 1) at week 24
- Incidence of adverse events and evaluation of other vital signs and safety laboratory measurements will also be used to assess the safety and tolerability of telitacicept

Eligibility Criteria

- Inclusion and exclusion criteria are outlined in **Figure 3**
- Eligible patients may also receive up to 2 stable concomitant medications (not counting cholinesterase inhibitors) for the treatment of gMG if they meet the stability criteria prior to baseline
  - Varying standard of care regimens will be allowed, including cholinesterase inhibitors, oral corticosteroids, and nonsteroidal immunosuppressive treatments
- Patients who have received prohibited immunosuppressants (pimecrolimus, vincristine, vinblastine, or cyclophosphamide) other than protocol-permitted stable concomitant medications, biologics, or other agents will be excluded
  - Washout periods will be required for any prior biologic or intravenous immunoglobulin use
- Patients will be excluded if they have a chronic or acute infection

Figure 3. Inclusion and Exclusion Criteria



AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; mAb, monoclonal antibody; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; QMG, Quantitative Myasthenia Gravis. [a]Typical pattern of weakness meeting the clinical criteria for diagnosis of myasthenia gravis as defined by the MGFA clinical classification II-IV. [b]Stable concomitant medications, with a limit of 2 (not counting cholinesterase inhibitors). Allowed medications include cholinesterase inhibitors, oral corticosteroids, and nonsteroidal immunosuppressive treatments. [c]However, patients with a thymoma diagnosed 3-5 years prior to screening may be eligible if the thymoma was at a localized stage and definitively treated with complete surgical resection. [d]Excludes adequately treated nonmelanoma skin cancer or any early-stage cancer considered cured with resection.

Study Locations

- Study locations are shown in **Figure 4**

Figure 4. Study Locations and Number of Sites

As of March 9, 2026.

CONCLUSIONS

- A global, phase 3, pivotal, multicenter, randomized, double-blind, placebo-controlled trial with a long-term OLE period is ongoing to evaluate the efficacy and safety of telitacicept in a heterogeneous patient population
- This study will add to the established efficacy and safety data from previous phase 2 and 3 studies conducted in China

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