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Phase 3 Trial Investigating Impact of Intravenous Efgartigimod in Anti-Acetylcholine Receptor Antibody-Negative Generalized Myasthenia Gravis

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INTRODUCTION

- Efgartigimod is an IgG1 antibody Fc fragment that has been engineered for increased affinity to FcRn compared to endogenous IgG, and is uniquely composed of the only part of the IgG antibody that normally binds FcRn[1]
- Efgartigimod selectively reduces IgG by blocking FcRn-mediated IgG recycling without impacting antibody production or other parts of the immune system, and does not decrease albumin[1-3]

Efgartigimod Mechanism of Action: Blocking FcRn

1. Efgartigimod and IgG are internalized[1,4]
2. Efgartigimod competes with endogenous IgG for binding to FcRn[1]
3. Unbound IgG enters the lysosomal degradation pathway[1,4]
4. Efgartigimod and fewer IgGs are recycled back into the bloodstream[1]

Efgartigimod · IgG antibody · IgG autoantibody · FcRn

RATIONALE

- gMG is a rare, chronic, neuromuscular autoimmune disease caused by pathogenic IgGs targeting the neuromuscular junction, resulting in impaired neuromuscular transmission and debilitating and potentially life-threatening muscle weakness and chronic fatigue[5]
- Approximately 15% of patients with gMG do not have antibodies directed against AChR, which is referred to as AChR-Ab- gMG[6]
- The AChR-Ab- gMG population is heterogeneous and includes patients with autoantibodies targeting other components of the neuromuscular junction, including MuSK and LRP4[7]
  - MuSK and LRP4 autoantibodies have been detected in ≈5%, and ≈1%-5% of patients with gMG, respectively, while ≈10% of patients have no identifiable autoantibodies[5,6,8,9]
  - In all known subgroups of acquired AChR-Ab- gMG, the disease is considered IgG mediated[6]
- Treatment for patients with AChR-Ab- gMG predominantly consists of off-label drug use, and efficacy has not been proven for immunosuppressive treatments such as corticosteroids and NSISTs[10,11]
- Patients with AChR-Ab- gMG are often either excluded from clinical trials or represent a small subpopulation of the enrolled population, which limits the ability to draw conclusions[12-16]
- Recent evidence suggests clinical outcomes for patients with AChR-Ab- gMG treated with currently available treatments are worse than for patients with AChR-Ab+ gMG[17,18]

OBJECTIVE — **To determine the efficacy and safety of 10 mg/kg IV efgartigimod compared with placebo in AChR-Ab- participants with gMG**

SUMMARY

ADAPT SERON is a randomized, double-blinded, placebo-controlled, phase 3, parallel-group trial evaluating efgartigimod IV in AChR-Ab- gMG

Participants will all have confirmed acquired gMG based on review of an MG Diagnostic Adjudication Committee

This Phase 3 trial will provide important data on the efficacy and safety of efgartigimod IV in the treatment of AChR-Ab- gMG

Recruitment is ongoing — **Estimated primary completion date: Summer 2025**

DESIGN

INCLUSION CRITERIA

- Has no known weakness in infancy and develops fatigable weakness ≥ age 16
- Confirmed diagnosis of acquired gMG that meets one of the criteria in both of the following:

Abnormal SFEMG/RNS **OR** MuSK-Ab seropositive	**AND**	History of positive edrophonium chloride test **OR** Demonstrated improvement in MG signs with treatments such as oral AChE inhibitors, PLEX, immunoabsorption, or IVIg/SCIg treatment

- AChR-Ab seronegative at screening (MuSK-Ab+/LRP4-Ab+ allowed)
- MGFA Class II, III, or IV
- MG-ADL total score ≥5 (>50% nonocular)
- Stable dose of gMG therapy prior to screening[a-c]

[a]NSISTs initiated ≥6 months before screening with no change in dose during the 3 months before screening. [b]Steroids initiated ≥3 months before screening, with no change in dose during the month before screening. [c]AChEI with no change in dose during the 2 weeks before screening.

EXCLUSION CRITERIA

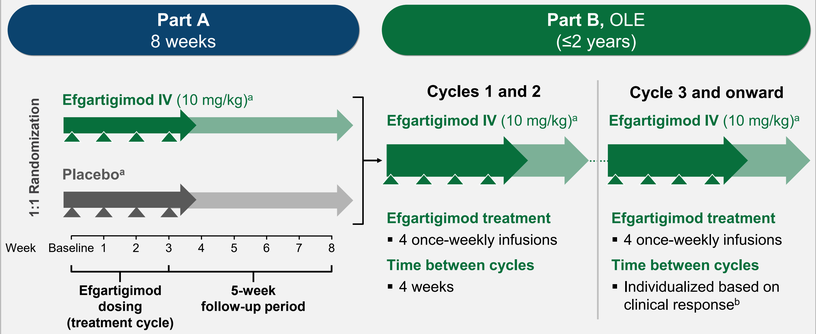
- Total IgG <4 g/L at screening
- Use of IVIg, SCIg, or intramuscular Ig within 4 weeks, any other investigational product within 3 months or 5 half-lives, monoclonal antibody within 6 months (eculizumab within 3 months), PLEX within 4 weeks, anti-CD20 or anti-CD19 antibody within 6 months, prior treatment with any CAR T-cell therapy or IL-6(R) inhibitor, prior treatment with an FcRn inhibitor
- Received a live or live-attenuated vaccine <4 weeks before screening
- History of malignancy
  - Adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or breast, or incidental histological findings of stage T1a or T1b prostate cancer are allowed
- Received a thymectomy <3 months before screening or thymectomy planned during study
- Active infection
- Documented lack of clinical response to PLEX
- Severe renal impairment with eGFR <30 mL/min/1.73 m^2 at screening

ADAPT SERON (ARGX-113-2308) TRIAL DESIGN

adapt SERON myasthenia gravis study

Efgartigimod IV Randomized, Double-Blinded, Placebo-Controlled, Phase 3, Parallel-Group Trial in AChR-Ab- gMG

Total anticipated enrollment:
110 AChR-Ab- Participants With Confirmed Acquired gMG Diagnosis Reviewed by MG Diagnostic Adjudication Committee



[a]Triangles indicate efgartigimod or placebo administration. [b]Time between cycles will be no shorter than 7 days since previous efgartigimod IV infusion.

ENDPOINTS

PRIMARY ENDPOINT

MG-ADL total score change from baseline to Day 29 (Week 4) in part A

SECONDARY ENDPOINTS

Key Secondary Endpoints

- QMG total score change from baseline to Day 29 (Week 4) in part A
- Proportion of participants who are both MG-ADL and QMG responders[a,b] in part A

Other Secondary Endpoints

- Proportion of participants with MSE (defined as an MG-ADL total score of 0 or 1)
- Proportion of participants who are MG-ADL responders[a] or QMG responders[b]
- Proportion of participants who are early MG-ADL responders[c]
- MG-ADL and QMG total score actual values and changes from baseline scores over time
- MG-QoL15r score change from baseline to Day 29 (Week 4) in part A
- MG-QoL15r and EQ-5D-5L VAS actual values and changes from baseline scores over time
- Incidence and severity of adverse events, serious adverse events, laboratory test results, vital signs, and electrocardiogram results
- Total IgG concentration actual values and percent changes from baseline over time

[a]MG-ADL responder is defined as a participant achieving ≥2-point reduction in the MG-ADL total score compared to baseline that is maintained for the next 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last administration of IMP in part A. [b]QMG responder is defined as a participant achieving ≥3-point reduction in the QMG score compared to baseline and maintained for the next 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last administration of IMP in part A. [c]Early MG-ADL responder is defined as a participant having onset of MG-ADL response no later than 2 weeks after the first administration of IMP in part A.

Scan here for more information on the ADAPT SERON website

ABBREVIATIONS
AChE, acetylcholinesterase; AChEI, acetylcholinesterase inhibitor; AChR, acetylcholine receptor; AChR-Ab, acetylcholine receptor antibody; CAR, chimeric antigen receptor; CD, cluster of differentiation; eGFR, estimated glomerular filtration rate; EQ-5D-5L VAS, EuroQuol 5-Dimension 5-Level Visual Analog Scale; Fc, fragment crystallizable region; FcRn, neonatal Fc receptor; gMG, generalized myasthenia gravis; Ig, immunoglobulin; IgG, immunoglobulin G; IL6(R), interleukin 6 receptor; IMP, investigational medicinal product; IV, intravenous; IVIg, intravenous Ig; LRP4, low-density lipoprotein receptor-related protein 4; LRP4-Ab, low-density lipoprotein receptor-related protein 4 antibody; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15r, Myasthenia Gravis Quality of Life 15-Item Questionnaire, Revised; MSE, minimal symptom expression; MuSK, muscle-specific tyrosine kinase; MuSK-Ab, muscle-specific tyrosine kinase antibody; NSIST, nonsteroidal immunosuppressive therapy; OLE, open-label extension; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; RNS, repetitive nerve stimulation; SCIg, subcutaneous Ig; SFEMG, single-fiber electromyography.

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ACKNOWLEDGMENTS AND DISCLOSURES:
The authors gratefully acknowledge the clinicians, patient organizations, and scientists who have collaborated on the design of this trial.
JFH: Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, PCORI, UCB, AcademicCME, Biologix, CheckRare CME, CoreEvitas, Curie bio, Hansa Biopharma, Amgen, Biohaven, Medscape CME, Merck EMB Serono, NMD, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron, Sanofi, TG Therapeutics, and Tolerantia AB. **JG, RHJ, FG,** and **SS:** argenx. Medical writing and editorial support for this presentation were provided by Precision.AQ and funded by argenx.

Presented at the American Academy of Neurology (AAN) Annual Meeting; April 5-9, 2025; San Diego, California