Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT) : a multicentre, randomised, placebo-controlled, phase 3 trial

Efficacy, Safety, and Tolerability of Efgartigimod in Patients with Generalized Myasthenia Gravis (gMG): Analysis of the Randomized Phase 3 ADAPT Study

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Summary (word count = 420)

Background

There is an unmet need for treatment options for generalized myasthenia gravis (gMG) that are effective, targeted, well tolerated, and can be used in a broad population of patients. We aimed to assess the efficacy and safety of efgartigimod (ARGX-113), a human IgG1 antibody Fc fragment engineered to reduce pathogenic IgG autoantibody levels, in patients with gMG

Methods

ADAPT (ClinicalTrials.gov: NCT03669588) was a randomized, double-blind, placebo-controlled, phase 3 trial of efgartigimod in gMG conducted at 56 neuromuscular academic and community centers in 15 countries. Patients with gMG were eligible to participate in the study, regardless of anti-acetylcholine receptor antibody (AChR-Ab) status, if they met the following criteria: Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 (more than 50% non-ocular), and on a stable dose of ≥1 treatment for gMG (acetylcholinesterase inhibitor, steroid and/or non-steroidal immunosuppressant treatment). Patients were randomized by Interactive Response Technology 1:1 to efgartigimod (10 mg/kg) or matching placebo administered as cycles of 4 weekly intravenous infusions repeated as needed, depending on clinical response. Patients, investigators, and clinical site staff were all unaware of treatment allocation. The primary endpoint was percentage of AChR-Ab+ patients who were MG-ADL responders (≥2-point MG-ADL improvement sustained for ≥4 weeks in the first treatment cycle [C1]). The primary analysis was completed on the AChR-Ab+ modified intent-to-treat population and the safety analysis included all randomized patients who received at least one dose of efgartigimod or placebo.

Findings

Between September 5, 2018 and November 26, 2019, 167 patients were randomized and treated. The majority were AChR-Ab+ (n=129, 77%). Most of AChR-Ab+ efgartigimod-

treated patients were MG-ADL responders (n=44/65, 67·7%) in C1 compared to placebo (n=19/64, 29·7%), with an odds ratio of 4.95 (95% CI 2.21 to 11.53, p<0.0001). Similar results were seen in other outcomes measures, successive cycles, and the overall population. A lower percentage of patients treated with efgartigimod (n=65/85, 77·4%) experienced treatment emergent adverse events than placebo treated (n=70/83, 84·3%). The majority of these events were mild or moderate in severity. Three patients in each treatment arm discontinued treatment during the study (3.6%). Efgartigimod reduced total IgG and AChR-Abs and was well tolerated overall.

Interpretation

Efgartigimod was well tolerated and efficacious in patients with gMG. Improvements in symptoms correlated with IgG and AChR-Ab reduction, demonstrating the utility of selective IgG reduction through FcRn blockade in gMG. The individualized dosing based on clinical response was a unique feature of ADAPT, and translation to clinical practice with longer term safety and efficacy data will be further informed by the Open Label Extension.

Funding

argenx.

Introduction (word count: 4481)

Generalized myasthenia gravis (gMG) is a rare, chronic autoimmune disease, causing debilitating and potentially life-threatening muscle weakness affecting ocular motility, swallowing, speech, mobility, and respiratory function, which can significantly impair independence and quality of life.[1]

The majority of patients with gMG (~85%) have IgG autoantibodies; most often directed against the skeletal muscle nicotinic acetylcholine receptor (AChR), and less frequently against muscle specific tyrosine kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP4).[2,3] A small percentage of patients have no identifiable antibody. These autoantibodies exert a direct pathogenic effect in gMG and their mechanisms of action include functional blockade, accelerated internalization and degradation of AChRs, and activation of complement.[4-7] These actions lead to reduced density of functional AChR and damage to the neuromuscular junction, resulting in impaired neuromuscular transmission.[4-7] The majority of AChR and LRP4 antibodies are of the IgG1 subtype, which can activate complement, whereas the IgG4 subtype, which includes MuSK-Ab, do not.[2,8-10]

Existing treatments, including corticosteroids and non-steroidal immunosuppressive therapies (NSISTs), broadly suppress the immune system and do not selectively target IgG autoantibodies that are central to gMG pathophysiology.[7] Moreover, these treatments frequently provide insufficient symptom relief and are associated with burdensome side effects such as glucose intolerance, weight gain, arterial hypertension, osteoporosis, gastrointestinal issues, bradycardia, and renal dysfunction, which can limit their use.[7,11] Another therapeutic approach has been to block complement activation, targeting one of the downstream pathogenic pathways triggered specifically by AChR antibodies (AChR-Ab).[12,13] Overall, there remains a significant unmet need for gMG treatment options that are effective, targeted, well tolerated and can be used in a broad population of patients.[2,14,15]

The neonatal Fc receptor (FcRn) is a MHC class I-like molecule that recycles IgG, extending its half-life approximately four times relative to other immunoglobulins that are not recycled by FcRn (e.g., IgM or IgA).[16] Following cellular uptake, the Fc region of an IgG antibody binds two FcRn receptors under acidic conditions in the endosome.[17] IgG bound to FcRn are rescued from lysosomal degradation and released at physiological pH outside the cell.[18-21] Therefore, FcRn perpetuates the availability of IgG autoantibodies in IgG mediated diseases such as gMG. The utility of removing autoantibodies in gMG has been demonstrated by the effectiveness of plasma exchange (PLEX) and immunoadsorption; however, their use is limited by availability and requirement for specialized facilities.[22] Blocking FcRn represents a rational therapeutic approach to target the key pathogenic driver in gMG.

Efgartigimod is a human IgG1 antibody Fc-fragment, a natural ligand of FcRn, that has been engineered for increased affinity to FcRn compared to endogenous IgG, whilst retaining the characteristic pH dependence.[23] It outcompetes endogenous IgG binding, thereby reducing IgG recycling and increasing IgG degradation.[23] In phase 1 and 2 trials, efgartigimod significantly reduced concentrations of all IgG subtypes without decreasing levels of other immunoglobulins or albumin, which is also recycled by FcRn.[23,24] These reductions correlated to clinically meaningful and sustained improvements in gMG symptoms and function. The phase 2 trial also provided insight into the protocol design for the phase 3 ADAPT study that aimed to assess the efficacy and safety of efgartigimod (ARGX-113), a human IgG1 antibody Fc fragment engineered to reduce pathogenic IgG autoantibody levels, in patients with gMG.[24]

Methods

Study Design

ADAPT was a randomized, double-blind, placebo-controlled, global, multicenter, phase 3 trial of efgartigimod (ARGX-113) in patients with gMG. Patients were recruited from 56 neuromuscular academic and community centers across 15 countries in North America,

Europe, and Japan (appendix p 2 - 12). Screening was 2 weeks, followed by a 26-week treatment period. Independent ethics committees and international review boards provided written approval for the study protocol and all amendments. The trial was conducted according to the principles outlined in the Declaration of Helsinki.

Participants

Adult patients with gMG, with or without AChR-Ab, were eligible if they were Myasthenia Gravis Foundation of America [MGFA] Class II to IV and had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 (with >50% due to non-ocular symptoms). Diagnosis was supported by a history of abnormal neuromuscular transmission tests, a positive edrophonium chloride test, or improvement with AChE inhibitors. Eligibility criteria also required patients to be on a stable dose of at least one gMG treatment (AChE inhibitors, corticosteroids and/or non-steroidal immunosuppressive therapies [NSISTs]), prior to screening and throughout the trial. There was no requirement for patients to have received or failed specific gMG therapies. Patients were excluded if they had received rituximab or eculizumab in the prior 6 months, undergone thymectomy within 3 months, had intravenous immunoglobulin (IVIg) or PLEX within 1 month of screening, had active hepatitis B, were seropositive for hepatitis C, seropositive for HIV with low CD4 count, had serum IgG levels <6 g/L at screening, or were pregnant. A complete list of inclusion and exclusion criteria is in the appendix (p 11 – 12). Potential patients were recruited through the investigators' practice or from a physicians' referral. All patients provided written informed consent before entering the study.

Randomization and Masking

Patients were randomized in a 1:1 ratio to either efgartigimod or placebo. Placebo was matched to efgartigimod in appearance and supplied in identical containers. Randomization was performed centrally using the Interactive Response Technology (IRT), utilizing both web and voice systems, by an independent company (SGS, Belgium, NV), who held randomization

156 codes until after the final database lock, based on three stratification factors: AChR-Ab status
157 (AChR-Ab+ vs. AChR-Ab-), NSISTs (patients taking vs. not), and Japanese nationality. The
158 stratification factors were selected to ensure consistency of effect across antibody status,
159 concomitant medication, and ethnicities. Due to the small number of patients anticipated at
160 individual centers, randomization was performed across, rather than within, the centers.
161 Investigators, patients, study personnel, clinic staff, and the funder remained masked to
162 treatment assignments for the duration of the study.

163 *Procedures*

164 Efgartigimod (10 mg/kg) or matching placebo were administered in treatment cycles of 4
165 weekly intravenous infusions. All patients received an initial cycle (C1) with subsequent cycles
166 administered according to individual clinical response, being initiated when MG-ADL score
167 was ≥5 (with >50% non-ocular) and, if the patient was a MG-ADL responder (see outcomes
168 section for definition) they no longer had a clinically meaningful improvement (CMI; defined
169 as having ≥2-point improvement in total MG-ADL score) compared to cycle baseline.
170 Subsequent cycles could commence no sooner than 8 weeks from initiation of the previous
171 cycle; a maximum of three cycles were possible in the 26-week study. Patients who required
172 rescue therapy were discontinued from study treatment. Patients who completed the study or
173 could not complete a cycle before study end (retreatment after day 126) were able to roll-over
174 to the ongoing open-label extension study (ADAPT+; NCT03770403).

175 Efficacy was assessed with the MG-ADL scale (patient-reported, physician-recorded outcome
176 measure; CMI ≥2-point reduction)[25]; Quantitative Myasthenia Gravis (QMG) score (physician-
177 evaluated, including quantitative measures; CMI ≥3-point reduction)[26], Myasthenia Gravis
178 Composite (MGC) scale (patient and physician evaluated measure; CMI ≥3-point reduction)[27];
179 the 15-item revised version of the Myasthenia Gravis Quality of Life (MG-QoL15r)[28]
180 questionnaire (patient-completed), and EQ5D quality of life scale (patient-completed).

Assessments were conducted weekly for 8 weeks following each cycle initiation and then every two weeks.

Outcomes

The primary efficacy endpoint was the percentage of AChR-Ab+ patients who were MG-ADL responders in C1. An MG-ADL responder was defined as a patient who had ≥2-point improvement (reduction) in MG-ADL score, sustained for ≥4 consecutive weeks with the first improvement occurring by week 4 of the cycle (one week after the 4^{th} infusion). Secondary endpoints were assessed in hierarchical order, as follows: 1) percentage of QMG responders (defined as a ≥3 point improvement in the total QMG score for ≥4 consecutive weeks with the first improvement occurring by week 4 of C1) in the AChR-Ab+ population; 2) percentage of MG-ADL responders in C1 in the overall population (i.e., AChR-Ab+ and AChR-Ab- patients); 3) percentage of time patients showed a CMI in MG-ADL score in the AChR-Ab+ population, up to day 126; 4) time from Day 28 (1 week after the 4^{th} infusion in C1) to not having CMI in the AChR-Ab+ population; and 5) percentage of "early MG-ADL responders" in C1 (MG-ADL responders with first MG-ADL improvement of ≥2 points occurring by week 2) in the AChR-Ab+ population.

Predefined exploratory endpoints assessed time to onset of effect; magnitude of effect, including percent of patients achieving minimal symptom expression (MSE; defined as MG-ADL score of 0 or 1) and proportion of patients who achieved increasing levels of MG-ADL and QMG score improvement in each cycle; duration of response in MG-ADL responders; repeatability of effect with second treatment cycle; and the change in MGC and MG-QoL15r scores.

Safety was assessed through incidence of adverse events (AEs) and changes in clinical laboratory values, vital signs and electrocardiogram (ECG).

Pharmacodynamic effects were analyzed using validated assays of total IgG, IgG subtypes (IgG1, IgG2, IgG3 and IgG4), and autoantibodies (anti-AChR antibodies for the AChR-Ab+ patients and antibodies against muscle-specific tyrosine kinase [MuSK-Ab] for the MuSK-Ab+ patients). The validated assays were a radioimmunoassay (IBL International, Germany) that used acetylcholine receptor labelled with ^{125}I-alpha-bungarotoxin for anti-AChR antibodies and an ELISA (IBL International, Germany) for anti-MuSK antibodies.

Statistical Analyses

The proportion of MG-ADL responders in the placebo group was hypothesized to be 30%. The treatment difference was assumed to be 35% for AChR-Ab+ patients and 5% for AChR-Ab- patients. A difference of total MG-ADL responder rate of 35% between placebo and efgartigimod primary AChR-Ab+ population is considered clinically relevant. In the phase 2 ARGX-113-1602 study, the total MG-ADL responder rate was observed to be 33% for placebo (3/12) and 75% (9/12) for efgartigimod. Sample size was based on allowing enrollment of up to 20% AChR-Ab- patients. Based on this quota, a sample size of 150 provided power of 96% in the primary population of AChR-Ab+ patients to detect a difference of 35% in proportion of responder with 120 patients. The sample size also provided power of 90% to detect a 29% difference in the proportion of responders in the overall population with a two-sided alpha level of 5%, allowing for a 10% dropout rate.

Efficacy analyses were performed in the modified Intention-To-Treat (mITT) population, including all randomized patients who had a valid baseline MG-ADL assessment and ≥1 post-baseline MG-ADL assessment. Safety analyses were performed in all patients who received ≥1 dose or part of a dose. Patients were discontinued from randomized treatment if they became pregnant, received rescue therapy (PLEX, IVIg, immunoadsorption, any new type of corticosteroid, increased dose of current steroid; rescue was permitted per protocol in case of new or worsening respiratory or bulbar symptoms or at least 2-point increase of individual non-

ocular MG-ADL items), developed a serious adverse event that could jeopardize the safety of the patient, or developed a bacterial/viral/fungal disease. After discontinuation, patients who did not withdraw consent were followed for safety and disease severity assessments through the rest of the trial.

Statistical analyses used SAS® (SAS Institute, Cary, NC, United States) version 9·2 or higher and the software package R, where applicable. The primary endpoint was tested by means of a two-sided exact test using a logistic regression model with baseline total score as covariate and the three stratification factors as variables. The treatment effect was presented as an odds ratio (OR) with 95% confidence interval (CI) and two-sided *p*-value. If the primary endpoint met significance at the 5% two-sided alpha level, secondary endpoints were tested at a 5% two-sided significance level in hierarchical order (**Table 2**) using a fixed sequence approach. The secondary endpoint percentage of QMG responders in C1 in the AChR-Ab+ population, MG-ADL responders in C1 in the overall population and percentage of "early MG-ADL responders" in C1 in the AChR-Ab+ population were tested suing the same logistic regression model as for the primary endpoint. Percentage of time patients showed a CMI in MG-ADL score in the AChR-Ab+ population was analyzed using an analysis of covariance (ANCOVA) model. In this analysis, randomized treatment group and the stratification variables were included as a factors, and baseline total MG-ADL score was included as a covariate. Time from Day 28 to not having CMI in the AChR-Ab+ population was estimated using Kaplan-Meier time to event analysis and compared by means of a stratified log-rank test, stratified for the stratification variables. Additional endpoints assessing efficacy, safety, pharmacodynamics, and immunogenicity were analyzed in a descriptive manner.

Role of the funding source

The funder was involved in study design, conduct and data collection; and was responsible for the protocol, statistical analysis plan, and clinical study report. Medical writing was contracted

by the sponsor and additional employees provided review of the manuscript. All authors had full access to study data, reviewed, edited and provided final approval of the manuscript content, and had final responsibility for the decision to submit for publication.

Results

A total of 216 patients were screened between September 5, 2018 and November 26, 2019, of whom 167 were randomized and treated (**Figure 1**); 129 (77%) were AChR-Ab+ and 38 (23%) were AChR-Ab- of whom six were MuSK-Ab positive. There were five treatment discontinuations in the efgartigimod group (three serious adverse events [SAE], one protocol deviation, and one rescue therapy) and 10 in the placebo group (three patients withdrew consent, two SAEs, two rescue therapy, two sponsor decision following SAEs, one prohibited medication).

Patient characteristics were representative of the general gMG population and were well balanced between the efgartigimod and placebo groups (**Table 1**), except more patients in the efgartigimod group had previously undergone thymectomy. The mean (SD) time since thymectomy in all patients was 10·84 (9·0) years.

Most patients (86%, n=) were receiving immunosuppressive treatment (steroids or NSISTs). Approximately 30% (48/167) of patients had never previously been treated with an NSIST. The mean baseline MG-ADL and QMG scores demonstrate significant disease burden despite ongoing gMG treatment.

The number of patients receiving 1, 2, or 3 cycles during the study is listed in **appendix p 13**. In efgartigimod treated patients the median duration of C1 (time from first infusion in C1 until first infusion in C2 or final visit of study) was 10 weeks (range 58-185 days) and for placebo the median duration was also 10 weeks (range 16 – 190 days).

AChR-Ab+ population

A significantly higher percentage of patients in the efgartigimod group (44/65, 67·7%) met the primary endpoint of MG-ADL responder in C1 than in the placebo group (19/64 [29·7%]; OR 4.95, 95% CI 2.21 to 11.53, p <0·0001; **Table 2**).

Additionally, a significantly greater proportion of patients in the efgartigimod group (41/65, 63·1%) were QMG responders (secondary endpoint) compared with 9/64 (14·1%) in the placebo group (OR 10.84, 95% CI 4.18 to 31.20, p <0·0001; **Table 2**) in C1.

Patients in the efgartigimod group had greater total mean score improvements in MG-ADL, QMG, MCG and MG-QoL15r in C1, with statistically significant differences from baseline observed from week 1 and sustained through week 7 in all measures (**Figure 2**). The maximum improvement in efgartigimod treated patients occurred at week 5 for MG-QoL15r and week 4 for other measures.

A greater percentage of patients in the efgartigimod group compared with placebo achieved higher levels of improvement in MG-ADL (up to 9-point reduction) and QMG (up to 10-point reduction) score at Week 4 (**Figure 3**). Forty percent (26/65) of patients in the efgartigimod group attained an MG-ADL score of 0 or 1 (MSE) in C1 compared with 11·1% (7/63) in placebo group (p <0·0001).

More patients in the efgartigimod treatment arm were early MG-ADL responders (**Table 2**). In the 44 AChR-Ab+ MG-ADL responders in the efgartigimod group, the onset of response occurred by week 2 in 84% of patients.

Efgartigimod treated patients showed a CMI in MG-ADL score for 48·7% of the time between start of study and day 126, compared with 26·6% of the same period in the placebo group (p = 0·0001, secondary endpoint; **Table 2**).

The median time from Day 28 to not having CMI over the course of the study was 35 days with efgartigimod and 8 days with placebo, respectively (p = 0·2604 log rank test, secondary endpoint; **Table 2**).

Among C1 MG-ADL responders, the duration of responder status was 6-7 weeks in 31·8% (14/44) of patients, 8-11 weeks in 22·7% (10/44) and 12 weeks or more in 34·1% (15/44).

In patients who received a second cycle, a greater proportion of efgartigimod patients (36/51 [70·6%]) were MG-ADL responders compared with placebo (11/43 [25·6%]), with similar rates to C1. Similar to C1, there was greater total mean score improvements in MG-ADL and QMG with efgartigimod than placebo in C2. Of the 44 AChR-Ab+ patients in the efgartigimod group who were MG-ADL responders in C1, 32 qualified for retreatment and 29 of these (90%) were MG-ADL responders again in C2. Among 21 patients in the efgartigimod group who were not MG-ADL responders during C1, 19 were retreated and seven of these (37%) were MG-ADL responders in C2. Six out of seven efgartigimod patients who received C3 were MG-ADL responders.

Subgroup analyses did not reveal any efficacy differences based on gender, age, or baseline MG-ADL. Concomitant use of NSISTs did also not alter efficacy as 70·4% (19/27) of AChR-Ab+ patients treated with efgartigimod, who were not on NSISTs, achieved responder status. In AChR-Ab+ efgartigimod treated patients with prior thymectomy 60% (27/45) were MG-ADL responders, compared to 85% (17/20) patients who had not previously undergone thymectomy.

Overall population

Results in the overall population were similar to those in the AChR-Ab+ population, including significantly more patients in the efgartigimod group (57/84 [67·9%]) who were MG-ADL responders in C1 than in the placebo group (31/83 [37·3%]; OR 3.70, 95% CI 1.85 to 7.58, $p<0·0001$, secondary endpoint; **Table 2**).

AChR-Ab- population

There was a similar number of MG-ADL responders in each treatment group in C1, 13/19 (68·4%) patients in the efgartigimod group and 12/19 (63·2%) patients in the placebo group. There were more QMG responders in the efgartigimod group than placebo in C1; 10 (52·6%) versus seven (36·8%) patients, respectively. Six (31·6%) patients in the efgartigimod group achieved MSE compared to three (15·8%) patients in the placebo group in C1.

A post hoc analysis assessed the percentage of patients who were both MG-ADL and QMG responders in C1, showing nine (47·4%) patients in the efgartigimod group and 4 (21·1%) patients in the placebo group.

Among the AChR-Ab- patients six were MuSK-Ab+, three in each treatment group. All six patients were MG-ADL responders in C1.

Pharmacodynamics

In AChR-Ab+ patients maximum mean reductions of 61·3% (0·9) and 57·6% (1·3) were observed in IgG and AChR-Abs respectively, one week after the fourth infusion in C1 (appendix p 14) and returned to baseline by week 12 (9 weeks after the last infusion of C1). Reductions were comparable across subtypes with maximum mean reductions of 67·6% (1·0) , 59·6% (1·7) , 63·2% (1·2) , and 52·0% (1·7) for IgG 1 through 4, respectively. Similar reductions in IgG and AChR-Abs were seen with each treatment cycle. However, no reductions in albumin levels were observed.

Safety and tolerability

No deaths occurred during the study in either the efgartigimod or placebo groups. The most frequent AEs were headache, nasopharyngitis, gastrointestinal symptoms, upper respiratory tract infections (URTI) and urinary tract infections (UTI) (**Table 3**). Headache, and GI symptoms were similar between groups, nasopharyngitis occurred in more placebo patients and URTI and UTI in more efgartigimod patients. Most AEs were mild or moderate in severity. Four efgartigimod treated patients experienced an SAE; thrombocytosis, rectal

adenocarcinoma, MG worsening (each leading to treatment discontinuation), and depression. In the placebo treated group, seven patients experienced an SAE, including cases of myocardial ischemia, atrial fibrillation, spinal ligament ossification (that led to treatment discontinuation). AEs related to infections were observed in 39 (46·4%) patients in the efgartigimod group and 31 (37·3%) in the placebo group. All infections were reported as mild to moderate severity except for three severe events; influenza and pharyngitis in efgartigimod and URTI in placebo group. Infusion related reactions were reported in three (3·6%) patients in the efgartigimod and eight (9·6%) patients in the placebo group; all were mild in severity. There were no clinically meaningful changes in hematology or chemistry parameters (including no decrease in albumin levels), ECG or vital signs in either group.

Discussion

The ADAPT phase 3 trial demonstrated efgartigimod was well tolerated and effective in patients with gMG. The reduction in disease burden, and improvement in strength and quality of life in patients with gMG, were consistent across four MG specific scales and these benefits were observed early, reproducible, and durable.

The study enrolled a broad gMG patient population, including both AChR-Ab+ and AChR-Ab- patients and with no requirement for patients to have received or failed specific MG medication. The majority of patients were receiving steroids and/or NSISTs; however, approximately 30% had not previously received an NSIST.

At enrollment, despite ongoing MG therapy, patients continued to experience disability with mean MG-ADL score of 9 and QMG score of 16. Treatment with efgartigimod was shown to provide significant, clinically meaningful, and durable clinical benefit to the majority of these patients. Many patients experienced improvement beyond the clinically meaningful threshold, achieving up to 9- and 10-point reductions in MG-ADL and QMG, respectively. Minimal or no symptoms (MSE) was achieved by 40% of AChR-Ab+ efgartigimod treated patients. The

majority of patients experienced benefit within two weeks of starting treatment. While 67·3% of AChR-Ab+ patients were MG-ADL responders with the first cycle, additional patients achieved this status with a second cycle, with 78·1% of patients achieving MG-ADL responder status during the study.

The early onset of action, observed benefit in patients with or without prior NSIST exposure, and the favorable tolerability profile suggests that efgartigimod may be able to be utilized throughout the treatment paradigm of patients with gMG. As previously discussed, AChR-Abs cause a net reduction of functional AChRs at the postsynaptic membrane. However, patients with gMG also have increased AChR synthesis and repopulation, shown through mRNA and protein production, presumably as compensatory mechanisms.[29,30] Due to this, the reduction of AChR-Abs by efgartigimod after one infusion could lead to a corresponding increase in AChRs at the postsynaptic membrane and potentially account for the early onset of effect.

While more patients in the efgartigimod group had previously undergone thymectomy, a post hoc analysis demonstrated that the proportion of patients who were MG-ADL responders was lower in patients with prior thymectomy. Therefore, the increased prevalence of thymectomy in the efgartigimod group did not appear to favor efgartigimod.

This phase 3 study tested efgartigimod administered in treatment cycles, with the frequency of cycles defined by the duration of clinical effect in each patient. This individualized approach to treatment according to patient's need proved effective, with reproducible efficacy following a second and third cycle**.**

Among AChR-Ab+ MG-ADL responders, one third maintained a CMI in MG-ADL score for more than 12 weeks, suggesting a portion of patients experience clinical benefit beyond the reduction in IgG and AChR-Ab. Production of sufficient AChR to restore the safety factor for neurotransmission may explain the prolonged effect in some patients, with appropriate reserves established to maintain neurotransmission even after return of AChR-Abs.[31]

The secondary endpoint of time from day 28 of C1 (one week after the last infusion) until the patient not having CMI was numerically greater in the AChR-Ab+ efgartigimod group than placebo (35 days compared to 8 days); however, it did not reach statistical significance (log rank test, p=0·2604). The log rank test was not the most appropriate as the data did not show proportional hazards. Patients were likely to require retreatment at some point in the future so the chance of the event occurring was not equal throughout the duration of the study. The Wilcoxon test did show significance, p=0·0133.

In AChR-Ab- efgartigimod treated patients, 68·4% achieved responder status, similar to that in AChR-Ab+ patients but there was an unexpectedly high response rate in the placebo group. A post hoc analysis of AChR-Ab- patients who were both MG-ADL and QMG responders in C1 demonstrated a treatment effect, suggesting efgartigimod may be effective in this patient population. There were only six patients with anti-MuSK-Ab's, 3 in each treatment group, and all 6 were MG-ADL responders in C1. Further information regarding the efficacy in AChR-Ab- patients will be gained in the ongoing open label extension trial.

Efgartigimod reduced IgG levels, with a maximum mean reduction in total IgG of 61·3% in AChR-Ab+ patients with similar reductions with each cycle and across IgG subtypes and similar reduction in the AChR-Ab- patients. The reduction in AChR autoantibodies was similar to that of IgG and both paralleled the improvements in symptoms. This demonstrated that selective removal of IgG is an effective treatment approach in gMG which is in line with the data available from PLEX in gMG, a treatment that removes autoantibodies and is considered highly efficacious but is limited in use due to its administrative challenges.

Existing treatments for gMG are associated with burdensome short and long-term side effects that can limit their utility. Efgartigimod was well tolerated in this study, with most AEs mild or moderate in severity and low incidence of infusion reactions. While headache was the most common AE observed, it occurred in equal number of patients in both treatment groups.

Efgartigimod did not reduce albumin levels demonstrating its selectivity for the IgG binding site of FcRn and suggesting it does not alter the function of FcRn.

The rate of infection is of special interest as patients with MG are predisposed to infections, likely exacerbated by concomitant immunosuppressive treatments.[32,33] In the efgartigimod treated group 46·4% of patients had an infection compared to 37·3% in placebo. Most infections were mild to moderate, with only two graded as severe in the efgartigimod treated patients. Whilst longer-term data is required to assess the risk of infection, these results are reassuring. Additionally, the action of efgartigimod is selective, with transient and incomplete reduction of IgG and no impact on other immunoglobulins. Pre-clinical models have also shown that IgG production is not impaired[34] Due to these factors, efgartigimod treated patients should retain the potential to mount an IgG immune response.

Strengths of this study included the randomized placebo-controlled design, using validated scales incorporating physician and patient assessment and endpoints requiring a combination of clinically meaningful improvement and sustained effect. The prolonged response requirement aimed to reduce the placebo effect and more reliably ascertain the treatment effect of efgartigimod. The study recruited a broad patient population of gMG patients. Limitations included the length of follow-up (which will be addressed by the open-label extension study). The retreatment criteria requiring patients MG-ADL score to return to less than 2-point reduction from baseline was a rigorous ADAPT study criteria and the utility in the real world will be determined in clinical practice.

In the phase 3 ADAPT trial, efgartigimod demonstrated efficacy in the treatment of patients with gMG. The improvements were observed early, significant, durable, and reproducible across multiple outcome measures. The results suggest that this novel mechanism of selective IgG reduction through blocking of FcRn with efgartigimod represents an effective and well tolerated treatment for patients with gMG.

Contributors

All authors had full access to the study design information and had final responsibility for the decision to submit for publication. ***JFH, VB, HM, AG, PU, TV, JV, RM*** contributed to the concept or design of the study. ***JFH, VB, TV, CK, SP, TM, HM, MB, RS, MS, AG, PU, TV, KU, JV, RM*** contributed to the analysis and interpretation of data. Cello Health produced the first draft of the paper based on input and direction from all authors. All authors provided input into subsequent drafts and reviewed and approved the final version for submission.

Declaration of Interests

J.F. Howard, Jr. has received research support from Alexion Pharmaceuticals, argenx, The Centers for Disease Control and Prevention (Atlanta, GA, USA), the Muscular Dystrophy Association, the National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), PCORI, and Ra Pharmaceuticals (now UCB), honoraria from Alexion Pharmaceuticals, argenx, Immunovant, Ra Pharmaceuticals (now UCB), Regeneron Pharmaceuticals and Viela Bio Inc. and non-financial support from Alexion Pharmaceuticals, argenx, Ra Pharmaceuticals (now UCB) and Toleranzia.

V. Bril has received research support from CSL, Grifols, UCB, Bionevia, Shire, and Octapharma.

T. Vu has served as a speaker for Alexion; consulting work for argenx and UCB; and participating in trials in MG sponsored by NIH, Alexion Pharmaceuticals, argenx, Ra, Viela Bio, UCB, and Grifols.

C. Karam has served on advisory boards for Acceleron, Akcea, Alexion, Alnylam, argenx, Biogen, CSL Behring, Cytokinetics and Sanofi-Genzyme, and received research grants from Genzyme and Akcea.

S. Peric reports following conflicts of interest, all outside this work. He has received lecture honoraria from Pfizer, Teva Actavis, Berlin Chemie Menarini, Mylan, Worwag, Adoc and Salveo; research grants from Kedrion, Octapharma and Argenx; consultant fees from argenx, Mylan and Roche; and travel grants from Octapharma, Kedrion, Teva Actavis, Sanofi Genzyme, Pfizer, Roche, Adoc and Berlin Chemie Menarini.

T. Margania has nothing to declare.

H. Murai has served as a paid consultant for Alexion Pharmaceuticals, argenx and Ra Pharma, and has received speaker honoraria from the Japan Blood Products Organization and research support from the Ministry of Health, Labor and Welfare, Japan.

M. Bilinska has nothing to declare.

R. Shakarishvili has nothing to declare.

M. Smilowski has nothing to declare.

A. Guglietta, P. Ulrichts, and T. Vangeneugden are full-time employees of argenx, Ghent, Belgium.

K. Utsugisawa has served as a paid consultant for argenx, Ra Pharma, UCB Pharma, Viela Bio and Regeneron Pharmaceuticals, and has received speaker honoraria from Alexion Pharmaceuticals and the Japan Blood Products Organization.

J. Verschuuren receives research support from Target to B consortium, Prinses Beatrix Spierfonds, and argenx and has been involved in trials or consultancies for argenx, Alexion, Ra pharma. He is coinventor on patent applications based on MuSK-related research. The

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R. Mantegazza has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with BioMarin, Catalyst, Alexion Pharmaceuticals, UCB, and argenx.

Data Sharing

argenx is committed to responsible data sharing regarding the clinical trials they fund. Included in this commitment is access to anonymized, individual and trial-level data (analysis datasets), and other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by qualified researchers who engage in rigorous independent scientific research, and will only be provided after review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months.

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Research In Context

Evidence before this study

PubMed database was searched up to November 2020 for relevant clinical studies in generalized myasthenia gravis. Key search terms included neonatal Fc receptor, IgG recycling, antibody fragment, and autoantibody reduction. While preclinical and early phase studies had been completed with some neonatal Fc receptor antagonists, no phase 3 studies in generalized myasthenia gravis were found. Additionally, while therapeutic plasma exchange had demonstrated the impact of IgG reduction, there were no previous pharmacological approaches to achieving such a targeted reduction in IgG. Finally, many of the studies in myasthenia gravis had been constrained by other factors such as only including patients who have acetyl choline receptor autoantibodies.

Added value of this study

While there are treatment options currently available to patients with generalized myasthenia gravis, they are frequently burdensome, carry substantial side effects, do not alleviate symptoms or are reserved for refractory patients. ADAPT was the largest clinical trial in generalized myasthenia gravis and the only one to include patients regardless of their autoantibody status. During the 26-week study, efgartigimod was well tolerated with most adverse events being either mild or moderate in severity. Additionally, significantly more patients treated with efgartigimod, compared to placebo, experienced clinically meaningful improvements in their Myasthenia-Gravis-Activities of Daily Living and Quantitative Myasthenia Gravis scores compared to patients who received placebo.

Implications of all the available evidence

The study used four validated myasthenia-specific outcome measures, utilizing both patient and physician reported information, to evaluate the effects of efgartigimod in patients with generalized myasthenia gravis. Importantly, the primary and first secondary endpoints required patients to not only have a clinically meaningful improvement in the associated outcome measure, but for it to persist for at least four weeks. The data suggests that reduction of pathogenic IgG antibodies through inhibition of neonatal Fc receptor recycling may be an effective approach to the treatment of generalized myasthenia gravis and potentially other IgG mediated autoimmune diseases.

Table 1. Baseline demographic and clinical characteristics

	All patients			AChR-Ab+	
	Efgartigimod (n = 84)	Placebo (n = 83)	Total (n = 167)	Efgartigimod (n = 65)	Placebo (n = 64)
Age, years	45·9 (14·4)	48·2 (15·0)	47·0 (14·7)	44·7 (15·0)	49·2 (15·5)
Female, n (%)	63 (75·0)	55 (66·3)	118 (70·7)	46 (70·8)	40 (62·5)
Race, n (%)[†]					
Asian	9 (10·7)	7 (8·4)	16 (9·6)	7 (10·8)	4 (6·3)
Black/African American	3 (3·6)	3 (3·6)	6 (3·6)	1 (1·5)	3 (4·7)
White	69 (82·1)	72 (86·7)	141 (84·4)	54 (83·1)	56 (87·5)
Time since gMG diagnosis, years	10·1 (9·0)	8·8 (7·6)	9·5 (8·4)	9·7 (8·3)	8·9 (8·2)
MGFA class at screening, n (%)[**]					
Class II	34 (40·5)	31 (37·3)	65 (38·9)	28 (43·1)	25 (39·1)
Class III	47 (56·0)	49 (59·0)	96 (57·5)	35 (53·8)	36 (56·3)
Class IV	3 (3·6)	3 (3·6)	6 (3·6)	2 (3·1)	3 (4·7)

Previous thymectomy, n (%)	59 (70·2)	36 (43·4)	95 (56·9)	45 (69·2)	30 (46·9)
AChR-Ab+, n (%)	65 (77·4)	64 (77·1)	129 (77·2)	65 (100)	64 (100)
MuSK-Ab+, n (%)	3 (3·6)	3 (3·6)	6 (3·6)	0	0
AChR/MuSK-Ab-, n (%)	16 (19·0)	16 (19·3)	32 (19·2)	0	0
Total MG-ADL score	9·2 (2·6)	8·8 (2·3)	9·0 (2·5)	9·0 (2·5)	8·6 (2·1)
Total QMG score	16·2 (5·0)	15·5 (4·6)	15·9 (4·8)	16·0 (5·1)	15·2 (4·4)
Total MGC score	18·8 (6·1)	18·3 (5·5)	18·5 (5·8)	18·6 (6·1)	18·1 (5·2)
Total MG-QoL15r score	16·1 (6·4)	16·8 (5·7)	16·4 (6·0)	15·7 (6·3)	16·6 (5·5)
≥1 Prior NSIST, n (%)	62 (73·8)	57 (68·7)	119 (71·3)	47 (72·3)	43 (67·2)
MG therapy at baseline, n (%)					
Any steroid	60 (71·4)	67 (80·7)	127 (76·0)	46 (70·8)	51 (79·7)
Any NSIST	51 (60·7)	51 (61·4)	102 (61·1)	40 (61·5)	37 (57·8)
Steroid + NSIST	43 (51·2)	44 (53·0)	87 (52·1)	34 (52·3)	31 (48·4)
No steroid nor NSIST	16 (19·0)	7 (8·4)	23 (13·8)	13 (20·0)	6 (9·4)

AChE, acetylcholinesterase; AChR-Ab+, acetylcholine receptor autoantibody positive; NSIST, non-steroidal immunosuppressive treatments; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; NSIST, non-steroidal immunosuppressant therapy; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.

*Data are mean (SD) unless otherwise noted.

†Only the most prevalent categories are shown.

**Percents may not total 100·0% due to roundin

Table 2. Summary of primary and secondary endpoints

	Population	Time frame	Efgartigimod	Placebo	OR, 95% CI, P-value
MG-ADL responder (primary endpoint)	AChR Ab +	Cycle 1	67·7% (44/65)	29·7% (19/64)	4.95, 2.21 to 11.53, <0·0001
QMG responder	AChR Ab +	Cycle 1	63·1% (41/65)	14·1% (9/64)	10.84, 4.18 to 31.20, <0·0001
MG-ADL responder	Overall	Cycle 1	67·9% (57/84)	37·3% (31/83)	3.70, 1.85 to 7.58, <0·0001
% of time with ≥2-point improvement in MG-ADL	AChR Ab +	Until day 126*	48·7%	26·6%	0·0001
Time from day 28 until no CMI	AChR Ab +	Full study	Median 35 days	Median 8 days	0·2604
Early MG-ADL responder	AChR Ab +	Cycle 1	56·9% (37/65)	25·0% (16/64)	Not Tested*

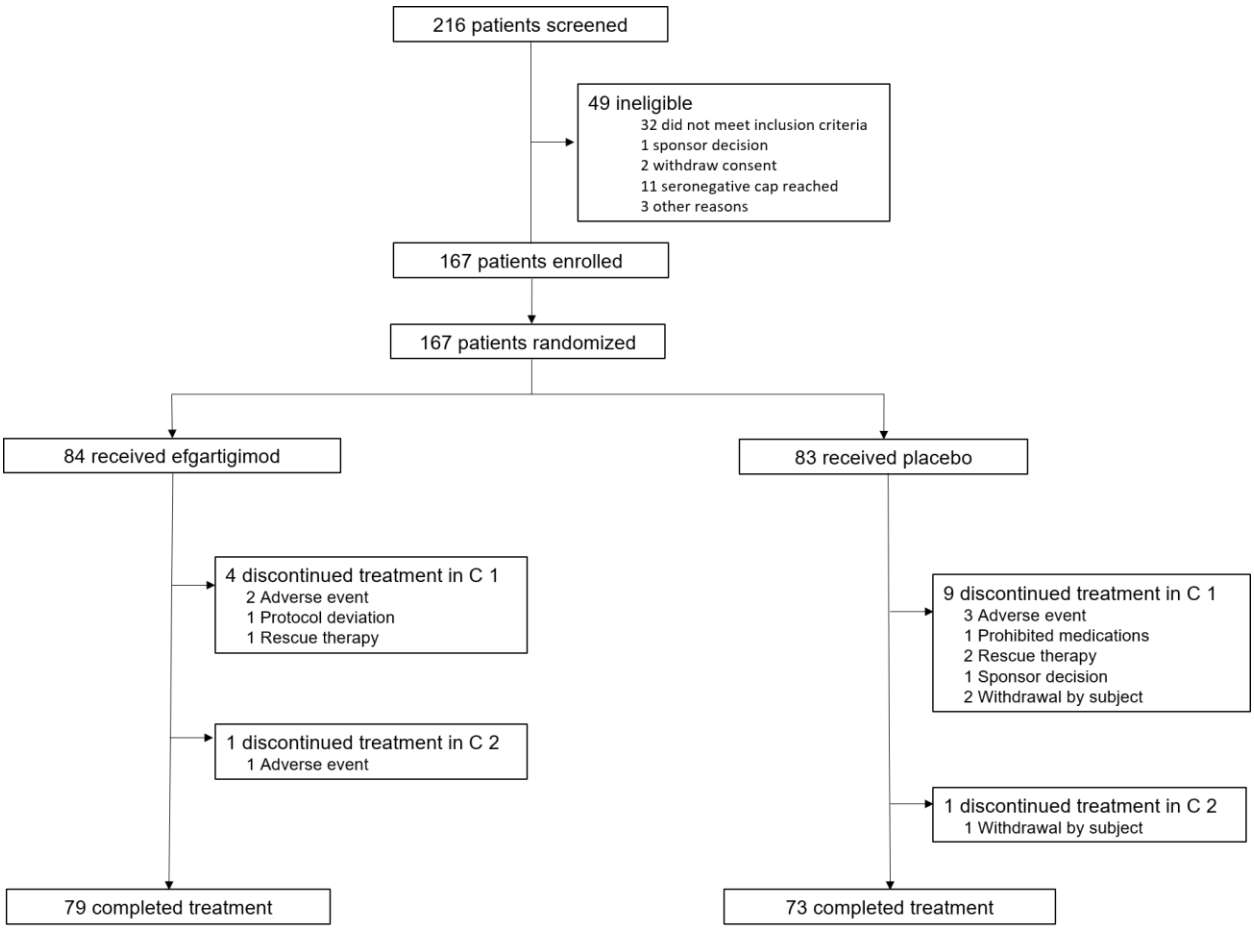
*secondary endpoints were tested in hierarchical order. The 5th secondary endpoint was not tested as the 4th secondary endpoint did not achieve statistical significance. CMI, clinically meaningful improvement.

Table 3. Summary of adverse events in all patients

	Efgartigimod (n = 84)	**Placebo (n = 83)**
Any AE	65 (77·4)	70 (84·3)
Any serious AE	4 (4·8)	7 (8·4)
Any AE leading to discontinuation of study drug	3 (3·6)	3 (3·6)
Any infection AE	39 (46·4)	31 (37·3)
≥1 Infusion-related reaction event	3 (3·6)	8 (9·6)
Most common adverse events		
Headache	24 (28·6)	23 (27·7)
Nasopharyngitis	10 (11·9)	15 (18·1)
Nausea	7 (8·3)	9 (10·8)
Diarrhea	6 (7·1)	9 (10·8)
Upper respiratory tract infection	9 (10·7)	4 (4·8)
Urinary tract infection	8 (9·5)	4 (4·8)

MG, myasthenia gravis; AE, adverse event.

Figure 1



C, cycle.

Figure 2

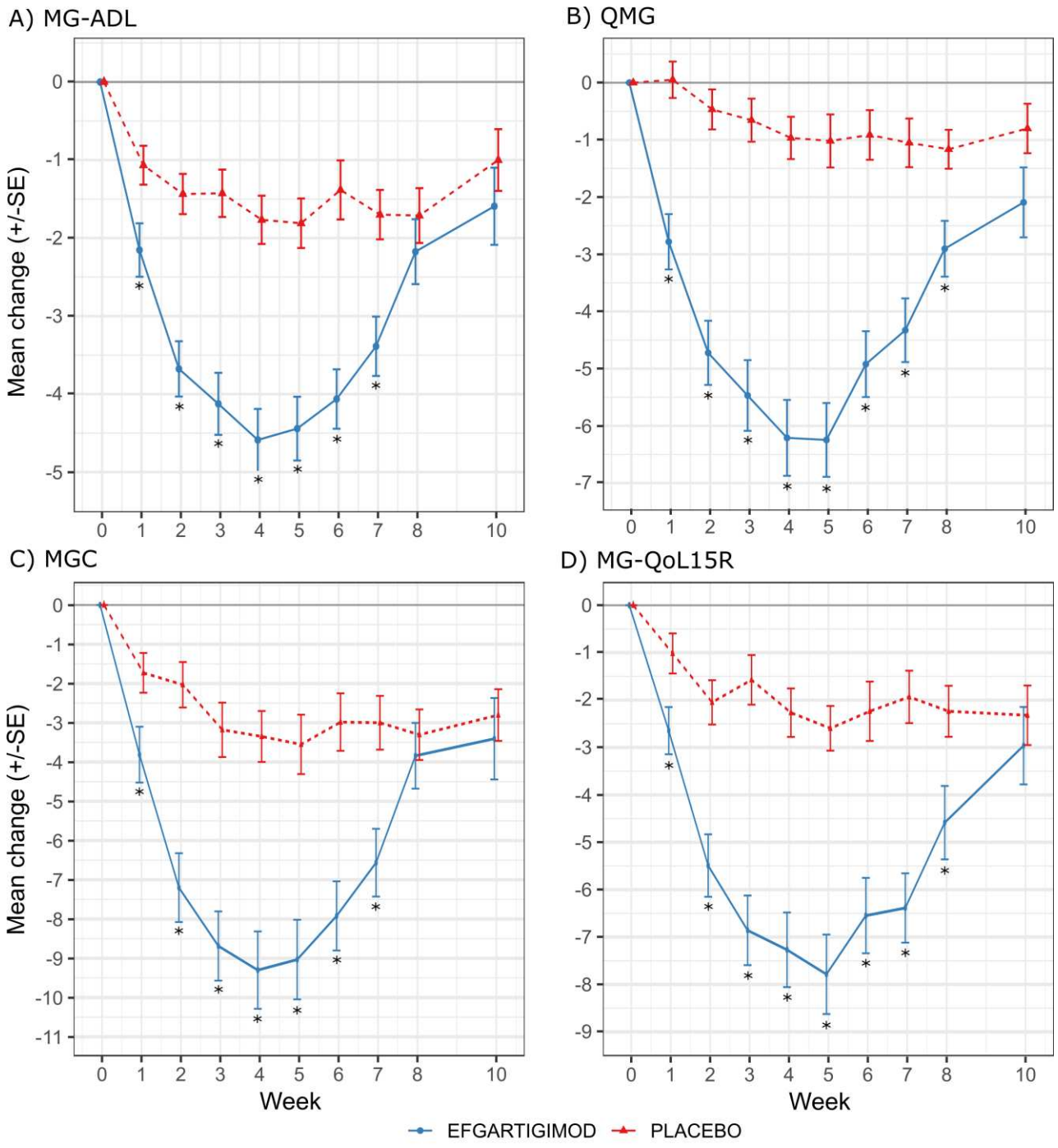

A) MG-ADL
B) QMG
C) MGC
D) MG-QoL15R
Mean change (+/-SE)
Week
EFGARTIGIMOD
PLACEBO

Figure 3

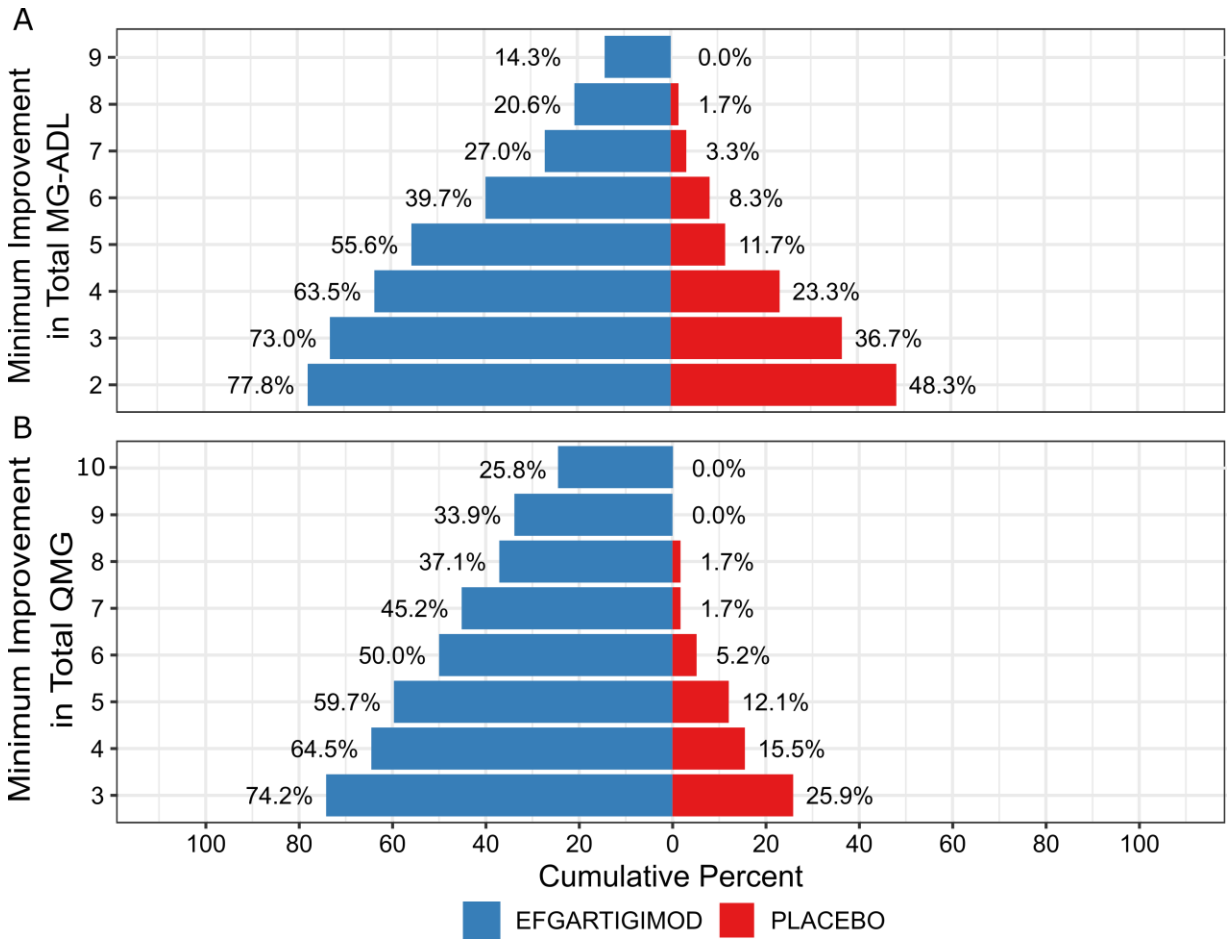

A
Minimum Improvement in Total MG-ADL
9
8
7
6
5
4
3
2
14.3%
0.0%
20.6%
1.7%
27.0%
3.3%
39.7%
8.3%
55.6%
11.7%
63.5%
23.3%
73.0%
36.7%
77.8%
48.3%
B
Minimum Improvement in Total QMG
10
9
8
7
6
5
4
3
25.8%
0.0%
33.9%
0.0%
37.1%
1.7%
45.2%
1.7%
50.0%
5.2%
59.7%
12.1%
64.5%
15.5%
74.2%
25.9%
100
80
60
40
20
0
20
40
60
80
100
Cumulative Percent
EFGARTIGIMOD
PLACEBO

Figure Legends:

Figure 1: Trial Profile

Figure 2: Change of four outcome scales during C1: Mean change over time of A) MG-ADL, B) QMG, C) MGC, and D) MG-QoL15R in AChR-Ab+ patients. Significance in improvement of efgartigimod treated patients compared to placebo was achieved at week 1 and maintained through week 7 for all scales, and week 8 for QMG and MG-QoL15R (at least $p < 0{\cdot}05 = *$). Error bars indicate standard error.

Figure 3: Minimum point improvement of primary and secondary outcome measures: Minimum improvements in C1 of A) MG-ADL and B) QMG one week after the last infusion of C1 (week 4) in AChR-Ab+ patients.