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

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*Study group members are in the appendix (pp 15–23)

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Summary

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

Methods ADAPT was a randomised, double-blind, placebo-controlled, phase 3 trial done at 56 neuromuscular academic and community centres in 15 countries in North America, Europe, and Japan. Patients aged at least 18 years with generalised myasthenia gravis were eligible to participate in the study, regardless of anti-acetylcholine receptor antibody status, if they had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 (>50% non-ocular), and were on a stable dose of at least one treatment for generalised myasthenia gravis. Patients were randomly assigned by interactive response technology (1:1) to efgartigimod (10 mg/kg) or matching placebo, administered as four infusions per cycle (one infusion per week), repeated as needed depending on clinical response no sooner than 8 weeks after initiation of the previous cycle. Patients, investigators, and clinical site staff were all masked to treatment allocation. The primary endpoint was proportion of acetylcholine receptor antibody-positive patients who were MG-ADL responders (≥2-point MG-ADL improvement sustained for ≥4 weeks) in the first treatment cycle. The primary analysis was done in the modified intention-to-treat population of all acetylcholine receptor antibody-positive patients who had a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment. The safety analysis included all randomly assigned patients who received at least one dose or part dose of efgartigimod or placebo. This trial is registered at ClinicalTrials.gov (NCT03669588); an open-label extension is ongoing (ADAPT+, NCT03770403).

Findings Between Sept 5, 2018, and Nov 26, 2019, 167 patients (84 in the efgartigimod group and 83 in the placebo group) were enrolled, randomly assigned, and treated. 129 (77%) were acetylcholine receptor antibody-positive. Of these patients, more of those in the efgartigimod group were MG-ADL responders (44 [68%] of 65) in cycle 1 than in the placebo group (19 [30%] of 64), with an odds ratio of 4·95 (95% CI 2·21–11·53, p<0·0001). 65 (77%) of 84 patients in the efgartigimod group and 70 (84%) of 83 in the placebo group had treatment-emergent adverse events, with the most frequent being headache (efgartigimod 24 [29%] *vs* placebo 23 [28%]) and nasopharyngitis (efgartigimod ten [12%] *vs* placebo 15 [18%]). Four (5%) efgartigimod-treated patients and seven (8%) patients in the placebo group had a serious adverse event. Three patients in each treatment group (4%) discontinued treatment during the study. There were no deaths.

Interpretation Efgartigimod was well tolerated and efficacious in patients with generalised myasthenia gravis. The individualised 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 ongoing open-label extension.

Funding argenx.

Introduction

Generalised myasthenia gravis is a rare, chronic, autoimmune disease that causes 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]

Most patients with generalised myasthenia gravis (about 85%) have IgG autoantibodies, most often directed against the skeletal muscle nicotinic acetylcholine receptor and less frequently against muscle-specific tyrosine kinase (MUSK) and low-density lipoprotein receptor-related protein 4 (LRP4).[2,3] A small proportion of patients have no identifiable antibodies. These autoantibodies exert a direct

Research in context

Evidence before this study

We searched PubMed up to Nov 5, 2020, for relevant clinical studies in generalised myasthenia gravis, with no language restrictions. Key search terms included "neonatal Fc receptor", "IgG recycling", "antibody fragment", and "autoantibody reduction". Although preclinical and early-phase studies had been completed with some neonatal Fc receptor antagonists, we found no phase 3 studies in generalised myasthenia gravis. Additionally, although therapeutic plasma exchange had shown the effect 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 acetylcholine receptor autoantibodies.

Added value of this study

Although there are treatment options available to patients with generalised myasthenia gravis, they are frequently burdensome, have substantial side-effects, do not alleviate symptoms, or are reserved for refractory patients. ADAPT was the largest clinical trial in patients with generalised 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 in the efgartigimod group than in the placebo group had clinically meaningful improvements in their Myasthenia Gravis Activities of Daily Living and Quantitative Myasthenia Gravis scores.

Implications of all the available evidence

The study used four validated myasthenia gravis-specific outcome measures, utilising both patient-reported and physician-reported information, to assess the effects of efgartigimod in patients with generalised myasthenia gravis. Notably, the primary and some secondary endpoints required patients to have a clinically meaningful improvement in the associated outcome measure, and for this improvement to persist for at least 4 weeks. The data suggest that reduction of pathogenic IgG antibodies through inhibition of neonatal Fc receptor recycling might be an effective approach to the treatment of a broad population of generalised myasthenia gravis and should encourage research in other IgG-mediated autoimmune diseases.

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See **Online** for appendix

pathogenic effect in generalised myasthenia gravis and their mechanisms of action include functional blockade, accelerated internalisation, and degradation of acetylcholine receptors and activation of complement.[4–7] These actions lead to reduced density of functional acetylcholine receptors and damage to the neuromuscular junction, resulting in impaired neuromuscular transmission.[4–7] Most acetylcholine receptor and LRP4 antibodies are of the IgG1 subtype, which can activate complement, whereas the IgG4 subtype, which includes MUSK antibodies, 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 generalised myasthenia gravis 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] Another therapeutic approach has been to block complement activation, targeting one of the downstream pathogenic pathways triggered specifically by acetylcholine receptor antibodies.[11,12] Overall, there remains a significant unmet need for generalised myasthenia gravis treatment options that are effective, targeted, well tolerated, and can be used in a broad population of patients.[2,13,14]

The neonatal Fc receptor (FcRn) is an MHC class I-like molecule that recycles IgG, extending its half-life by about four times that of other immunoglobulins that are not recycled by FcRn (eg, IgM or IgA).[15] Following cellular uptake, the Fc region of an IgG antibody binds two FcRn receptors under acidic conditions in the endosome.[16] IgGs bound to FcRn are rescued from lysosomal degradation and released at physiological pH outside the cell.[17–20] Therefore, FcRn perpetuates the availability of IgG autoantibodies in IgG-mediated diseases such as generalised myasthenia gravis. The utility of removing autoantibodies in generalised myasthenia gravis has been demonstrated by the effectiveness of plasma exchange and immunoadsorption; however, their use is limited by availability and requirement for specialised facilities.[21] Blocking FcRn is a rational therapeutic approach to target the key pathogenic driver in generalised myasthenia gravis.

Efgartigimod (ARGX-113) is a human IgG1 antibody Fc-fragment, a natural ligand of FcRn, that has been engineered for increased affinity to FcRn compared with endogenous IgG while retaining the characteristic pH dependence.[22] It outcompetes endogenous IgG binding, thereby reducing IgG recycling and increasing IgG degradation.[22] 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.[22,23] These reductions were associated with clinically meaningful and sustained improvements in generalised myasthenia gravis symptoms and activities of daily living. The phase 3 ADAPT study aimed to assess the safety and efficacy of efgartigimod, in patients with generalised myasthenia gravis.[23]

Methods

Study design

ADAPT was a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial of efgartigimod in patients with generalised myasthenia gravis. Patients were recruited from 56 neuromuscular academic and community centres across Japan and 14 countries in Europe and North America (appendix pp 2–11). 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

Patients aged at least 18 years with generalised myasthenia gravis, with or without acetylcholine receptor antibodies, were eligible if their disease was categorised as Myasthenia Gravis Foundation of America class II to IV and they had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 (with >50% of the MG-ADL score due to non-ocular symptoms). Diagnosis was supported by a history of abnormal neuromuscular transmission tests, a positive edrophonium chloride test, or improvement with acetylcholinesterase inhibitors. Eligibility criteria also required patients to be on a stable dose of at least one treatment for generalised myasthenia gravis (ie, acetylcholinesterase inhibitors, corticosteroids, or NSISTs) before screening and throughout the trial. There was no requirement for specific generalised myasthenia gravis therapies.

Patients were excluded if they had received rituximab or eculizumab in the 6 months before screening, undergone thymectomy within 3 months, had intravenous immunoglobulin or plasma exchange 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 less than 6 g/L at screening, or were pregnant. A complete list of inclusion and exclusion criteria is in the appendix (pp 11–12). Potential patients were recruited through the investigators' practice or via physician referral. All patients provided written informed consent before starting the study.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to either efgartigimod or placebo. Placebo was matched to efgartigimod in appearance and supplied in identical containers. Randomisation was performed centrally using interactive response technology, using both web and voice systems, by an independent company (SGS, Zwijnaarde, Belgium) that held randomisation codes until after the final database lock. Randomisation was based on three stratification factors: acetylcholine receptor antibody status (positive *vs* negative), NSISTs (taking *vs* not taking), and Japanese nationality (yes *vs* no). The stratification factors were selected to ensure consistency of effect across antibody status, concomitant medication, and ethnicities. Due to the small number of patients anticipated at individual centres, randomisation was done across, rather than within, the centres. Investigators, patients, study personnel, clinic staff, and the funder remained masked to treatment assignments for the duration of the study.

Procedures

Patients were screened for the study during a 2-week period, which was followed by a 26-week treatment period. Efgartigimod (10 mg/kg) or matching placebo was administered as four infusions per cycle (one infusion per week). After each cycle there was a period of at least 5 weeks of follow-up. All patients received an initial cycle, with subsequent cycles administered according to individual clinical response when MG-ADL score was at least 5 (with >50% MG-ADL non-ocular) and, if the patient was an MG-ADL responder, when they no longer had a clinically meaningful decrease (MG-ADL clinically meaningful improvement defined as having ≥2-point improvement in total MG-ADL score) compared with baseline. Subsequent cycles could commence no sooner than 8 weeks from initiation of the previous cycle; a maximum of three cycles were possible in the 26-week study. Patients who required rescue therapy were discontinued from study treatment. Patients who completed the study or could not complete a cycle before study end (retreatment after day 126) were able to rollover to the ongoing open-label extension study (ADAPT+; NCT03770403).

Efficacy was assessed with the MG-ADL scale (patient-reported, physician-recorded outcome measure);[24] Quantitative Myasthenia Gravis (QMG) score (physician assessed, including quantitative measures; clinically meaningful improvement ≥3-point reduction),[25] Myasthenia Gravis Composite (MGC) scale (patient and physician assessed; clinically meaningful improvement ≥3-point reduction);[26] the 15-item revised version of the Myasthenia Gravis Quality of Life (MG-QOL15r)[27] questionnaire (patient completed), and EQ5D quality of life scale (patient completed).

Assessments were done weekly for 8 weeks after initiation of each cycle and then every 2 weeks up to 26 weeks.

Pharmacodynamic effects were analysed using validated assays of total IgG, IgG subtypes (IgG1, IgG2, IgG3, and IgG4), and autoantibodies (anti-acetylcholine receptor antibodies for the acetylcholine receptor antibody-positive patients and antibodies against MUSK for the MUSK antibody-positive patients). The validated assays were a radioimmunoassay (IBL International, Hamburg, Germany) that used acetylcholine receptor labelled with ^{125}I-α-bungarotoxin for anti-acetylcholine receptor antibodies and an ELISA (IBL International) for anti-MUSK antibodies.

Outcomes

The primary efficacy endpoint was the proportion of acetylcholine receptor antibody-positive patients who were MG-ADL responders in the first treatment cycle. An

MG-ADL responder was defined as a patient who had at least a 2-point improvement (reduction) in MG-ADL score, sustained for at least 4 consecutive weeks, with the first improvement occurring by week 4 of the cycle (1 week after the fourth infusion). Secondary endpoints were assessed in hierarchical order, as follows: (1) proportion 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 cycle 1) in the acetylcholine receptor antibody-positive population; (2) percentage of MG-ADL responders in cycle 1 in the overall population (ie, acetylcholine receptor antibody-positive and antibody-negative patients); (3) proportion of time patients showed a clinically meaningful improvement in MG-ADL score in the acetylcholine receptor antibody-positive population, up to day 126; (4) time from day 28 (1 week after the fourth infusion in cycle 1) to not having clinically meaningful improvement in the acetylcholine receptor antibody-positive population; and (5) proportion of early MG-ADL responders in cycle 1 (MG-ADL responders with first MG-ADL improvement of ≥2 points occurring by week 2) in the acetylcholine receptor antibody-positive population.

Safety was assessed through incidence of adverse events and changes in clinical laboratory values and vital signs, and on electrocardiograms. Tertiary endpoints were pharmacodynamics and immunogenicity.

Predefined exploratory endpoints assessed time to onset of effect; magnitude of effect, including proportion of patients achieving minimal symptom expression (defined as MG-ADL score of 0 or 1) and proportion of patients with 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 Myasthenia Gravis Composite and MG-QOL15r scores.

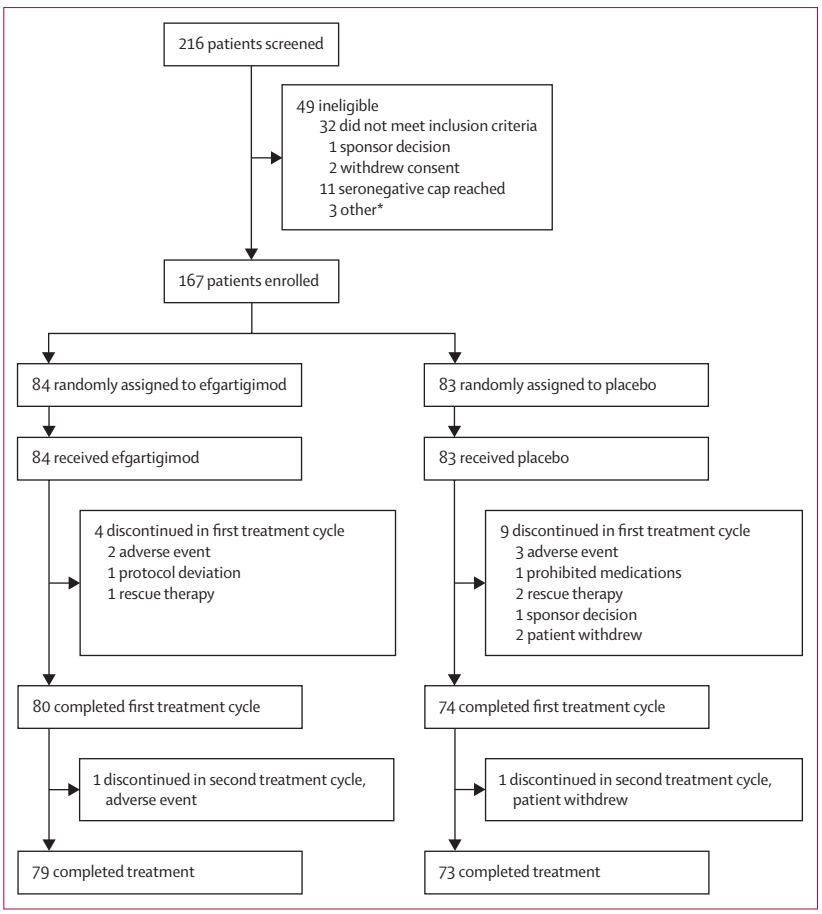

Figure 1: **Trial profile**
*Absence of laboratory results on the day before the final day of the screening period.

Statistical analysis

The proportion of MG-ADL responders in the placebo group was hypothesised to be 30%. The treatment difference was assumed to be 35% for acetylcholine receptor antibody-positive patients and 5% for acetylcholine receptor antibody-negative patients. A difference of total MG-ADL responder rate of 35% between the placebo and efgartigimod primary acetylcholine receptor antibody-positive population is considered clinically relevant. In the phase 2 ARGX-113-1602 study,[23] the total MG-ADL responder rate was 33% for placebo (three of 12) and 75% (nine of 12) for efgartigimod. Sample size was based on allowing enrolment of up to 20% acetylcholine receptor antibody-negative patients. Based on this quota, a sample size of 150 provided power of 96% in the primary population of acetylcholine receptor antibody-positive patients to detect a difference of 35% in the proportion of responders with 120 patients. The sample size also provided a power of 90% to detect a 29% difference in the proportion of responders in the overall population with a two-sided α level of 5%, allowing for a 10% dropout rate.

Efficacy analyses were done in the modified intention-to-treat population, including all randomly assigned patients who had a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment. Safety analyses were done in all patients who received at least one dose or part of a dose. Patients were discontinued from treatment if they became pregnant, received rescue therapy (plasma exchange, intravenous immunoglobulin, immunoadsorption, any new type of corticosteroid, or 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 jeopardise the safety of the patient, or developed a bacterial, viral, or fungal infection (evaluated on a case-by-case basis). After discontinuation, patients who did not withdraw consent were followed up for safety and disease severity assessments through the rest of the trial.

Statistical analyses were done using SAS, version 9.2 or higher, and the software package R, where applicable. The

	All patients		Acetylcholine receptor antibody-positive patients	
	Efgartigimod group (n=84)	Placebo group (n=83)	Efgartigimod group (n=65)	Placebo group (n=64)
Age, years	45·9 (14·4)	48·2 (15·0)	44·7 (15·0)	49·2 (15·5)
Sex				
Female	63 (75%)	55 (66%)	46 (71%)	40 (63%)
Male	21 (25%)	28 (34%)	19 (29%)	24 (38%)
Race				
Asian	9 (11%)	7 (8%)	7 (11%)	4 (6%)
Black or African American	3 (4%)	3 (4%)	1 (2%)	3 (5%)
White	69 (82%)	72 (87%)	54 (83%)	56 (88%)
Other*	3 (4%)	1 (1%)	3 (5%)	1 (2%)
Time since generalised myasthenia gravis diagnosis, years	10·1 (9·0)	8·8 (7·6)	9·7 (8·3)	8·9 (8·2)
MGFA class at screening				
II	34 (40%)	31 (37%)	28 (43%)	25 (39%)
III	47 (56%)	49 (59%)	35 (54%)	36 (56%)
IV	3 (4%)	3 (4%)	2 (3%)	3 (5%)
Previous thymectomy	59 (70%)	36 (43%)	45 (69%)	30 (47%)
Acetylcholine receptor antibody-positive	65 (77%)	64 (77%)	65 (100%)	64 (100%)
MUSK antibody-positive	3 (4%)	3 (4%)	0	0
Acetylcholine receptor or MUSK antibody-negative	16 (19%)	16 (19%)	0	0
Total MG-ADL score	9·2 (2·6)	8·8 (2·3)	9·0 (2·5)	8·6 (2·1)
Total Quantitative Myasthenia Gravis score	16·2 (5·0)	15·5 (4·6)	16·0 (5·1)	15·2 (4·4)
Total Myasthenia Gravis Composite score	18·8 (6·1)	18·3 (5·5)	18·6 (6·1)	18·1 (5·2)
Total MG-QOL15r score	16·1 (6·4)	16·8 (5·7)	15·7 (6·3)	16·6 (5·5)
At least one previous NSIST	62 (74%)	57 (69%)	47 (72%)	43 (67%)
Myasthenia gravis therapy at baseline				
Any steroid	60 (71%)	67 (81%)	46 (71%)	51 (80%)
Any NSIST	51 (61%)	51 (61%)	40 (62%)	37 (58%)
Steroid and NSIST	43 (51%)	44 (53%)	34 (52%)	31 (48%)
No steroid or NSIST	16 (19%)	7 (8%)	13 (20%)	6 (9%)

Data are mean (SD) or n (%). MG-ADL=Myasthenia Gravis Activities of Daily Living. MGFA=Myasthenia Gravis Foundation of America. MG-QOL15r=15-item revised version of the Myasthenia Gravis Quality of Life. NSIST=non-steroidal immunosuppressant therapy. *Includes American Indian or Alaska Native (n=2) and multiple (n=1) for the efgartigimod group, and not reported for the placebo group (n=1).

Table 1: **Baseline demographic and clinical characteristics**

primary endpoint was tested by means of a two-sided exact test using a logistic regression model with baseline total score as a covariate and the three stratification factors as variables. The treatment effect was presented as an odds ratio (OR) with 95% CI and two-sided p value. If the primary endpoint met significance at the 5% two-sided α level, secondary endpoints were tested at a 5% two-sided significance level in hierarchical order using a fixed-sequence approach. The secondary endpoints of QMG responders in cycle 1 in the acetylcholine receptor antibody-positive population, MG-ADL responders in cycle 1 in the overall population, and percentage of early MG-ADL responders in cycle 1 in the acetylcholine receptor antibody-positive population were tested using the same logistic regression model as for the primary endpoint. Percentage of time patients showed a clinically meaningful improvement in MG-ADL score in the acetylcholine receptor antibody-positive population was analysed using an ANCOVA model. In this analysis, randomised treatment group and the stratification variables were included as factors, and baseline total MG-ADL score was included as a covariate. Time from day 28 to not having clinically meaningful improvement in the acetylcholine receptor antibody-positive 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 analysed in a descriptive manner. This study is registered at ClinicalTrials.gov (NCT03669588).

Role of the funding source

The funder of the study had a role in study design, data collection, data interpretation, data analysis, and writing of the report.

Results

216 patients were screened between Sept 5, 2018, and Nov 26, 2019, of whom 167 (84 in the efgartigimod group and 83 in the placebo group) were enrolled, randomly assigned, and treated (figure 1). 129 (77%) were acetylcholine receptor antibody-positive and 38 (23%) were acetylcholine receptor antibody-negative, of whom six (4%) were MUSK antibody-positive. There were five treatment discontinuations in the efgartigimod group and ten in the placebo group.

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

Most patients (144 [86%] of 167) were receiving immunosuppressive treatment (steroids or NSISTs). 48 (29%) had never previously been treated with an NSIST. The mean baseline MG-ADL and QMG scores demonstrate substantial disease burden despite ongoing generalised myasthenia gravis treatment.

The number of cycles of assigned treatment received by patients during the study is in the appendix (p 13). In efgartigimod-treated patients, the median duration of cycle 1 (time from first infusion in cycle 1 until first infusion in cycle 2 or final visit of study) was 10 weeks (IQR 71–113 days) and for placebo-treated patients, the median duration was 10 weeks (71–141 days).

A significantly higher proportion of acetylcholine receptor antibody-positive patients in the efgartigimod group (44 [68%] of 65) were MG-ADL responders in cycle 1 (primary endpoint) than in the placebo group (19 [30%] of 64; OR 4·95 [95% CI 2·21–11·53], p<0·0001; table 2). Additionally, a significantly greater proportion of patients

	Efgartigimod group	Placebo group	OR (95% CI)	p value
MG-ADL responder in cycle 1 (primary endpoint)	44/65 (68%)	19/64 (30%)	4·95 (2·21–11·53)	<0·0001
Quantitative Myasthenia Gravis responder in cycle 1	41/65 (63%)	9/64 (14%)	10·84 (4·18–31·20)	<0·0001
MG-ADL responder in cycle 1 (all patients)	57/84 (68%)	31/83 (37%)	3·70 (1·85–7·58)	<0·0001
Percentage of time with ≥2-point improvement in MG-ADL up to day 126	48·7%	26·6%	..	0·0001
Median time from day 28 until no clinically meaningful improvement, days	35 (18–71)	8 (1–57)	..	0·26
Early MG-ADL responder (cycle 1)	37/65 (57%)	16/64 (25%)	..	Not assessed*

Data are n/N (%), or median (IQR), unless stated otherwise. Analyses were done in acetylcholine receptor antibody-positive patients unless otherwise stated. MG-ADL=Myasthenia Gravis Activities of Daily Living. *Secondary endpoints were tested in hierarchical order. The fifth secondary endpoint was not assessed because the fourth secondary endpoint was not significant.

Table 2: **Summary of primary and secondary endpoints**

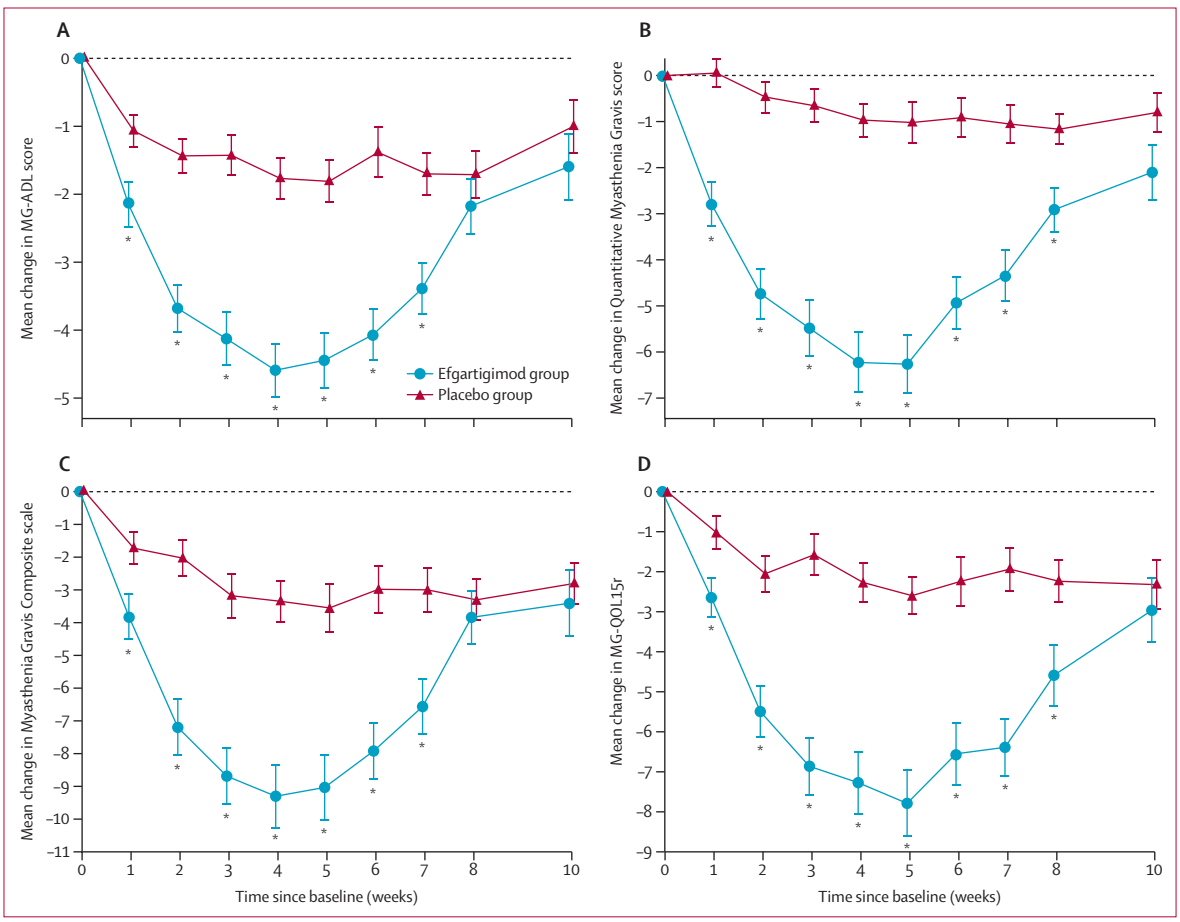

Figure 2: **Change in MG-ADL (A), Quantitative Myasthenia Gravis score (B), Myasthenia Gravis Composite scale (C), and MG-QOL15r (D) during cycle 1, in acetylcholine receptor antibody-positive patients**

Error bars show standard error. MG-ADL=Myasthenia Gravis Activities of Daily Living. MG-QOL15r=15-item revised version of the Myasthenia Gravis Quality of Life questionnaire. *p<0·05.

in the efgartigimod group (41 [63%] of 65) were QMG responders in cycle 1 than in the placebo group (nine [14%] of 64; OR 10·84 [95% CI 4·18–31·20], p<0·0001; table 2).

Patients in the efgartigimod group had greater total mean score improvements in MG-ADL, QMG, MCG, and MG-QOL15r in cycle 1, 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 proportion of patients in the efgartigimod group than in the placebo group achieved higher levels of improvement in MG-ADL (up to 9-point reduction) and

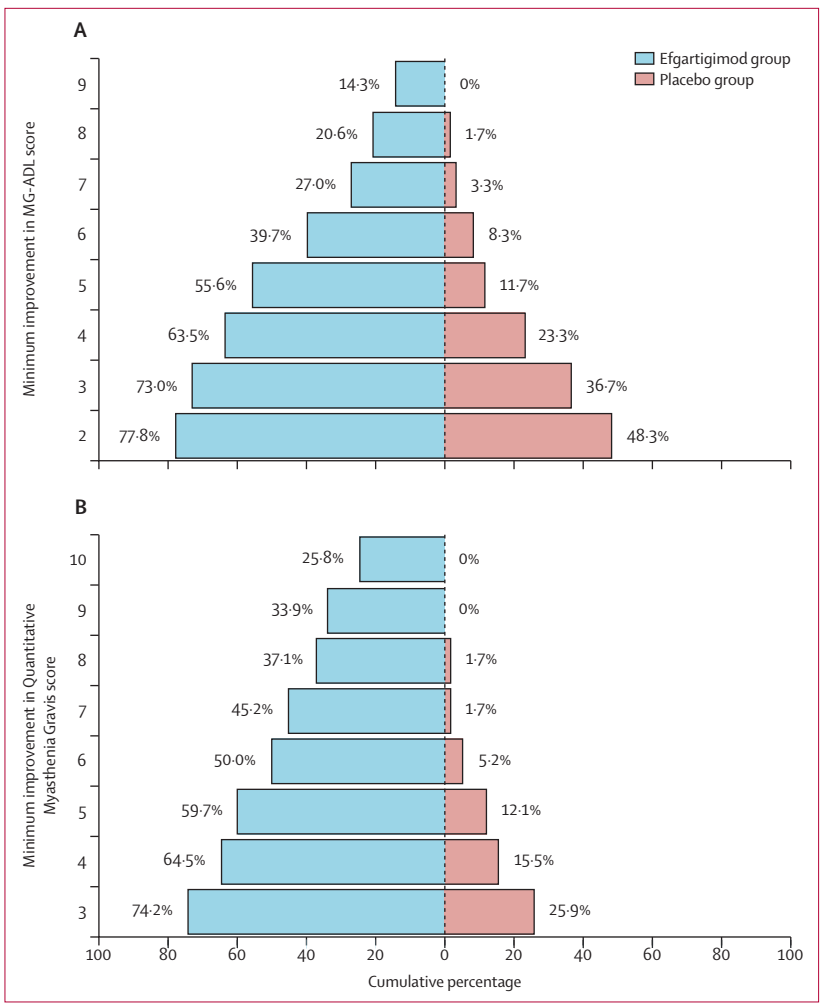

Figure 3: **Minimum point improvement in MG-ADL (A) and Quantitative Myasthenia Gravis (B) score in cycle 1, in acetylcholine receptor antibody-positive patients**
Minimum improvements 1 week after the last infusion of cycle 1 (week 4). MG-ADL=Myasthenia Gravis Activities of Daily Living.

QMG (up to 10-point reduction) score at week 4 (figure 3). 26 (40%) of 65 patients in the efgartigimod group attained an MG-ADL score of 0 or 1 (minimal symptom expression) in cycle 1 compared with seven (11%) of 63 in the placebo group (p<0·0001).

More patients in the efgartigimod group than the placebo group were early MG-ADL responders (table 2). In the 44 acetylcholine receptor antibody-positive MG-ADL responders in the efgartigimod group, the onset of response occurred by week 2 in 37 (84%) patients.

Efgartigimod-treated patients showed a clinically meaningful improvement 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; table 2).

The median time from day 28 to not having clinically meaningful improvement over the course of the study was 35 days (IQR 18–71) with efgartigimod and 8 days (1–57) with placebo (p=0·26 log-rank test; table 2). Although a log-rank test was not significant, a Wilcoxon test done post hoc was significant (p=0·013).

Among cycle 1 MG-ADL responders, the duration of responder status was 6–7 weeks in 14 (32%) of 44 patients, 8–11 weeks in ten (23%) patients, and 12 weeks or more in 15 (34%) patients (data not shown).

In patients who received a second cycle, a greater proportion of patients in the efgartigimod group (36 [71%] of 51) were MG-ADL responders compared with the placebo group (11 [26%] of 43), with similar rates to cycle 1. Similar to cycle 1, there was a greater total mean score improvement in MG-ADL and QMG in the efgartigimod group than in the placebo group in the second treatment cycle (data not shown). Of the 44 acetylcholine receptor antibody-positive patients in the efgartigimod group who were MG-ADL responders in cycle 1, 32 qualified for retreatment and 29 (90%) of these were MG-ADL responders again in cycle 2. Among 21 patients in the efgartigimod group who were not MG-ADL responders during cycle 1, 19 were retreated and seven (37%) of these were MG-ADL responders in cycle 2. Six (86%) of seven patients in the efgartigimod group who received a third cycle were MG-ADL responders (data not shown).

Predefined exploratory analyses did not show any efficacy differences based on gender, age, or baseline MG-ADL (data not shown). Concomitant use of NSISTs also did not affect efficacy, with 18 (72%) MG-ADL responders of the 25 acetylcholine receptor antibody-positive patients in the efgartigimod group who were not on NSISTs. Of the 45 acetylcholine receptor antibody-positive efgartigimod-treated patients with previous thymectomy, 27 (60%) were MG-ADL responders, compared with 17 (85%) of 20 patients who had not previously undergone thymectomy.

Results in the overall population were similar to those in the acetylcholine receptor antibody-positive population, including significantly more patients in the efgartigimod group (57 [68%] of 84) who were MG-ADL responders in cycle 1 than in the placebo group (31 [37%] of 83; OR 3·70 [95% CI 1·85–7·58], p<0·0001; table 2).

Predefined exploratory analyses showed that in acetylcholine receptor antibody-negative patients, there was a similar number of MG-ADL responders in each treatment group in cycle 1: 13 (68%) of 19 patients in the efgartigimod group versus 12 (63%) of 19 in the placebo group. There were more QMG responders in the efgartigimod group than in the placebo group in cycle 1: ten (53%) versus seven (37%) patients. Six (32%) patients in the efgartigimod group achieved minimal symptom expression in cycle 1 versus three (16%) in the placebo group (data not shown).

A post-hoc analysis of acetylcholine receptor antibody-negative patients assessed the proportion of patients who were both MG-ADL and QMG responders in cycle 1: nine (47%) of 19 patients in the efgartigimod group and four (21%) of 19 in the placebo group. Among the

acetylcholine receptor antibody-negative patients, six were MUSK antibody-positive, three in each treatment group. All six patients were MG-ADL responders in cycle 1.

In acetylcholine receptor antibody-positive patients, there were mean maximum reductions of 61·3% (SD 0·9) in IgG and 57·6% (1·3) in acetylcholine receptor antibodies, 1 week after the fourth infusion in cycle 1 (appendix p 14). Levels returned to baseline by week 12 (9 weeks after the last infusion of cycle 1). Reductions were similar across subtypes, with mean maximum reductions of 68% (1·0) for IgG1, 60% (1·7) for IgG2, 63% (1·2) for IgG3, and 52% (1·7) for IgG4. Similar reductions in IgG and acetylcholine receptor antibodies were seen with each treatment cycle. However, no reductions in albumin levels were observed.

No deaths occurred during the study in either the efgartigimod or placebo groups. 65 (77%) of 84 patients in the efgartigimod group and 70 (84%) of 83 in the placebo group had adverse events, with the most frequent being headache, nasopharyngitis, nausea, diarrhoea, upper respiratory tract infections, and urinary tract infections (table 3). Incidence of headache was similar between groups; nausea, diarrhoea, and nasopharyngitis occurred in more placebo patients, and upper respiratory tract infections and urinary tract infections occurred in more efgartigimod patients. Most adverse events were mild or moderate in severity, with nine (11%) patients with severe events in the efgartigimod group and eight (10%) in the placebo group. Four (5%) efgartigimod-treated patients had a serious adverse event, which were thrombocytosis, rectal adenocarcinoma, myasthenia gravis worsening (each leading to treatment discontinuation), and depression. In the placebo group, seven (8%) patients had a serious adverse event, including one case each of myocardial ischaemia, atrial fibrillation, and spinal ligament ossification, which all led to treatment discontinuation. The remaining events were upper respiratory infection, spinal compression fracture, myasthenia gravis worsening, and myasthenia gravis crisis. Adverse events related to infections occurred in 39 (46%) patients in the efgartigimod group and 31 (37%) in the placebo group. All infections were reported as mild-to-moderate severity except for three severe events, which were influenza and pharyngitis in the efgartigimod group and upper respiratory tract infections in the placebo group. Infusion-related reactions were reported in three (4%) patients in the efgartigimod group and eight (10%) in the placebo group, all mild in severity. There were no clinically meaningful changes in haematology or chemistry parameters (including no decrease in albumin levels), electrocardiograms, or vital signs in either group.

	Efgartigimod group (n=84)	Placebo group (n=83)
Any adverse event	65 (77%)	70 (84%)
Any serious adverse event	4 (5%)	7 (8%)
Any adverse event leading to discontinuation of study drug	3 (4%)	3 (4%)
Any infection	39 (46%)	31 (37%)
Infusion-related reaction event	3 (4%)	8 (10%)
Most common adverse events		
Headache	24 (29%)	23 (28%)
Nasopharyngitis	10 (12%)	15 (18%)
Nausea	7 (8%)	9 (11%)
Diarrhoea	6 (7%)	9 (11%)
Upper respiratory tract infection	9 (11%)	4 (5%)
Urinary tract infection	8 (10%)	4 (5%)

Data are n (%).

Table 3: **Summary of adverse events in all patients**

Discussion

The ADAPT phase 3 trial showed that efgartigimod was well tolerated and efficacious in patients with generalised myasthenia gravis. The reduction in disease burden and improvement in strength and quality of life in patients with generalised myasthenia gravis were consistent across four myasthenia gravis-specific scales, and these benefits were observed early and were reproducible and durable.

The study enrolled a broad population of patients with generalised myasthenia gravis, including both antibody-positive and acetylcholine receptor antibody-negative patients, with no requirement for patients to have had specific myasthenia gravis medication. Most patients were receiving steroids or NSISTs; however, about 30% had not previously received an NSIST.

At enrolment, despite ongoing myasthenia gravis therapy, patients still had poor scores on the myasthenia gravis strength and function scales. Treatment with efgartigimod provided significant, clinically meaningful, and durable clinical benefit to most of these patients. Many patients had improvement beyond the clinically meaningful threshold, achieving up to 9-point reductions in MG-ADL and 10-point reductions in QMG. Minimal symptom expression was achieved by 40% of acetylcholine receptor antibody-positive efgartigimod-treated patients. Most patients had a clinically meaningful improvement in MG-ADL within 2 weeks of starting treatment. Although 68% of acetylcholine receptor antibody-positive patients were MG-ADL responders with the first treatment cycle, 78% of patients achieved this status during the study with further treatment cycles.

The early onset of action, observed benefit in patients with or without previous NSIST exposure, and the favourable tolerability profile suggest that efgartigimod might be able to be used throughout disease continuum of patients with generalised myasthenia gravis. Acetylcholine receptor antibodies cause a net reduction of functional acetylcholine receptors at the postsynaptic membrane. However, patients with generalised myasthenia gravis also have increased acetylcholine receptor synthesis and repopulation, shown through mRNA and

protein production, presumably as compensatory mechanisms.[28,29] Because of this, the reduction of acetylcholine receptor antibodies by efgartigimod after one infusion could lead to a corresponding increase in acetylcholine receptors at the postsynaptic membrane and potentially account for the early onset of effect.

Although more patients in the efgartigimod group had previously undergone thymectomy, a post-hoc analysis showed that the proportion of patients who were MG-ADL responders was lower in patients with previous thymectomy. Therefore, the increased prevalence of thymectomy in the efgartigimod group did not appear to favour 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 individualised approach to treatment according to patient's need proved effective, with reproducible efficacy after a second and third cycle.

A third of acetylcholine receptor antibody-positive MG-ADL responders maintained a clinically meaningful improvement in MG-ADL score for more than 12 weeks, suggesting that a proportion of patients have clinical benefit beyond the reduction in IgG and acetylcholine receptor antibodies. Production of sufficient acetylcholine receptor to restore the safety factor for neurotransmission might explain the prolonged effect in some patients, with appropriate reserves established to maintain neurotransmission even after return of acetylcholine receptor antibodies to normal levels.[30]

The secondary endpoint of time from day 28 of cycle 1 (1 week after the last infusion) until the patient not having a clinically meaningful improvement was numerically greater in the acetylcholine receptor antibody-positive efgartigimod group than placebo (35 days compared to 8 days); however, it was not significant (log-rank test, p=0·26). The log-rank test was not the most appropriate test, because 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.

68% of acetylcholine receptor antibody-negative efgartigimod-treated patients had a response, similar to that in acetylcholine receptor antibody-positive patients, but there was an unexpectedly high response rate in the placebo group. A post-hoc analysis of acetylcholine receptor antibody-negative patients who were both MG-ADL and QMG responders in cycle 1 showed a treatment effect, suggesting efgartigimod might be effective in this patient population. There were only six patients with anti-MUSK antibodies, three in each treatment group, and all six were MG-ADL responders in cycle 1. Further information regarding the efficacy in acetylcholine receptor antibody-negative patients will be gained in the ongoing open-label extension trial.

Efgartigimod reduced IgG levels in acetylcholine receptor antibody-positive patients, with similar reductions with each cycle and across IgG subtypes and a similar reduction in the antibody-negative patients. The reduction in acetylcholine receptor autoantibodies was similar to that of IgG, and both paralleled the improvements in symptoms. This showed that selective removal of IgG is an effective treatment approach in generalised myasthenia gravis, which is in line with the data available from plasma exchange, a treatment that removes autoantibodies and is considered highly efficacious but is limited by its administrative challenges.

Existing treatments for generalised myasthenia gravis are associated with burdensome short-term and long-term side-effects that can limit their use. Efgartigimod was well tolerated in this study, with most adverse events mild or moderate in severity and low incidence of infusion reactions. Although headache was the most common adverse event, it occurred in equal numbers of patients in both treatment groups. Efgartigimod did not reduce albumin levels, demonstrating its selectivity for the IgG binding site of FcRn and suggesting that it does not alter the function of FcRn.

The rate of infections is of special interest because patients with myasthenia gravis are predisposed to infections, probably exacerbated by concomitant immunosuppressive treatments.[31,32] In the efgartigimod-treated group, 46% of patients had an infection compared with 37% in the placebo group. Most infections were mild to moderate, with only two graded as severe in the efgartigimod-treated patients. Although longer term data are 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 effect on other immunoglobulins. Preclinical models have also shown that IgG production is not impaired.[33] Because of these factors, efgartigimod-treated patients should retain the potential to mount an IgG immune response.

Strengths of this study include the randomised 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. A broad population of patients with generalised myasthenia gravis was recruited.

Study limitations included the length of follow-up, which will be addressed by the ongoing open-label extension study. The retreatment criteria requiring patients' MG-ADL score to return to less than a 2-point reduction from baseline was a rigorous ADAPT study criterion and the usefulness in the real world will be established in clinical practice. The inclusion of acetylcholine receptor antibody-negative patients was important due to the limited treatment options these patients have and their lack of inclusion in previous clinical trials. However, only a few of these patients were recruited, and the trial

was not statistically powered to assess efficacy in this population.

The results of the phase 3 ADAPT trial suggest that the novel mechanism of selective IgG reduction through blocking of FcRn with efgartigimod is an effective and well tolerated treatment for patients with generalised myasthenia gravis.

Contributors

All authors had full access to the study design information and all data in the study and had final responsibility for the decision to submit for publication. JFH, VB, HM, AG, PU, TVa, JV, and RM contributed to the concept or design of the study. All authors contributed to the analysis and interpretation of data. JFH, AG, PU, and TVa accessed and verified the data in the study. Cello Health Communications, a medical writing company, produced the first draft of the paper based on input and direction from all authors. 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.

Declaration of interests

JFH 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 (NIH; including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), Patient Centered Outcomes Research Institute, and Ra Pharmaceuticals (now UCB); honoraria from Alexion Pharmaceuticals, argenx, Immunovant, Ra Pharmaceuticals (now UCB), Regeneron Pharmaceuticals, and Viela Bio; and non-financial support from Alexion Pharmaceuticals, argenx, Ra Pharmaceuticals (now UCB), and Toleranzia. VB has received research support from Commonwealth Serum Laboratories, Grifols, UCB, Bionevia, Shire, and Octapharma. TVu has served as a speaker for Alexion; has done consulting work for argenx and UCB; and participated in trials in myasthenia gravis sponsored by NIH, Alexion Pharmaceuticals, argenx, Ra, Viela Bio, UCB, and Grifols. CK 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. SP reports 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, all outside the submitted work. HM 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. AG, PU, and TVa are full-time employees of argenx, Ghent, Belgium. KU 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. JV receives research support from Target to B consortium, Prinses Beatrix Spierfonds, and argenx; has been involved in trials or consultancies for argenx, Alexion, and Ra pharma; JV is coinventor on patent applications based on MUSK-related research; and is a member of the European Reference Network for Rare Neuromuscular Diseases; and JV's institution received royalties from Immuno-Biological Laboratories. RM has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with BioMarin, Catalyst, Alexion Pharmaceuticals, UCB, and argenx. All other authors declare no competing interests.

Data sharing

argenx is committed to responsible data sharing regarding the clinical trials they fund. Included in this commitment is access to anonymised, 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 and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months. Requests can be submitted to ESR@argenx.com.

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