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ADIS DRUG EVALUATION

Efgartigimod: A Review in Generalised Myasthenia Gravis

Hannah A. Blair[1]

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Abstract

Efgartigimod (Vyvgart®; Vyvgart® Hytrulo) is a neonatal fragment crystallizable receptor (FcRn) antagonist indicated for the treatment of generalised myasthenia gravis (gMG) in adults who are acetylcholine receptor (AChR) antibody positive (Ab+). Efgartigimod is approved for both intravenous (IV) and subcutaneous (SC) use. In a pivotal phase III trial, IV efgartigimod was associated with significant and clinically meaningful improvements in myasthenia gravis symptoms and reductions in disease burden. The beneficial effects of IV efgartigimod were reproducible, durable and maintained over the long term. IV efgartigimod also improved health-related quality of life (HRQOL). In another phase III trial, SC efgartigimod PH20 was noninferior to IV efgartigimod in reducing total immunoglobulin G levels. Clinical improvement with SC efgartigimod PH20 was consistent with that of IV efgartigimod and was reproducible over the long term. Efgartigimod was generally well tolerated; the most common adverse events were headache and infections (with IV efgartigimod) and injection-site reactions (with SC efgartigimod PH20). Although further long-term data are required, IV and SC formulations of efgartigimod provide effective, generally well-tolerated and flexible treatment options for adults with AChR Ab+ gMG.

Plain Language Summary

Generalised myasthenia gravis (gMG) is a chronic, autoimmune disorder caused by impaired communication between the nerves and muscles. Recently, new targeted therapies have been developed for gMG, including FcRn antagonists such as efgartigimod (Vyvgart®; Vyvgart® Hytrulo). Efgartigimod works by reducing circulating levels of disease-causing antibodies. The drug is available as an IV infusion or an SC injection. In patients with gMG, IV efgartigimod significantly reduced disease burden and improved myasthenia gravis symptoms. These beneficial effects were long-lasting and repeatable across multiple treatment cycles. IV efgartigimod provided consistent clinically meaningful improvement over the long term (up to 17 treatment cycles) and was generally well tolerated. The efficacy and tolerability of SC efgartigimod PH20 was consistent with that of IV efgartigimod. The most common adverse events were headache and infections (with IV formulation) and injection-site reactions (with SC formulation). Thus, efgartigimod is an effective and generally well-tolerated treatment option for adults with gMG, with the flexibility of IV or SC administration.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.27048220.

1 Introduction

Myasthenia gravis is a chronic autoimmune disorder characterized by muscle weakness due to impaired neuromuscular transmission [1, 2]. It is rare, with an annual incidence of 3–28 cases per million. The disease can be broadly classified as ocular or generalised [1, 2]. The clinical defining feature of myasthenia gravis is fatigable muscle weakness, which may affect ocular, bulbar, limb and respiratory muscles [1–3]. The underlying pathogenesis of myasthenia gravis involves autoantibodies that bind to the acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4. In most (80–90%) cases of myasthenia gravis, immunoglobulin (Ig) G antibodies are directed against AChRs on the postsynaptic

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✉ Hannah A. Blair
demail@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

Efgartigimod: clinical considerations in gMG
First FcRn antagonist to be approved for gMG
Available as IV and SC formulations
Improves myasthenia gravis symptoms, reduces disease burden and improves HRQOL in AChR Ab+ patients
Beneficial effects are reproducible, durable and maintained over the long term
Generally well tolerated

membrane of the neuromuscular junction [1–3]. These autoantibodies bind to AChRs, leading to complement-mediated destruction of AChRs and dysfunction of the neuromuscular junction [1, 2]. Pathogenic AChR autoantibodies also impair the function of AChR by preventing acetylcholine from binding to the receptor [2].

Traditionally, patients with myasthenia gravis have been treated with acetylcholinesterase inhibitors (AChEIs), corticosteroids, nonsteroidal immunosuppressive therapies (NSISTs), biologicals, intravenous immunoglobulins (IVIg), therapeutic plasma exchange (PLEX) and thymectomy [1–5]. However, 10–20% of patients do not respond to immunosuppressive therapy, which is also associated with treatment-limiting adverse events (AEs) [3, 4]. An improved understanding of the pathophysiology of myasthenia gravis has led to the development of new targeted therapeutic approaches [1–5]. One such approach involves inhibition of the neonatal fragment crystallizable receptor (FcRn), which maintains IgG levels by protecting antibodies from lysosomal degradation and recycling them back into the circulation [1–5].

Intravenous (IV) efgartigimod (Vyvgart®) was the first FcRn antagonist to be approved for the treatment of generalised myasthenia gravis (gMG) [6, 7]. A subcutaneous (SC) formulation of efgartigimod co-formulated with recombinant human hyaluronidase PH20 (Vyvgart® Hytrulo; hereafter referred to as SC efgartigimod PH20) is now also available. Both formulations of efgartigimod are approved in several regions worldwide, including the USA [8, 9], the EU [10] and China [11], for the treatment of gMG in adults who are AChR antibody positive (Ab+), and in Japan (VYVDURA®), for the treatment of gMG in adults with an inadequate response to treatment with steroids or NSISTs, regardless of AChR antibody status [12]. This article reviews the efficacy and tolerability of IV efgartigimod and SC efgartigimod PH20 in this patient population and briefly summarizes the pharmacological properties of efgartigimod.

2 Pharmacodynamics of Efgartigimod

Efgartigimod is a humanized IgG1-derived Fc fragment of the za allotype [8, 9, 13]. It has been engineered for increased affinity to FcRn at both neutral and acidic pH, with an equilibrium dissociation constant (K_D) of 320 nM at pH 7.4 and a K_D of 14.2 nM at pH 6.0 [13]. Binding of efgartigimod to FcRn inhibits its interaction with IgG, thereby reducing levels of circulating IgG (including pathogenic IgG autoantibodies) [10, 13]. This targeted reduction of IgG levels occurs without reducing levels of other immunoglobulins or albumin and without increasing cholesterol levels [10, 13].

IV efgartigimod rapidly reduced serum IgG levels in a murine model of MuSK myasthenia gravis [14] and in cynomolgus monkeys [13]. IV efgartigimod also improved muscle weakness and fatigability in myasthenic mice relative to control [14]. In phase I trials in healthy volunteers, single and multiple ascending doses of IV efgartigimod [13] and SC efgartigimod PH20 [15] reduced total IgG levels from baseline, but did not alter serum levels of other immunoglobulins or albumin [13]. Total IgG levels returned to baseline ≈8 weeks after the last IV infusion [13].

In an exploratory phase II trial [16] and in the phase III ADAPT trial [17] (Sect. 4.1.1) in AChR Ab+ patients with gMG, four once-weekly IV infusions of efgartigimod 10 mg/kg per cycle rapidly decreased serum IgG levels and AChR antibody levels from baseline. Rapid and sustained IgG reductions were observed across all subtypes of IgG and during subsequent treatment cycles [16, 17]. Total IgG and AChR antibody levels returned to baseline levels ≈7–8 weeks after the last IV infusion [16, 17]. In the ADAPT+ open-label extension (OLE; Sect. 4.1.1.2), reductions in total IgG, IgG subtypes and AChR antibody levels were consistent with those seen in ADAPT [18].

In a phase I trial in healthy volunteers, SC efgartigimod PH20 had similar pharmacodynamic effects as IV efgartigimod in terms of reducing total IgG levels [15]. The phase III ADAPT-SC trial (Sect. 4.2.1) confirmed the pharmacodynamic noninferiority of SC efgartigimod PH20 1000 mg to IV efgartigimod 10 mg/kg in patients with gMG [19]. The primary endpoint of ADAPT-SC was the percentage change from baseline in total IgG levels at week 4 and the prespecified noninferiority margin was 10%. At week 4, after one cycle of treatment (four once-weekly administrations), the least squares mean (LSM) change from baseline in total IgG level was −66.4% in patients who received SC efgartigimod PH20 and −62.2% in patients who received IV efgartigimod (LSM difference −4.2% 95% CI −7.73 to −0.66; $p < 0.0001$ for noninferiority). Similar results were seen in the AChR Ab+ population (−66.9% vs −62.4%; LSM difference −4.5%; 95% CI −8.53 to −0.46; $p < 0.0001$). Total IgG

levels returned to near baseline levels by week 10. Reductions from baseline in AChR antibody levels were similar in the SC and IV treatment groups and paralleled the reductions in total IgG [19].

3 Pharmacokinetics of Efgartigimod

Efgartigimod exhibits linear pharmacokinetics [8, 10], with a geometric mean accumulation ratio of 1.12 [10]. Exposure of efgartigimod increases in a dose-proportional manner following IV doses up to 50 mg/kg (i.e. 5 x the recommended dosage) [8] and SC doses up to 1750 mg (i.e. 1.75 x the recommended dosage) [9]. In the ADAPT-SC trial in patients with gMG (Sect. 4.2.1), exposure of IV efgartigimod 10 mg/kg and SC efgartigimod PH20 1000 mg was comparable following one treatment cycle (four once-weekly administrations) [15]. The estimated bioavailability of SC efgartigimod PH20 is 77% [9]. The volume of distribution of efgartigimod is 15–20 L [8–10].

The expected metabolic pathway for efgartigimod (and hyaluronidase [9]) involves degradation to small peptides and amino acids by proteolytic enzymes [8–10]. Following a single dose of IV efgartigimod 10 mg/kg in healthy volunteers, < 0.1% of the dose was recovered in urine [8, 9]. Efgartigimod has a terminal half-life of 80–120 h (3–5 days) [8–10] and a clearance of 0.128 L/h [10].

Age, sex, race and body weight did not have any clinically relevant effects on efgartigimod pharmacokinetics [8–10, 15]. Dedicated pharmacokinetic studies have not been conducted in patients with renal or hepatic impairment [8–10]. However, in a population pharmacokinetic analysis, patients with mild renal impairment [estimated glomerular filtration rate (eGFR) 60–89 mL/min/1.73 m^2] had a 22% (IV efgartigimod) or 11% (SC efgartigimod PH20) increase in efgartigimod exposure relative to that in patients with normal renal function [8, 9]. The effect of moderate (eGFR 30–59 mL/min/1.73 m^2) and severe (eGFR < 30 mL/min/1.73 m^2) renal impairment on the pharmacokinetics of efgartigimod is unknown [10]. Hepatic impairment is not expected to influence efgartigimod pharmacokinetics [8–10].

3.1 Drug Interactions

No formal drug interaction studies have been conducted with efgartigimod [8–10]. However, because efgartigimod is not metabolized by CYP450 enzymes, interactions between efgartigimod and concomitant drugs that are substrates, inducers or inhibitors of CYP450 enzymes are not expected [8, 9]. Efgartigimod may decrease exposure to drugs that bind to the human FcRn (e.g. immunoglobulin products, monoclonal antibodies, antibody derivatives containing the human FcRn domain of the IgG subclass). Plasma exchange, plasmapheresis and immunoadsorption may decrease circulating concentrations of efgartigimod [10].

Due to its mechanism of action (e.g. reduction of IgG levels), efgartigimod has the potential to interfere with the response to vaccines [8–10]. However, healthy volunteers who received IV efgartigimod mounted effective humoral immune responses to a pneumococcal vaccine [20]. Likewise, IV efgartigimod-treated patients with gMG participating in the ADAPT (Sect. 4.1.1) or ADAPT+ (Sect. 4.1.1.2) trials mounted antigen-specific IgG responses to pneumococcal, influenza and COVID-19 vaccines [21]. Administration of live or live-attenuated vaccines during efgartigimod treatment is not recommended [8–10].

4 Therapeutic Efficacy of Efgartigimod

4.1 Intravenous Efgartigimod

The efficacy of IV efgartigimod in patients with gMG was initially demonstrated in an exploratory, multinational, randomized, double-blind, phase II trial [16]. In this trial, relative to placebo, patients who received four once-weekly IV infusions of efgartigimod 10 mg/kg demonstrated rapid and significant clinical improvement (assessed on four efficacy scales). Most patients achieved persistent (≥ 6 weeks) disease improvement [16]. Based on these findings, the efficacy of efgartigimod was subsequently evaluated in the multinational, randomized, double-blind, phase III ADAPT trial [17] (Sect. 4.1.1). These data are supported by the long-term results of ADAPT+, an up to 3-year OLE of ADAPT [18] (Sect. 4.1.1.2). The effectiveness of IV efgartigimod in the real-world setting is also discussed (Sect. 4.1.2).

4.1.1 ADAPT Trial

The ADAPT trial enrolled patients aged ≥ 18 years with gMG, with or without AChR antibodies [17]. Inclusion criteria were Myasthenia Gravis Foundation of America (MGFA) class II–IV disease; a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5 (> 50% non-ocular); and a history of abnormal neuromuscular transmission tests, a positive edrophonium chloride test, or improvement with AChEIs. All patients were receiving stable doses of ≥ 1 gMG treatment (i.e. NSISTs, steroids or AChEIs). Following stratification based on AChR antibody status (positive vs negative), concomitant NSISTs (yes vs no) and Japanese nationality (yes vs no), patients were randomized to receive a treatment cycle comprising four once-weekly IV infusions of efgartigimod 10 mg/kg ($n = 84$) or placebo ($n = 83$). After the first cycle, patients could receive one or two additional cycles according to individual clinical response (i.e.

Table 1 Efficacy of intravenous efgartigimod in patients with generalised myasthenia gravis in the phase III ADAPT trial

ADAPT trial [17]	IV EFG 10 mg/kg ($n = 65$)	PL ($n = 64$)	OR (95% CI)
Primary endpoint			
MG-ADL response[a] in cycle 1 (% of pts)	68*	30	4.95 (2.21–11.53)
Secondary endpoints[b]			
QMG response[c] in cycle 1 (% of pts)	63*	14	10.84 (4.18–31.20)
MG-ADL response[d] in cycle 1 in overall population (% of pts)	68*	37	3.70 (1.85–7.58)
Proportion of time with CMI[e] up to day 126 (%)	48.7*	26.6	
Median time from day 28 until no CMI (days)	35	8	
Early MG-ADL[f] response in cycle 1[g] (% of pts)	57	25	

Unless otherwise stated, all efficacy endpoints were assessed in the modified intention-to-treat population of AChR Ab+ pts

Ab+ antibody positive, *Ab–* antibody negative, *AChR* acetylcholine receptor, *CMI* clinically meaningful improvement, *EFG* efgartigimod, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *OR* odds ratio, *PL* placebo, *pts* patients, *QMG* Quantitative Myasthenia Gravis

*$p \leq 0.0001$ vs PL

[a]A ≥2-point improvement in MG-ADL score sustained for ≥4 consecutive weeks, with the first improvement occurring by week 4

[b]Secondary endpoints were assessed hierarchically in the order presented

[c]A ≥3-point improvement in total QMG score for ≥4 consecutive weeks, with the first improvement occurring by week 4

[d]All randomized pts, including AChR Ab– pts (EFG $n = 84$ and PL $n = 83$)

[e]A ≥2-point improvement from baseline in MG-ADL score

[f]A ≥2-point improvement in MG-ADL score sustained for ≥4 consecutive weeks, with the first improvement occurring by week 2

[g]Statistical analysis was not performed due to the lack of statistical significance for the previous secondary endpoint

MG-ADL score of ≥5 and when an MG-ADL responder no longer had a ≥2-point improvement from baseline in MG-ADL total score). Subsequent cycles could commence ≥8 weeks after initiation of the previous cycle [17].

The primary endpoint was the proportion of AChR Ab+ patients with an MG-ADL response in the first treatment cycle [17]. An MG-ADL response was defined as a ≥2-point improvement (reduction) in MG-ADL score sustained for ≥4 consecutive weeks, with the first improvement by week 4 (i.e. 1 week after the last infusion of the cycle). Baseline demographic and clinical characteristics were generally well balanced between treatment groups. However, more patients in the efgartigimod group had previously undergone thymectomy than in the placebo group (70% vs 43%). In these patients, the median time since thymectomy was 10.8 years. Most patients were female (71%), had MGFA class II or III disease (96%), were AChR Ab+ (77%) and were receiving immunosuppressive treatment (86%) [17].

IV efgartigimod was more effective than placebo in improving myasthenia gravis symptoms and reducing disease burden in AChR Ab+ patients with gMG [17]. Significantly more efgartigimod than placebo recipients achieved an MG-ADL response in the first cycle (primary endpoint; Table 1). Efgartigimod was also significantly more effective than placebo for the first three hierarchically tested secondary endpoints: the proportion of patients achieving a Quantitative Myasthenia Gravis (QMG) response in the first cycle; the proportion of MG-ADL responders in the overall patient population in the first cycle; and the proportion of time with clinically meaningful (i.e. ≥2-point) improvement (CMI) in MG-ADL score up to day 126 (Table 1). The median time from day 28 until no CMI was not significantly different between treatment groups; therefore, statistical analysis of the next secondary endpoint (the proportion of patients with an early MG-ADL response in the first cycle) was not performed (Table 1). Clinical improvement was seen as early as 1 week after the first infusion [17].

Overall, more IV efgartigimod than placebo recipients achieved higher levels of improvement in MG-ADL score (up to 9-point reduction) and QMG score (up to 10-point reduction) by week 4 [17]. The proportion of patients achieving minimal symptom expression (MSE; i.e. MG-ADL score of 0 or 1) was significantly higher with efgartigimod than with placebo (40% vs 11%; $p < 0.0001$). Efgartigimod recipients had significantly ($p < 0.05$) greater improvements from baseline in MG-ADL, QMG and Myasthenia Gravis Composite (MGC) scores during the first cycle than placebo recipients; these improvements were seen as early as week 1 and were sustained through week 7 [17]. In a post hoc analysis, efgartigimod was associated with a significant reduction in the risk of exacerbation (i.e. a 3-point worsening in QMG score; 21% vs 44%; $p = 0.0016$) and numerically lower rates of all-cause hospitalization [11.4 vs 28.3 per 100 patient-years (PY)] and gMG-related hospitalization (2.8 vs 8.5 per 100 PY) compared with placebo [22].

The clinical benefit of IV efgartigimod was reproducible after subsequent cycles [17]. Among patients who received a second cycle, 71% of efgartigimod recipients achieved an MG-ADL response compared with 26% of placebo recipients. Of the 29 patients who did not respond to efgartigimod during cycle 1, 19 were retreated and seven (37%) achieved an MG-ADL response during cycle 2 [17].

According to predefined exploratory and post hoc subgroup analyses, the benefits of IV efgartigimod over placebo were seen regardless of sex [17, 23], age [17], baseline MG-ADL scores [17], concomitant medications (NSISTs, steroids and/or AChEIs) [17, 24], history of thymectomy [17], affected muscle group subdomains (bulbar, ocular, limb/gross motor, respiratory) [25], prior treatment failures [26], disease duration [27] and body weight [28]. However, among AChR Ab– patients, the proportion of MG-ADL responders was similar in both treatment groups (68% with efgartigimod and 63% with placebo) [17]. The proportion of patients achieving a QMG response was 53% with efgartigimod and 37% with placebo [17].

4.1.1.1 Health-Related Quality of Life IV efgartigimod was associated with rapid, significant, durable and reproducible improvements in health-related quality of life (HRQOL) in AChR Ab+ patients with gMG [29]. HRQOL was assessed using the Myasthenia Gravis-Quality of Life 15-item revised (MG-QOL15r), a disease-specific measure assessing mobility, disease symptoms, general contentment and emotional well-being, with higher scores indicating worse quality of life, and the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L), a standardized measure of health status, with higher scores indicating better quality of life. Efgartigimod was associated with significantly greater reduction in MG-QOL15r scores and significantly greater increase in EQ-5D-5L utility scores compared with placebo. Significant between-group differences were seen as early as week 1 ($p < 0.01$) and were maintained for up to 8 weeks ($p < 0.05$) in both cycle 1 and cycle 2. EQ-5D-5L visual analogue scale (VAS) scores were also significantly increased with efgartigimod relative to placebo, with these improvements maintained up to week 5 in both treatment cycles [29]. Improvements in MG-ADL scores with efgartigimod were associated with higher EQ-5D-5L utility scores, with each unit improvement in MG-ADL leading to a significant ($p < 0.001$) utility increase of 0.0233 [30].

4.1.1.2 Long-Term Efficacy The beneficial effects of IV efgartigimod in patients with gMG were maintained over the long term [18]. Patients who completed the ADAPT trial (or who were eligible for a treatment cycle but could not complete the cycle by week 26 of ADAPT) were eligible to enter ADAPT+. The primary and key secondary objectives were to evaluate long-term safety and tolerability (Sect. 5); efficacy was also assessed. All patients received four once-weekly IV infusions of efgartigimod 10 mg/kg per cycle. The number of treatment cycles was determined according to individual clinical response [18]. Patients who completed ADAPT+ were eligible to enter ADAPT-SC+ (Sect. 4.2.2).

At the time of the final interim analysis (data cutoff 31 January 2022), 145 patients had received ≥ 1 dose of efgartigimod [18]. The mean duration of treatment plus follow-up was 548 days and patients received a maximum of 17 treatment cycles, corresponding to 217.6 PY of observation. In AChR Ab+ patients, the mean change in MG-ADL and QMG scores during the first cycle was −5.0 and −4.7, respectively. Similar results were seen in AChR Ab– patients (−5.3 and −5.2, respectively). Most AChR Ab+ patients had CMI in MG-ADL (i.e. ≥ 2-point reduction) and QMG (i.e. ≥ 3-point reduction) that were maintained in each cycle for up to 10 cycles, with a substantial proportion of patients demonstrating improvements well beyond clinically meaningful thresholds [18].

In a post hoc analysis in AChR Ab+ patients with ≥ 1 year of combined follow-up between ADAPT and ADAPT+ ($n = 95$), sustained clinical improvement with IV efgartigimod was associated with fewer treatment cycles [18]. In the entire cohort, the annualized mean number of cycles was 4.7 cycles per year. The average time between cycles (i.e. from the last infusion of the previous cycle to the first infusion of the subsequent cycle) was ≥ 9 weeks in 37% of patients (≈ 4 cycles per year). Overall, 24% of patients received ≤ 3 cycles per year, 18% received ≤ 2 cycles per year and 6% received 1 cycle per year [18].

4.1.2 In the Real-World Setting

Data from the real-world setting support the efficacy of IV efgartigimod for the treatment of gMG. Clinical experience in the USA [31–33], the UK [34], Italy [35, 36], China [37] and Japan [38] confirmed that weekly infusions of IV efgartigimod led to CMI in patients with gMG.

In the largest of these studies, which was conducted in the USA, data were obtained from 705 patients with gMG who initiated IV efgartigimod and enrolled in a patient support programme [32]. At baseline, all patients had an MG-ADL score of ≥ 2 (mean 8.6). The number of efgartigimod cycles initiated ranged from 1 to 13 (mean 3.8). The largest observed 'cohort-wide response' was a 5.8-point mean reduction from baseline in MG-ADL score with 93% of patients experiencing CMI. The largest observed MG-ADL responses were 78.8%, 67.4%, 61.0% and 57.1% in the bulbar, ocular, limb/gross motor and respiratory subdomains, respectively. At their best state, 78% of patients had achieved an MG-ADL score of ≤ 4 and 36% of patients had achieved MSE [32].

In a retrospective cohort study of US insurance claims-based data in patients with gMG ($n = 316$), IV efgartigimod was associated with a significant reduction in oral corticosteroid usage [39]. Six months after initiating efgartigimod, the average oral corticosteroid dosage had significantly ($p < 0.001$) decreased from 18.6 mg/day to 13.5 mg/day. Almost half (46%) of patients were able to reduce their average oral corticosteroid dosage by ≥ 5 mg/day [39].

4.2 Subcutaneous Efgartigimod PH20

The efficacy of SC efgartigimod PH20 in patients with gMG was investigated in the randomized, open-label, multicentre, phase III ADAPT-SC trial [19] (Sect. 4.2.1), which was primarily designed to evaluate the pharmacodynamic noninferiority of SC efgartigimod PH20 compared with IV efgartigimod (Sect. 2). These data are supported by the interim results of ADAPT-SC+, an ongoing OLE of ADAPT-SC, which was designed to assess the long-term tolerability of SC efgartigimod PH20 [19, 40] (Sect. 4.2.2).

4.2.1 ADAPT-SC Trial

ADAPT-SC enrolled patients aged ≥ 18 years with MGFA class II–IV gMG and an MG-ADL total score of ≥ 5 (> 50% non-ocular) who were receiving a stable dose of ≥ 1 gMG treatment (NSISTs, steroids or AChEIs) [19]. They were randomized to receive SC efgartigimod 1000 mg co-formulated with PH20 2000 U/mL ($n = 55$) or IV infusions of efgartigimod 10 mg/kg ($n = 55$) once weekly for 4 weeks (i.e. one treatment cycle) followed by 7 weeks of post-treatment follow-up. Most (83%) patients were AChR Ab+ [19].

Clinical improvement was consistent between SC efgartigimod PH20 and IV efgartigimod in patients with gMG [19]. In the overall population, the proportions of MG-ADL and QMG responders were similar with SC efgartigimod PH20 versus IV efgartigimod (Table 2). The mean change from baseline in MG-ADL and QMG total scores at week 4 was similar in the SC and IV treatment groups (Table 2). The proportion of patients achieving MSE at any time point was also similar in both treatment groups. CMI was seen as early as week 1 in both treatment groups, with maximal improvement in MG-ADL and QMG scores observed at week 4. Up to one-third of patients in both treatment groups experienced MG-ADL and QMG improvements well beyond clinically meaningful thresholds (Table 2) [19].

Results in the AChR Ab+ population ($n = 91$) were similar to those in the overall population in terms of MG-ADL and QMG response rates, change from baseline in MG-ADL and QMG total scores and achievement of MSE and CMI (Table 2) [19]. Modest clinical improvements were also seen in AChR Ab– patients ($n = 19$). In this population, the MG-ADL response rate was 60% with SC efgartigimod PH20 and 56% with IV efgartigimod; corresponding QMG response rates were 50% and 44% [19].

4.2.2 Long-Term Efficacy

Long-term (up to 3 years) treatment with SC efgartigimod PH20 was associated with early, consistent and reproducible clinical improvement in patients with gMG, according to interim results of ADAPT-SC+ [19]. Patients who completed ADAPT-SC ($n = 105$) or ADAPT+ ($n = 73$) were eligible to enter ADAPT-SC+. All patients received individualized treatment cycles of four once-weekly administrations of SC efgartigimod 1000 mg co-formulated with PH20 2000 U/mL. Patients could start a new treatment cycle without a worsening MG-ADL score [19].

Through January 2022, a total of 164 patients received ≥ 1 dose of SC efgartigimod PH20, with a mean duration of follow-up of 169.7 days (72.1 PY of exposure) [19]. In the overall population, the mean change from baseline in MG-ADL total score at week 4 was −4.0, −3.8 and −4.1 in cycles 1 through 3, respectively. The proportions of patients achieving MSE at any time point were 30%, 31% and 36% in cycles 1 through 3, respectively. Most (88%) patients in ADAPT-SC+ were considered to be adequately trained in self-administration of SC efgartigimod PH20, with nearly 60% of patients able to self-administer at home by cycle 3. Among patients who had previously received IV efgartigimod in ADAPT+ or ADAPT-SC, 71% preferred SC efgartigimod PH20 and 29% preferred IV efgartigimod or had no preference [19].

The long-term efficacy of SC efgartigimod PH20 was also demonstrated in the AChR Ab+ ($n = 141$) [40] and AChR Ab– ($n = 38$) populations [41], at a later data cutoff of December 2022 (mean study duration of 412.9 days; maximum 585 days) [40]. Across cycles 1–9, the proportion of AChR Ab+ patients achieving MSE ranged from 36% to 44%, the proportion achieving CMI in MG-ADL at week 4 ranged from 76% to 82% and the mean change from baseline in MG-ADL score at week 4 ranged from −4.1 to −4.7 [40]. Among AChR Ab– patients, 68–90% experienced CMI in MG-ADL and 12–19% achieved MSE across multiple cycles [41].

SC efgartigimod PH20 was associated with consistent and reproducible improvements in HRQOL (assessed using the MG-QOL15r and EQ-5D-5L VAS) in both the AChR Ab+ [42] and AChR Ab– [41] populations.

5 Tolerability of Efgartigimod

IV efgartigimod was generally well tolerated in patients with gMG [17, 18]. In ADAPT, the incidence of AEs was 77% with IV efgartigimod and 84% with placebo [17].

Table 2 Efficacy of subcutaneous efgartigimod in patients with generalised myasthenia gravis in the phase III ADAPT-SC trial

ADAPT-SC trial [19]	Overall population		AChR Ab+ population	
	SC EFG PH20 ($n = 55$)	IV EFG ($n = 55$)	SC EFG PH20 ($n = 45$)	IV EFG ($n = 46$)
MG-ADL response[a] (% of pts)	69	69	71	72
QMG response[b] (% of pts)	66	52	69	53
Mean change from BL in MG-ADL total score at week 4	−5.1	−4.7	−5.3	−4.6
Mean change from BL in QMG total score at week 4	−6.1	−5.2	−6.5	−5.4
MSE[c] at any time point (% of pts)	37	38	46	41
CMI in MG-ADL[d] at week 4 (% of pts)	90	91	93	91
CMI in QMG[e] at week 4 (% of pts)	81	71	84	81
CMI in MG-ADLd at week 10 (% of pts)	57	63	62	67
≥ 7-point improvement in MG-ADL total score at any time point (% of pts)	25	30		
≥ 8-point improvement in QMG total score at any time point (% of pts)	33	29		

Efficacy analyses were performed in the intention-to-treat population

Ab+ antibody positive, *AChR* acetylcholine receptor, *BL* baseline, *CMI* clinically meaningful improvement, *EFG* efgartigimod, *IV* intravenous, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *MSE* minimal symptom expression, *pts* patients, *QMG* Quantitative Myasthenia Gravis

[a]A ≥ 2-point reduction from BL in MG-ADL score for ≥ 4 consecutive weeks after onset, with onset occurring ≥ 1 week after last dose

[b]A ≥ 3-point reduction from BL in QMG score for ≥ 4 consecutive weeks after onset, with onset occurring ≥ 1 week after last dose

[c]MG-ADL total score of 0 or 1

[d]A ≥ 2-point reduction from BL in MG-ADL total score

[e]A ≥ 3-point reduction from BL in QMG score

Most AEs were mild to moderate in severity. The most common (incidence ≥ 10% of patients and higher than with placebo) AEs with efgartigimod were headache (29% vs 28% with placebo), upper respiratory tract infection (11% vs 5%) and urinary tract infection (10% vs 5%). Serious AEs occurred in 5% of efgartigimod recipients and 8% of placebo recipients, while AEs leading to discontinuation of treatment occurred in 4% of patients in both groups [17].

SC efgartigimod PH20 and IV efgartigimod were generally well tolerated in ADAPT-SC [19]. The overall incidence of AEs was 67% with SC efgartigimod PH20 and 51% with IV efgartigimod. Most AEs were mild to moderate in severity. The most common (incidence ≥ 10% of patients) AEs were injection-site reactions (ISRs; 38% with SC efgartigimod PH20 vs 2% with IV efgartigimod), headache (13% vs 13%), COVID-19 (4% vs 0%) and myasthenia gravis (11% vs 2%). The incidence of serious AEs was 15% with SC efgartigimod PH20 and 7% with IV efgartigimod, and 4% of patients discontinued SC efgartigimod PH20 due to AEs [19].

5.1 Long-Term Tolerability

The long-term tolerability profile of IV efgartigimod was generally consistent with that seen in short-term trials [18]. Over 217.5 PY of follow-up (data cutoff 31 January 2022) in ADAPT+, the incidence of treatment-emergent AEs (TEAEs) was 85% (3.60 events per PY of follow-up). The most common (incidence ≥ 10% of patients) TEAEs were infections (55%; 0.75 events/PY), headache (25%; 0.45 events/PY), COVID-19 (15%; 0.11 events/PY), nasopharyngitis (14%; 0.11 events/PY), infusion-related reactions (IRRs; 10%; 0.10 events/PY) and diarrhoea (10%; 0.09 events/PY). Serious TEAEs occurred in 23% of patients (0.24 events/PY) and 8% of patients discontinued treatment due to TEAEs (0.06 events/PY). There were five fatal TEAEs (0.02 events/PY), none of which were related to IV efgartigimod [18].

The long-term tolerability profile of SC efgartigimod PH20 was consistent with that of IV efgartigimod, with no new safety signals observed [40]. Over 193.4 PY of follow-up (data cutoff December 2022) in ADAPT-SC+, the incidence of AEs with SC efgartigimod PH20 was 85% (9.0 events/PY). The most common (incidence ≥ 10% of patients) AEs were injection-site erythema (29%; 1.7 events/PY), COVID-19 (22%; 0.2 events/PY), headache (20%; 0.6 events/PY), nasopharyngitis (16%; 0.2 events/PY), diarrhoea (13%; 0.2 events/PY), injection-site pain (12%; 0.2 events/PY), injection-site pruritus (11%; 0.2 events/PY) and injection-site bruising (10%; 0.2 events/PY). Grade ≥ 3 AEs occurred in 20% of patients (0.4 events/PY) and serious AEs occurred in 18% of patients (0.3 events/PY). Four patients discontinued treatment due to AEs. There were four fatal AEs (< 0.1 events/PY), none of which were related to SC efgartigimod PH20 [40].

5.2 Adverse Events of Special Interest

Efgartigimod can increase the risk of infections [8–10], as can some concomitant medications (e.g. immunosuppressants) [43]. In ADAPT, infections (mostly mild to moderate in severity) occurred in 46% of IV efgartigimod recipients and 37% of placebo recipients [17]. In ADAPT+, the overall incidence of infections with IV efgartigimod was 55% (0.75 events/PY), and the incidence did not increase with subsequent treatment cycles [18]. In ADAPT-SC, infections (mostly mild to moderate in severity) occurred in 18% of patients in the SC efgartigimod PH20 group and 16% of patients in the IV efgartigimod group [19]. In ADAPT-SC+, the overall incidence of infections with SC efgartigimod PH20 was 51% (1.0 events/PY) [40]. Patients should be monitored for signs and symptoms of infection during treatment with efgartigimod [8–10]. In patients with an active infection, or if serious infection occurs, efgartigimod should be delayed or withheld until the infection has resolved [8–10].

IRRs, ISRs and hypersensitivity reactions may occur with efgartigimod [8–10]. In ADAPT, IRRs occurred in 4% of IV efgartigimod recipients and 10% of placebo recipients, all of which were mild in severity [17]. In ADAPT+, the incidence of IRRs with IV efgartigimod was 10% (0.10 events/PY) [18]. In ADAPT-SC, ISRs were the most commonly reported AE in the SC efgartigimod PH20 group (Sect. 5) [19]. All ISRs were mild or moderate in severity, and most were transient, resolved without treatment and did not lead to discontinuation of efgartigimod [19]. In ADAPT-SC+, the overall incidence of ISRs with SC efgartigimod PH20 was 46% (3.2 events/PY) [40]. There were no serious or grade ≥ 3 ISRs and none led to discontinuation of treatment [40]. The incidence of ISRs decreased with each injection of the treatment cycle in ADAPT-SC (from 22% of patients with injection 1 to 10% with injection 4) [19] and over subsequent treatment cycles in ADAPT-SC+ (from 35% of patients in cycle 1 to 10% in cycle 9). Patients should be monitored for signs and symptoms of IRRs, ISRs and hypersensitivity reactions during treatment with efgartigimod [10]. Reactions should be treated with appropriate supportive therapies [8–10]. Subsequent injections/infusions should be administered with caution, with consideration given to close observation, slower infusion rates and/or pre-medications [8, 9].

Like all therapeutic proteins, efgartigimod has the potential for immunogenicity [8]. In ADAPT-SC, anti-drug antibodies (ADAs) were detected in 20% of patients following treatment with IV efgartigimod and in 35% of patients following treatment with SC efgartigimod PH20, with 4% of patients in both groups developing neutralizing antibodies [19]. In ADAPT+, 16% of patients developed ADAs following long-term treatment with IV efgartigimod, mostly during the first treatment cycle [18]. Although data are limited [8, 9], the presence of ADAs did not appear to affect the pharmacokinetics, efficacy or safety of efgartigimod [18, 19].

6 Dosage and Administration

In the USA, efgartigimod is indicated for the treatment of gMG in adult patients who are AChR Ab+ [8, 9]. In the EU [10] and in China [11], efgartigimod is indicated as an add-on to standard therapy in adult patients with gMG who are AChR Ab+. Efgartigimod is also approved in Japan for the treatment of gMG in adults with an inadequate response to treatment with steroids or NSISTs, regardless of AChR antibody status [12].

Efgartigimod is approved for IV or SC use [8–10]. IV efgartigimod is administered as a 1-h infusion once weekly for 4 weeks as one cycle; the recommended dosage is 10 mg/kg (or 1200 mg in patients weighing ≥ 120 kg) [8, 10]. SC efgartigimod PH20 is injected over 30–90 s at a dosage of 1000 mg (1008 mg in the EU [10]) once weekly for 4 weeks as one cycle [9, 10]. Subsequent treatment cycles can be administered according to clinical evaluation [8–10]. The US prescribing information states that SC efgartigimod PH20 must be administered by a healthcare professional [9], while the EU summary of product characteristics states that patients or caregivers may administer SC efgartigimod PH20 at home after adequate training from a healthcare professional [10].

Dosage adjustments are not required in elderly patients, patients with mild renal impairment or patients with hepatic impairment [8–10]. Due to a lack of data, the use of efgartigimod during pregnancy or breastfeeding should only be considered if the clinical benefit outweighs the risks [8–10]. Consult local prescribing information for further details regarding contraindications, warnings and precautions, drug interactions and use in special populations.

7 Place of Efgartigimod in the Management of Generalised Myasthenia Gravis

The primary goal for the treatment of gMG, as appointed by the MGFA task force, is achievement of a minimal manifestation status (i.e. no symptoms or functional limitations but mild weakness in some muscles), with only mild AEs that do not require intervention [44]. International consensus guidelines for the management of myasthenia gravis recommend the AChEI pyridostigmine as first-line therapy, with corticosteroids reserved for patients who do not respond to an adequate trial of pyridostigmine. Other recommended subsequent-line treatments include NSISTs, IVIg and PLEX [44].

Novel targeted therapeutics with improved efficacy and favourable tolerability profiles may represent a new approach

to the management of gMG [4]. Along with efgartigimod [6, 7], the FcRn antagonist rozanolixizumab [45] and several complement inhibitors (i.e. eculizumab [46], ravulizumab [47] and zilucoplan [48]) have been approved for the treatment of gMG, and are generally used as second- or third-line options for patients with severe and/or refractory disease [49]. German [50] and Nordic [51] guidelines recommend efgartigimod as an option for the symptomatic second-line treatment of severe, refractory myasthenia gravis. As the most recent international treatment guidelines [44] were published prior to the approval of efgartigimod, updates are awaited with interest.

Approval of IV efgartigimod was based on data from the pivotal phase III ADAPT trial (Sect. 4.1.1). In this trial, IV efgartigimod was associated with significant and clinically meaningful improvements in myasthenia gravis symptoms and reductions in disease burden in patients with AChR Ab+ gMG. These benefits were observed early and were seen across multiple gMG-specific rating scales. Of note, over two-thirds of patients in the efgartigimod group achieved improvement beyond the clinically meaningful threshold (Sect. 4.1.1). The efficacy of IV efgartigimod was reproducible and durable, with consistent improvements observed with each subsequent treatment cycle (Sects. 4.1.1 and 4.1.1.2). Sustained duration of clinical improvement warranted fewer treatment cycles per year (Sect. 4.1.1.2), providing further support for the use of an individualized treatment approach [17, 18].

gMG can have a substantial negative impact on mental, physical and relational HRQOL [29, 30]. Patients with gMG often have comorbid depression and/or anxiety, both of which are predictors of worsening HRQOL [29]. Indeed, a substantial proportion of patients in the ADAPT trial reported anxiety/depression at baseline. Despite patients being on stable doses of ≥ 1 gMG treatment, baseline EQ-5D-5L health utility scores were also relatively low, highlighting the burden of disease [29]. IV efgartigimod led to rapid and significant improvements in HRQOL which were durable, reproducible and strongly correlated with improvements in clinical symptoms (Sect. 4.1.1.1).

Data from real-world studies of IV efgartigimod in patients with gMG were generally consistent with those seen in clinical trials (Sect. 4.1.2). Although treatment with IV efgartigimod was associated with CMI in the real-world setting, patient numbers in most studies were relatively small. It should also be noted that patients in the largest real-world study had an MG-ADL score of ≥ 2 at baseline (Sect. 4.1.2), while patients in the ADAPT trial had an MG-ADL score of ≥ 5 at baseline (Sect. 4.1.1). Patients with lower MG-ADL scores would be unlikely to attain MSE. Larger-scale and longer-term data are necessary to assess the effectiveness of efgartigimod in real-world clinical practice.

Conventional treatments for gMG are frequently associated with burdensome AEs that limit their use [3, 4]. Among the newer targeted treatments, complement inhibitors carry boxed warnings on the risk of life-threatening and fatal meningococcal infections [46–48]. IV efgartigimod was generally well tolerated in the ADAPT trial, with most AEs being mild or moderate in severity (Sect. 5). IV efgartigimod was also generally well tolerated over the long term (Sect. 5.1). The most common TEAEs in ADAPT+ were headache and infections (Sect. 5.1). Severe infections were uncommon, and the incidence of infection did not increase with subsequent cycles of IV efgartigimod (Sect. 5.2), possibly as a result of selective IgG reduction [18]. This is an important finding, given that patients with gMG are at increased risk of infections due to predisposition and the use of concomitant immunosuppressive therapy [17].

The US and EU labels for efgartigimod were extended to include SC efgartigimod PH20 [9, 10] based on data from the phase III ADAPT-SC trial (Sects. 2 and 4.2.1). In this trial, SC efgartigimod PH20 was noninferior to IV efgartigimod in reducing total IgG levels (Sect. 2) in patients with gMG, and clinical improvement was consistent between both formulations (Sect. 4.2.1). Interim results from the ongoing ADAPT-SC+ trial (Sect. 4.2.2) demonstrated that clinical improvement with SC efgartigimod PH20 was consistent and reproducible over the long term (≤ 3 years). The tolerability of SC efgartigimod PH20 was generally consistent with that of IV efgartigimod (Sect. 5). Almost half of patients experienced localized ISRs with the SC formulation (Sect. 5.2). However, most reactions were not serious or severe, did not result in treatment discontinuation and became less frequent over subsequent treatment cycles (Sect. 5.2).

More convenient administration has become the focus of recent development of gMG treatments [49]. Of the approved complement inhibitors, eculizumab and ravulizumab are both administered via IV infusion [46, 47], while zilucoplan can be self-administered once daily via SC injection [48]. Rozanolixizumab is administered as a SC infusion once weekly for 6 weeks [45] and other FcRn antagonists currently in development will likely require IV infusions every 2–4 weeks or SC injections every 1–2 weeks. Efgartigimod is approved for both IV and SC use (Sect. 6). The SC formulation was developed to provide patients with an alternative route of administration, allowing for a more individualized and flexible approach to treatment. SC efgartigimod PH20 may improve patient convenience, with delivery taking 30–90 s compared with a 1-h IV infusion (Sect. 6). More than two-thirds of patients in ADAPT-SC+ indicated a preference for SC efgartigimod PH20 over IV efgartigimod (Sect. 4.2.2). The SC formulation also offers the potential (after adequate training) for self- and caregiver-supported administration at home (Sect. 6). Indeed, by treatment cycle 3 of ADAPT-SC+, almost 60% of patients were able to self-administer SC efgartigimod PH20 at home

(Sect. 4.2.2). To further inform alternative treatment regimens, a randomized, open-label, phase IIIb trial (ADAPT-NXT) is assessing the efficacy and tolerability of continuous (10 mg/kg every 2 weeks) versus fixed cycles (four once-weekly infusions of 10 mg/kg per cycle) of IV efgartigimod in patients with gMG [52]. Final results are awaited with interest.

To date, no studies have directly compared efgartigimod with other gMG treatments. Systematic reviews, network meta-analyses and/or matching-adjusted indirect comparisons have demonstrated some differences in efficacy and tolerability between efgartigimod and other targeted therapies for gMG, including rozanolixizumab, complement inhibitors and B-cell therapies (e.g. belimumab, rituximab) [53–57]. However, given the limitations of indirect comparisons, these results should be interpreted with caution. Randomized head-to-head trials comparing the efficacy and tolerability of efgartigimod with other approved treatments would be valuable in determining their relative roles in the management of gMG.

The economic burden of gMG on both patients and caregivers is large [58]. A pharmacoeconomic model combining data from ADAPT and a real-world study found that add-on therapy with efgartigimod reduced total productivity losses per gMG patient by ≈27% compared with conventional therapy alone [58]. In another analysis using data from phase III trials, the costs associated with achieving a 1-point improvement in QMG score, one additional patient with minimal clinically important difference in QMG, and one additional patient with MSE were lower for efgartigimod than for IVIg and eculizumab [59]. A Canadian cost-effectiveness analysis found that, over a lifetime horizon, IV efgartigimod was cost effective compared with chronic immunoglobulins [60]. However, according to the Institute for Clinical and Economic Review, efgartigimod has an incremental cost-effectiveness ratio that greatly exceeds the price needed to reach traditional cost-effectiveness thresholds [61]. The UK National Institute for Health Care and Excellence (NICE) does not recommend efgartigimod as a cost-effective use of National Health Service resources; however, the NICE guidance for efgartigimod in gMG is not yet finalized [62]. Given the high costs of FcRn antagonists (and complement inhibitors) [51, 61], further robust cost effectiveness analyses are warranted. A direct cost comparison of efgartigimod versus IVIg relative to symptom improvement would be of particular interest.

In conclusion, although further long-term data are required to fully determine the place of efgartigimod in the management of gMG, IV and SC formulations of efgartigimod provide effective, generally well-tolerated and flexible treatment options for adult patients with AChR Ab+ gMG.

Data Selection for Efgartigimod: 164 records identified

Duplicates removed	0
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	54
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	48
Cited efficacy/tolerability articles	27
Cited articles not efficacy/tolerability	35

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were efgartigimod, ARGX 113, ARGX-113, EFG PH20 SC, PH20 SC, Vyvgart, Hytrulo; generalized myasthenia gravis, myasthenia gravis, myasthenia, gMG, generalized MG. Records were limited to those in English language. Searches last updated 16 September 2024

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