10 August 2022
EMA/OD/0000083237
EMADOC-1700519818-876279
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Vyvgart (Efgartigimod alfa)
Treatment of myasthenia gravis
EU/3/18/1992

Sponsor: Argenx

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Un on

Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Efgartigimod alfa
Other name(s)	Efgartigimod alfa
International Non-Proprietary Name	-
Tradename	Vyvgart
Orphan condition	Treatment of myasthenia gravis
Sponsor's details:	Argenx Industriepark-Zwijnaarde 7 9052 Gent Oost-Vlaanderen Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	argenx BVBA
COMP opinion	15 February 2018
EC decision	21 March 2018
EC registration number	EU/3/18/1992
Post-designation procedural history	
Sponsor's name change	Name change from argenx BVBA to Argenx – EC letter of 01 September 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Thalia Marie Estrup Blicher/Alexandre Moreau
Applicant	Argenx
Application submission	30 July 2021
Procedure start	19 August 2021
Procedure number	EMA/H/C/005849/0000
Invented name	Vyvgart
Proposed therapeutic indication	Treatment of adult patients with generalised myasthenia gravis Further information on Vyvgart can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/medicines/human/EPAR/vyvgart)
CHMP opinion	23 June 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Penninga / Cécile Dop
Sponsor's report submission	16 February 2022
COMP discussion	14-16 June 2022
COMP opinion (adoption via written procedure)	24 June 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing efgartigimod alfa was considered justified based on non-clinical and on preliminary clinical data showing improvement of relevant functional endpoints and symptoms scores;
- the condition is life-threatening and chronically debilitating due to recurrent crisis characterised by muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing. Crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment;
- the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing efgartigimod alfa will be of significant benefit to those affected by the condition. The sponsor has provided clinical data showing improvement of clinical scores and quality of life on top of standard of care with the proposed product. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Myasthenia gravis (MG) is an autoimmune disorder characterised by a combination of weakness and fatigability of skeletal muscles, including ocular, bulbar, limb, and respiratory muscles. Weakness is the result of an IgG antibody mediated, T-cell dependent immunological reaction against proteins in the postsynaptic membrane of the neuromuscular junction (NMJ) of skeletal muscles (nicotinic acetylcholine receptors [AChR] and/or receptor-associated proteins). Patients present with muscle weakness, which typically worsens with continued activity (fatigue) and improves on rest. Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease (Drachman, 2001). Remissions are rarely complete or permanent.

Antibodies are present at NMJ, the site of pathology (Engel et al, 1979). About 80% to 90% of patients have detectable antibodies against the nicotinic AChR on the postsynaptic muscle membrane at the NMJ. Another 3% to 7% of patients have antibodies directed against MuSK, another NMJ protein.

The approved therapeutic indication "*Vyvgart is indicated as an add-on to standard therapy for the treatment of adult AChR-Ab seropositive generalized Myasthenia Gravis (MG) patients"* falls within the scope of the designated orphan condition "Treatment of myasthenia gravis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The course of MG is often variable. Exacerbations and remissions may occur, particularly during the first few years of the disease. However, remissions are rarely complete or permanent. Myasthenia gravis might impair vision (diplopia and ptosis), facial muscles, chewing, speech, swallowing, walking, or talking. Difficulty in swallowing may occur because of weakness of the palate, tongue, or pharynx, which could lead to nasal regurgitation and aspiration of liquids or foods with the risk of a dangerous and difficult to treat infection of the upper and lower airways. Dysphagia and respiratory failure are factors known to be caused by MG, and several reports have highlighted the importance of dysphagia and aspiration precipitating a myasthenic crisis. Fifteen to 20% of myasthenic patients are affected by myasthenic crisis at least once in their lives. Myasthenic crisis is a life-threatening complication of MG where the majority of patients require endotracheal intubation and mechanical ventilation.

The diagnosis of MG in AChR-antibody-seropositive patients has been associated with increased estimated mortality rates (1.41 compared to healthy individuals) especially in patients with late-onset disease (>50 years old at onset) (Hansen et al, 2016).

The condition is therefore both life threatening and chronically debilitating.

Number of people affected or at risk

In the initial ODD (Orphan Drug Designation) for efgartigimod for treatment of MG in 2018, the COMP agreed on a prevalence estimate of approximately 2 per 10,000 persons (EMA 2018). The estimate was supported by literature references identified through a literature search in July 2017. This search has now been conducted again, covering publications available up until 31 May 2021.

A total of 19 European literature references published after 2010 provided direct prevalence estimates from established epidemiological data for populations in the EEA (Table 1).

Table 1: Prevalence of MG in the EEA

Reference	Country	Prev year	Data source	Prevalence (per 10,000 persons)
Andersen et al, 2010	Norway	2008	National Prescription Database	1.3
Andersen et al, 2014	Norway	2008	National Prescription Database	1.3
Aragonès et al, 2017	Spain	2013	County-based re.g.ister	3.3
Boldingh et al, 2015a	Netherlands	2015	Hospital Records	1.7
Boldingh et al, 2015b	Norway	2015	Hospital Records	1.4
Cetin et al, 2012	Austria	2009	National hospital discharge re.g.ister	1.6
Fang et al, 2015	Sweden	2010	National health and population re.g.isters	2.5
Foldvari et al, 2015	Hungary	2007	Hospital discharge records	1.7
García Estévez et al, 2020	Spain	2018	Hospital Records	2,6
Lefter et al, 2017	Ireland	2013	Hospital Records	1.5
Martinka et al, 2018	Slovakia	2015	Hospital Records (National reference center)	2.5
Montomoli et al, 2012	Italy	2008	Neurological Institute MG database, all case collection	2.4
Pallaver et al, 2011	Italy	2009	Multiple information sources	1.3
Sabre et al, 2017	Estonia	2014	Hospital Records	2.3
Sabre et al, 2017	Sweden	2014	Hospital Records	2.0
Santos et al, 2016	Portugal	2013	Hospital Records	1.1
Sardu et al, 2012	Italy	2009	GPs	3.5
Westerberg and Punga, 2020	Sweden	2016	National re.g.ister	3.6
Zieda et al, 2018	Latvia	2015	Hospital Records	1.1

The average prevalence of MG published for populations in Europe between 2010 and today is 2.04 per 10,000 people (range 1.1 to 3.6). For the prevalence values calculated since 2015 (Boldingh et al, 2015a; García Estévez et al, 2020, Martinka et al, 2018, Westerberg and Punga, 2020; Zieda et al, 2018), the average is higher 2.45/10,000, range 1.1 to 3.6). Due to the very small number of publications, and the small patient samples, it cannot be determined if this increase is indeed indicative of a general trend towards higher prevalence. Therefore, the previously accepted prevalence estimate of approximately 2 in 10,000 persons in the European Union (EU) is still considered to be applicable.

The COMP supported a prevalence estimate of approximately 2 in 10,000 persons in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The below table provides an overview of therapies currently used for MG (Table 2). The table also indicates which of these medicinal products are authorised for use in the condition in the EU.

Table 2. Therapies Currently Used for Myasthenia Gravis (modified from sponsors original Table 10)

Therapy	**Mechanism of Action (MoA) & Side Effects/Limitations**	**Approval Status (national and centrally)**
AChE inhibitors; e.g. Pyridostigmine, Neostigmine, Distigmine, Ambenonium	MoA Acetylcholine breakdown inhibition, increasing its availability in the NMJ Limitations Short-acting and often need to be taken several times daily (Grob et al, 2008; Gilhus et al, 2019) Reduced efficacy in AChR-Ab seronegative population	Approved for the treatment of MG
Eculizumab	MoA Complement inhibitor, prevents C5 cleavage and inhibits IgG autoantibody-initiated complement activation Limitations Limited to treatment of refractory gMG (Gilhus, 2017) Limited to AChR-Ab seropositive [28] Increased risk of Neisseria meningitidis infection and the need for vaccination prior to commencing treatment (Soliris Product information, 2021).	Approved for the treatment of AChR-Ab positive patients with refractory gMG
Corticosteroids More commonly used: oral prednisone	MoA Nonspecific immunosuppression Limitations Widespread short- and long-term adverse effects (Schneider-Gold et al, 2019; Pascuzzi et al, 1984; Liu et al, 2013; Mehndiratta et al, 2014)	Approved for the treatment of MG in some member states only (e.g., in Germany)
NSISTs More commonly used: Azathioprine, cyclosporine, and mycophenolate Also used: tacrolimus,	MoA Multiple nonspecific mechanisms of action, including suppression of B and T cells Limitations Delayed onset of action. Various side effects, including liver and bone marrow toxicities, malignancies, and increased risk of infection for	Azathioprine tablets approved since 2004 for treatment of MG in some member states. Oral suspension (Jayempi®) recently approved in the EU following an application under Art 10(3) of Directive 2001.83

methotrexate, and cyclophosphamide	the more commonly used NSIDs (Hart et al, 2007; Mantegazza et al, 2011; Skeie et al, 2010)	based on Imurek approved in Germany
Intravenous immunoglobulins (IVIg) (e.g., Gamunex)	MoA Multiple mechanisms postulated including effects on autoantibodies, B and T cells Limitations IVIg use is limited in patients who are at risk of renal dysfunction and a history of hypertension or risk factors for thrombotic events (Privigen package insert, 2017) Burdensome administration Supply chain shortages are common Nausea, headache, fever, hypotension or hypertension, local skin reactions, IgA deficiency, allergic reactions (Privigen package insert, 2017)	Gamunex approved in MG for treatment of severe acute exacerbations in some member states only.
Rituximab	MoA B-cell depletion Limitations Nausea, infections, infusion-related problems Progressive multifocal leukoencephalopathy Eliminates B lymphocytes causing broad immunosuppression	Off-label use. Not approved for the treatment of MG

AChE=acetylcholinesterase; AChR-Ab=acetylcholine receptor – antibody; C5=complement component 5; gMG=generalised myasthenia gravis; IgA=immunoglobulin A; IgG=immunoglobulin G; IVIg=intravenous immunoglobulin; MG=myasthenia gravis; NMJ=neuromuscular junction; NSIST=nonsteroidal immunosuppressive drug

The mainstays of the routine management of MG are defined in international consensus guidelines, most recently in the International Consensus Guidance for Management of Myasthenia Gravis (Narayanaswami et al, 2021). This guidance includes the following recommendations:

- The AChE inhibitor pyridostigmine should be part of the initial treatment in most patients with MG.
- Corticosteroids or NSIST therapy for patients who have not met treatment goals after an adequate trial of pyridostigmine. NSISTs may be used alone when corticosteroids cannot be used. NSISTs that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus.
- Patients with refractory MG may be treated with chronic IVIg and chronic plasmapheresis/plasma exchange (PLEX) as maintenance therapy, cyclophosphamide, Rituximab.

It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Patients must be monitored for potential adverse effects and complications from immunosuppression and changing treatment may be required.

Thymectomy is recommended to be considered early in disease in patients aged 18–50 years who have non-thymomatous generalised MG (gMG), AChR-Ab seropositive patients who have failed to respond to immunotherapy or who have intolerable side effects. It may also be considered in patients without AChR-Abs (Hehir and Silvestri, 2018).

The guidance states that eculizumab should be considered in the treatment of severe, refractory, gMG in patients that are AChR-Ab positive (Hehir and Silvestri, 2018).

Significant benefit

For the evaluation of significant benefit of efgartigimod (Vyvgart) and in view of the therapeutic indication, medicinal products from the following drug classes are considered satisfactory methods and are therefore of relevance for this evaluation: **AChE inhibitors, NSISTs** and **corticosteroids**. The monoclonal antibody eculizumab is only indicated for the treatment of (AChR-Ab+) patients with refractory MG. Other treatment options such as the short-term immune therapies of plasmapheresis/ plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) are indicated and used in a subset of the MG population in which efgartigimod approval is not being sought (i.e., patients with refractory MG and/or severe acute exacerbations).

The sponsor claims that efgartigimod will be of significant benefit over relevant existing treatments for those affected by that condition, based on the following considerations:

Efgartigimod demonstrated superior efficacy as add-on to standard of care therapy versus standard of care therapy plus placebo, in adult AChR-Ab seropositive patients with gMG in a randomised, controlled clinical trial (pivotal study ARGX-113-1704). Standard of care therapy included AChE inhibitors, NSISTs and corticosteroids. Efgartigimod was studied in patients who were symptomatic despite receiving at least one concomitant gMG therapy and 88.4% of the AChR-Ab+ patients in the study were receiving an AChEi, either alone in combination with steroids or NSIST. A total of 19 patients (13 in the efgartigimod group and 6 in the placebo group) received concomitant AChE inhibitors as sole concomitant therapy during cycle 1. As shown in Table 3, in the efgartigimod group, 11 (84.6%) patients were MG-ADL responders compared to 1 (16.7%) patient in the placebo group. The response difference (95% CI) of 67.9% (32.3; 100.0) demonstrated a benefit of efgartigimod treatment compared to AChE inhibitor monotherapy. Similar results were seen in QMG scores (8/13[61.5%] versus 1/6 [16.7%]).

Table 3: MG-ADL Responders During Cycle 1 in AChR-Ab Seropositive Population by Concomitant AChE Inhibitor Status in Study ARGX-113-1704 (mITT Analysis Set)

	MG-ADL	
	EFG (N=68) n (%)	**PBO (N=64) n (%)**
Concomitant AChE inhibitor only	13 (100)	6 (100)
Response	11 (84.6)	1 (16.7)
Δ in Response (95% CI)	67.9% (32.3; 100.0)	

Source: ARGX-113-1704 - Pharmaceuticals and Medicinal Devices Agency (PMDA) Questions Table 5.1
Δ=change; AChE=acetylcholinesterase; AChR-Ab=acetylcholine receptor antibody; CI=confidence interval; EFG=efgartigimod; MG-ADL=Myasthenia Gravis Activities of Daily Living; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; PBO=placebo; MG-ADL responder criterion: ≥2-point improvement in MG-ADL total score sustained for ≥4 consecutive weeks

In study ARGX-113-1704, 79.2% of AChR-Ab seropositive patients were receiving steroids and 59.7% were receiving NSISTs demonstrating these therapies were not adequately treating their gMG. Efgartigimod has demonstrated efficacy in these patients. Additionally, subgroup analyses of patients who were receiving steroids, or were receiving NSISTs during the study show that efgartigimod treatment provided benefit, demonstrating a major clinical benefit over these treatments (see Table 4).

Table 1: MG-ADL Responders During Cycle 1 in the AChR-Ab Seropositive Population in Patients Treated With Concomitant NSIST and Corticosteroids and the Full AChR-Ab Seropositive Patient Group in Study ARGX-113-1704 (mITT Analysis Set)

	Efgartigimod n/N (%)	**Placebo n/N (%)**
MG-ADL Responders		
Concomitant steroid	29/46 (63.0)	15/51 (29.4%)
Concomitant NSIST	25/38 (65.8%)	11/37 (29.7%)
Full AChR-Ab Seropositive Patient Group	44/65 (67.7%)	19/64 (29.7%)
QMG Responders		
Concomitant steroid	31/46 (67.4)	7/51 (13.7)
Concomitant NSIST	23/40 (57.5%)	2/37 (5.4%)
Full AChR-Ab Seropositive Patient Group	41/65 (63.1%)	9/64 (14.1%)

ARGX-113-1704 CSR Table 14.2.1.5.1
AChR-Ab=acetylcholine receptor antibody; MG-ADL=Myasthenia Gravis Activities of Daily Living; QMG=Quantitative Myasthenia Gravis; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported; N=number of patients in the analysis set

With regards to significant benefit of efgartigimod vs. eculizumab, data shows that efgartigimod is effective in treating patients that would not qualify for treatment with eculizumab. Eculizumab is authorised for the treatment of AChR-Ab seropositive patients with refractory gMG while the therapeutic indication for efgartigimod is not restricted to patients with refractory gMG. AChR-Ab seropositive patients with refractory gMG represent only approximately 10% of gMG patients and efgartigimod offers treatment to approximately 80 to 85% of the MG population with gMG.

The sponsor also presents data from an indirect comparison of efficacy between efgartigimod and eculizumab. Mean improvement in MG-ADL score was 1.0 point greater for efgartigimod than for eculizumab with a 95% credible interval (CrI) of 0.8 to 1.2. The robustness and clinical relevance of these findings is however questioned. The sponsor also points out that following the initiation of treatment with efgartigimod clinical response has been shown to be obtained within 2 weeks of the initial infusion in the majority of patients. Time to treatment effect can take up to 6 to 12 months with NSISTs.

The COMP also took note of feedback obtained from patient and consumer organisations during the MA review of Vyvgart by CHMP. The specific feedback concerning Vyvgart pertained to its dosing frequency and administration modality. Vyvgart is administered as a 1-hour IV infusion in cycles. One cycle consists of one infusion per week for 4 weeks The frequency of treatment cycles may vary by patient.

In conclusion, significant benefit over relevant authorised therapies is considered to be established by the COMP. This is based on the efficacy data from the pivotal randomised, placebo-controlled 26-week study (ARGX-113-1704). Vyvgart demonstrated superior efficacy as add-on to standard of care therapy including AChE inhibitors, NSISTs and/or corticosteroids, versus standard of care therapy plus placebo, in adult AChR-Ab seropositive patients with gMG. Improvements pertained to the following primary and secondary efficacy endpoints: 1) % responders in Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, 2) % responders in the Quantitative Myasthenia Gravis (QMG) scale, and 3) %

of Time of Clinically Meaningful Improvement in the AChR-Ab seropositive population. The COMP concluded that this represents a clinically relevant advantage over currently authorised therapies.

4. COMP position adopted on 24 June 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of myasthenia gravis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expression, chewing, talking, and swallowing. Recurrent myasthenic crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Vyvgart may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data showing improved efficacy of Vyvgart when used as adjunct treatment to standard of care, including acetylcholinesterase inhibitors, nonsteroidal immunosuppressive drugs and/or corticosteroids, as compared to standard of care. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Vyvgart, efgartigimod alfa, for treatment of myasthenia gravis (EU/3/18/1992) is not removed from the Community Register of Orphan Medicinal Products.