NEW DRUG APPROVAL

Brand Name	Vyvgart™
Generic Name	efgartigimod alfa-fcab
Drug Manufacturer	Argenx BV

New Drug Approval

FDA approval date: December 17, 2021

Review designation: Orphan

Type of review: Biologic License Application (BLA): 761195

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Acquired myasthenia gravis is a relatively uncommon disorder, with prevalence rates that have increased to about 20 per 100,000 in the US population. This autoimmune disease is characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest. In about two-thirds of the patients, the involvement of extrinsic ocular muscle presents as the initial symptom, usually progressing to involve other bulbar muscles and limb musculature, resulting in generalized myasthenia gravis. Although the cause of the disorder is unknown, the role of circulating antibodies directed against the nicotinic acetylcholine receptor in its pathogenesis is well established. As this disorder is highly treatable, prompt recognition is crucial.

In about 10% of myasthenia gravis patients, symptoms are limited to EOMs, with the resultant condition called ocular MG (oMG). Sex and age appear to influence the occurrence of myasthenia gravis. Below 40 years of age, female: male ratio is about 3: 1; however, between 40 and 50 years as well as during puberty, it is roughly equal. Over 50 years, it occurs more commonly in males. Childhood MG is uncommon in Europe and North America, comprising 10% to 15% of MG cases. In Asian countries though, up to 50% of patients have onset below 15 years of age, mainly with purely ocular manifestations.

Efficacy

The efficacy of Vyvgart™ for the treatment of generalized myasthenia gravis (gMG) in adults who are AChR antibody positive was established in a 26-week, multicenter, randomized, double-blind, placebo-controlled trial (Study 1; NCT03669588).

Study 1 enrolled patients who met the following criteria at screening:

- Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV.
- MG-Activities of Daily Living (MG-ADL) total score of ≥ 5.
- On stable dose of MG therapy prior to screening, that included acetylcholinesterase (AChE) inhibitors, steroids, or non-steroidal immunosuppressive therapies (NSISTs), either in combination or alone.
- IgG levels of at least 6 g/L.

A total of 167 patients were enrolled in Study 1 and were randomized to receive either Vyvgart™ 10mg/kg (1200 mg for those weighing 120 kg or more) (n=84) or placebo (n=83). The majority of patients (n=65 for Vyvgart™; n=64 for placebo) were positive for AChR antibodies. At baseline, over 80% of patients in each group received AChE inhibitors, over 70% in each treatment group received steroids, and approximately 60% in each treatment group received NSISTs, at stable doses.

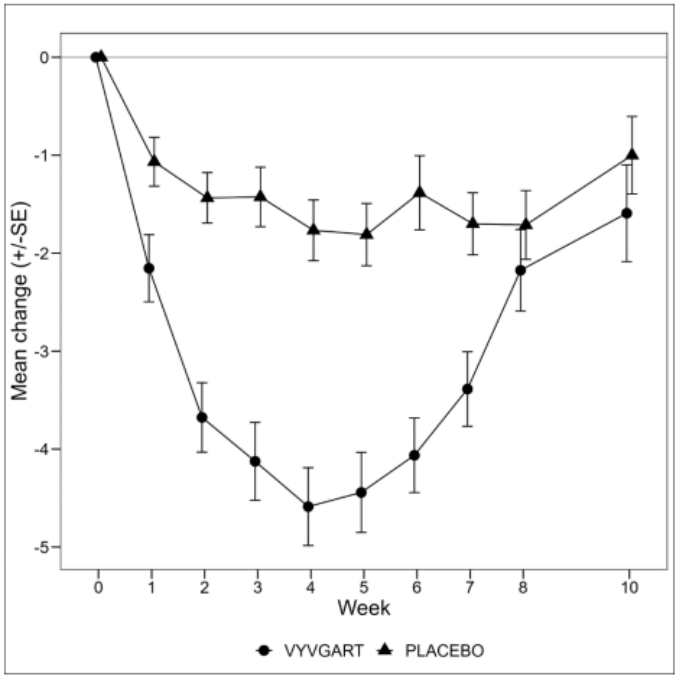
The primary efficacy endpoint was the comparison of the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the AChR-Ab positive population. A statistically significant difference favoring Vyvgart™ was observed in the MG-ADL responder rate during the first treatment cycle [67.7% in the Vyvgart™-treated group vs 29.7% in the placebo-treated group (p < <0.0001)].
The efficacy of Vyvgart™ was also measured using the Quantitative Myasthenia Gravis (QMG) total score which is a 13-item categorical grading system that assesses muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total possible score ranges from 0 to 39, where higher scores indicate more severe impairment. In this study, a QMG responder was defined as a patient who had a 3-point or greater reduction in the total QMG score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after last infusion of the cycle.
The secondary endpoint was the comparison of the percentage of QMG responders during the first treatment cycle between both treatment groups in the AChR-Ab positive patients. A statistically significant difference favoring Vyvgart™ was observed in the QMG responder rate during the first treatment cycle [63.1% in the Vyvgart™-treated group vs 14.1% in the placebo-treated group (p < 0.0001)].

Table 1: MG-ADL and QMG Responders During Cycle 1 in AChR-Ab Positive Patients (mITT Analysis Set)

	VYVGART n=65 %	Placebo n=64 %	P-value	Odds Ratio (95% CI)
MG-ADL Responders	67.7	29.7	< 0.0001	4.951 (2.213, 11.528)
QMG Responders	63.1	14.1	< 0.0001	10.842 (4.179, 31.200)

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; CI = confidence interval;
Logistic regression stratified for AChR-Ab status (if applicable), Japanese/Non-Japanese and standard of care, with baseline MG-ADL as covariate / QMG as covariates
Two-sided exact p-value

Figure 1 shows the mean change from baseline on the MG-ADL during cycle 1.



Safety

ADVERSE EVENTS

In a placebo-controlled study (Study 1) in patients with gMG, 84 patients received Vyvgart™ 10 mg/kg. Of these 84 patients, approximately 75% were female, 82% were White, 11% were Asian, and 8% were of Hispanic or Latino ethnicity. The mean age at study entry was 46 years (range 19 to 78).

The minimum time between treatment cycles, specified by study protocol, was 50 days. On average, Vyvgart™-treated patients received 2 cycles in Study 1. The mean and median times to the second treatment cycle were 94 days and 72 days from the initial infusion of the first treatment cycle, respectively, for Vyvgart™-treated patients.

Adverse reactions reported in at least 5% of patients treated with Vyvgart™ and more frequently than placebo are summarized in Table 1.

Table 1: Adverse Reactions in ≥ 5% of Patients Treated with VYVGART and More Frequently than in Placebo-Treated Patients in Study 1 (Safety Population)

Adverse reaction	VYVGART (N=84) %	Placebo (N=83) %
Respiratory tract infection	33	29
Headache[1]	32	29
Urinary tract infection	10	5
Paraesthesia[2]	7	5
Myalgia	6	1

[1]Headache includes migraine and procedural headache.
[2]Paraesthesia includes oral hypoesthesia, hypoesthesia, and hyperesthesia.

WARNINGS & PRECAUTIONS

Infections: Vyvgart™ may increase the risk of infection. The most common infections observed in Study 1 were urinary tract infection (10% of Vyvgart™ treated patients compared to 5% of placebo-treated patients) and respiratory tract infections (33% of Vyvgart™ treated patients compared to 29% of placebo-treated patients). A higher frequency of patients who received Vyvgart™ compared to placebo were observed to have below normal levels for white blood cell counts (12% versus 5%, respectively), lymphocyte counts (28% versus 19%, respectively), and neutrophil counts (13% versus 6%, respectively). The majority of infections and hematologic abnormalities were mild to moderate in severity.

Hypersensitivity Reactions: It includes rash, angioedema, and dyspnea, were observed in Vyvgart™ treated patients. In clinical trials, hypersensitivity reactions were mild or moderate, occurred within one hour to three weeks of administration.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Efgartigimod alfa is a human immunoglobulin G1 (IgG1) antibody fragment that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG, including the abnormal antiacetylcholine receptor (AChR)

antibodies that are present in patients with generalized myasthenia gravis (gMG). In patients with myasthenia gravis who test positive for the AChR antibody, the AChR antibodies interfere with communication between nerves and muscles, resulting in weakness.

Dose & Administration

ADULTS

Weight less than 120 kg: 10 mg/kg once weekly intravenous for 4 weeks.

Weight 120 kg or more: 1,200 mg once weekly intravenous for 4 weeks.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 400 mg in 20 mL (20 mg/mL) single-dose vial.