Policy Number	**RX501.141**
Policy Effective Date	**01/01/2024**
Policy End Date	**03/14/2025**

Efgartigimod alfa-fcab or Efgartigimod alfa and hyaluronidase-qvfc

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-

reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Efgartigimod alfa-fcab (Vyvgart®) or Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo) **may be considered medically necessary** for the treatment of generalized myasthenia gravis (MG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive AND the following criteria are met:

- Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV; AND
- MG-Activities of Daily Living (MG-ADL) total score of ≥5; AND
- 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; AND
- Will **NOT** use efgartigimod alfa-fcab or efgartigimod alfa and hyaluronidase-qvfc concurrently with other biologics used to treat Myasthenia Gravis (e.g., rituximab, eculizumab, IVIG).

Efgartigimod alfa-fcab (Vyvgart™) or Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo) **are considered experimental, investigational and/or unproven** for all other indications, and when the above criteria are not met.

Policy Guidelines

None.

Description

Myasthenia gravis (MG) is a neuromuscular disorder that causes muscle weakness and muscle fatigue. It is an autoimmune disease where the immune system, which normally protects the body from foreign organisms, mistakenly attacks itself. MG is caused by an error in the transmission of nerve impulses to muscles, which occurs when normal communication between the nerve and muscle is interrupted at the neuromuscular junction, the spot where nerve cells connect with the muscles they control. (1, 2)

Normally when electrical signals or impulses travel down a motor nerve, the nerve endings release a neurotransmitter called acetylcholine that binds to sites called acetylcholine receptors

on the muscle. The binding of acetylcholine to its receptor activates the muscle and causes a muscle contraction.

In myasthenia gravis, antibodies (immune proteins produced by the body's immune system) block, alter, or destroy the receptors for acetylcholine at the neuromuscular junction, which prevents the muscle from contracting. This is most often caused by antibodies to the acetylcholine receptor itself, but antibodies to other proteins, such as MuSK (Muscle-Specific Kinase) protein, also can impair transmission at the neuromuscular junction.

Myasthenia gravis affects both men and women and occurs across all racial and ethnic groups. It most commonly impacts young adult women (under 40) and older men (over 60), but it can occur at any age, including childhood. Myasthenia gravis is not inherited nor is it contagious. Occasionally, the disease may occur in more than one member of the same family.

Clinical Features

Most individuals with myasthenia gravis develop weakness and drooping of the eyelids (ptosis); weakness of eye muscles, resulting in double vision (diplopia); and excessive muscle fatigue following activity. Additional features commonly include weakness of facial muscles; impaired speech (dysarthria); difficulties chewing and swallowing (dysphagia); and weakness of the upper arms and legs (proximal limb weakness). In addition, in about 10 percent of patients, affected individuals may develop potentially life-threatening complications due to severe involvement of muscles used during breathing (myasthenic crisis). (1, 2)

In those with more generalized disease or "generalized myasthenia gravis," affected muscles may include those of the eyes, face, jaw, and throat region; arm and leg (limb) muscles; and muscles involved in breathing (respiratory muscles).

Clinical Classification

The Myasthenia Gravis Foundation of America (MGFA) clinical classification divides MG into 5 main classes and several subclasses. Designed to identify subgroups of patients who share distinct clinical features or severity of disease that may indicate different prognoses or responses to therapy, it should not be used to measure clinical outcome.

- Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
- Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

    - IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb. (3)

The Myasthenia Gravis–specific Activities of Daily Living scale (MG-ADL)
The Myasthenia Gravis–specific Activities of Daily Living scale (MG-ADL) was developed in the late 1990s to assess the status of symptoms and activities in MG.11 It is an 8-item, patient reported questionnaire that can be completed in 2–3 minutes with no need for specialized equipment or training. (4) See Table 1.

Table 1. MG Activities of Daily Living (MG-ADL) Profile

Grade	0	1	2	3	Score (0, 1, 2, 3)
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependent	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to	None	Mild, sometimes users arms	Moderate, always uses arms	Severe, requires assistance	

arise from a chair					
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Each activity is scored 0-3; and all scores are totaled to represent the overall MG-ADL score.

Treatment
Treatment for MG may include a thymectomy, the removal of the thymus gland which often is abnormal in individuals with MG. Monoclonal antibodies that target the process by which acetylcholine antibodies injure the neuromuscular junction may be used. Anticholinesterase medications slow the breakdown of acetylcholine at the neuromuscular junction and improve transmission and increase muscle strength. Immunosuppressive drugs improve muscle strength by suppressing the production of abnormal antibodies.

Regulatory Status
Efgartigimod alfa-fcab (Vyvgart®) is a human immunoglobulin G1 (IgG1)-derived Fc fragment (fragment, crystallized) of the za allotype. It binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG. The U.S. Food and Drug Administration (FDA) granted approval of Vyvgart on Dec. 17, 2021 through their fast-track process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The FDA also designated Vyvgart as an orphan drug. (5, 6)

In 2023, the FDA approved efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo) for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Vyvgart Hytrulo is a coformulation of efgartigimod alfa and hyaluronidase. Efgartigimod alfa is a human IgG1 antibody fragment that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. This effect is transient, and permeability of the subcutaneous tissue is restored within 24 to 48 hours. (7)

Rationale

This policy was developed in January 2022 and is based on the U.S. Food and Drug Administration labeled indications as well as a search of literature in the PubMed database.

Efgartigimod alfa-fcab (Vyvgart®)
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). (6)

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). Baseline characteristics were similar between treatment groups. Patients had a median age of 46 years at screening (range: 19 to 81 years) and a median time since diagnosis of 9 years. Seventy-one percent were female, and 84% were White. Median MG-ADL total score was 9, and median Quantitative Myasthenia Gravis (QMG) total score was 16. 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.

Patients were treated with Vyvgart at the recommended dosage regimen.

The efficacy of Vyvgart was measured using the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) which assesses the impact of gMG on daily functions of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. A total score ranges from 0 to 24, with the higher scores indicating more impairment. In this study, an MGADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle.

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)].

The results are presented in Table 2.

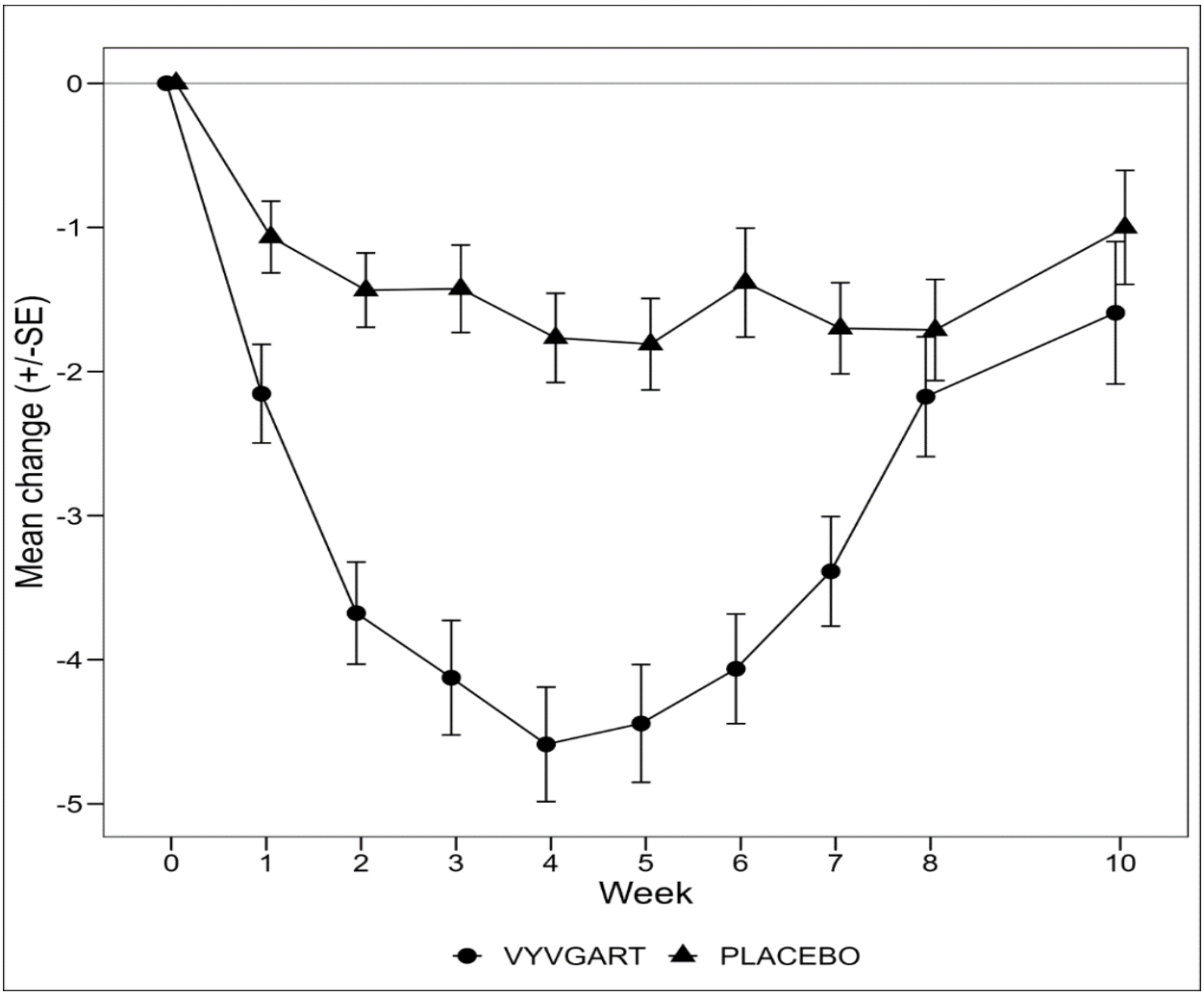
Table 2. MG-ADL and QMG Responders During Cycle 1 in AChR-Ab Positive Patients (mITT Analysis Set)

	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; AChR-Ab: anti-acetylcholine receptor antibody; 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.

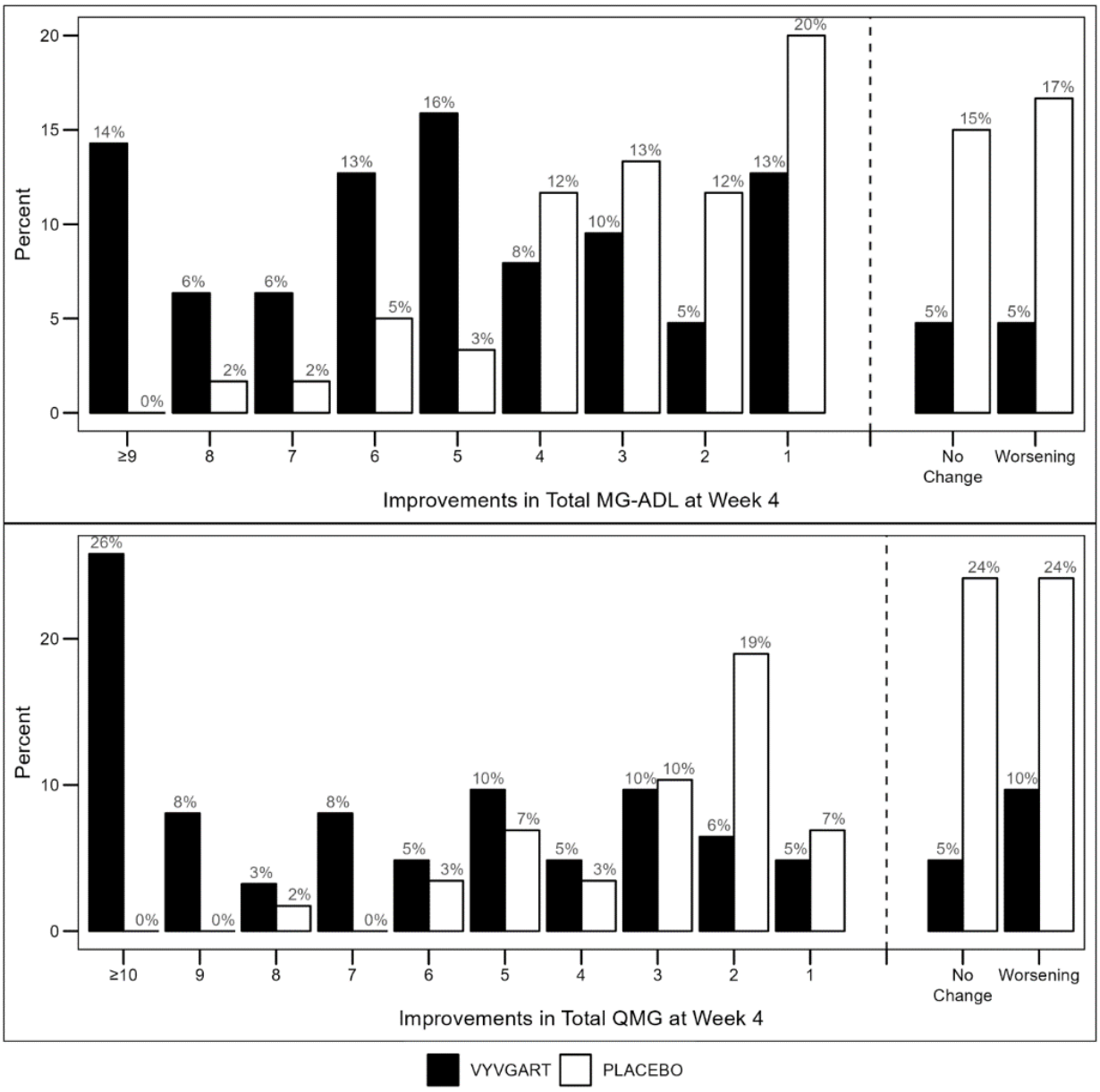
Figure 1: Mean Change in Total MG-ADL From Cycle 1 Baseline Over Time in AChR-Ab Positive Patients (mITT Analysis Set)



MG-ADL: Myasthenia Gravis Activities of Daily Living; AChR-Ab: anti-acetylcholine receptor antibody; mITT: modified intent-to treat

Figure 2 shows the distribution of response on the MG-ADL and QMG during cycle 1, four weeks after the first infusion with Vyvgart.

Figure 2: Percentage of Patients with MG-ADL and QMG Total Score Change 4 Weeks Post Initial Infusion of the First Cycle in AChR-Ab Positive Population



MG-ADL: Myasthenia Gravis Activities of Daily Living; QMG: Quantitative Myasthenia Gravis; AChR-Ab: anti-acetylcholine receptor antibody

Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo)

Study 1 (described below) which established the effectiveness of efgartigimod alfa-fcab for the treatment of generalized myasthenia gravis (gMG) in adults who are AChR antibody positive was conducted with efgartigimod alfa-fcab intravenous formulation. In Study 2, Vyvgart Hytrulo demonstrated a comparable pharmacodynamic effect on AChR antibody reduction as compared to the efgartigimod alfa-fcab intravenous formulation, which established the efficacy of Vyvgart Hytrulo. (7)

<u>Study 1 (Efgartigimod Alfa-fcab Intravenous)</u>

The efficacy of efgartigimod alfa-fcab intravenous (EFG IV) for the treatment of 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 EFG IV 10mg/kg (1200 mg for those weighing 120 kg or more) (n=84) or placebo (n=83). Baseline characteristics were similar between treatment groups. Patients had a median age of 46 years at screening (range: 19 to 81 years) and a median time since diagnosis of 9 years. Seventy-one percent were female, and 84% were White. Median MG-ADL total score was 9, and median Quantitative Myasthenia Gravis (QMG) total score was 16. The majority of patients (n=65 for EFG IV; 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.

Patients were treated with 10 mg/kg EFG IV administered as an intravenous infusion over one hour once weekly for 4 weeks. In patients weighing 120 kg or more, EFG IV was administered as 1200 mg per infusion. Subsequent treatment cycles were administered based on clinical evaluation, but no sooner than 50 days from the start of the previous treatment cycle.

The efficacy of EFG IV was measured using the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) which assesses the impact of gMG on daily functions of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. A total score ranges from 0 to 24, with the higher scores indicating more impairment. In this study, an MG-ADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle.

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 EFG IV was observed in the MG-ADL responder rate during the first treatment cycle [67.7% in the EFG IV-treated group vs 29.7% in the placebo-treated group ($p < 0.0001$)].

The efficacy of EFG IV 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 EFG IV was observed in the QMG responder rate during the first treatment cycle [63.1% in the EFG IV-treated group vs 14.1% in the placebo treated group (p <0.0001)].

The results are presented in Table 3.

Table 3. MG-ADL and QMG Responders During Cycle 1 in AChR-Ab Positive Patients (mITT Analysis Set)

	EFG IV 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)

AChR-Ab: anti-acetylcholine receptor antibody positive; EFG IV: Efgartigimod alfa-fcab intravenous; 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

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J3490, J3590, J9332, J9334

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2024	Document updated with literature review. Coverage revised to add Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo) to the medically necessary and experimental, investigational and/or unproven statements. Reference 7 added; others revised. Title changed from Efgartigimod alfa-fcab.
05/01/2022	New medical document. Efgartigimod alfa-fcab (Vyvgart™) may be considered medically necessary for the treatment of generalized myasthenia gravis (MG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive when additional criteria listed in the policy are met. Efgartigimod alfa-fcab (Vyvgart™ is considered experimental, investigational

	and/or unproven for all other indications, and when the above criteria are not met.