HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VYVGART HYTRULO safely and effectively. See full prescribing information for VYVGART HYTRULO.

VYVGART® HYTRULO (efgartigimod alfa and hyaluronidase-qvfc) injection, for subcutaneous use
Initial U.S. Approval: 2023

----------RECENT MAJOR CHANGES----------

Contraindications (4)	12/2023
Warnings and Precautions (5.2, 5.3)	12/2023

----------INDICATIONS AND USAGE----------

VYVGART HYTRULO is a combination of efgartigimod alfa, a neonatal Fc receptor blocker, and hyaluronidase, an endoglycosidase, indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. (1)

----------DOSAGE AND ADMINISTRATION----------

- See Full Prescribing Information for instructions on dosage, preparation, and administration. (2.1, 2.2, 2.3, 2.4)
- Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle with VYVGART HYTRULO. (2.1)
- Administer by a healthcare professional only. (2.2)
- For subcutaneous use with a winged infusion set. (2.2)
- The recommended dose is 1,008 mg / 11,200 units (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered subcutaneously over approximately 30 to 90 seconds in cycles of once weekly injections for 4 weeks. (2.3)
- Administer subsequent treatment cycles based on clinical evaluation; safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 1,008 mg efgartigimod alfa and 11,200 units hyaluronidase per 5.6 mL (180 mg/2,000 units per mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

VYVGART HYTRULO is contraindicated in patients with serious hypersensitivity to efgartigimod alfa products, to hyaluronidase, or to any of the excipients of VYVGART HYTRULO. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Delay administration of VYVGART HYTRULO to patients with an active infection. Monitor for signs and symptoms of infection in patients treated with VYVGART HYTRULO. If serious infection occurs, administer appropriate treatment and consider withholding VYVGART HYTRULO until the infection has resolved. (5.1)
- Hypersensitivity Reactions: Anaphylaxis, hypotension leading to syncope, angioedema, dyspnea, rash, and urticaria have occurred in patients treated with VYVGART HYTRULO or intravenous efgartigimod alfa-fcab product. If a hypersensitivity reaction occurs, the healthcare professional should institute appropriate measures if needed or the patient should seek medical attention. (4, 5.2)
- Infusion-Related Reactions: If a severe infusion-related reaction occurs, initiate appropriate therapy; consider the risks and benefits of readministering. If a mild to moderate infusion-related reaction occurs, may rechallenge with close clinical observation, slower infusion rates, and pre-medications. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 10%) in patients with gMG treated with efgartigimod alfa-fcab were respiratory tract infections, headache, and urinary tract infection.

Additional common adverse reactions with VYVGART HYTRULO are injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Argenx at 1-833-argx411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Closely monitor for reduced effectiveness of medications that bind to the human neonatal Fc receptor. When concomitant long-term use of such medications is essential for patient care, consider discontinuing VYVGART HYTRULO and using alternative therapies. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VYVGART HYTRULO is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination

Because VYVGART HYTRULO causes transient reduction in IgG levels, immunization with live-attenuated or live vaccines is not recommended during treatment with VYVGART HYTRULO. Evaluate the need to administer age-appropriate immunizations according to immunization guidelines before initiation of a new treatment cycle with VYVGART HYTRULO *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

2.2 Important Dosage and Administration Instructions

VYVGART HYTRULO is to be administered by a healthcare professional only.

VYVGART HYTRULO is for subcutaneous use only and administered with a winged infusion set *[see Dosage and Administration (2.4)].* Do not administer intravenously.

Do not dilute VYVGART HYTRULO.

2.3 Recommended Dose and Dose Schedules

The recommended dosage of VYVGART HYTRULO is 1,008 mg / 11,200 units (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered subcutaneously over approximately 30 to 90 seconds in cycles of once weekly injections for 4 weeks.

Administer subsequent treatment cycles according to clinical evaluation. The safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.

If a scheduled dose is missed, VYVGART HYTRULO may be administered up to 3 days after the scheduled time point. Thereafter, resume the original dosing schedule until the treatment cycle is completed.

2.4 Preparation and Administration Instructions

Use aseptic technique when preparing and administering VYVGART HYTRULO. Do not shake the vial. Each vial is for one time use only. Avoid exposure to direct sunlight.

<u>Preparation</u>

- Take the VYVGART HYTRULO vial out of the refrigerator at least 15 minutes before

injecting to allow it to reach room temperature *[see How Supplied/Storage and Handling (16)].* Do not use external heat sources.

- Check that the VYVGART HYTRULO solution is yellowish, clear to opalescent.
- Parenteral medicine products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Do not use if opaque particles or other foreign particles are present.
- Withdraw the entire content of VYVGART HYTRULO from the vial using a polypropylene syringe and an 18G stainless steel transfer needle.
- Remove large air bubbles, if present.
- Each vial contains overfill to compensate for liquid loss during preparation and to compensate for the priming volume of the winged infusion set.
- VYVGART HYTRULO does not contain preservatives. Administer immediately after preparation.

Administration

- To administer VYVGART HYTRULO use a winged infusion set made of polyvinyl chloride (PVC), 25G, 12 inches tubing, maximum priming volume of 0.4 mL.
- Remove the transfer needle from the syringe and connect the syringe to the winged infusion set.
- Prior to administration, fill the tubing of the winged infusion set by gently pressing the syringe plunger until the plunger is at 5.6 mL. There should be solution at the end of the winged infusion set needle.
- Choose an injection site on the abdomen (at least 2 to 3 inches away from the navel).
  - Do not inject on areas where the skin is red, bruised, tender, hard, or into areas where there are moles or scars.
  - Rotate injection sites for subsequent administrations.
- Inject VYVGART HYTRULO subcutaneously into a pinched skin area at an angle of about 45 degrees over 30 to 90 seconds.
- Localized injection site reactions may occur after VYVGART HYTRULO is administered. *[see Adverse Reactions (6.1)]*.
- Discard any unused portions of medicine remaining in the vial, the syringe and the winged infusion set.
- Healthcare professionals should monitor for clinical signs and symptoms of hypersensitivity reactions for at least 30 minutes after administration. If a hypersensitivity reaction occurs, the healthcare professional should institute appropriate measures if needed or the patient should seek medical attention *[see Warnings and Precautions (5.2)].*

3 DOSAGE FORMS AND STRENGTHS

Injection: 1,008 mg efgartigimod alfa and 11,200 units hyaluronidase per 5.6 mL (180 mg/2,000 units per mL) as yellowish, clear to opalescent solution, in a single-dose vial.

4 CONTRAINDICATIONS

VYVGART HYTRULO is contraindicated in patients with serious hypersensitivity to efgartigimod alfa products, to hyaluronidase, or to any of the excipients of VYVGART HYTRULO. Reactions have included anaphylaxis and hypotension leading to syncope *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

VYVGART HYTRULO may increase the risk of infection. The most common infections observed in Study 1 were urinary tract infection (10% of efgartigimod alfa-fcab-treated patients compared to 5% of placebo-treated patients) and respiratory tract infections (33% of efgartigimod alfa-fcab-treated patients compared to 29% of placebo-treated patients) *[see Adverse Reactions (6.1) and Clinical Studies (14)]*. A higher frequency of patients who received efgartigimod alfa-fcab 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. Delay VYVGART HYTRULO administration in patients with an active infection until the infection is resolved. During treatment with VYVGART HYTRULO, monitor for clinical signs and symptoms of infections. If serious infection occurs, administer appropriate treatment and consider withholding VYVGART HYTRULO until the infection has resolved.

Immunization

Immunization with vaccines during VYVGART HYTRULO treatment has not been studied. The safety of immunization with live or live-attenuated vaccines and the response to immunization with any vaccine are unknown. Because VYVGART HYTRULO causes a reduction in IgG levels, vaccination with live-attenuated or live vaccines is not recommended during treatment with VYVGART HYTRULO. Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle with VYVGART HYTRULO.

5.2 Hypersensitivity Reactions

In clinical trials, hypersensitivity reactions, including rash, angioedema, and dyspnea were observed in patients treated with VYVGART HYTRULO or intravenous efgartigimod alfa-fcab. Urticaria was also observed in patients treated with VYVGART HYTRULO. Hypersensitivity reactions were mild or moderate, occurred within one hour to three weeks of administration, and did not lead to treatment discontinuation.

Anaphylaxis and hypotension leading to syncope have been reported in postmarketing experience with intravenous efgartigimod alfa-fcab. Anaphylaxis and hypotension occurred during or within an hour of administration and led to infusion discontinuation and in some cases to permanent treatment discontinuation.

Healthcare professionals should monitor for clinical signs and symptoms of hypersensitivity reactions for at least 30 minutes after administration *[see Dosage and Administration (2.4)]*. If a hypersensitivity reaction occurs, the healthcare professional should institute appropriate measures if needed or the patient should seek medical attention. VYVGART HYTRULO is contraindicated in patients with a history of serious hypersensitivity to efgartigimod alfa products, to hyaluronidase, or

to any of the excipients of VYVGART HYTRULO *[see Contraindications (4)]*.

5.3 Infusion-Related Reactions

Infusion-related reactions have been reported with intravenous efgartigimod alfa-fcab in postmarketing experience. The most frequent symptoms and signs were hypertension, chills, shivering, and thoracic, abdominal, and back pain. Infusion-related reactions occurred during or within an hour of administration and led to infusion discontinuation. If a severe infusion-related reaction occurs, initiate appropriate therapy. Consider the risks and benefits of readministering VYVGART HYTRULO following a severe infusion-related reaction. If a mild to moderate infusion-related reaction occurs, patients may be rechallenged with close clinical observation, slower infusion rates, and pre-medications.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of efgartigimod alfa in patients with gMG was established in a double blinded placebo-controlled study with efgartigimod alfa-fcab administered intravenously (Study 1) and its open-label extension, and in an active-controlled study of VYVGART HYTRULO administered subcutaneously (Study 2) and its open-label extension.

Adverse Reactions with Efgartigimod Alfa-fcab Intravenous

In clinical studies, the safety of efgartigimod alfa-fcab administered intravenously has been evaluated in 246 patients who received at least one dose of efgartigimod alfa-fcab, including 57 patients exposed to at least 7 treatment cycles and 8 patients exposed to at least 10 treatment cycles.

In a placebo-controlled study (Study 1) in patients with gMG, 84 patients received efgartigimod alfa-fcab 10 mg/kg *[see Clinical Studies (14)]*. 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 to initiate a subsequent cycle, specified by study protocol, was 50 days from the start of the previous treatment cycle. On average, efgartigimod alfa-fcab-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 efgartigimod

alfa-fcab-treated patients.

Adverse reactions reported in at least 5% of patients treated with efgartigimod alfa-fcab and more frequently than placebo are summarized in Table 1. The most common adverse reactions (reported in at least 10% of efgartigimod alfa-fcab-treated patients) were respiratory tract infection, headache, and urinary tract infection.

Table 1: Adverse Reactions in at least 5% of Patients Treated with Efgartigimod Alfa-fcab Intravenously (EFG IV) and More Frequently than in Placebo-Treated Patients in Study 1 (Safety Population)

Adverse reaction	**EFG IV** (N=84) %	**Placebo** (N=83) %
Respiratory tract infection	33	29
Headache*	32	29
Urinary tract infection	10	5
Paraesthesia†	7	5
Myalgia	6	1

Headache includes migraine and procedural headache.

†*Paraesthesia includes oral hypoesthesia, hypoesthesia, and hyperesthesia.*

Adverse Reactions with VYVGART HYTRULO

In an active-controlled study in patients with gMG (Study 2), 110 patients were randomized and received one cycle of once weekly administrations for 4 weeks (4 administrations total), of either VYVGART HYTRULO subcutaneously (n=55) or efgartigimod alfa-fcab intravenously (n=55) at recommended doses *[see Dosage and Administration (2.2)]*. The open-label extension of Study 2 included some patients who switched from efgartigimod alfa-fcab IV to VYVGART HYTRULO.

The most common adverse reactions (reported in at least 10% of VYVGART HYTRULO-treated patients) were injection site reactions and headache.

In Study 2, injection site reactions occurred in 38% of patients receiving VYVGART HYTRULO. These were injection site rash, erythema, pruritus, bruising, pain, and urticaria.
In Study 2 and its open-label extension (n = 168), all injection site reactions were mild to moderate in severity and did not lead to treatment discontinuation. The majority occurred within 24 hours after administration and resolved spontaneously. Most injection site reactions occurred during the first treatment cycle, and the incidence decreased with each subsequent cycle.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of efgartigimod alfa products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions including anaphylaxis and hypotension, and

infusion-related reactions *[see Warnings and Precautions (5.2 5.3)].*

7 DRUG INTERACTIONS

7.1 Effect of VYVGART HYTRULO on Other Drugs

Concomitant use of VYVGART HYTRULO with medications that bind to the human neonatal Fc receptor (FcRn) (e.g., immunoglobulin products, monoclonal antibodies, or antibody derivates containing the human Fc domain of the IgG subclass) may lower systemic exposures and reduce effectiveness of such medications. Closely monitor for reduced effectiveness of medications that bind to the human neonatal Fc receptor. When concomitant long-term use of such medications is essential for patient care, consider discontinuing VYVGART HYTRULO and using alternative therapies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of VYVGART HYTRULO or efgartigimod alfa containing products during pregnancy. There was no evidence of adverse developmental outcomes following the intravenous administration of efgartigimod alfa at up to 100 mg/kg/day in rats and rabbits (see Data).

The background rate of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Therefore, efgartigimod alfa may be transmitted from the mother to the developing fetus.

As VYVGART HYTRULO is expected to reduce maternal IgG antibody levels, reduction in passive protection to the newborn is anticipated. Risk and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to VYVGART HYTRULO in utero *[see Warnings and Precautions (5.1)].*

Data

Animal Data

VYVGART HYTRULO for subcutaneous injection contains efgartigimod alfa and hyaluronidase *[see Description (11)]*.

Efgartigimod alfa:

- Intravenous administration of efgartigimod alfa (0, 30, or 100 mg/kg/day) to pregnant rats and rabbits throughout organogenesis resulted in no adverse effects on embryofetal development in either species. Maternal efgartigimod alfa exposures at the highest no-effect doses were approximately 8 and 62 times, respectively, that in humans at the recommended human dose (RHD) of 1008 mg.
- Intravenous administration of efgartigimod alfa (0, 30, or 100 mg/kg/day) to rats throughout gestation and lactation resulted in no adverse effects on pre- or postnatal development. Maternal exposures at the highest no-effect dose were approximately 13 times that in humans at the RHD.

Hyaluronidase:
- In a study in which hyaluronidase (human recombinant) was administered by subcutaneous injection to pregnant mice throughout organogenesis, increased embryofetal mortality and decreased fetal body weights were observed at the highest doses tested. The no-effect dose for adverse effects on embryofetal development in the mouse was approximately 1800 times the dose of hyaluronidase at the recommended human dose (RHD) of VYVGART HYTRULO (1,008 mg efgartigimod alfa and 11,200 U hyaluronidase), on a U/kg basis.
- There were no adverse effects on pre- and postnatal development following subcutaneous administration of hyaluronidase (human recombinant) to mice throughout gestation and lactation at doses up to 5,000 times the dose of hyaluronidase at the RHD of VYVGART HYTRULO, on a U/kg basis.

8.2 Lactation

Risk Summary

There is no information regarding the presence of efgartigimod alfa or hyaluronidase, from administration of VYVGART HYTRULO, in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYVGART HYTRULO and any potential adverse effects on the breastfed infant from VYVGART HYTRULO or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of VYVGART HYTRULO did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger adult patients.

8.6 Renal Impairment

No dose adjustment of VYVGART HYTRULO is needed for patients with mild renal impairment. There are insufficient data to evaluate the impact of moderate renal impairment (eGFR 30-59

mL/min/1.73 m²) and severe renal impairment (eGFR <30 mL/min/1.73 m²) on pharmacokinetic parameters of VYVGART HYTRULO *[see Clinical Pharmacology (12.3)].*

11 DESCRIPTION

VYVGART HYTRULO is a coformulation of efgartigimod alfa and hyaluronidase (human recombinant).

Efgartigimod alfa, a neonatal Fc receptor blocker, is a human immunoglobulin G1 (IgG1) -derived Fc fragment (fragment, crystallized) of the za allotype, produced in Chinese hamster ovary (CHO) cells. The efgartigimod alfa Fc fragment is a homodimer consisting of two identical peptide chains each consisting of 227 amino acids linked together by two interchain disulfide bonds with affinity for FcRn. The molecular weight of efgartigimod alfa is approximately 54 kDa.

Hyaluronidase (human recombinant) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. Hyaluronidase (human recombinant) is a glycosylated single-chain protein produced by Chinese hamster ovary cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (human recombinant) has a molecular weight of approximately 61 kDa.

VYVGART HYTRULO (efgartigimod alfa and hyaluronidase-qvfc) injection is a sterile, preservative free, yellowish, clear to opalescent solution supplied in a single-dose vial for subcutaneous injection.

Each 5.6 mL single-dose vial of VYVGART HYTRULO contains 1,008 mg efgartigimod alfa and 11,200 units hyaluronidase (human recombinant). Each mL of solution contains 180 mg of efgartigimod alfa, 2,000 units of hyaluronidase (human recombinant) and histidine (1.4 mg), L-histidine hydrochloride monohydrate (2.2 mg), methionine (1.5 mg), polysorbate 20 (0.4 mg), sodium chloride (5.8 mg), sucrose (20.5 mg), and water for injection, USP, at a pH of 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

In Study 1 *[see Clinical Studies (14)],* the pharmacological effect of efgartigimod alfa-fcab was assessed by measuring the decrease in serum IgG levels and AChR autoantibody levels. In patients testing positive for AChR antibodies and who were treated with efgartigimod alfa-fcab intravenous, there was a reduction in total IgG levels relative to baseline. Decrease in AChR autoantibody levels followed a similar pattern. A decrease in AChR-Ab was associated with a

clinical response in AChR-Ab positive patients, as measured by the change from baseline in MG-ADL total score.

In Study 2, the pharmacological effect of VYVGART HYTRULO administered subcutaneously (SC) at 1,008 mg / 11,200 Units was compared to efgartigimod alfa-fcab administered intravenously at 10 mg/kg (EFG IV) in gMG patients. The maximum mean reduction in AChR-Ab level was observed at week 4, with a mean reduction of 62.2% and 59.7% in the VYVGART HYTRULO SC and efgartigimod alfa-fcab IV arm, respectively. The decrease in total IgG levels followed a similar pattern. The 90% confidence intervals for the geometric mean ratios of AChR-Ab reduction at day 29 and $AUEC_{0\text{-}4w}$ (area under the effect-time curve from time 0 to 4 weeks post dose) were within the range of 80% to 125%, indicating no clinically significant difference between the two formulations.

12.3 Pharmacokinetics

Efgartigimod alfa exposures were approximately dose-proportional up to the highest subcutaneously tested dose of VYVGART HYTRULO (1750 mg, 1.75 times the recommended dosage).

Distribution

The volume of distribution is 15 to 20L.

Metabolism and Elimination

Efgartigimod alfa and hyaluronidase are expected to be degraded by proteolytic enzymes into small peptides and amino acids.

The terminal half-life is 80 to 120 hours (3 to 5 days).

After a single intravenous dose of 10 mg/kg efgartigimod alfa-fcab in healthy subjects, less than 0.1% of the administered dose was recovered in urine.

Specific Populations

Age, Sex and Race

A population pharmacokinetics analysis assessing the effects of age, body weight, sex, and race did not suggest any clinically significant impact of these covariates on efgartigimod alfa exposures.

Body Weight

A population pharmacokinetics analysis suggests that the influence of body weight on efgartigimod alfa exposure after administration of VYVGART HYTRULO SC 1008 mg was limited and not clinically relevant.

Patients with Renal Impairment

No dedicated pharmacokinetic study has been performed in patients with renal impairment.

A population PK analysis of data from the VYVGART HYTRULO clinical studies indicated that patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m²) had 11% increase in exposure relative to the exposure in patients with normal renal function *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

No dedicated pharmacokinetic study has been performed in patients with hepatic impairment. Hepatic impairment is not expected to affect the pharmacokinetics of efgartigimod alfa.

Drug Interaction Studies

Clinical drug interactions studies have not been performed with efgartigimod alfa.

P450 Enzymes

Efgartigimod alfa is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Drug Interactions with Other Drugs or Biological Products

Efgartigimod alfa may decrease concentrations of compounds that bind to the human FcRn *[see Drug Interactions (7.1)]*.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of VYVGART HYTRULO or of other efgartigimod products.

In up to 10 weeks treatment in Study 2, the incidence of anti-efgartigimod alfa antibodies was 35% (19/55) following treatment with VYVGART HYTRULO and 20% (11/55) in patients receiving intravenous efgartigimod alfa-fcab. For both IV and SC arms, neutralizing anti-efgartigimod alfa antibodies were detected in 4% (2/55) of patients. Some neutralizing antibodies may not be detected by the assay. The available data are too limited to make definitive conclusions regarding immunogenicity and the effect on pharmacokinetics, safety, or efficacy of VYVGART HYTRULO.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VYVGART HYTRULO for subcutaneous injection contains efgartigimod alfa and hyaluronidase *[see Description (11)]*.

Carcinogenesis and Mutagenesis

No studies have been conducted to assess the carcinogenic potential of efgartigimod alfa.

No studies have been conducted to assess the genotoxic potential of efgartigimod alfa.

No carcinogenicity or genotoxicity studies were conducted for human recombinant hyaluronidase.

Impairment of Fertility

Intravenous administration of efgartigimod alfa (0, 30, or 100 mg/kg/day) to male and female rats prior to and during mating and continuing in females through gestation day 7 resulted in no adverse effects on fertility. Efgartigimod alfa exposures at the highest no-effect dose were approximately 12 times that in humans at the recommended human dose of 1008 mg.
There were no effects on reproductive tissues in monkeys following subcutaneous administration of hyaluronidase (human recombinant) doses up to approximately 1,200 times the dose of hyaluronidase at the recommended human dose (RHD) of VYVGART HYTRULO (1,008 mg efgartigimod alfa and 11,200 U hyaluronidase) on a U/kg basis for 39 weeks. No systemic exposure to hyaluronidase was observed at doses up to approximately 120 times the dose of hyaluronidase at the RHD of VYVGART HYTRULO, on a U/kg basis.

14 CLINICAL STUDIES

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 *[see Clinical Pharmacology (12.2)]*.

Study 1 (Efgartigimod Alfa-fcab Intravenous)

The efficacy of efgartigimod alfa-fcab intravenous (EFG IV) 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 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 7 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 2.

Table 2: 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)

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

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)

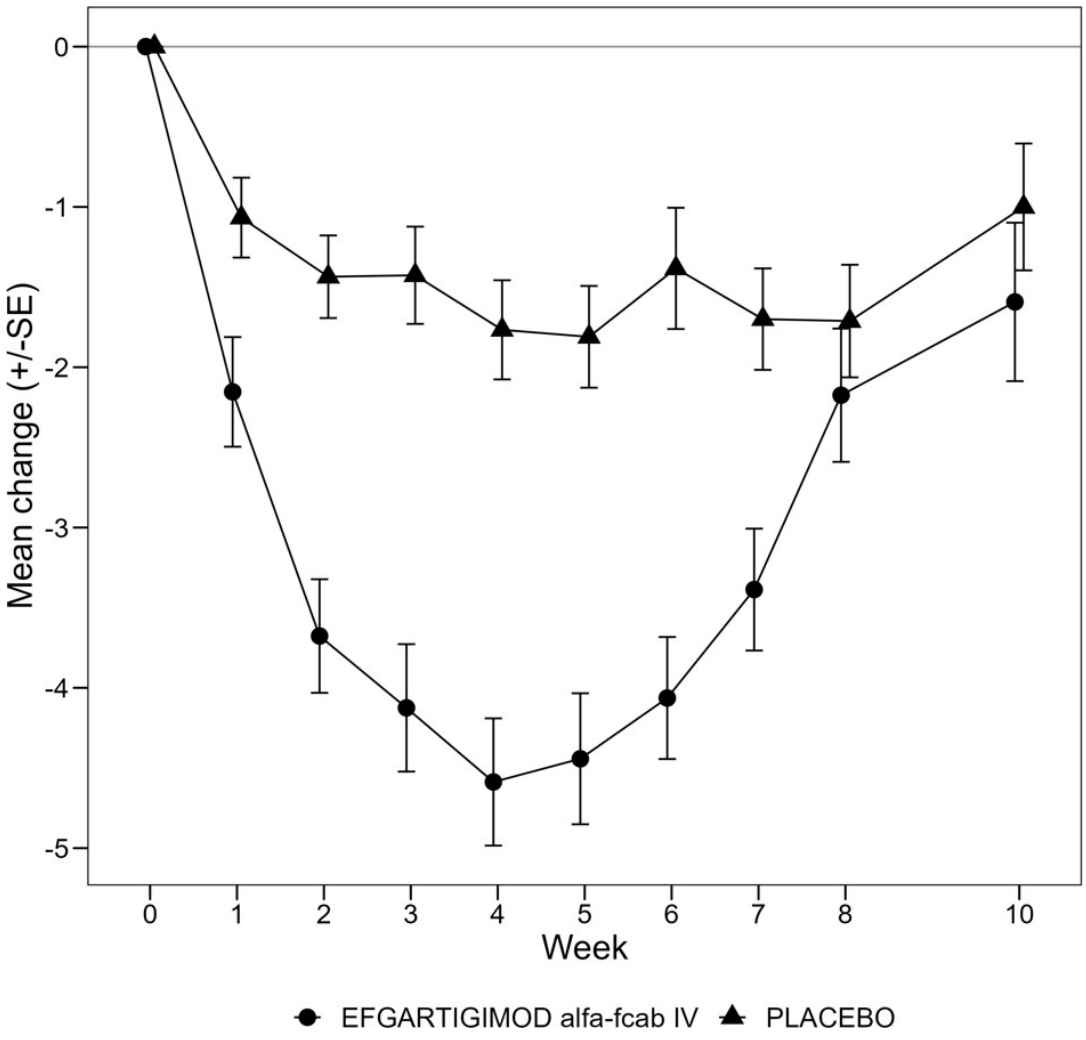
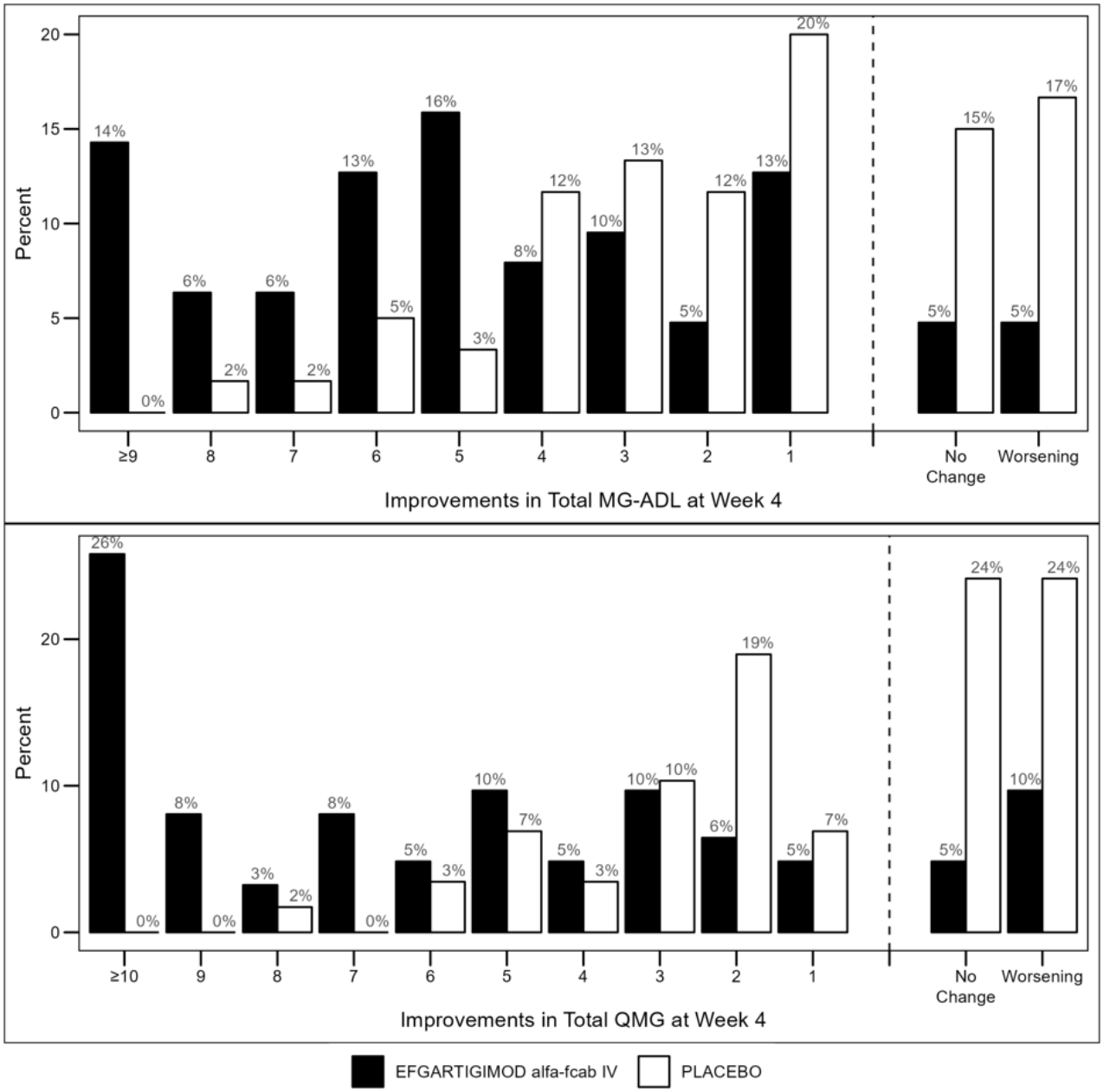


Figure 2 shows the distribution of response on the MG-ADL and QMG during cycle 1, four weeks after the first infusion with EFG IV.

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 Patients



16 HOW SUPPLIED/STORAGE AND HANDLING

VYVGART HYTRULO (efgartigimod alfa and hyaluronidase-qvfc) injection is a preservative free, sterile, yellowish, clear to opalescent solution supplied as one single-dose vial per carton containing 1,008 mg efgartigimod alfa and 11,200 units hyaluronidase per 5.6 mL (180 mg/2,000 units per mL): (NDC 73475-3102-3).

Store VYVGART HYTRULO vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. Do not shake.

If needed, unopened vials may be stored in the original carton for up to 3 days at room temperature at 20°C to 25°C (68°F to 77°F) for a single period before administration or returned to refrigeration. Do not store the vial at room temperature more than one time. Record the date removed from and the date returned to the refrigerator on the carton.

17 PATIENT COUNSELING INFORMATION

Infections

Instruct patients to communicate any history of infections to the healthcare provider and to contact their healthcare provider if they develop any symptoms of an infection. Advise patients to complete age-appropriate vaccines according to immunization guidelines prior to initiation of a new treatment cycle with VYVGART HYTRULO. Administration of live or live-attenuated vaccines is not recommended during treatment with VYVGART HYTRULO *[see Warnings and Precautions (5.1)].*

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including angioedema and anaphylaxis, have occurred in patients who were treated with efgartigimod alfa products. Inform patients about the signs and symptoms of these reactions, and advise patients to contact their healthcare provider immediately if these occur *[see Warnings and Precautions (5.2)].*

Infusion-Related Reactions

Advise patients of the potential risk of infusion-related reactions, which can include hypertension, chills, shivering, and chest, abdominal, and back pain *[see Warnings and Precautions (5.3)].*

Manufactured by:

argenx BV
Industriepark 7
9052 Zwijnaarde, Belgium
U.S. License No. 2217

Halozyme Therapeutics, Inc.
12390 El Camino Real
San Diego, CA 92130
U.S. License No. 2187

Distributed by:

argenx US, Inc.
33 Arch Street

Boston, MA 02110