EU RISK MANAGEMENT PLAN

VYVGART (EFGARTIGIMOD [ARGX-113])

Data lock point for this RMP	02 Mar 2022	Version number	2.6
Date of final sign-off	05 Jun 2024		

Details of This RMP Submission

Version number	2.6
Rationale for submitting an updated RMP	RMP for inclusion in a variation (Type II) submission
Summary of significant changes in this RMP	Addition of a new formulation (efgartigimod pre-filled syringe)

Other RMP Versions Under Evaluation:

RMP version number	Submitted on	Procedure number
2.5	05 Jun 2024	EMEA/H/C/005849/II/tba

Details of the Currently Approved RMP

Version number of last agreed RMP	2.4
Approved within procedure	EMEA/H/C/005849/II/0014
Date of approval (Competent authority opinion date)	11 April 2024

SIGNATURE PAGE

The efgartigimod EU Risk Management Plan version 2.6 has been approved by

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European Union Qualified Person Responsible for Pharmacovigilance (EU-QPPV) Date

argenx BV

EU-QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization applicant's EU-QPPV. The electronic signature is available on file.

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PART I PRODUCT(S) OVERVIEW

Table Part I-1: Product Overview

Active substance (INN or common name)	Efgartigimod alfa (efgartigimod)
Pharmacotherapeutic group (ATC Code)	Immunosuppressants, selective immunosuppressant (L04AA58)
Marketing authorization applicant	argenx BV
Medicinal products to which this RMP refers	1
Invented name(s) in the European economic area (EEA)	Vyvgart
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: biotherapeutic Human recombinant immunoglobulin G1 (IgG1)-derived Fc fragment produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.
	Summary of mode of action: Efgartigimod is a human IgG1 antibody fragment engineered for increased affinity to Fc Receptor (FcRn). Efgartigimod binds to FcRn, resulting in the reduction of circulating IgG including autoantibodies levels. Efgartigimod does not reduce the levels of other immunoglobulins (IgA, IgD, IgE, or IgM), or those of albumin.
	Important information about its composition: <u>Intravenous (IV) formulation:</u> Efgartigimod is formulated as a concentrate for solution for intravenous infusion and contains sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, sodium chloride, arginine hydrochloride, polysorbate 80, and water for injections, at a pH of approximately 6.7. <u>Subcutaneous (SC) formulation (efgartigimod PH20 SC):</u> Efgartigimod is formulated as a solution for subcutaneous injection and contains recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sodium

	chloride, sucrose, and water for injections, at a pH of approximately 6.0. SC formulation in a pre-filled syringe: Efgartigimod is formulated as a solution for subcutaneous injection, in a pre-filled syringe, and contains rHuPH20, L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sodium chloride, sucrose, and water for injections, at a pH of approximately 6.0.
Hyperlink to the product information	Module 1.3.1, SmPC, Labelling and Package Leaflet
Indication(s) in the EEA	Vyvgart is indicated as an add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.
Dosage in the EEA	IV formulation: The recommended dose is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. In patients weighing 120 kg or more, the recommended dose is 1200 mg (3 vials) per infusion. SC formulation: The recommended dose is 1000 mg administered subcutaneously in cycles of once-weekly injections for 4 weeks. IV and SC formulation: Subsequent treatment cycles are administered according to clinical evaluation. The frequency of treatment cycles may vary by patient. If a scheduled dosing is not possible, treatment may be administered up to 3 days before or after the scheduled time point. Thereafter, the original dosing schedule should be resumed until the treatment cycle is completed. If a dose needs to be delayed for more than 3 days, the dose should not be administered to ensure 2 consecutive doses are given with an interval of at least 3 days.
Pharmaceutical form and strengths	IV formulation: Sterile, colorless to slightly yellow, clear to slightly opalescent concentrate for solution for infusion. Each 20 mL single-dose vial delivers 400 mg efgartigimod at a concentration of 20 mg/mL. SC formulation: Yellowish, clear to opalescent solution for injection. Each 5.6 mL single-dose vial contains 1000 mg of efgartigimod (180 mg/mL).

	<u>SC formulation in a pre-filled syringe:</u> Pre-filled syringe content has a yellowish, clear to opalescent color. Each pre-filled syringe contains 1000 mg of efgartigimod in 5.0 mL (200 mg/mL).
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Generalized Myasthenia Gravis

Incidence, prevalence, and demographics of the target population

A meta-analysis of 63 studies, conducted in 2021, estimated a worldwide prevalence of myasthenia gravis (MG) of 124 per million persons (range: 106-145).[1] Per continent, the highest prevalence was reported in America with 190 per million persons (range: 150-238) and Africa with 152 per million persons (range: 69-302). A lower prevalence was reported in Asia (109 per million persons; range: 64-179) and Europe (100 per million persons; range: 82-122).

Myasthenia gravis occurs in both genders, at all ages, and in all races.[2,3] The most common age of MG onset is between 20 and 40 years. In this age group, about 60% of patients are women. In older age groups, men are affected more often and the disease is often misdiagnosed. As a result, there is a bimodal distribution with a female predominance in the second to third decade of life and male predominance in the sixth to eighth decade.[4,5,6] Childhood MG (onset <15 years) seems to be higher in the Asian population.[6,7]

Risk factors for the disease

Risk factors for MG include female gender, autoimmune diseases, and thymus diseases.

Female gender

The overall female-to-male ratio has been considered to be 3:2, with a female predominance in younger adults (ie, patients aged 20-30 years) and a slight male predominance in older adults (ie, patients older than 50 years).[2,8]

A gender bias is observed for single nucleotide polymorphisms in the human leukocyte antigen (HLA)-locus, suggesting female-specific alleles have an increased risk for MG. Moreover, sex hormones play a pivotal role in the gender bias in autoimmunity in general and in MG in particular.[9]

Autoimmune diseases

People with a personal or family history of autoimmune diseases are at increased risk of developing MG. The development of autoimmunity generally requires a genetic predisposition in addition to being exposed to a triggering environmental factor. Monozygotic MG twin concordance is estimated to be about 35%, supporting the central role of environmental factors in MG etiology.[10] The major histocompatibility complex region represents the most important genetic risk factor for most autoimmune diseases.[11,12] Genetic studies have mainly pointed at specific HLA alleles implicated in MG susceptibility; however, recently both TNFAIP3-interacting protein 1 and tyrosine phosphatase nonreceptor 22 were indicated to be associated with MG in a genome-wide association study. Several genes converging on the NF-κB signaling

pathway also seem to be associated with MG. Epigenetic modulation of gene expression by specific microRNAs has been associated with a variety of autoimmune diseases, including MG.[9]

Thymus diseases

The thymus plays a central role in the pathophysiology of MG due to the presence of key elements of the myasthenic autoimmune process, such as antigen presenting cells, T and B cells. Approximately 80% of patients with MG have thymic abnormalities; up to 70% of patients have thymic hyperplasia, 10% to 15% of thymomas, and in 15% to 20% thymus is normal or regressive, ie, atrophic and replaced with fat tissue.[13]

Thymomas in MG are usually of the cortical subtype (World Health Organization type B) and 50% of patients with thymoma develop MG.[14]

Main treatment options

Therapies currently used for the treatment of generalized myasthenia gravis (gMG) are shown in Table Part II: Module SI-1. Therapeutic options for gMG include mainly acetylcholinesterase (AChE) inhibitors that increase availability of acetylcholine in the neuromuscular junction (NMJ) and immunosuppressants.[15,16,17] Plasmapheresis/plasma exchange (PLEX) and intravenous immunoglobulins (IVIgs) are typically used for treatment of severe exacerbations of gMG.[15,18,19] Thymectomy is also frequently performed in patients with MG. However, considerable variation exists in the management of gMG and treatment is not standardized.[20,21] There is a lack of consensus in choice of immunosuppressive agent, and widespread use of particular agents, even though available data from a randomized controlled study does not support their use in MG.[21,22,23] The use of corticosteroids and several nonsteroidal immunosuppressive therapies for the treatment of gMG are based on observational rather than high-quality, randomized controlled clinical studies.[23,24,25,26,27]

Even with current treatments, many patients with gMG are substantially burdened by the disease and have symptoms and morbidities that negatively impact their quality of life.[28,29] Approximately 90% of patients with gMG are unable to maintain normal muscle strength without medication[15,20] and 10% to 15% of patients are refractory to available treatments.[30,31] Furthermore, many therapeutic agents are associated with an increased risk of serious side effects, are inconvenient for the patient, or are unavailable.[28,32,33,34] Long-term use of corticosteroids (eg, prednisone) is associated with serious side effects such as hypertension, diabetes, osteoporosis, and gastrointestinal effects.[23,35,36] Long-term use of nonspecific immunosuppressants like azathioprine, mycophenolate mofetil, and methotrexate may be associated with severe side effects that vary by agent but can include liver and bone marrow toxicities, malignancies, and increased risk of infection.[37,38,39] PLEX is a lengthy and burdensome procedure[40] and is usually conducted in a hospital or specialized clinical setting. IVIgs shortages are a global concern that could impact patient care.[41]

Eculizumab is approved as a treatment for adult patients with gMG who are AChR-Ab seropositive; in the European Union (EU), it is limited to the treatment of patients who are also refractory to current gMG treatment options. Ravulizumab is approved as an add-on to standard therapy for the treatment of adult patients with gMG who are AChR Ab-seropositive. Both of these complement inhibitors are contraindicated in patients with unresolved *Neisseria*

meningitidis infection or patients who are not vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics for 2 weeks after vaccination.[20,42,43]

Table Part II: Module SI-1: Other Therapies Used for the Treatment of Myasthenia Gravis

Therapy	Mechanism of Action	Side Effects/Limitations	Approval Status
AChE inhibitors More commonly used: pyridostigmine and neostigmine	Acetylcholine breakdown inhibition, increasing its availability in the NMJ	Short-acting and often needs to be taken several times daily	US: Approved Japan: Approved EU: Approved
Corticosteroids More commonly used: oral prednisone	Nonspecific immunosuppression	Widespread short- and long-term adverse effects	US: Not approved Japan: Approved EU: Not approved
Nonsteroidal immunosuppressive drugs (NSIDs) More commonly used: Azathioprine, cyclosporine, and mycophenolate Also used: tacrolimus, methotrexate, and cyclophosphamide	Multiple mechanisms of action, including suppression of B and T cells[18]	Various side effects, including liver and bone marrow toxicities, malignancies, and increased risk of infection for the more commonly used NSIDs[2,18]	US: Not approved Japan: Approved EU: Not approved in all member states
Intravenous immunoglobulins	Multiple mechanisms postulated including effects on autoantibodies, B and T cells	• IVIg use is limited in patients who are at risk of renal dysfunction and those who have a history of hypertension or risk factors for thrombotic events • Burdensome administration • Supply chain shortages are common • Nausea, headache, fever, hypotension or hypertension, local skin reactions, IgA deficiency, allergic reactions	US: Not approved Japan: Approved EU: Not approved

Therapy	Mechanism of Action	Side Effects/Limitations	Approval Status
Plasma exchange	Removal of autoantibodies and complement components	• Invasive procedure • Hospitalization required • Its use is limited by requirements for specialist administration and venous access issues	US: Not approved Japan: Approved EU: Not approved
Rituximab[44]	B cell depletion	• Nausea, infections, infusion-related problems • Progressive multifocal leukoencephalopathy	US: Not approved Japan: Not approved EU: Not approved
Eculizumab[45]	Complement inhibitor, prevents C5 cleavage and inhibits IgG autoantibody-initiated complement activation	• Limited to treatment of refractory MG • Increased risk of *Neisseria meningitidis* infection and the need for vaccination prior to commencing treatment	US: Approved Japan: Approved EU: Approved
Ravulizumab[43]	Complement inhibitor, reduction of terminal complement complex C5b-9 deposition at the NMJ	• Increased risk of *Neisseria meningitidis* infection and the need for vaccination prior to commencing treatment	US: Approved Japan: Not approved EU: Approved

AChE=acetylcholinesterase; AChR-Ab=anti-acetylcholine receptor antibody; C5=complement component 5; EU=European Union; gMG=generalized myasthenia gravis; IgA=immunoglobulin A; IgG=immunoglobulin G; IVIg=intravenous immunoglobulin; MG=myasthenia gravis; NMJ=neuromuscular junction; NSIDs=nonsteroidal immunosuppressive drugs; US=United States

Natural history including mortality and morbidity

Although most patients initially present with ocular symptoms, more than 80% of patients will progress to gMG within 2 years.[15] In an older study[46] in which 1487 patients with MG were followed between 1940 and 1985 for a mean of 18 years, it was shown that in 14% of the patients, the disease remained clinically localized to the extraocular muscles and in the remaining 86% the disease became generalized, which causes generalized muscle weakness.[15] A more recent population-based study conducted in the US found that 51% of patients with MG presented with isolated ocular involvement, with 55% of these patients converting to gMG within 5 years.[47] Generalized muscle weakness affects multiple muscle groups leading to difficulties in mobility, speech, swallowing, and vision, as well as impaired respiratory function and extreme fatigue.[48] This can proceed to potentially life-threatening weakness of respiratory muscles requiring intubation or noninvasive ventilation, termed myasthenic crisis, estimated to affect up to 20% of patients with MG at least once in their lives.[49]

Mortality rates (MRs) were high with older MG therapies. From 1940 to 1957, management of the disease relied on anticholinesterase compounds, endotracheal intubation or tracheostomy and

negative pressure assisted ventilation for respiratory failure, and thymectomy (26% of patients) and thymomectomy (8% of patients). During this time, 31% of patients with gMG died of the disease, 32% improved, 23% remained unchanged, 10% went into remission, and only 5% were worse during the last year than during the worst of the first 3 years. From 1958 to 1965, management of respiratory failure was improved by positive pressure and volume controlled ventilation and improved intensive care. Mortality fell to 14%, and a higher proportion remained unchanged. From 1966 to 1985, when more than half the patients received adrenal cortical steroids, mortality fell to 7% and the proportion that improved rose to 47%.[46]

With current treatment, which combines cholinesterase inhibitors, immunosuppressive drugs, plasmapheresis, immunotherapy, and supportive care in an intensive care unit setting (when appropriate), mortality has decreased further. A study in US hospitals showed that the overall in-hospital MR was 2.2%, and 4.47% for patients in MG crisis. Older age and respiratory failure were the predictors of death.[6,50]

MG has been reported to increase mortality. A nationwide population-based study in Denmark, published in 2015, assessed mortality in 702 AChR-Ab seropositive patients with MG diagnosed between 1985 and 2005, compared to 7020 matched controls. Overall mortality was higher in patients with MG with a mortality rate ratio (MRR) of 1.41 (95% CI: 1.24-1.60) with highest mortality in the first 5 years after diagnosis (MRR: 1.67 [1.41-1.98]).[51] In another nationwide register-based study of 4559 Swedish patients with MG between 2006 and 2016, the MR did not differ from that of the Swedish general population; however, the authors found that MG was the most commonly recorded ultimate cause of death, affecting as many as 10% of both female and male patients with MG.[52]

Morbidity results from intermittent impairment of muscle strength, which leads to difficulties in mobility, speech, swallowing, and vision, and impaired respiratory function and extreme fatigue. Up to 20% of patients have a potentially life-threatening myasthenic crisis, with respiratory failure requiring mechanical ventilation.[2,49,53] In addition, the medications used to control the disease may produce adverse effects.

Approximately 10% of patients fail to respond adequately to current therapies and are considered treatment refractory, or treatment intolerant, and up to 80% fail to achieve complete stable remission despite existing therapies.[54] Although patients with autoantibodies to MuSK (anti-MuSK positive) are more likely to become treatment refractory than those with autoantibodies to the acetylcholine receptor (anti-AChR positive); each of these serotypes (anti-MuSK positive, anti-AChR positive, anti–low-density lipoprotein receptor-related protein 4 [LRP4] positive) is substantially represented in the refractory MG population. Other risk factors for becoming treatment refractory include history of thymoma or thymectomy and female gender.[34]

Patients with refractory MG have more exacerbations and MG-related hospitalizations than patients with nonrefractory disease and are also more likely to have certain comorbidities such as renal disease and hypertension.[55]

Important comorbidities:

Comorbidities are frequent in patients with MG (73%) and they might worsen the prognosis of MG. The most frequently associated disorders are dyslipidaemia (60%), diabetes mellitus (20%), dysthyroidism (19%), hypertension (16%), and other autoimmune diseases (7%). Among the autoimmune diseases, thyroiditis is the most common followed by rheumatoid arthritis and systemic lupus erythematosus. The autoimmune comorbidities vary in different subgroups of MG. Patients with MG with a comorbid disease are at higher risk for myasthenic crisis and more often require emergency room visits.[56,57]

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

A panel of in vivo and in vitro studies, including single- and repeated-dose toxicity and reproductive toxicity studies have been performed. These studies are considered to have adequately assessed the nonclinical safety profile of efgartigimod.

Consistently reported findings in all repeated-dose toxicity studies were related to pharmacology and included reversible decreases in endogenous IgG linked to decreases in globulin with unchanged albumin, IgM, and IgA levels.

There was no nonclinical safety finding identified that was considered relevant for humans; therefore, no risk was added to the identified and potential risks in Part II: Module SVII and Part II: Module SVIII.

Brief explanations on nonclinical findings are provided in the table below.

Table Part II: Module SII-1: Nonclinical Safety Findings

Key Safety Findings	Relevance to Human Use
Toxicity	
Single- and repeated-dose toxicity	
Single- and repeated-dose IV toxicity studies were conducted in rat (up to 4 weeks) and cynomolgus monkey (up to 6 months) at doses up to 100 mg/kg. Kupffer cell hyperplasia/hypertrophy were reported in the rat as an immune reaction to efgartigimod that constitutes a foreign protein to the nonclinical species. In the 4-week study in cynomolgus monkey, transient signs of activated lymphocytes and monocytes and mild increases in alanine transaminase (ALT)/liver histopathology were noted as a reaction to endotoxins present in this particular batch of test article. Endotoxin content in drug substance batches intended for human use is adequately controlled and this result is not relevant for the situation in humans. Efgartigimod was well tolerated locally and systemically in the 6-month toxicity study in cynomolgus monkey and no safety findings were reported. A 12-week repeated-dose toxicity study with efgartigimod SC without rHuPH20 and efgartigimod SC comixed with rHuPH20 was conducted in cynomolgus monkey at doses up to 100 mg/kg. No systemic findings were reported. Local signs of inflammation at the injection sites were transient and mild in grading.	Signs of a transient activation of the immune system in nonclinical species were not consistently observed and are not translatable to humans. There were no relevant safety findings reported that indicated a risk to humans.

Key Safety Findings	Relevance to Human Use
No local findings were reported in a single-dose local tolerance study in rabbit with efgartigimod SC comixed with rHuPH20.	
Influence on active immunity	
A GLP-compliant nonclinical T-cell dependent antibody response (TDAR) safety study in cynomolgus monkey was conducted. Efgartigimod treatment did not impair T-cell and B-cell activation after administration of a well-defined antigen. The antigen-specific IgG response observed under efgartigimod treatment was slightly lower compared to controls. After cessation of treatment, no difference in the IgG response to a booster dose was observed between active and control groups. The levels of antigen-specific IgM were not influenced.	No safety findings were reported. There was no influence on generation of a T-cell dependent immune response.
Reproductive toxicity	
Toxicity studies investigating male and female fertility, maternal toxicity, embryo-fetal development, and postnatal development have been conducted in 2 species. Efgartigimod up to a high dose of 100 mg/kg/day given daily was shown to have no teratogenic effects in rat and rabbit and did not adversely affect male and female fertility, or any other reproductive and developmental performance in rat.	There were no safety findings reported in reproductive toxicity studies in rat and rabbit.
Genotoxicity	
Genotoxicity studies were not performed and are not mandated for biotherapeutics.	Not applicable
Carcinogenicity	
Carcinogenicity studies were not performed and are not mandated for biotherapeutics.	Not applicable
Safety pharmacology	
Cardiovascular system, including potential for QT interval prolongation	
Safety pharmacology cardiovascular system endpoints were included in toxicity studies in cynomolgus monkey. No influence was reported on cardiovascular vital signs.	No safety findings were reported.
Nervous system	
Safety pharmacology endpoints on respiratory and central nervous system tolerability were included in a pharmacokinetic and safety pharmacology study in cynomolgus monkey. No influence was reported on vital signs of the respiratory and central nervous system.	No safety findings were reported.

Key Safety Findings	Relevance to Human Use
Nephrotoxicity	
No safety findings were reported in general toxicity studies in rat and cynomolgus monkey.	No safety findings were reported.
Hepatotoxicity	
Transient findings of a mild increase in ALT that were related with reversible liver findings in histopathology were reported in one 4-week toxicity study in cynomolgus monkey. These findings were linked to the presence of endotoxins present in this particular batch of test article and were not confirmed in other studies.	Findings are not translatable to humans as they were linked to impurities in the test article and not to efgartigimod. There were no relevant safety findings reported with regards to hepatotoxicity.

ALT=alanine aminotransferase; GLP=Good Laboratory Practice; IgG=immunoglobulin G; IV=intravenous; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

Table Part II: Module SII-2: Summary of Nonclinical Safety Concerns

Summary of Nonclinical Safety Concerns	
Important identified risks	There were no important risks identified from the nonclinical studies.
Important potential risks	Consistently reported findings in toxicity studies were related to the intended pharmacology and included decreases in endogenous IgG. Decreases in IgG levels could increase the risk of infections.
Missing information	There is no information on potential transfer of efgartigimod from mother to developing fetus; however, no safety findings were reported in reproductive toxicity studies. There is no information on the excretion of efgartigimod into breast milk; however, no safety findings were reported in a reproductive toxicity study in which efgartigimod was administered to rat until lactation day 7.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

Data were grouped into an IV formulation pooling and a SC formulation pooling.

The IV pooling block consists of data from all patients with gMG who received efgartigimod IV 10 mg/kg in the completed studies ARGX-113-1602 and ARGX-113-1704, and data from study ARGX-113-1705 up to the 31 Jan 2022 data cutoff date. Data observed while patients were receiving placebo in study ARGX-113-1704 are excluded from the pooling.

The SC pooling block consists of data from all patients with gMG who received efgartigimod SC 1000 mg (efgartigimod PH20 SC) in the completed study ARGX-113-2001 and data from the ongoing study ARGX-113-2002 up to the 02 Mar 2022 data cutoff date. Data from patients who received efgartigimod IV in study ARGX-113-2001 are excluded from the pooling.

In the study protocols, a cycle is the time from the first day investigational medicinal product (IMP) is administered in cycle n (Cn) until the first day IMP is administered in the next cycle, cycle n+1 (Cn+1). A cycle comprised a treatment cycle (TC) and an intertreatment cycle (ITC) of indeterminant length, depending on the patient. The TC included a 3-week treatment period in which patients received IMP every 7 days (weekly) for 4 administrations. At the end of each TC, patients entered an ITC period when they received only their concomitant gMG treatment. The length of the ITC period varied by patient, and for each patient by cycle depending on clinical response.

The efgartigimod IV-treated patients with gMG pooling includes 3 studies:

- ARGX-113-1602: a phase 2, randomized, double-blinded, placebo-controlled study of efgartigimod IV
- ARGX-113-1704: a phase 3, randomized, double-blinded, placebo-controlled study of efgartigimod IV
- ARGX-113-1705: an open-label follow-on to study ARGX-113-1704

Treatment consisted of efgartigimod IV 10 mg/kg intravenously infused over 2 hours (ARGX-113-1602) or 1 hour (ARGX-113-1704 and ARGX-113-1705) weekly for 4 infusions (each TC).

The efgartigimod SC-treated patients with gMG pooling includes 2 studies:

- ARGX-113-2001: a phase 3, randomized, open-label, parallel-group study to compare efgartigimod SC with efgartigimod IV
- ARGX-113-2002: an open-label extension to ARGX-113-2001. Participants from ARGX-113-1705 rolled over to ARGX-113-2002 also

Treatment consisted of efgartigimod SC 1000 mg weekly for 4 injections.

Exposure to efgartigimod in this population is summarized in Table Part II: Module SIII-1-Table Part II: Module SIII-8 for all patients by duration, age group and gender, by ethnic origin and race, and baseline AChR-Ab status, respectively.

Table Part II: Module SIII-1: Duration of Exposure - IV Pooling

Cumulative number of patients who received efgartigimod		164
Cumulative number of infusions		4862
Total duration under treatment and follow-up (days, median [range])		664.5 (42-1080)
Cycle	**Number of patients per treatment cycle**	**Treatment cycle duration (days, median [range])[a]**
Cycle 1	164	72.0 (42-825)
Cycle 2	144	71.0 (7-565)
Cycle 3	128	61.5 (15-491)
Cycle 4	116	62.0 (4-603)
Cycle 5	105	57.0 (35-192)
Cycle 6	98	57.0 (32-203)
Cycle 7	84	57.0 (25-194)
Cycle 8	79	57.0 (25-148)
Cycle 9	70	57.0 (29-164)
Cycle 10	64	57.0 (36-148)
Cycle 11	56	57.0 (42-107)
Cycle 12	44	52.0 (7-112)
Cycle 13	31	56.0 (22-110)

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Table 14.1.1.2.3, 14.1.1.2.5, 14.1.1.2.7, 14.1.3.2.1, and 14.1.3.2.2
IV=intravenous
[a] The cycle duration is the number of days from the first infusion of a cycle to the first infusion of the next cycle or the data cutoff date, whichever comes first; therefore, the duration of an individual patient's last cycle may appear shorter.

Table Part II: Module SIII-2: Duration of Exposure - SC Pooling

Cumulative number of patients who received efgartigimod		168
Cumulative number of injections		2123
Total duration under treatment and follow-up (days, median [range])		187 (7-311)
Cycle	**Number of patients per treatment cycle**	**Treatment cycle duration (days, median [range])[a]**
Cycle 1	168	70.5 (7-246)
Cycle 2	149	52.0 (2-106)
Cycle 3	117	50.0 (7-129)
Cycle 4	80	50.0 (3-86)
Cycle 5	38	28.0 (1-52)
Cycle 6	8	11.5 (3-45)

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.1.1.1.3 and 14.1.3.1.1
SC=subcutaneous
[a] The individual cycle duration is the number of days from the first injection of a cycle to the first injection of the next cycle or the data cutoff date, whichever comes first; therefore, the duration of an individual participant's last cycle may appear shorter when considering all cycles.

Table Part II: Module SIII-3: Age Group and Gender - IV Pooling

Age Group	**Number of Patients**		**Number of Infusions**
	M	**F**	
≥18 to <65 years	31	107	4166
≥65 years	16	10	696
Number of Infusions	**M**	**F**	**Total**
	1560	3302	4862

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.1.1.2.6, 14.1.2.2.1.2 and 14.1.3.2.2
F=Female; IV=intravenous; M=Male

Table Part II: Module SIII-4: Age Group and Gender - SC Pooling

Age Group	Number of Patients		Number of Injections
	M	F	
≥18 to <65 years	40	92	1696
≥65 years	19	17	427
Number of Injections	**M**	**F**	**Total**
	760	1363	2123

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.1.2.1.1.2 and 14.1.3.1.2
F=Female; M=Male; SC=subcutaneous

Table Part II: Module SIII-5: Exposure by Ethnic Origin and Race - IV Pooling

Ethnic Origin	Number of Patients	Number of Infusions
Japanese	11	332
Hispanic or Latino	9	370
Not Hispanic or Latino	143	4156
Not reported	1	4
Race	**Number of Patients**	**Number of Infusions**
Caucasian/White	143	4258
Asian	13	352
Other	8	252

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.1.1.2.6 and 14.1.3.2.2
IV=intravenous

Table Part II: Module SIII-6: Exposure by Ethnic Origin and Race - SC Pooling

Ethnic Origin	Number of Patients	Number of Injections
Japanese	14	180
Hispanic or Latino	5	47
Not Hispanic or Latino	149	1896
Not reported	0	0
Race	**Number of Patients**	**Number of Injections**
Caucasian/White	151	1903
Asian	14	180
Other	3	40

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.1.2.1.1.1 and 14.1.3.1.2
SC=subcutaneous

Table Part II: Module SIII-7: Exposure by Baseline AChR-Ab Status - IV Pooling

Baseline AChR-Ab Status	Number of Patients	Number of Infusions
AChR-Ab seropositive	127	3705
AChR-Ab seronegative	37	1157

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.1.1.2.6 and 14.1.3.2.2
AChR-Ab=anti-acetylcholine receptor antibody; IV=intravenous

Table Part II: Module SIII-8: Exposure by Baseline AChR-Ab Status - SC Pooling

Baseline AChR-Ab Status	Number of Patients	Number of Injections
AChR-Ab seropositive	137	1681
AChR-Ab seronegative	31	442

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.1.2.1.1.1 and 14.1.3.1.2
AChR-Ab=anti-acetylcholine receptor antibody; SC=subcutaneous

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Program

Pregnant and lactating women	
Reason for exclusion	Efgartigimod was not tested in pregnant and lactating women. No clinical data are available in this population.
Is it considered to be included as missing information?	Yes
Rationale (if not included as missing information)	Not applicable
MGFA Class I and V patients	
Reason for exclusion	Class I (ie, ocular MG) is not part of the intended label indication of generalized MG. Class V (severe and life-threatening MG) requires urgent care management; efgartigimod has not been studied in this disease state.
Is it considered to be included as missing information	No
Rationale (if not included as missing information)	These patients are not part of the intended population.
HBV (only active infection), HCV, or HIV (only if associated with clinical signs/symptoms of AIDS)	
Reason for exclusion	Efgartigimod has not been studied in patients with aforementioned infections and the potential effect of FcRn antagonism on the specific immune response is not known.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	This is covered under the important potential risk of serious infections.
Severe bacterial, viral, or fungal infection	
Reason for exclusion	Efgartigimod has not been studied in patients with aforementioned infections and the potential effect of FcRn antagonism on the specific immune response is not known.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	This is covered under the important potential risk of serious infections.

Vaccination with live/attenuated vaccines (only if given less than 4 weeks prior to screening)	
Reason for exclusion	Due to its mode of action, theoretically efgartigimod could interfere with the efficacy or safety of recently administered vaccines. Currently, there are no data in patients having received live/attenuated vaccines during treatment with efgartigimod.
Is it considered to be included as missing information?	Yes
Rationale (if not included as missing information)	Not applicable
Use with monoclonal antibodies	
Reason for exclusion	Due to its mode of action, theoretically, efgartigimod could interfere with the efficacy/safety of other IgGs. Currently, there are no data to support this.
Is it considered to be included as missing information?	Yes
Rationale (if not included as missing information)	Not applicable
Total IgG level <6 g/L	
Reason for exclusion	Low serum levels of total IgG at baseline (<6 g/L) could be further reduced by treatment with efgartigimod compromising the IgG immune response.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	The risk is related to the development or reactivation of infections and is covered under the important potential risk of serious infections.

AIDS=acquired immunodeficiency syndrome; FcRn=neonatal crystallizable fragment receptor; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IgG=immunoglobulin G; IMP=investigational medicinal product; MG=myasthenia gravis; MGFA=Myasthenia Gravis Foundation of America

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs

Table Part II: Module SIV-2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Population with relevant different ethnic origin	IV formulation: 11 Japanese patients in total receiving 332 infusions. SC formulation: 14 Japanese patients in total receiving 180 injections.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Patients with relevant comorbidities	
Patients with hepatic impairment	No patients with severe, moderate, or mild hepatic impairment were enrolled in the clinical development program.
Patients with renal impairment	IV formulation: No patients with severe renal impairment were enrolled. 6 patients with moderate renal impairment were included and in total received 176 infusions. 55 patients with mild renal impairment were included and in total received 1480 infusions. SC formulation: 1 patient with severe renal impairment was included and in total received 13 injections. 3 patients with moderate renal impairment were included and in total received 27 injections. 35 patients with mild renal impairment were included and in total received 418 injections.
Patients with cardiovascular impairment	Patients with unstable cardiovascular disease, as deemed by the investigator, were excluded from the clinical studies. No patients with clinically significant QT or PR prolongation were enrolled in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.

Type of Special Population	Exposure
Patients with a disease severity different from inclusion criteria in clinical studies	Not included in the clinical development program.

Source: Module 5.3.5.1, ARGX-113-1704 CSR, Tables 14.3.4.1.2 and 14.1.2.3.3; Module 5.3.5.3, ARGX-113-9021-9031-ISS, Module Tables 14.1.2.2.1.1, 14.1.3.2.2, 14.1.2.1.1.6, 14.1.2.1.1.1, and 14.1.3.1.2

PART II: MODULE SV POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

The exposure information is based on data from Vyvgart Patient Support Programs and 6 specialty pharmacies and does not include Vyvgart treatment via buy & bill channels such as at an infusion center.

SV.1.2 Exposure

As of 02 Mar 2022, 121 patients received at least 1 dose of Vyvgart.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

There is no nonclinical or clinical evidence that efgartigimod has potential for drug abuse.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Procedural headache (IV formulation only)
- Myalgia
- Injection site reactions (SC formulation only)

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered to by prescribers:

- Bronchitis
- Upper respiratory tract infection
- Urinary tract infection

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Potential Risk 1: Serious Infections

Risk-benefit impact:

As efgartigimod induces a transient lowering in IgG levels, there is a potential risk for infections associated with the lowered IgG levels.

There is no clinical evidence linking the use of efgartigimod with an increase in serious infections (defined as any infection meeting the seriousness criteria for an individual case safety report). The majority of infections observed in patients treated with efgartigimod were mild or moderate, and transient. The most common infections observed in clinical studies were upper respiratory tract infections. None of the patients who received efgartigimod treatment had opportunistic infections. The type and severity of reported infectious events seen during

development were comparable to what was observed in the placebo group and in a noninterventional cohort study of infections in patients with MG relative to the general population.[58]

Important Potential Risk 2: Malignancies

Risk-benefit impact:

Efgartigimod causes a selective and transient decrease in the serum level of IgG. This could theoretically impair the immune response to cancer.

During the clinical development program, an imbalance was observed between neoplasms reported in patients treated with efgartigimod and patients receiving placebo, with a higher number of events being reported in patients treated with efgartigimod. All malignant neoplasms were assessed as not related to efgartigimod by the investigator. Available data on other IgG-reducing agents or treatments do not suggest a correlation between IgG reduction and an increased risk of developing any type of cancer. Immunosuppressants, which patients with MG take concomitantly with efgartigimod, can impair the immune response to cancer.

Missing Information 1: Use in Pregnant Women

Risk-benefit impact:

Pregnant patients were excluded from the clinical development program. There is evidence that maternal antibodies, including therapeutic monoclonal antibodies, are transferred from mother to fetus. Further data on the safety of efgartigimod in pregnant patients will be collected via routine pharmacovigilance activities and treatment of pregnant women with Vyvgart should be considered if the clinical benefit outweighs the risks.

Missing Information 2: Effect on Vaccination Efficacy and the Use of Live/Attenuated Vaccines

Risk-benefit impact:

Patients who received a vaccination (eg, influenza vaccine) within 4 weeks before screening were excluded from the clinical studies ARGX-113-1602 and ARGX-113-1704. Vaccination (except for live and live-attenuated vaccines), when administered at least 48 hours predose or 48 hours postdose of IMP, was allowed during clinical studies ARGX-113-1704 and ARGX-113-1705, following a protocol amendment, and during clinical studies ARGX-113-2001 and ARGX-113-2002. Currently, no data are available on the use of vaccines in combination with efgartigimod. The safety of immunization with live or live-attenuated vaccines and the response to immunization with vaccines are unknown. Vaccines should be administered according to immunization guidelines and at least 4 weeks before the initiation of treatment with efgartigimod. For patients who are on treatment with efgartigimod, vaccination with live or live-attenuated vaccines is not recommended. For all other vaccines, vaccination should take place at least 2 weeks after the last administration of a TC and 4 weeks before initiating the next cycle.

Missing Information 3: Use with Monoclonal Antibodies

Risk-benefit impact:

Patients who received monoclonal antibodies within 6 months of IMP dosing were excluded from the clinical studies. Efgartigimod may decrease concentrations of compounds that bind to the human FcRn, ie, immunoglobulin products, monoclonal antibodies (mAbs), or antibody derivatives containing the human Fc domain of the IgG subclass. Patients receiving Vyvgart while receiving monoclonal antibodies should be closely monitored for intended efficacy response for those products.

Missing Information 4: Use in Patients With Moderate and Severe Renal Impairment

Risk-benefit impact:

Patients with renal impairment were not excluded from the clinical studies. However, due to a low number of enrolled patients with moderate or severe renal impairment, there are limited safety and efficacy data in these patients. The molecular weight of efgartigimod is approximately 54 kDa, which is at the boundary of molecules that are renally filtered. No specific dose adjustment is recommended in patients with mild renal impairment.

Missing Information 5: Long-term Safety of Efgartigimod Treatment

Risk-benefit impact:

There are limited data available on the use of efgartigimod beyond 2 years. As Vyvgart is intended to be used as a chronic therapy, further data will be collected on the safety of long-term treatment with efgartigimod.

Missing Information 6: Use in Immunocompromised Patients

Risk-benefit impact:

Patients with a low serum level of total IgG at baseline (<6 g/L) were excluded from the clinical studies because efgartigimod induces a transient lowering of IgG, which could thus further reduce these levels, compromising the IgG immune response. Patients with MG with other concomitant autoimmune diseases considered by the investigator as having no impact on the study assessments were eligible for participation in the clinical studies. However, because of a low number of enrolled patients with MG with other concomitant autoimmune diseases, including patients with impaired immunity, there are limited safety and efficacy data on these patients.

The observed reductions in total antibodies were specific to IgG as no relevant decrease in all the other types of antibodies (IgA, IgD, IgE, IgM) nor albumin levels were observed.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

The missing information "Effect on vaccination efficacy and the use of live/attenuated vaccines" was updated to "Use with live/attenuated vaccines."

The effect on vaccination efficacy was removed as missing information because data became available from ARGX-113-2102, a placebo-controlled clinical study to evaluate the immune response to the polyvalent pneumococcal vaccine, PNEUMOVAX 23, and from a post hoc analysis of existing samples from completed clinical studies with efgartigimod.

A nonclinical TDAR study did not indicate a lack of immune response against a model antigen. In ARGX-113-2102, efgartigimod administration before or at the time of vaccination with PNEUMOVAX 23 did not interfere with vaccine-induced humoral immunity in healthy adults. Efgartigimod formulation for IV administration was well tolerated in participants vaccinated with PNEUMOVAX 23; all TEAEs were nonserious and mild to moderate in severity.
The post hoc analysis showed that FcRn inhibition does not reduce existing protective antibody titers below protective levels, nor does it impact the ability of participants to mount an immune response after vaccination.[59]

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Potential Risk: Serious Infections

Medical Dictionary for Regulatory Activities (MedDRA): Infections and Infestations System Organ Class (SOC)

Potential mechanisms:

Efgartigimod induces a transient lowering of IgG.

Evidence sources and strength of evidence:

No evidence for an increased risk of serious infections (defined as any infection meeting the seriousness criteria for an individual case safety report) with the use of efgartigimod was seen in the clinical development program. The majority of infections observed in patients treated with efgartigimod were mild or moderate, and transient. The type and severity of infections observed in patients treated with efgartigimod was comparable to that observed in patients receiving placebo and their frequency did not increase with repeated cycles of treatment. None of the patients who received efgartigimod treatment had opportunistic infections.

Vyvgart (efgartigimod) binds to a specific protein in the body, called neonatal FcRn. Efgartigimod binds to and blocks FcRn, which results in a transient lowering of a type of antibody called IgG. In patients testing positive for AChR antibodies, the maximum mean percentage decrease in total IgG levels compared to baseline reached 61% 1 week after the last infusion of the initial treatment cycle and returned to baseline levels 9 weeks after the last infusion. For efgartigimod SC, total IgG and AChR-Ab reduction followed a similar time course

to that seen with IV. Similar effects were also observed for all subtypes of IgG. This lowering of IgG levels could increase the risk of infections.

The observed reductions in total antibodies were specific to IgG as no relevant decrease in all the other types of antibodies (IgA, IgD, IgE, IgM) nor albumin levels were observed. Additionally, due to the mode of action of efgartigimod of blocking FcRn, no impact on IgG production is expected.

Given the potential mechanism of action of Vyvgart, serious infections are considered an important potential risk.

Characterization of the risk:

Table Part II: Module SVII-1: TEAE Frequency (95% CI), Seriousness, Outcomes, and Severity of Infections in Clinical Studies With Efgartigimod IV

	All Efgartigimod IV-Treated Patients With gMG (N=164) n (%) m
Infections and infestations SOC	**101 (61.6) 229**
95% confidence interval Clopper-Pearson	(53.7; 69.1)
Seriousness	
Serious	9 (5.5) 11
Outcomes	
Fatal	1 (0.6)
Not recovered/not resolved	6 (3.7)
Recovering/resolving	6 (3.7)
Recovered/resolved with sequelae	1 (0.6)
Recovered/resolved	86 (52.4)
Missing	1 (0.6)
CTCAE grades	
Grade 1	35 (21.3)
Grade 2	55 (33.5)
Grade 3	9 (5.5)
Grade ≥4	2 (1.2)
Missing	0

Sources: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.3.1.2.1.1, 14.3.1.2.3.1, 14.3.1.2.9.5, and 14.3.1.2.9.6
CTCAE=Common Terminology Criteria for Adverse Events; gMG=generalized myasthenia gravis; IV=intravenous m=number of events; N=number of patients in the analysis set; n=number of patients with event; SOC=system organ class; TEAE=treatment-emergent adverse event

Table Part II: Module SVII-2: TEAE Frequency (95% CI), Seriousness, Outcomes, and Severity of Infections in ARGX-113-1704 (Efgartigimod IV)

	Efgartigimod IV (N=84) n (%) m	**Placebo** (N=83) n (%) m
Infections and infestations SOC	**39 (46.4) 56**	**31 (37.3) 42**
Difference in AE rate	9.1	
95% confidence interval Clopper-Pearson	(-6.1; 24)	
Seriousness		
Serious	0	1 (1.2)
Outcomes		
Fatal	0	0
Not recovered/not resolved	0	1 (1.2)
Recovering/resolving	1 (1.2)	0
Recovered/resolved	38 (45.2)	30 (36.1)
Missing	0	0
CTCAE grades		
Grade 1	18 (21.4)	17 (20.5)
Grade 2	19 (22.6)	13 (15.7)
Grade 3	2 (2.4)	1 (1.2)
Grade ≥4	0	0
Missing	0	0

Sources: Module 5.3.5.1, ARGX-113-1704, Tables 14.3.1.1.2, 14.3.1.1.2.3, 14.3.1.4.2, 14.4.21, and 14.4.22
AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; m=number of events; N=number of patients in the analysis set; n=number of patients with event; SOC=system organ class; TEAE=treatment-emergent adverse event

Table Part II: Module SVII-3: TEAE Frequency (95% CI), Seriousness, Outcomes, and Severity of Infections in Clinical Studies With Efgartigimod SC

	All Efgartigimod SC-Treated Patients With gMG (N=168) n (%) m
Infections and infestations SOC	**57 (33.9) 91**
95% confidence interval Clopper-Pearson	(26.8; 41.6)
Seriousness	
Serious	6 (3.6) 8
Outcomes	
Fatal	1 (0.6)
Not recovered/not resolved	1 (0.6)
Recovering/resolving	0
Recovered/resolved with sequelae	1 (0.6)
Recovered/resolved	51 (30.4)
Missing	3 (1.8)
CTCAE grades	
Grade 1	26 (15.5)
Grade 2	24 (14.3)
Grade 3	5 (3.0)
Grade ≥4	2 (1.2)
Missing	0

Sources: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Tables 14.3.1.1.1.1, 14.3.1.1.2.1, 14.3.1.1.3.1, 14.3.1.1.9.5, 14.3.1.1.9.6

CTCAE=Common Terminology Criteria for Adverse Events; gMG=generalized myasthenia gravis; m=number of events; N=number of patients in the analysis set; n=number of patients with event; SC=subcutaneous; SOC=system organ class; TEAE=treatment-emergent adverse event

Risk factors and risk groups:

Underlying immunodeficiency conditions, either acquired or due to immunosuppressive drugs, represent a general risk factor for serious infections. The risk increases with more pronounced impairment of the immune system.

Preventability:

Clinical signs and symptoms of infections should be monitored during treatment with Vyvgart. In patients with an active infection, the benefit-risk of maintaining or withholding treatment with

Vyvgart should be considered until the infection has resolved. If serious infections occur, delaying treatment with Vyvgart should be considered until the infection has resolved.

Impact on the risk-benefit balance of the product:

The severity and seriousness of infections observed in the clinical program do not impact the risk-benefit balance of Vyvgart.

Public health impact:

The impact on public health is expected to be low based on the frequency and severity of serious infections that have been seen during clinical studies and the prevalence of the treated disease.

Important Potential Risk: Malignancies

Standardized MedDRA Queries (SMQ): Malignancies

Potential mechanism:

Efgartigimod causes a selective and transient decrease in the serum level of IgG. This could theoretically impair the immune response to cancer.

Evidence sources and strength of evidence:

During the clinical development program, an imbalance was seen between neoplasms in patients treated with efgartigimod and patients receiving placebo, with 11 events of neoplasms observed in 8 patients treated with efgartigimod IV (1 in study ARGX-113-1704 and 10 in 7 patients in study ARGX-113-1705) and only 1 event observed in the placebo group. In patients treated with efgartigimod SC, 2 events of neoplasms were observed in 2 patients in study ARGX-113-2002 (none were observed in study ARGX-113-2001). All malignant neoplasms were assessed as not related to efgartigimod by the investigator.

Available data on other IgG-reducing agents or treatments do not suggest a correlation between IgG reduction and an increased risk of developing any type of cancer. No literature could be found associating chronic use of plasma exchange, immunoadsorption, and plasmapheresis therapies reducing IgGs with the development of malignancies. Immunosuppressants, which patients with MG take concomitantly with efgartigimod, can impair the immune response to cancer. Therefore, malignancies are considered an important potential risk.

Characterization of the risk:

Table Part II: Module SVII-4: TEAE Frequency (95% CI), Seriousness, Outcomes, and Severity of Malignancies in Clinical Studies With Efgartigimod IV

	All Efgartigimod IV-Treated Patients With gMG (N=164) n (%) m
Malignancies SMQ - Narrow	**8 (4.9) 11**
95% confidence interval Clopper-Pearson	(2.1; 9.4)
Seriousness	
Serious	5 (3.0)
Outcomes	
Fatal	1 (0.6)
Not recovered/not resolved	2 (1.2)
Recovering/resolving	1 (0.6)
Recovered/resolved with sequelae	0
Recovered/resolved	4 (2.4)
Missing	0
CTCAE grades	
Grade 1	1 (0.6)
Grade 2	2 (1.2)
Grade 3	2 (1.2)
Grade ≥4	3 (1.8)
Missing	0

Sources: ARGX-113-9031 – EMA outputs, Table 99.9
CTCAE=Common Terminology Criteria for Adverse Events; gMG=generalized myasthenia gravis; IV=intravenous; m=number of events; N=number of patients in the analysis set; n=number of patients with event; SMQ=standardized MedDRA queries; TEAE=treatment-emergent adverse event

Table Part II: Module SVII-5: TEAE Frequency (95% CI), Seriousness, Outcomes, and Severity of Malignancies in ARGX-113-1704 (Efgartigimod IV)

	Efgartigimod IV (N=84) n (%) m	**Placebo** (N=83) n (%) m
Malignancies SMQ - Narrow	**1 (1.2) 1**	**1 (1.2) 1**
Difference in AE rate	−0.0	
95% confidence interval Clopper-Pearson	(−5.6; 5.6)	
Seriousness		
Serious	1 (1.2)	0
Outcomes		
Fatal	0	0
Not recovered/not resolved	1 (1.2)	0
Recovering/resolving	0	0
Recovered/resolved	0	1 (1.2)
Missing	0	0
CTCAE grades		
Grade 1	0	1 (1.2)
Grade 2	0	0
Grade 3	1 (1.2)	0
Grade ≥4	0	0
Missing	0	0

Sources: ARGX-113-1704 – EMA questions, Table 999.9
AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; N=number of patients in the analysis set; n=number of patients with event; m=number of events; SMQ=standardized MedDRA queries; TEAE=treatment-emergent adverse event

Table Part II: Module SVII-6: TEAE Frequency (95% CI), Seriousness, Outcomes, and Severity of Malignancies in Clinical Studies With Efgartigimod SC

	All Efgartigimod SC-Treated Patients With gMG (N=168) n (%) m
Malignancies SMQ - Narrow	2 (1.2) 2
95% confidence interval Clopper-Pearson	(0.1; 4.2)
Seriousness	
Serious	1 (0.6)
Outcomes	
Fatal	1 (0.6)
Not recovered/not resolved	0
Recovering/resolving	0
Recovered/resolved with sequelae	0
Recovered/resolved	1 (0.6)
Missing	0
CTCAE grades	
Grade 1	1 (0.6)
Grade 2	0
Grade 3	0
Grade ≥4	1 (0.6)
Missing	0

Sources: Module 5.3.5.3, ARGX-113-9021-ISS post-hoc analysis, Tables 99.9
CTCAE=Common Terminology Criteria for Adverse Events; gMG=generalized myasthenia gravis; m=number of events; N=number of patients in the analysis set; n=number of patients with event; SC=subcutaneous; SMQ=standardized MedDRA queries; TEAE=treatment-emergent adverse event

Risk factors and risk groups:

Risk factors for malignancy include traditional risk factors such as advancing age, smoking, drinking alcohol, obesity, sun exposure, radiation and chemicals exposure, hormonal disturbance, and family history.

Preventability:

Routine prevention measures should be followed according to clinical guidelines that describe how to screen and monitor malignancies to prevent and/or manage malignant neoplasms.

Impact on the risk-benefit balance of the product:

Malignancy is an important potential risk that could impact the benefit-risk balance due to its seriousness. However, due to the debilitating nature of gMG, the benefit-risk balance of Vyvgart remains positive. Should the risk be confirmed, minimization measures will be put in place to maintain the positive benefit-risk balance.

Public health impact:

The public health impact is expected to be limited due to the rarity of gMG.

SVII.3.2 Presentation of the Missing Information

Missing Information: Use in Pregnant Women

Evidence source:

Pregnant patients were excluded from the clinical studies. The safety of efgartigimod in pregnant women is unknown. Antibodies, including therapeutic monoclonal antibodies, are known to be actively transported across the placenta (after 30 weeks of gestation) by binding to the FcRn and therefore efgartigimod has the potential for being transmitted from the mother to the developing fetus. There is no evidence of adverse developmental outcomes following the administration of efgartigimod at up to 100 mg/kg/day in rat and rabbit.

As efgartigimod is expected to reduce maternal antibody levels, and is also expected to inhibit the transfer of maternal antibodies to the fetus, reduction in passive protection to the newborn is anticipated.

Population in need of further characterization:

Further data collection on the use of efgartigimod in pregnant patients, to characterize the safety of efgartigimod in these patients, will be done through routine pharmacovigilance activities.

Missing Information: Use With Live/Attenuated Vaccines

Evidence source:

Patients who received a vaccination within 4 weeks before screening were excluded from the clinical studies ARGX-113-1602 and ARGX-113-1704. Vaccination, except for live and live-attenuated vaccines, when administered at least 48 hours predose or 48 hours postdose of IMP, was allowed during the clinical study ARGX-113-1704 and ARGX-113-1705, following a protocol amendment, and during clinical studies ARGX-113-2001 and ARGX-113-2002.

The safety of immunization with live and live-attenuated vaccines and the response to immunization with these vaccines during treatment with efgartigimod are unknown. Theoretical concerns are that live and live-attenuated vaccines are potentially pathogenic.

Population in need of further characterization:

Patients receiving live/attenuated vaccines while receiving efgartigimod treatment.

Missing Information: Use with Monoclonal Antibodies

Evidence source:

Patients who received monoclonal antibodies within 6 months of dosing were excluded from the clinical studies. No information is available on the effect of concomitant administration of monoclonal antibodies with efgartigimod. Efgartigimod may decrease serum concentrations of compounds that bind to the human FcRn, ie, immunoglobulin products, mAbs, or antibody derivatives containing the human Fc domain of the IgG subclass, which may affect the intended efficacy response of those products.

Population in need of further characterization:

Patients receiving monoclonal antibodies while receiving efgartigimod administration.

Missing Information: Use in Patients With Moderate and Severe Renal Impairment

Evidence source:

Patients with renal impairment were not excluded from the clinical studies. However, due to a low number of enrolled patients with moderate or severe renal impairment, there are limited safety and efficacy data in these patients.

The molecular weight of efgartigimod is approximately 54 kDa, which is at the boundary of molecules that are renally filtered.

The effect of renal function marker estimated glomerular filtration rate [eGFR] as a covariate in a population PK analysis showed a reduced clearance resulting in a limited increase in exposure in patients with mild renal impairment (eGFR 60-89 mL/min/1.72 m^2). Clinical data show that mild renal impairment does not affect the overall tolerability profile of efgartigimod.

Population in need of further characterization:

Patients with moderate or severe renal impairment treated with efgartigimod.

Missing Information: Long-term Safety of Efgartigimod Treatment

Evidence source:

As of 31 Jan 2022, the maximum duration of treatment with efgartigimod and follow-up was 1080 days with a median duration of 664.5 days, in patients who received efgartigimod IV 10 mg/kg. Overall, the duration of treatment combined with follow-up was at least 12 months for 125 patients, at least 18 months for 105 patients, and at least 24 months for 63 patients. No clinically significant cumulative toxicities have been identified.

Population in need of further characterization:

Patients treated with efgartigimod beyond 2 years.

Missing Information: Use in Immunocompromised Patients

Evidence source:

Patients with a low serum level of total IgG at baseline (<6 g/L) were excluded from the clinical studies because efgartigimod induces a transient lowering of IgG, which could thus further reduce these levels, compromising the IgG immune response. Patients with MG with other concomitant autoimmune diseases considered by the investigator as having no impact on the study assessments were eligible for participation in the clinical studies. However, because of a low number of enrolled patients with MG with other concomitant autoimmune diseases, including those with impaired immunity, there are limited safety and efficacy data on these patients. The observed reductions in total antibodies were specific to IgG as no relevant decrease in all the other types of antibodies (IgA, IgD, IgE, IgM) nor albumin levels were observed.

Population in need of further characterization:

Immunocompromised patients treated with efgartigimod.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII-1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious infections Malignancies
Missing information	Use in pregnant women Use with live/attenuated vaccines Use with monoclonal antibodies Use in patients with moderate and severe renal impairment Long-term safety of efgartigimod treatment Use in immunocompromised patients

PART III PHARMACOVIGILENCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities are deemed sufficient to manage the risk.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Malignancies:

Description	Purpose	Safety Concern(s) Addressed
Targeted follow-up questionnaire (see Annex 4)	Monitoring, standardized collection, and documentation of malignancies to detect patterns	Malignancies

III.2 Additional Pharmacovigilance Activities

Post-authorization Safety Study (ARGX-113-PASS-2208) Summary

Study short name and title:

A non-interventional, post-authorisation safety study of patients treated with efgartigimod alfa.

Rationale and study objectives:

The purpose of this study is to evaluate the overall long-term safety of efgartigimod including the occurrence of serious infections in patients with gMG treated with efgartigimod compared to patients with gMG not exposed to efgartigimod.

Study design:

This is a noninterventional, prospective PASS.

Patients will be treated and observed according to normal clinical practice. No visits or investigations outside of normal clinical practice will be required. Enrollment of patients will occur during a period of 5 years. Follow-up of patients will continue for 5 years from the time the last patient has been enrolled. Patients will be followed regardless of whether they continue or discontinue efgartigimod. Assuming a 5-year enrollment period this will allow for a maximum of 10 years of follow-up and a minimum of 5 years.

Study population:

Patients diagnosed with gMG who are starting commercial efgartigimod or are within their first cycle of efgartigimod at enrollment and patients diagnosed with gMG who have never received efgartigimod.

Milestones:

Start of data collection: Q2 2024

Last patient enrolled: Q2 2029

End of data collection: Q2 2034

Study progress report: yearly (except at the time of the interim and final report)

First interim report: Q2 2028

Second interim report: Q2 2032

Final study report: Q2 2035

Pregnancy Post-Authorization Safety Study (ARGX-113-PAC-2206) Summary

Study short name and title:

A worldwide pregnancy safety study to assess maternal, foetal, and infant outcomes following exposure to efgartigimod alfa during pregnancy and/or breastfeeding.

Rationale and study objectives:

There are no studies of efgartigimod exposure in pregnant women. Pregnant and breastfeeding patients were excluded from the clinical studies. The safety of efgartigimod in pregnant and breastfeeding women is unknown.

This pregnancy safety study will assess maternal, fetal, and infant outcomes following exposure to efgartigimod during pregnancy and/or breastfeeding.

Study design:

This is a noninterventional prospective PASS.

Enrollment will occur over approximately 8.25 years, and data will be collected for up to 10 years after the date of the first patient's enrollment to enable complete capture of the infant outcomes for all enrolled pregnancies with live-births. All infants exposed in utero and/or through breastfeeding will be followed through 12 months of age with the exception of an infant death or loss to follow-up. Pregnant women will be followed from the time of enrollment until their pregnancy outcome is known (ie, maximum of 9 months).

Study population:

Pregnant women exposed to efgartigimod any time within 25 days before conception or any time during pregnancy, and women exposed to efgartigimod only during breastfeeding.

Milestones:

Start of data collection: Q4 2023

Last patient enrolled: Q1 2031

End of data collection: Q4 2032

First interim report: Q4 2024

Following interim reports: annually

Final study report: Q2 2034

Malignancy Post-Authorization Safety Study Summary

Study short name and title:

Post-authorisation safety study (PASS) to evaluate the risk of malignancies in patients with myasthenia gravis (MG) treated with efgartigimod.

Rationale and study objectives:

Malignancies are considered an important potential risk.

This safety study is to evaluate the long-term risk of malignancies in patients with MG treated with efgartigimod compared with patients with MG receiving any other MG therapy who do not have malignancy history in the lookback period.

Study design:

This is a multinational, longitudinal database cohort study.

Patient enrollment in the study will begin following the launch of efgartigimod and will continue for up to 5 years via database refreshes. Patients will be followed up from study entry up to approximately 5 to 10 years.

Study population:

The study population consists of an efgartigimod cohort of patients with an MG diagnosis who have initiated efgartigimod and a reference cohort of patients with an MG diagnosis who have not initiated efgartigimod but are receiving any other MG therapy.

Milestones:

To be confirmed.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Post-authorization safety study/ ARGX-113-PASS-2208 Planned	To evaluate the overall long-term safety of efgartigimod including the occurrence of serious infections in patients with gMG treated with efgartigimod compared to patients with gMG not exposed to efgartigimod.	• Long-term safety of efgartigimod treatment • Serious infections • Malignancies • Use with live/attenuated vaccines • Use with monoclonal antibodies • Use in patients with moderate and severe renal impairment • Use in immunocompromised patients	Protocol	14 Dec 2023
			First interim report	Q2 2028
			Final report	Q2 2035

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Pregnancy post-authorization safety study/ ARGX-113-PAC-2206 Planned	To assess maternal, fetal, and infant outcomes following exposure to efgartigimod during pregnancy and/or breastfeeding	• Use in pregnant women	Protocol	14 Dec 2023
			First Interim report	Q4 2024
			Final report	Q2 2034
Malignancy post-authorization safety study Planned	To evaluate the long-term risk of malignancies in patients with MG treated with efgartigimod compared with patients with MG receiving any other MG therapy who do not have malignancy history in the lookback period.	• Malignancies	Protocol	TBC
			First interim report	TBC
			Final report	TBC

gMG=generalized myasthenia gravis, PASS=post-authorization safety study, Q2=second quarter, Q4=fourth quarter; TBC=to be confirmed

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table Part V-1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious infections	Routine risk communication: • SmPC section 4.4 • SmPC section 4.8 • PL section 2 • PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring for infections are included in SmPC section 4.4 • Recommendation to the patient to inform their doctor if they have any infections before using Vyvgart in PL section 2 Other routine risk minimization measures beyond the Product Information: None
Malignancies	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

Safety Concern	Routine Risk Minimization Activities
Use in pregnant women	Routine risk communication: • SmPC section 4.6 • PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that the treatment of pregnant women with Vyvgart should only be considered if the clinical benefit outweighs the risk is included in SmPC section 4.6 • Recommendation to the patient to ask for advice before taking Vyvgart when pregnant or planning to have a baby in PL section 2 Other routine risk minimization measures beyond the Product Information: None
Use with live/attenuated vaccines	Routine risk communication: • SmPC section 4.4 • SmPC section 4.5 • PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for use of vaccines is included in SmPC section 4.4 • Recommendation to the patient to inform their doctor if they have received or plan to be vaccinated in PL section 2 Other routine risk minimization measures beyond the Product Information: None
Use with monoclonal antibodies	Routine risk communication: • SmPC section 4.5 • PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for treatment with antibodies are included in SmPC section 4.5 • Recommendation to the patient to inform their doctor if they are using or might use other medicines in PL section 2 Other routine risk minimization measures beyond the Product Information: None

Safety Concern	Routine Risk Minimization Activities
Use in patients with moderate and severe renal impairment	Routine risk communication: • SmPC section 4.2 • SmPC section 5.2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None
Long-term safety of efgartigimod treatment	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None
Use in immunocompromised patients	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

PL=package leaflet, SmPC=summary of product characteristics

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Table Part V-1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table Part V-2: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infections	Routine risk minimization measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Malignancies	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire for malignancies Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208) • Malignancy PASS
Use in pregnant women	Routine risk minimization measures: • SmPC section 4.6 • PL section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Pregnancy PASS (ARGX-113-PAC-2206)
Use with live/attenuated vaccines	Routine risk minimization measures: • SmPC section 4.4 • SmPC section 4.5 • PL section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use with monoclonal antibodies	Routine risk minimization measures: • SmPC section 4.5 • PL section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Use in patients with moderate and severe renal impairment	Routine risk minimization measures: • SmPC section 4.2 and 5.2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Long-term safety of efgartigimod treatment	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Use in immunocompro-mised patients	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)

PASS=post-authorization safety study, PL=package leaflet, SmPC=summary of product characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR VYVGART (EFGARTIGIMOD)

This is a summary of the risk management plan (RMP) for Vyvgart. The RMP details important risks of Vyvgart, how these risks can be minimized, and how more information will be obtained about Vyvgart risks and uncertainties (missing information).

Vyvgart's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vyvgart should be used.

This summary of the RMP for Vyvgart should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vyvgart's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Vyvgart is used together with standard therapy to treat adults with generalized myasthenia gravis (gMG), an autoimmune disease that causes muscle weakness. It contains efgartigimod alfa as the active substance and it is given by intravenous infusion or subcutaneous injection (see SmPC).

Further information about the evaluation of Vyvgart benefits can be found in Vyvgart EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/vyvgart.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Vyvgart, together with measures to minimize such risks and the proposed studies for learning more about Vyvgart's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including periodic safety update reports (PSUR) assessments so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Vyvgart is not yet available, it is listed under “missing information” below.

II.A List of Important Risks and Missing Information

Important risks of Vyvgart are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vyvgart. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table II-1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Serious infections Malignancies
Missing information	Use in pregnant women Use with live/attenuated vaccines Use with monoclonal antibodies Use in patients with moderate and severe renal impairment Long-term safety of efgartigimod treatment Use in immunocompromised patients

II.B Summary of Important Risks

Important Potential Risk: Serious Infections	
Evidence for linking the risk to the medicine	No evidence for an increased risk of serious infections (defined as any infection meeting the seriousness criteria for an individual case safety report) with the use of efgartigimod was seen in the clinical development program. The majority of infections observed in patients treated with efgartigimod were mild or moderate, and transient. The type and severity of infections observed in patients treated with efgartigimod was comparable to that observed in patients receiving placebo and their frequency did not increase with repeated cycles of treatment. None of the patients who received efgartigimod treatment had opportunistic infections.

	Vyvgart (efgartigimod) binds to a specific protein in the body, called neonatal Fc Receptor (FcRn). Efgartigimod binds to and blocks FcRn, which results in a transient lowering of a type of antibody called immunoglobulin G (IgG). In patients testing positive for acetylcholine receptor (AChR) antibodies, the maximum mean percentage decrease in total IgG levels compared to baseline reached 61% 1 week after the last infusion of the initial treatment cycle and returned to baseline levels 9 weeks after the last infusion. For efgartigimod SC, total IgG and AChR-Ab reduction followed a similar time course to that seen with IV. Similar effects were also observed for all subtypes of IgG. This lowering of IgG levels could increase the risk of infections. The observed reductions in total antibodies were specific to IgG as no relevant decrease in all the other types of antibodies (IgA, IgD, IgE, IgM) nor albumin levels were observed. Additionally, due to the mode of action of efgartigimod of blocking FcRn, no impact on IgG production is expected. Given the potential mechanism of action of Vyvgart, serious infections are considered an important potential risk.
Risk factors and risk groups	Underlying immunodeficiency conditions, either acquired or due to immunosuppressive drugs, represent a general risk factor for serious infections. The risk increases with more pronounced impairment of the immune system.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-authorization safety study of patients treated with efgartigimod (ARGX-113-PASS-2208)
Important Potential Risk: Malignancies	
Evidence for linking the risk to the medicine	During the clinical development program, an imbalance was seen between neoplasms in patients treated with efgartigimod and patients receiving placebo, with 11 events of neoplasms observed in 8 patients treated with efgartigimod IV (1 in study ARGX-113-1704 and 10 in 7 patients in study ARGX-113-1705) and only 1 event observed in the placebo group. In patients treated with efgartigimod SC, 2 events of neoplasms were observed in 2 patients in study ARGX-113-2002 (none were observed in study ARGX-113-2001). All malignant neoplasms were assessed as not related to efgartigimod by the investigator. Available data on other IgG-reducing agents or treatments do not suggest a correlation between IgG reduction and an increased risk of developing any type of cancer. No literature could be found associating chronic use of plasma exchange, immunoadsorption,

	and plasmapheresis therapies reducing IgGs with the development of malignancies. Immunosuppressants, which patients with MG take concomitantly with efgartigimod, can impair the immune response to cancer. Therefore, malignancies are considered an important potential risk.
Risk factors and risk groups	Risk factors for malignancy include traditional risk factors such as advancing age, smoking, drinking alcohol, obesity, sun exposure, radiation and chemicals exposure, hormonal disturbance, and family history.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-authorization safety study of patients treated with efgartigimod (ARGX-113-PASS-2208) • Malignancy post-authorization safety study
Missing Information: Use in Pregnant Women	
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.6 • PL section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Pregnancy post-authorization safety study (ARGX-113-PAC-2206)
Missing Information: Use With Live/Attenuated Vaccines	
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 and 4.5 • PL section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-authorization safety study of patients treated with efgartigimod (ARGX-113-PASS-2208)

Missing Information: Use With Monoclonal Antibodies	
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.5 • PL section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-authorization safety study of patients treated with efgartigimod (ARGX-113-PASS-2208)
Missing Information: Use in Patients With Moderate and Severe Renal Impairment	
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2 and 5.2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-authorization safety study of patients treated with efgartigimod (ARGX-113-PASS-2208)
Missing Information: Long-term Safety of Efgartigimod Treatment	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-authorization safety study of patients treated with efgartigimod (ARGX-113-PASS-2208)
Missing Information: Use in immunocompromised patients	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-authorization safety study of patients treated with efgartigimod (ARGX-113-PASS-2208)

PL=package leaflet, SmPC=summary of product characteristics

II.C Post-Authorization Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligations of Vyvgart.

II.C.2 Other Studies in Post-Authorization Development Plan

Post-authorization Safety Study – ARGX-113-PASS-2208

Purpose of the study: to evaluate the overall long-term safety of efgartigimod including the occurrence of serious infections in patients with gMG treated with efgartigimod compared to patients with gMG not exposed to efgartigimod.

Pregnancy Post-Authorization Safety Study – ARGX-113-PAC-2206

Purpose of the study: There are no studies of efgartigimod exposure in pregnant women. Pregnant and breastfeeding patients were excluded from the clinical studies. The safety of efgartigimod in pregnant and breastfeeding women is unknown.

This pregnancy safety study will assess maternal, fetal, and infant outcomes following exposure to efgartigimod during pregnancy and/or breastfeeding.

Malignancy Post-Authorization Safety Study

Purpose of the study: Malignancies are considered an important potential risk.

This safety study is to evaluate the long-term risk of malignancies in patients with MG treated with efgartigimod compared with patients with MG receiving any other MG therapy who do not have malignancy history in the lookback period.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific adverse reaction follow-up questionnaires for Malignancies:

Targeted follow-up questionnaire for serious adverse event MALIGNANCY

Please complete this form and send it back to: safety@argenx.com

Event description (Malignancy)

Causal relationship between the event and Vyvgart	**Event dates / duration** (dd/mmm/yyyy)	**Outcome of the event**	**Action taken with Vyvgart due to the event?**	**Therapy dates and cycle**
☐ Related Please add rationale: _____ ☐ Not related Please provide plausible alternative cause: _____	Start date: _____ End date: _____ Duration: _____	☐ Fatal ☐ Resolved ☐ Resolving ☐ Not resolved ☐ Resolved with sequelae: _____ ☐ Unknown	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Not applicable	Start date: _____ End date: _____ Cycle number: _____

- Event: *Please provide diagnosis.*
- Description of event *(eg, symptoms, location of primary malignancy, staging)* Click or tap here to enter text.
- Is the malignancy localized? ☐ Yes ☐ No
  If not, please provide details on further locations. Click or tap here to enter text.
- Was biopsy performed? ☐ Yes ☐ No
  If available, please provide report or information about grading and histological typing, including immunophenotyping. Click or tap here to enter text.
- Please provide current treatment for malignancy. Click or tap here to enter text.

Diagnosis and tests

Were any of the following diagnostic tests performed? Please provide copies of the tests or check all that apply and specify test(s), dates, and results.

☐ Imaging tests (eg, X-ray, CT scan, MRI scan, PET scan, mammogram, PSA screening) Click or tap here to enter text.

☐ Exploratory surgery, Endoscopic exams. Click or tap here to enter text.

☐ Bone marrow aspiration. Click or tap here to enter text.

☐ Blood tests, urine tests, biomarkers. Click or tap here to enter text.

☐ EBV serology, other viral serology tests (eg, HIV, HCV) test. Click or tap here to enter text.

☐ Other relevant tests? Click or tap here to enter text.

Patient history and risk factors

Does the patient have a history of any of the following prior to the start of, or concomitantly with the use of Vyvgart*? Please, check all that apply and provide details as applicable.*

☐ Infection ☐ UV exposure, PUVA/AUV ☐ Vaccination for HPV. Click or tap here to enter text.

☐ Smoking ☐ Yes / ☐ No. Duration (packs/years). Click or tap here to enter text.

☐ Alcohol abuse. Click or tap here to enter text.

☐ Personal history of malignancy. If yes, provide diagnosis, date of diagnosis, location. Click or tap here to enter text.

☐ Genetic investigations. Click or tap here to enter text.

☐ Immunosuppression conditions (eg, HIV, transplantation, autoimmune diseases). Click or tap here to enter text.

☐ Exposure to carcinogens (environmental, occupational, exposure to chemicals). Click or tap here to enter text.

For skin cancer: Please provide patient's skin characteristics:

☐ Lighter natural skin color ☐ Olive, brown, or black skin ☐ Brown eyes

Immunosuppression therapy

Please indicate the generic drug name/s, treatment duration and dates of immunosuppression therapy/ies:

Generic drug name	**Start date**	**Stop date or total duration**	**Indication**
Past therapy			
Concurrent therapy			

Patient's immune status

Please provide test results prior to treatment with Vyvgart *and at the time of the adverse event.*

Name of test	**Unit / normal value**	**Test result**	**Date of sample**
White blood cells *(prior)*			
White blood cells *(at event)*			
IgG levels *(prior)*			
IgG levels *(at event)*			
CD4/CD8 count *(prior)*			
CD4/CD8 count *(at event)*			
CD19 count (B cells) *(prior)*			
CD19 count (B cells) *(at event)*			
CD20 count (NK cells) *(prior)*			
CD20 count (NK cells) *(at event)*			

Concomitant treatments

Concomitant treatments (Suspected drugs are marked with *)	**Daily dose**	**Route**	**Dates Start – Stop** (dd/mmm/yyyy)		**Cause of prescription**

Reporter's details

Name: Job title: Date:

Address: Telephone: Signature:

Email:

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable.

Abbreviations

AChE	acetylcholinesterase
AChR	acetylcholine receptor
AChR-Ab	anti-acetylcholine receptor antibody
AE	adverse events
ALT	alanine transaminase
CTCAE	Common Terminology Criteria for Adverse Events
eGFR	estimated glomerular filtration rate
EU	European Union
FcRn	neonatal crystallized fragment receptor
gMG	generalized myasthenia gravis
HLA	human leukocyte antigen
Ig	immunoglobulin
IMP	investigational medicinal product
ITC	intertreatment cycle
IVIg	intravenous immunoglobulin
mAbs	monoclonal antibodies
MedDRA	medical dictionary for regulatory activities
MG	myasthenia gravis
MR	mortality rate(s)
MRR	mortality rate ratio
MuSK	muscle-specific tyrosine kinase
NMJ	neuromuscular junction

NSID	nonsteroidal immunosuppressive drug
PASS	post-authorization safety study
PLEX	plasma exchange
PNEUMOVAX 23	polyvalent pneumococcal vaccine
PT	preferred term
SmPC	summary of product characteristics
SMQ	standardized MedDRA queries
SOC	system organ class
TC	treatment cycle
TDAR	T-cell dependent antibody response
TEAE	treatment-emergent adverse event
US	United States (of America)