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

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Compound: Efgartigimod alfa (VYVGART)

Sponsor

argenx BV

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Title	A non-interventional, post-authorisation safety study of patients treated with efgartigimod alfa.
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Active substance	Efgartigimod alfa (efgartigimod)
Medicinal product	VYVGART
Product reference	H005849
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Marketing authorisation holder (MAH) & license holders	argenx BV
Joint post-authorisation safety study (PASS)	No
Research question and objectives	A non-interventional 10-year Post-Authorization Safety Study (PASS) in a post-marketing setting comparing cohorts of patients with gMG treated with efgartigimod to those treated with other MG medication, in order to estimate the incidence rates of serious infection and other safety events. **Primary Objective** • To evaluate the overall long-term safety of efgartigimod including the occurrence of serious infections in generalized myasthenia gravis (gMG) patients treated with efgartigimod compared to gMG patients not exposed to efgartigimod. **Exploratory Objectives** • To evaluate the safety of efgartigimod in immunocompromised patients • To evaluate the safety of efgartigimod administered to patients treated with monoclonal antibodies • To evaluate the safety of efgartigimod in patients receiving live/attenuated vaccine • To evaluate the safety of efgartigimod in patients with moderate to severe renal impairment
Regions and countries of study	Europe & United States (US)
Author	argenx BV

Marketing Authorization and License Holders

MAH & License holders	argenx BV Industriepark Zwijnaarde 7 9052 Gent Belgium
MAH contact person	Mrs. [redacted]

Sponsor Approval

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the Declaration of Taipei, and all applicable local laws and regulations, including, without limitation, data privacy laws and regulations.

Name and Title	**Date (DD MMM YYYY)**	**Signature**
[redacted] MD PhD Chief Medical Officer		See appended signature page
[redacted] MD Vice President Head Global Patient Safety		See appended signature page
[redacted] MD PhD Qualified Person for Pharmacovigilance		See appended signature page

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
AChE	Acetylcholinesterase
AChR	Acetylcholine Receptor
ATC	Anatomical Therapeutic Chemical
CDC	Centre for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FcRn	Fragment crystallisable Receptor
GDPR	General Data Protection Regulation
gMG	Generalised Myasthenia Gravis
HCP	Healthcare Professional
ICF	Informed Consent Form
IEC	Independent Ethics Committee

Abbreviation	**Definition**
IRB	Institutional Review Board
Ig	Immunoglobulin
IV	Intravenous
IVIg	Intravenous Immunoglobulins
LRP4	Lipoprotein Receptor-Related Protein 4
MedDRA	Medical Dictionary for Regulatory Activities
MAH	Marketing Authorisation Holder
MG	Myasthenia Gravis
MuSK	Muscle-Specific Tyrosine Kinase
MyaReg	Deutsches Myaesthenie Register
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PLEX	Plasmapheresis/Plasma Exchange
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
RMP	Risk Management Plan
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Query
SOC	System Organ Class
UK	United Kingdom
US	United States
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

Sponsor	argenx BV
Contract research organization	United BioSource LLC

4. ABSTRACT

Title

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

Rationale and Background

Myasthenia gravis (MG) is an autoimmune disease caused by immunoglobulin G (IgG) antibodies against postsynaptic antigens at the neuromuscular junction. IgG autoantibodies impair neuromuscular transmission by binding to acetylcholine receptors (AChR), muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4).

Myasthenia gravis can be classified into various subgroups based upon antibody status, age of onset and/or degree of muscle involvement. Ocular symptoms are the most common initial presentation of disease and about two thirds of ocular MG patients progress to generalised MG (gMG) within the first 2-3 years (Anil 2020).

Efgartigimod alfa (efgartigimod) is a human IgG1 antibody fragment engineered for increased affinity to the neonatal Fragment crystallisable Receptor (FcRn). Efgartigimod binds to FcRn, resulting in the reduction of circulating IgG including IgG autoantibodies. Efgartigimod does not affect the levels of other immunoglobulins (IgA, IgD, IgE, or IgM), or those of albumin.

In the United States (US), efgartigimod is approved for the indication of gMG in adult patients who are AChR antibody positive and in the European Union (EU) it is approved as an add-on to standard therapy for the treatment of adult patients who are AChR antibody positive.

The purpose of this study is to evaluate the important potential risks and missing information as set out in the EU Risk Management Plan (RMP) in a larger patient population for a longer duration than in clinical trials and under conditions of normal clinical practice.

Research Question and Objectives

A non-interventional 10-year Post-Authorization Safety Study (PASS) in a post-marketing setting comparing cohorts of patients with gMG treated with efgartigimod to those treated with other MG medication, in order to estimate incidence rates of serious infection and other safety events.

Primary objective

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

Exploratory objectives

- To evaluate the safety of efgartigimod in immunocompromised patients.
- To evaluate the safety of efgartigimod administered to patients treated with monoclonal antibodies.
- To evaluate the safety of efgartigimod in patients receiving live/attenuated vaccine.
- To evaluate the safety of efgartigimod in patients with moderate to severe renal impairment

Study Design

This is a non-interventional, prospective, post authorisation safety study.

Patients with gMG who are expected to start treatment with efgartigimod at enrolment or are within their first cycle of efgartigimod at enrolment will be eligible to enrol into the efgartigimod cohort. Patients with gMG who have not been exposed to efgartigimod and for whom it is not planned to start treatment with efgartigimod at enrolment will be eligible to enrol into the non-efgartigimod cohort.

Enrolment of patients will be over at least a 5-year period. The follow up of patients will continue for 5 years from the time the last patient has been enrolled. Patients will be followed up regardless of whether they continue or discontinue efgartigimod.

In order to minimise heterogenicity between the two cohorts, patients in the efgartigimod cohort will be matched at enrollment with a patient in the non-efgartigimod cohort for the following criteria:

- Age (± 5 years)
- Myasthenia Gravis -Activities of Daily Living (MG-ADL) score (0-5, 5-9, and >9) (Wolfe, 1999)
- Region (within EU and within US)

Population

Inclusion Criteria (efgartigimod cohort)

1. Patients diagnosed with gMG who are expected to start commercial efgartigimod at enrolment or who are within their first cycle of efgartigimod at enrolment
2. Have provided appropriate written informed consent

Inclusion Criteria (non-efgartigimod cohort)

1. Patients diagnosed with gMG who have not been exposed to efgartigimod and for whom it is not planned to start treatment with efgartigimod at enrolment
2. Have provided appropriate written informed consent

Exclusion Criteria

None

Data Sources

Data will be extracted from the patient's medical records by site personnel and entered into the electronic data capture (EDC) on an ongoing basis.

Study Size

It is anticipated that 340 patients will be enrolled in each cohort as per the inclusion criteria above.

Data Analysis

Categorical endpoints will be summarised using counts and percent; continuous endpoints will be summarised using mean, standard deviation, median, minimum and maximum values. Statistical analysis will be mainly descriptive in nature using metrics such as incidence proportion, exposure-adjusted incidence rate, confidence intervals, etc. Details of the analysis plan will be specified in the Statistical Analysis Plan (SAP).

Milestones

Milestones are estimated and are dependent upon the date of the Pharmacovigilance Risk Assessment Committee (PRAC) approval of the protocol. Patient enrolment will begin within 6 months of PRAC approval, and the end of data collection will be 10 years after the start of data collection. Interim reports will be submitted in years 4 and 8 after the start of data collection, with study progress reports submitted annually in the intervening years. The final study report is estimated to be submitted 1 year after the end of data collection.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	**Planned date**
Submission of study protocol for Pharmacovigilance Risk Assessment Committee (PRAC) approval	28 November 2022
Approval of study protocol by PRAC	To Be Determined
Registration in European Union Post-Authorisation Study (EU PAS) Register*	At time of PRAC approval of protocol
Start of data collection/first patient enrolled*	Within 6 months after PRAC approval
Last patient enrolled*	5 years after start of enrolment
End of data collection*	10 years after start of data collection
Study progress report*	Year 1 after start of data collection
Study progress report*	Year 2 after start of data collection
Study progress report*	Year 3 after start of data collection
Interim report of study results*	Year 4 after start of data collection
Study progress report*	Year 5 after start of data collection
Study progress report*	Year 6 after start of data collection
Study progress report*	Year 7 after start of data collection
Interim report of study results*	Year 8 after start of data collection
Study progress report*	Year 9 after start of data collection
Study progress report*	Year 10 after start of data collection
Final report of study results*	Estimated 1 year after end of data collection

* timelines may change depending upon Pharmacovigilance Risk Assessment Committee (PRAC) protocol approval date

7. RATIONALE AND BACKGROUND

Myasthenia gravis (MG) is an autoimmune disease caused by immunoglobulin G (IgG) antibodies against postsynaptic antigens at the neuromuscular junction. IgG autoantibodies impair neuromuscular transmission by binding to acetylcholine receptors (AChR), muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4).

From an immunological point of view, approximately 80% of patients with MG have detectable antibodies against AChR. These patients are known as AChR antibody positive.

The estimated prevalence rate for MG is 77.7 per million persons (range 15–179) and the estimated incidence rate is 5.3 per million person-years (range 1.7–21.3) [Carr 2010].

MG occurs in both genders, at all ages, and in all races [Carr 2010, McGrogan 2010]. 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 [Philips 2004, Spillane 2012].

MG can be classified into various subgroups based upon antibody status, age of onset and/or degree of muscle involvement. Ocular symptoms are the most common initial presentation of disease and about two thirds of ocular MG patients progress to generalised MG (gMG) within the first 2-3 years (Anil 2020).

A considerable variation exists in the management of gMG, and treatment is not standardized. Current treatment options include acetylcholinesterase (AChE) inhibitors, and long-term immune therapies with immunosuppressive agents such as corticosteroids, azathioprine, cyclosporine, and mycophenolate, but tacrolimus, methotrexate, and cyclophosphamide are also used. There is no consensus on the choice of immunosuppressive agent. Thymectomy is also a treatment option for patients with generalised MG. Monoclonal antibodies such as eculizumab or rituximab are used for more refractory cases [Vyvgart EPAR].

Short term immune therapies such as plasmapheresis/plasma exchange (PLEX) and intravenous immunoglobulins (IVIg) are typically used for treatment of severe exacerbations of gMG [Vyvgart EPAR].

With the exception of AChE inhibitors, the complement inhibitor eculizumab, and a liquid formulation of azathioprine, which have received regulatory approval in Europe for the treatment of gMG, all other existing therapies are used off-label [Vyvgart EPAR].

In the United States (US), efgartigimod is approved for the indication of gMG in adult patients who are AChR antibody positive and in the EU it is approved as an add-on to standard therapy for the treatment of adult patients who are AChR antibody positive.

The recommended dose of efgartigimod is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Subsequent treatment cycles are administered according to clinical evaluation. The frequency of treatment cycles may vary by patient.

In the EU Risk Management Plan (RMP) for efgartigimod, serious infections, is considered to be an important potential risk. As efgartigimod induces a transient lowering in IgG levels, there is a potential

risk for infections associated with the lowered IgG levels. In the randomized placebo-controlled study of 167 patients ARGX-113-1704, 84 patients with gMG were exposed to efgartigimod and the most frequently observed adverse reactions were upper respiratory infections (10.7% in the efgartigimod patients and 4.8% in the placebo patients) and urinary tract infections (9.5% in the efgartigimod patients and 4.8% in the placebo patients). In the patients who received efgartigimod, these events were ≤ Grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE). Overall, treatment emergent infections were reported in 46.4% of patients treated with efgartigimod and 37.3% of patients treated with placebo. The frequency of infections in the efgartigimod treated patients did not increase with repeated cycles of treatment. There were no serious infections or opportunistic infections in the efgartigimod treated patients. This study will evaluate the occurrence of serious infections in gMG patients treated with efgartigimod in the real world setting under conditions of normal clinical practice compared to gMG patients who are not treated with efgartigimod.

During clinical development of the IV formulation, in the efgartigimod phase 3 placebo-controlled 26 week clinical study, ADAPT, there were 2 reported neoplasm events, 1 (1.2%) in the efgartigimod treatment arm and 1 (1.2%) in the placebo treatment arm.

During the ADAPT open-label extension study, ADAPT+, all patients received efgartigimod. Up until the data analysis cut-off date of 01February2021, for a mean duration of exposure of 363 days, there were 7 (5.0%) patients with a reported neoplasm: 3 (4.1%) in the efgartigimod – efgartigimod group and 4 (6.1%) in the placebo to efgartigimod group. The maximum number of cycles completed as of the 01February2021 database cut-off was 10 cycles. All malignant neoplasms were assessed as not related to efgartigimod by the investigator. The safety data reported in the efgartigimod studies in MG patients and available data for other IgG reducing agents or treatments do not suggest a correlation between IgG reduction and an increased risk of developing cancer. The etiology of cancer is complex. Literature on cancer immune responses does not suggest that a selective reduction of IgG, without lowering other immunoglobulin isotypes such as IgM, or affecting cell-mediated immunity, would generally increase the risk of developing cancers or have an effect on factors that promote carcinogenesis. Efgartigimod lowers IgG levels with no relevant decrease in all the other types of antibodies (IgA, IgD, IgE, IgM) or in albumin levels. Immunosuppressants, which patients with gMG take concomitantly with efgartigimod alfa, can impair the immune response to cancer. Regardless, malignancy has been included as an important potential risk in the EU RMP. Therefore, malignant events will be collected as events of interest throughout the PASS study.

The long-term safety of efgartigimod is considered to be missing information. As of 01 Feb 2021, the maximum duration of treatment with efgartigimod and follow-up was 721 days with a median duration of 451 days, in patients who received efgartigimod intravenously (IV) 10 mg/kg. Overall, the duration of treatment combined with follow-up was at least 6 months for 143 patients, at least 12 months for 118 patients, and at least 18 to <24 months for 33 patients. No clinically significant cumulative toxicities have been identified.

This study will evaluate the overall long-term safety of efgartigimod including the occurrence of serious infections in gMG patients treated with efgartigimod compared to gMG patients not exposed to efgartigimod over a maximum 10 year period under conditions of normal clinical practice.

In the EU RMP, use of efgartigimod in immunocompromised patients, in patients with moderate to severe renal impairment, in patients taking concomitant monoclonal antibodies and in patients receiving

live/attenuated vaccines is considered to be missing information as efgartigimod has not been studied in these patient populations. This post authorisation safety study will include these patient populations according to normal clinical practice. If these patients are enrolled into the study, the safety of efgartigimod will be assessed in these patient populations.

8. RESEARCH QUESTION AND OBJECTIVES

A non-interventional Post-Authorization Safety Study (PASS) in a post-marketing setting comparing cohorts of patients with gMG treated with efgartigimod to those treated with other MG medication for 10 years, in order to estimate incidence rates of serious infection and other safety events.

Primary Objective

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

Exploratory Objectives

- To evaluate the safety of efgartigimod in immunocompromised patients
- To evaluate the safety of efgartigimod administered to patients treated with monoclonal antibodies
- To evaluate the safety of efgartigimod in patients receiving live/attenuated vaccine
- To evaluate the safety of efgartigimod in patients with moderate to severe renal impairment

9. RESEARCH METHODS

9.1 Study Design

This is a non-interventional, prospective, post authorisation safety study.

Patients with gMG who are expected to start treatment with efgartigimod at enrolment or are within their first cycle of efgartigimod at enrolment will be eligible to enrol into the efgartigimod cohort. Patients with gMG who have not been exposed to efgartigimod and for whom it is not planned to start treatment with efgartigimod at enrolment will be eligible to enrol into the non-efgartigimod cohort. It is anticipated that 340 patients will be enrolled in each cohort.

Patients will be treated and observed according to normal clinical practice. Participation in this study does not limit the physicians` clinical decision making as to the most appropriate treatment for the patient during the course of the study. No visits or investigations outside of normal clinical practice will be required. The enrolled patients will be followed prospectively until end of study participation, loss to follow up, consent withdrawal, or death, whichever comes first. All adverse events (AEs) will be collected throughout the duration of the study.

Enrolment of patients will be over a 5-year period. The 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 enrolment period this will allow for a maximum of 10 years of follow-up and a minimum of 5 years. A patient will be considered to be an efgartigimod exposed patient if he/she has received at least one dose of efgartigimod.
In order to minimise heterogenicity between the two cohorts, patients in the efgartigimod cohort will be matched at enrollment with a patient in the non-efgartigimod cohort for the following criteria:

- Age (± 5 years)
- Myasthenia Gravis -Activities of Daily Living (MG-ADL) score (0-5, 5-9, and >9) (Wolfe, 1999)
- Region (within EU and within US)

9.2 Setting

This study will be conducted in the EU, the United Kingdom (UK) and the US at clinics which manage patients with gMG. The number of sites and countries is dependent upon market access and market launch. It is anticipated that in addition to the US, countries will include, but not be limited to, Germany, France, Italy and UK. If feasible, data may also be collected from the Deutsches Myasthenie Register (MyaReg) which is a German MG registry.

All eligible patients from each participating site will be invited to participate in the study in order to minimise selection bias. For eligible patients who do not enrol, the reason for non-enrolment will be collected by the site and maintained in a non-enrolment log. At the end of the enrolment period , aggregate, non-identifiable data from the non-enrolment log will be provided to the sponsor.

9.2.1 Selection of Study Population

Patients with gMG who are expected to start treatment with efgartigimod at enrolment or are within their first cycle of efgartigimod at enrolment will be eligible to enrol into the efgartigimod cohort. Patients with gMG who have not been exposed to efgartigimod and for whom it is not planned to start

treatment with efgartigimod at enrolment will be eligible to enrol into the non-efgartigimod cohort.

Physicians participating in the study will be instructed to invite all patients who meet study eligibility criteria to enrol until the enrolment period is closed.

Inclusion Criteria (efgartigimod cohort)

1. Patients diagnosed with gMG who are expected to start commercial efgartigimod at enrolment or who are within their first cycle of efgartigimod at enrolment
2. Have provided appropriate written informed consent

Inclusion Criteria (non-efgartigimod cohort)

3. Patients diagnosed with gMG who have not been exposed to efgartigimod and for whom it is not planned to start treatment with efgartigimod at enrolment
4. Have provided appropriate written informed consent

Exclusion Criteria

None

9.2.2 Study Procedures

Patient care will follow the normal treatment practices in the respective country and at the specific site. All patients in the study will receive care according to usual clinical practice, and clinical care will not be mandated by the protocol. No additional visits or investigations will be performed beyond usual clinical practice. The choice of ongoing medical treatment for the duration of the study will be made independently by the physician in the regular course of practice and will not be influenced by participation in this study.

Patient enrolment will be over a 5-year period. The 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. Thus, patients enrolled at the beginning of the study may be followed for a maximum period of 10-years.

Efgartigimod or any other treatment will not be provided by or paid for by argenx. Assessments are as per standard of care and will not be provided by or paid for by argenx.

9.2.3 Schedule of Assessments

No mandatory visits, tests, or assessments are required for this study. All visits will be scheduled and conducted according to the clinical site's normal clinical practice. Data will be extracted by the site from the medical record and entered via a secure web-based Electronic Data Capture (EDC) system following clinic visits. Patients will be provided with regular reminders to notify sites of AEs in between clinic visits. AEs should be reported in accordance with the requirements in Section 11.

The Clinical Research Associate (CRA)/monitor will monitor whether data entry is occurring and, if needed, conduct contact calls with the sites to ensure sites are remaining compliant to the requirements of the study and that adequate follow-up and contact is being made by the site with their patients.

9.2.4 Participation Strategies

Every effort will be made to ensure adequate follow-up and ongoing contact with patients.

The consenting patient/legal guardian will complete a patient/legal guardian contact form (including physical address, mailing address, phone number, and e-mail address) and will also be asked to identify one or more secondary contacts such as the patient's primary care physician and one or more other persons. This information will remain at the site and will not be entered into the study database. This information will be used by the site to provide the patient/legal guardian with study update materials and/or current information as it becomes available. This information will also be used to minimise loss to follow-up.

In the event a physician retires, or discontinues participation from the study, a transition plan will be put in place to enable continuing participation by the patient. In the event a patient moves to a new location or chooses to leave their current physician or treatment center, patients/legal guardians will be provided with information as to how to locate a participating physician in their area or how to provide the study information to a new physician who may not be participating yet.

The goal of these strategies is to enhance patient retention, potentially resulting in a lower drop-out rate and improved quality of data. Over the course of a long-term study, patients may become lost to follow-up due to medical or social reasons.

9.2.5 Loss to Follow-up

If there has been no data entered by the site for an enrolled patient within 6 months of the last data entry time point, the study management team will contact the site to confirm the patient's status and whether the patient is still under the Healthcare Professional's (HCP) care. If the patient is still participating in the study, the study management team will remind the site that data must be entered into the EDC at least within 3 months of new data for each enrolled patient and will confirm with the site when the data will be entered. If the patient is no longer being treated by this HCP, the study management team will attempt to identify and obtain any new HCP information and will establish contact with the new HCP to ensure the patient's data continues to be collected in the study. If the patient has not reported any data to the site or the site has not been able to contact the patient/or secondary contacts to obtain patient status for at least 12 months then a patient will be considered lost to follow-up.

9.3 Variables

Electronic case report forms (eCRFs) will be specifically designed for the collection of data from this study. An overview of the categories of study variables (raw data) to be collected for each enrolled patient is summarized in Table 1. There may be some missing data if any assessments are not performed as part of normal clinical practice.

Table 1: Study Variables*

Category	Variables	Baseline	Follow up
Confirmation of eligibility, demographics, study status	• Date of appropriate informed consent for study enrolment • Eligibility assessment • Demographic characteristics	✓	
Past and current medical history	• Relevant medical history including key co-morbidities (including past history of infections)	✓	

Category	Variables	Baseline	Follow up
	• Immune status (immunocompromised or immunocompetent)	✓	✓
gMG Disease	• Date of diagnosis	✓	
	• Criteria used for diagnosis of gMG	✓	
	• Antibody status (AChR, MuSK, anti-LRP4)/date	✓	
	• Clinical classification (Myasthenia Gravis Foundation of America recommendations) (Jaretzki, 2000)	✓	✓
	• Previous myasthenia crises	✓	
	• Thymectomy o Date o Histology	✓	✓
	• MG-ADL questionnaire	✓	✓
Renal function	• Estimated glomerular filtration rate (eGFR)	✓ (Most recent prior to initiation of efgartigimod therapy)	✓
gMG treatments in period from diagnosis prior to enrollment (excluding efgartigimod)	• Drug name, start and stop dates o Acetylcholinesterase inhibitors o Corticosteroids o Other immunosuppressants (specify) o Monoclonal antibodies (specify) o Plasmapheresis/plasma exchange acute o Plasmapheresis/plasma exchange chronic o IVIg therapy acute o IVIg therapy chronic o Other	✓	
gMG treatments at or following enrollment (excluding efgartigimod)	• Drug name, dose, start and stop dates o Acetylcholinesterase inhibitors o Corticosteroids o Other Immunosuppressants (specify) o Monoclonal antibodies (specify) o Plasmapheresis/plasma exchange acute o Plasmapheresis/plasma exchange chronic o IVIg therapy acute o IVIg therapy chronic o Other	✓	✓

Category	Variables	Baseline	Follow up
Efgartigimod treatment	• Date of administration • Reason for interruption during cycle of treatment • Reason for permanent discontinuation whilst on study	✓	✓
Other comedications at or following enrollment for conditions other than gMG	• Drug name, start and stop dates • Indication	✓	✓

Live/attenuated vaccinations 2 months prior to enrollment to 2 months after last Vyvgart dose	• Live/attenuated vaccine
	  ○ Vaccine
	  ○ Date
		✓	✓

Adverse Events (AEs)/Serious Adverse Events (SAEs)	• AEs, SAEs		✓
Events of interest	See Table 2		✓

*All variables will be collected ONLY if available as part of routine clinical practice

A patient will be considered to be an efgartigimod exposed patient if he/she has received at least one dose of efgartigimod.

Additionally, taking into account the variable follow up time and time interval between cycles, the following will be measured for efgartigimod:

- Number of administrations per year
- Total duration of the exposure
- Total number of administrations

The exposure time window of efgartigimod is 56 days +/-3 days after the last dose.
Events of interest in this study will be pre-specified as per Table 2 below.

Table 2: Pre-specified events of interest

Event of interest	Definition	Measurement
Serious infection	Any serious adverse event coded to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of Infection and Infestation. See Section 11 for definition of Serious.	Proportion of patients who report serious infections during the course of the study in the efgartigimod treated cohort compared to the non-efgartigimod cohort. Incidence rate of serious infections per patient-years exposed in the efgartigimod treated cohort compared to the non-efgartigimod cohort.
Malignancy	Any adverse event (AE) within the Standardised MedDRA Query (SMQ) *Malignancies (Narrow).*	Proportion of patients who report events of malignancy during the course of the study in the efgartigimod treated cohort compared to the non-efgartigimod cohort. Incidence rate of events of malignancy per patient-years exposed in the efgartigimod treated cohort compared to the non-efgartigimod cohort.
Adverse event (AE)	Any untoward medical occurrence in a patient administered a pharmaceutical product or device and that does not necessarily have a causal relationship between the product and the event. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding) or symptom temporally associated with a medicinal product, whether or not related to the medicinal product.	Proportion of patients who report AEs during the course of the study in the efgartigimod treated cohort compared to the non-efgartigimod cohort. Incidence rate of AEs per patient-years exposed in the efgartigimod treated cohort compared to the non-efgartigimod cohort.
Serious adverse event (SAE)	As per definition in Section 11.	Proportion of patients who report SAEs during the course of the study in the efgartigimod treated cohort compared to the non-efgartigimod cohort. Incidence rate of SAEs per patient-years exposed in the efgartigimod treated cohort compared to the non-efgartigimod cohort.

AEs (serious and non-serious) in immunocompromised patients	Immunocompromised definition (moderate or severe) based upon Centre for Disease Prevention (CDC) People Who Are Immunocompromised | CDC.	Proportion of AEs/SAEs reported in immunocompromised patients and immunocompetent patients in the efgartigimod cohort. Incidence rate of AEs/SAEs per patient-years exposed in immunocompromised patients and immunocompetent patients in the efgartigimod cohort.
AEs (serious and non-serious) in patients treated with monoclonal antibodies	Patients receiving monoclonal antibodies other than FcRn (e.g., adalimumab, tocilizumab, ixekizumab, rituximab) within 6 months prior to efgartigimod administration.	Proportion of AEs/SAEs reported in patients treated with monoclonal antibodies vs patients not treated with monoclonal antibodies in the efgartigimod cohort. Incidence rateof AEs/SAEs per patient-years exposed in patients treated with monoclonal antibodies vs patients not treated with monoclonal antibodies in the efgartigimod cohort.
AEs (serious and non-serious) in patients treated with live attenuated vaccine	Patients receiving live/attenuated vaccine (e.g., live-attenuated flu vaccine, measles, mumps and rubella, polio, smallpox, chickenpox, yellow fever, Japanese encephalitis, shingles, rotavirus) in the period of 4 weeks prior to or 2 weeks after efgartigimod administration.	Proportion of AEs/SAEs reported in patients who have received live/attenuated vaccine vs patients who have not received live/attenuated vaccine in the efgartigimod cohort. Incidence rateof AEs/SAEs per patient-years exposed in patients who have received live/attenuated vaccine vs patients who have received live/attenuated vaccine in the efgartigimod cohort.
AEs (serious and non-serious) in patients with moderate to severe renal impairment	Moderate renal impairment: eGFR 30-59 mL/min/1.73 m^2 Severe renal impairment: eGFR < 30 mL/min/1.73 m^2	Proportion of AEs/SAEs reported in patients with moderate renal impairment vs patients who have normal renal function in the efgartigimod cohort. Incidence rateof AEs/SAEs per patient-years exposed in patients with moderate renal impairment vs patients who have normal renal function in the efgartigimod cohort. Proportion of AEs/SAEs reported in patients with severe renal impairment vs patients who have normal renal function in the efgartigimod cohort.

		Incidence rate of AEs/SAEs per patient-years exposed in patients with severe renal impairment vs patients who have normal renal function in the efgartigimod cohort.

9.4 Data Sources

Data will be extracted from the patient's medical records by site personnel. Once written informed consent has been obtained, study site personnel will complete the data collection for each patient. Follow-up data for patient visits will be recorded in the patient chart in accordance with the clinical site's standard of care or clinical judgment. All data will be extracted from medical records and entered into the EDC on an ongoing basis.

The technologies used for this study (e.g., EDC) will be compliant with Title 21 Code of Federal Regulations (CFR) Part 11, EudraLex Annex 11, the General Data Protection Regulation (GDPR), and local data privacy requirements, and will be evaluated on an ongoing basis throughout the duration of the study to ensure upgrades are made when necessary.

If feasible, data may also be collected from the MyaReg.

9.5 Study Size

A sample size of 340 patients in each of the two cohorts is proposed (680 patients in total). Recruitment will be over a 5 year period and patients will be followed for 5 years from the time the last patient is enrolled. Thus maximum follow up will be 10 years.

The estimated prevalence rate for MG is 77.7 per million persons (range 15-179) and the estimated incidence rate is 5.3 per million person-years (range 1.7–21.3).

Myasthenia gravis occurs in both genders, at all ages, and in all races. However, for sample size calculations it is proposed to use the reported serious infection prevalence in MG patients.

Statistical analysis in this study will be descriptive and exploratory, and not aimed to confirm or reject predefined hypotheses.

Sample size calculation is driven by the precision of the estimated incidence proportion of serious infection assuming similar incidence proportion to the background.

In a population-based cohort study of 3823 MG patients (Kassardjian 2020) followed for a mean of 5.4 (Standard Deviation [SD]=3.8) years, 33.4% of patients experienced a serious infection which included both emergency department visits and hospitalisation with primary diagnosis of infection. In a retrospective chart review of 358 MG patients (Prior 2018) over a 10-year period, 19% of patients experienced infection. In the argenx-sponsored ADAPT+ study final analysis with 145 efgartigimod patients followed for a mean of 1.7 years (SD=0.7), 6.2% of patients experienced at least one serious infection (serious adverse event with SOC term "Infections and Infestations").

For the current study, serious infection incidence proportion is assumed to be 20% considering varied follow-up time and definitions of serious infection in the literature and argenx-sponsored trial.

The sample size needed to achieve a 5% precision (half-width) is presented in Table 3 below with the following assumptions:

- An incidence proportion of 20% for serious infections among patients receiving efgartigimod.
- Two-sided 95% exact binomial confidence limits based on the Clopper-Pearson method.

Table 3: Precision calculations for different incidence proportions

Number of Patients	Expected Incidence Proportion	Expected Number of Patients with Event*	Lower Limit of 95% Confidence Interval (CI) of Observed Incidence Proportion	Upper Limit of 95% CI of Observed Incidence Proportion
215	15%	32	10.5%	20.5%
245	18%	44	13.4%	23.4%
264	**20%**	**52**	**15.3%**	**25.3%**
282	22%	62	17.3%	27.3%
306	25%	76	20.2%	30.2%

*Rounded down to the nearest whole number

A sample size of 270 is recommended to achieve 5% precision (half width). Considering a drop-out rate of 20%, 340 patients in each arm are needed.

To provide further justification about detecting potential increased risk given the calculated sample size above, the power calculation is presented in Table 4 below assuming 20% incidence proportion in the comparator arm and varied increased incidence proportions in the treatment arm with two-sided 0.05 alpha level using normal approximation. With 270 patients who complete the study in each arm, there is 84% power to detect an 11% risk increase.

Table 4: Power calculations to detect potential increased risk

Risk Increase	Expected Proportion for Comparator Arm	Expected Proportion for Treatment Arm	Completion Status	Sample Size in Each Arm	Power
9%	20%	29%	Completers Only	270	69%
10%	20%	30%	Completers Only	270	77%
11%	**20%**	**31%**	**Completers Only**	**270**	**84%**
12%	20%	32%	Completers Only	270	89%
9%	20%	29%	Completers + 30 Drop-outs	300	73%
10%	**20%**	**30%**	**Completers + 30 Drop-outs**	**300**	**81%**
11%	20%	31%	Completers + 30 Drop-outs	300	88%
12%	20%	32%	Completers + 30 Drop-outs	300	92%
9%	20%	29%	Completers + 60 Drop-outs	330	77%
10%	**20%**	**30%**	**Completers + 60 Drop-outs**	**330**	**85%**
11%	20%	31%	Completers + 60 Drop-outs	330	90%
12%	20%	32%	Completers + 60 Drop-outs	330	94%

Owing to the study design with 5-year enrollment and 5-year follow-up, patients will be followed between 5 to 10 years. A discontinued patient enrolled early and discontinued not soon after enrollment will be included in the analysis with possible long follow-up time. For example, the first enrolled patient discontinued at year 6 will have longer follow-up time than the last enrolled patient who has only 5-year

follow-up at maximum. Therefore, early discontinued patient may still contribute high-quality information with acceptable follow-up time to the analysis. Additional power analysis is provided in Table 4 assuming 270 completers +30 and +60 early discontinued patients being included in the analysis, and there is >80% power to detect a 10% risk increase.

9.6 Data Management

Data will be collected and entered in eCRFs within a validated EDC system that is compliant with all regulatory requirements. The web-based EDC system aims to serve as a transparent tool to collect and manage data and track study progress at the patient level. Data in the EDC system are kept in a central location.

Site staff will be trained by the sponsor representative or delegate to perform the chart abstraction, including data entry and how to retrieve and respond to data queries in the EDC system. It is assumed that participating sites will be able to complete data entry into the eCRFs via the EDC system.

The sponsor representative or delegate will supervise and perform site management and monitoring as described in the study-specific monitoring plan. All participating sites will only have access to view and enter the data for their own patients. Only data required by the protocol for the purposes of the study should be collected.

The patient's routine clinical care treating physician has the ultimate responsibility for the collection and reporting of all clinical, safety, and treatment data entered into the eCRF and ensuring any other data collection forms (source documents) are accurate, authentic/original, attributable, complete, consistent, legible, timely, enduring, and available when required. The eCRFs must be electronically signed by the treating physician or by an authorized staff member to attest that the data contained on the eCRFs are true, complete, accurate and verifiable to source records. The argenx representative or delegate will inform sites when it is time for eCRF sign-off to occur.

Each site will maintain a Patient Identification list linking the patient to the Patient Identification within the EDC. Only the treating physician and/or authorised personnel will be able to identify the patient based on the Patient Identification list, which will be held only at the site.

The Investigator must permit study-related monitoring, audits, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review, and regulatory agency inspections and provide direct access to source data documents.

9.7 Data Analysis

The Full Population will be all patients enrolled.

The Safety Population will include all patients enrolled who have taken at least one dose of efgartigimod for the efgartigimod cohort and all patients enrolled into the non-efgartigimod cohort. All analysis will be based on the Safety Population.

Unless otherwise specified, categorical endpoints will be summarised using counts and percent; continuous endpoints will be summarised using mean, standard deviation, median, minimum and maximum values. Statistical analysis will be mainly descriptive in nature using metrics such as

incidence proportion, exposure-adjusted incidence rate, confidence intervals, etc. Details of the analysis plan will be specified in the Statistical Analysis Plan (SAP).

Primary objective

Descriptive statistics will be used to summarise the long-term safety of efgartigimod, including the occurrence of events of serious infections, in gMG patients treated with efgartigimod compared to gMG patients not exposed to efgartigimod. The number and percentage of patients with AEs/SAEs will be presented. The rate per person-year exposure with a 95% CI will be constructed using asymptomatic normal approximation.

Although no formal hypothesis will be tested in the study, statistical models will be used to test the difference of incidence between treatment cohorts (efgartigimod vs. comparator). Two base models which are widely used to model incidence proportion and incidence rate adjusted by potential confounders will be used:

1. To model incidence proportions, a logistic regression model will be used including patients with event vs. patients without event as the response variable and treatment group and country as covariates.
2. To account for varied follow-up time, a Cox regression model will be used with time to the first occurrence of event for each patient as the response variable, treatment group and country as covariates .

Countries with small sample sizes will be combined with other countries based on the geographic locations. Other covariates may be added to the above base models as described below.

Balance of the baseline measures, including age, MG-ADL score and region matched at enrollment and other demographic and disease characteristics, will be assessed. The imbalanced measures which are considered to be potential confounders based on clinical judgement will be added to the above base models as covariates. If a large number of imbalanced potential confounders are identified after the enrollment is complete, a propensity score method will be applied instead. More details will be given in the SAP.

Subgroup analyses will be performed using descriptive statistics on the subset of patients who remained on efgartigimod throughout the duration of the PASS. In addition, subgroup analyses of treatment cycle per year or administration per year (four administrations in one cycle if not interrupted), subgroup analyses of time since the last administration of efgartigimod prior to the event occurrence in intervals of every 4 weeks will be performed, and subgroup analysis of patients using efgartigimod as add-on or single treatment will be performed if sample size allows. Since one patient may have multiple same events with different time to the last administration, one patient may be assigned to multiple time intervals.

Events of Interest

Statistical analysis of malignancy and other events of interest will follow the same method as those for serious infections

Exploratory objectives

Descriptive statistics will be used to summarise the long-term safety of efgartigimod for specific subgroups. The number and percentage of patients with AEs/SAEs will be presented. The rate per person-year exposure with a 95% CI will be constructed using asymptomatic normal approximation. This will be done for the following subgroups:

- immunocompromised patients and immunocompetent patients.
- patients treated with monoclonal antibodies and patients not treated with monoclonal antibodies.
- patients who have received live/attenuated vaccine and patients who have not received live/attenuated vaccine.
- patients with moderate to severe renal impairment and patients with normal renal function or mild renal impairment.

Missing values

No imputation will be applied to occurrence of serious infection, malignancy or other safety events.

For baseline measures which are potential confounders, descriptive analysis and balance assessment will be based on observed cases. The missing values of imbalanced potential confounders used as covariates in the statistical modelling will be imputed using the mean from non-missing values for continuous variables or a missing category for categorical variables.

Coding

Concomitant medications will be coded according to the World Health Organization (WHO) -Drug Dictionary. Patients with concomitant medications will be summarised by Anatomical Therapeutic Chemical (ATC) class and Preferred Term (PT) using descriptive statistics described above using the Full Population.

All AEs will be coded by PT and associated primary SOC using the MedDRA dictionary. The electronic case report AE form collects the verbatim term for MedDRA coding. AEs will be presented by SOC and PT using descriptive statistics described above using the Safety Population.

Details of the data analysis will be outlined in the SAP.

Representativeness of the study population

The characteristics of the enrolled population will be analysed after study enrolment is completed; baseline characteristics will be compared to the characteristics of the gMG population from real world studies in the literature to identify any potential differences. Details on this comparison will be included in the SAP.

9.8 Quality Control

argenx has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and applicable regulatory guidelines. As such, in order to fulfil these obligations and to maintain current knowledge of the study progress, the Contract Research Organisation (CRO) monitors or representatives will regularly contact the clinical sites either by telephone or in-person visits. Regular inspection of the study data will be conducted in order to assess patient enrolment, compliance with protocol procedures, and completeness and accuracy of data entered on the study. Verification of eCRF data against original source documents, and occurrence of SAEs may be done at selected sites and/or for selected patients.

9.8.1 Monitoring

Monitoring details describing strategy, including definition of trial critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plans.

9.8.2 Inspection and Auditing Procedures

The purpose of an audit or inspection is to assess whether ethics, regulatory, and quality requirements are fulfilled.

argenx or its representative may conduct audits at the clinical sites including, but not limited to, presence of required documents, the informed consent process, and comparison of case report forms (CRFs) with source documents. All medical records and source data must be available for audit. The site agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the site during or after the study. Site personnel should contact argenx immediately if this occurs and should cooperate fully with regulatory authorities or other audits conducted in a reasonable manner.

9.8.3 Source Document Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records, computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study will be maintained by the site and made available for inspection by authorized persons. The original signed informed consent form (ICF) for each patient shall be filed with records kept by the site and a copy shall be given to the patient.

9.8.4 Record Maintenance

Records will be retained in accordance with the applicable local regulations. All essential study documents, including records of patients, source documents, signed ICFs, and eCRFs, must be kept by the Investigator for at least 10 years from study termination/completion or until instructed in writing by argenx that records may be destroyed or forwarded to argenx. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data

generated during this study. Such documentation is subject to audit by argenx or its representatives, and inspection by regulatory authorities.

If an Investigator moves, withdraws from the study, or retires, the responsibility for maintaining the records must be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed to by argenx.

9.9 Limitations of the Research Methods

Patient-selection bias is a consideration, as motivation to consent to join the study can vary between patients for different reasons. Also, if prescribers and patients are not willing to participate, selection bias may occur, resulting in limited generalisability of the results. All eligible patients at each site will be invited to participate minimising the selection bias. Sites will maintain a log of eligible patients who are not participating in the study and the reasons for non-participation. This data will be provided in aggregate and anonymously to argenx for evaluation of differences between participants and non-participants.

Furthermore, the characteristics of the enrolled population will be analysed after study enrolment is completed; baseline characteristics will be compared to the characteristics of the MG population from real world studies in the literature to identify any potential differences. Information on this comparison will be added to the SAP.

This study is observational in nature and will gather data on standard clinical practice without the constraints of a clinical trial setting. Consequently, there are no protocol mandated procedures, and the collection of data will be limited to what is undertaken in normal clinical practice. This may result in missing data if a procedure has not been performed. This risk has been minimised by ensuring variables are limited to meet the study objectives and are aligned, as far as is possible, to the expected normal clinical practice. The handling of missing data will be specified in the SAP. It would be considered whether a complete records' analysis would be valid, or whether multiple imputation or an alternative approach would likely offer benefits as well as consider a sensitivity analysis regarding the missingness mechanism. The results will be reported, including a description of the missing data, details on how the missing data were addressed, and the results from all analyses.

The study design includes an efgartigimod cohort and a comparator cohort of non-efgartigimod treated patients. The duration of the study is a maximum of 10 years (5 years of enrolment and 5 years of follow up). Over this time period, standard of care for the treatment of gMG is likely to evolve with the introduction of new medicinal products such as ultomiris (recently approved) and rozanolixizumab and zilucoplan (currently under review with an approval expected by end of 2023) and the potential for patients to switch treatments during this time. The comparator group, and indeed the efgartigimod group, will therefore be heterogenous in terms of treatments, thus limiting the interpretability of the results.

Furthermore, in countries where efgartigimod is marketed, it is likely that the efgartigimod cohort and the comparator cohort will differ in terms of disease severity with the more severe patients receiving efgartigimod. Thus, there will be an inherent selection bias. This could be solved by recruiting the comparator patients from countries where efgartigimod is not marketed. However, this will introduce further biases in terms of differing standards of care.

9.10 Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PATIENTS

Prior to any data collection under this protocol, a written ICF must be signed by the patient/legal guardian in accordance with local practice and regulations. Information about the study will be explained to the patient/legal guardian where appropriate including advice that the patient can withdraw from the study at any time. A copy of the ICF, signed and dated by the patient/legal guardian, must be given to the patient/legal guardian. Confirmation of a patient/legal guardian's informed consent must be documented in the patient's medical records prior to any data collection under this protocol. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and argenx.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

Documents that are not for submission to the study (e.g., ICF), will be maintained by the site in strict confidence, except to the extent necessary to allow monitoring by argenx or its representative, and auditing by argenx and regulatory authorities. No documents identifying patients by name will leave the clinical site and patient identity will remain confidential in all publications related to the study.

Prior to the collection of any study related data, IRB/IEC approval of the protocol, informed consent, and all patient enrolment materials will be obtained in each country and for each site, as applicable. The study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, applicable privacy laws, and local regulations for each participating site.

This study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, the Guide on Methodological Standards in Pharmacoepidemiology issued by The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), Guideline on Good Pharmacovigilance Practices Module VIII Post Authorisation Safety Studies and the Declaration of Taipei.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

argenx or its designee will follow all applicable local and national regulatory requirements related to safety reporting. Study investigators must also comply with the applicable regulatory requirements for reporting of serious events to the IRB/IEC/Ethics Committees/Regulatory authorities (if applicable) responsible for reviewing information from the study at their site. All serious and non-serious AEs, pregnancies, and special situations will be collected. Once the treating physician becomes aware of AEs and SAEs should be reported to the sponsor on an AE/SAE Report Form as soon as possible, but no later than within 24 hours for Serious AEs and 7 calendar days for non-serious AEs, pregnancies and special situations of the site becoming aware of the event, along with an assessment of severity and causality. argenx will receive, process and submit these reports to the relevant health authorities as appropriate.

All AEs will be collected from signing the informed consent until the end of study participation, loss to follow up, consent withdrawal or death. After the initial AE/SAE report, the treating physician should make every effort to follow each participant until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. The action taken for AEs occurring in the efgartigimod cohort should be provided by the treating physician.

11.1 Definitions

AE: Any untoward medical occurrence in a patient administered a pharmaceutical product or device and that does not necessarily have a causal relationship between the product and the event. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding) or symptom temporally associated with a medicinal product, whether or not related to the medicinal product.

SAE: Any untoward medical occurrence which:

- Results in death.
- Is life-threatening: The term life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongs hospitalization: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event will be considered serious. When in doubt as to whether hospitalization occurred or was necessary, the AE is considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from screening will not be collected as an AE.
- Results in persistent or permanent disability or incapacitation: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include events of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that can interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Results in a congenital anomaly or birth defect.
- Other situations: Any important medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above, should also be reported as an SAE.

Special situations:

- Off-label use: situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
- Overdose: administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
- Misuse of a medicinal product: situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse of a medicinal product: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Drug exposure during pregnancy and/or breast-feeding.
- Lack of efficacy/effectiveness.
- Medication errors: are broadly defined as any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not.
- Occupational exposure: this refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation.
- Suspected Drug-drug interaction.
- (Suspicion of) Transmission of infectious agent.

Causality Assessment (relationship to efgartigimod):

The treating physician is obligated to assess the relationship between efgartigimod and each occurrence of each AE/SAE as related or not related. The treating physician will use clinical judgment to determine whether there is reasonable possibility that efgartigimod caused the AE. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to efgartigimod administration, will be considered and investigated

Related means that the AE cannot be explained by the participant's medical condition, other therapies, or an accident. The temporal relationship between the AE and efgartigimod administration is compelling and/or follows a known or suspected response pattern concerning that efgartigimod.

Not related means that the AE can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident. No plausible temporal or biologic relationship exists between the efgartigimod and the AE.

There could be situations in which an AE/SAE has occurred and the treating physician has minimal information to include in the initial report. However, it is very important that the treating physician always assess causality for every event before the initial transmission of the AE/SAE data. The treating physician could change his/her opinion of causality in light of follow-up information and send an AE/SAE follow-up report with the updated causality assessment.

Severity

The severity of AEs and SAEs will be graded as mentioned below:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (e.g., preparing meals, shopping for groceries or clothes, using the telephone)
- **Grade 3:** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- **Grade 4:** Life-threatening consequences or urgent intervention indicated
- **Grade 5:** Death related to AE

NOTE: An AE that is assessed as severe may not necessarily meet the criteria for an SAE. Severe is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe. Grade 4 and 5 AEs are always assessed as serious (i.e., SAE).

Outcome assessment

One of five outcomes listed below must be recorded:

- **Recovered/Resolved** – The event has stopped. The stop date of the event must be recorded.
- **Recovering/Resolving** – The subject is clearly recovering from an event. The event is not yet completely resolved.
- **Not Recovered/Not Resolved** – The event is still ongoing. (Could include stable and commensurate with ongoing disease processes).
- **Recovered/Resolved with sequelae** – The event has reached a state where no further changes are expected, and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.
  The stop date of the event must be recorded. In case of an SAE, the sequelae should be specified.
- **Fatal** – The subject has died as a consequent of the event.
- **Unknown** – Unknown to investigator, e.g., subject lost to follow up.

Action taken:

- **Withdrawal -** the permanent discontinuation of efgartigimod when the participant stops receiving efgartigimod before the end of the study and does not resume receiving efgartigimod.

- **Interruption**- the temporary discontinuation of efgartigimod when the participant discontinues receiving efgartigimod before the end of the study and resumes once the cause for the discontinuation has been resolved

Pregnancy

If pregnancy is reported, the treating physician will record the pregnancy information on the appropriate form and submit it to the sponsor within 7 calendar days of learning of the pregnancy in the female participant or the female partner of the male participant. The participant and pregnant female partner, if consented, will be followed to determine the outcome of the pregnancy. The treating physician will collect follow-up information on the participant/pregnant female partner and the neonate and forward it to the sponsor. While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported accordingly.

Contact details to report AEs/SAEs and Pregnancies to the sponsor:
•Email: safety@argenx.com

•Fax: +1-833-874-7325

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be summarised in annual reports and a final study report that, after review and approval by argenx, will be communicated to the European Medicines Agency and other national competent authorities if required, within the agreed timeframe as shown in Section 6. The protocol and an abstract of results will be posted as per guidelines for studies meeting the criteria for PASS in the EU PAS Register. The study will be registered in the EU PAS register prior to enrolment of the first patient.

The results of this study can be published or presented at scientific meetings. If so, the investigator agrees to submit all manuscripts or abstracts to argenx before submission. This allows argenx to protect proprietary information and provide comments. argenx will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, argenx will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and consistent with the International Committee of Medical Journal Editors authorship requirements.

13. REFERENCES

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14. INVESTIGATOR PROTOCOL SIGNATURE PAGE

Protocol Title: A non-interventional, post-authorisation safety study of patients treated with efgartigimod alfa

Protocol Number:

Protocol Version: Version 1.0

Date: 14 December 2023

I have reviewed the content of this protocol and agree to participate in the study and adhere to all regulations that govern the conduct of this study.

Site Principal Investigator Name (printed):

Site Address:

Site Principal Investigator's Signature	Signature Date

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the Investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A non-interventional (NIS), post-authorisation safety study (PASS) of patients with generalised myasthenia gravis.

EU PAS Register® number: To be determined
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Study is observational and does not test a hypothesis

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2; 9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1
	4.2.2 Age and sex	☒	☐	☐	9.3
	4.2.3 Country of origin	☒	☐	☐	9.3
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☒	☐	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Details will be provided in the Statistical Analysis Plan

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.5

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	11
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Detail will be provided in the SAP

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.4; 9.8.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias?	☒ ☐	☐ ☒	☐ ☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol:	
Date:	
Signature:	

Signature Page for VV-CLIN-002108 v4.0

Approval	[redacted] 09-Jan-2024 [redacted]
Approval	[redacted] 09-Jan-2024 [redacted]
Approval	[redacted] 10-Jan-2024 [redacted]

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