PASS Protocol	
Drug Substance	Efgartigimod alfa
Study Code	ARGX-113-PASS-2316
Edition Number	
Date	24 July 2025

Post-Authorisation Safety Study (PASS) to Evaluate the Risk of Malignancies in Patients with Myasthenia Gravis (MG) Treated with Efgartigimod

Protocol version identifier	Final v1.0
Date of last version of protocol	11 July 2025
EU PAS Registration Number:	N/A
Active Substance:	efgartigimod alfa
Medicinal Product:	VYVGART® (concentrate for solution for infusion; and solution for injection)
Product Reference:	H005849
Procedure Number:	EMEA/H/C/005849/MEA/007.3
Marketing Authorisation Holder(s):	argenx BV
Joint PASS:	No
Research Question and Objectives:	***Primary objective*** To evaluate the long-term risk of malignancies overall and by type in patients with myasthenia gravis (MG) treated with efgartigimod compared to MG patients on any other MG therapy and who do not have malignancy history in the lookback period. ***Secondary objectives*** In MG patients treated with efgartigimod compared to MG patients on any other MG therapy:

	• To evaluate the long-term risk of malignancies overall and by type in MG patients with malignancy history in the lookback period
	• To evaluate the long-term risk of malignancies by duration of efgartigimod exposure
	• To evaluate the long-term risk of malignancies in subpopulations with increased risk of malignancy:
	  ○ Elderly – age 65 years and older
	  ○ Chronic use (i.e., ≥1 year) of corticosteroids
	
	Exploratory objectives
	• To evaluate the long-term risk of malignancies in MG patients treated with other neonatal fragment crystallizable receptor (FcRn) antagonists
	• To assess time to the first occurrence of malignancy overall and specified by type of malignancy
	
	In MG patients treated with efgartigimod and MG patients on any other MG therapy:
	• To assess healthcare resource utilization including:
	  ○ The number of hospitalisations (including MG related)
	  ○ The number of emergency room (ER) visits
	  ○ The number of MG exacerbations and MG crises if available

Countries of Study:	United Kingdom (UK), France, and United States (US)
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Marketing authorisation holder(s)

Marketing authorisation holder(s) (MAH)	argenx BV
MAH contact person	[redacted]

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2 List of abbreviations

Abbreviation	Meaning
AChE	Acetylcholinesterase
AChR	Acetylcholine Receptors
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutical Chemical
BMI	Body Mass Index
CCAM	Common Classification of Medical Procedures
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CIP	Code Identifiant de Présentation (French national identification code of each presentation of a pharmaceutical product)
CPRD	Clinical Practice Research Datalink
CPT	Current Procedural Terminology
CRO	Contract Research Organisation
EHR	Electronic Health Record
EMA	European Medicines Agency
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	Emergency Room
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
FcRn	neonatal Fragment crystallizable Receptor
gMG	generalized Myasthenia Gravis
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HAS	Haute Autorité de Santé
HCPCS	Healthcare Common Procedure Coding System
HES	Hospital Episode Statistics
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INCa	Institut National du Cancer (French National Cancer Institute)
IR	Incidence Rate
IRB	Institutional Review Board
IRR	Incidence Rate Ratio

Abbreviation	Meaning
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
IVIg	Intravenous Immunoglobulins
LRP4	Lipoprotein Receptor-related Protein 4
MAH	Market Authorisation Holder
MG	Myasthenia Gravis
MuSK	Muscle-Specific tyrosine Kinase
NDC	National Drug Code
NIHR	National Institute for Health Research
OPCS	Office of Population Censuses and Survey
PASS	Post-Authorisation Safety Study
PLEX	Plasmapheresis/Plasma Exchange
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person-Year
QMS	Quality Management Software
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SNDS	Système National Des Données De Santé (French national health data system)
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie (French national health insurance information system)
SNOMED	Systematized Medical Nomenclature for Medicine
SOP	Standard Operating Procedure
UCD	Unité Commune de Dispensation
UK	United Kingdom
US	United States

3 Responsible parties

This study protocol has been reviewed and approved by the undersigned persons. It is confirmed that the information and guidance given in this protocol complies with scientific principles, European Medicines Agency (EMA) post-authorisation safety study (PASS) guidance document, (1) the applicable guidelines (Good Pharmacovigilance Practices [GVP] Module VIII) (EMA 2017), (2) the Declaration of Helsinki in the latest relevant version and the applicable legal and regulatory requirements (World Medical Association [WMA] 1964).

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4 Abstract

Title	Post-Authorisation Safety Study (PASS) to Evaluate the Risk of Malignancies in Patients with Myasthenia Gravis (MG) Treated with Efgartigimod Based on Protocol Version 1.0 [24 July 2025]
Rationale and background	Efgartigimod alfa is an immunomodulator, a first-in-class biologic indicated for the treatment of patients with generalized MG (gMG) in various jurisdictions including the United States (US), Japan, United Kingdom (UK), and the European Union (EU). In the US, efgartigimod is approved for the indication of gMG in adult patients who are acetylcholine receptor (AChR) antibody positive and in the EU and UK it is approved as an add-on to standard therapy for the treatment of adult patients who are AChR antibody positive. In the EU Risk Management Plan (RMP), malignancy is considered an Important Potential Risk. As part of the additional pharmacovigilance activities agreed to at the time of marketing authorisation of efgartigimod in the Europe, argenx is undertaking a cohort study in several healthcare databases (France, UK and US) to evaluate if there is an increased risk of malignancies with exposure to efgartigimod.

Research question and objectives	This study aims to assess the risk of malignancy in patients with MG exposed to at least one (1) dose of efgartigimod compared to MG patients with no record of exposure to efgartigimod by analysing data from two claims databases (US Optum Market Clarity, and France le Système National des Données de Santé [SNDS], and one electronic medical record [EMR] database UK Clinical Practice Research Datalink [CPRD]).
	
	Primary objective
	
	To evaluate the long-term risk of malignancies overall and by type in patients with MG treated with efgartigimod compared to MG patients on any other MG therapy and who do not have malignancy history in the lookback period, in a real-world setting.
	
	Secondary objectives
	
	In MG patients treated with efgartigimod compared to MG patients on any other MG therapy:
	• To evaluate the long-term risk of malignancies overall and by type in MG patients with malignancy history in the lookback period
	• To evaluate the long-term risk of malignancies by duration of efgartigimod exposure
	• To evaluate the long-term risk of malignancies in subpopulations with increased risk of malignancy:
	  ○ Elderly – age 65 years and older
	  ○ Chronic use (i.e., ≥1 year) of corticosteroids
	
	Exploratory objectives
	• To evaluate the long-term risk of malignancies in MG patients treated with other neonatal fragment crystallizable receptor (FcRn) antagonists
	• To assess time to the first occurrence of malignancy overall and specified by type of malignancy in MG patients treated with efgartigimod and MG patients on any other MG therapy
	• To assess healthcare resource utilization including:

	○ The number of hospitalisations (including MG-related) ○ The number of emergency room (ER) visits ○ The number of MG exacerbations and MG crises if available
Study design	This multinational, longitudinal database cohort study will identify patients who are newly treated with efgartigimod and who have a diagnostic code for MG (efgartigimod cohort). A patient will be considered an efgartigimod exposed patient if he/she has received at least one (1) dose of efgartigimod. For each patient entering the efgartigimod cohort, the date of the first efgartigimod exposure in the database (either through an intravenous [IV] infusion or subcutaneous [SC] injection) will be their index date for the study. The reference cohort will consist of patients with a diagnosis code for MG without efgartigimod exposure but are on any other therapy for the treatment of MG during the study period. The index date for each patient in the reference cohort will be assigned as the same index date as the corresponding matched efgartigimod patient. Within each database, efgartigimod initiators will be matched 2:1 (reference: efgartigimod) by (1) age at index date (+/- 5 years), (2) sex, (3) Charlson Comorbidity Index (CCI) and (4) duration of prior use of other MG treatment as matching variables prior to and including the index date or within 6 months of the index date. Patient accrual into the study will begin following the launch of efgartigimod (differs by country), allowing for a lag between actual exposure dates and appearance of the medication record/procedure in each of the data sources, and will continue for up to 5 years via database refreshes (assumed to be annual). To achieve a desired sample size across all databases, a minimum of approximately 1,358 patients will be needed in the efgartigimod cohort and 2,716 matched patients in the reference cohort. Patients will be followed from study entry to at least 10 years following inclusion in the study. If efgartigimod uptake is slower than expected, patient accrual may need to be extended to reach the required sample size. Analyses will be first conducted independently within each data source to maintain the strengths and unique data features of the individual data sources, and a meta-analysis that combines summary results from each country will then be conducted for the final study report after the country-specific analyses are completed.
Population	The observational study will identify two (2) cohorts from each selected database: • Efgartigimod Cohort: Patients with an MG diagnosis and who have initiated efgartigimod • Reference Cohort: Patients with an MG diagnosis and who have not initiated efgartigimod but are on any other therapy for the treatment of MG. Immunoglobulins and plasmapheresis are not considered here, as they are usually used for acute management of MG crisis. All patients in the study will have a minimum of 3 years of continuous coverage in the database prior to their cohort entry date. The 3-year minimum prior to index date (lookback period) is required to reliably characterise a patient based on relevant malignancy history, as well as use of other medications prior to initiation of the index medication. The lookback period is also required to reliably identify true initiators of efgartigimod. This lookback period may vary by different data sources. As for the EU databases, a 3-year lookback period is required for US database. However, this period could be adjusted to 1 or 2 years for US database if data for

	the full period are not available. In that case, sensitivity analyses will be performed for subgroups with 1-2, 2-3 and >3 years lookback period if sample size allows.
Variables	In this study, a patient will be considered an efgartigimod exposed patient if he/she has received at least one (1) dose of efgartigimod. Exposure to efgartigimod IV and SC starts with the initial exposure date for the medication found in the patient record (patient's index date).,. Considering 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 study outcome of interest is long-term risk of malignancies in patients with MG initiating treatment with efgartigimod and MG patients not treated with efgartigimod but are on any other therapy for the treatment of MG. Outcome variables will include (1) category of malignancy(ies); and (2) date of malignancy diagnosis(ses) in a patient's follow up period. Risk factors for malignancy will be evaluated as potential covariates for study analysis. The covariates will include clinical characteristics, medication use, and medical procedures coded in the databases that could be used to provide a complete description of the cohort and subpopulations. All covariates will be collected based on data availability in the selected databases.
Data sources	The selected data sources for this analysis must contain key variables that will enable the study exposure, study cohort, analysis subpopulations and study outcomes. Three (3) data sources have been identified for the study: • UK: CPRD • France: SNDS • US: Optum Market Clarity
Study size	Statistical analysis in this study will be exploratory, and not aimed to confirm or reject predefined hypotheses. Instead of considering enrolled patients up-front at the start of study, sample size calculation is based on the number of patients included in the final analysis. It is anticipated that 829 and 681 cumulative efgartigimod-treated patients in UK and France up to year 2028, and 90% and 100% will be captured in the CPRD and SNDS databases, respectively. 1200 patients are anticipated in Optum database. Factors that may decrease the number of patients in the final analysis include inclusion/exclusion criteria, lost to follow-up, failure to match to reference, no malignancy history in the look-back period, etc. Therefore, 30% of the patients in CPRD or SNDS are assumed to be excluded from the final analysis, and this percentage increases to 50% in Optum owing to higher loss-to-follow-up rate and shorter look-back period. A total of 1,599 efgartigimod-treated patients combining all 3 databases are anticipated to be included in the final analysis. An adjusted sample size of 1358 efgartigimod-treated patients are needed to achieve >80% power.
Data analysis	Descriptive statistics will be used to analyse baseline demographic information, co-morbid conditions, and concomitant medication use. For each outcome of interest, the incidence rate (IR), with 95% confidence intervals (CIs), will be calculated. IRs will be calculated within each

<table>
<tr><td></td><td>individual database by dividing the number of events for each outcome by the total person-time at risk. A Poisson distribution will be assumed to compute 95% CIs for IRs.

Furthermore, the incidence rate ratio (IRR) and corresponding 95% CIs will be used to compare the malignancy events among the efgartigimod exposed cohort vs. the reference cohort. The calculations will be performed separately for each individual database and across all three (3) databases as a meta-analysis according to published methods.

A sensitivity analysis based on the intention-to-treat principle will be conducted to ensure the continued monitoring of safety outcomes, irrespective of any treatment modifications throughout the follow-up period</td></tr>
<tr><td>Milestones</td><td>The date of data collection commencement is driven by when efgartigimod is commercially launched in each study country.

<table>
<tr><th>Milestone</th><th>Planned date</th></tr>
<tr><td>Submission of revised study protocol for PRAC approval</td><td>02 April 2024</td></tr>
<tr><td>Submission of second revision study protocol for PRAC approval</td><td>20 August 2024</td></tr>
<tr><td>Submission of third revision of study protocol for PRAC approval</td><td>19 December 2024</td></tr>
<tr><td>Submission of fourth revision of study protocol for PRAC approval</td><td>29 April 2025</td></tr>
<tr><td>Submission of fifth revision of study protocol for PRAC approval</td><td>11 July 2025</td></tr>
<tr><td>Estimated approval of study protocol by PRAC</td><td>24 July 2025</td></tr>
<tr><td>Registration in the EU PAS register</td><td>August 2025</td></tr>
<tr><td>Start of data collection</td><td>September 2026</td></tr>
<tr><td>End of data collection</td><td>September 2038</td></tr>
<tr><td>Final report of study results</td><td>September 2039</td></tr>
</table>

Abbreviations: EU PAS register = European Union electronic Register of Post-Authorisation Studies; PRAC = Pharmacovigilance Risk Assessment Committee.</td></tr>
</table>

5 Amendments and updates

None.

6 Milestones

The date of data collection commencement is driven by when efgartigimod is commercially launched in each study country. Efgartigimod has been accessible to patients in the United States (US) since December 2021 and was launched in the European Union (EU) in August 2022.

Milestone	Planned date
Submission of the study protocol for PRAC approval	31 October 2023
Submission of revised study protocol for PRAC approval	02 April 2024
Submission of revised study protocol for PRAC approval #2	20 August 2024
Submission of revised study protocol for PRAC approval #3	19 December 2024
Submission of revised study protocol for PRAC approval #4	29 April 2025
Submission of revised study protocol for PRAC approval #5	July 2025
Estimated approval of study protocol by PRAC	July 2025
Registration in the EU PAS register	August 2025
Start of data collection[1]	September 2026
End of data collection[2]	September 2036
Progress report 1[3]	September 2028
Interim report 1[4]	September 2030
Interim report 2	September 2032
Interim report 3	September 2034
Interim report 4	September 2036
Interim report 5	September 2038
Final report of study results	September 2039

EU PAS register = European Union electronic Register of Post-Authorisation Studies; PRAC = Pharmacovigilance Risk Assessment Committee.

[1] Due to the retrospective design of the study, data collection (accrual of data in the datasets) has already occurred prior to access to data. Start and end dates of access to data will differ by study country. Access to data will occur in databases in countries with earliest launch of efgartigimod first (US). For each country, the overall study period will be from the time of efgartigimod launch in that country and will continue for 10 years.

[2] The end of data collection may vary by country, depending on the start of data collection in the country's database.

[3] A progress report will be provided two years after the start of data collection.

[4] Interim reports will be provided at year 4 (considering the latency period for a malignancy to develop) following the start of data collection, and then every two (2) years through the end of study follow up.

7 Rationale and background

Myasthenia gravis

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). Approximately 80% of patients with MG have detectable antibodies against AChR. The estimated

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

A considerable variation exists in the management of generalized myasthenia gravis (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. Thymectomy is also a treatment option for patients with generalised MG. Monoclonal antibodies such as eculizumab, ravulizumab 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 or refractory cases of gMG in hospital settings (Vyvgart EPAR).

Background rates of cancer in MG population

The literature evaluating the association between autoimmune diseases and the risk of cancer is scarce and presents vast heterogeneity (Gilhus 2015). Studies vary in sample size and designs, from site based retrospective chart-review studies to large-scale national administrative database analyses. Retrospective studies on the incidence of malignancies in MG reported a cumulative incidence for extrathymic malignancies ranging from 2.8% to 11.7%, over an observation period of 8 years or longer (Basta 2014; Citterio 2009; Evoli 1998; Levin 2005; Liu 2012; Wakata 2006). The above-mentioned studies evaluating incidence rates for specific malignancies have demonstrated that the risk of some malignancies is higher in patients with MG. However, the studies are heterogeneous with respect to the design, populations, sample size, and analyses. Thus, there is no conclusive evidence due to conflicting results observed among studies. Furthermore, the studies do not consistently evaluate the role of MG therapy on incidence of malignancy, despite the established association of non-steroidal immunosuppressants with some categories of malignancies such as lymphomas.

Association between thymoma and MG

Many patients with MG have thymic abnormalities, with 10% to 15% having a thymic malignancy (Estephan 2022; Gilhus 2015; McGrogan 2010). In a study in Taiwan, the incidence rate for thymoma in patients with MG was 24.94 per 10, 000 person years, with a 118.47-fold increased risk of thymus cancer (hazard ratio, 118.47; 95% (confidence interval [CI], 42.57, 329.71) over the comparison cohort with no history of MG (Yeh 2014). In a systematic literature review, the incidence of thymoma was 21% in patients with MG, with a higher risk in males and patients older than 40 years at the onset of MG. The majority of the patients with thymoma had noninvasive thymoma (Mao 2012).

The presence of thymoma in patients with MG has been evaluated as a risk factor for extra-thymic malignancy, with inconsistent results. A study evaluating extrathymic malignancies in thymoma patients with and without MG showed that patients with thymoma have a significantly increased risk of extrathymic malignancies, which is unaffected by a coexisting autoimmune disease such as MG and is not specific for any type of cancer. While some studies reported a higher odds ratio for extrathymic malignancies in patients with MG with thymoma (1.9 [Citterio

2009] and 1.73 [Evoli 1998]), no statistically significant association was observed in other studies (Basta 2014; Levin 2005; Liu 2012).

Extrathymic malignancies in MG

Several autoimmune disorders and immunosuppressive therapies have been linked to an increased risk of malignancies (Hemminki 2012; Hemminki 2020; Giat 2017). The rates of extrathymic malignancies have been evaluated in various studies in patients with MG. However, most of these studies have methodological limitations, making comparisons difficult. The studies vary in design, sample size, populations, reporting periods, and have limitations including incomplete follow-up, selection biases for the MG group, insufficient control matching, low number of patients, and lack of stratification (Gilhus 2015). Therefore, different studies often have conflicting results.

Some type of cancers have been reported in the population but are likely due to the background therapy, such as lymphomas and some solid tumours such as prostate cancer.

The autoimmune pathology of MG and the oncogenic thymic influence in thymomatous MG may predispose patients to further develop malignancies of various types. Thymic malignancy is estimated to be prevalent in 10–15% of patients with MG (Estephan 2022; Gilhus 2015; McGrogan 2010), and the incidence of extrathymic malignancies after onset of MG ranges between 2.8–11.7% based on review of the published literature (Basta 2014; Citterio 2009; Evoli 1998; Levin 2005; Liu 2012; Wakata 2006). While there is some data on the overall incidence of malignancies associated with MG for consideration, there is insufficient evidence to draw concrete conclusions on the risk of specific types of malignancy and risk factors of malignancies associated with MG, due to diversities in patient characteristics, treatment patterns, different calendar years and duration of study observation and geographic area of where studies were conducted.

Efgartigimod alfa

Efgartigimod alfa is an immunomodulator, a first-in-class biologic, and has a novel mechanism of action. It is a human IgG antibody Fc fragment that binds to FcRn (neonatal fragment crystallizable receptor), resulting in reduction (but not depletion) in serum IgG, including levels of autoantibodies. Efgartigimod does not reduce the levels of other immunoglobulin isotypes (IgA, IgD, IgE, or IgM) or albumin and does not hamper T cell–dependent antibody responses and cellular immune response.

Efgartigimod alfa has marketing authorization for the treatment of patients with gMG in various jurisdictions including the US, Japan, United Kingdom (UK), and the EU. In the US, efgartigimod is approved for the indication of gMG in adult patients who are AChR antibody positive and in the EU and UK it is approved as an add-on to standard therapy for the treatment of adult patients who are AChR antibody positive.

The recommended intravenous (IV) dose of efgartigimod is 10 mg/kg as a 1-hour infusion. The recommended efgartigimod dose administered by a subcutaneous (SC) injection is 1,000 mg efgartigimod alfa to be administered weekly for 4 weeks per cycle. Subsequent treatment cycles

are administered according to clinical evaluation. The frequency of treatment cycles may vary by patient.

Review of literature on cancer immune responses does not suggest that a selective reduction of IgG, without lowering other immunoglobulin isotypes or affecting cell-mediated immunity, would generally increase the risk of developing cancers or have an effect on factors that promote carcinogenesis (Monroy-Iglesias 2022). Evidence from toxicity safety studies has not shown an association between efgartigimod exposure and an increased risk for the development or progression of malignancy.

Study Rationale

In efgartigimod controlled and uncontrolled clinical studies, malignancies have been reported. All reported malignancies were assessed as not being related to efgartigimod. All had confounding factors such as age, medical history, prior or concomitant medications, or limited duration of exposure to efgartigimod. The safety data from studies with efgartigimod in patients with gMG combined with additional data for other immunoglobulin γ (IgG)-reducing agents or treatments did not suggest a correlation between IgG reduction and an increased risk of developing malignancy.

The immune response to cancer is complex and the role of IgG has not been fully elucidated as it can be both procarcinogenic and anti-carcinogenic. However, literature remains controversial and some publications suggest that considering the role of IgGs in tumour-associated immunity and the role of FcRn in antitumour immune surveillance, there is a theoretical risk of developing malignancy in patients treated with efgartigimod. As the mechanism of action of efgartigimod is novel with limited safety data, the role of IgG in the immune response to cancer remains unclear.

However, as the immune response to cancer is complex and the role of IgG reduction has not been fully elucidated, and malignancies have been detected in long-term clinical trials with efgartigimod, the marketing authorisation holder (MAH) considers malignancies an important potential risk in the EU Risk Management Plan (RMP). Several approaches will be used to monitor malignancies in an exposed population. First, routine pharmacovigilance activities will provide ongoing monitoring of all malignancy cases identified through spontaneous adverse event (AE) reports. Second, malignancies will be evaluated as a clinical outcome of interest in the PASS (post-authorisation safety study) of patients treated with efgartigimod (ARGX-113-PASS-2208) over a total duration of 10 years.

Third, and most comprehensively, a retrospective cohort study in several healthcare databases (France, UK, and US) will be conducted with a primary objective to evaluate if there is an increased risk of malignancies with exposure to efgartigimod. These three (3) data sources were identified through an in-depth feasibility assessment that evaluated multiple US and EU healthcare databases to assess if they met the key criteria for conducting a retrospective study to evaluate malignancy risk in efgartigimod-exposed patients. Retrospective databases have been widely used to evaluate the risk of malignancy outcomes in exposed populations. Studies conducted in these databases are considered an acceptable approach to generate evidence to enable a more comprehensive safety profile for a marketed medicinal product. The design of this database safety study is presented in this protocol.

8 Research question and objectives

This study aims to assess the risk of malignancy in patients with MG exposed to at least one (1) dose of efgartigimod compared to MG patients with no record of exposure to efgartigimod by analysing data from two (2) claims databases (US Optum Market Clarity, and France le Système National des Données de Santé [SNDS]), and one electronic medical record (EMR) database UK Clinical Practice Research Datalink [CPRD]).

Primary objective

To evaluate the long-term risk of malignancies overall and by type in patients with MG treated with efgartigimod compared to MG patients on any other MG therapy and who do not have malignancy history in the lookback period[1], in a real-world setting.

Note: the malignancy categories will include thymic and non-thymic (all other types); non-thymic will be further categorized into solid tumours by organ and hematopoietic/lymphoid and related

Secondary objectives

In MG patients treated with efgartigimod compared to MG patients on any other MG therapy:

- To evaluate the long-term risk of malignancies overall and by type in MG patients with malignancy history in the lookback period
- To evaluate the long-term risk of malignancies by duration of efgartigimod exposure
- To evaluate the long-term risk of malignancies in subpopulations with increased risk for malignancy:
    - elderly – age 65 years and older
    - chronic use (i.e., ≥1 year) of corticosteroids

Exploratory objectives

- To evaluate the long-term risk of malignancies in MG patients treated with other FcRn antagonists
- To assess time to the first occurrence of malignancy overall and by type of malignancy in MG patients treated with efgartigimod and MG patients on any other MG therapy:
- To assess healthcare resource utilization including:
    - The number of hospitalisations (including MG-related)
    - The number of emergency room (ER) visits, and
    - The number of MG exacerbations and MG crises if available.

[1] A lookback period is a period prior to patients' initiation of index medication (cohort entry) to reliably characterise a patient based on relevant malignancy history, as well as other baseline covariates.

9 Research methods

9.1 Study design

This multinational, longitudinal database cohort study will identify patients who are newly treated with efgartigimod and have a diagnostic code for MG (efgartigimod cohort). A patient will be considered an efgartigimod exposed patient if he/she has received at least one (1) dose of efgartigimod.

For each patient entering the efgartigimod cohort, the date of the first efgartigimod exposure in the database (either through an IV infusion or SC injection) will be their index date for the study. Only new users of efgartigimod will be included in this cohort, that is, a patient who receives a first prescription, or first dispensing, or has a first procedure code for efgartigimod during the study period and without a prescription or a dispensing or a procedure code for efgartigimod in the previous 12 months.

A reference cohort will also be selected with a 2:1 ratio to the efgartigimod cohort to provide an overall, real-world assessment of malignancy risk in patients receiving efgartigimod. The reference cohort will consist of patients with a diagnosis code for MG without efgartigimod exposure but is on any other therapy for the treatment of MG during the study period. The index date for each patient in the reference cohort will be assigned as the same index date as the corresponding matched efgartigimod patient.

Identification of patients in the reference cohort will be based on selected matching variables in the patient's history (prior to and including the index date) or within 6 months of the index date. More specifically, within each database, efgartigimod initiators will be matched 2:1 (reference: efgartigimod) by (1) age at index date (+/- 5 years), (2) sex, (3) Charlson Comorbidity Index (CCI)[2] and (4) duration of prior use of other MG treatment as matching variables prior to and including the index date or within 6 months of the index date.

Patient accrual into the study will begin following the launch of efgartigimod (differs by country), allowing for a lag between actual exposure dates and appearance of the medication record/procedure in each of the data sources, and will continue for up to 5 years via database refreshes (assumed to be annual). To achieve a desired sample size across all databases, a minimum of approximately 1,358 patients will be included in the efgartigimod cohort and 2,716 matched patients in the reference cohort. Accrual of patients into the study cohorts will be monitored annually. Patients will be followed from study entry to at least 10 years following inclusion in the study. If efgartigimod uptake is slower than expected, patient accrual may need to be extended to reach the required sample size.

[2] CCI is a method of predicting mortality by classifying or weighting comorbid conditions and has been widely utilized by health researchers to measure burden of disease and case mix. Nineteen (19) conditions are included in the index. Each condition is assigned a weight from 1 to 6, based on severity of the disease and estimated 1-year mortality, and these weights from the comorbidities were added to give a singular numeric score which will act as a way of quantifying current health status.

The study will assess the occurrence of any malignancy according to International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes, which will be grouped according to the ICD-10 classification system (or to the ICD revision valid at time of analysis). More specifically, the first incidence of and time to any malignancy (incidence rate of events of malignancy per PYs exposed in the efgartigimod treated cohort compared to the reference cohort), as well as incidence rate ratio (IRR) will be estimated.

The study will be conducted in validated longitudinal data sources that provide a good representation of the overall healthcare experience in the countries of interest. Analyses will be first conducted independently within each data source to maintain the strengths and unique data features of the individual data sources (e.g., claims data will have highly detailed medication exposure information including days of supply for medications dispensed through outpatient pharmacies; EMR data from clinical settings will have increased outcome validity), and most importantly, to check data integrity (e.g., covariates availability, preliminary study results) across all data sources. A meta-analysis that combines summary results from each country will then be conducted for the final study report after the country-specific analyses are completed.

9.2 Setting

The observational study will identify two (2) cohorts from each targeted database:

- Efgartigimod Cohort: Patients with an MG diagnosis and who have initiated efgartigimod
- Reference Cohort: Patients with an MG diagnosis and who have not initiated efgartigimod but are on any other therapy for the treatment of MG. Immunoglobulins and plasmapheresis are not considered here, as they are usually used for acute management of MG crisis.

9.2.1 Patient selection (cohort entry)

The overall study population of interest consists of patients with MG and who have initiated efgartigimod and their matched non-exposed cohorts (i.e., reference cohort), who meet study eligibility criteria. Detailed coding algorithms for MG diagnosis ascertainment may vary across databases and will be described in the Statistical Analysis Plan (SAP).

Patient selection for efgartigimod and reference cohorts will occur concurrently and will start when efgartigimod exposure begins to appear in patient records in the database. The earliest cohort entry date (i.e., a patient's index date) for a country depends on the launch date of efgartigimod in that country. To qualify for cohort entry, patients must fulfil the following inclusion criteria.

Inclusion Criteria (efgartigimod cohort)

1. 18 years or older at index date (the date of the first efgartigimod exposure in the database);

2. Patients diagnosed with MG who have initiated efgartigimod[3];
3. Patients continuously covered in the data source for at least 3 years before their respective cohort entry date.

Inclusion Criteria (reference cohort)

1. 18 years or older at matched index date.
2. Patients diagnosed with MG who have not initiated efgartigimod treatment, but are on any other therapy for MG.
3. Patients continuously covered in the data source for at least 3 years before their respective cohort entry date.

All patients in the study will have a minimum of 3 years of continuous coverage in the database prior to their cohort entry date. The 3-years minimum prior to index date (lookback period) is required to reliably characterise a patient based on relevant malignancy history, as well as use of other medications prior to initiation of the index medication. The lookback period is also required to reliably identify true initiators of efgartigimod. This lookback period may vary by different data sources: As for the EU databases, a 3-year lookback period is required for US database. However, this period could be adjusted to 1 or 2 years for US database if data for the full period are not available. In that case, sensitivity analyses will be performed for subgroups with 1-2, 2-3 and >3 years lookback period if sample size allows.

9.2.2 Study observation period

The first interim report will be submitted to the European Medicines Agency (EMA) at year 4 following the start of data collection, and then will be submitted on a biennial basis (i.e., five interim reports in total for the entire study period). Each patient selected will be followed from his/her respective index date until the earliest occurrence of:

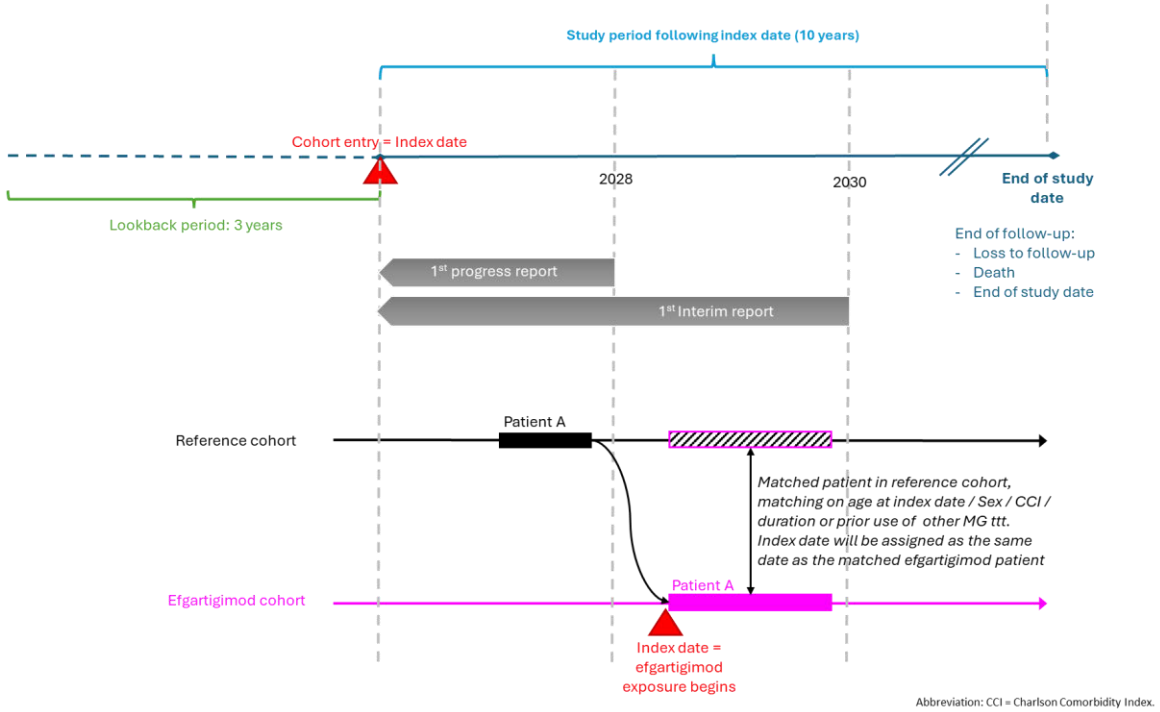
- Loss to follow-up (i.e., patient no longer covered in the data source)
- Death (NOTE: The approach for evaluation of death outside of a hospital setting will differ by database)
- End of study follow-up period (10 years after the last patient selected per database)

The cohorts are considered to have dynamic inclusion periods. At each interim analysis, the cohort populations and patient matching will be redefined. Patients in the reference cohort who have switched from any other MG treatment to efgartigimod will be considered as having

[3] Only new users of efgartigimod will be included in the efgartigimod cohort, that is, patient who receives a first prescription, or dispensing, or has a procedure code for efgartigimod during the study period, and without a prescription or dispensing or a procedure code for efgartigimod in the previous 12 months.

reached the end of their follow-up period at the time of the switch and will thus be censored from the reference group but counted in the efgartigimod group.

Figure 1. Study observational period



9.2.2.1 Switch from reference cohort to efgartigimod cohort or multiple cumulative exposure to efgartigimod during study period

It is anticipated that during the study period, patients who are in the reference cohort at study entry may initiate efgartigimod at a later time; or patients who are in the efgartigimod cohort at study entry may reinitiate efgartigimod a long time following their index exposure.

Details on handling patients who switch therapies or with multiple cumulative exposure to efgartigimod is briefly described in section 13 Data analysis and will be elaborated in the SAP.

9.3 Variables

Variables that will be evaluated to determine subpopulations of interest include patient demographics and exposure to non-steroid immunosuppressants.

Risk factors for malignancy will be evaluated as potential covariates for study analysis.

Exposure to MG therapies will be captured:

- Efgartigimod

- Non-efgartigimod maintenance therapies, including:
    - Acetylcholinesterase (AChE) inhibitors
    - Corticosteroids
    - Non-steroidal immunosuppressants
    - Monoclonal antibodies

The following variables will be collected to assess the impact of healthcare resource utilization:

- Hospitalisations
- MG-related hospitalisations
- ER visits
- MG exacerbations, when available in the database
- MG crises

These variables will also be collected during the look-back period if possible.

9.4 Efgartigimod exposure definition and measurements

Efgartigimod is administered in cycles of 4 weekly administrations followed by an efgartigimod-free period. The initiation of the next cycle is based on clinical need.

This schedule of administration is based on results of clinical trials that showed that clinical response is following or even exceeding the duration of IgG reduction. Majority of patients receive 5-7 cycles per year which has been confirmed in real world studies (Bhavaraju-Sanka 2024).

In this study, a patient will be considered an efgartigimod exposed patient if he/she has received at least one (1) dose of efgartigimod. Exposure to efgartigimod IV and SC starts with the initial exposure date for the medication found in the patient record (patient's index date). It is determined that consecutive doses administered greater than 21 days apart will be considered a different cycle.

Based on these elements, the following treatment patterns will be identified:

- Ever used: patients who receive 1 administration to up to 1 cycle (ie., max. of 4 once weekly administration with less than 21 days between).
- Infrequent use: patients who have a *Medication Possession Ratio* (MPR) < 60%. MPR is defined as the sum of drug supply days covered by each cycle (28+21= 49 days) divided by the time elapsed between the first supply and the end of the follow-up period.
- Continuous use: patients who have received ≥ 2 subsequent cycles without any interruption of more than 120 days between cycles.
- Intermittent use: patients who have at least one interruption of more than 120 days between two consecutive cycles. If sample size permits, the intermittent group may be stratified according to MPR subclasses.

- Discontinuation is defined as a gap period of at least 120 days after the last claim/prescription/dispensing.

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 coding algorithms to identify efgartigimod exposure vary across different databases. In the US database (i.e., Optum), the coding algorithm will consist of relevant National Drug Code (NDC) and/or Healthcare Common Procedure Coding System (HCPCS) Level II procedure codes. In Europe, relevant anatomical therapeutical chemical (ATC) codes will be used to identify efgartigimod. UK CPRD uses a different medication coding system. The details of product codes associated with efgartigimod in selected databases will be provided in the SAP.

9.5 Outcomes

The study outcome of interest is long-term risk of malignancies in patients with MG initiating treatment with efgartigimod and MG patients not treated with efgartigimod, but are on any other therapy for the treatment of MG. Malignancies (examples mentioned in Table 1) will be identified in each of the study databases primarily by using coding algorithms based on International Classification of Disease. Currently Revision 10 is valid, however revisions of the ICD is expected and therefore the version valid at the time of analysis will be used. The algorithms may also consist of relevant procedure codes, and/or results from relevant laboratory tests whenever appropriate and available in the database. All final coding algorithms and detailed code lists will be provided in the SAP.

Table 1. Examples of types of malignancy to be collected, subject to the valid ICD version.

Event of interest	Types of Malignancy	Measurement
Malignancy	• Malignant neoplasms of lips, oral cavity and pharynx • Malignant neuroendocrine tumours • Secondary neuroendocrine tumours • Malignant neoplasms of digestive organs • Malignant neoplasms of respiratory and intrathoracic organs • Malignant neoplasms of bone and articular cartilage	Incidence rate of events of malignancy by type per patient-years exposed in the efgartigimod treated cohort compared to the reference cohort. Incidence rate ratio and corresponding 95% CIs will be used to compare the malignancy events among the efgartigimod exposed cohort vs. the reference cohort. The calculations will be performed

	• Melanoma and other malignant neoplasms of skin • Malignant neoplasms of mesothelial and soft tissue • Malignant neoplasms of breast • Malignant neoplasms of female genital organs • Malignant neoplasms of male genital organs • Malignant neoplasms of urinary tract • Malignant neoplasms of eye, brain and other parts of central nervous system • Malignant neoplasms of thyroid and other endocrine glands • Malignant neoplasms of ill-defined, other secondary and unspecified sites • Malignant neoplasms of lymphoid, hematopoietic and related tissue • Thymic malignancies • In-situ carcinoma	separately for each individual database and across all three (3) databases as a meta-analysis according to published methods.

Abbreviation: CI = confidence interval.

Each category of malignancy presented in Table 1 will be assessed individually. If possible, adjudication through review of medical charts will occur for malignancy cases identified through coding algorithms in the claims databases used to conduct the study.

Outcome variables will include:

- Category of malignancy(ies)
- Date of malignancy diagnosis(ses) in a patient's follow-up period

9.6 Covariates

This study is designed to describe real-world outcomes associated with the use of efgartigimod. The covariates to be collected include any clinical characteristics, medication use, and medical procedures coded in the databases that could be used to provide a complete description of the cohorts and subpopulations. Baseline covariates observed in the patient's medical history and other relevant factors prior to the study drug initiation will be assessed.

It is anticipated that not all variables can be collected in the three (3) selected databases; therefore, all covariates will be collected based on data availability. The following list of *a priori* covariates will be evaluated. A more detailed description of relevant covariates and their use in the analysis will be described in the SAP.

1. Cohort identification
    - Date(s) of a diagnosis of MG (health care setting) to approximate disease duration (new-/old-onset)
2. Demographic factors
    - Gender
    - Ethnicity/race (if allowed)
    - Patient's age at his/her index date
    - Thymoma (with or without thymectomy), if present in database (date, indication, histology)
    - [Supplementary variables]
        - Comorbidities
            - CCI will be calculated based on comorbidities identified in the lookback period in the selected databases.
        - Serological testing of MG diagnosis, if available
        - MG Disease severity, if available
3. Lifestyle variables[4], if available
    - Smoking
    - Body mass index (BMI)
    - Alcohol consumption
4. MG treatment
    - Prior and current treatments, e.g.
        - Anticholinesterase agent
        - Corticosteroids
        - Chronic non- steroidal immunosuppressants
        - Monoclonal antibodies
        - Plasmapheresis/plasma exchange
        - IVIg therapy
    - Duration of exposure of prior and current treatments, if available
    - [Supplementary variables]

[4] May only be available in EMR database(s) but not claims administration databases.

- Cumulative dose for each line of therapy, if available, and if not, number of distinct concomitant MG treatments (mono-, double or triple therapy)

5. Concomitant treatments

- Type of treatment and duration (for selected concomitant medications)
- [Supplementary variables]
  - Duration of exposure for each treatment
  - Cumulative dose of each treatment, if available

9.7 Subpopulations

Subpopulations with increased risk of malignancies will be established by reviewing all patient history in the lookback period, and will be defined as follows:

1. Elderly, age 65 years and older at their index date
2. Chronic use (i.e., ≥1 year) of corticosteroids

Lists of relevant codes will be included in the SAP.

10 Data sources

The study will be conducted using

- UK: CPRD
- France: SNDS
- US: Optum Market Clarity

10.1 Clinical Practice Research Datalink (CPRD)

Jointly sponsored by the Medicines and Healthcare Products Regulatory Agency and the National Institute for Health Research (NIHR), CPRD collects de-identified patient data from a network of general practitioner (GP) practices across the UK.

- Primary care data are linked to other health related data to provide a longitudinal, representative UK health dataset (e.g., linkage to Hospital Episode Statistics [HES]). Patient metrics include demographics (e.g., year of birth, gender, registration dates), medical history (e.g., event dates, diagnosis, symptoms, risk factors, comorbidities, referrals, laboratory results), prescriptions (e.g., prescription dates, therapeutic class, ingredient, dosage, duration), and clinical data (e.g., blood pressure, height, weight, immunizations, life habits such as smoking and alcohol use).
- HES data covers all National Health Service (NHS) Clinical Commissioning Groups in England including private patients treated in NHS hospitals and patients receiving care in treatment centres funded by the NHS. Each HES record provides a comprehensive picture about an individual admitted to an NHS hospital and their care, including

clinical information and diagnoses and procedures, dates of admission and discharge, and demographics include gender and ethnicity.

- There are >40 million patient lives in CPRD Aurum and >20 million patients in CPRD GOLD, including 15 million currently registered.
- For >30 years, research has informed clinical guidance and best practice, resulting in over 2,000 peer-reviewed publications.

10.2 Système National des Données de Santé (SNDS)

SNDS covers the entire population of France - 67 million residents. Each person is identified by a unique, anonymous number. Since 2006, SNDS has recorded information on all outpatient care (including drugs, imaging, and laboratory tests) and inpatient care (including diagnoses and procedures performed, coded according to the common classification of medical procedures—CCAM). The health expenditure for patients with long term diseases, such as cancer and diabetes, is fully reimbursed, and their diagnosis is recorded according to ICD-10 codes. SNDS has been extensively used in France to conduct real life studies, especially on the use, safety, and efficacy.

10.3 Optum Market Clarity

The Optum Market Clarity database includes deidentified data from medical and pharmacy claims and linked electronic health record (EHR) data for over 100 million unique, integrated patient lives from over 150 US payers, including commercial, Medicaid and Medicare plans. The database includes medical and pharmacy claims from United HealthCare, the largest insurer in the US, as well as partner claims from other insurers and clearinghouses. These claims are then linked with EHR data primarily from integrated delivery networks as well as some ambulatory networks. The database includes 20,000+ mapped clinical variables, diagnosis codes, signs and symptoms, biomarkers, laboratory and test results; it can also have natural language processing applied to unstructured clinical notes.

10.4 Coding Systems for CPRD, SNDS, and Optum

Table 2 below provides details on the diagnosis and medication coding systems for each of the 3 databases that will be used to conduct the study, as well as potential validity concerns.

Table 2. Coding system and potential validity concerns for CPRD, SNDS, and Optum

	Diagnosis	Medication	Potential Validity Concerns
CPRD	ICD-10 (HES) & medcode (CPRD) & SNOMED	Product code & medcode & OPCS (PLEX)	EMR system that captures physician recorded diagnosis, procedures. In general, data from CPRD are considered reliable.
SNDS	ICD-10	UCD (hospital) & CIP (retail) & CCAM procedures codes	The SNIIRAM has been largely recognised by the French authorities (INCa, HAS) as a powerful tool for epidemiologic studies. The main limitations are

			induced by the nature of the claims database, that require algorithms to increase the precision.
OPTUM	ICD-10 & ICD-9	CPT & HCPCS	A claim is limited to reimbursement purposes, therefore, algorithms may be required to increase the precision.

Abbreviations: CCAM = common classification of medical procedures; CIP = Code Identifiant de Présentation; CPT = Current Procedural Terminology; CPRD = Clinical Practice Research Datalink; EMR = electronic medical record; HAS = Haute Autorité de Santé; HCPCS = Healthcare Common Procedure Coding System; HES = Hospital Episode Statistics; ICD-10 = International Classification of Diseases, Tenth Revision (valid in 2024, revision valid at time of analysis will be used); INCa = French National Cancer Institute; OPCS = Office of Population Censuses and Survey; SNDS = le Système National des Données de Santé ; SNIIRAM = Système national d'information inter-régimes de l'Assurance maladie; SNOMED = Systematized Medical Nomenclature for Medicine; UCD = Unité Commune de Dispensation.

11 Study size

Statistical analysis in this study will be exploratory, and not aimed to confirm or reject predefined hypotheses. Instead of considering enrolled patients up-front at the start of study, sample size calculation is based on the number of patients included in the final analysis.

Since the variation under a random-effect model assuming heterogeneity across databases consists of both within-database and between-database variation and the number of patients will only impact the within-database variance, a two-step method for sample size calculation is conducted: 1) calculate the unadjusted sample size using inequality test assuming no heterogeneity among databases as if all patients were from one single database; 2) calculate the adjusted sample size by multiplying an adjustment factor to the unadjusted sample size assuming moderate heterogeneity. The feasibility of patient accrual based on projected cumulative number of patients in the databases is discussed considering factors that may impact the final number of patients, such as loss to follow-up, malignancy history, etc.

A real-world study using Optum database conducted by argenx showed malignancy incidence rate of 73.6 per 1,000 PY in MG population (data not published). An exploratory analysis using the result from the eculizumab Phase III study (NCT01997229) and its extension study (NCT02301624) (Mantegazza 2021 and Results from clinicaltrials.gov) showed malignancy incidence rate of 42.0 per 1,000 PY for eculizumab-treated patients (data not published). With this wide range of observed incidences in MG populations, a spectrum of malignancy incidence rates was explored with upper and lower bound of 73.6 and 42.0 per 1,000 PY.

Under the fix-effect model assuming a common effect size and variance it is demonstrated that the variance of the combined effect will be the same regardless of the distribution of sample size in each database (Borenstein 2010). Therefore, the sample size calculation can be conducted based on the overall number of patients. Using a two-sided inequality test for two (2) Poisson rates (Zhu 2017) the unadjusted sample size is shown in Table 3 with 5% significance level, >85% power and rate ratio 1.3 under alternative hypothesis. The follow-up time is assumed to be 6 or

8 years based on the study design. The calculation is conducted using the power and sample size software PASS 2023. A total of 679 efgartigimod patients are needed assuming no heterogeneity (Power Analysis and Sample Size Software (2023) (NCSS, LLC. Kaysville, Utah, US [ncss.com/software/pass]).

To account for the increased variance owing to between-database variation under random-effect model if heterogeneity exists, the unadjusted sample size is multiplied by the adjustment factor of $1/(1-I^2)$ (Wetterslev 2009) where I^2 is the heterogeneity measure. Assuming moderate heterogeneity of $I^2 = 0.5$ the adjustment factor equals to 2. The adjusted sample size is therefore two (2) times of the unadjusted sample size and shown in Table 3. A total of 1358 efgartigimod-treated patients are needed with a rate ratio of 1.3 under alternative hypothesis, 6-year follow-up and background rate of 42.0 per 1,000 PY to achieve >85% power.

Table 3. Sample size calculation

Background Rate in 1000PY	Follow-up Year	Rate Ratio under Alternative Hypothesis	Unadjusted Sample Size in Efgartigimod Cohort	Adjusted Sample Size* in Efgartigimod Cohort
42.0	6	1.3	**679**	**1358**
	8	1.3	509	1018
60.0	6	1.3	475	950
	8	1.3	357	714
73.6	6	1.3	384	768
	8	1.3	288	576

* Adjusted sample size = unadjusted sample size × 2, where 2 is calculated from $1/(1-I^2)$ assuming moderate heterogeneity of $I^2 = 0.5$

To further demonstrate the ability to detect difference between two (2) cohorts, power analysis is conducted using two-sided inequality test (H_0: rate ratio=1 vs. H_a: rate ratio ≠ 1) for two (2) Poisson rates (Zhu, 2017) with 5% significance level and rate ratios of 1.2, 1.3, 1.4, 1.5, 2, 3 and 4. Table 4 shows that there are >80% power in most scenarios under the adjusted sample size of 1358.

Table 4. Power calculation

Background Rate in 1000PY	Follow-up Year	Rate Ratio under Alternative Hypothesis	Power
42.0	6	1.2	54.20%
		1.3	86.13%
		1.4	97.90%
		1.5	99.84%
		2	100.00%
		3	100.00%
		4	100.00%

Background Rate in 1000PY	Follow-up Year	Rate Ratio under Alternative Hypothesis	Power
	8	1.2	66.46%
		1.3	94.03%
		1.4	99.60%
		1.5	99.99%
		2	100.00%
		3	100.00%
		4	100.00%
60.0	6	1.2	69.45%
		1.3	95.36%
		1.4	99.76%
		1.5	100.00%
		2	100.00%
		3	100.00%
		4	100.00%
	8	1.2	81.34%
		1.3	98.76%
		1.4	99.98%
		1.5	100.00%
		2	100.00%
		3	100.00%
		4	100.00%
73.6	6	1.2	78.39%
		1.3	98.17%
		1.4	99.96%
		1.5	100.00%
		2	100.00%
		3	100.00%
		4	100.00%
	8	1.2	88.69%
		1.3	99.67%
		1.4	100.00%
		1.5	100.00%
		2	100.00%
		3	100.00%
		4	100.00%

It is anticipated that 829 and 681 cumulative efgartigimod-treated patients in UK and France up to year 2028, and 90% and 100% will be captured in the CPRD and SNDS databases, respectively. 1200 patients are anticipated in Optum database. Factors that may decrease the number of patients in the final analysis include inclusion/exclusion criteria, lost to follow-up, failure to match

to reference, no malignancy history in the look-back period, etc. Therefore, 30% of the patients in CPRD or SNDS are assumed to be excluded from the final analysis, and this percentage increases to 50% in Optum owing to higher loss-to-follow-up rate and shorter look-back period. A total of 1,599 efgartigimod-treated patients combining all 3 databases are anticipated to be included in the final analysis, which is greater than the sample size calculated above. Therefore, it is feasible to have sufficient efgartigimod-treated patient and achieve satisfactory power in the analysis.

Table 5. Anticipated efgartigimod-treated patients included in the final analysis

Database (Country)	Cumulative Patients by Country	% Captured in Database	Projected Patients in Database	% Included in Study	Sample Size in Each Database	Total Sample Size
CPRD (UK)	829	90%	746	70%	522	1,599
SNDS (France)	681	100%	681	70%	477	
Optum (US)	-	-	1,200	50%	600	

Abbreviations: CPRD = Clinical Practice Research Datalink; SNDS = le Système National des Données de Santé; UK = United Kingdom; US = United States.

12 Data management

Data management will be in accordance with the Sponsor's designated contract research organisation (CRO)'s standard operating procedures (SOPs) regarding external data management which outline the procedures for establishing a data agreement, conducting a data intake analysis, performing data load and verification, executing data backups, defining data retention and destruction timelines. Additional SOPs may be applicable depending on the format of the data files to be delivered by the providers.

Furthermore, data protection and privacy procedures will be followed to ensure data files received from providers are processed for specific study purposes and only those requiring data access will have access to the data. This also ensures data are accurate and not kept longer than needed, and defines logical and physical data security standards which meet regulatory guidelines. Data transferred from the providers will be stored in a dedicated application instance for the MAH.

13 Data analysis

An SAP will be prepared once the protocol is approved by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The SAP will provide analytical methods that are applicable across all databases, as well as addressing database-specific differences that may need to be applied. These differences may include conventions for handling specific data elements of interest that define exposure, diagnoses, covariates, and subpopulations of interest.

More specifically, descriptive statistics will be used to analyse baseline demographic information, co-morbid conditions, and concomitant medication use. For each outcome of interest, the IR, with 95% CIs, will be calculated. IRs will be calculated within each individual database by dividing the number of events for each outcome by the total person-time at risk. A Poisson distribution will be assumed to compute 95% CIs for IRs.

13.1 Analysis populations

All primary and secondary analyses will be conducted in two (2) study cohorts:

1. Efgartigimod cohort: patients with an MG diagnosis and who have initiated efgartigimod for the treatment of MG
2. Reference cohort: patients with an MG diagnosis and who have not initiated efgartigimod, but who are on any other therapy for the treatment of MG

In the exploratory analysis, the long-term risk of malignancies will be evaluated in:

- FcRn cohort: patients with an MG diagnosis and who have initiated other FcRn antagonists for the treatment of MG

13.2 Primary analysis

The IRR and corresponding 95% CIs will be used to compare the malignancy events among the efgartigimod exposed cohort vs. the reference cohort. The calculations will be performed separately for each individual database and across all three (3) databases as a meta--analysis according to published methods.

A quasi-Poisson regression model will be used to estimate the incidence rate ratio between cohorts with number of event occurrences as the response variable, cohort and age as covariates and follow-up time as offset. Scale/overdispersion parameter will be used to account for potential over- or under-dispersion.

In addition, the balance of baseline measures, including matching variables (i.e. age, sex, CCI and duration of previous MG treatment) 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 quasi-Poisson model as additional covariates.

- Age will be adjusted as a covariate in the quasi-Poisson model to account for the increased malignancy risk over time, no matter balanced or not. And age-specific incidence rates and incidence rate ratio between cohorts can be calculated.
- Concomitant and/or previous use of monoclonal antibody will be adjusted as a covariate in the quasi-Poisson model to account for any potential imbalance.

The primary analyses will be performed on an “as-treated” basis. To this end, patients will contribute person time until the first occurrence of the following events: death, loss to follow-up, end of study period, or a switch from any MG treatment to efgartigimod (for the reference cohort). For the analyses performed based on “as-treated” basis, the time before switching to efgartigimod for the reference cohort will be counted toward the overall person-time but not the time after switching.

A sensitivity analysis based on the intention-to-treat principle will be conducted to ensure the continued monitoring of safety outcomes, irrespective of any treatment modifications throughout the follow-up period. For the sensitivity analyses performed based on "intent-to-treat" basis, both the time before and after switching will be counted. Sensitivity analysis will be described as noted in section 13.5.

Duration of follow-up time with and without censoring by cohort will be summarized and compared. The percentages of patients with different reasons of censoring will be summarized by cohort. Details of the analysis will be given in the Statistical Analysis Plan

13.3 Subgroup analysis

Analyses of the primary outcome will be repeated for each of the following subpopulations:

1. Elderly - aged 65 and older years at their index date
2. Chronic use (i.e., ≥1 year) of corticosteroids

13.4 Sensitivity analysis

Sensitivity analyses may be considered for scenarios that patients remain on efgartigimod who do not switch vs. patients who take efgartigimod and switch to a different therapy. The sensitivity analysis in this study will be exploratory in nature. Results from subgroup and sensitivity analyses will be presented and discussed in the final report, but it is not the intent to provide any inferential statistics.

- Intention-to-treat analysis will be carried out, in which patients will be censored at death, loss to follow-up, end of study period.
- Sensitivity analyses will be performed for subgroups with 1-2, 2-3 and >3 years lookback period in the US database if sample size allows.
- A sensitivity analysis will be performed for users of efgartigimod as a first-line treatment only if the number of patients allows for it.
- Depending on the number of efgartigimod-using MG patients identified as likely to have been included in the clinical trials, a sensitivity analysis will be carried out by including only patients with a minimum wash-out period of 2 months after the end of the clinical trials.
- To evaluate the potential bias of including events of malignancy occurring within the first year of initiation of efgartigimod or a reference drug, a sensitivity analysis will be conducted that excludes events occurring within the first 12 months after a patient's study index date.
- To take into account the various reference treatments to which efgartigimod can be added and compared a sensitivity analysis will be performed. In this analysis the reference cohort will be defined according to the type of concomitant treatment given

in addition to efgartigimod (if the number of patients allows). The risk of cancer will thus be assessed between the following treatment groups:

- Users of efgartimod added to symptomatic treatment (i.e. anticholinesterase agent) vs. Users of symptomatic treatment;
- Users of efgartimod added to corticosteroids vs. Corticosteroids users;
- Users of efgartimod added to chronic non-steroidal immunosuppressants vs. Chronic non-steroidal immunosuppressants users;
- Users of efgartimod added to any chronic immunosuppressants (including corticosteroids) vs. any chronic immunosuppressants users;
- Users of efgartigimod vs other monoclonal antibodies users
- Users of efgartigimod without concomitant or previous use of another monoclonal antibody vs users of other MG therapies without concomitant or previous use of any monoclonal antibody.

In this analysis patients will contribute person time until the first occurrence of the following events: death, loss to follow-up, end of study period, or a switch from any MG treatment to efgartigimod (for the reference cohort). For the sensitivity analyses performed based on "intent-to-treat" basis, both the time before and after switching will be counted.

Additional considerations regarding the sensitivity analyses will be addressed in the SAP.

13.5 Exploratory analysis

The long-term risk of malignancies will be explored within a potential new cohort of MG patients who are treated with other FcRn antagonists, if sufficient patients can be identified for this patient cohort.

The study will also assess time to the first occurrence of malignancy overall and specified by type of malignancy using a Fine and Gray model in order to take into account a potential competitive risk for death and cumulative incidence curves will be provided. The index date will be the first claim of efgartimod (for the efgartimod cohort) or other MG treatment (for the reference cohort). The proportional hazards assumption will be checked using statistical tests and graphical diagnostics based on the cumulative sums of residuals. If the assumption is violated, an interaction term with time will be added in the model. The study will also assess the healthcare resource utilization (e.g., number of hospitalisations [including MG-related], ER visits, and MG exacerbations and crises) between the efgartigimod and reference cohorts. This exploratory analysis will be descriptive only; details will be provided in the SAP.

In order to assess the robustness of the results, a Proportional Hazard Model (Cox model) will be performed as a sensitivity analysis with providing cumulative incidence curves.

An exploratory analysis of the CPRD dataset (UK) to identify the extent of recorded MG related information will be performed and if feasible, analysis will be adjusted for disease severity.

13.6 Methods for addressing the potential for outcome misclassification in the claims databases

- Optum: to reduce the potential for false positive malignancy cases based on ICD-10 diagnosis codes in administrative claims database, an algorithm for malignancy case definition will be used that requires at least 2 malignancy diagnoses (within the same site) that are separated by >=30 days.
- SNDS: the SNDS has becoming largely recognised by the French authorities as a powerful tool of pharmacoepidemiology and some guidance and algorithm have been published for the community and one in particular for cancer(Méthode | L'Assurance Maladie (ameli.fr)).

14 Quality control

The SOP and work instructions of the sponsor's designated CRO will be used to guide the conduct of the study. These procedures include internal quality audits of the data, consistency of collected data, validation of coding, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Written programming will be reviewed independently. All key study documents, such as the SAP and study reports, will undergo quality control and senior scientific review.

The study will be executed in line with all applicable regulations and guidelines, such as the Guide on Methodological Standards in Pharmacoepidemiology, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols, and the International Society of Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices, as well as the data vendor's quality management system.

The SOP and work instructions of the MAH will be used to oversee the execution and conduct of the study by the CRO. These procedures include pre-qualification and in-process quality audits of the CRO's quality management software (QMS) and contracted services. Additionally, the Vendor Relationship Manual will be put in place and will include:

- Performance metrics
- Routine oversight activities
- CRO Governance meetings

The Vendor has SOPs in place which address the extent of source data verification, validation of endpoints, storage of records and archiving of the statistical programming performed to generate the results. These SOPs will be followed in this study.

15 Limitations of the research methods

This real-world observational study utilises data collected in administrative claims and EMR databases and is subject to limitations inherent to all database studies:

- There is no definitive coding algorithm to distinguish a generalized MG diagnosis vs. an ocular MG diagnosis in databases, although the indication for efgartigimod is specifically for patients with a gMG diagnosis. In this study, an algorithm for MG case ascertainment will be developed to identify the appropriate base cohort in the selected databases.
- Information concerning the malignancy may not be available in the selected claims databases such as Optum or SNDS. When evaluating risk of malignancies among patients with malignancy history, the study will not be able to distinguish if the current malignancy outcome is a new primary malignancy or a recurrence or metastases of the original primary malignancy.
- The lookback period is 1 to 3 years for the Optum database and up to 3 years for the EU and UK databases. However, this lookback period may not be sufficient to capture all important baseline data elements for this study. For instance, the possibility of obtaining the date of first diagnosis is low. In CPRD and SNDS, duration can be obtained if the first diagnosis is during the 3-year lookback period. However, if MG has been ongoing during the 3-year lookback period, duration of MG can only be given as >3 years. Limited continuous coverage for patients with MG in the Optum database may impact the study as follows:
    - Lack of continuity of coverage prior to a patient's study index date (efgartigimod initiation) may impact accurately evaluating:
        - Potential baseline confounders (e.g., thymectomy [date, indication, histology], thymoma [without thymectomy], malignancy history)
        - Duration of MG
        - Age at initial MG diagnosis
        - Treatment history (e.g., prior and baseline MG treatments)
    - Lack of continuity of coverage post drug initiation (efgartigimod or the reference drug) may impact ability to reliably evaluate risk of malignancy
        - Associated with repeated exposure to efgartigimod over time (e.g., dose, duration)
        - With a long latency period (e.g., 5+ years following efgartigimod initiation)
- Missing data are expected, particularly for certain covariates such as geography. Missingness will be assessed by comparing patients with missing data to those without missing data. The degree to which including or excluding those with

missingness may bias the findings will be estimated. This will also depend on the proportion of a given covariate that is missing. Methods such as multiple imputation may be needed if it is determined that their use may introduce bias.

- While Optum Market Clarity database is the largest insurer in the US covering over 100 million unique patients, it has a limited continuous coverage period for patients with MG according to a cohort study[5] conducted among the MG patients in the Optum database.
- The primary use of the data from the three (3) selected databases is not for research purposes but to facilitate and record information relating to billing or patient management; therefore, available information only reflects what is pertinent to the primary use of the data rather than a meticulous record of every detail of testing or examination. However, the data sources of this PASS were selected based on a thorough evaluation of the variables to ensure complete and reliable capture of primary outcomes.
- Potential for misclassification of patient's exposure status can arise for several reasons in a retrospective database study:
- In an EMR database such as CPRD, prescription for a medication cannot guarantee that the patient has taken the medication. Therefore, the study may have misclassification of patients' exposure status.
    - Potential misclassification for patients exposed to efgartigimod before product launch (i.e., prevalent users):
        - In France, data on patients during the time they have been treated in the early access program will be available in the French SNDS database and hence will be included in the study as incident users. If a patient was exposed to efgartigimod in a clinical trial in France, the clinical trial exposure will not be captured in SNDS. If these patients are then exposed to commercial efgartigimod, the prior exposure in a clinical trial will not be captured and these patients will not be able to be identified as prevalent users.
        - In the UK, data from a patient exposed to efgartigimod in a clinical trial or in an Expanded Access/Compassionate Use Program may be present in the CPRD database if the electronic medical records for that patient are part of the data set and if the treating physician has recorded that the patient was exposed to efgartigimod. The CPRD database consists only of data from sites who have agreed to participate and is not

[5] An internal position paper developed by argenx, titled "Malignancies with efgartigimod in generalized myasthenia gravis".

inclusive of all sites in the UK. Hence, it cannot be determined for certain if such patients will be included.

- As Optum is a US claims database, data during the time a patient was exposed to efgartigimod in a clinical trial is not included. Thus, there is the possibility of prevalent users not being identified. However, this is unavoidable when utilizing a claims database in the US.

  Misclassifying prevalent efgartigimod users as new users would have the effect of inducing selection bias by retaining only healthy users and excluding those who discontinue treatment following early adverse events (depletion of susceptible). This could lead to an underestimation of cancer risk estimate. However, given that few patients have been enrolled in the efartigimod clinical trials and early access programmes and that the UK EAMS (Early Access to Medicines Scheme) programme encourages patients to continue taking efgartigimod once it is marketed and reimbursed, as it was set up before efgartigimod was reimbursed, few patients should be affected by this issue. The effect of this potential selection bias on the point estimate is thus likely to be minimal.

    - In claims databases such as Optum and SNDS, dispensing of oral medications are consolidated into a total pharmacy expense during an inpatient hospital stay, preventing the identification of any individual exposure during the visit. This potential for immeasurable time bias is primarily a concern for (1) hospital stays that last more than a few days and (2) oral treatments for MG that could impact malignancy risk. This potential source of misclassification will be addressed as follows:

        - Medication dispensing in the weeks prior to admission and following a discharge of a hospital visit with a length of stay that exceeds 1 week will be reviewed. If dispensing for a medication is observed in the prior or post hospitalisation period, then exposure to the same medication will be imputed to have occurred throughout the hospitalisation stay as well.

- Inability to control precisely for unmeasured confounders such as:
    - Severity of MG
    - Disease duration, which cannot be reliably measured in claims databases that represent patients' healthcare experience only during the time of enrolment in covered insurance plans. The date of the initial MG diagnosis may not be available due to limited *historical enrolment* prior to the study index date.
    - History of malignancy that may not have been identified in the databases
    - Lifestyle variables that are typically not available in the claims databases, or only intermittently collected in the EMR database(s)

- Other factors that may contribute to the cell mutation (e.g., genetic) as malignancy is a multifactorial disease

- There is potential for prevalent user bias in favour of the reference cohort that may result from prior use of non-efgartigimod MG therapies by patients in the efgartigimod cohort prior to initiating efgartigimod.
- Latency to cancer can only be estimated using models (Nadler 2014) and can range from 2 years to decades. It is therefore not possible to detect all types of cancer in an observational study.

16 Other aspects

N/A.

17 Protection of human subjects

This study will comply with scientific principles, EMA PASS study guidance document, the applicable guidelines (GVP Module VIII) (EMA 2017), the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements (WMA 1964).

Informed consent is not applicable for a database analysis study because only de-identified data will be used. Research using anonymised databases should not require Independent Ethics Committee (IEC) review and approval and specific patient authorisation for each use of the data (ISPE Guidelines for GPP).

The database providers will keep confidential any information provided by the Sponsor (including this protocol) related to this observational study and all data and records generated in the course of conducting the study, and will not use the information, data, or records for any purpose other than conducting the study. These restrictions do not apply to: 1) information which becomes publicly available through no fault of the database provider, 2) information which is necessary to disclose in confidence to an Institutional Review Board (IRB) solely for the evaluation of the study, or 3) study data which may be published.

18 Management and reporting of adverse events/adverse reactions

Given the information available within the Optum, CPRD and SNDS databases used for this study is deidentified, extraction of AEs data will not be conducted. Only data related to the study objectives (i.e., all events of malignancies) will be captured and summarised in interim safety analyses and final study report.

18.1 Definitions

18.1.1 Definition of AE

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign

(including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

18.1.2 Definition of serious adverse event

A serious AE (SAE) corresponds to any untoward medical occurrence that at any dose results in:

- Death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

18.1.3 Definition of adverse drug reactions

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from:

- the use of a medicinal product within the terms of the marketing authorisation
- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse, and medication errors
- occupational exposure

The definition of an ADR implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

18.2 Collection of adverse events

Although AE information is not being actively solicited via this protocol, all ADRs that are inadvertently discovered and has an identifiable patient must be reported to argenx by email or fax.

Email: safety@argenx.com

Fax : +1 833 874-7325

One or more of the following qualifies a patient as identifiable: sex, age [or category, for example “elderly”], date of birth, initials, hospital, or other identifying item. In order for an event to be classified as an ADR, the database medical record should clearly indicate that the treating physician considered there to be a possible causal relationship between the AE and efgartigimod.

19 Plans for disseminating and communicating study results

Registration in the ENCePP register is planned. A progress report will be provided two (2) years after the start of data collection, which will present information on enrolment in the study cohorts, overall and by country (i.e., database). Interim results will be provided at year four (4) following the start of data collection, and then will be submitted on a biennial basis to the EMA; and a final study report will be provided one (1) year after the end of data collection if additional time is required to meet enrolment numbers to the EMA and to the competent authority of each country where the study is being conducted.

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	N/A		
2	N/A		

Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

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: Post-Authorisation Safety Study to Evaluate the Risk of Malignancies in Patients with Myasthenia Gravis Treated with Efgartigimod

EU PAS Register® number: **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[6]	☒	☐	☐	6
	1.1.2 End of data collection[7]	☒	☐	☐	
	1.1.3 Progress report(s)	☐	☐	☒	

[6] 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.

[7] Date from which the analytical dataset is completely available.

Section 1: Milestones	Yes	No	N/A	Section Number
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:	☒	☐	☐	
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)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	8, 9.1
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
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))	☒	☐	☐	9.1
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)	☒	☐	☐	18

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.1, 9.2
	4.2.3 Country of origin	☒	☐	☐	9.1, 9.2
	4.2.4 Disease/indication	☒	☐	☐	9.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.1, 9.2
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)	☒	☐	☐	9.4
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)	☒	☐	☐	9.4
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?	☒	☐	☐	9.4

Comments:

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?	☒	☐	☐	9.5
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.5

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
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)	☐	☐	☒	
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)	☒	☐	☐	13.5

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)	☒	☐	☐	9.6, 15
7.2	Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☐	☐	☒	
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)	☐	☐	☒	

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)	☒	☐	☐	10
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	10

Section 9: Data sources		Yes	No	N/A	Section Number
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.6, 10
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)	☒	☐	☐	9.1, 9.4
	9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.1, 9.2
	9.2.3 Covariates and other characteristics? (e.g. ,age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.5
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

All coding algorithms for MG diagnosis, exposure, outcome and covariates will be described in the SAP.

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	13
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	11
10.3	Are descriptive analyses included?	☒	☐	☐	13
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.6
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?	☒	☐	☐	13.4

Comments:

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)	☒	☐	☐	14
11.2 Are methods of quality assurance described?	☒	☐	☐	14
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	14

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?	☐	☒	☐	
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)	☒	☐	☐	11

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?	☒	☐	☐	17
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	17, 18

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?	☐	☐	☒	

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)?	☒	☐	☐	19
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	19

Comments:

Name of the main author of the protocol: _____

Date: dd/month/year _____

Signature: _____

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Approval	[redacted]
Approval	[redacted]

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