PASS Protocol	
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A Worldwide Pregnancy Safety Study to Assess Maternal, Foetal, and Infant Outcomes Following Exposure to Efgartigimod alfa during Pregnancy and/or Breastfeeding

Protocol version identifier:	2.0
Date of last version of protocol:	05 September 2023
EU PAS Registration Number:	Study to be registered
Active Substance:	efgartigimod alfa
Medicinal Product:	VYVGART®
Product Reference:	H0005849
Procedure Number:	EMEA/H/C/005849/MEA 004.2
Marketing Authorisation Holder(s) (MAH):	argenx BV
Joint PASS:	No
Research Question and Objectives:	The objectives of this pregnancy safety study are to describe: • pregnancy outcomes of women who were exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy • the prevalence of major and minor congenital malformations (MMCM) identified in foetuses, neonates, and infants through 12 months of age who were exposed to efgartigimod *in utero* • the incidence of other events of interest identified in neonates and infants through 12-months of age who were exposed to efgartigimod *in utero* or during breastfeeding • pregnancy complications in women who were exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy
Countries of Study:	All countries where efgartigimod is marketed
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Marketing authorisation holder(s)

MAH(s)	argenx BV
MAH contact person	[redacted]

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Abbreviation	Meaning
AChR	acetylcholine receptor
ACOG	American College of Obstetricians and Gynecologists
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AFP	alpha-fetoprotein
AJOG	American Journal of Obstetrics and Gynecology
AMC	arthrogryposis multiplex congenita
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
ART	assisted reproductive technology
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CRF	case report form
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
CVS	chorionic villus sampling
DMP	data management plan
DNA	deoxyribonucleic acid
EDD	estimated delivery date
EFPIA	European Federation of Pharmaceutical Industries and Association
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
EUROCAT	European Network for Population-based Registries for the Epidemiological Surveillance of Congenital Anomalies
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FTT	failure to thrive
gMG	generalized myasthenia gravis
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCG	human chorionic gonadotropin
HCP	healthcare provider
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICF	informed consent form

Abbreviation	Meaning
ICMJE	International Committee of Medical Journal Editors
ICSR	individual case safety report
IEC	Independent Ethics Committee
IgG(1)	immunoglobulin G and immunoglobulin G1
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IUGR	intrauterine growth restriction
LMP	last menstrual period
LRP4	lipoprotein-related protein 4
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Market Authorization Holder
MCM	major congenital malformation
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MHLW	Ministry of Health, Labour and Welfare
MMCM	major and minor congenital malformation
MRP	medical review plan
MuSK	muscle-specific kinase
NBDPN	National Birth Defects Prevention Network
NDI	National Death Index
OB/GYN	obstetrician/gynaecologist
OWH	Office on Women's Health
PAS	post-authorisation study
PASS	post-authorisation safety study
PDR	Prescriber's Digital Reference
PER	pregnancy exposure registry
PIH	pregnancy-induced hypertension
PMR	post-marketing requirement
PPROM	preterm premature rupture of membranes
PRAC	Pharmacovigilance Risk Assessment Committee
PROM	premature rupture of membranes
Q3	quarter 3
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SAR	severe adverse reaction
SCC	study coordinating centre
SD	standard deviation
SME	subject matter expert
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Abbreviation	Meaning
TORCH	toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV
UBC	United BioSource LLC
UL	upper limit
US	United States
WHO	World Health Organization

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) study guidance document, (1) the applicable guidelines (Good Pharmacovigilance Practice [GVP] Module VIII), (2) the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

[redacted], MD PhD Chief Medical Officer argenx	See appended signature page Signature Date
[redacted], MD Vice President, Head of Global Patient Safety argenx	See appended signature page Signature Date
[redacted], MD PhD Qualified Person for Pharmacovigilance argenx	See appended signature page Signature Date
Amy Miller, RPh, PharmD Principal Investigator United BioSource LLC	Signature DocuSigned by: [redacted]

4. Abstract

Title	A Worldwide Pregnancy Safety Study to Assess Maternal, Foetal, and Infant Outcomes Following Exposure to Efgartigimod during Pregnancy and/or Breastfeeding Version 2.0 [December 2023]
Rationale and background	VYVGART (efgartigimod) was approved on 17 December 2021 by the Food and Drug Administration (FDA) for the treatment of generalized myasthenia gravis (gMG) in adults who test positive for the acetylcholine receptor (AChR) antibody (FDA 2021). The product also received approval on 20 January 2022 for gMG (only when treatment with steroids or non-steroidal anti-inflammatory drugs does not lead to sufficient response) by Japan's Ministry of Health, Labour and Welfare (MHLW) (argenx 2022). The Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion, on 23 June 2022, for efgartigimod as an add-on therapy for the treatment of adult patients with gMG who are AChR antibody positive. There are no studies of efgartigimod exposure in pregnant women. Pregnant and breastfeeding patients were excluded from the clinical studies. The safety of efgartigimod in pregnant and breastfeeding women is unknown. In order to better describe the safety profile of efgartigimod when used during pregnancy, the Sponsor is conducting a safety study to collect and evaluate the effect of efgartigimod on the pregnancy outcomes, and on the health and development of infants exposed in utero and/or through breast milk. The absence of comprehensive research on human pregnancy exposures to efgartigimod and the potential for females of reproductive potential to be exposed to the product make such a study an essential component of the ongoing program of pharmacoepidemiologic studies on the safety of efgartigimod.
Research question and objectives	This pregnancy safety study will assess maternal, foetal, and infant outcomes following exposure to efgartigimod during pregnancy and/or breastfeeding. The study is being conducted to fulfil requests from both the FDA and the EMA. The objectives of this pregnancy safety study are to describe: • pregnancy outcomes of women who were exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy • the prevalence of major and minor congenital malformations (MMCM) identified in foetuses, neonates, and infants through 12 months of age who were exposed to efgartigimod in utero • the incidence of other events of interest identified in neonates and infants through 12-months of age who were exposed to efgartigimod in utero or during breastfeeding • pregnancy complications in women who were exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy
Study design	This is a multi-country safety study of pregnant women exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy. Women exposed

to efgartigimod only during breastfeeding will also be eligible to enrol. Background rates of major congenital malformations (MCMs), which will be obtained from populations within the same countries/regions as the countries/regions in which the efgartigimod-exposed pregnancies were reported, will be used as reference rates.

Specifically, data from the United States (US), European union (EU), and Japan will be used to determine expected rates in each of these regions, respectively, as described below.

US - Historically the overall prevalence of MCMs in the Metropolitan Atlanta Congenital Defects Program (MACDP) is approximately 3% of live births and has been stable with 2.8% prevalence in 1978 to 3.0% prevalence in 2005 (test for trend p = 0.19) (Rynn 2008). The most recent background MCM rate was reported as 3% based on the Centers for Disease Control and Prevention (CDC) Birth Defects homepage (CDC 2020a).

EU - European data reported MCM prevalence of 23.8 per 1,000 (or 2.38%) births for 2000-2004, and live birth prevalence of 19.9 per 1,000 birth or (1.99%) (EUROCAT Central Registry 2009).

Japan - A recent study from Japan reported MCM prevalence of 298.6 per 10,000 (or 2.99%) births for 2011–2014 for malformations identified either at birth or 1 month of age. (Mezawa 2019).

Background rates from a myasthenia gravis (MG) population not exposed to efgartigimod will be considered as an additional comparator. Published literature will be reviewed to determine if reliable background rates of MCM in an MG population without efgartigimod exposure are available, for each of the geographic regions represented in the efgartigimod-exposed population (US, EU, and Japan). If available contemporary data sources of MG population cannot distinguish specific exposures and, therefore, cannot be used to provide background MCM rates on a non-efgartigimod exposed population of patients with MG, data on MCM prevalence for the time period prior to efgartigimod commercial availability in each region will be used.

Enrolment will take place for about 8.25 years and collect follow- up data for up to 10 years following the date of the first patient's enrolment, to enable complete capture of the infant outcomes for all enrolled pregnancies with live-birth deliveries. All infants exposed in utero and/or through breastfeeding will be followed through 12 months of age with the exception of an infant death or loss to follow-up). Pregnant women will be followed from the time of enrolment until their pregnancy outcome is known (i.e., maximum of 9 months).

Analyses will follow a detailed statistical analysis plan (SAP), and the results will be descriptive. The study is not intended to test pre-defined statistical hypotheses.

Two (2) mutually exclusive subgroups of the pregnancy safety study population are defined as follows, depending on whether or not the woman is still pregnant at the time of enrolment.

Retrospective Pregnancy: woman is no longer pregnant at time of study enrolment but was exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy.

	Prospective Pregnancy: woman is pregnant or breastfeeding at time of study enrolment. All enrolment and follow-up data will be collected directly from the patient and her healthcare providers (HCPs). Pregnant women may be referred from any ongoing efgartigimod observational studies and clinical trials.
Population	Eligible women will be actively recruited from the US, Japan, and all additional countries that have received authorization for efgartigimod marketing at the time of protocol approval. Recruitment will be expanded over the course of the pregnancy safety study, as efgartigimod continues to be approved in additional countries. In the US and other countries where direct patient contact is allowed, women can self-enrol into the pregnancy safety study or may be enrolled by their HCP. In all other countries, the patient will be enrolled into the study by her HCP. In countries where the pregnant women are enrolled by HCPs, evidence of assessment of all eligibility criteria by the physician or a delegate, as well as enrolment of a pregnant patient in the pregnancy safety study, should be documented in her medical records. Inclusion criteria: 1. Women with exposure to efgartigimod any time within 25 days prior to conception or any time during pregnancy, or women with exposure to efgartigimod during breastfeeding. The timeframe of 25 days prior to conception is calculated based on five times the efgartigimod half-life, which is 3 to 5 days.[1] 2. Written informed consent or eConsent (depending on country regulations) (for adolescents under the age of majority, written informed assent or eConsent by the pregnant minor (where applicable) and written informed consent or eConsent by the parent/legal guardian). There are no exclusion criteria.
Variables	**Exposure variables include:** The following information related to each efgartigimod exposure will be captured: • Administration date during pregnancy or in the 25-day period prior to conception • Dose and any dose change(s) **Covariates include:** • Exposure during pregnancy (by trimester) to tobacco, alcohol, illicit drug use and other teratogenic exposure • Preconception care including pregnancy planning, fertility assessment and preconception screening • Concomitant medications

[1] VYVGART. Summary of Product Characteristics. Accessed on 14 April 2023, from https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf

	○ By trimester and any time during pregnancy ○ In neonates and infants through 12 months of age **<u>Outcomes variables include:</u>** • Pregnancy outcomes ○ Spontaneous abortion ○ Elective or therapeutic abortion ○ Foetal death/stillbirth ○ Molar or ectopic pregnancy ○ Live birth ▪ Preterm delivery ▪ Full-term delivery • Congenital malformations (CDC 2020b) identified in the developing foetus, neonate, or infant ○ MCMs ○ Minor congenital malformations • Other events of interest identified in the developing neonate and infant ○ Hospitalizations for serious illness ○ Potential adverse reactions to medications ○ Growth and development milestones as described by the Centers for Disease Control and Prevention (CDC 2021) or other accepted standard assessment ○ Infant developmental deficiency (CDC 2021) ○ Postnatal growth deficiency or failure to thrive (FTT) ○ Neonatal and infant mortality ○ Infections ○ Transient neonatal myasthenia ○ Vaccination status and reactions to the vaccines • Maternal complications of pregnancy, including but not limited to: ○ Premature rupture of membranes (PROM) ○ Preterm PROM (PPROM) ○ Pre-eclampsia ○ Gestational hypertension ○ Eclampsia ○ Severe pregnancy-induced hypertension (PIH) ○ Proteinuria ○ Gestational diabetes ○ Intrauterine growth restriction (IUGR) ○ Polyhydramnios • Maternal infections • Measures of foetal growth deficiency (e.g., small for gestational age)
Data sources	Data will be collected by various methods, when and/or if applicable, including telephone interviews conducted by the study coordinating centre (SCC) with the woman and her HCPs, reports sent to the SCC from spontaneous reports received by

	argenx, and medical records obtained for identified MCMs. In countries where HCP sites are enrolled, reports will come from the HCPs and their sites. For reports received after pregnancy outcome, applicable information will be collected from the patient (where allowed) and from her HCP and the infant's HCP (if applicable for a live birth). Region-specific analyses will be performed to address potential variation in data (e.g., completeness of medical event documentation) by method of data collection. Birth outcome data provided by the woman will be verified, whenever possible, by an HCP. A subject matter expert (SME), a teratologist or a specialist with similar expertise, will adjudicate all reports of MMCM.
Study size	Sample size is driven by the expected number of women of childbearing age who are prescribed efgartigimod and become pregnant. Given that MG is (1) a rare disease and (2) a potentially debilitating and clinically severe condition, the number of prospectively enrolled pregnancies over the 8.25-year enrolment period is expected to be approximately 279 .
Data analysis	Statistical analyses will be descriptive in nature. The study is not intended to test pre-defined statistical hypotheses. The prevalence of MCM among live births and 95% confidence intervals (CIs) will be calculated using the exact binomial distribution and compared to the MCM prevalence in the general population (country-specific) as reported in published literature and if possible, to an MG population without efgartigimod exposure (country-specific). The prevalence of minor congenital malformation among live births and 95% confidence intervals (CIs) will be calculated using the exact binomial distribution. A formal SAP will include details of all planned analyses and presentation of study data. Depending on the endpoint, the analysis population will be one of the following: pregnancies, live births, foetuses and breastfed infants. Pregnancy outcomes include the number of women with a pregnancy, number of women with pregnancy complete (includes spontaneous abortion, elective abortion, molar or ectopic pregnancy, foetal death/stillbirth, preterm delivery, and live birth), number of pregnancies ongoing, number of pregnancies with outcome lost to follow-up, number of known foetuses. Results will be presented for all enrolled pregnancies overall as well as separately according to whether a pregnancy was enrolled prospectively and retrospectively. Additionally, results will be presented by (1) type of recruitment method whenever sufficient numbers of exposed pregnancies are available to support this analysis, and (2) region. Endpoints characterizing a live birth include sex, estimated gestational age, size relative to gender, weight, length, head circumference, APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores at time points reported, medications/treatments, tests/procedures performed and any associated diagnoses. Live birth characteristics will be summarized using descriptive statistics by number of live births with the exception of maternal complications which will be by enrolled pregnancies. Rates of MCM and rates of minor congenital malformation will be computed for pregnancies where pregnancies with multiple foetuses will be considered as having an MCM if at least one of the foetuses or infants have an MCM or minor congenital malformation. Rates will also be computed for MCM relative to foetuses and live births.

	A 2-sided 95% CI for these rates will be calculated using exact Clopper-Pearson methods (Clopper-Pearson 1934). Summary statistics of feeding patterns will be calculated including rate of breastfeeding, duration, exclusivity of breastfeeding, degree of formula supplementation and milk production and rate of infection.
Milestones	The date of data collection commencement is driven by the PRAC approval on the study protocol.

Milestone	Planned date
Registration in the EU post-authorisation studies (PAS) register	December 2023
Start of data collection[1]	December 2023
First interim report	December 2024
End of data collection	December 2032
Final report of study results	June 2034
[1] *Interim reports will be provided annually.*	

5. Amendments and updates

None.

6. Milestones

The initial planned dates for key milestones in this study are outlined below.

The expected study start date is December 2023. The planned end of data collection is anticipated by December 2032. The study will collect data for approximately 10 years. Patient enrolment will occur over 8.25 years, allowing women who become pregnant at the end of the enrolment period to complete gestation and one year of infant follow-up.

Interim progress reports will be submitted to the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) annually through the end of study date. The final study report will be submitted to FDA and EMA in June 2034, or earlier should the study end at an earlier timepoint with agreement from the Health Agencies.

Milestone	Planned date
Initial submission of study protocol to PRAC	25 November 2022
Submission of revised study protocol for PRAC approval	19 September 2023
Estimated approval of study protocol by PRAC	December 2023
Registration in EU-PAS Register*	December 2023

Milestone	Planned date
Start of data collection/first patient enrolled*	December 2023
Last patient enrolled*	February 2031
End of data collection*	December 2032
Interim report 1*	December 2024
Interim report 2*	December 2025
Interim report 3*	December 2026
Interim report 4*	December 2027
Interim report 5*	December 2028
Interim report 6*	December 2029
Interim report 7*	December 2030
Interim report 8*	December 2031
Interim report 9*	December 2032
Interim report 10*	December 2033
Final report of study results*	June 2034

Abbreviations: EU-PAS=European Union Post-Authorisation Study Register; PRAC=Pharmacovigilance Risk Assessment Committee.

7. Rationale and background

Myasthenia gravis (MG) is a rare autoimmune disease in which antibodies (acetylcholine receptor [AChR], muscle-specific kinase [MuSK], and lipoprotein-related protein 4 [LRP4]) bind to the postsynaptic muscle membrane at the neuromuscular junction. Therapy is symptomatic, with options including immunosuppressive drugs (e.g., acetylcholine esterase inhibitor pyridostigmine, prednisone/prednisolone, azathioprine), thymectomy, and supportive therapy such as physical training. Of the two clinical types of MG (ocular and generalized), generalized MG (gMG) is more common, accounting for approximately 80 - 85 percent of cases. Generalized myasthenia gravis is also more debilitating than ocular, as multiple muscle groups are affected and involvement of oropharyngeal or respiratory muscles can lead to serious complications including death (Hehir 2018, Gilhus 2017).

7.1 Incidence and prevalence

There are variations in MG prevalence and incidence both among and within countries, which may be attributable to small patient numbers, reference size of the catchment population, clinical report source (usually clinics and hospitals), case ascertainment method, and extrapolation to the catchment population. Prevalence and incidence vary between urban (city) and rural areas (D'Alessandro 1991, Howard 2015). Biological factors may contribute to the rate variation, as the occurrence of MG is influenced by sex, age, and race (Trouth 2012). Worldwide, MG has a prevalence rate of <1 per 10,000 persons and an incidence of 0.3 per 10,000 persons per year (Hehir 2018).

A recent Republic of Moldova publication, which synthesized MG epidemiology data available through 2019 from studies around the world, reported that Argentina had the highest incidence (61.33 per million person-years), followed by Sweden (29 per million person-years) and Australia (24.9 per million person-years). The global incidence rate of AChR antibody- positive MG ranges between 4 and 18 per million person-years (Bubuioc 2021). Epidemiological data from population-based epidemiological studies and the Myasthenia Gravis Foundation of America (MGFA) indicated that the MG incidence is ≤4 persons per 10,000 population per year, and the MG prevalence is <2 persons per 10,000 population in the US. This prevalence indicates an estimate of 56,000–123,000 patients in Europe and 60,000 patients in the US (Howard 2015).

The worldwide incidence and prevalence have been rising steadily over the past decades. These increases are attributed to greater awareness of the disease and improvements in diagnostic antibody testing (e.g., anti-AChR antibody receptor assay), increasing longevity, and treatment of the disease leading to better survival (Phillips 2003, Carr 2010). A bimodal age distribution has been consistently observed, with two peaks of incidence: early-onset MG in the third decade (mostly females) and late-onset MG in the elderly (mostly males). As with most autoimmune diseases, MG is more prevalent in women than in men. In early-onset MG, the female: male ratio is 3:1 (Hehir 2018). Asian populations report more cases of early-onset MG, which is more often ocular MG (Bubuioc 2021).

Efgartigimod (efgartigimod alfa) is a human recombinant immunoglobulin 1 (IgG1)-derived Fc fragment produced in Chinese hamster ovary by recombinant deoxyribonucleic acid (DNA) technology. Efgartigimod is a first-in-class neonatal Fc receptor (FcRn) antagonist that blocks FcRn recycling of IgG. This blocking reduces IgG levels, representing a therapeutic approach to autoimmune diseases mediated by IgG autoantibodies (Akilesh 2007, Latvala 2017, Roopenian 2007, Ward 2003). Efgartigimod does not affect the levels of other immunoglobulins (IgA, IgD, IgE or IgM), or those of albumin.

VYVGART (efgartigimod alfa) was approved on 17 December 2021 by the FDA for the treatment of gMG in adults who test positive for the AChR antibody (FDA 2021). The product also received approval on 20 January 2021 for the gMG (only when treatment with steroids or non- steroidal anti-inflammatory drugs does not lead to sufficient response) by Japan's Ministry of Health, Labour and Welfare (MHLW) (argenx 2022). The Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion, on 23 June 2022, for efgartigimod as an add-on therapy for the treatment of adult patients with gMG who are AChR antibody positive.

7.2 MG during pregnancy and impact to the infant

MG is common during the second and third decades of life, coinciding in females with the age of maximal fertility and active family planning. Most women remain stable during pregnancy if their symptoms are controlled before conception. Their fertility is near normal. Women with MG do not have a higher risk of an infant with genetic disorders or structural defects, with the exception of foetal arthrogryposis multiplex congenita (AMC). This complex condition occurs in <1 percent of babies of mothers with MG. Foetal AMC is thought to result due to transplacental transfer of maternal autoantibodies against the foetal-type of AChR after 14–16 weeks (Cimpoca-Raptis 2021, Gilhus 2020, Waters 2019). A Taiwanese study conducted in two nationwide population-

based datasets did not demonstrate statistically significant differences in risk of adverse pregnancy outcomes (e.g., low birthweight, preterm birth, caesarean sections and babies born small for gestational age) in pregnant women with MG compared with a comparator cohort of randomly selected pregnant women without MG (Wen 2009).

Pyridostigmine, prednisolone, and azathioprine as treatments to control disease symptoms are generally regarded as safe during pregnancy. Mycophenolate, methotrexate and cyclophosphamide are contraindicated because of their teratogenic risk and should not be used by women with the potential to become pregnant. Rituximab should also be discontinued prior to a pregnancy as it may cause an altered neonatal immune response (Cimpoca-Raptis 2021, Gilhus 2020, Waters 2019, Sanders 2016).

Around 10–20 percent of new-borns of mothers with MG develop transient neonatal myasthenia during the first few days after birth due to transfer of antibodies AChR or MuSK across the placenta. The symptoms, usually mild with some sucking and swallowing difficulties, typically last days to a few weeks and are treatable with acetylcholinesterase inhibitors (Waters 2019). In a Norwegian nationwide cohort, 5 out of 125 MG babies had confirmed neonatal myasthenia and another 10 were transferred to a neonatal ward (Gilhus 2020).

7.3 Efgartigimod exposure during pregnancy and breast-feeding

Antibodies including therapeutic monoclonal antibodies are known to be actively transported across the placenta (after 30 weeks of gestation) by binding to the FcRn (Latvala 2017, Pentsuk 2009). Therefore, efgartigimod alfa may be transmitted from the mother to the developing foetus, as antibodies including therapeutic monoclonal antibodies are known to be actively transported across the placenta (after 30 weeks of gestation) by binding to the FcRn. Therefore, efgartigimod may be transmitted from the mother to the developing foetus. As efgartigimod is expected to reduce maternal antibody levels and in addition blocks the active transfer of maternal antibodies, reduction in passive protection to the new-born is expected.

There are no studies of efgartigimod exposure in pregnant women. Therefore, the assessment of potential risks of adverse outcomes associated with exposure during pregnancy is based on animal data. Toxicity studies investigating male and female fertility, maternal toxicity, embryo-foetal development, and postnatal development were conducted for efgartigimod alfa administered in rats and rabbits. Efgartigimod alfa, up to the high dose of 100 mg/kg/day, was shown to have no teratogenic effects in the rat and rabbit and did not adversely affect male and female fertility or any other reproductive and developmental performance in rats. Observed rates of morbidity or loss of offspring were within historical background rates (Pentsuk 2009).

To better describe the safety profile of efgartigimod when used during pregnancy, the Sponsor is conducting a global pregnancy safety study to collect and evaluate the effect of efgartigimod on the pregnancy outcomes, and on the health and development of infants exposed in utero and/or through breast milk. The absence of comprehensive research on human pregnancy exposures to efgartigimod and the potential for females of reproductive potential to be exposed to the product makes such a study an essential component of the ongoing program of pharmacoepidemiologic studies on the safety of efgartigimod.

In an effort to assure that the pregnancy safety study collects, analyses, and presents information that is useful to the HCPs and other stakeholders, the pregnancy safety study will conform to the FDA Guidance for Industry: Post-approval Pregnancy Safety Studies (2019), Guidelines for Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment (2005), and International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (2008). Additionally, the pregnancy safety study will be carried out in accordance with guidelines and regulations of European Medicines Agency (EMA) (EMA 2005) as well as EMA guidelines on good pharmacovigilance practices and applicable local laws and regulations. Recommendations by other relevant organizations will be followed (European Federation of Pharmaceutical Industries and Association (EFPIA) 2014).

8. Research question and objectives

This global pregnancy safety study will assess maternal, foetal, and infant outcomes following exposure to efgartigimod during pregnancy. The study is being conducted to fulfil the following FDA post-marketing requirement at the time of VYVGART approval to monitor the safety profile of efgartigimod during pregnancy and/or breastfeeding (post-marketing requirement [PMR] 4202-1):

> *"Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to VYVGART (efgartigimod) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing foetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol."*

This study is also being conducted to address the efgartigimod safety concern of 'use in pregnant women' identified in the EU Risk Management Plan (RMP).

The objectives of this pregnancy safety study are to describe:

- pregnancy outcomes of women who were exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy
- the prevalence of major and minor congenital malformations (MMCM) identified in foetuses, neonates, and infants through 12 months of age who were exposed to efgartigimod in utero
- the incidence of other events of interest identified in neonates and infants through 12-months of age who were exposed to efgartigimod in utero or during breastfeeding
- pregnancy complications in women who were exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy

9. Research methods

9.1 Study design

This is a multi-country safety study of pregnant women exposed to efgartigimod during pregnancy or any time within 25 days prior to conception. Infants exposed in utero or through breastfeeding will be followed through 12 months of age. Analyses will follow a detailed statistical analysis plan (SAP), and the results will be descriptive. The study is not intended to test pre-defined statistical hypotheses. argenx BV is the study Sponsor.

Two (2) mutually exclusive subgroups of the pregnancy safety study population are defined as follows, depending on whether the woman is still pregnant at the time of enrolment.

Retrospective Pregnancy: woman is no longer pregnant at the time of study enrolment but exposed to efgartigimod any time within 25 days prior to conception or any time during the pregnancy.

Prospective Pregnancy: woman is pregnant or breastfeeding at the time of study enrolment.

Eligible women will be recruited from the US, Japan, and all additional countries that have received authorization for efgartigimod marketing at the time of protocol approval. Recruitment will be expanded over the course of the pregnancy safety study, as efgartigimod continues to be approved in additional countries. An external historical control will be used as a comparator. Background rates of major congenital malformations (MCMs) will be obtained from populations within the same countries/regions as the countries in which the efgartigimod-exposed pregnancies were reported. Specifically, data from the US, EU, and Japan will be used to determine expected rates in each of these regions, as described below.

US - Historically the overall prevalence of MCMs in the Metropolitan Atlanta Congenital Defects Program (MACDP) is approximately 3% of live births and has been stable with 2.8% prevalence in 1978 to 3.0% prevalence in 2005 (test for trend p = 0.19) (Rynn 2008). The most recent background MCM rate was reported as 3% based on the CDC Birth Defects homepage (CDC 2020a).

EU - European data reported MCM prevalence of 23.8 per 1,000 (or 2.38%) births for 2000-2004, and live birth prevalence of 19.9 per 1,000 birth or (1.99%) (EUROCAT Central Registry 2009).

Japan - A recent study from Japan reported MCM prevalence of 298.6 per 10,000 (or 2.99%) births for 2011–2014 for malformations identified either at birth or 1 month of age. (Mezawa 2019).

Background rates from an MG population not exposed to efgartigimod will be considered as an additional comparator. Published literature will be reviewed to determine if reliable background rates of MCMs in an MG population without efgartigimod exposure are available, for each of the geographic regions represented in the efgartigimod-exposed population (US, EU, and Japan). Contemporary data sources will be investigated to identify availability of this information. If

identified data sources cannot distinguish specific exposures and, therefore, cannot be used to provide background MCM rates on a non-efgartigimod exposed population of patients with MG, data on MCM prevalence for the time period prior to efgartigimod commercial availability in each region will be used.

The pregnancy safety study is expected to start no later than December 2023 and will enrol all eligible pregnancies with exposure to efgartigimod during pregnancy or any time within 25 days prior to conception. The earliest launch date of efgartigimod was in the US (January 2022), followed by a launch date of May 2022 in Japan.

Information on pregnancies that occur in women exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy will be collected by the VYVGART Study Coordinating Centre (SCC) from healthcare providers (HCPs) who are treating pregnant women with efgartigimod, and from the pregnant women. The SCC will also collect information on secondary contacts from the pregnant women (i.e., individuals both within and outside her household who will know her whereabouts should she become lost to follow-up). Secondary contacts will be used to update the woman's contact information if needed, not to collect clinical data on the woman or her baby. The SCC will conduct a proactive, multipronged outreach as indicated in Section 9.2.5 of this protocol to encourage reporting of pregnancy exposures and enrolment into the study.

All enrolment and follow-up data will be collected directly from the patient and her HCPs. Pregnant women may also be referred from any ongoing efgartigimod observational studies and clinical trials. Once a patient in an observational study provides consent to be enrolled in this study, the SCC will collect the overarching enrolment data from the respective study and then the subsequent follow-up information will be collected directly from the HCP and the patient.

The SCC will collect the patient's written consent or eConsent (depending on country regulations) and a Release of Medical Information Form directly from the patient (if applicable). In instances where the HCP initially reported the pregnancy, the HCP may obtain the patient's written consent or eConsent. The consent and a medical release form will allow the SCC to contact the patient's prescriber, obstetrician, treating physician and other HCPs and the infant's paediatric HCP. Once consent is obtained, the SCC will obtain enrolment information from the patient and from the HCP(s) using a structured questionnaire. The SCC will follow patients at specified time-points throughout their pregnancies and live births through 12 months of age.

As the pregnancy safety study is observational, medical treatment for each pregnant woman and infant should be consistent with routine local clinical practice and will not be mandated or required in any way by the safety study protocol. No additional diagnostic or monitoring procedures will be applied. The choice of ongoing medical treatment for the duration of the pregnant patient's and infant's participation in the safety study will be made independently by their HCPs in the regular course of practice and will not be influenced by their participation in this observational study.

The safety study will enrol pregnant women with efgartigimod exposure for 8.25 years and collect follow-up data for up to 10 years following the date of the first patient's enrolment, to enable

complete capture of the infant outcomes for all enrolled pregnancies with live-birth deliveries. Pregnant women will be followed until their pregnancy outcome is known. Infants will be followed through 12 months of age. Data will also be collected for pregnancies in which the outcome was known prior to enrolment in the study.

9.1.1 Study endpoints

The endpoints are:

- Pregnancy outcomes
  - Spontaneous abortion
  - Elective or therapeutic abortion
  - Foetal death/stillbirth[2]
  - Molar or ectopic pregnancy
  - Live birth[3]
    - Preterm delivery
    - Full-term delivery
- Congenital malformations (CDC 2020b) identified in the developing foetus, neonate, or infant
  - MCMs
  - Minor congenital malformations
- Other events of interest identified in the developing neonate and infant
  - Hospitalizations for serious illness
  - Potential adverse reactions to medications
  - Growth and development milestones as described by the Centers for Disease Control and Prevention (CDC 2021) or other accepted standard assessments
  - Infant developmental deficiency[4] (CDC 2021)
  - Postnatal growth deficiency or failure to thrive (FTT)[5]

[2] If gestational age is unknown, a foetus weighing ≥ 350g.
[3] Birth of a living foetus at ≥ 20 gestational weeks or, if gestational age is unknown, a foetus weighing ≥ 350 g.
[4] Failure to achieve the developmental milestones for chronological age, as defined by the CDC. Infant developmental deficiency will be evaluated at 3, 6, 9, and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development) separately.
[5] Weight in < 10th percentile for sex and chronological age on standard growth charts. Postnatal growth deficiency will be evaluated at 3, 6, 9, and 12 months of infant age. For the determination of postnatal growth deficiency, the study will utilize the sex-specific international growth reference standards from the World Health Organization for children ages 0 to 24 months. The World Health Organization growth standards are recommended for use in the US for infants and children 0 to 2 years of age.

- Neonatal and infant mortality[6]
- Infections
- Transient neonatal myasthenia
- Vaccination and vaccine reactions

- Maternal complications of pregnancy, including but not limited to:
  - Premature rupture of membranes (PROM)
  - Preterm PROM (PPROM)[7]
  - Pre-eclampsia[8] (American College of Obstetricians and Gynecologists [ACOG] 2020)
  - Gestational hypertension[9] (American Journal of Obstetrics and Gynecology [AJOG] 2000)
  - Eclampsia[10] (ACOG 2020)
  - Severe pregnancy-induced hypertension
  - Proteinuria
  - Gestational diabetes
  - Intrauterine growth restriction (IUGR)
  - Polyhydramnios
- Maternal infections
- Measures of foetal growth deficiency (e.g., small for gestational age[11]) (Kozuki 2015)

[6] Neonatal mortality is defined as death of a live-born infant within 28 days of life; infant mortality is defined as death of a live-born infant >28 days but within 1 year of life.
[7] Membrane rupture before labour that occurs before 37 weeks of gestation.
[8] A disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term, and proteinuria. Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:
- Thrombocytopenia: Platelet count less than 100 x 109/L
- Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary oedema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms.

[9] A systolic blood pressure 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure.
[10] The convulsive manifestation of the hypertension disorders of pregnancy and is among the more severe manifestations of the disease. Eclampsia is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial haemorrhage, or drug use.
[11] Weight at birth in < 10th percentile for sex and gestational age using standard growth charts for full and preterm live-born infants. For the determination of SGA, the study will use the sex-specific international growth reference standards from the International Foetal and New-born Growth Consortium for the 21st Century (INTERGROWTH-21st) for those born between 24$^{0/7}$ and 42$^{6/7}$ gestational weeks. The INTERGROWTH-21st standards are the latest available global reference standards representing
[1]

9.2 Setting

The pregnancy safety study will actively pursue and attempt to capture all pregnancies that meet the eligibility criteria in the countries where efgartigimod is marketed. In the US and other countries where direct patient contact is allowed, women can self-enrol into the pregnancy safety study or may be enrolled by their HCP. In all other countries, the patient will be enrolled into the pregnancy safety study by her HCP.

9.2.1 Target population

All pregnancies occurring in any country where efgartigimod is approved to be marketed and in which the pregnant patient has been exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy are eligible for enrolment. In countries where the pregnant women are enrolled by HCPs, evidence of assessment of all eligibility criteria by the physician or a delegate, as well as enrolment of a pregnant patient in the safety study, should be documented in her medical records.

9.2.2 Patient selection

All pregnancies occurring in any country where efgartigimod is approved to be marketed and in which the pregnant patient has been exposed to efgartigimod any time within 25 days prior to conception or any time during pregnancy are eligible for enrolment. In countries where the pregnant women are enrolled by HCPs, evidence of assessment of all eligibility criteria by the physician or a delegate, as well as enrolment of a pregnant patient in the safety study, should be documented in her medical records.

Inclusion criteria

1. Women with exposure efgartigimod any time within 25 days prior to conception or any time during a pregnancy, or women with exposure to efgartigimod during breastfeeding. The timeframe of 25 days prior to conception is calculated based on five times the efgartigimod half-life, which is 3 to 5 days).[12]
2. Written informed consent or eConsent (depending on country regulations) (for adolescents under the age of majority, written informed assent or eConsent by the pregnant minor [where applicable] and written informed consent or eConsent by the parent/legal guardian).

Exclusion criteria

There are no exclusion criteria.

contemporary information from an international, multi-ethnic, diverse population, and have been specifically developed for modern research.

[12] https://www.ema.europa.eu/en/documents/product-information/efgartigimod-epar-product-information_en.pdf

9.2.3 Patient withdrawal

In this pregnancy safety study, withdrawal from the study is independent of the underlying therapy and will not affect the pregnant patient's medical care. A patient may withdraw from the study at any time and without giving a reason. If a patient wants to terminate pregnancy safety study participation, no further data will be collected. In case a patient would like to withdraw the consent given earlier, she should inform her HCP and the HCP should document the withdrawal in the case report form (CRF) as well as in the medical records. All data collected prior to the date of her withdrawal will be included in the study unless otherwise specified. If the request to withdraw is made to the SCC, the SCC will document this in the study database. Once the patient is withdrawn, the SCC will make no further attempt to contact her or her HCP.

9.2.4 Replacement

Enrolment in the pregnancy safety study is ongoing through 8.25 years. At the end of enrolment, women who drop out will not be replaced (e.g., withdrawal, loss to follow-up).

9.2.5 Recruitment of pregnant women

In the US and other countries where direct outreach is possible, proactive outreach will occur to solicit reports of women exposed to efgartigimod during pregnancy. Direct to prescriber HCP awareness mailings targeting prescriber lists will be done at least annually, using distribution data and other data to obtain lists of active prescribers. Information will be sent requesting that they identify any women who become pregnant while exposed to efgartigimod and invite them to participate in the pregnancy safety study. The limitations to generalizability of the pregnancy safety study population are described in Section 9.9.

The goal for effective outreach is to ensure that all HCPs who have direct contact with pregnant women being treated with efgartigimod or their infants are completely familiar with the pregnancy safety study and are able to educate and communicate information about the safety study to appropriate pregnant women. The pregnancy safety study will use effective recruitment strategies (DeWard 2014) that have also proven to be effective in previous pregnancy safety studies.

The following list provides initial strategies that will be considered to recruit eligible women into the pregnancy safety study. Strategies may be added over the course of the study as new methods for identifying women with potential to qualify for the study become available.

- Create a efgartigimod pregnancy safety study website
- Link to the pregnancy safety study on argenx's efgartigimod website
- Establish a direct mail campaign to prescribers, other HCPs, and women with MG in countries where direct patient contact is allowed
- Develop a Patient Brochure to be provided to HCPs and women and to be available on the website (with translations as needed, depending on the countries in which efgartigimod is marketed)

- Provide study information to patients in the age range of 15–50 years who are treated with efgartigimod through the designated Specialty Pharmacy as applicable
- Provide study information to investigators of ongoing efgartigimod studies, including expanded access programs, post-marketing studies, and investigator-initiated studies
- Collaborate with Patient Advocacy Groups and Medical Societies
- Establish a central SCC which will use call scripts for standard responses to HCPs and women about the pregnancy safety study
- Provide training to argenx Field Support about the pregnancy safety study
- Provide training to the My VYVGART Path Patient Support Program staff regarding enrolment into the study
- Establish a toll-free number and study website address printed on the US Prescribing Information and Medication Guide and other country labels where applicable
- Post the pregnancy safety study on the FDA Pregnancy Exposure Registry website (www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries)
- Post the pregnancy safety study on the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) https://www.encepp.eu/encepp/studiesDatabase.jsp

Additionally, spontaneous adverse event cases that report a pregnancy with exposure to efgartigimod will be another source to identify potentially eligible women for the study (either potential retrospective or prospective cases), assuming the case reports contain sufficient detail to contact the patient or her HCP(s).

The SCC will work with argenx to obtain a list of prescribers outside of the US who are treating women with efgartigimod, so that efgartigimod prescribers can be sent information about this pregnancy safety study and the importance of prompt reporting of pregnancies to the SCC in order to ensure that the site will promptly report any exposed pregnancy. In those countries, all communication with HCPs will follow local rules and regulations. When an eligible pregnancy is identified by a site, all the necessary documents to activate the site for the study will be obtained.

Details on each strategy are provided in the Table 1 below.

Table 1 Methods to Identify and Recruit Women into the Efgartigimod Pregnancy Safety Study

Recruitment Activity	Method
Efgartigimod Pregnancy Safety Study Website	The website will include: • Home • About the Pregnancy Safety Study • Why Enrol • Do You Qualify • Report a Pregnancy • Link to the Patient Informed Consent, Patient Brochure and the Medical Information Release form
Direct Mail Campaign to Prescribers and Other HCPs who Treat Women with Myasthenia Gravis	Direct to HCP awareness mailings targeting efgartigimod prescriber lists obtained by argenx and lists of specialists known to treat women with myasthenia gravis including investigators of ongoing efgartigimod observational studies, expanded access programs and post-marketing studies.
Direct Email to Women Using Lists Obtained through External Patient opt-in databases. (US only)	Direct to patient awareness emails targeting women of childbearing age with myasthenia gravis using lists obtained through external patient opt-in databases (e.g., Clinical Connections).
Patient Brochures	The brochure will include: • About the Pregnancy Safety Study • Why Enrol • Do You Qualify • Frequently Asked Questions • Contact Information for the SCC The patient brochure will be available on the website, included in the HCP letter, and in any mailings to women or Patient Advocacy Groups and will be available in multiple languages.
Collaborate with Patient Advocacy Groups and Medical Societies	Relationships will be established with the National Organization for Rare Disorders, the Myasthenia Gravis Foundation of America, the Muscular Dystrophy Association, Conquer Myasthenia Gravis, the European Myasthenia Gravis Association, Japan Myasthenia Gravis Association and other specialty networks and patient advocacy groups to inform them of the study and elicit support. Outreach will begin within 30 days after the launch of the pregnancy safety study website.
Central Study Coordinating Centre	The SCC will be staffed with clinical nurses with experience in conducting interviews with women to obtain pregnancy information and trained in handling the sensitivities surrounding both positive and negative pregnancy outcomes (El-Khorazaty 2007). They will respond to inbound calls regarding the study and enrol women who are interested in participating.

Recruitment Activity	Method
My efgartigimod Path	The My efgartigimod Path Patient Support Program can be used to provide a pregnancy safety study brochure and invitation letter to females of reproductive age that they identify.
Field Support Outreach	The Efgartigimod Medical Science Liaisons will inform physicians and institutions about the pregnancy safety study and direct them to the study website and the SCC.
argenx Pharmacovigilance Department	The Pharmacovigilance Department will send spontaneous pregnancy reports to the SCC for review and follow-up for potential patient enrolment into the pregnancy safety study.
Toll-free Number and pregnancy safety study Website Address Printed on the Prescribing Information and in the Medication Guide (in the US)	Under the FDA Pregnancy and Labelling Rule requirements, if there is a pregnancy registry/study for the product, relevant contact information must be included in product labelling under the subheading Pregnancy Safety Study and in the Patient Counselling Information.
Pregnancy Surveillance Program Listed on the FDA Pregnancy Exposure Registry Website	The FDA's Office on Women's Health (OWH) maintains an online list of pregnancy registries that are actively enrolling women to raise awareness about pregnancy registries and connect consumers and HCPs to pregnancy studies. The pregnancy safety study listing will be submitted to OWH.
Pregnancy Safety Study information included on a mobile drug reference like Epocrates, Prescriber's Digital Reference (PDR) or Medscape	Information can be added to these reference sources so that when a prescriber looks up efgartigimod, they would see pregnancy safety study information/messaging.

Abbreviations: FDA=Food and Drug Administration; HCP=Healthcare provider; MG=Myasthenia Gravis; OWH=Office on Women's Health; PDR=Prescriber's Digital Reference; SCC=Study Coordinating Centre; US=United States.

The different methods for recruiting pregnant woman with efgartigimod exposure into the study might impact study results for several reasons, including differences in:

- the underlying adverse pregnancy outcome risk profiles of pregnant women between recruitment methods (e.g., socioeconomic status [SES], prenatal care, smoking and alcohol use)
- the lost to follow-up rate

Outcome rates by type of recruitment method will be presented for methods that have sufficient number of exposed pregnancies to support this analysis. The Data Analysis section of the protocol (Section 9.7) describes this analysis.

9.2.6 Representativeness

The inclusion criteria for this pregnancy safety study are broad to represent the general exposed population, e.g., exposure to efgartigimod during pregnancy or any time within 25 days prior to conception and provision of informed consent. There are no exclusion criteria. All pregnant women who are identified as meeting the eligibility criteria will be invited to enrol in the

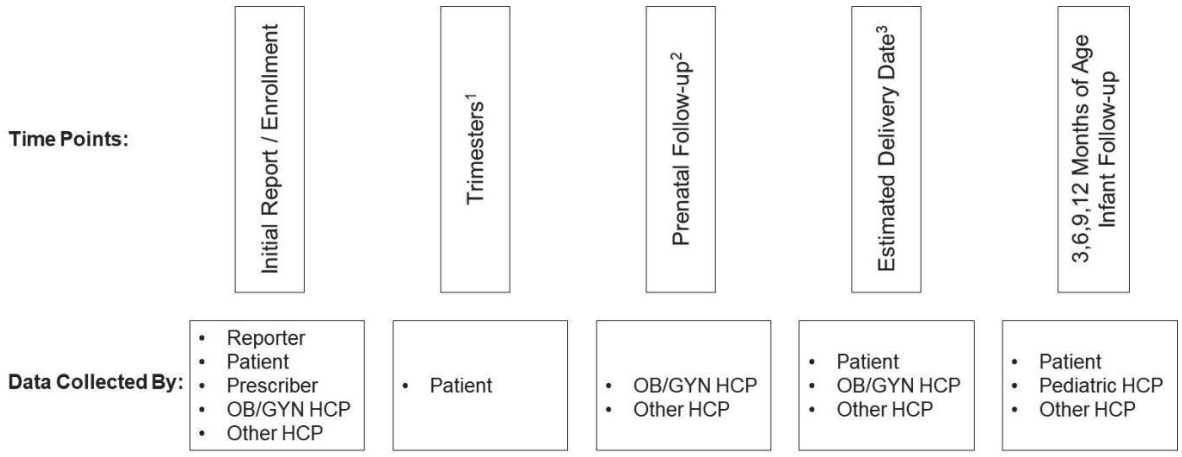
pregnancy safety study by the SCC or their treating HCP(s). However, women who agree to enrol in the pregnancy safety study may not be generalizable to the overall population of women of childbearing age being treated with efgartigimod and may represent particularly high-risk pregnancies. Additionally, those who enrol after the pregnancy outcome is known may be more likely to report adverse outcomes than women who have enrolled in the pregnancy safety study without knowledge of the pregnancy outcome.

9.2.7 Study visits

No mandatory visits, tests, or assessments are required for this pregnancy safety study. Pregnant women and infants will be treated according to the standard of care.

A Study Contact Schedule (Figure 1) is provided below to indicate the contacts per time point.

Figure 1 Pregnancy Surveillance Study Contact Schedule



Abbreviations: HCP = Healthcare Provider; OB/GYN = Obstetrician/Gynecologist
[1]Trimesters Follow-up: Tri 1-14 weeks ± 2 weeks, Tri 2-21 weeks ± 2 weeks, Tri 3-34 weeks ± 2 weeks
[2]Prenatal Follow-up: 34 weeks ± 2 weeks
[3]Estimated Delivery Date: 40 weeks ± 2 weeks

9.2.7.1 Initial report/enrolment

The following information will be collected at Enrolment from the pregnant patient or prescribing HCP. The SCC will review the information collected and will follow-up with the pregnant patient, where possible, and with the prescriber for supplemental information if needed. Since an exposed pregnancy can be reported at any time, the SCC is trained to collect the appropriate data based on the pregnancy status and outcome. The data to be collected will be documented on a CRF and are aligned with the appropriate time points but could be requested as soon as the outcome is reported or collected later based on the actual delivery date.

- Reporter (HCP, enrolled woman, other)
  - Date of report
  - Type of reporter

  - Name of reporter
  - Contact information of pregnant patient (name, address, phone, email)
    - Preferred method of contact
    - Secondary contact information
  - Pregnancy status
  - Names of efgartigimod prescriber and other HCPs
    - Name of efgartigimod prescriber and contact information
    - Name of obstetrician/gynaecologist (OB/GYN) or other HCP providing care for the pregnant mother and contact information
- Name of paediatrician or other HCP providing care for the infant (if determined, depending on timing of enrolment) and contact information
- Consent
  - Date of written consent or eConsent, and written assent or eConsent where required
- Enrolment in another observational study or pregnancy registry (yes/no)
- Eligibility criteria
- Maternal demographics (collection of complete data may not be possible in all regions)
  - Birth date, race and ethnic origin (in countries where permitted)
  - Level of education
  - Pre-pregnancy height and weight and Body Mass Index
- Obstetrical history
  - Number of previous pregnancies and outcome of each
  - Complications in previous pregnancies
  - Previous foetal/neonatal abnormalities
- Maternal medical history
  - MG disease history
    - Date of diagnosis
    - Medications and procedures (e.g., thymectomy, folic acid)
  - MG antibody type(s) (AChR, MuSK, LRP4, other, none, unknown)
  - Concomitant disease
  - Vaccination history (e.g., coronavirus disease 2019 [COVID-19], rubella)

- Family history of MCM
  - Relevant maternal/paternal family history of pregnancy complications/MCM
- History of infections (toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV [TORCH] and papillomavirus)

- Pregnancy information
  - Date of last menstrual period (LMP) for women enrolled prospectively (i.e., currently pregnant)
  - Estimated date of conception (pregnancy start date) hierarchy is based on the data collected. If all data are available, the estimated date of conception uses #1 to estimate the pregnancy start date:
    i. Date of conception = first day of the LMP date[13] + 14 days
    ii. Date of conception = Estimated gestational age using ultrasound, if collected
  - Estimated delivery date (EDD)
    - Method of EDD calculation from HCP
      - LMP
      - Ultrasound
      - Assisted reproductive technology (ART)
  - Number of foetuses
  - Pregnancy confirmed by serum Human Chorionic Gonadotropin (HCG)
  - Method of pregnancy conception, including in vitro fertilization
  - Pregnancy complications
  - Prenatal testing
    - Type (amniocentesis, ultrasound, chorionic villus sampling [CVS], glucose tolerance, maternal serum screening, alpha-fetoprotein [AFP], genetic, other)
  - Outcome – if reported retrospectively
  - Pregnancy report type (prospective, retrospective)
- Medication use any time within 25 days prior to conception and during pregnancy
  - Exposure to efgartigimod

[13] First day of LMP, defined as $0^{0/7}$ gestational weeks, will be calculated as estimated delivery date minus 280 days (40 weeks).

- Administration dates, and reason(s) for any treatment interruption or discontinuation
- Trimesters[14] of exposure (1, 2, 3)
- Gestational age at time of exposure in weeks/days (if available)
- Dose for each administration

- Exposure to known teratogenic medications (e.g., mycophenolate mofetil, methotrexate, cyclophosphamide)
  - First start date, dose, stop date or ongoing
  - Trimesters of exposure (1, 2, 3)
  - Gestational age at time of exposure in weeks/days (if available)
- Other concurrent medication use (prescription and non-prescription including pre-natal vitamins)
  - Indication
  - First start date, dose, stop date or ongoing
  - Trimesters of exposure (1, 2, 3)
  - Gestational age at time of exposure in weeks/days (if available)
- Possible risk factors (social and environmental)
  - Alcohol use
  - Smoking
  - Illicit drug use
  - Any potentially teratogenic exposures other than treatments for MG (e.g., occupational, environmental)
  - Diagnostic imaging (dates, type of imaging, area of examination)
  - Infections (rubella; toxoplasmosis; herpes; cytomegalovirus; syphilis [TORCH], papillomavirus)
  - Other

[14] Gestational weeks $2^{0/7}$ to $13^{6/7}$ will be considered the first trimester; gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester; gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester.

9.2.7.2 Trimester follow-up with the pregnant woman

In countries where direct data collection is possible, data will be collected at these time points directly from the pregnant patient if the pregnancy is still ongoing. In all other countries, the HCP will determine the status of the pregnancy and collect these data to report to the SCC.

End of 1st Trimester: Follow-up will be collected at 14 weeks ± 2 weeks gestation. If enrolment and baseline data collection fall within this window (i.e., 12-16 weeks gestation), follow-up will not be requested until the 2nd trimester.

Mid 2nd Trimester: Follow-up will be collected at 21 weeks ± 2 weeks gestation.

Mid 3rd Trimester: Follow-up will be collected at 34 weeks ± 2 weeks gestation.

The following information will be collected from the pregnant patient at each trimester:

- Source of information
- Date of contact
- Change in current pregnancy status
- Current gestational age in weeks and days at time of follow-up by ultrasound or LMP date
- Pregnancy status/outcome (i.e., ongoing pregnancy, miscarriage, live birth, spontaneous loss, elective or therapeutic termination, ectopic or molar pregnancy, foetal death, pregnancy complications)
- Gestational age at pregnancy outcome (weeks, days)
- Efgartigimod administration dates, and reason(s) for any treatment interruption or discontinuation
- Changes in other medications (new, continuing or discontinued)
- Changes in concurrent conditions and risk factors, including any new concurrent conditions
- Changes in maternal contact information
- Changes in maternal HCP and/or paediatrician contact information
- Changes in secondary contact information
- Adverse Events (AEs) and Serious Adverse Events (SAEs): maternal and foetal
- Infections (including aetiology; severity; treatment; duration; outcome)
- Targeted prenatal testing (to be collected from pregnant patient if it is not provided by her HCP)
    - Type (amniocentesis, ultrasound, CVS, glucose tolerance, maternal serum screening, AFP, genetic, other) and dates

- Evidence of a structural defect (specify defect)
- Gestational age at time of diagnosis

9.2.7.3 Prenatal follow-up with the HCP

Pregnancy information will be collected at this time point from the obstetric HCP, treating physician, and other HCPs if needed. Follow-up with the pregnant patient's HCPs will be collected at 34 weeks ± 2 weeks gestation. The following information will be collected from the HCP:

- Source of information
- Date of contact
- Pregnancy status and outcome, including risk factors and changes in medical condition and medications
- Efgartigimod administrations and dates, and reason(s) for any treatment interruption or discontinuation
- Current gestational age in weeks and days at time of follow-up by ultrasound or LMP date
- Targeted prenatal testing
  - Type (amniocentesis, ultrasound, CVS, glucose tolerance, maternal serum screening, AFP, genetic, other) and dates
  - Evidence of a structural defect (specify defect)
  - Gestational age at time of diagnosis
- Changes in maternal contact information
- Pregnancy-related AEs and SAEs: maternal

9.2.7.4 Estimated date of delivery follow-up with the pregnant patient and/or HCP

Follow-up will be collected at 40 weeks ± 2 weeks gestation.

The following information will be collected from the pregnant patient (where possible), the OB/GYN HCP, paediatric HCP, and other HCPs as needed, at the time of the EDD Follow-up. This information will also be collected from women whose pregnancy outcome was known at the time of enrolment (i.e., retrospectively enrolled women).

- Source of information
- Date of contact
- Outcome and date of outcome (e.g., live birth, stillbirth)
  - Factors which may have contributed to the outcome (e.g., efgartigimod,

other medications, prenatal maternal infection, or fever-causing illness)

- If elective termination, specify primary reason (e.g., identified MCM, increased risk of an MCM, non-medical reasons, other)
- Method of delivery (spontaneous or induced)
  - If induced, reason for induction
- Pregnancy complications
  - Obstetric and delivery complications [PROM, PPROM, pre-eclampsia/gestational hypertension/eclampsia/severe pregnancy- induced hypertension (PIH)/proteinuria, gestational diabetes, IUGR, polyhydramnios, other]
- Gestational age at pregnancy outcome (weeks)
- Number of foetuses/new-borns
  - For each:
    - Infant gender
    - Birth weight (kilogram)
    - Birth length (cm)
    - Head circumference (cm)
    - Apgar (Appearance, Pulse, Grimace, Activity, and Respiration) scores (per local practice)
    - MMCM
      - MMCM description(s)
      - Association with efgartigimod exposure (if HCP reported)
      - Other factors which may have contributed to MMCM
    - Tests/procedures performed and any associated diagnoses
    - Medications/treatments
    - Infant overall status
    - Transient neonatal myasthenia (time of onset, symptoms, severity, duration, medications and other treatment, method of diagnosis)

- Pregnancy-related adverse events of special interest (AESIs) (e.g., infection) and SAEs: maternal and neonate/infant
- Allergic reactions
- Breastfeeding
  - Exclusive/partial lactation

9.2.7.5 Infant 3, 6, 9, and 12 months of age follow-up

Information at this time point will be collected from the infant's HCP. If additional information is needed, the mother will be contacted in countries where direct contact is possible.

Follow-up will be collected at age 3, 6, 9 and 12 months of age ± 2 weeks. Information will be collected for each infant if there was a multiple birth.

If the woman is breastfeeding the SCC will contact the woman when the infant is 3, 6, 9 and 12 months of age to obtain data on lactation.

The following information will be collected from the infant's paediatric HCP for each infant (if multiple birth):

- Source of information
- Date of contact
- Infant length, weight, and head circumference
- Relevant testing/procedures performed and any associated diagnoses
- MMCM
    - MMCM description(s)
    - Association with efgartigimod exposure (if HCP reported)
    - Other factors that may have contributed to the MMCM
- Infections
    - Type (e.g., urinary tract, respiratory)
    - Etiologic agent (if available)
    - Duration
    - Treatment
    - Outcome
- Allergic reactions
- Vaccinations
    - For each vaccine, the following information will be collected:
        - Name
        - Date
        - Dose
        - Any adverse reaction – if yes, provide details

- Growth and development measurements (validated tool(s) used as part of assessment, if any)
    - Growth alteration (height, weight)
    - Infant developmental deficiency for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development)
    - Physiologic function (locomotor activity)
    - Result of assessment
    - Diagnosis or problem identified, if any
    - Action taken (e.g., close monitoring, additional testing, medication/treatments)
    - Association with efgartigimod exposure (if HCP reported)
- Any hospitalizations for serious conditions
- AESI and SAEs: infant

9.2.8 Loss to follow-up

To reduce the number of pregnant women or infants who become lost to follow-up, in countries where it is allowed, the pregnant woman will be asked to provide her preferred method of contact (telephone, email, text) and to designate two secondary contacts at the time of enrolment. Secondary contacts are individuals both within and outside the pregnant patient's household who will know her whereabouts should she become lost to follow-up. In countries where contact can only be made with the HCP, the SCC will contact the HCP using multiple follow-up methods (e.g., fax, telephone, postal mail, or email) based on prior success or HCP contact preference to minimize the occurrence of missing data.

If the requested data are not obtained within the appropriate timeframe, at least 4 attempts will be made to contact the pregnant woman and/or the HCP within 3 months of last follow-up contact to obtain information about the outcome of the pregnancy before a case is considered lost to follow-up. If needed, and where allowed, the SCC will contact her secondary contacts.

Resources such as the National Death Index (NDI) in the US and other local or regional vital status registers, where available, may be searched for any patient considered lost to follow-up; however, these sources have long lag times so the matching with the NDI cannot begin until at least 2 years after a patient has been designated as lost to follow-up. All data collected prior to considering the pregnant woman lost to follow-up will be used for analysis and reporting purposes to the extent possible.

9.3 Variables

The SCC or the HCP will collect study-relevant data for each pregnant woman and document it in the CRF.

9.3.1 Exposure definition

Women who are exposed to at least one dose of efgartigimod during pregnancy or any time within 25 days prior to conception. The following information related to each efgartigimod exposure will be captured in the study's data collection tool:

- Administration date during pregnancy or in the 25 day period prior to conception
- Dose and any dose change(s)

9.3.2 Covariates

Covariates to be included include:

- Exposure during pregnancy (by trimester) to tobacco, alcohol, illicit drug use and other teratogenic exposure
- Preconception care including pregnancy planning, fertility assessment and preconception screening
- Concomitant medications
  - By trimester and any time during pregnancy
  - In neonates and infants through 12 months of age

9.3.3 Outcomes

9.3.3.1 Pregnancy outcomes

Pregnancy outcomes will be classified into one of the following mutually exclusive categories and are defined in Table 2 below:

- Spontaneous abortion
- Elective or therapeutic abortion
- Foetal death/stillbirth
- Molar or ectopic pregnancy
- Live birth
  - Preterm delivery
  - Full-term delivery

An attempt will be made to assess all outcomes for the presence of MCM.

Table 2 Definitions for Pregnancy Outcomes

Event	Definition
Spontaneous abortion*	Any loss of a foetus due to natural causes less than 20 weeks gestation as a spontaneous abortion (ACOG 2022a, World Health Organization [WHO]/Centers for Disease Control and Prevention [CDC] /International Clearinghouse for Birth Defects Surveillance and Research [ICBDSR] 2014). If available, data from gross or pathological examination of the abortus or foetus will be evaluated for structural defects.
Elective/Induced (therapeutic) abortion	Elective or induced abortion is the termination of pregnancy through medical or surgical procedures (ACOG 2022b, WHO/CDC/ICBDSR 2014). If available, data from gross or pathological examination of the abortus or foetus will be evaluated for structural defects.
Foetal death/Stillbirth*	Foetal death or stillbirth refers to foetuses born dead at > 20 weeks gestation or weighing > 500 grams. Foetal death occurring > 20 weeks but less than 28 weeks gestation is considered an early foetal loss. Foetal death occurring > 28 weeks is considered a late foetal loss (ACOG 2022c). If available, data from gross or pathological examination of the abortus or foetus will be evaluated for structural defects. * The pregnancy safety study will make the final classification between foetal death/stillbirth and spontaneous abortion based on gestational age and weight. If these parameters are not available, the pregnancy safety study will accept the classification indicated by the HCP.
Live Birth	A live birth refers to a complete expulsion from its mother of a surviving neonate breathing or showing any evidence of life such as a heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, whether the umbilical cord has been cut or the placenta is attached (WHO/CDC/ICBDSR 2014). Live birth will also be reported based on the timing of the delivery. Preterm delivery is defined as births delivered prior to 37 completed weeks of gestation per 100 births. Gestational age is based on the obstetric estimate of gestation (CDC 2019, Martin 2018).
Ectopic or Molar Pregnancy	Any reported ectopic or molar pregnancy will be sub-classified in the respective pregnancy outcome including induced abortion, live birth, or spontaneous pregnancy loss (National Birth Defects Prevention Network [NBDPN] 2014).

9.3.3.2 Major and minor congenital malformations major congenital malformations

Congenital anomalies comprise a wide range of abnormalities of body structure or function that are present at birth and are of prenatal origin. For efficiency and practicality, the focus is commonly on major structural anomalies. These are defined as structural changes that have significant medical, social, or cosmetic consequences for the affected individual, and typically require medical intervention.

9.3.3.3 Major congenital malformations

The study has adopted the term MCM for an abnormality that may often be referred to as a "congenital abnormality" or a "birth defect" and defines MCM according to the following criteria:

1. any major structural defect diagnosed with signs/symptoms, using the selected major congenital anomalies list extracted from the Birth defects surveillance: a manual, CDC (Table 3) (CDC 2020b).

Table 3 Selected Major Congenital Malformations

External	Internal

• Neural tube defects
  ○ Anencephaly
  ○ Craniorachischisis
  ○ Iniencephaly
  ○ Encephalocele
  ○ Spina bifida
• Microcephaly
• Microtia/Anotia
• Orofacial clefts
  ○ Cleft lip only
  ○ Cleft palate only
  ○ Cleft lip and palate
• Exomphalos (omphalocele)
• Gastroschisis
• Hypospadias
• Reduction defects of upper and lower limbs
• Talipes equinovarus/club foot
	• Congenital heart defects
	  ○ Hypoplastic left heart syndrome
	  ○ Common truncus
	  ○ Interrupted aortic arch
	  ○ Transposition of great arteries
	  ○ Tetralogy of Fallot
	  ○ Pulmonary valve atresia
	  ○ Tricuspid valve atresia
	• Oesophageal atresia/tracheoesophageal fistula
	• Large intestinal atresia/stenosis
	• Anorectal atresia/stenosis
	• Renal agenesis/hypoplasia

Chromosomal • Trisomy 21 (Down syndrome)	

Source: Box 1.1 Selected major congenital anomalies retrieved from https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html> on 15 July 2022

2. on a case-by-case basis, through evaluator review and agreement from external advisors (if required), any structural defect (that satisfy criterion 1 or 2) detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, foetus, or deceased infant will be included, if available, to increase the sensitivity of pregnancy study monitoring.

To maintain as much consistency with the CDC birth defect surveillance system as possible without missing a potential signal, only cases meeting the CDC MACDP criteria will be counted for the primary analyses. Additionally, risk estimates will not include outcomes that are not associated with efgartigimod exposure (e.g., genetic syndromes, prematurity-related outcomes, positional effects). The CDC guidelines disqualify the following as MCM: (1) those findings that are present in infants with outcomes at < 36 weeks gestational age or if gestational age is unavailable, weighing < 2500 grams, and are attributed to prematurity alone, such as patent ductus arteriosus, patent foramen ovale, and inguinal hernias, and (2) infants with only transient or infectious conditions, or biochemical abnormalities, who are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized MCM.

9.3.3.4 Minor congenital malformations

Minor structural defect is a defect which occurs in less than 4% of the population but which has neither cosmetic nor functional significance to the child (e.g., complete 2,3 syndactyly of the toes) (Chambers 2001).

Categorization of Defects

Structural defects will be separated into one of three groups based on developmental pathogenesis. The major purpose for doing so is to consider biologic plausibility. Defects will be categorized into malformations, deformations, and/or disruptions defined as follow:

Malformation: an arrest at a normal stage of embryologic differentiation or development, e.g., a cleft lip.

Deformation: a defect due to deformation of a structure which has previously formed normally. The defect is usually due to mechanical forces such as uterine constraint, e.g., a club foot.

Disruption: a defect due to destruction of a structure which has previously formed normally. Such disruptive defects may be of vascular, infectious or mechanical origin, e.g., amniotic band disruption.

Minor Structural Defects Excluded as Outcomes

Birthmarks: *birthmarks will not be included.*

Variations of normal (in general population): *features on the physical examination which occur in greater than 4% of the population and have no cosmetic or functional significance for the child, e.g., 2, 3 syndactyly of the toes less than one-third of the distance to the tip of the third phalanx, will not be included.*

Deformational defects: *those deformational defects that do not require casting or surgery will not be included.*

Minor congenital anomalies, although more prevalent among the population, are structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual. Table 4 presents examples of external minor congenital malformations, which include hydrocele, single palmar crease and clinodactyly (CDC 2020b). A complete list of minor congenital malformations is available in Appendix B of the CDC Birth Defects Surveillance Toolkit (CDC 2019).

Table 4 Selected External Minor Congenital Malformations

• Absent nails Accessory tragus • Anterior anus (ectopic anus) Auricular tag or pit • Bifid uvula or cleft uvula Branchial tag or pit Camptodactyly • Cup ear • Cutis aplasia (if large, this is a major anomaly) Ear lobe crease • Ear lobe notch Ear pit or tag • Extra nipples (supernumerary nipples) Facial asymmetry • Hydrocele • Hypoplastic fingernails • Hypoplastic toenails Iris coloboma	• Lop ear Micrognathia Natal teeth Overlapping digits Plagiocephaly • Polydactyly type B tag, involves hand and foot Preauricular appendage, tag or lobule Redundant neck folds • Rocker-bottom feet Single crease, fifth finger • Single transverse palmar crease Single umbilical artery • Small penis (unless documented as micropenis) Syndactyly involving second and third toes Tongue-tie (ankyloglossia) • Umbilical hernia Undescended testicle • Webbed neck (pterygium colli)

Source: Box 1.2 Selected external minor congenital anomalies retrieved from https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html on 15 July 2022

9.3.3.5 Other events of interest in neonates and infants through 12 months of age

Events of interest occurring in developing neonates and infants will include:

- Hospitalizations
- Death
- Concomitant medications and vaccinations
- Growth and development milestones as described by the CDC 2021 or other accepted standard assessment
- Infant developmental deficiency (CDC 2021)
- Postnatal growth deficiency or failure to thrive
- Neonatal and infant mortality
- Others specific to efgartigimod/MG (e.g., infections, transient myasthenia gravis)
- Transient neonatal myasthenia (time of onset, severity, duration, medications and other treatment, method of diagnosis)

9.3.3.6 Maternal complications

Maternal complications of pregnancy will include but not be limited to:

- PROM
- PPROM
- Pre-eclampsia
- Gestational hypertension
- Eclampsia
- Severe PIH
- Proteinuria
- Gestational diabetes
- Polyhydramnios
- Infections or others specific to MG
- Pre-term delivery
- Measures of foetal growth deficiency (small for gestational age)

9.3.4 Classification and evaluation of outcomes

A subject matter expert (SME), a teratologist or a specialist with similar expertise, will adjudicate all reports of MMCM to (1) determine if the event meets the criteria for a particular MMCM; and (2) provide a causality assessment. All documents provided to the SME will be anonymized. The SME will evaluate the anonymized individual reports of MMCM to determine if there is an increase in a specific type(s) of MMCM. In cases of complex congenital malformations, additional specialists will be asked to adjudicate the MMCM(s), as needed. Additionally, if there are any cases with MMCM identified in abortions (spontaneous/therapeutic/elective) a thorough analysis of products of conception will be reviewed and adjudicated by the specialist if the information is available.

9.3.5 Lactation and breastfed infants

When an infant is being breastfed, the key variables of interest from birth through 12 months of age for infants will include the pattern of breastfeeding including:

- Date initiated and duration
- Exclusivity
- Degree of formula supplementation
- Milk production

9.4 Data sources

Data will be collected by various methods, when and/or if applicable, including telephone interviews conducted by the SCC with the woman and her HCPs, reports sent to the SCC from spontaneous reports received by argenx, and medical records obtained for identified MCMs. In countries where HCP sites are enrolled, reports will come from the HCPs and their sites. For reports received after pregnancy outcome, applicable information will be collected from the patient (where allowed) and from her HCP and the infant's HCP (if applicable for a live birth). Region-specific analyses will be performed to address potential variation in data (e.g., completeness of medical event documentation) by method of data collection.

For medical data collected from the HCP, if the HCP is unable to provide the data directly to the SCC, a paper copy of the CRF will be sent to the HCP for completion based on the specific data points that need to be collected to reduce burden on the HCP, i.e., the form will be pre-populated with known information for the HCP to confirm in order to reduce burden. Birth outcome data provided by the woman will be verified, whenever possible, by an HCP and any MMCM will be confirmed by the SME.

9.5 Study size

Participation in the study is voluntary. Sample size is driven by the expected number of women prescribed efgartigimod and the number that become pregnant. Given that MG is (1) a rare disease and (2) a potentially debilitating and clinically severe condition, the number of prospectively enrolled pregnancies over the 8.25-year enrolment period is expected to be approximately 279 pregnancies. This enrolment estimate assumes a 5% loss to follow-up based on experience with prior pregnancy programmes. Because the projection is low this study will not have sufficient power to make a statistical comparison against a non-exposed control group however it will be sufficient to compare against an external historical control. For this study the Prevalence of MCM from the MACDP will be used as a benchmark for the background rate. Historically the overall prevalence of MCMs in the MACDP is approximately 3% of live births and has been stable with 2.8% prevalence in 1978 to 3.0% prevalence in 2005 (test for trend p = 0.19) (Rynn 2008). The most recent background MCM rate was reported as 3% based on the CDC Birth Defects homepage (CDC 2020a). European data reported MCM prevalence of 23.8 per 1,000 (or 2.38%) births for 2000-2004, and live birth prevalence of 19.9 per 1,000 birth or (1.99%) (EUROCAT Central Registry 2009). A recent study from Japan reported MCM prevalence of 298.6 per 10,000 (or 2.99%) births for 2011–2014 for malformations identified either at birth or 1 month of age (Mezawa 2019).

The analyses will look at rates of MCMs relative to number of pregnancies, number of live births (projected to be 0.65[15]*(.95*279, 265) or 173) and foetuses[16] (projected to be 1.01*(0.95*279, 265) or 268) (Curtin 2013, Ventura 2012). Based on the upper limit (UL) of the 95% exact CI in Table 5, a sample size of 200 live births will be sufficient to rule out MCM rates in live births

[15] 0.65 live birth rate was obtained from Curtin 2013.

[16] Includes live and non-live foetuses.

> 6.7%, and sufficient to rule out MCM rates per pregnancies or per foetus > 6.4% if the underlying rate is 3%.

Table 5 Study Sample Size and 95% Confidence Interval Width for an Underlying Rate of 2 or 3%

Sample size	95% UL where underlying rate is 2%	95% UL where underlying rate is 3%
100	7.0%	8.5%
175	5.3%	6.7%
200	5.0%	6.4%
300	4.3%	5.6%
400	3.9%	5.2%

Abbreviation: UL=upper limit.

To provide further justification about detecting potential increased risk, the power calculation for MCM prevalence is presented in Table 6 below assuming 2% or 3% background incidence proportion using exact binomial test with 0.05 alpha level. With 265 enrolled efgartigimod-exposed pregnancies, there is approximately 80% power to detect a 3% risk increase assuming 2% background proportion or 4% risk increase assuming 3% background proportion. The actual alpha level is also given in the table for the exact binomial test.

Table 6 Power Calculations for Different Background Incidence Proportions of MCM

Risk Increase	Background Incidence Proportion	Sample Size	Power	Actual Alpha Level
2%	2%	265	49%	0.024
3%	**2%**	**265**	**78%**	**0.024**
4%	2%	265	93%	0.024
5%	2%	265	98%	0.024
2%	3%	265	35%	0.028
3%	3%	265	63%	0.028
4%	**3%**	**265**	**84%**	**0.028**
5%	3%	265	94%	0.028

Should the target sample size be achieved earlier than the 8.25 years of enrolment, the Sponsor will discuss with FDA whether the study can be stopped. Similarly, should the enrolment target not be achieved in the designated time frame, the Sponsor will review the data with FDA to determine whether the enrolment period should be extended.

9.6 Data management

The Contract Research Organization (CRO) will serve as the SCC. The SCC will provide overall study management, obtain Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the study in all countries, and complete any other regulatory obligations for study conduct. The SCC will assist participating sites where local ethics review is required. In the US and in any other countries where direct contact is possible with the pregnant woman, the SCC will collect data directly from the pregnant woman and her HCPs as well as the infant's HCPs. The SCC will enter all data into the study database and will prepare the interim and final reports.

The CRO will develop the data collection system. The CRF will be part of the data capture system which allows documentation of all variables and covariates in a standardized way. Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP).

Data will be collected on a paper CRF by the SCC or by the HCP who will submit the CRF to the SCC. The SCC staff will enter the data into the study database using double data entry. Discrepancies will be adjudicated by an independent reviewer.

All medication and therapeutic procedures documented in the CRF will be coded using the latest version of the World Health Organization Drug Global dictionary implemented at the time of database lock for coding of prior and concomitant medication.

Any diagnoses/diseases/event terms documented in the CRF will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version implemented at time of database lock:

- Co-morbidities (medical history, concomitant diseases)
- AEs

For information on quality control, refer to Section 9.8.

A DMP will be developed as part of the program materials along with the CRF and coding instructions. Data are entered into the study database within seven days of receipt. Data are double entered and reviewed for quality control simultaneously. The SCC will review all data as they are obtained for potentially reportable safety-related information and will triage the cases to argenx for processing and regulatory submission within 24 hours of receipt.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be descriptive. The study is not intended to test pre-defined statistical hypotheses. The prevalence of MCM among live births and 95% CIs will be calculated using the exact binomial distribution and compared to the MCM prevalence in the general population (country or region-specific) as reported in published literature and if possible, to an MG population without efgartigimod exposure (country or region-specific). The prevalence of minor

congenital malformations among live births and 95% CIs will be calculated using the exact binomial distribution.

A formal SAP will include details of all planned analyses and presentation of study data. Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and n and percent for categorical variables. A Kaplan-Meier analysis will be performed to present time between last efgartigimod exposure and each of the two adverse pregnancy outcomes for which an 'event date' can be established: spontaneous abortion and foetal death/stillbirth. The SAP will be finalized before the first annual analysis and is kept as a stand-alone document.

When the same data points are provided by the woman and the HCP and are contradictory, the data obtained by the HCP will be used in the analysis.

9.7.1.1 Prospective vs. Retrospective Cases

Bias may occur when some abnormal results or outcome information are known prior to enrolment; therefore, pregnant women are advised to enrol in the study as soon as their pregnancy is known, preferably in the first trimester before the condition of the foetus has been assessed through prenatal testing, including ultrasound, amniocentesis and genetic testing. In order to determine the impact of such a bias (i.e., as a result of recalling exposures and other medical history differently once it is known that a pregnancy is compromised), cases will be characterized as either prospective or retrospective. The criterion for prospective enrolment is that, at the time of enrolment, the woman is currently pregnant whether or not the woman has had prenatal testing. The criterion for retrospective enrolment is that at the time of enrolment, the woman is no longer pregnant.

Pregnancy reports will be categorized by prospective and retrospective and a listing of pregnant women by this classification and a listing of any MCM by this classification will be presented. A sensitivity analyses will be conducted that evaluates outcomes separately for pregnancies classified as prospective versus retrospective (see Data Analysis Section 9.7).

9.7.2 General methods

In countries where data can be collected directly from pregnant woman, data may be provided to the SCC by the pregnant women or their HCPs via telephone interview conducted by the SCC or from paper based CRFs submitted via mail or fax by HCPs. The SCC will enter the data into a validated study database using double data entry. In other countries, an HCP who identified an eligible pregnancy will be contracted by the SCC to perform follow-up of the pregnancy and the neonate/infant. The HCP will provide the requested data to the SCC for entry into the study database.

An SME, a teratologist or a specialist with similar expertise, will adjudicate all reports of MMCM. For all summary analyses, the adjudicated values will be used if they differ from the initially reported values. Both original and adjudicated values will be reported in listings.

Identified MCM will be reviewed individually and in aggregate to identify any possible patterns or trends reported.

Results will be presented by type of recruitment method whenever sufficient numbers of exposed pregnancies are available to support this analysis. Additionally, results will be presented by method of data collection to compare the frequency of adverse outcomes identified through the following two data collection methods: (1) solicited approaches such as interviews with the enrolled woman or her HCP and (2) unsolicited approaches such as spontaneous adverse event reports received by argenx or the SCC. Due to expected small sample sizes, these analyses will be presented across all geographic regions. Cases of adverse events identified in the study that are considered to be causally related to efgartigimod exposure will be described separately.

9.7.3 Analysis datasets

Depending on the endpoint, the analysis population will be pregnancies, live births, foetuses or neonates and infants. Each analysis will refer to one or more of the populations described in this section.

9.7.3.1 All pregnant women analysis set

This set includes all enrolled pregnant women who have met the inclusion criteria and provided consent, regardless of whether the pregnant patient was enrolled prospectively or retrospectively. It is possible for a woman to be represented more than once if the woman had more than 1 exposed pregnancy. Each pregnancy will be considered an independent unit even if a woman has more than one qualifying pregnancy as concomitant risk factors (e.g., age, smoking status) may change over time. For pregnancies with multiple foetuses the pregnancy will be considered of having an outcome of interest if at least one foetus has the outcome of interest.

9.7.3.2 Live births (including neonates and infants)

This is the set of all live births regardless of whether the mother was enrolled prospectively or respectively.

9.7.3.3 Foetuses

This set includes all live births, foetal death, and early terminations (spontaneous or elective) regardless of whether the woman was enrolled prospectively or retrospectively.

9.7.3.4 Breastfed infants

This analysis set includes infants with an outcome of a live birth and who are breastfed and includes infants where efgartigimod exposure only occurred during lactation.

9.7.4 Description of statistical analyses

9.7.4.1 Enrolment disposition and baseline information

Summaries using descriptive statistics (defined above) using the All Pregnant Women Analysis set will be provided for:

- Disposition
- Demographics
- Baseline characteristics and obstetric and medical history
- Efgartigimod exposure by peri-conception, trimester, and any time during pregnancy
- Concomitant medications and supplements by trimester and any time during pregnancy
- Tobacco, alcohol, illicit drugs, and other teratogenic exposure during pregnancy by trimester and any time during pregnancy.

All outcomes will be presented for retrospective and prospective pregnancies, and all pregnant women analysis. Denominators for percentages will be number of pregnant women in each category.

Details of these analysis are provided in the SAP.

9.7.4.2 Pregnancy and foetal outcomes

An overall summary of pregnancy outcomes will be presented. Outcomes include the number of women with a pregnancy, number of women with pregnancy complete (includes spontaneous abortion, elective abortion, molar or ectopic pregnancy, foetal death/stillbirth, preterm delivery, and live birth), number of pregnancies ongoing, number of pregnancies with outcome lost to follow-up, number of known foetuses. Results will be presented for all enrolled pregnancies overall as well as separately according to whether a pregnancy was enrolled prospectively and retrospectively. Additionally, results will be presented by (1) type of recruitment method whenever sufficient numbers of exposed pregnancies are available to support this analysis, and (2) region.

Rules for combining data across forms:

The data sources for pregnancy outcome include the trimester follow-up form, the estimated date of delivery form and the infant follow-up form (if EDD form is missing). Pregnancy status to be reported will primarily come from the trimester follow-up forms but may be updated by the EDD or infant follow-up forms as follows:

- Pregnant women with a trimester follow-up form and a pregnancy status of “ongoing” will have the status updated to the most recent Trimester or EDD.

- If there is an Infant follow-up form, the pregnancy status will switch from "ongoing" to "pregnancy complete".

9.7.4.3 Live births

Endpoints characterizing a live birth include sex, estimated gestational age, size relative to gender, weight, length, head circumference, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores (or as per local practice) at time points reported, medications/treatments, tests/procedures performed and any associated diagnoses.

Live birth characteristics will be summarized using descriptive statistics by number of live births with the exception of maternal complications which will be by enrolled pregnancies.

All outcomes will be presented separately for the following categories of pregnancies that resulted in live births:

- pregnancy outcome is known at the time of enrolment (i.e., retrospective cases and traditional prospective cases);
- pregnancy outcome is not known at enrolment; and
- all pregnancies that end in live birth

Summary of data related to lactation will be presented for lactating women or breast-fed infants, as appropriate. The number of lactating women, and the number of breastfed infants will be presented for 3, 6, 9 and 12 months of age.

9.7.4.4 Major and minor congenital malformations in foetuses, live births (neonates and infants)

An important outcome of interest is MMCM as classified using the selected major and minor congenital anomalies list. Rates of MCM and rates of minor congenital malformation will be computed for pregnancies where pregnancies with multiple foetuses will be considered as having an MCM or minor congenital malformation if at least one of the foetuses or infants has an MCM or minor congenital malformation. Rates will also be computed for MMCM and MCM relative to foetuses and live births. A 2-sided 95% CI for these rates will be calculated using exact Clopper-Pearson methods (Clopper-Pearson 1934). Analysis will be repeated by trimester of first exposure and by the timing and duration of exposure during pregnancy, with the exposure window of interest for MMCM being the first trimester.

9.7.4.5 Other events of interest in live births (neonates and infants)

Two MG complications (arthrogryposis multiplex and pulmonary hypoplasia) are the events of interest in live births. Other events of interest occurring in developing neonates and infants will include hospitalizations, medications, growth and development milestones, infant developmental deficiency (social/emotional, language/communication, cognitive, and

movement/physical development), infections, vaccinations, transient neonatal myasthenia and neonatal or infant mortality.

9.7.4.6 Breastfed infants

Summary statistics of feeding patterns including rate of breastfeeding, duration, exclusivity of breastfeeding, degree of formula supplementation and milk production and rate of infection.

9.7.4.7 Maternal complications

Obstetric and delivery complications (PROM, PPROM, pre-eclampsia, gestational hypertension, eclampsia, severe PIH, proteinuria, gestational diabetes, IUGR, infection, polyhydramnios, other) will be summarized using descriptive statistics with all complications reported on the CRF. The all pregnancies analysis set will be used for this analysis. Newly diagnosed conditions are defined as not being listed as chronic at baseline. Conditions reported on trimester follow-up or EDD forms will be compared to conditions reported on baseline forms. Any event reported on the baseline form will not be considered as a new condition.

9.7.4.8 Sensitivity analysis

A sensitivity analysis will present study outcomes for the following two subgroups of prospectively enrolled pregnancies (i.e., woman is still pregnant at time of enrolment):

- 'Pure' prospective pregnancies at enrolment (i.e., no pre-natal testing in advance of enrolment)
- Prospective pregnancies with pre-natal testing prior to enrolment.

9.7.4.9 Serious adverse events and adverse events of special interest

SAEs and AESI such as infections will be presented in frequency tables of the SAEs and AESI observed. Listings of all SAEs and AESI will also be provided for pregnant women and neonates/infants.

9.8 Quality control

9.8.1 Data quality

argenx has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles, standard treatment practices and regulations. argenx or representatives will visit the SCC to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by argenx.

When an HCP is enrolled in an area where data collection directly from the pregnant woman is not allowed, the involved site personnel will be sufficiently trained on the background and objectives of the pregnancy safety study and on ethical as well as regulatory obligations. Investigators and site personnel will have the chance to discuss and develop a common

understanding of the protocol and the CRF. They will be trained on the importance to ensure that all relevant study data should be retrievable from the pregnant patient's medical records.

All observations will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried, and the data will be validated. A check for duplicate documented pregnant women will be done.

Detailed information on checks for completeness, accuracy, plausibility, and validity are given in the DMP.

Medical review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the medical review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the medical review will be described in the MRP.

National and international data protection laws as well as regulations on observational studies will be followed. Databases used for capturing documentation will be validated according to FDA Code of Federal Regulations (CFR) Title 21, Part 11 (FDA 2003). These regulations describe the criteria to consider whether electronic records including e-signatures are reliable and generally equivalent to paper records and handwritten signatures. They mandate access controls to ensure that only authorized individuals can use the system; additionally, a computer- generated audit trail must be in place to record the date and time of any actions to create, modify, or delete electronic records.

The DMP, MRP and validation documentation are kept as stand-alone documents.

9.8.2 Quality review

Since most data are collected from post marketing setting, no source data verification will be conducted.

9.9 Limitations of the research methods

The primary limitation of a study utilizing volunteers is selection bias. Women who agree to enrol in the study may represent particularly high risk pregnancies. The generalizability of the study results will be limited due to the low numbers of pregnancies expected and will be only generalizable to women fitting the profile of the sample of women who enrol. Retrospective case reports are thought to be subject to further bias in that adverse outcomes may be more likely to be reported, and there is no known denominator of exposed persons for the retrospective period. The comparison of study data with external MACDP, European Network for Population-based Registries for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) or other external sources is limited in that data from these sources do not necessarily represent the same populations.

Another limitation of the study relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, i.e., at 7 through 9 weeks post-LMP or less, will not be measured in a study that enrols women after recognition of pregnancy.

The prevalence rate denominator excludes foetal losses (spontaneous abortions, induced abortions, or foetal deaths) for which no MCM have been detected, since in most cases it is unknown what percentage of these pregnancies consist of potentially normal outcomes or MCM. The study will attempt to obtain information on MCM detected at the time of the outcome. However, the malformation status of the aborted foetus may not be known. A sensitivity analysis will be performed including stillbirths and elective terminations where an MCM has been identified as the denominator.

Efgartigimod uptake over the next several years could potentially impact patient enrolment into the study. The expected counts of efgartigimod uptake in the US and EU, based on updated marketing forecasts, indicate that the minimum number of 265 exposed pregnancies is a realistic target over the 8.25-year recruitment period; however, it is possible that slower-than-expected prescribing of efgartigimod in the next few years in one or more regions could impact the ability to recruit eligible women into the study. Every effort will be made to maximize recruitment by (1) targeting clinical settings with larger MG patient populations; (2) contacting disease-centric Patient Advocacy Groups and Medical Societies, and (3) focusing on geographical regions that have higher uptake of the product.

Enrolled pregnancies for which outcome information for the full study follow-up period (i.e., up to 21 months for pregnancies that result in a live birth) is unobtainable will be considered “lost to follow-up”. It is possible that outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases that the loss to follow-up may have on the analysis. However, if sample sizes are large enough, efforts at comparing some of the characteristics of each group will be conducted in an attempt to address this potential source of bias. Additionally, patient demographics and clinical characteristics for pregnancies lost to follow-up will be compared to pregnancies with documented outcomes to determine if and how groups differ and what impact any potential difference may have on interpretation of study results. It is important to note, however, that based on experience with other pregnancy exposure registries (PERs), a high retention rate is generally achieved because of consistently maintaining contact with the enrolled pregnant women and the HCPs (mother and baby) throughout the study.

In addition, the one-year follow-up period for infants with exposure in utero or during breastfeeding will preclude the study from evaluating risk of neurodevelopmental disorders with latency periods that exceed one year. However, the follow-up time of one year for infants is standard practice for a post-marketing safety study to evaluate risks of adverse outcomes among infants exposed either in utero or during breast-feeding.

There is a potential for missing data. In general, missing observations will not be imputed in the analysis of individual questions or items unless otherwise specified. Partial dates will be imputed

using the earliest possible date of the missing range, i.e., in general, “1” for missing day and January for missing month. Additional rules may apply where the earliest day is date of last LMP. These rules will be specified in the SAP. All summary statistics for individual responses will be performed on actual data. However, statistics will be performed on imputed partial dates when needed, for example, estimation of gestational age or estimating exposure. Details will be described in the SAP.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

Prior to any data collection under this protocol, an informed consent must be provided by the woman, in accordance with local practice, law or regulation. Information about the study will be explained to the woman. In countries where it is allowed, eConsent will be obtained. In all others, written consent will be necessary. Women will be sent a copy of the informed consent form (ICF) that was discussed with them, and they may voluntarily choose to sign and return the ICF. The ICF must not be altered without the prior agreement of the relevant IRB or IEC and argenx.

All information obtained during the conduct of the study with respect to the woman’s state of health will be regarded as confidential.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for argenx, the IRB/IEC, or any regulatory agency worldwide to review files as they relate to this study. Only the patient’s unique number on the CRFs will identify her.

Documents that are not for submission to argenx will be maintained by the SCC in strict confidence, except to the extent necessary to allow monitoring by argenx, and auditing by argenx and regulatory authorities. No documents identifying women by name will leave the SCC, and patient identity will remain confidential in all publications related to the study.

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

This study will be conducted in accordance with the GPPs issued by the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (2008), the Guide on Methodological Standards in Pharmacoepidemiology (2010) issued by European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.

Every patient has the right to withdraw consent from the program at any time. A patient’s participation will terminate immediately upon her request. In case a patient would like to withdraw the consent given earlier, she should inform her physician, or the SCC and s/he should document the withdrawal in the CRF as well as in the medical records. All information already

collected as part of the program will be retained for analysis unless specified otherwise by the woman. The request for withdrawal from the program must be made by writing to the SCC. The SCC will document the request in the database. Once the woman is withdrawn, the SCC will make no further attempt to contact the patient or her HCP.

argenx may terminate the program at any time. In case of premature termination or suspension of the program, the SCC in conjunction with argenx will promptly inform the participating women and HCPs, regulatory authorities, and IRB/IECs of the termination or suspension and the reason for that action.

11. Management and reporting of adverse events/adverse reactions

11.1 Definition of adverse events

Adverse event (AE): Any untoward medical occurrence in a pregnant woman administered a pharmaceutical product and which does not necessarily have to have a causal relationship (association) with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the product.

Adverse events and SAEs related to pregnancy, lactation and breastfeeding are the focus of this study and will be presented using MedDRA (version in effect at the time) Preferred Terms related to pregnancy, lactation, and breastfeeding.

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

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

An adverse drug reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between efgartigimod and an occurrence is suspected. The study will collect the necessary information that will be applied to all maternal and infant adverse events to evaluate whether a causal relationship between efgartigimod exposure and event is suspected.

Interruption or discontinuation of efgartigimod as a result of an ADR, reported by either the women or her HCP, will be captured on a data collection form that will specify the reason for the action taken.

Serious adverse event/serious adverse drug reaction: An AE or ADR is serious if it:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization

  A hospitalization or prolongation of hospitalization will not be regarded as a SAE if at least 1 of the following exceptions is met:

  - the admission results in a hospital stay of less than 12 hours;
  - the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study);
  - the admission is not associated with an AE (e.g., social hospitalization for purpose of respite care).

  However, it should be noted that invasive treatment during any hospitalization may fulfil the criterion of 'medically important' and as such may be reportable as an SAE dependent on the clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.
- results in persistent or significant disability or incapacity
- is a congenital anomaly, birth defect or foetal mental impairment
- is medically significant:
  - Medical and scientific judgment should be exercised in deciding whether an AE/ADR may be considered serious (due to an important medical event) because it jeopardizes the health of the pregnant woman or infant or may require intervention to prevent another serious condition (death, a life-threatening condition, hospitalization or persistent or significant disability)

Special situations (irrespective if a clinical event has also occurred)

- Drug-drug or drug-food interaction
- Drug use during lactation or breast-feeding
- Lack of effectiveness
- Overdose
- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / medication errors

11.2 Collection and reporting

All reports of pregnancy will be forwarded to the argenx Pharmacovigilance Department within 24 hours for entry into the safety database. Follow-up information obtained by the pregnancy safety study will be forwarded following the same process. The safety study will limit active solicitation of AEs to specific pregnancy outcomes, and they will be classified as SAEs. These actively solicited SAEs include MCM, low birth weight infant, preterm birth, SAB, stillbirth, induced abortion, molar pregnancy, and ectopic pregnancy. In addition to actively solicited SAEs, any maternal death will be reported as individual case safety reports (ICSRs) to the sponsor's Pharmacovigilance Department. The argenx Pharmacovigilance Department will forward all applicable valid ICSRs of actively sought AEs in pregnancy data to the appropriate regulatory authorities within the required timeframe, as required by regulations.

For women enrolled in the study, exposure in pregnancy to any other product for which the sponsor is the market authorization holder (MAH) will be collected and reported within 1 business day of awareness. The argenx Pharmacovigilance Department will be responsible for assessing the seriousness of these events. Annual periodic safety update reports will provide data on exposure in pregnancy reported to the study. For all non-pregnancy outcomes-related AEs/ADRs, the standard procedures that are in place for spontaneous reporting will be followed.

The documentation of any AE/ADR/SAE/serious adverse reaction (SAR) or special scenario cases ends with the completion of the observation period of the pregnant woman or the infant.

However, any AE/ADR/SAE/SAR or special scenario cases – regardless of the relationship and the seriousness – occurring up to seven days after the last dose of efgartigimod within the study period has to be documented and forwarded to argenx within the given timelines, even if this period goes beyond the end of observation.

12. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov" and in the EU-PAS register (ENCePP) prior to enrolment of the first patient. Results will be disclosed in a publicly available database within the standard timelines.

Annual interim progress reports will be provided to the FDA and EMA on an annual basis for the duration of the pregnancy safety study. The final study report will be submitted at the conclusion of the study. The interim analysis will consist of summaries of enrolment data and summaries of pregnancy outcomes. Medically confirmed outcomes will be distinguished from maternally reported (i.e., unconfirmed) outcomes. Listings of all other data including MMCMs will be provided. In addition, updates on recruitment and retention strategies and a table of all pharmacovigilance cases of pregnancy for women not enrolled in the study will be included. Final study results will be reported on the US-based www.clinicaltrials.gov website in alignment with the guidance provided by Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) that establishes the standard for transparent and thorough reporting of observational research. (von Elm 2008)

12.1 Publications

argenx may prepare one or more manuscripts for publication including a description of the study methods and one describing the results of this observational study. Any manuscripts will be submitted to a peer-reviewed journal or submitted as abstracts/presentations at medical congresses under the oversight of argenx. argenx is committed to adhering to the prevailing standards for "Good Publication Practice". Current guidelines and recommendation will be followed (e.g., GPP3 Guidelines, STROBE), as well as the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE). (ICMJE 2019, Battisti 2015, von Elm 2008) No individual investigator may publish on the results of this study, or their own enrolees, without prior approval from argenx.

12.2 Audits and inspections

Members of argenx's Quality Assurance and external auditors appointed by argenx or designees may conduct an audit of the SCC at any time before, during, or after completion of the study. The Central Investigator at the SCC will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other regulatory agencies worldwide may also conduct an inspection of the study. If informed of such an inspection, the SCC will notify argenx immediately. The SCC will ensure that the auditors have access to study site facilities, source documentation, and all study files.

12.3 Source document maintenance

Patient medical records will be collected in order to adjudicate primary outcomes with medical chart review. Patient information is not redacted from the medical records. All source documents from this program will be maintained by the SCC and made available for audits and inspections by authorized persons. Informed consents collected written and electronically, as permitted by law or regulation, are collected and saved in a secure file. Signed ICFs will be filed by the SCC with the women's records.

12.4 Retention of records

The SCC must retain all study records required by argenx and by the applicable regulations in a secure and safe facility. The SCC must consult an argenx representative before disposal of any study records and must notify argenx of any change in the location, disposition, or custody of the study files. The SCC or designee must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., patient charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

The SCC should retain patient identifiers for at least 25 years after the completion or discontinuation of the pregnancy safety study. Patient files and other source data must be kept

for the maximum period of time permitted by the vendor, but not less than 25 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with argenx. argenx must be notified and will assist with retention should the SCC be unable to continue maintenance of patient files for the full 25 years. It is the responsibility of argenx to inform the SCC as to when these documents no longer need to be retained.

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Annex 1. List of Stand-alone Documents

Number	Document reference number	Date	Title
1			
2			

Annex 2. List of Known Teratogens

Adapted from:

Fine JS. Reproductive and perinatal principles. In: Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, Flomenbaum NE, eds. Goldfrank's Toxicologic Emergencies. 11th ed. McGraw-Hill Education; 2019. http://accesspharmacy.mhmedical.com/content.aspx?bookid=2569 Accessed March 30, 2020

The patient's list of non-efgartigimod medications will be compared against the list of known medications classified as teratogens (Table 7) to identify any teratogenic exposure. Questions on exposure during pregnancy to other teratogens (Table 8) will be included as part of the Enrolment data collection form completed by the mother.

Table 7 Medications Classified as Teratogens

Medications		
Teratogen	**Reported Effects**	**Comments**
Alkylating agents (e.g., busulfan, chlorambucil, cyclophosphamide, mechlorethamine, nitrogen mustard)	Growth retardation, cleft palate, microphthalmia, hypoplastic ovaries, cloudy corneas, renal agenesis, malformations of digits, cardiac defects other anomalies	10%–50% malformation rate, depending on the agent. Cyclophosphamide-induced damage requires cytochrome P450 oxidation.
Aminopterin, methotrexate (amethopterin)	Hydro- or microcephaly; meningoencephalocele; anencephaly; abnormal cranial ossification; cerebral hypoplasia; growth retardation; eye, ear, and nose malformations; cleft palate; malformed extremities or fingers; reduction in derivatives of first branchial arch; developmental delay	Folate antagonists inhibit dihydrofolate reductase. High rate of malformations.
Amiodarone	Transient neonatal hypothyroidism, with or without goitre; hyperthyroidism	Amiodarone contains 39% iodine by weight. Small to moderate risk from 10 weeks to term for thyroid dysfunction.
Androgens	Virilization of the female external genitalia: clitoromegaly, labioscrotal fusion	Dose dependent. Stimulates growth of sex steroid receptor–containing tissue.

Medications		
Teratogen	**Reported Effects**	**Comments**
Angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptors blockers	Foetal or neonatal death, prematurity, oligohydramnios, neonatal anuria, IUGR, secondary skull hypoplasia, limb contractures, pulmonary hypoplasia	Significant risk of effects related to chronic foetal hypotension during second or third trimester. If used during early pregnancy, can be switched during first trimester.
Carbamazepine	Upslanting palpebral fissures, epicanthal folds, short nose with long philtrum, fingernail hypoplasia, developmental delay, NTD	1% risk for NTD. Risk of other malformations is unquantified. Risk is increased in setting of therapy with multiple antiepileptics, particularly valproic acid. Mechanism involves an epoxide intermediate. High-dose folate is recommended to prevent NTDs.
Diethylstilbesterol (DES)	*Female offspring:* vaginal adenosis, clear cell adenocarcinoma of the vagina, irregular menses, reduced pregnancy rates, increased rate of preterm deliveries, increased perinatal mortality and spontaneous abortion *Male offspring:* epididymal cysts, cryptorchidism, hypogonadism, diminished spermatogenesis	A synthetic nonsteroidal oestrogen that stimulates oestrogen receptor–containing tissue. 40%–70% risk of morphologic changes in vaginal epithelium. Risk of carcinoma is approximately one in 1,000 for exposure before the 18th gestational week. Most women exposed to DES in utero can conceive and deliver normal children.
Fluconazole	Craniosynostosis, orbital hypoplasia, humeral radial synostosis, femoral bowing	Risk related to high-dose (400–800 mg/d), chronic, parenteral use. Single 150-mg oral dose probably safe.
Iodine and iodine-containing products	Thyroid hypoplasia after the eighth week of development	High doses of radioiodine isotopes can additionally produce cell death and mitotic delay. Tissue- and organ-specific damage depends on the specific radioisotope, dose, distribution, metabolism, and localization.

Medications		
Teratogen	**Reported Effects**	**Comments**
Lithium carbonate	Ebstein anomaly	Controversial association. Low risk.
Methimazole	Aplasia cutis, skull hypoplasia, dystrophic nails, nipple abnormalities, hypo- or hyperthyroidism	Small risk of anomalies or goitre with first trimester exposure. Hypothyroidism risk after 10 weeks of gestation.
Methylene blue (intraamniotic injection)	Haemolytic anaemia, neonatal jaundice, possible intestinal atresia,	Used to identify twin amniotic sacs during amniocentesis.
Misoprostol	Vascular disruptive phenomena (e.g., limb reduction defects); Moebius syndrome (paralysis of sixth and seventh facial nerves)	Synthetic prostaglandin E1 analog. Effects observed in women after unsuccessful attempts to terminate pregnancy.
Mycophenolate mofetil	Microtia, orofacial cleft, coloboma, hypertelorism, micrognathia, conotruncal CHD, agenesis of the corpus callosum, oesophageal atresia, digital hypoplasia	Immunosuppressive xenobiotic used in transplant recipients, inhibits inosine monophosphate dehydrogenase and blocks de novo purine synthesis in T and B lymphocytes.
Oxazolidine-2,4-diones (trimethadione, paramethadione)	Foetal trimethadione syndrome: V- shaped eyebrows; low-set ears with anteriorly folded helix; high-arched palate; irregular teeth; CNS anomalies; severe developmental delay; cardiovascular, genitourinary, and other anomalies	An 83% risk of at least one major malformation with any exposure; 32% die. Characteristic facial features are associated with chronic exposure.
Paroxetine	Cardiovascular malformations, mostly VSD and ASD	Possible small (1%) increased risk. Possible risk with other SSRIs has not been quantified.
Penicillamine	Cutis laxa, hyperflexibility of joints	Copper chelator—copper deficiency inhibits collagen synthesis or maturation. Few case reports; low risk.

Medications		
Teratogen	**Reported Effects**	**Comments**
Phenytoin	Foetal hydantoin syndrome: microcephaly, intellectual disability, cleft lip or palate, hypoplastic nails or phalanges, characteristic facies— low nasal bridge, inner epicanthal folds, ptosis, strabismus, hypertelorism, low-set ears, wide mouth	Effects seen with chronic exposure. A 5%–10% risk of typical syndrome, 30% risk of partial syndrome. Risks confounded by those associated with epilepsy itself and use of other antiepileptics.
Quinine	Hypoplasia of eighth nerve, deafness, abortion	Effects related to high doses used as abortifacients.
Retinoids (isotretinoin, etretinate, high-dose vitamin A)	Spontaneous abortions; micro- or hydrocephalus; deformities of cranium, ears, face, heart, limbs, liver	Retinoids can cause direct cytotoxicity, alter apoptosis, and inhibit migration of neural crest cells. For isotretinoin, 38% risk of malformations; 80% are CNS malformations. Effects are associated with vitamin A doses of 25,000–100,000 units/day. Exposures below 10,000 IU/day present no risk to foetuses. Topical retinoids are not considered a reproductive risk.
Streptomycin	Hearing loss	Rare reports.
Tetracycline	Yellow, grey-brown, or brown staining of deciduous teeth, hypoplastic tooth enamel	Effects seen after 4 months of gestation because tetracyclines must interact with calcified tissue.
Thalidomide	Limb phocomelia, amelia, hypoplasia, congenital heart defects, renal malformations, cryptorchidism, abducens paralysis, deafness, microtia, anotia	~20% risk for exposure during days 34–50 of gestation.
Trimethoprim	NTD, oral clefts, hypospadias, and cardiovascular defects	~1% risk of NTD for first trimester exposure. Mechanism is folic acid inhibition.

Medications		
Teratogen	**Reported Effects**	**Comments**
Valproic acid	Spina bifida, ASD, cleft palate, hypospadias, polydactyly, craniosynostosis, cognitive deficits	Risk for spina bifida is ~1%, but the risk for dysmorphic facies is greater. Risk is confounded by risks associated with epilepsy itself or use of other anticonvulsants.
Vitamin D	Possible association with supravalvular aortic stenosis, elfin facies, and intellectual disability	Large doses of vitamin D disrupt cellular calcium regulation. Genetic susceptibility plays a role.
Warfarin	Foetal warfarin syndrome: nasal hypoplasia, chondrodysplasia punctata, brachydactyly, skull defects, abnormal ears, malformed eyes, CNS malformations, microcephaly, hydrocephalus, skeletal deformities, intellectual disability, spasticity	10%–25% risk of malformation for first trimester exposure, 3% risk of haemorrhage, 8% risk of stillbirth. Bleeding is an unlikely explanation for effects produced in the first trimester. CNS defects occur during the second or third trimesters and are related to bleeding.

Abbreviations: ASD=atrial septal defect; CHD=congestive heart disease; CNS=central nervous system; IUGR=intrauterine growth restriction; NTD=neural tube defect; SSRI=selective serotonin reuptake inhibitor; VSD=ventricular septal defect.

Data from Brent RL. Environmental causes of human congenital malformations: The pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. Pediatrics. 2004;113:957-968; Nulman I, et al. Teratogenic drugs and chemicals in humans. In: Koren G, ed. Medication Safety in Pregnancy and Breastfeeding. New York: McGraw-Hill; 2007:21-30; and Polifka JE, Friedman JM. Medical genetics: 1. Clinical teratology in the age of genomics. CMAJ. 2002;167:265-273.

Table 8 Other Teratogens

Other Teratogens		
Teratogen	**Reported Effects**	**Comments**
Carbon monoxide	Cerebral atrophy, intellectual disability, microcephaly, convulsions, spastic disorders, intrauterine death	With severe maternal poisoning, high risk for neurologic sequelae.
Cocaine	IUGR, microcephaly, neurobehavioral abnormalities, vascular disruptive phenomenon (limb amputation, cerebral infarction, visceral or urinary tract abnormalities)	Vascular disruptive effects because of decreased uterine blood flow and foetal vascular effects from first trimester through the end of pregnancy.

Other Teratogens		
Teratogen	**Reported Effects**	**Comments**
Ethanol	FAS: pre- or postnatal growth retardation, intellectual disability, fine motor dysfunction, hyperactivity, microcephaly, maxillary hypoplasia, short palpebral fissures, hypoplastic philtrum, thinned upper lips, joint, digit anomalies	Neither a threshold for effects nor a safe dose has been identified. Partial expression or other congenital anomalies. Increased incidence of spontaneous abortion, premature delivery, and stillbirth; neonatal withdrawal.
Lead	Lower scores on developmental tests	Higher risk when maternal lead is >10 mcg/dL.
Methyl mercury, mercuric sulfide	Normal appearance at birth; cerebral palsylike syndrome after several months; microcephaly, intellectual disability, cerebellar symptoms, eye or dental anomalies	Inhibits enzymes, particularly those with sulfhydryl groups. In acute poisoning, the foetus is 4–10 times more sensitive than an adult.
Polychlorinated biphenyls	Cola-colored children; pigmentation of gums, nails, and groin; hypoplastic, deformed nails; IUGR; abnormal skull calcifications	Cytotoxic xenobiotic. Body residue can affect subsequent offspring for up to 4 years after exposure. Most cases followed high consumption of PCB-contaminated rice oil; 4%–20% of offspring were affected.
Radiation, ionizing	Microcephaly, intellectual disability, eye anomalies, growth retardation, visceral malformations	Significant doses of radiation from diagnostic or therapeutic sources produce cell death and mitotic delay. There is no measurable risk with x-ray exposures of 5 rads or less at any stage of pregnancy.
Smoking	Placental lesions, IUGR, increased perinatal mortality, increased risk of SIDS, neurobehavioral effects such as learning deficits and hyperactivity.	Possible mechanisms include vasoconstriction (nicotine effect); hypoxia secondary to hypoperfusion, CO, and CN; and altered development of neurons and neural pathways via stimulation of nicotinic acetylcholine receptors.

Abbreviations: IUGR=intrauterine growth restriction, FAS=foetal alcohol syndrome, PCB=polychlorinated biphenyl, SID=sudden infant death syndrome, CO=carbon monoxide, CN=cyanide.

Annex 3. 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: A Worldwide Pregnancy Safety Study to Assess Maternal, Foetal, and Infant Outcomes Following Exposure to Efgartigimod (efgartigimod alfa) During Pregnancy and/or Breastfeeding

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[17]	☒	☐	☐	
1.1.2 End of data collection[18]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	6.0
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[17] 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.
[18] Date from which the analytical dataset is completely available.

Comments:

Exact dates are not provided because PRAC's approval on the study protocol is pending.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.0, 8.0
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?	☒	☐	☐	
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?	☒	☐	☐	9.1
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)	☒	☐	☐	11.2

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1, 9.4
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	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.2.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.7
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2, 9.2.5

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)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1, 9.5

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?	☒	☐	☐	9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.5, 9.7
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)	☒	☐	☐	9.3.1, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.3, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.2, 9.4
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))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Are stratified analyses included?	☒	☐	☐	9.7.4.8
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3, 9.7.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.4.8

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)	☒	☐	☐	9.6, 9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.3.4

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				9.9
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)	☒	☐	☐	9.4, 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.0
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.0

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.0

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.0

Comments:

Name of the main author of the protocol: _____

Date: dd/month/year

Signature: _____

Annex 4. Central Investigator Protocol Signature Page

Protocol Title: A Worldwide Pregnancy Safety Study To Assess Maternal, Foetal, and Infant Outcomes Following Exposure to Efgartigimod (efgartigimod alfa) During Pregnancy and/or Breastfeeding

Protocol Number: ARGX-113-2206

Protocol Version: v.2.0

Protocol Date: 14 December 2023

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

Study Principal Investigator Name (printed): **Amy Miller, RPh, PharmD**

Site Address: **933 Canyon Road, Morgantown, WV 26508, USA**

Signature Page for VV-CLIN-002440 v6.0

Approval	[redacted]
Approval	[redacted]
Approval	[redacted]

Signature Page for VV-CLIN-002440 v6.0

DocuSign

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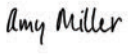
Amy Miller Amy.Miller@UBC.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 1711CA7E-6FDD-481E-8F68-AA824C48A98F [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17-Jan-2024 | 08:35 Viewed: 17-Jan-2024 | 14:32 Signed: 17-Jan-2024 | 14:33

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Witness Events	Signature	Timestamp

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	17-Jan-2024 | 08:35
Certified Delivered	Security Checked	17-Jan-2024 | 14:32
Signing Complete	Security Checked	17-Jan-2024 | 14:33
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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	Final release versions of Internet Explorer® 6.0 or above (Windows only); Mozilla Firefox 2.0 or above (Windows and Mac); Safari™ 3.0 or above (Mac only)
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	Allow per session cookies

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