# NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

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|---|---|
| **TITLE:** | **SATRALIZUMAB SINGLE-ARM PREGNANCY SAFETY STUDY: A GLOBAL, OBSERVATIONAL, SINGLE-ARM, 10-YEAR STUDY OF PREGNANCY AND INFANT OUTCOMES IN SATRALIZUMAB-EXPOSED WOMEN WITH NEUROMYELITIS OPTICA SPECTRUM DISORDER** |
| **PROTOCOL NUMBER:** | WN42856 |
| **VERSION NUMBER:** | 1.0 – 17 September 2021 |
| **AUTHOR:** | [redacted] PhD, MSc<br>F. Hoffmann-La Roche Ltd.<br>Grenzacherstrasse 124, 4070 Basel<br>Switzerland<br><br>[redacted] PhD, MSc<br>IQVIA<br>3 Forbury Place, 23 Forbury Rd<br>Reading RG1 3JH<br>United Kingdom |
| **EU PAS REGISTER NUMBER:** | To be registered |
| **STUDIED MEDICINAL PRODUCT:** | ENSPRYNG® (satralizumab) |
| **DATE FINAL:** | See electronic date stamp below |

## FINAL PROTOCOL APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 20-Sep-2021 11:52:35 | [redacted] EU QPPV | [redacted] |
| 20-Sep-2021 12:01:06 | Company Signatory | |
| 20-Sep-2021 13:05:16 | Company Signatory | |

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|---|---|
| **ACTIVE SUBSTANCE:** | L04AC19: satralizumab |
| **PROCEDURE NUMBERS:** | IND 118183; BLA 761149<br>EMEA/H/C/004788 |
| **JOINT PASS:** | No |
| **RESEARCH QUESTION AND OBJECTIVES:** | To collect and describe maternal, fetal and infant adverse outcomes among women with neuromyelitis optica spectrum disorder (NMOSD) exposed to satralizumab during the 6 months prior to the last menstrual period (LMP) or at any time during pregnancy.<br>The objectives of this study are as follows:<br>• To observe and report selected adverse pregnancy and birth outcomes (i.e., spontaneous abortions, fetal deaths/stillbirths, elective terminations, and preterm births) and pregnancy complications in women with NMOSD exposed to satralizumab during the defined exposure window<br>• To observe and report selected adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development) at birth and through the first year of life of infants from pregnancies in women with NMOSD exposed to satralizumab during the defined exposure window |
| **COUNTRIES OF STUDY POPULATION:** | At least 5 countries including the US and Europe |
| **MARKETING AUTHORIZATION HOLDER (MAH):** | Roche Registration GmbH<br>Emil-Barell-Strasse 1<br>D-79639 Grenzach-Wyhlen<br>Germany |
| **MAH CONTACT PERSON:** | [redacted]<br>Roche Products Limited<br>Hexagon Place, 6 Falcon Way,<br>Shire Park, Welwyn Garden City, |

| | |
|---|---|
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I agree to conduct the study in accordance with the current protocol.

Treating Physician's Name (print)

Treating Physician's Signature

Date

Please return a copy of this form to IQVIA. Please retain the signed original for your study files.

# 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AQP4 | aquaporin 4 |
| BMI | body mass index |
| CDC | Centers for Disease Control |
| CNS | central nervous system |
| CRF | case report form |
| CRO | contract research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| eCRF | electronic case report form |
| EC | Ethics Committee |
| EDC | electronic data capture |
| EDD | estimated date of delivery |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centers for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| EUROCAT | European Concerted Action on Congenital Anomalies and Twins |
| FDA | U.S. Food and Drug Administration |
| GPP | Good Pharmacoepidemiology Practices |
| HCP | Health Care Professional |
| ICF | informed consent form |
| IgG | immunoglobulin G |
| IRB | Institutional Review Board |
| LMP | last menstrual period |
| MAH | marketing authorization holder |
| MS | multiple sclerosis |
| NCI | National Cancer Institute |
| NMO | neuromyelitis optica |
| NMOSD | neuromyelitis optica spectrum disorder |
| PAS | post authorization study |
| PMR | post marketing requirement |
| RMP | risk management plan |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SDV | source data verification |
| SmPC | summary of product characteristics |
| US | United States |
| USPI | United States prescribing information |

## 2. RESPONSIBLE PARTIES

### Protocol Development Responsible

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## 3. SYNOPSIS

| | |
|---|---|
| **TITLE:** | **SATRALIZUMAB SINGLE-ARM PREGNANCY SAFETY STUDY: A GLOBAL, OBSERVATIONAL, SINGLE-ARM, 10-YEAR STUDY OF PREGNANCY AND INFANT OUTCOMES IN SATRALIZUMAB-EXPOSED WOMEN WITH NEUROMYELITIS OPTICA SPECTRUM DISORDER** |
| **PROTOCOL NUMBER:** | WN42856 |
| **VERSION NUMBER:** | 1.0 – 17 September 2021 |
| **DATE OF SYNOPSIS:** | See electronic date stamp on the cover page |
| **EU PAS REGISTER NUMBER:** | To be registered |
| **STUDIED MEDICINAL PRODUCT:** | ENSPRYNG® (satralizumab) |
| **SCIENTIFIC RESPONSIBLE MAIN AUTHOR:** | [redacted] MD<br>[redacted] PhD, MSc.<br>[redacted]<br>F. Hoffmann-La Roche Ltd. |
| **PHASE:** | IV, non-interventional study |
| **INDICATION:** | Neuromyelitis optica spectrum disorder |
| **MARKETING AUTHORIZATION HOLDER:** | Roche Registration GmbH<br>Emil-Barell-Strasse 1<br>D-79639 Grenzach-Wyhlen<br>Germany |

### Rationale and Background

Neuromyelitis optica (NMO), originally known as Devic's disease, is a rare, chronic, autoimmune, inflammatory, demyelinating disorder of the central nervous system (CNS) that affects mainly the optic nerve and/or spinal cord (Huda 2019). The discovery in 2004 of a pathogenic autoantibody biomarker revolutionized its diagnosis and therapeutic development (Lennon 2004; Weinshenker 2006); in 2015, the International Panel for Neuromyelitis Optica Diagnosis defined the unifying term "neuromyelitis optica spectrum disorder" (NMOSD) that included serologic testing for aquaporin 4 (AQP4) immunoglobulin G (IgG) antibodies and distinguished between AQP4-IgG seropositive and seronegative NMOSD (Wingerchuk 2015).

NMOSD is clinically characterized by relapsing optic neuritis and/or transverse myelitis attacks associated with neurologic symptoms such as visual impairment, ambulation difficulties, sensory disturbances, and/or bowel and bladder dysfunction. Fatigue and pain are also common symptoms of NMOSD and significantly impact the patient's quality of life. Disability accumulates with each relapse, and if undiagnosed and untreated, disability accrual can lead to mobility problems, paralysis, blindness or death in a few years (Wingerchuk 1999). NMOSD predominantly affects women (4- to 5-fold compared

to men), and although higher frequencies have been reported in non-Caucasian populations, NMOSD prevalence is considered to be approximately 4-10 cases per 100,000 individuals worldwide (Asgari 2011; Flanagan 2016).

Because of its overlapping clinical manifestations and relapsing presentation, NMOSD can be confused with other CNS demyelinating disorders such as multiple sclerosis (MS). However, NMOSD is histopathologically and radiologically distinct from MS, has a worse prognosis, and has a pathophysiology that is unresponsive to typical MS treatment (Weinshenker 2007). Unlike in MS, secondary progression is uncommon in NMOSD. Other distinguishing features of NMOSD include an even stronger female preponderance, longitudinally extensive spinal cord lesions (more than three vertebral segments), and absence of oligoclonal IgG bands in the cerebrospinal fluid (Jacob 2013). Early and accurate diagnosis of these distinct conditions is of great importance for patient care given their different treatments (Lana-Peixoto 2019).

Satralizumab (ENSPRYNG®) is a humanized interleukin-6 (IL-6) receptor blocking monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) in August 2020 for treatment of adults with anti-AQP4 antibody positive NMOSD. In June 2021, the European Medicines Agency (EMA) approved satralizumab as monotherapy or in combination with immunosuppressive therapies for the treatment of NMOSD in adult and adolescent patients from 12 years of age who are AQP4-IgG seropositive. Its approval was based primarily on the results of two randomized placebo-controlled trials (NCT02073279, Traboulsee 2020; NCT02028884, Yamamura 2019) that demonstrated a reduction in the risk of protocol-defined relapse >74% for AQP4-IgG positive patients receiving satralizumab and a favorable safety profile (Hemingway 2020). Satralizumab (ENSPRYNG®) has been approved in more than 50 countries and is currently under review by other Health Authorities worldwide.

There are no adequate data on the developmental risks associated with use of satralizumab during pregnancy or lactation. The randomized controlled clinical trials excluded women who were pregnant or breastfeeding, and female participants of reproductive potential were required to use reliable means of contraception. In animal studies, no adverse effects on maternal animals or fetal development were observed in monkeys with administration of doses up to 50 mg/kg/week; the concentrations of satralizumab in breast milk were very low (<0.9% of the corresponding maternal plasma levels).

In humans, monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Human IgGs are excreted in human milk. Nevertheless, no information is available on the presence of satralizumab in human milk, its effects on milk production, the potential for its absorption in the infant, or its effects on the breastfed infant.

It is not known whether satralizumab can affect pregnancy outcomes or infant outcomes in humans. However, satralizumab might theoretically affect pregnancy outcomes and infant outcomes in the following ways:

- By direct exposure of the fetus to satralizumab, which is assumed to occur after the 16$^{th}$ week of gestation as receptor-mediated transplacental transfer of IgG; this is minimal during the first trimester of pregnancy
- Indirectly due to effects of satralizumab on the placenta
- By exposure of the infant to satralizumab in human milk

This satralizumab study will be conducted to fulfill an FDA postmarketing requirement (PMR) (3920-1) for a single-arm pregnancy safety study. This study has also been included as the additional pharmacovigilance activity for the missing information of ‘Use in pregnant and breastfeeding women’ in the EU Risk Management Plan (RMP).

## Research Question and Objectives

This global, observational, single-arm, 10-year study will collect and describe maternal, fetal, and infant adverse outcomes among women with NMOSD exposed to satralizumab during the 6 months prior to the last menstrual period (LMP) or at any time during pregnancy.

### Objectives

The objectives for this pregnancy safety study are as follows:

To observe and report selected adverse pregnancy and birth outcomes (i.e., spontaneous abortions, fetal deaths/stillbirths, elective terminations, preterm births) and pregnancy complications in women with NMOSD exposed to satralizumab during the defined exposure window

To observe and report selected adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development) at birth and through the first year of life of infants from pregnancies in women with NMOSD exposed to satralizumab during the defined exposure window

## Study Design

This single-arm pregnancy safety study will collect primary data from satralizumab-exposed pregnant women, their obstetric provider, and their satralizumab prescriber, as well as from the infant's health care provider (HCP) throughout the first year of life for live births. Women who have been exposed to satralizumab during the 6 months prior to their LMP or at any time during pregnancy will be eligible for participation. Inclusion of exposures prior to the LMP is based on the pharmacokinetic characteristics of satralizumab. Dosing and treatment duration of satralizumab as part of this non-interventional study is at the discretion of the physician in accordance with local labeling. The study duration is expected to be a maximum of 10 years. A different duration may be adopted based on the number of cases reported and in agreement with Health Authorities.

Participants may enroll in this pregnancy safety study prospectively or retrospectively (i.e., when the first contact with the patient takes place after a pregnancy outcome has occurred).

### Description of Study

The design of this pregnancy safety study is consistent with relevant guidelines and recommendations (Food and Drug Administration 2019; European Medicines Agency 2005; Andrews 2008; Gliklich 2014).

This is a worldwide, non-interventional, single-arm, 10-year study on the safety of satralizumab in women with NMOSD and their infants.

Outcomes and variables of interest will be collected from patients and their healthcare providers (HCPs) (e.g., neurologist, obstetrician) during pregnancy and from patients and the infant's HCP (e.g., pediatrician) through 1 year after birth. Participants may enroll in this pregnancy exposure study prospectively or retrospectively (e.g., after a pregnancy outcome has occurred). Patient enrollment is voluntary; any woman with NMOSD exposed to satralizumab within 6 months of their LMP or any time during pregnancy according to national labeling and local standard of care will be eligible for enrollment in each targeted country. As this study is a single-arm study, no minimal sample size is required for formal statistical comparisons. The Sponsor will utilize awareness strategies to maximize the enrollment of satralizumab-exposed pregnant women with NMOSD.

The total duration of participation is up to 21 months, and the total duration of the study is approximately 10 years. Given the rarity of NMOSD, data will be collected in at least 5 countries including the United States (US) and Europe based on the drug approval dates and drug access, as well as the country size and the local drug uptake.

**Studied Medicinal Product**

Satralizumab (ENSPRYNG®) as per local labeling.

**Exposure definition**

Satralizumab exposure from 6 months prior to the LMP through pregnancy will be recorded including dosing, dates, and mode of administration during each trimester of pregnancy.

Concomitant medication prescribed for NMOSD or other ongoing conditions and vaccines during the observation period will be recorded from 6 months prior to the LMP.

**Population**

Pregnant patients may be enrolled prospectively or retrospectively from the postmarketing setting or other clinical or observational studies of satralizumab.

Pregnancies will be classified as prospective if the outcome of the pregnancy is unknown at the time of enrollment. Retrospective pregnancies include women for whom the pregnancy outcome (e.g., live birth, stillbirth, elective or spontaneous abortion) is known prior to enrollment in the study. Women who have had prenatal testing prior to enrollment that could determine the status of the fetus (e.g., amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late term ultrasound) will be considered prospective pregnancies. However, women who have received first-trimester prenatal screening prior to enrollment, in which either aneuploid disorders or genetic disorders that cause major congenital malformations may have been detected, will be considered retrospective pregnancies.

Patients must meet the following criteria for study entry:

Patient informed consent (written or verbal as per local regulations or Ethics Committee requirements) obtained prior to enrollment. Where applicable, consent must be obtained from the patient's parent, guardian, or legally authorized representative, and the patient should provide assent per local and national requirements. Consent will be obtained in compliance with any country or region specific regulations and requirements.

Ability to comply with the study protocol.

Diagnosed with AQP4 antibody seropositive NMOSD.

Prospective or retrospective pregnancy with documented exposure to satralizumab during the 6 months prior to the LMP or at any time during the pregnancy.

There are no exclusion criteria for this study.

**Variables**

Only variables, obtained according to routine clinical practice and following objectives can and should be documented in this study.

Variables will be collected according to the below schedule for prospective patients. For retrospectively enrolled patients (i.e., patients enrolled after the pregnancy outcome is known), all information on the pregnancy and any infant outcomes detailed below will be collected at study entry. If the infant of a retrospectively enrolled patient is <1 year old, they will be prospectively followed until 1 year of age.

The following variables will be collected during the study, as part of the local routine clinical practice, as available:

Study entry:

Documentation of informed consent

Reporter of information (e.g., patient, obstetrician, satralizumab prescriber)

Maternal demographics and general characteristics (e.g., age, occupation/employment status, education level, race/ethnicity, height, weight, body mass index [BMI])

Patient, secondary contact, and HCP contact information (obstetrician, satralizumab prescriber, infant HCP, if possible). This information is confidential and remains at the coordinating center; it is not recorded in the electronic case report form (eCRF).

Maternal lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use) from estimated date of conception

Current pregnancy information (e.g., LMP, method of conception, gestational age, estimated date of delivery [EDD], date and results of any prenatal tests, number of fetuses)

Maternal medical history:

- Pregnancy history (e.g., parity, gravidity, previous preterm births, previous spontaneous abortions or elective or therapeutic terminations, reason for any elective or therapeutic termination, previous pregnancy complications, history of congenital malformations)
- Surgical and medical history, including significant medical conditions other than NMOSD (e.g., diabetes, high blood pressure)
- NMOSD disease history (including treatment history, disease duration, date of the last relapse and relapse severity, most recent Expanded Disability Status Scale [EDSS] score, NMOSD biomarker status if available)
- Comorbid conditions
- Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, preterm births, chromosomal anomalies, developmental delays)
- Family NMOSD history

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation or delayed treatment [if applicable], mode of administration [self-administration, HCP, caregiver])

Current and prior medication use from 6 months prior to the LMP (including other NMOSD treatments, teratogenic medications, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic disease)

Paternal information:

The following paternal variables are optional, depending on the availability and willingness of fathers to provide informed consent:

- Age
- Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, preterm births, chromosomal anomalies, developmental delays)
- Comorbid conditions and medical history including significant medical conditions
- Teratogenic or genotoxic medications, which may cause DNA mutagenesis, used in the 3 months prior to LMP

<u>Follow-up during pregnancy (during each trimester, approximately at 14, 21, and 34 weeks of gestation):</u>

Date of contact

Reporter of information (e.g., patient, obstetrician, satralizumab prescriber)

Changes in contact information (maternal, secondary contact, and mother's HCP). This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Changes in pregnancy status:

- Gestational age (estimated based on the date of LMP, unless ultrasound results provide an updated estimate)
- Weight
- Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasound scans, amniocentesis, maternal serum alpha-fetoprotein screen, screening for chromosomal abnormalities, glucose screen, blood group, and Rh factor)
- Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
  - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
  - Autopsy results and pathology reports, if available
- Changes in NMOSD disease status (including treatment changes, relapses, EDSS score)

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation or delayed treatment [if applicable], mode of administration [self-administration, HCP, caregiver])

Changes in comorbid conditions

Current maternal lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)

Current medications (including other NMOSD drugs, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

Serious adverse events (SAEs) related to pregnancy, including pregnancy complications

<u>Pregnancy outcome follow-up (approximately 4 weeks after pregnancy outcome):</u>

Date of contact and date of pregnancy outcome or gestational age (in weeks)

Changes in contact information; contact information for infant's HCP. This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Reporter of information (e.g., patient, obstetrician, HCP)

Pregnancy outcome (e.g., live birth, stillbirth, spontaneous abortion, elective or therapeutic termination)

- Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
- Autopsy results and pathology reports, if available
- Mode of delivery (vaginal delivery, assisted delivery/cesarean section, type of anesthesia)
- Presentation at delivery (vertex, non-vertex)

Maternal weight at end of pregnancy

Changes in NMOSD disease and treatment status since last follow-up, if applicable

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable], mode of administration [self-administration, HCP, caregiver])

Changes in comorbid conditions

Current maternal lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)

Current medications (including other NMOSD drugs, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

Infant characteristics:

- Gestational age at birth
- Sex
- Birth weight
- Length at birth
- Head circumference at birth
- Birth order (for multiple births) and number of fetuses
- Apgar score (1, 5, and 10 minutes)
- Congenital malformations noted (including description and attribution)
- Laboratory values and laboratory test dates, if available (e.g., neutrophil count, platelet count, liver enzymes, and bilirubin)
- Vaccination information

Breastfeeding (yes vs. no) and duration of breastfeeding, if applicable

SAEs related to pregnancy

Infant SAEs and selected non-serious AEs which include severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response

Pediatric follow-up (approximately at infant age 12, 26, and 52 weeks after birth):

Reporter of information (e.g., patient, infant HCP)

Changes in contact information (maternal, secondary contact, mother's HCP, and infant's HCP). This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Infant characteristics:

- Feeding behavior (including breastfeeding)
- Weight
- Length
- Head circumference
- Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the Centers for Disease Control and Prevention [Centers for Disease Control and Prevention 2016])
- Laboratory values, if available (e.g., neutrophil count, platelet count, liver enzymes, and bilirubin)
- Evidence of any new congenital malformations and growth alterations since last follow-up
- Vaccination information

Infant SAEs and selected non-serious AEs which include severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response

Maternal satralizumab use (dates, dose, dosing frequency, mode of administration, reason for discontinuation [if applicable])

Maternal concomitant medications (including other NMOSD drugs, corticosteroids, vaccinations, medications to treat other chronic diseases)

Early termination of study participation contact, if applicable:

Reporter of information (e.g., patient, obstetrician, HCP)

Changes in contact information (maternal, secondary contact, mother's HCP, and infant's HCP). This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Assessments appropriate for the time of withdrawal

Reason for study withdrawal

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable], mode of administration [self-administration, HCP, caregiver])

Other medications (including other NMOSD drugs, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

Pregnancy status:

- Gestational age
- Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, screening for chromosomal abnormalities, glucose screen, blood group, and Rh factor)
- Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
  - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
  - Autopsy results and pathology reports, if available

Infant characteristics (for live births):

- Gestational age at birth
- Sex
- Birth weight
- Length at birth
- Head circumference at birth
- Birth order (for multiple births) and number of fetuses
- Apgar score (1, 5, and 10 minutes)
- Congenital malformations noted (including description and attribution)
- Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the Centers for Disease Control and Prevention [Centers for Disease Control and Prevention 2016])
- Laboratory values, if available (e.g., neutrophil count, platelet count, liver enzymes, and bilirubin)
- Breastfeeding (yes vs. no) and duration of breastfeeding, if applicable

SAEs related to pregnancy, infant SAEs, and selected non-serious infant adverse events (AEs) which include severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response

## Data Sources

Patients' data will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the eCRF as soon as they become available.

Data will be obtained through questionnaires administered to patients and/or their HCPs (NMOSD treating HCP, obstetrician or infant HCP), and will be recorded on the eCRFs by the coordinating center. Treating physicians will provide information from patient's charts and will be the preferred source of information for medically related data elements.

## Study Size/Determination of Sample Size

All eligible women will be enrolled in the pregnancy safety study. No formal sample size is required for such a study design as no formal statistical hypotheses will be tested. NMOSD is a rare disease, and recruitment of patients is dependent on several factors. Approval and uptake of new medications such as satralizumab are unpredictable and have the potential to impact the feasibility of enrolling satralizumab-exposed women in each targeted country. In addition, the expected pace of exposure to pregnant women and the willingness of pregnant women to participate in such a study are both difficult to predict.

To mitigate these challenges, the Sponsor will develop study awareness strategies as well as outreach and retention efforts aiming to ensure that target populations are being reached, actively engaged, and retained over time in the study. Increased awareness of the study will use multiple approaches aimed towards both HCPs and patients, such as social media, paper and electronic media, and scientific conferences. Study retention efforts may include the following: general study eNewsletters to HCPs and an optional (opt-in) communications program (e.g., engagement e-mails, SMS/e-mail/call reminders, and thank-you messages for patients and SMS/ e-mail/call reminders for HCPs).

## Data Analysis

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the study sample.

If there are sufficient numbers of patients enrolled in the pregnancy safety study, descriptive statistics will be reported using summary tables and figures (where appropriate). Continuous variables will be summarized using mean, standard deviation, range (min-max), median and interquartile range. Categorical variables will be summarized using counts and proportions (%). The number of patients with non-missing data will be presented.

The analysis will qualitatively describe patients enrolled in the study. The source of information (patient or HCP) will also be included in the descriptions.

Demographic information, maternal clinical characteristics and other factors that may affect pregnancy and infant outcomes will be described.

The frequency of selected adverse pregnancy outcomes, pregnancy complications and adverse infant outcomes will be estimated. All descriptive outcome analyses will be conducted on an overall basis (i.e., combining data from all patients irrespective of whether the outcome of the pregnancy was known at the time of enrollment) and also separately for prospective and retrospective pregnancies. When sample size permits, analyses will be stratified by earliest trimester of satralizumab exposure (including a subgroup with preconception exposure), prenatal screening result (positive vs. negative for aneuploid disorders or genetic disorders that cause major congenital malformations), as well as by maternal age, race/ethnicity, gestational age at enrollment, NMOSD biomarker status, elective or therapeutic pregnancy termination status and other relevant factors. Retrospective-pregnancy analyses may be stratified by prenatal screening status, if sample size permits. If possible, a sensitivity descriptive analysis of

major congenital malformations will exclude women exposed to any known teratogenic medications during pregnancy.

**Interim Analyses**

Interim progress reports will be provided to the Health Authorities yearly. If at least five new pregnancies have been reported between two interim analyses, descriptive statistics will be provided; otherwise, a qualitative progress report will be submitted.

## Milestones

**Start Date of Study:**

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database. The planned start date is approximately by Q2 2022.

**End of Study**

The end of the study will be the date from which the last data collected from the last subject is recorded in the study database. The planned end of study date is Q4 2032. In addition, the Sponsor may decide to terminate the study at any time.

**Length of Study**

This study will last approximately 10 years.

# 4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorization Holder (MAH) or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: none.

# 5. MILESTONES

Planned approximate study milestones are given in the following table.

| Milestone | Planned Date |
|---|---|
| Registration of protocol in the EU PAS register | To be determined |
| Start of data collection | Q2 2022 |
| End of data collection | Q4 2032 |
| Study progress report | Annually |
| Interim analysis | Annually [1] |
| Final report of study results | Q4 2033 |
| Registration of the results in the EU PAS register | To be determined |

[1] Interim analyses will be conducted every year provided that at least five new pregnancies have occurred between two interim analyses.

EU = European Union; PAS = post-authorization study.

# 6. RATIONALE AND BACKGROUND

## 6.1 STUDY RATIONALE

Neuromyelitis optica (NMO), originally known as Devic's disease, is a rare, chronic, autoimmune, inflammatory, demyelinating disorder of the central nervous system (CNS) that affects mainly the optic nerve and/or spinal cord (Huda 2019). The discovery in 2004 of a pathogenic autoantibody biomarker revolutionized its diagnosis and therapeutic development (Lennon 2004; Weinshenker 2006); in 2015, the International Panel for Neuromyelitis Optica Diagnosis defined the unifying term "neuromyelitis optica spectrum disorder" (NMOSD) that included serologic testing for aquaporin 4 (AQP4)

immunoglobulin G (IgG) antibodies and distinguished between AQP4-IgG seropositive and seronegative NMOSD (Wingerchuk 2015).

NMOSD is clinically characterized by relapsing optic neuritis and/or transverse myelitis attacks associated with neurologic symptoms such as visual impairment, ambulation difficulties, sensory disturbances, and/or bowel and bladder dysfunction. Fatigue and pain are also common symptoms of NMOSD and significantly impact the patient's quality of life. Disability accumulates with each relapse, and if undiagnosed and untreated, disability accrual can lead to mobility problems, paralysis, blindness or death in a few years (Wingerchuk 1999). NMOSD predominantly affects women (4- to 5-fold compared to men), and although higher frequencies have been reported in non-Caucasian populations, NMOSD prevalence is considered to be approximately 4-10 cases per 100,000 individuals worldwide (Asgari 2011; Flanagan 2016).

Because of its overlapping clinical manifestations and relapsing presentation, NMOSD can be confused with other CNS demyelinating disorders such as multiple sclerosis (MS). However, NMOSD is histopathologically and radiologically distinct from MS, has a worse prognosis, and has a pathophysiology that is unresponsive to typical MS treatment (Weinshenker 2007). Unlike in MS, secondary progression is uncommon in NMOSD. Other distinguishing features of NMOSD include an even stronger female preponderance, longitudinally extensive spinal cord lesions (more than three vertebral segments), and absence of oligoclonal IgG bands in the cerebrospinal fluid (Jacob 2013). Early and accurate diagnosis of these distinct conditions is of great importance for patient care given their different treatments (Lana-Peixoto 2019).

Satralizumab (ENSPRYNG®) is a humanized interleukin 6 (IL-6) receptor blocking monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) in August 2020 for treatment of adults with anti-AQP4 antibody positive NMOSD. In June 2021, the European Medicines Agency (EMA) approved satralizumab as monotherapy or in combination with immunosuppressive therapies for the treatment of NMOSD in adult and adolescent patients from 12 years of age who are AQP4-IgG seropositive. Its approval was based primarily on the results of two randomized placebo-controlled trials (NCT02073279, Traboulsee 2020; NCT02028884, Yamamura 2019) that demonstrated a reduction in the risk of protocol-defined relapse >74% for AQP4-IgG positive patients receiving satralizumab and a favorable safety profile (Hemingway 2020). Satralizumab (ENSPRYNG®) has been approved in more than 50 countries and is currently under review by other Health Authorities worldwide.

For information on the condition under observation and on satralizumab, please refer to the most recent version of the United States prescribing information (USPI) and summary of product characteristics (SmPC).

## 6.2 STUDY BACKGROUND

Congenital malformations, structural (e.g., cleft lip/palate, heart defects, neural tube defects, heart defects, abnormal limbs) and functional/developmental (e.g., sensory problems, metabolic disorders, nervous system problems, degenerative disorders), affect about 3.0 per 100 live births in the United States (US) (Centers for Disease Control and Prevention 2008) and are the leading cause of infant death (about 20% of all infant deaths) (Matthews 2015). The European Surveillance of Congenital Anomalies (EUROCAT) estimated the prevalence of congenital anomalies as 23.9 per 1,000 live births from 2003–2007 (Dolk 2010).

Results from small retrospective studies and case reports indicate that pregnancy can worsen NMOSD activity (with increased frequency of relapses, particularly in the postpartum/post-abortion period; Shosha 2017; Tong 2018; Collongues 2021) and might contribute to disease onset (Klawiter 2017). It is unknown whether NMOSD has an impact on the risk of adverse pregnancy and infant outcomes. Some studies have suggested higher risks of pregnancy complications in NMOSD patients, particularly spontaneous abortions and pre-eclampsia (Nour 2016; Shosha 2017). However, available data are insufficient to confirm and accurately estimate the risk of adverse obstetric outcomes in this population (D'Souza 2020; Mao-Draayer 2020).

There are no adequate data on the developmental risks associated with use of satralizumab during pregnancy or lactation. The randomized controlled clinical trials excluded women who were pregnant or breastfeeding, and female participants of reproductive potential were required to use reliable means of contraception. In animal studies, no adverse effects on maternal animals or fetal development were observed in monkeys with administration of doses up to 50 mg/kg/week (US prescribing information 2020); the concentrations of satralizumab in breast milk were very low (<0.9% of the corresponding maternal plasma levels).

In humans, monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Human IgGs are excreted in human milk. Nevertheless, no information is available on the presence of satralizumab in human milk, its effects on milk production, the potential for its absorption in the infant or its effects on the breastfed infant.

It is not known whether satralizumab can affect pregnancy outcomes or infant outcomes in humans. However, satralizumab might theoretically affect pregnancy outcomes and infant outcomes in the following ways:

- By direct exposure of the fetus to satralizumab, which is assumed to occur after the 16th week of gestation as receptor-mediated transplacental transfer of IgG; this is minimal during the first trimester of pregnancy
- Indirectly due to effects of satralizumab on the placenta
- By exposure of the infant to satralizumab in human milk

This satralizumab study will be conducted to fulfill an FDA postmarketing requirement (PMR) (3194-3) for a single-arm pregnancy safety study. This study has also been included as the additional pharmacovigilance activity for the missing information of 'Use in pregnant and breastfeeding women' in the EU Risk Management Plan (RMP).

# 7. RESEARCH QUESTION AND OBJECTIVES

## 7.1 RESEARCH QUESTION

This global, observational, single-arm, 10-year study will collect and describe maternal, fetal and infant adverse outcomes among women with NMOSD exposed to satralizumab during the 6 months prior to the last menstrual period (LMP) or at any time during pregnancy.

## 7.2 OBJECTIVES

The objectives of this pregnancy safety study are as follows:

To observe and report selected adverse pregnancy and birth outcomes (i.e., spontaneous abortions, fetal deaths/stillbirths, elective terminations, and preterm births) and pregnancy complications (gestational diabetes, pre-eclampsia and other hypertensive disorders of pregnancy, antenatal bleeding, placenta previa, postpartum hemorrhage, preterm labor, premature rupture of membranes, small-for-gestational-age fetus or intrauterine growth restriction, others) in women with NMOSD exposed to satralizumab during the defined exposure window

To observe and report selected adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development) at birth and through the first year of life of infants from pregnancies in women with NMOSD exposed to satralizumab during the defined exposure window

# 8. RESEARCH METHODS

## 8.1 STUDY DESIGN

### 8.1.1 Overview of Study Design

The design of this single-arm pregnancy safety study is consistent with relevant guidelines and recommendations (Food and Drug Administration 2019; European Medicines Agency 2005; Andrews 2008; Gliklich et al. 2014).

This is a global, non-interventional, single-arm, 10-year study on the safety of satralizumab in women with NMOSD and their infants exposed to the study drug during the 6 months prior to the LMP or at any time during the pregnancy. Inclusion of exposures prior to the LMP is based on the pharmacokinetic characteristics of satralizumab. Based on the average satralizumab terminal half-life of 30 days reported in the two randomized controlled trials, it is expected that satralizumab would be eliminated from the body approximately 4.9 months after the last administration. Accounting for the interpatient variability range of 22 - 37 days, a 6-month window prior to LMP is considered appropriate. Dosing and treatment duration of satralizumab as part of this

non-interventional study is at the discretion of the physician in accordance with local clinical practice and local labeling.

Outcomes and variables of interest will be collected from patients and their healthcare providers (HCPs) (e.g., neurologist, obstetrician) during pregnancy and from patients and the infant's HCP (e.g., pediatrician) through 1 year after birth. Participants may enroll in this pregnancy exposure study prospectively or retrospectively (e.g., after a pregnancy outcome has occurred). Patient enrollment is voluntary; any woman with NMOSD exposed to satralizumab according to national labeling and local standard of care during pregnancy will be eligible for each targeted country. As this study is a single-arm study, no minimal sample size is required for formal statistical comparisons. The Sponsor will utilize awareness strategies to maximize the enrollment of satralizumab-exposed pregnant women with NMOSD.

The total duration of participation is up to 21 months (9 months of pregnancy and 1 year of infant follow-up), and the total duration of the study is approximately 10 years (the last patient will be expected to enroll no later than 8 years and 3 months after the first patient entering the study). Given the rarity of NMOSD, data will be collected in at least 5 countries including the US and Europe based on the drug approval dates and drug access, as well as the country size and the local drug uptake.

**Start Date of Study:**
The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database.

**End of Study:**
The end of the study will be the date from which the last data collected from the last subject is recorded in the study database. A data collection overview is provided in Appendix 2.

### 8.1.2 Rationale for Study Design

The FDA PMR (3920-1) requested a single-arm pregnancy safety study, which has been designed in accordance with the FDA's Post approval Pregnancy Safety Studies Guidance for Industry (Food and Drug Administration 2019). The data elements and design setting will allow the MAH to assess and report pregnancy complications and birth outcomes for satralizumab-exposed pregnancies. This study has also been included as the additional pharmacovigilance activity for the missing information of 'Use in pregnant and breastfeeding women' in the EU RMP.

## 8.2 SETTING

HCPs who treat patients with NMOSD including investigators involved in ongoing or future clinical studies of satralizumab will be informed of the study and asked to refer any patient who becomes pregnant to the appropriate study coordinating center. Reporting of pregnancy exposures to satralizumab is voluntary, and pregnancies should be reported

as early as possible, ideally before prenatal testing has been performed. However, reports from all eligible pregnancies will be included in the study.

### 8.2.1 Centers

This study will be conducted in at least 5 countries including the US and Europe based on the drug approval dates and drug access, as well as the country size and the local drug uptake. Each country will have at least one coordinating center that is responsible for obtaining informed consent and for all patient and HCP contacts during the study.

Additional countries may be added to the study depending upon the availability of eligible patients.

### 8.2.2 Study Population

Pregnant patients may be enrolled prospectively or retrospectively from the postmarketing setting or other clinical or observational studies of satralizumab. In order to reduce bias that may occur if outcome information is known prior to enrollment, women should be enrolled in the study as soon as their pregnancy is known, preferably in the first trimester.

Pregnancies will be classified as prospective if the outcome of the pregnancy is unknown at the time of enrollment. Retrospective pregnancies include women for whom the pregnancy outcome (e.g., live birth, stillbirth, congenital malformation) is known prior to enrollment in the study. Women who have had prenatal testing prior to enrollment that could determine the status of the fetus (e.g., amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late term ultrasound) will be considered prospective pregnancies. However, women who have received first-trimester prenatal screening prior to enrollment, in which either aneuploid disorders or genetic disorders that cause major congenital malformations may have been detected, will be considered retrospective pregnancies (see Figure 1 for a depiction of the definitions of prospective and retrospective pregnancies).

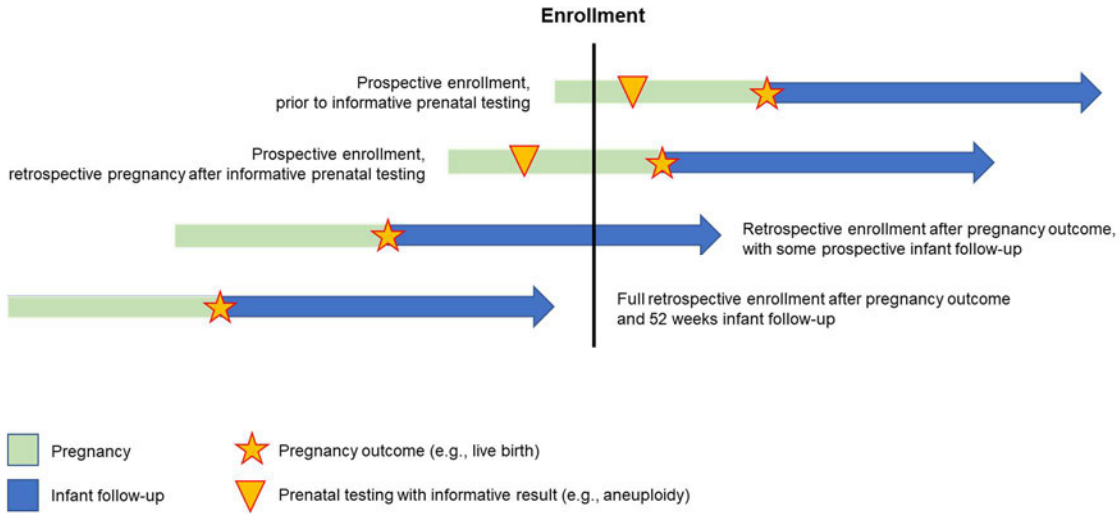



**Figure 1 Definition of retrospective and prospective pregnancies.**

Patients must meet the following criteria for study entry:

Patient informed consent (written or verbal as per local regulations or EC requirements) obtained prior to enrollment. Where applicable, consent must be obtained from the patient's parent, guardian, or legally authorized representative, and the patient should provide assent per local and national requirements. Consent will be obtained in compliance with any country or region specific regulations and requirements.

Ability to comply with the study protocol.

Diagnosed with AQP4 antibody seropositive NMOSD.

Prospective or retrospective pregnancy with documented exposure to satralizumab during the 6 months prior to the LMP or at any time during the pregnancy.

There are no exclusion criteria for this study.

### 8.2.3 Recruitment and Retention

Complete details of study awareness, outreach, and retention efforts will be described in the Recruitment and Retention Plan, and may include the following methods to (1) increase awareness of the pregnancy safety study by using multiple approaches aimed toward HCPs and patients, such as social media, paper and electronic media, and scientific conferences; (2) evaluate awareness of the pregnancy safety study periodically; (3) accept data from multiple sources; (4) minimize the burden on HCPs; (5) ongoing communications with HCPs and patients via a general study eNewsletters to HCPs and an optional (opt-in) communications programs (e.g., engagement e-mails, SMS/e-mail/call reminders, and thank-you messages for patients and SMS/ e-mail/call reminders for HCPs); and (6) and minimize the burden on subjects. All activities in this plan will be reviewed on a regular basis.

#### 8.2.3.1 Pregnancy Safety Study Awareness

The pregnancy safety study will utilize awareness strategies that have appeared to be effective in other pregnancy safety studies. Increased awareness of the pregnancy safety study will use multiple approaches aimed toward both HCPs and patients, such as social media, paper and electronic media, and scientific conferences. Study awareness activities and content will be evaluated on a regular basis ensuring target populations are being reached yet minimizing any burden on the recipients. Channels for providing feedback on pregnancy safety study material and corresponding with potential HCPs and patients will be detailed in the Recruitment and Retention Plan.

#### 8.2.3.2 Outreach Efforts

Active outreach will occur to obtain reports of women with NMOSD who are exposed to satralizumab during pregnancy. Outreach efforts may include the following:

Discussion of the pregnancy safety study with investigators participating in satralizumab clinical studies, with periodic written reminders

Collaboration with investigators of independent NMOSD pregnancy registries

Notification of the pregnancy safety study to practitioners who may prescribe satralizumab, as well as NMOSD education and support groups, via the following:

- EU Post Authorization Study (PAS) Register (if EU countries are included)
- Investigator awareness electronic flyer
- Investigator referral letters
- HCP introduction letters

Recruitment of patients is dependent on several factors: uptake of new medications such as satralizumab is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets in the US and other potential countries under study. In addition, the expected pace of exposure to pregnant women and the willingness of pregnant women to participate in a pregnancy safety study are both difficult to predict. Continuous monitoring of patient recruitment (comparing projections and observed rates) will allow for strategies to be employed in response to any recruitment challenges.

#### 8.2.3.3 Retention Efforts

Pregnancy safety study retention efforts for prospective cases will include (but will not be limited to) general study eNewsletters to HCPs and optional (opt-in) study communications including: engagement e-mails, SMS/e-mail/Call reminders and thank-you messages for patients, and SMS/ e-mail/call reminders for HCPs. Compensation will be issued (where allowed by local regulations) to all patients and/or HCPs for data collected. As detailed in Post approval Pregnancy Safety Studies Guidance for Industry, study design, and approach and factors for determining if a single-arm pregnancy safety study should continue will be routinely evaluated (Food and Drug Administration, 2019). The projected versus observed drop-out rates will be continuously monitored. Retention planning will be performed in advance as part of the Recruitment Risk Management with

triggers for implementation of actions identified, as well as steps to take if the rate of patient completion decreases. Retention efforts for both HCPs and the patients will be documented in the Recruitment and Retention Plan. Steps to ensure recruitment and retention of patients in the pregnancy safety study include actions for implementation at study start, in addition to actions that could be implemented as the study progresses and new enrollment information becomes available.

### 8.2.4 Dosage, Administration and Compliance of Studied Product(s)

The marketed drug will be used in the study; dosing and treatment duration collected as part of this non-interventional study are at the discretion of the physician in accordance with local labeling.

### 8.2.5 Concomitant Medication and Treatment

Concomitant medication prescribed for concomitant diseases of special interest and treatment for NMOSD at the beginning of the observation period or introduced during the observation period will be documented in the case report form (CRF) from 6 months prior to the LMP until discontinuation of the treatment if applicable.

## 8.3 VARIABLES

Only variables, obtained according to routine clinical practice and collected according to the study objectives can and should be documented in this study.

### 8.3.1 Exposure Definition

This is an observational pregnancy safety study. No study medication is provided as part of participation.

Satralizumab exposure from 6 months prior to the LMP through pregnancy will be recorded, including dosing and dates of administration during each trimester of pregnancy.

### 8.3.2 Outcome Variables

#### 8.3.2.1 Spontaneous Abortions

A spontaneous abortion is defined as loss of a fetus due to natural causes at <20 weeks of gestation. If available, information from gross or pathologic examination of the abortus or fetus will be evaluated for structural and chromosomal defects.

#### 8.3.2.2 Fetal Death or Stillbirth

Fetal death or stillbirth refers to the death of a fetus at ≥20 weeks of gestation. In the event of a stillbirth or fetal death, full pathology details will be requested and examined for structural or chromosomal defects. The final classification between fetal death/stillbirth and spontaneous abortion will be based on gestational age.

#### 8.3.2.3 Live Birth

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate.

#### 8.3.2.4 Elective or Therapeutic Pregnancy Terminations

Elective or therapeutic pregnancy terminations are defined as any induced or voluntary fetal loss during pregnancy. If available, data from pathologic examination of the abortus or fetus will be evaluated for structural and chromosomal defects. The reason for elective or therapeutic termination will be collected.

#### 8.3.2.5 Preterm Birth

A live birth will be classified as preterm if it occurs prior to 37 weeks of gestation (www.cdc.gov). Early preterm (<34 weeks), late preterm (34–36 weeks), early term (37-38 weeks) are additional stratifications that may be considered during the analysis.

#### 8.3.2.6 Congenital Malformations

Congenital malformations will be classified according to the European Concerted Action on Congenital Anomalies and Twins (EUROCAT) classification system. All potential congenital malformations will be evaluated using all available medical records. The classification of the potential congenital malformations will be based upon adjudication by an independent teratologist not affiliated with the pregnancy safety study who will be blinded to the specific NMOSD treatment. The exact grouping of congenital malformations will mirror classification systems used in EUROCAT.

Major malformations are those that have significant medical, social or cosmetic consequences, and typically require surgical intervention or are life-threatening (e.g., cleft lip, spina bifida). Minor malformations pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences, rarely requiring surgical intervention (e.g., single palmar crease, clinodactyly). Both major and minor congenital malformations identified up to 1 year of age by the mother or by the infant's pediatrician via the dysmorphological examination conducted as part of the standard of care will be included in the analysis.

#### 8.3.2.7 Size for Gestational Age at Birth

All live births will be classified as small, appropriate or large for gestational age using the Centers for Disease Control (CDC) and Prevention definitions of birth weight below the $10^{th}$ percentile, between the $10^{th}$ and $90^{th}$, and above the $90^{th}$ percentile for age, respectively.

#### 8.3.2.8 Low Birth Weight

An infant with low birth weight will be classified as weighing under 2500 g. Very low birth weight are infants who weigh less than 1500 g, and moderate birth weight ranges between 1500 g and 2499 g; these are additional stratifications that may be considered during the analysis.

#### 8.3.2.9 Failure to Thrive

An infant may be diagnosed as failing to thrive by his/her treating physician using criteria such as a significant weight or weight-for-height deceleration. Any reported instances of failure to thrive will be captured.

#### 8.3.2.10 Ectopic Pregnancies

Any reported ectopic pregnancy will be sub-classified in the respective pregnancy outcome, including induced termination, maternal death, or spontaneous pregnancy loss.

#### 8.3.2.11 Molar Pregnancies

Any reported molar pregnancy will be sub-classified in the respective pregnancy outcome, including induced termination, maternal death, or spontaneous pregnancy loss.

#### 8.3.2.12 Hospitalization of Infants

AEs requiring or prolonging inpatient hospitalization will be collected as SAEs (Section 10.1.1.2). Any infant hospitalization (other than a standard post birth hospital stay) will be collected as part of SAE data collection.

#### 8.3.2.13 Selected Infant Adverse Events

In addition to all SAEs in infants, the following infant non-serious AEs will be captured:

- Infections (NCI CTCAE Grade 3 and above)
- Inadequate vaccine response

#### 8.3.2.14 Neonatal Death

A neonatal death is defined as a death occurring in a neonate prior to 28 days of life. In the event of a neonatal death, full pathological details will be requested, and any structural or congenital defects detected will be evaluated.

#### 8.3.2.15 Perinatal Death

Perinatal death is defined as the death of an infant between 28 days of life and 12 weeks of life. In the event of a perinatal death, full pathological details will be requested, and any structural or congenital defects will be evaluated.

#### 8.3.2.16 Infant Death

Infant death is defined as the death of an infant occurring between 12 and 52 weeks of life. In the event of an infant death, full pathological details will be requested, and any structural or congenital defects will be evaluated.

#### 8.3.2.17 Maternal Death

Maternal death is defined as the death of a pregnant woman during pregnancy, labor, or delivery. Maternal deaths for up to 12 weeks after delivery will also be reported and full pathology details will be requested.

#### 8.3.2.18 Gestational Diabetes

Gestational diabetes will be based on HCP reported diagnosis. It is often characterized by the development of carbohydrate intolerance with first onset or first recognition during pregnancy; a record of an oral glucose tolerance test during pregnancy will also be accepted for data collection, where available.

#### 8.3.2.19 Pre-eclampsia

Primary pre-eclampsia will be based on HCP reported diagnosis. It is often defined as the presence of hypertension on two occasions at least 4 hours apart after 20 weeks' gestation (in a woman with a previously normal blood pressure) and proteinuria; or in the absence of proteinuria, a new-onset hypertension accompanied by 1 of the following conditions: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms.

#### 8.3.2.20 Pregnancy-Induced Hypertension

High blood pressure (elevated: systolic between 120-129 and diastolic <80 mmHg; Stage 1 hypertension: systolic between 130-139 or diastolic between 80-89 mmHg; Stage 2 hypertension: systolic at least 140 or diastolic at least 90 mmHg) associated with pregnancy, as diagnosed by the treating HCP.

#### 8.3.2.21 Antenatal Bleeding

Bleeding from or in to the genital tract, occurring from 24 weeks of pregnancy and prior to the birth of the baby (in the majority of cases the bleeding is vaginal and obvious, but the syndrome includes bleeding contained within the uterine cavity, the intraperitoneal space, or the retroperitoneal space) based on HCP reported diagnosis.

#### 8.3.2.22 Placenta Previa

Physician-diagnosed placenta previa: when the baby's placenta fully or partially covers the mother's cervix.

#### 8.3.2.23 Postpartum Hemorrhage

Total blood loss >500 mL after vaginal delivery or >1000 mL after cesarean section, as reported by the treating HCP.

#### 8.3.2.24 Preterm Labor

Preterm labor will be based on HCP reported diagnosis. It is often defined as regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy. Any interventions or treatments provided to the patient as a result of preterm labor will be collected.

#### 8.3.2.25 Premature Rupture of Membranes

Clinically confirmed rupture of the amniotic sac prior to 37 weeks' gestation.

#### 8.3.2.26 Small-for-gestational-age (SGA) fetus and intrauterine growth restriction (IUGR)

SGA is defined as fetal abdominal circumference or estimated fetal weight <10th centile; IUGR implies a pathological restriction of the genetic growth potential, with growth-restricted fetuses manifesting evidence of fetal compromise. SGA and IUGR will be based on HCP reported diagnosis.

### 8.3.3 Information Collected from Consenting Patients and Healthcare Providers

Variables will be collected according to the below schedule for prospective patients. For retrospectively enrolled patients (i.e., patients enrolled after the pregnancy outcome is known), all information on the pregnancy and any infant outcomes detailed below will be collected at the study entry. If the infant of a retrospectively enrolled patient is <1 year old, they will be prospectively followed until 1 year of age.

The following variables will be collected during the study, as part of the local routine clinical practice, as available:

#### 8.3.3.1 Study Entry

Documentation of informed consent

Reporter of information (e.g., patient, obstetrician, satralizumab prescriber)

Maternal demographics and general characteristics (e.g., age, occupation/employment status, education level, race/ethnicity, height, weight, body mass index [BMI])

Patient, secondary contact, and HCP contact information (obstetrician, satralizumab prescriber, infant HCP, if possible). This information is confidential and remains at the coordinating center; it is not recorded in the eCRF.

Maternal lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use) from estimated date of conception

Current pregnancy information (e.g., LMP, method of conception, gestational age, estimated date of delivery [EDD], date and results of any prenatal tests, number of fetuses)

Maternal medical history:

- Pregnancy history (e.g., parity, gravidity, previous preterm births, previous spontaneous abortions or elective or therapeutic terminations, reason for any elective or therapeutic termination, previous pregnancy complications, history of congenital malformations)
- Surgical and medical history, including significant medical conditions other than NMOSD (e.g., diabetes, high blood pressure)
- NMOSD disease history (including treatment history, disease duration, date of the last relapse, and relapse severity, most recent Expanded Disability Status Scale [EDSS] score, NMOSD biomarker status if available)

- Comorbid conditions
- Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, preterm births, chromosomal anomalies, developmental delays)
- Family NMOSD history

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation or delayed treatment [if applicable], mode of administration [self-administration, HCP, caregiver])

Current and prior medication use from 6 months prior to the LMP (including other NMOSD treatments, teratogenic medications, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic disease)

Paternal information:

The following paternal variables are optional, depending on the availability and willingness of fathers to provide informed consent.

- Age
- Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, preterm births, chromosomal anomalies, developmental delays)
- Comorbid conditions and medical history including significant medical conditions
- Teratogenic or genotoxic medications, which may cause DNA mutagenesis, used in the 3 months prior to the LMP

#### 8.3.3.2 Follow-up during pregnancy (during each trimester, approximately at 14, 21, and 34 weeks of gestation):

Date of contact

Reporter of information (e.g., patient, obstetrician, satralizumab-prescriber)

Changes in contact information (maternal, secondary contact, and mother's HCP). This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Changes in pregnancy status:

- Gestational age (estimated based on the date of LMP, unless ultrasound results provide an updated estimate)
- Weight
- Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasound scans, amniocentesis, maternal serum alpha-fetoprotein screen, screening for chromosomal abnormalities, glucose screen, blood group, and Rh factor)
- Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)

        - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
        - Autopsy results and pathology reports, if available
    - Changes in NMOSD disease status (including treatment changes, relapses, EDSS score)

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation or delayed treatment [if applicable], mode of administration [self-administration, HCP, caregiver])

Changes in comorbid conditions

Current maternal lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)

Current medications (including other NMOSD drugs, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

Serious adverse events (SAEs) related to pregnancy, including pregnancy complications

#### 8.3.3.3 Pregnancy outcome follow-up (approximately 4 weeks after pregnancy outcome):

Date of contact and date of pregnancy outcome or gestational age (in weeks)

Changes in contact information; contact information for infant's HCP. This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Reporter of information (e.g., patient, obstetrician, infant HCP)

Pregnancy outcome (e.g., live birth, stillbirth, spontaneous abortion, elective or therapeutic termination)

- Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
- Autopsy results and pathology reports, if available
- Mode of delivery (vaginal delivery, assisted delivery/cesarean section, type of anesthesia)
- Presentation at delivery (vertex, non-vertex)

Maternal weight at end of pregnancy

Changes in NMOSD disease and treatment status since last follow-up, if applicable

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable], mode of administration [self-administration, HCP, caregiver])

Changes in comorbid conditions

Current maternal lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)

Current medications (including other NMOSD drugs, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

Infant characteristics:

- Gestational age at birth
- Sex
- Birth weight
- Length at birth
- Head circumference at birth
- Birth order (for multiple births) and number of fetuses
- Apgar score (1, 5, and 10 minutes)
- Congenital malformations noted (including description and attribution)
- Laboratory values and laboratory test dates, if available (e.g., neutrophil count, platelet count, liver enzymes, and bilirubin)
- Vaccination information

Breastfeeding (yes vs. no) and duration of breastfeeding, if applicable

SAEs related to pregnancy

Infant SAEs and selected non-serious AEs which include severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response

#### 8.3.3.4 Pediatric follow-up (approximately at infant age 12, 26, and 52 weeks after birth):

Reporter of information (e.g., patient, infant HCP)

Changes in contact information (maternal, secondary contact, mother's HCP, and infant's HCP). This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Infant characteristics:

- Feeding behavior (including breastfeeding)
- Weight
- Length
- Head circumference
- Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the Centers for Disease Control and Prevention [Centers for Disease Control and Prevention 2016])

- Laboratory values, if available (e.g., neutrophil count, platelet count, liver enzymes and bilirubin)
- Evidence of any new congenital malformations and growth alterations since last follow-up
- Vaccination information

Infant SAEs and selected non-serious AEs which include severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response

Maternal satralizumab use (dates, dose, dosing frequency, mode of administration, reason for discontinuation [if applicable])

Maternal concomitant medications (including other NMOSD drugs, corticosteroids, vaccinations, medications to treat other chronic diseases)

#### 8.3.3.5 Early termination of study participation contact, if applicable:

Reporter of information (e.g., patient, obstetrician, HCP)

Changes in contact information (maternal, secondary contact, mother's HCP, and infant's HCP). This information is confidential and remains at the coordinating center. It is not recorded in the eCRF.

Assessments appropriate for the time of withdrawal

Reason for study withdrawal

Satralizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable], mode of administration [self-administration, HCP, caregiver])

Other medications (including other NMOSD drugs, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

Pregnancy status:

- Gestational age
- Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, screening for chromosomal abnormalities, glucose screen, blood group, and Rh factor)
- Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
  - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
  - Autopsy results and pathology reports, if available

Infant characteristics (for live births):

- Gestational age at birth
- Sex

- Birth weight
- Length at birth
- Head circumference at birth
- Birth order (for multiple births) and number of fetuses
- Apgar score (1, 5, and 10 minutes)
- Congenital malformations noted (including description and attribution)
- Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the Centers for Disease Control and Prevention [Centers for Disease Control and Prevention 2016])
- Laboratory values, if available (e.g., neutrophil count, platelet count, liver enzymes and bilirubin)
- Breastfeeding (yes vs. no) and duration of breastfeeding, if applicable

SAEs related to pregnancy, infant SAEs, and selected infant non-serious adverse events (AEs) which include severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response

## 8.4 DATA SOURCES

### 8.4.1 Data Sources

Data will be obtained through questionnaires administered to patients and/or their HCPs (NMOSD treating HCP, obstetrician or infant HCP) and will be recorded on the eCRFs by the coordinating center. Treating physicians will provide information from patient's charts and will be the preferred source of information for medically related data elements.

### 8.4.2 Collection of Data on the eCRF

Patients' data will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the eCRF as soon as they become available.

#### 8.4.2.1 Data Collected during the Observation Period

After a patient provides consent, the coordinating center will obtain demographic and contact information in addition to baseline information at the time of enrollment. Retrospective cases where the pregnancy outcome (e.g., live birth, stillbirth, elective or spontaneous abortion) occurs prior to study enrollment will provide retrospective information on exposures and events during pregnancy when they enroll in the study. All patient and HCP contact information will be confidential and will remain at the coordinating center. The coordinating center will then contact the patient each trimester to update contact information and ascertain the occurrence of pregnancy outcomes or other events (Figure 2).

Expected contacts with patients:

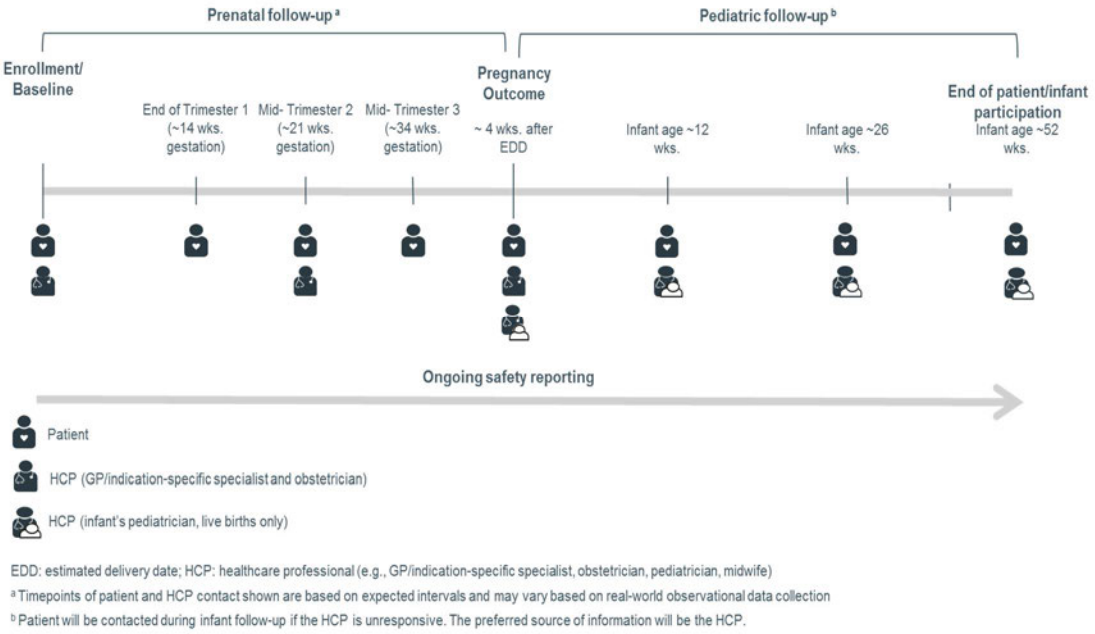
- Enrollment
- End of Trimester 1 (approximately 14 gestational weeks)
- Mid-Trimester 2 (approximately 21 gestational weeks)
- Mid-Trimester 3 (approximately 34 gestational weeks)
- EDD plus 4 weeks
- Birth plus 12 weeks, 26 weeks, and 52 weeks (live births only)

Expected contacts with the patient's HCPs (satralizumab prescriber, obstetrician):

- Enrollment
- Mid-Trimester 2 (approximately 21 gestational weeks)
- EDD plus 4 weeks

Expected contacts with the infant's HCP (live births only):

- EDD plus 4 weeks
- Birth plus 12 weeks
- Birth plus 26 weeks
- Birth plus 52 weeks




EDD: estimated delivery date; HCP: healthcare professional (e.g., GP/indication-specific specialist, obstetrician, pediatrician, midwife)

[a] Timepoints of patient and HCP contact shown are based on expected intervals and may vary based on real-world observational data collection

[b] Patient will be contacted during infant follow-up if the HCP is unresponsive. The preferred source of information will be the HCP.

**Figure 2 Expected contacts with patients, patient's HCPs or infant's HCP.**

At each follow-up timepoint, there will be at least three attempts to contact the patient and/or the HCP via phone, e-mail, fax, and mail, as appropriate, approximately ten business days apart. If data are obtained after a follow-up interval is passed, the coordinating center will accept and enter the data and continue follow-up of the patient. If an HCP is not responsive at the time points described above, the patient will be asked to provide the information contained on the HCP worksheets. If the HCP then responds to contact, their information will supersede the patient-reported information. At all timepoints, the type of reporter (patient, obstetrician, satralizumab prescriber, or infant HCP) will be recorded.

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

If the patient experiences an adverse pregnancy outcome or has an elective or therapeutic termination or a termination of unknown cause, the HCP and patient will be encouraged to report the outcome to the coordinating center as soon as possible. In the event of an elective or therapeutic termination, spontaneous abortion, fetal death or stillbirth, communications with the patients will cease after the pregnancy outcome information has been obtained.

Please see Appendix 2 for the data collection overview (as per standard of care).

#### 8.4.2.2 Data Collected at Study Completion

All patients should have either the postpartum or the end of study data collection at 52 weeks postpartum (infant age 12 months), depending on the pregnancy outcome. The end of study data collection will also be completed if the patient discontinues from the study prematurely.

Please see Appendix 2 for the data collection overview at the postpartum or the end of study data collection if available.

#### 8.4.2.3 Loss to Follow-Up

For study purposes, patients will be considered lost to follow-up if any time-based assessment is missed and the corresponding data have not been received by the coordinating center after making additional follow-up attempts using all contact methods available (e.g., phone, fax, registered letter; see Section 8.4.2.1). At least three attempts will be made, up to 4 months after the expected date of the missed assessment. The case will be reopened if additional information is later obtained. All HCPs and secondary contacts will also be contacted prior to considering a patient lost to follow-up. All data collected prior to the patient being lost to follow-up will be used for analyses, if possible. For analysis purposes, the date of discontinuation will be recorded as the date of last contact.

#### 8.4.2.4 Safety Data Collection

Only SAEs related to pregnancy, infant SAEs, and selected non-serious infant AEs through the first year of life, as described in Section 8.3, are required to be recorded in the eCRF during the total observation period. For clinical AEs, serious and non-serious, physician's assessment of severity (using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) and relationship to therapy (i.e., related or unrelated) will be recorded as described in Appendix 3. HCPs will report SAEs related to pregnancy and infants to the coordinating center that will enter them in the eCRF. See Section 10 for a full description of safety procedures.

## 8.5 STUDY SIZE

All eligible women will be enrolled in the pregnancy safety study, and no formal statistical hypotheses will be tested. Due to the study design, no formal sample size is required for statistical comparisons. NMOSD is a rare disease and recruitment of patients is dependent on several factors. Approval and uptake of new medications such as satralizumab are unpredictable and have the potential to impact the feasibility of enrolling satralizumab-exposed women in each targeted country. In addition, the expected pace of exposure to pregnant women and the willingness of pregnant women to participate in such a study are both difficult to predict.

## 8.6 DATA MANAGEMENT

### 8.6.1 Data Quality Assurance

IQVIA, a contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC). Coordinating centers will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the coordinating centers, which the coordinating centers will resolve electronically in the EDC system.

The MAH will perform oversight of the data management of this study. The CRO will produce eCRF specifications for the study based on the MAH's templates including quality checking to be performed on the data.

Data will be periodically transferred electronically from the CRO to the MAH, and the MAH's standard procedures will be used to handle and process the electronic transfer of these data.

The eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures. The CRO will comply with the MAH 's procedures regarding archiving and record management.

### 8.6.2 Electronic Case Report Forms

eCRFs are to be completed using a MAH-approved EDC system. Coordinating centers will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the MAH and should be handled in accordance with instructions from the MAH.

All eCRFs should be completed by designated trained coordinating center staff. eCRFs should be reviewed and electronically signed and dated by the coordinating center investigator or a designee.

At the end of the study, the coordinating center will receive the data related to its patients in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgment of receipt of the data is required.

See Figure 3 for details about coordinating center operations and data flow.

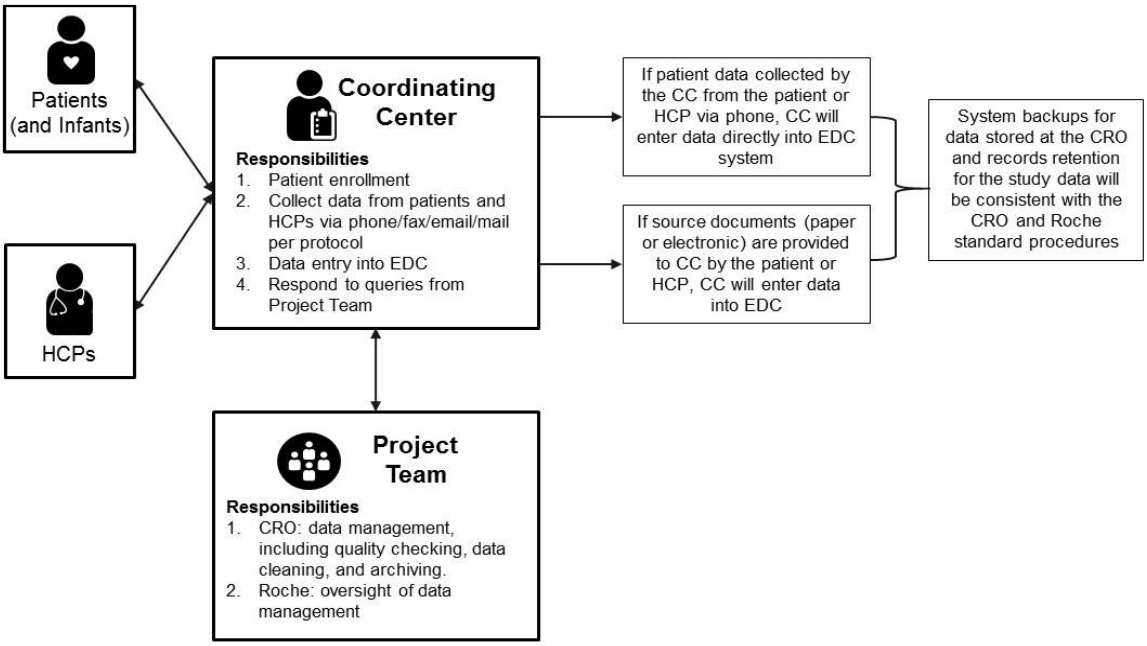



**Figure 3 Coordinating center operations and data flow.**
CC: Coordinating center, CRO: Contract research organization, EDC: Electronic data capture, HCPs: Health care practitioners.

### 8.6.3 Source Data Documentation

The sponsor Operations Representative will perform ongoing source data verification (SDV) as defined in the Study Monitoring Plan to confirm that critical protocol data (i.e., source data) entered in the eCRF by authorized coordinating center personnel are accurate, complete and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Study Monitoring Plan. The Study Monitoring Plan defines which kind of source data - if available from clinical routine - can be used for documentation into CRF. No additional source data creation beyond routine is allowed.

Source documents that are required to verify the validity and completeness of data entered in the CRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 8.8.3.

To facilitate SDV, the coordinating center investigators must provide the MAH direct access to applicable source documents and reports for study-related monitoring, MAH audits, and IRB/EC review. The participating coordinating centers must also allow inspection by applicable Health Authorities.

## 8.7 DATA ANALYSIS

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the study sample. Full details of the statistical analysis will be described in the statistical analysis plan (SAP).

If there are sufficient numbers of patients enrolled in the pregnancy safety study, descriptive statistics will be reported using summary tables and figures (where appropriate). Continuous variables will be summarized using mean, standard deviation, range (min-max), median and interquartile range. Categorical variables will be summarized using counts and proportions (%). The number of patients with non-missing data will be presented.

### 8.7.1 Safety Analyses

The analysis will qualitatively describe patients enrolled in the study in term of patient disposition, information on NMOSD diagnosis, satralizumab treatment and treatment changes during pregnancy and infant follow-up, loss to follow-up and reasons for loss to follow-up, pregnancy outcomes, pregnancy complications and neonatal/infant outcomes. The source of information (patient or HCP) will also be included in the descriptions.

Demographic information, maternal clinical characteristics and other factors that may

affect pregnancy and infant outcomes will be described.

The frequency of selected adverse pregnancy outcomes, pregnancy complications and adverse infant outcomes will be estimated. All descriptive outcome analyses will be conducted on an overall basis (i.e., combining data from all patients irrespective of whether the outcome of the pregnancy was known at the time of enrollment) and also separately for prospective and retrospective pregnancies. For pregnancy complications, the outcome analyses will account for the timing of the presentation, excluding events that occur before the exposure to satralizumab. When sample size permits, analyses will be stratified by earliest trimester of satralizumab exposure (including a subgroup with preconception exposure), prenatal screening result (positive vs. negative for aneuploid disorders or genetic disorders that cause major congenital malformations), as well as by maternal age, race/ethnicity, gestational age at enrollment, NMOSD biomarker status, NMOSD disease activity (active relapsing course vs. no relapse during the observation period), exposure to other medications for NMOSD during the observation period (yes vs. no), elective or therapeutic pregnancy termination status and other relevant factors. Retrospective-pregnancy analyses may be stratified by prenatal screening status, if sample size permits. If possible, a sensitivity descriptive analysis of major congenital malformations will exclude women exposed to any known teratogenic medications during pregnancy.

### 8.7.2 Interim/Final Analysis and Timing of Analyses

Interim progress reports will be provided to the Health Authorities yearly. If at least five new pregnancies have been reported between two interim analyses, descriptive statistics will be provided, otherwise, a qualitative progress report will be submitted.

## 8.8 QUALITY CONTROL

### 8.8.1 Study Documentation

The coordinating center must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (ICFs) and documentation of IRB/EC and governmental approval/notification. In addition, at the end of the study, the coordinating center principal investigator will receive the patient data, which include an audit trail containing a complete record of all changes to data.

The MAH shall ensure that the dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

### 8.8.2 Coordinating Center Audits and Inspections

The coordinating center will permit the MAH to audit facilities and records relevant to this study.

The coordinating center will also permit national and local Health Authorities to inspect facilities and records relevant to this study.

### 8.8.3 Retention of Records

Archiving at the coordinating center has to be for at least five years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by the MAH for at least 25 years after completion of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the MAH. Written notification should be provided to the MAH prior to transferring any records to another party or moving them to another location.

All supporting functional parties will comply with the MAH procedures regarding archiving and record management.

### 8.8.4 Administrative Structure

#### 8.8.4.1 External Advisors

A qualified independent teratologist or other appropriate birth defect expert will be used throughout the study for evaluation of congenital malformations and other significant findings. Other experts in relevant specialties will also be consulted by the MAH as deemed necessary by the external advisors.

## 8.9 LIMITATIONS OF THE RESEARCH METHOD

Although all possible measures will be taken to ensure the quality and robustness of the data, there are several limitations inherent to the study design that should be acknowledged.

Spontaneous abortions most frequently occur in early pregnancy, likely before the pregnancy is recognized. Even if the pregnancy is recognized and confirmed, it is possible that the pregnancy may not be reported to the study if the loss occurred before enrollment into the study. Not capturing all early pregnancy losses will likely lead to an underestimation of the true early pregnancy loss rate. There is no reason to believe that this study will be differentially impacted by this bias even though the spontaneous early losses may be underestimated, the relative rate compared with the other registries should not be affected.

Reporting outcomes in this study is voluntary and it is possible that not all patients will complete all of the follow-up assessments. If data from a patient and their HCPs are unattainable, the patient will be considered lost to follow-up. It is possible that the

outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Comparisons of the characteristics of patients with completed information and those lost to follow-up will be conducted in an attempt to address this potential bias.

This study plans to enroll both retrospective patients (women where the pregnancy outcome is known, prior to enrollment in the study, either positive or negative) and prospective patients (women where the pregnancy outcome is unknown prior to enrollment in the study). Patients who have been informed about a potential adverse pregnancy outcome prior to enrollment in the study may differentially recall their exposures during early pregnancy and may also have changed their exposures after learning of the outcome. Patients may also change their willingness to take part in the study after learning the outcome. These differences may lead to recall or selection bias, which we will attempt to address with the stratification analyses by retrospective and prospective enrollment status.

Safety pregnancy studies are descriptive by design and have inherent methodological limitations for the quantification of risks between a given exposure and selected outcomes. In order to reduce the potential effect of confounding, the study will collect variables relevant to the evaluation of exposures during pregnancy to contextualize the results according to the confounding factors (e.g., by stratification), particularly those related to NMOSD therapies other than satralizumab. It is unlikely that pregnant women will completely stop their maintenance therapy given the severity of NMOSD relapses. Therefore, exposure to other drugs might introduce bias. Similarly, there is evidence that suggests NMOSD is associated with some pregnancy complications and adverse pregnancy outcomes (e.g., pre-eclampsia, miscarriage, preterm birth), therefore, it is possible that NMOSD may be a confounder in the relationship between satralizumab and some of the pregnancy-related outcomes evaluated as part of the study objectives.

Residual confounding due to unmeasured confounding factors is also likely and its magnitude on the study outcomes is impossible to predict.

There is potential for channeling bias by label indication due to the severity of NMOSD at baseline and patient relapse history. Baseline severity of NMOSD will be captured to assess the degree of confounding by indication through utilization of NMOSD measures of progression (e.g. EDSS).

# 9. PROTECTION OF HUMAN SUBJECTS

## 9.1 PATIENT DISCONTINUATION

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following:

Patient withdrawal of consent at any time

Patient is lost to follow-up.

### 9.1.1 Discontinuation from Treatment with Studied Medicinal Product

The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol.

### 9.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF page. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

### 9.1.3 Study and Site Discontinuation

The MAH has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

Patient enrollment is unsatisfactory

Patient safety

The MAH will notify the coordinating center if the study is placed on hold, or if the MAH decides to discontinue the study.

The MAH has the right to replace a coordinating center at any time. Reasons for replacing a coordinating center may include, but are not limited to, the following:

Excessively slow recruitment

Poor protocol adherence

Inaccurate or incomplete data recording

Non-compliance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) or any other pertinent local law or guideline

## 9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

If applicable, the study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

## 9.3 INFORMED CONSENT

The MAH's sample ICF (and ancillary sample ICFs such as a Child's Assent or the Infant's Biological Father ICF for collection of paternal variables, if applicable) will be

provided to each coordinating center. If applicable, it will be provided in a certified translation of the local language. The MAH must review and approve any proposed deviations from the MAH's sample ICFs or any alternate Consent Forms proposed by the coordinating center (collectively, the “Consent Forms”) before IRB/EC submission. The final Consent Forms approved by the IRB/EC must be provided to the MAH for archiving and for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or, when relevant, the patient’s legally authorized representative before start of documentation of his or her data in the CRF. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to first documentation of this patient’s data in the eCRF.

For the purposes of follow-up with the infant’s HCP, the patient will be expected to provide proxy informed consent on behalf of the infant. Where possible, this proxy consent will be included in the patient’s informed consent signed at enrollment. Otherwise, prior to the collection and entry of postpartum and through 1-year follow-up data, the coordinating center will be required to obtain informed consent from the patient on behalf of the infant (where required, consent of both parents will be sought). Study staff from the CRO will provide reminders to coordinating centers at appropriate time points to ensure the proxy infant consent is obtained.

By signing the form, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable) and the possibility of monitoring activities. It is the accountability of the coordinating center principal investigator for ascertaining that the subject has comprehended the information and to obtain written informed consent from each patient participating in the study.

A copy of each signed Consent Form must be provided to the patient or the patient’s legally authorized representative. All signed and dated Consent Forms must remain in each patient’s study file or in the coordinating center file and must be available for verification by Site Operations Representative at any time.

For coordinating centers in the US, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the coordinating center utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval and other processes outlined above apply except that IRB review and approval may not be required per coordinating center policies.

## 9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

In addition to the requirements for collecting and reporting pregnancy-related SAEs, infant SAEs and relevant infant AEs to the MAH, coordinating center principal investigators must comply with requirements for AE reporting to the local health authority and IRB/EC.

## 9.5 CONFIDENTIALITY

The MAH maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any MAH location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

The MAH, including affiliates, collaborators and licensees may use study data labeled with the patient ID numbers. Study data may also be shared with independent researchers or government agencies, but only after personal information that can identify the patient has been removed. Patients' study data may be combined with other patient's data and/or linked to other data collected from the patients. Patients' study data may be used to help better understand why people get diseases, how to best prevent, diagnose and treat diseases, and to develop and deliver access to new medicines, medical devices, and healthcare solutions to advance patient care.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local Health Authorities, MAH monitors, representatives, and collaborators, and the IRB/EC for each coordinating center, as appropriate.

## 9.6 FINANCIAL DISCLOSURE

Coordinating center principal investigators will provide the MAH with sufficient, accurate financial information in accordance with local regulations to allow the MAH to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Coordinating center principal investigators are responsible for

providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e. last data collection).

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

## 10.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

### 10.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products. Products are not considered "studied" anymore after the end of the wash out period following their discontinuation. For safety reporting requirements for non-studied medicinal products, see Section 10.2.

Safety assessments will consist of monitoring and recording SAEs related to pregnancy, any infant SAEs, and selected infant non-serious AEs which include severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response.

#### 10.1.1.1 Adverse Events

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 3

Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

#### 10.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder) and Other Non-serious Adverse Events

**Serious Adverse Events**

A SAE is any AE that meets any of the following criteria:

Is fatal (i.e., the AE actually causes or leads to death)

Is life-threatening (NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

Requires or prolongs inpatient hospitalization (see A)

Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)

Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine

Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Obstetric complications and pregnancy outcomes that fall into the above categories are defined as pregnancy-related SAEs in this study and should be reported to the coordinating center.

A pregnancy outcome is as outlined in Section 8.3.2 and covers:

Spontaneous abortion
Fetal loss including stillbirth
Ectopic pregnancy
Molar pregnancy
Congenital malformation
Elective or therapeutic pregnancy terminations
Preterm birth

Normal delivery and elective cesarean sections performed for non-medical reasons (i.e., scheduling, personal preference) and their related hospitalizations will not be considered pregnancy-related SAEs, unless, in the view of the reporter, the hospitalization was prolonged due to a complication.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Appendix 3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF (for detailed instructions, see Appendix 3).

### Non-Serious Adverse Events

In neonates and infants, the following non-serious AEs will be collected during their first year of life: severe infections of NCI CTCAE severity Grade 3 and above and inadequate vaccine response and coded according to the appropriate level of MedDRA Classification.

### Exemption of Specific Adverse Events from Collection

Product-specific pregnancy registries often fail to provide clinically meaningful information because of inadequate enrollment. Enrollment in registries may be low, as

HCPs may not have sufficient time to spend time with patients discussing the pregnancy safety study, enroll patients, and complete eCRFs or send medical records (U.S. Food and Drug Administration 2014).

Therefore, in order to balance successful pregnancy safety data collection requirements to fulfill the study objectives and to minimize the administrative burden for HCPs, only pregnancy-related SAEs and all infant SAEs will be collected in this study; in addition, severe infections (NCI CTCAE Grade 3, 4 and 5) and inadequate vaccine response in infants aged 1 year or less will also be collected.

Other AEs, including SAEs not related to pregnancy, will not be collected in this registry. These AEs/SAEs will be reported to the Sponsor via the pharmacovigilance system, as for any spontaneous reporting of AEs.

Other non-serious AEs and any other safety information not falling under the definitions above will not be collected as part of the study. All non-pregnancy related SAEs and AEs for patients enrolled in the study and receiving satralizumab must be reported to Roche Safety department to be processed following standard pharmacovigilance practices.

### 10.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The coordinating center is accountable for ensuring that all pregnancy-related SAEs, infant SAEs and selected infant AEs collected as per protocol (see Section 10.1.1.1 for definition) are recorded in the AE section of the CRF and reported to the MAH in accordance with instructions provided in this section and in Section 10.1.3.

For each AE recorded in the AE section of the CRF, the coordinating center will make an assessment of seriousness (see Section 10.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

#### 10.1.2.1 Adverse Event Reporting Period

Coordinating centers will seek information on pregnancy-related SAEs, infant SAEs and selected infant AEs at each patient and HCP contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or by HCPs, will be recorded in the AE section of the CRF.

Once the patient is enrolled in the study, pregnancy-related SAEs, infant SAEs and selected infant AEs will be collected until the end of the corresponding observation period, i.e., until a pregnancy outcome is reported or until the infant's first year of life, unless the patient withdraws from the study prematurely. After this period, the coordinating center is not required to actively monitor patients for AEs.

#### 10.1.2.2 Procedures for Recording Adverse Events

HCPs and coordinating centers should use correct medical terminology/concepts when reporting and collecting pregnancy-related SAEs, infant SAEs and selected infant AEs to the coordinating center that will be recording the AEs in the AE section of the CRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the CRF.

See Appendix 3 for further specific instruction regarding:

Diagnosis versus signs and symptoms

Adverse Events occurring secondary to other Adverse Events

Persistent or recurrent Adverse Events

Deaths

- All events with an outcome or consequence of death should be classified as SAEs and reported to the MAH immediately. In certain circumstances, however, suspected adverse reactions with fatal outcome may not be subject to expedited reporting (see Section 10.3). All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the CRF and immediately reported to the MAH

Hospitalization or Prolonged Hospitalization

### 10.1.3 Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

#### 10.1.3.1 Immediate Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

Certain events require immediate reporting to allow the MAH and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The HCP must report such events to the MAH immediately; under no circumstances should reporting take place more than 24 hours after the HCP learns of the event. The following is a list of events that the HCP must report to the MAH within 24 hours after learning of the event, regardless of relationship to study medicine:

SAEs

The HCP must report new significant follow-up information for these events to the MAH immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

New signs or symptoms or a change in the diagnosis

Significant new diagnostic test results

Change in causality based on new information

Change in the event's outcome, including recovery

Additional narrative information on the clinical course of the event

For reports of pregnancy-related SAEs and infant SAEs, including follow-up, coordinating centers should record all case details that can be gathered immediately (i.e., within 24 hours of the coordinating center learning of the event) in the AE page of the CRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

If an HCP or a patient reports any non-pregnancy-related SAEs, these SAEs must be forwarded to Roche for processing as a spontaneous report (refer to local product label for relevant contact details).

HCPs must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

#### 10.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For selected infant AEs, including follow-up reports, coordinating centers must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

If an HCP or a patient reports any non-pregnancy-related AEs, these AEs must be forwarded to Roche to process as a spontaneous report for satralizumab events.

#### 10.1.3.3 If EDC System is Temporarily Unavailable or not Used

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) or within 30 days for non-serious AEs, using the fax number or e-mail address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

### 10.1.4 Follow-Up of Patients after Adverse Events

#### 10.1.4.1 HCP Follow-Up

The HCP should follow each pregnancy-related SAE, infant SAE and selected infant AE until the event has resolved to baseline grade or better, the event is assessed as stable

by the HCP, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to satralizumab until a final outcome can be reported.

During the study period, resolution of pregnancy-related SAEs, infant SAEs and selected infant AEs (with dates) should be documented in the AE section of the CRF and in the patient's medical record to facilitate SDV.

#### 10.1.4.2 Marketing Authorization Holder Follow-Up

For all pregnancy-related SAEs, infant SAEs and selected infant AEs, the MAH or a designee may follow up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## 10.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED PRODUCTS

Although AE information is not being actively solicited for non-studied products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a product) that come to their attention to the MAH of the suspected product, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed product, even in the absence of adverse events:

Pregnancy

Breastfeeding

Abnormal laboratory findings

Overdose, abuse, misuse, off-label use, medication error or occupational exposure

Reports of lack of efficacy

Product quality defects and falsified medicinal products

Data related to a suspected transmission of an infectious agent via a medicinal product

Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the HCP/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

## 10.3 REPORTING OF PRODUCT COMPLAINTS WITHOUT ADVERSE EVENTS

Report Roche product complaints without AE, where Product Complaint is any written or oral information received from a complainant that alleges deficiencies related to Identity,

Quality, Safety, Strength, Purity, Reliability, Durability, Effectiveness, or Performance of a product after it has been released and distributed to the commercial market, to basel.complaint_manager_pharma@roche.com. Report non-Roche-product complaints as per local regulation.

## 11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the MAH is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the MAH prior to submission for publication or presentation. This allows the MAH to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, the MAH will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of MAH personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate MAH personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the MAH, except where agreed otherwise.

### Specification of publication plan

Roche plans to publish the design of the single-arm pregnancy safety study and final results.

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# Appendix 1 List of Stand-Alone Documents Not Included in the Protocol



European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

## 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:**
SATRALIZUMAB PREGNANCY SURVEILLANCE STUDY: A GLOBAL, OBSERVATIONAL, SINGLE ARM, 10-YEAR STUDY OF PREGNANCY AND INFANT OUTCOMES IN SATRALIZUMAB EXPOSED WOMEN WITH NEUROMYELITIS OPTICA SPECTRUM DISORDER

**EU PAS Register® number:** To be registered
**Study reference number (if applicable):** WN42856

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 5 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 5 |
| 1.1.3 Progress report(s) | ☒ | ☐ | ☐ | 5 |
| 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | 5 |
| 1.1.5 Registration in the EU PAS Register® | ☒* | ☐ | ☐ | 5 |
| 1.1.6 Final report of study results | ☒ | ☐ | ☐ | 5 |

Comments:

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| * Registration in the EU PAS register will occur after the FDA approved protocol is registered on ClinicalTrials.gov. |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 6 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 7 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 8.2.2 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

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| **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) | ☒ | ☐ | ☐ | 8.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 8.1 |
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☐ | ☐ | ☒ | |

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

| **Section 3: Study design** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 3.4 | Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☐ | ☐ | ☒ | |
| 3.5 | Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 10 |

Comments:

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| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 8.2.2 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | 8.1 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | 8.2.2 |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 8.1 |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 8.1, 8.2.2 |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 8.1 |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 8.2.2 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 8.1, 8.3.1 |
| 5.2 | Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 5.3 | Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 8.1, 8.3.1 |
| 5.4 | Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 8.3.1 |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | 8.1 |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☐ | ☐ | ☒ | |

Comments:

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| **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? | ☒ | ☐ | ☐ | 7.2 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 8.3.2 |
| 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) | ☒ | ☐ | ☐ | 8.3.2 |
| 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:

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| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☒ | ☐ | ☐ | 8.7 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 8.9 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 8.9 |

Comments:

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| **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:

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| **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) | ☒ | ☐ | ☐ | 8.3 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 8.3 |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 8.3 |
| 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) | ☒ | ☐ | ☐ | 8.3 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 8.3 |
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 8.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☐ | ☒ | |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 8.3.2 |
| 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:

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| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 8.7 |
| 10.2 Is study size and/or statistical precision estimated? | ☐ | ☐ | ☒ | |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 8.7 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 8.7 |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.5 Does the plan describe methods for analytic control of confounding? | ☐ | ☐ | ☒ | |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☐ | ☒ | |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 8.7 |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 8.7 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 8.6.1, 8.8 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 8.6.1, 8.8 |
| 11.3 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 8.8.4.1 |

Comments:

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| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 8.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 8.9 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | ☒ | ☐ | ☐ | 8.9 |
| 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) | ☒ | ☐ | ☐ | 8.1, 8.5 |

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? | ☒ | ☐ | ☐ | 9.4 |

| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☒ | ☐ | ☐ | 9.4 |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 9.5 |

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? | ☒ | ☐ | ☐ | 4 |

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)? | ☒ | ☐ | ☐ | 11 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 11 |

Comments:

| |
|---|
| |

Name of the main author of the protocol: [redacted], PhD, MSc

Date: dd/Month/year

Signature: _____

# Appendix 2 Data Collection Overview (as per Standard of Care)

| Data Collection [a] | Enrollment | Prenatal Follow-Up | | | Pregnancy Outcome | Pediatric Follow-Up | Early Termination of Study Participation Contact |
|---|---|---|---|---|---|---|---|
| | | End 1st Trimester (~14 weeks) | Mid 2nd Trimester (~21 weeks) | Mid 3rd Trimester (~34 weeks) | ~4 weeks after EDD | Infant Age 12, 26, and 52 Weeks | End of Patient Participation in Study |
| Informed consent [b] | x | | | | | | |
| Inclusion/exclusion criteria | x | | | | | | |
| Patient demographics and characteristics | x | | | | | | |
| Medical history | x | | | | | | |
| NMOSD disease and treatment history [n] | x | | | | | | |
| Pregnancy history, and current pregnancy information [c] | x | | | | | | |
| Lifestyle factors [d] | x | x | x | x | x | | |
| Prior and concomitant medications [e] | x | x | x | x | x | | |
| Satralizumab treatment [f] | x | x | x | x | x | | x |
| Comorbid conditions | x | x | x | x | x | | |
| NMOSD disease status [g] | | x | x | x | x | | |
| Current pregnancy status | | x | x | x | | | x [h] |
| Gestational age (weeks) | | x | x | x | x | | x [h] |
| Pregnancy outcome [i] | | | | | x | | x [h] |
| Infant characteristics | | | | | x [j] | x [k] | x [h] |
| Infant abnormalities [l] | | | | | x | x | x [h] |

| Data Collection [a] | Enrollment | Prenatal Follow-Up | | | Pregnancy Outcome | Pediatric Follow-Up | Early Termination of Study Participation Contact |
|---|---|---|---|---|---|---|---|
| | | End 1st Trimester (~14 weeks) | Mid 2nd Trimester (~21 weeks) | Mid 3rd Trimester (~34 weeks) | ~4 weeks after EDD | Infant Age 12, 26, and 52 Weeks | End of Patient Participation in Study |
| SAEs related to pregnancy, infant SAEs, and selected non-serious infant AEs[m] | x | x | x | x | x | x | x [h] |
| Reason for early termination of study participation | | | | | | | x |

AE = adverse event; EDD = estimated date of delivery; EDSS = Expanded Disability Status Scale; LMP = last menstrual period; NMOSD = neuromyelitis optica spectrum disorder; SAE = serious adverse event.

[a] Available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice. For retrospectively enrolled patients (e.g., after the pregnancy outcome), all information on the pregnancy and any infant outcomes will be collected at the study entry. If the infant of the retrospectively enrolled patient is <1-year-old they, infant data collection will follow the pediatric follow-up schedule above..

[b] Written or verbal informed consent must be obtained before any data collection (per local regulations or Ethics Committee requirements).

[c] Includes previous pregnancy outcomes, detailed family history including pregnancy complications, adverse pregnancy outcomes and developmental abnormalities, and information about baseline risks.

[d] Includes smoking, caffeine consumption, alcohol use, and illicit drug use.

[e] Prior and concomitant medications up to 6 months prior to the LMP.

[f] Includes start and stop dates, dose, dosing frequency, and reason for discontinuation (if applicable).

[g] Changes in NMOSD disease status and NMOSD relapses since enrollment including EDSS, if available

[h] If applicable.

[i] Includes live birth, stillbirth, spontaneous abortion, elective or therapeutic termination, reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), and autopsy results and pathology reports, if available.

[j] Includes gestational age at birth, sex, weight, length, head circumference, birth order (for multiple births) and number of fetuses, laboratory values (if available), Apgar scores (1, 5, and 10 minutes), any congenital malformations noted (including description and attribution), and vaccination information.

[k] Includes feeding behavior (including breastfeeding), weight, length, head circumference, developmental milestones, laboratory values (if available), evidence of any new congenital malformations and growth alterations since last follow-up, and vaccination information.

[l] Detailed information on any infant abnormalities identified after infant birth.

[m] Reported throughout the study or until study discontinuation as applicable.

[n] Including treatment history, disease duration, date of the last relapse and relapse severity, biomarker status, most recent EDSS score, if available.

# Appendix 3 Methods for Assessing and Recording Adverse Events

3.1 Assessment of Severity of Adverse Events

3.2 Assessment of Causality of Adverse Events

3.3 Procedures for recording Adverse Events

## Appendix 3.1 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

**Adverse Event Severity Grading Scale**

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c] |
| 4 | Life-threatening consequences or urgent intervention indicated [d] |
| 5 | Death related to AE [d] |

Note: Based on the NCI CTCAE (v4.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a “significant medical event,” it must be reported as an SAE (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.1.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.1.

## Appendix 3.2 Assessment of Causality of Adverse Events

HCPs and coordinating centers should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study medicine, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

Temporal relationship of event onset to the initiation of study medicine

Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)

Known association of the event with the study medicine or with similar treatments

Known association of the event with the disease under study

Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal product.

## Appendix 3.3 Procedures for recording Adverse Events

### Appendix 3.3.1 Diagnosis versus Signs and Symptoms

For pregnancy-related SAEs, infant SAEs and selected infant AEs, a diagnosis (if known) should be recorded in the AE section of the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

### Appendix 3.3.2 Adverse Events Occurring Secondary to Other Events

In general, pregnancy-related SAEs, infant SAEs and selected infant AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary pregnancy-related SAE, infant SAE or selected infant AE that is separated in time from the initiating event should be recorded as an independent event in the AE section of the CRF. For example:

If severe and persistent vomiting during pregnancy (i.e., hyperemesis gravidarum) results in severe dehydration, both events should be reported separately on the CRF.

If infant neutropenia is accompanied by a severe infection, both events should be reported separately on the CRF.

All AEs should be recorded separately in the AE section of the CRF if it is unclear as to whether the events are associated.

### Appendix 3.3.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Persistent pregnancy-related SAEs, infant SAEs and selected infant AEs should only be recorded once in the AE section of the CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent infant AE becomes more severe, the most extreme severity should also be recorded in the AE section of the CRF. If the event becomes serious, it should be reported to the MAH immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 10.1.3.1 for reporting instructions). The AE section of the CRF should be updated by changing the event from "non-serious" to

"serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of a pregnancy-related SAEs, infant SAEs or selected infant AE should be recorded separately in the AE section of the CRF.

### Appendix 3.3.4 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to the MAH (see Section 10.1.3.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE section of the CRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

### Appendix 3.3.5 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in Section 10.1.1.2), except as outlined below.

The following hospitalization scenarios are <u>not</u> considered to be SAEs:

Hospitalization for respite care

Hospitalization for a preexisting condition, provided that all of the following criteria are met:

- The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
- The patient has not suffered an AE.

### Appendix 3.3.6 Safety data other than Adverse Events

Pregnancy-related SAEs, including adverse pregnancy outcomes (e.g., spontaneous abortion, fetal death/stillbirth, elective or therapeutic termination of pregnancy, preterm

birth, others) and pregnancy complications (e.g., gestational diabetes, pre-eclampsia and other hypertensive disorders of pregnancy, antenatal bleeding, placenta previa, postpartum hemorrhage, preterm labor, premature rupture of membranes, small for gestational age fetus or intrauterine growth restriction, others) (see section 8.3.2), as well as infant SAEs (including hospitalizations other than for the standard post-birth hospital stay) and selected non-serious infant AEs including severe infections (NCI CTCAE Grade 3 and above) and inadequate vaccine response should be recorded in an appropriate section of the CRF and reviewed on an ongoing basis.