**Official Title:** A Phase IV Multicenter, Open-Label Study Evaluating B Cell Levels in Infants Potentially Exposed to Ocrelizumab During Pregnancy – The Minore Study

**NCT Number:** NCT04998812

**Document Date:** Protocol Version 3: 05-Jun-2023

**PROTOCOL**

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|---|---|
| **TITLE:** | **A PHASE IV, MULTICENTER, OPEN-LABEL STUDY EVALUATING B-CELL LEVELS IN INFANTS POTENTIALLY EXPOSED TO OCRELIZUMAB DURING PREGNANCY – *THE MINORE STUDY*** |
| **PROTOCOL NUMBER:** | MN42988 |
| **VERSION NUMBER:** | 3 |
| **EUDRACT NUMBER:** | 2021-000062-14 |
| **IND NUMBER:** | 100593 |
| **NCT NUMBER:** | NCT04998812 |
| **TEST PRODUCT:** | Ocrelizumab (RO4964913) |
| **AUTHORS:** | [redacted] (Medical Monitor) [redacted] |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **APPROVAL:** | *See electronic signature and date stamp on the final page of this document.* |

## PROTOCOL HISTORY

| Protocol | |
|---|---|
| **Version** | **Date Final** |
| 3 | See electronic date stamp on the final page of this document. |
| 2 | 31 March 2022 |
| 1 | 4 March 2021 |

## PROTOCOL AMENDMENT, VERSION 3*:*
## RATIONALE

Protocol MN42988 has been primarily amended with the following key changes in response to the U.S. Food and Drug Administration feedback. Changes, along with rationale, are summarized below.

- The available evidence of pregnancy and infant outcomes in women receiving ocrelizumab for the treatment of multiple sclerosis (MS) has been updated to present data from an analysis performed with a cut-off date of 31 March 2022, replacing data from an analysis up to 31 March 2021 (Section 1.3).
- In the endpoint for the exploratory objective "to evaluate the evolution of B-cell levels between birth and the first year of life", language has been clarified that trajectory (absolute and percentage changes) of B-cell (CD19+ cell) levels in the infant will be measured from Week 6 of life to 1 month after the first or second dose of the measles, mumps and rubella (MMR) vaccine or Month 13 of age in case MMR vaccine is not planned to be administered (Section 2 [Table 1]).
- The phrase "to include but not be limited to" that was used to describe the planned laboratory assessments has been removed and details of the assessments (including markers of lymphocyte subtypes [T-, B-, and NK-cells]) added (Sections 2 [Table 1], 4.5.2.7, and 4.5.3.2 [Tables 3 and 4], and Appendix 1).
- Language has been amended to remove the estimation that approximately 50% of enrolled women should have potential fetal exposure (i.e., received their last dose of ocrelizumab $<3$ months before the last menstrual period [LMP] or during the first trimester [up to gestational Week 13]) (Sections 3.1, 3.1.1 [Figure 1], 3.1.2, and 6.1).
- The sample size has been updated from approximately 44 to approximately 33 pregnant women with clinically isolated syndrome (CIS) or MS. Given that women with CIS or MS are not routinely treated with ocrelizumab shortly before the LMP or during pregnancy and, therefore, represent a special population, the reduction in sample size increases the feasibility to conduct and conclude the study in a timely manner (Sections 3.1, 3.1.1 [Figure 1], 4.1 and 6.1).
- It has been clarified that all visit samples to be collected during the pregnancy and early postpartum period may be collected by home nurse visit, to reduce patient burden (Section 3.1.3).
- The total length of the study has been increased from approximately 25 months to approximately 33 months, due to the extension of the enrollment period from approximately 8 months to approximately 16 months (Section 3.2).
- Language has been modified to clarify that relative exclusions related to medications is according to medication washout period (Section 4.1.2).
- Rituximab has been removed from the list of medications with washout period of 6 months and added to the list of medications with 12-month washout period (Section 4.1.2).

- Language has been included to detail that the Expanded Disability Status Scale (EDSS) assessment may also be performed by the investigator via telephone, using a specific licensed questionnaire that has been included in Appendix A4–2 (Section 4.5.2.6).
- The B-cell subsets that are part of the list of planned maternal laboratory assessments have been specified (Section 4.5.2.7 [Table 2]).
- Language has been added to clarify that while vaccination schedules are not exactly the same from country to country, all participating countries are expected to provide the specific vaccines for the planned titer assessments (Section 4.5.3.2).
- The list of antibody titers of responses to vaccines administered as per local practice has been updated to detail that the following may be included: anti-measles antibody (Ab) IgG, anti-rubella Ab IgG, anti-mumps Ab IgG, PCV-13 Ab (all serotypes), anti-tetanus toxoid IgG, anti-diphtheria IgG, *Bordetella pertussis* Ab IgG, hepatitis B surface Ab, *Hemophilus influenza* B IgG (Section 4.5.3.2 [Table 4]).
- A section has been added detailing how the investigator can contact Medical Monitors, for patient safety; subsequent sections have been renumbered (Section 5.1.3.2).
- Due to the reduction in sample size, language has been amended to reduce the number of evaluable infants expected in this study from at least 40 to approximately 30 (Section 6.1).
- The precisions (width of the two-sided 95% CIs based on normal approximation) for different event rates (an “event” is defined as B-cell levels below the lower limit of normal) presented in Table 5 have been amended for a sample size of 30; the precisions for a sample size of 40 infants, with a subgroup of 20 infants whose mothers received the last dose of ocrelizumab 0 to 3 months before the LMP or during the first trimester, have been removed. Additionally, language has been included to detail that if no event is observed from the 30 infants during the study, there is a 95% confidence that the event rate is below 0.114 (Section 6.1).
- The population of the primary estimand has been amended to include infants exposed to ocrelizumab up to 6 months before the mother’s LMP or during the first trimester (up to gestational Week 13) of pregnancy and not exposed after the first trimester (infants’ full analysis set) (Section 6.4.1).
- A reference to Appendix 7 (B-cell reference ranges by week of life [absolute and percentage counts]) has been added (Section 6.4.1).
- Language has been added to detail the intercurrent events of the primary estimand (Section 6.4.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section 8.4).

- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).
- The EDSS by telephone questionnaire has been included in the protocol (Appendix 4 [Appendix A4-2]).
- An appendix detailing B-cell reference ranges by week of life (absolute and percentage counts) has been added (Appendix 7).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. The amendment represents cumulative changes to the original protocol.

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| **AUTHORS:** | [redacted] (Medical Monitor) [redacted] |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your study monitor.

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE IV, MULTICENTER, OPEN-LABEL STUDY EVALUATING B-CELL LEVELS IN INFANTS POTENTIALLY EXPOSED TO OCRELIZUMAB DURING PREGNANCY – *THE MINORE STUDY*** |
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| **IND NUMBER:** | 100593 |
| **NCT NUMBER:** | NCT04998812 |
| **TEST PRODUCT:** | Ocrelizumab (RO4964913) |
| **PHASE:** | Phase IV |
| **INDICATION:** | Multiple Sclerosis |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**Background**

The most recent report combining clinical trial and post-marketing experience suggests no increased risk of adverse pregnancy/fetal outcomes with ocrelizumab use, including in those pregnancies considered to have fetal ocrelizumab exposure (hypothetically, an embryo/fetus is considered exposed *in utero* if the last infusion of ocrelizumab was within 3 months of conception, during pregnancy, or if the date was unknown). However, very limited systematic data are available to date on laboratory outcomes (particularly B-cell levels) and infections in infants potentially exposed to ocrelizumab during pregnancy, and no information on their ability to mount immune responses.

**Objectives and Endpoints**

This study will evaluate the potential placental transfer of ocrelizumab in women with clinically isolated syndrome (CIS) or multiple sclerosis (MS) [in line with the locally approved indications] whose last dose of ocrelizumab was administered any time from 6 months before the last menstrual period (LMP) through to the first trimester (up to gestational Week 13) of pregnancy, and the corresponding pharmacodynamic effects (B-cell levels) in the infant. Specific objectives and corresponding endpoints for the study are outlined below.

| Objectives | Corresponding Endpoints |
|---|---|
| Primary Outcome Measure | |
| • To evaluate whether infants potentially exposed to ocrelizumab during pregnancy present with postpartum B-cell depletion | • Proportion of infants with B-cell levels (CD19+ cells, absolute counts) below the LLN, measured at Week 6 of life |
| Secondary Outcome Measures | |
| • To evaluate B-cell levels in infants potentially exposed to ocrelizumab during pregnancy | • B-cell levels (CD19+ cells, absolute counts and percentage of lymphocytes) measured at Week 6 of life |

| Objectives | Corresponding Endpoints |
|---|---|
| Secondary Outcome Measure (cont.) | |
| • To evaluate whether there is placental transfer of ocrelizumab from the mother to the infant | • Serum concentration of ocrelizumab in the umbilical cord blood at birth (target time frame of blood sampling: within 1 hour after delivery)<br>• Serum concentration of ocrelizumab in the infant at Week 6 of life |
| • To evaluate whether infants potentially exposed to ocrelizumab during pregnancy are able to mount humoral immune responses to clinically relevant vaccines | • Mean titers of antibody immune response(s) to common childhood vaccinations with full or partial doses given prior to 1 year, which include responses to *diphtheria, tetanus, pertussis*, Hib, PCV-13, MMR, and HBV<br>• Proportion of infants with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines |
| • To evaluate the levels of ocrelizumab in the mother during pregnancy | • Serum concentration of ocrelizumab in the mother during pregnancy (time frame of blood sampling: Week 24–30, Week 35) and at delivery (time frame of blood sampling: within 24 hours after delivery) |
| Safety Objectives | |
| • To evaluate the safety of ocrelizumab in the mother, and the safety of infants potentially exposed to ocrelizumab | • Rate and nature of adverse events in the mother throughout the study, including changes in clinical and laboratory results<br>• Rate and nature of adverse events in the infant throughout the study, including infections and hospitalizations |
| • To evaluate pregnancy and neonatal outcomes | • Proportion of pregnancies resulting in live births (term and preterm, with and without congenital anomalies), therapeutic abortions, or stillbirths<br>• Infant characteristics at birth, including but not limited to body weight, head circumference and length |
| Exploratory Objectives | |
| • To evaluate the infant's growth velocity and developmental milestones in the first year of life | • Assessment of growth velocity based on age-adjusted body length, weight and head circumference, using growth charts according to the WHO Child Growth Standards, as well as absolute values, at Months 2, 4, 6, 9, and 12<br>• Assessment of child developmental milestones in the domains of communication, gross motor, fine motor, problem solving, and personal-social at Months 2, 4, 6, 9, and 12, using the ASQ-3 |
| • To evaluate humoral immunity to clinically relevant pathogens in mothers during pregnancy | • Mean titers of antibody immune response(s) to vaccinations, measured in the third trimester (time frame of blood sampling: Week 35)<br>• Percentage of women with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines (time frame of blood sampling: Week 35) |

| Objectives | Corresponding Endpoints |
|---|---|
| Exploratory Objectives (cont.) | |
| | • **Note:** Immune responses to the following may be included: measles, mumps, rubella, *tetanus*, diphtheria, pertussis, varicella zoster, *Streptococcus pneumoniae*, HBV, and SARS-CoV-2; along with nucleocapsid and spike protein titers; only for those mothers who have received the vaccine, as per local clinical practice) |
| • To measure disease activity in mothers during pregnancy and postpartum | • Number of MS relapses during pregnancy and postpartum (clinical relapses)<br>• Mean change from baseline in the EDSS score over the course of the study |
| • To detect presence of neuroaxonal damage in the mother during pregnancy and postpartum | • sNfL levels during pregnancy (second trimester [time frame of blood sampling: Week 24–30], third trimester [time frame of blood sampling: Week 35] and at delivery [time frame of blood sampling: within 24 hours after delivery]) and postpartum (in line with ocrelizumab administration timepoints) |
| • To evaluate the evolution of B-cell levels between birth and the first year of life | • Trajectory (absolute and percentage changes) of B-cell (CD19+ cell) levels in the infant *from* Week 6 of life *to* 1 month after the first or second dose of MMR vaccine *or* Month 13 of age *in case MMR vaccine is not planned to be administered* |
| ASQ-3 = Ages and Stages Questionnaire, version 3; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; MMR = measles, mumps, and rubella; MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; sNfL = serum neurofilament light chain; WHO = World Health Organization. | |

## STUDY DESIGN

### DESCRIPTION OF STUDY

This is a prospective, multicenter, open-label study in women with CIS or MS (in line with the locally approved indications) receiving commercial ocrelizumab up to 6 months before the LMP or during the first trimester (up to gestational Week 13), due to accidental exposure, or in whom a decision to treat with ocrelizumab was taken as part of routine clinical practice.

Note on referral to sites: Pregnant and lactating women with MS are often treated in a decentralized way between specialized and non-specialized centers. It is difficult to predict at which clinical sites eligible women will be identified; and activation of new sites that identify potential women is not viable since it could take several months, and would not be achieved in time to screen the women while they still meet the protocol inclusion criteria. By using established networks and pregnancy registries for referral, the study could be completed in a timely manner. For these reasons, women may be referred to study sites; and study visits may be home-based (conducted by a mobile nurse, and by the investigator using telemedicine [i.e., remotely]). Implementation of these elements will depend on local requirements as well as agreement by the investigator, and capacity to use telemedicine. The investigators will be informed about the approach that may be used in their country.

The study will consist of the following periods.

- Screening/baseline period (between gestational Week 24 and 30): After providing written informed consent, women will enter a screening period between gestational Weeks 24 and 30, after the morphological scan (usually done at gestational Week 18–20). Women fulfilling the inclusion/exclusion criteria with accidental ocrelizumab exposure, or in whom a decision to treat with ocrelizumab was taken as part of routine clinical practice, will be enrolled; *some* of the*se* women should have potential fetal exposure (i.e., have received their last dose of ocrelizumab < 3 months before the LMP or during the first trimester [up to gestational Week 13]). Exposure to ocrelizumab includes administration of an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days for women initiating treatment with ocrelizumab, or a single 600 mg infusion (in 500 mL 0.9% sodium chloride) for women already on treatment with ocrelizumab. The baseline visit will be combined with the screening visit. To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. The scheduled obstetric blood glucose test should preferably be conducted at the screening/baseline visit rather than at a separate visit.
- Pregnancy and early postpartum period (up to Week 6 of life): Laboratory and clinical assessments during the third trimester (gestational Week 35 [± 14 days]), will be performed in accordance with planned prenatal care visits, whenever possible. To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. *All* visit samples may be collected by home nurse visit. At birth, a blood sample will be collected from the umbilical cord (only for live births; no collection should occur in the event of a pregnancy interruption [i.e., therapeutic abortion or stillbirth]). The target time frame for collection will be within 1 hour after delivery; the actual time of collection after delivery will be recorded. At week 6 (± 7 days) of the infant's life (or equivalent age for preterm births, i.e., gestational week at birth < 37 weeks). At Week 6 (± 7 days) of the infant's life, a blood sample will be collected from the infant (at an on-site visit, or by a home nurse visit) for measurement of B-cell levels (the primary endpoint). Ocrelizumab must not be administered after the woman is enrolled in the study and until the infant's birth. Treatment with commercial ocrelizumab may be resumed at any time after birth for women who decide not to breastfeed. Some women may decide to resume treatment with ocrelizumab whilst breastfeeding. For those women, treatment with ocrelizumab should be restarted after collection of the infant blood sample at Week 6 of life (± 7 days) if possible, but the decision is left to the discretion of the woman and the investigator.

  If the woman switches to another DMT postpartum, the infant blood sample at Week 6 of life (± 7 days) will only be collected if the woman is not breastfeeding.
- Vaccination period (after Week 6 of life and up to 1 month [+ 30 days] after the first or second dose of MMR vaccine, or at Month 13 of age [+ 30 days] if the MMR vaccine is not planned to be administered): Both mother and the infant will enter an extension phase, which will continue approximately until the infant reaches 13 months of age. This is designed to evaluate whether infants potentially exposed to ocrelizumab during pregnancy are able to mount humoral immune responses to clinically relevant vaccines. Infant laboratory assessments will be performed 1 month (+ 30 days) after the first dose of MMR vaccine (if first dose is administered at 11 months of age or later), 1 month (+ 30 days) after the second dose of MMR vaccine (if first dose is administered before 11 months of age), or at Month 13 of chronological age (+ 30 days) if MMR vaccine is not planned to be administered (as per local clinical practice, vaccinations may include *diphtheria, tetanus, pertussis*, Hib, PCV-13, HBV, and MMR). Additionally, infants will continue to be followed up for growth (age-adjusted body length, weight and head circumference) and developmental milestones up to 12 months of age. Growth charts following the WHO Child Growth Standards, absolute values and the ASQ-3 questionnaires will be used; other standard measurements recorded by e.g., the pediatrician as part of routine post-natal care may also be used. Post-natal timings of ocrelizumab infusions every 6 months and laboratory/clinical assessments in the mother may occur at different time points than infant assessments.

In case the mother decides to switch to another DMT or to stop DMT after birth, no laboratory/clinical assessments will be performed for the mother. However, the infant blood sample 1 month (+30 days) after the first or second dose of MMR vaccine (or at Month 13 of age [+30 days]) will still be collected.

- A structured telephone interview will be conducted by site personnel every 3 months postpartum (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's or infant's health status (including the occurrence of MS relapses in the woman and use of new concomitant medications) and possible adverse events in both the woman and the infant (particularly infections); women will also be asked if the ASQ-3 form is being filled out. No telephone contact is needed in weeks where the woman is performing on-site visits.
- Follow-up visit after early discontinuation: Women who decide to discontinue the study (this includes discontinuation of the mother or discontinuation of the infant by the mother, or discontinuation at the investigator's discretion) will be invited to attend an early study discontinuation visit (which may be conducted virtually or by telephone) as soon as possible. Depending on the timing of discontinuation, the following is recommended:
- *Discontinuation before birth:* Collection of pregnancy outcome and infant outcomes in the first year of life as per standard pharmacovigilance procedures.
- *Discontinuation after birth and before Week 6 of life of the infant:*
  - Collection of pregnancy outcome and infant outcomes in the first year of life as per standard pharmacovigilance procedures
  - If the mother decides to stop participating at Week 6 of life (± 7 days), attempts to collect the infant sample at Week 6 of life (± 7 days) should be made, and before discontinuation
  - If the mother switches to another DMT and is breastfeeding, the infant sample at Week 6 of life (± 7 days) should not be collected
- *Discontinuation after Week 6 of life of the infant:* Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures.

**Number of Women**

This study will enroll approximately 33 pregnant women with CIS or MS (in line with the locally approved indications).

**End of Study**

The end of the study is defined as the date of the last assessment (vaccine response titers measured 1 month [+30 days] after the first or second dose of MMR vaccine, or at Month 13 of age (+30 days) if MMR vaccine is not planned to be administered) for the last infant.

**Length of Study**

The total length of the study, from screening of the first woman to the end of the study, is expected to be approximately 33 months. This includes an enrollment period of approximately 16 months and subject participation of approximately 17 months.

**Target Population**

**Inclusion Criteria**

Women must meet the following criteria for study entry:

- An informed consent form (ICF) for participation of the maternal subject and her unborn (for collection of blood samples, infant demographics and adverse event data) is signed and dated by the subject. Where applicable, the written ICF with respect to the infant is also signed and dated by the holder of parental rights as designated by the maternal subject.
- Able and willing to comply with the study protocol, in the Investigator's judgment.
- Age 18–40 years, inclusive, at screening.
- Have a diagnosis of MS or CIS (in line with the locally approved indications).
- Currently pregnant with singleton pregnancy at gestational Week ≤30 at enrollment.

- *Note:* Gestational age will be determined by LMP and first trimester ultrasound so long as there is less than 1 week's difference in the projected due date. If there is over 1 week's difference, then the ultrasound alone will be used. For cases where the LMP is not known, then the earliest ultrasound will be used. For cases of in vitro fertilization (IVF), the projected dates from the IVF procedure will be preferentially used.
- Documentation that first (12-week) and second (18–20-week) obstetric ultrasound (prenatal screening) has been conducted before enrollment.
- Documentation that the last exposure to ocrelizumab occurred up to 6 months before the LMP before the woman became pregnant OR during the first trimester of pregnancy (up to gestational Week 13 inclusive).

  *Note:* Exposure to ocrelizumab includes administration of an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days for women initiating treatment with ocrelizumab, or a single 600 mg infusion (in 500 mL 0.9% sodium chloride) for women already on treatment with ocrelizumab.

**Exclusion Criteria**

Women who meet any of the following criteria will be excluded from study entry:

- Last exposure to ocrelizumab > 6 months before the woman's LMP or later than the first trimester of pregnancy (i.e., after gestational Week 13).
- Gestational age at enrollment > 30 weeks.
- Non-singleton pregnancy.
- Received the last dose of ocrelizumab at a different posology other than per the local prescribing information.
- Social circumstances (e.g., home relocation) that may preclude a woman from participating in the study.

Exclusions related to obstetric and gynecological health

- Lack of access to ultrasound prenatal care as part of standard clinical practice.
- Women in whom aneuploid disorders or genetic disorders that cause major congenital malformations have been detected during first trimester prenatal screening (e.g., ultrasound, amniocentesis, genetic testing, nuchal translucency screening, chorionic villus sampling), or in whom any fetal anomalies (i.e., fetal biometry, fetal anatomy) have been detected during the morphology scan at around or before gestational Week 18–20.
- Documented history of disorders associated with adverse pregnancy outcomes, including but not limited to, the following:
  - History of preterm birth (gestational age < 37 weeks) for any indication with or without fetal malformations
  - History of spontaneous abortion (miscarriage) after the first trimester (i.e., after gestational Week 13)
  - History of stillbirth (defined as fetal loss at gestational age > 22 weeks)
  - History of pre-eclampsia/eclampsia
  - History of a cervical pathology or intervention which may increase the risk of cervical incompetence (e.g., history of cervical cerclage, prior cervical conization or prior loop electrosurgical excision procedure [LEEP])
- Prior or current history of any other gynecological or obstetric disease considered by the investigator to be associated with a high risk of adverse pregnancy outcomes in the current pregnancy.

Exclusions related to general health

- Lack of peripheral venous access.
- Pre-pregnancy body mass index (BMI) > 35 kg/m$^2$.

- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study.
- Prior or current history of primary or secondary immunodeficiency, or woman in an otherwise severely immunocompromised state. The woman may be re-screened and included if condition resolves.
- Significant and uncontrolled disease, such as cardiovascular (including cardiac arrhythmia and hypertension), pulmonary (including obstructive pulmonary disease), neurological, psychiatric (e.g., psychosis), renal, hepatic, endocrine (e.g., diabetes, thyroid disorders), or gastrointestinal or any other significant disease that may preclude a woman from participating in the study.
- Women with known active malignancies or being actively monitored for recurrence of malignancy including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin). Women with *in situ* carcinoma of the cervix of the uterus, even if excised and resolved with documented clean margins on pathology, are excluded from the study.
- Prior or current history of alcohol or drug abuse, or current use of tobacco.

Exclusions related to laboratory findings

- Any abnormal screening laboratory value that is clinically relevant will be retested only once in order to rule out any progressive or uncontrolled underlying condition. The last value before study entry must meet study criteria.

  Women with positive screening tests for hepatitis B, determined by a positive hepatitis B surface antigen (HBsAg) result (current infection) or positive hepatitis B core antibody (HBcAb) titers (previous infection) will be excluded. Women with documented history of hepatitis B virus (HBV) vaccination or positive hepatitis B surface antibody (HBsAb) titers are eligible.

Note: based on local Ethics Committees or National Competent Authority requirements, additional local diagnostic testing may be required for selected women or selected centers to exclude tuberculosis, Lyme disease, human T-lymphotropic virus 1 associated myelopathy (HAM), human immunodeficiency virus (HIV), hepatitis C virus infection (HCV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the investigator.

Exclusions related to medications

*Absolute exclusions*

- Drugs known to have teratogenic effects including but not limited to certain anticonvulsants (even if used for pain management), antibiotics such as tetracyclines or fluoroquinolones.
- Planned treatment with interferons, glatiramer acetate, or pulsed corticosteroids as a bridging therapy after the last ocrelizumab dose before enrollment and throughout pregnancy.

*Relative exclusions (according to medication washout period)*

- Treatment with one of the following agents prior to the last ocrelizumab dose or prior to the LMP, whichever occurred first:
  - Treatment with siponimod or ponesimod within 10 days
  - Treatment with mycophenolate within 6 weeks
  - Treatment with fingolimod within 2 months
  - Treatment with ozanimod within 3 months
  - Treatment with alemtuzumab within 4 months
  - Treatment with mitoxantrone, methotrexate, ofatumumab or cladribine within 6 months

  - Treatment with cyclophosphamide *or rituximab* within 12 months
- Treatment with natalizumab within 12 weeks prior to the LMP
- Treatment with teriflunomide within the last two years, unless measured plasma concentrations are less than 0.02 mg/L. If levels are above 0.02 mg/L or not known, an accelerated elimination procedure will be implemented before screening visit. One of the following elimination procedures can be used:
  - Cholestyramine 8 g administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated
  - Alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days
- Treatment with any investigational agent within 6 months or five half-lives of the investigational drug (whichever is longer) prior to the last ocrelizumab dose or prior to the LMP, whichever occurred first.

**STUDIED MEDICINAL PRODUCTS**

The study treatment is commercial ocrelizumab. Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labelling (USPI; SmPC).

**Statistical Methods**

**Primary Analysis**

The primary analysis will be performed after the last blood draw at Week 6 *of life* to examine B-cell levels in infants.

The proportion of infants with B-cell levels below the LLN will be calculated and the corresponding two-sided Clopper-Pearson 95%CI will be presented.

The B-cell levels at Week 6 of life will be analyzed using descriptive statistics. Mean, corresponding 95% CI, SD, and other statistics will be presented.

Stillbirths and abortions of any type will not be included in the primary B-cell analysis.

**Determination of Sample Size**

The study will include approximately *33* pregnant women.

There is no formal sample size calculation, as no confirmatory hypothesis testing is planned. The primary analysis will be descriptive. Considering a 10% dropout rate, *approximately 30* evaluable infants are expected. A further investigation will be performed on the subgroup of infants whose mothers received the last dose of ocrelizumab 0–3 months before the LMP or during the first trimester.

The precisions (width of the two-sided 95% CIs based on normal approximation) for different event rates (an "event" is defined as B-cell levels below the LLN) are shown in the following table. If no event is observed from the *30* infants during the study, there is a 95% confidence that the event rate is below *0.114*.

| *Sample Size* | *Number of Events* | *Event Rate* | *Precision* |
|---|---|---|---|
| *30* | *1* | *0.033* | *0.165* |
| *30* | *2* | *0.067* | *0.195* |
| *30* | *3* | *0.100* | *0.222* |
| *30* | *4* | *0.133* | *0.244* |
| *30* | *5* | *0.167* | *0.262* |

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AESI | adverse events of special interest |
| *APGAR* | *Appearance, Pulse, Grimace, Activity, and Respiration* |
| ASQ-3 | Ages and Stages Questionnaire version 3 |
| BMI | body mass index |
| CIS | clinically isolated syndrome |
| CRO | contract research organization |
| DMT | disease-modifying therapy |
| EC | Ethics Committee |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EDSS | Expanded Disability Status Scale |
| EU | European Union |
| FAS | full analysis set |
| FDA | (U.S.) Food and Drug Administration |
| FSS | functional systems scores |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transpeptidase |
| HAM | human T-lymphotropic virus 1 associated myelopathy |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCP | healthcare professional |
| Hib | *Hemophilus influenzae* type b |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| ICH | International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICF | Informed Consent form |
| IMP | investigational medicinal product |
| IND | investigational new drug |
| IRB | Institutional Review Board |
| IRR | infusion-related reaction |
| *IV* | *intravenous* |

| Abbreviation | Definition |
|---|---|
| IVF | in vitro fertilization |
| LEEP | loop electrosurgical excision procedure |
| LLN | lower limit of normal |
| LMP | last menstrual period |
| MAH | marketing authorization holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMR | measles, mumps, and rubella |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| *NK* | *natural killer (cell)* |
| PCV-13 | 13-valent pneumococcal conjugate vaccine |
| PML | progressive multifocal leukoencephalopathy |
| PPMS | primary-progressive multiple sclerosis |
| QLT | quality tolerance limits |
| RMS | relapsing multiple sclerosis |
| RRMS | relapsing-remitting multiple sclerosis |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SmPC | Summary of Product Characteristics |
| sNfL | serum neurofilament light chain |
| SOC | system organ class |
| SPMS | secondary progressive multiple sclerosis |
| USPI | U.S. Prescribing Information |
| WHO | World Health Organization |

# 1. BACKGROUND

## 1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the CNS that affects approximately 1 million people in the United States and 2.8 million worldwide (Multiple Sclerosis International Federation 2020). MS primarily affects young adults, with 70%–80% of patients having an age of onset (i.e., initial visit to a physician) between 20 and 40 years (Anderson et al. 1992; Noonan et al. 2002), and has a strong gender bias, with approximately 64%–70% of diagnosed patients being women (Goodin 2014).

Multiple sclerosis is clinically categorized into three phenotypic disease patterns distinguished by the occurrence and timing of relapses as well as disability progression relative to disease onset: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary-progressive MS (PPMS; Lublin et al. 2014). RRMS is the most frequent disease course and develops as the initial presentation in approximately 85% of patients at approximately 30 years of age (Confavreux et al. 2000; Leray et al. 2015). If left untreated, in up to 80% of such patients, the disease advances to a secondary progressive stage (SPMS) within approximately 10–20 years depending on the natural history cohort (Koch et al. 2010; Kremenchutzky et al. 2006; Tremlett et al. 2008; Weinshenker et al. 1989). PPMS is the diagnosis at disease onset in around 15% of patients, and is characterized by a pattern of sustained deterioration of their neurological function from the onset. Around 5% of patients with PPMS will experience relapses and periods of remission throughout the disease course (Lublin et al. 2014). Clinically isolated syndrome (CIS) is considered to be an early part of the spectrum of MS phenotypes and should be followed to determine subsequent disease course (Lublin et al. 2014).

The clinical signs and symptoms in MS can occur in isolation or in combination, and can include weakness, spasticity, gait and coordination imbalances, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Tanasescu et al. 2014). Current diagnosis of definite MS involves both clinical (history and neurological exam) and paraclinical evidence (for example, magnetic resonance imaging [MRI], lumbar puncture, or evoked potentials; Polman et al.2011; Thompson et al. 2018).

The current therapeutic approach in MS involves symptomatic treatment, treatment of acute relapses, and disease-modifying therapies (DMTs). Disease-modifying therapies are the mainstay for the pharmacological treatment of MS. These therapies aim to decrease the clinical relapse rate, slow the development of MS-related neurological damage and disease progression, and concomitant inflammation within the CNS. Licensed DMTs have a range of mechanisms of action and can be immunomodulatory, anti-inflammatory, or immunosuppressive drugs (Reich et al. 2018).

## 1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets and eliminates CD20-expressing B-cells (Klein et al. 2013), which are believed to play a critical role in MS. Efficacy and safety of ocrelizumab has been demonstrated in one Phase II and three Phase III randomized controlled clinical trials. In two double-blind, double-dummy Phase III global relapsing multiple sclerosis (RMS) trials (OPERA I [Study WA21092] and OPERA II [Study WA21093]), ocrelizumab 600 mg administered every 24 weeks demonstrated superior efficacy over subcutaneous interferon beta (IFNβ)-1a 44 μg three times weekly (Hauser et al. 2017). Efficacy outcomes were consistent between trials and across the primary and key clinical and imaging secondary endpoints. Similarly, in a Phase III global PPMS trial (ORATORIO [Study WA25046]), ocrelizumab 600 mg demonstrated statistically significant superiority compared with placebo across several disability and imaging endpoints (Montalban et al. 2017).

Based on the results from these Phase III trials, ocrelizumab was approved for use in patients with RMS (which includes CIS, RRMS and active SPMS) and PPMS in the United States, whereas in the European Union (EU) it was approved for relapsing or primary-progressive forms of MS. The use of ocrelizumab in countries where it has been approved is governed by the applicable local label.

## 1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Most patients with MS are women in their reproductive years (Albor et al. 2017; Trojano et al. 2012). Family planning is therefore an important consideration for women with MS who are receiving treatment with DMTs. Women are usually advised to discuss treatment options with their healthcare professional (HCP) prior to family planning, and in many instances, it may be recommended, or even required, that a woman discontinue her treatment with DMTs during pregnancy planning or once pregnancy is confirmed (Hellwig et al. 2020). However, this may lead to an increased risk of relapses during the period between DMT discontinuation and the start of the potential protective effects of pregnancy (Confavreux et al. 1998). For example, severe rebound relapses during pregnancy have been reported as early as 1 month after stopping fingolimod and 3–4 months after stopping natalizumab (Langer–Gould et al. 2019). In addition, there is evidence that approximately 30% of women with MS experience a relapse in the first 3 months after delivery (Vukusic et al. 2004).

Ocrelizumab may be a suitable treatment option for women with MS planning to become pregnant because of its prolonged immunomodulatory effects. The terminal half-life of ocrelizumab (26 days on average) provides a window of opportunity for a woman to become pregnant when B-cells remain undetectable despite the medication already being cleared from the body, or not being able to cross the placental barrier. Currently, the ocrelizumab labeling (Summary of Product Characteristics [SmPC], U.S. Prescribing Information [USPI]) stipulates that contraceptives should be used during ocrelizumab treatment, and for 6 months (United States) or 12 months (EU) after the last dose.

The 6-month contraceptive requirement in the US label reflects the pharmacokinetic properties of ocrelizumab, including the lack of transfer across the placenta during the first trimester of pregnancy owing to its conformation as an IgG1 antibody (Kane and Acquah 2009).

### Available Evidence

In an embryofetal development study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity, or embryotoxicity following ocrelizumab treatment at 75/100 mg/kg (loading dose/study dose). Reductions in B-cells (the anticipated pharmacological effect) in maternal and fetal peripheral blood were observed. In two pre- and postnatal development studies in cynomolgus monkeys, administration of ocrelizumab from gestational Day 20 to at least parturition was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. The maternal doses administered in these studies resulted in maximum serum concentrations ($C_{max}$) that were 4.5- to 21-fold above those anticipated in the clinical setting (for a 600 mg dose). There were five neonatal deaths; one attributed to weakness due to premature birth accompanied by opportunistic bacterial infection, one due to an infective meningoencephalitis involving the cerebellum of the neonate from a dam with an active bacterial infection (mastitis), and three with evidence of jaundice and hepatic damage, with suspected viral etiology (possibly a polyomavirus). The course of these five confirmed or suspected infections could potentially have been impacted by B-cell depletion. Newborn offspring of animals exposed to ocrelizumab were noted to have depleted B-cell populations during the postnatal phase (Ocrelizumab Investigator's Brochure, version 20.0, November 2021).

As of 31 March 202*2*, *2020* MS pregnancies exposed to ocrelizumab were reported in the ocrelizumab global safety database which includes reports from clinical trials and spontaneous post-marketing (*Oreja-Guevara et al. 2022*). *Seven hundred five pregnancies* were considered to have fetal ocrelizumab exposure (an embryo/fetus is considered exposed in utero if the last infusion of ocrelizumab was within 3 months of conception, during pregnancy, or if the date was unknown), *433* had no fetal exposure, and *882* had unknown exposure. Among women with fetal exposure, *207* received the last ocrelizumab dose during the first trimester of pregnancy. Overall, *1064* pregnancies had known outcomes. Pregnancy outcomes irrespective of fetal exposure status were as follows: *there* were *809* (*76.0*%) live births, *72* (*6.8*%) elective/therapeutic abortions, *158* (*14.8*%) spontaneous abortions, *6* (*0.6*%) stillbirths, *2 (0.2%) intrauterine/fetal death,* and *17* (*1.6*%) ectopic pregnancies. *Two hundred sixty-six pregnancies* were ongoing, and *690* were lost to follow-up or had unknown/not reported outcomes *(Oreja-Guevara et al. 2022)*. These results remain in line with previous analyses (*Dobson et al. 2021*) and within the expected epidemiological range (CDC 2008; Geissbühler et al. 2015; Friend et al. 2016; Thiel et al. 2016; Lopez-Leon et al. 2020), suggesting no increased risk of adverse pregnancy/fetal outcomes (including

spontaneous abortions, stillbirth and malformations) with ocrelizumab use. In a prospective cohort study of 88 pregnancies in 81 women with MS or other neurological diseases who were treated with rituximab or ocrelizumab ≤12 months before the last menstrual period (LMP; Kümpfel et al. 2021), the overall prevalence of major congenital abnormalities was 3.3% (n=2; a ventricular septum defect and an atrium septum defect with pulmonary stenosis, both in women with RRMS who received ocrelizumab during pregnancy). This rate was similar to the rate seen in pregnancies of unexposed women from the same registry. Pregnancy outcomes in this study were similar between groups, except that there were significantly more preterm births in the group exposed after the LMP (45.5% [n=5 of 13]; vs. 9.8% [n=4 of 47] in the group with exposure <6 months before the LMP and n=0 of 8 in the group exposed >6 months but ≤12 months before the LMP; p=0.019).

Reduced B-cell levels at birth have been reported in an infant born to a mother exposed to ocrelizumab during the second trimester of pregnancy, following relapse activity post-alemtuzumab. However, two months later, B-cell levels were normal (Ciplea et al. 2020). The authors also reported a case where exposure to ocrelizumab occurred during the first trimester, in which B-cell levels in the infant returned to normal at 39 days postpartum (Ciplea et al. 2020). Another case of second trimester ocrelizumab exposure in a patient with RRMS transitioning off natalizumab resulted in no neonatal B-cell depletion, no infections, and normal infant development, despite B-cell depletion in the mother at delivery (Rolfes et al. 2020).

### Supporting Evidence from Other Anti-CD20 Therapies

Data from other anti-CD20 monoclonal antibodies also suggest no increased risk of adverse pregnancy/infant outcomes. In fact, two classes of monoclonal antibodies, natalizumab and CD20-depleting agents, rituximab and ocrelizumab, are considered highly effective therapy options for women at a high risk of pregnancy-related MS relapses (Ciplea et al. 2020). A retrospective cohort study of 74 pregnancies in 55 women treated with rituximab for MS, of whom 9 (12%) had accidental first trimester exposure, found no increase in adverse pregnancy outcomes compared with expected rates. Of the 38 live births, adverse pregnancy outcomes were: 3 preterm deliveries (including 1 set of twins), 1 neonatal death (preterm twin), and 1 perinatal stroke (full-term). There were no stillbirths, chorioamnionitis, or major malformations. Fifteen (27%) women had at least one first trimester miscarriage, of whom 8 (53%) had a history of infertility (Smith et al. 2020). In a systematic review evaluating the safety of rituximab treatment before and during pregnancy in women with MS and neuromyelitis optica spectrum disorders, 102 pregnancies with rituximab use within 6 months of conception were identified, of which 78 resulted in live births and 12 in spontaneous abortions (Das et al. 2018). Based on the available data, some clinicians propose that contraception may be discontinued as early as 4 weeks after the last dose of anti-CD20 antibodies (ocrelizumab or rituximab; Langer-Gould 2019).

### Uncertainties and Need for Additional Evidence

The recent report combining clinical trial and post-marketing experience (data cut-off 31 March *2022*; *Oreja-Guevara et al. 2022*) extends the knowledge on pregnancy outcomes in women with MS treated with ocrelizumab. However, very limited systematic data are available to date on laboratory outcomes (particularly B-cell levels) and infections in infants potentially exposed to ocrelizumab during pregnancy, and no information on their ability to mount immune responses. Given that 1) a large proportion of patients with MS are women of reproductive age, 2) ocrelizumab has a favorable benefit/risk profile in non-pregnant patients and a suitably prolonged pharmacodynamic effect and 3) to date no increased risk of adverse pregnancy outcomes is seen with accidental exposure to ocrelizumab during pregnancy, further investigation is required.

While the knowledge on pregnancy outcomes upon ocrelizumab exposure will be extended through a dedicated pregnancy registry (Wormser et al. 2018) and a multi-source post-marketing study (MELODIC; Margulis et al. 2018), a dedicated prospective interventional study to specifically evaluate the placental transfer of ocrelizumab in women with MS and the corresponding pharmacodynamic effects in infants is required and justified. This is part of the Sponsor's broader research effort to investigate the benefit/risk of exposure to ocrelizumab during pregnancy and lactation, which is currently considered missing information.

## 2. OBJECTIVES AND ENDPOINTS

This study will evaluate the potential placental transfer of ocrelizumab in women with CIS or MS (in line with the locally approved indications) whose last dose of ocrelizumab was administered anytime from 6 months before the LMP through to the first trimester of pregnancy (up to gestational Week 13), and the corresponding pharmacodynamic effects, particularly B-cell levels, in the infants.

Specific objectives and corresponding endpoints for the study are outlined below.

### Table 1 Objectives and Corresponding Endpoints

| Objectives | Corresponding Endpoints |
|---|---|
| Primary Outcome Measure | |
| • To evaluate whether infants potentially exposed to ocrelizumab during pregnancy present with postpartum B-cell depletion | • Proportion of infants with B-cell levels (CD19+ cells, absolute counts) below the LLN, measured at Week 6 of life |

*ASQ-3 = Ages and Stages Questionnaire, version 3; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; MMR = measles, mumps, and rubella; MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; sNfl = serum neurofilament light chain; WHO = World Health Organization.*

## Table 1 Objectives and Corresponding Endpoints (cont.)

| Objectives | Corresponding Endpoints |
|---|---|
| Secondary Outcome Measures | |
| • To evaluate B-cell levels in infants potentially exposed to ocrelizumab during pregnancy | • B-cell levels (CD19+ cells, absolute counts and percentage of lymphocytes) measured at Week 6 of life |
| • To evaluate whether there is placental transfer of ocrelizumab from the mother to the infant | • Serum concentration of ocrelizumab in the umbilical cord blood at birth (target time frame of blood sampling: within 1 hour after delivery)<br>• Serum concentration of ocrelizumab in the infant at Week 6 of life |
| • To evaluate whether infants potentially exposed to ocrelizumab during pregnancy are able to mount humoral immune responses to clinically relevant vaccines | • Mean titers of antibody immune response(s) to common childhood vaccinations with full or partial doses given prior to 1 year, which include responses to *diphtheria, tetanus, pertussis*, Hib, PCV-13, MMR, and HBV<br>• Proportion of infants with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines |
| • To evaluate the levels of ocrelizumab in the mother during pregnancy | • Serum concentration of ocrelizumab in the mother during pregnancy (time frame of blood sampling: Week 24–30, Week 35) and at delivery (time frame of blood sampling: within 24 hours after delivery) |
| Safety Objectives | |
| • To evaluate the safety of ocrelizumab in the mother, and the safety of infants potentially exposed to ocrelizumab | • Rate and nature of adverse events in the mother throughout the study, including changes in clinical and laboratory results<br>• Rate and nature of adverse events in the infant throughout the study, including infections and hospitalizations |
| • To evaluate pregnancy and neonatal outcomes | • Proportion of pregnancies resulting in live births (term and preterm, with and without congenital anomalies), therapeutic abortions, or stillbirths<br>• Infant characteristics at birth, including but not limited to body weight, head circumference and length |

*ASQ-3 = Ages and Stages Questionnaire, version 3; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; MMR = measles, mumps, and rubella; MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; sNfl = serum neurofilament light chain; WHO = World Health Organization.*

## Table 1 Objectives and Corresponding Endpoints (cont.)

| Objectives | Corresponding Endpoints |
|---|---|
| Exploratory Objectives | |
| • To evaluate the infant's growth velocity and developmental milestones in the first year of life | • Assessment of growth velocity based on age-adjusted body length, weight and head circumference, using growth charts according to the WHO Child Growth Standards, as well as absolute values, at Months 2, 4, 6, 9, and 12<br>• Assessment of child developmental milestones in the domains of communication, gross motor, fine motor, problem solving, and personal-social at Months 2, 4, 6, 9, and 12, using the ASQ-3 |
| • To evaluate humoral immunity to clinically relevant pathogens in mothers during pregnancy | • Mean titers of antibody immune response(s) to vaccinations, measured in the third trimester (time frame of blood sampling: Week 35.<br>• Percentage of women with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines (time frame of blood sampling: Week 35.<br>• **Note:** Immune responses to the following may be included: measles, mumps, rubella, *tetanus*, diphtheria, pertussis, varicella zoster, ***Streptococcus pneumoniae***, HBV, and SARS-CoV-2; along with nucleocapsid and spike protein titers; only for those mothers who have received the vaccine, as per local clinical practice) |
| • To measure disease activity in mothers during pregnancy and postpartum | • Number of MS relapses during pregnancy and postpartum (clinical relapses)<br>• Mean change from baseline in the EDSS score over the course of the study |
| • To detect presence of neuroaxonal damage in the mother during pregnancy and postpartum | • sNfL levels during pregnancy (second trimester [time frame of blood sampling: Week 24–30], third trimester [time frame of blood sampling: Week 35] and at delivery [time frame of blood sampling: within 24 hours after delivery]) and postpartum (in line with ocrelizumab administration timepoints) |

*ASQ-3 = Ages and Stages Questionnaire, version 3; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; MMR = measles, mumps, and rubella; MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; sNfl = serum neurofilament light chain; WHO = World Health Organization.*

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Objectives | Corresponding Endpoints |
|---|---|
| Exploratory Objectives (cont.) | |
| • To evaluate the evolution of B-cell levels between birth and the first year of life | • Trajectory (absolute and percentage changes) of B-cell (CD19+ cell) levels in the infant *from* Week 6 of life *to* 1 month after the first or second dose of MMR vaccine *or* Month 13 of age *in case MMR vaccine is not planned to be administered* |

ASQ-3 = Ages and Stages Questionnaire, version 3; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; MMR = measles, mumps, and rubella; MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; sNfl = serum neurofilament light chain; WHO = World Health Organization.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

This is a prospective, multicenter, open-label study in women with CIS or MS (in line with the locally approved indications) receiving commercial ocrelizumab up to 6 months before the LMP or during the first trimester of pregnancy (up to gestational Week 13), due to accidental exposure, or in whom a decision to treat with ocrelizumab was taken as part of routine clinical practice.

Note on referral to sites: Pregnant and lactating women with MS are often treated in a decentralized way between specialized and non-specialized centers. It is difficult to predict at which clinical sites eligible women will be identified; and activation of new sites that identify potential women is not viable since it could take several months, and would not be achieved in time to screen the women while they still meet the protocol inclusion criteria. By using established networks and pregnancy registries for referral, the study could be completed in a timely manner. For these reasons, women may be referred to study sites; and study visits may be home-based (conducted by a mobile nurse, and by the investigator using telemedicine [i.e., remotely]). Implementation of these elements will depend on local requirements as well as agreement by the investigator, and capacity to use telemedicine. The investigators will be informed about the approach that may be used in their country.

This study will enroll approximately *33* pregnant women with CIS or MS, some of whom should have potential fetal exposure (i.e., received their last dose of ocrelizumab <3 months before the LMP or during the first trimester [up to gestational Week 13]). Laboratory and clinical assessments will be performed as described in the Schedule of Assessments presented in Appendix 1. The study will consist of the following periods:

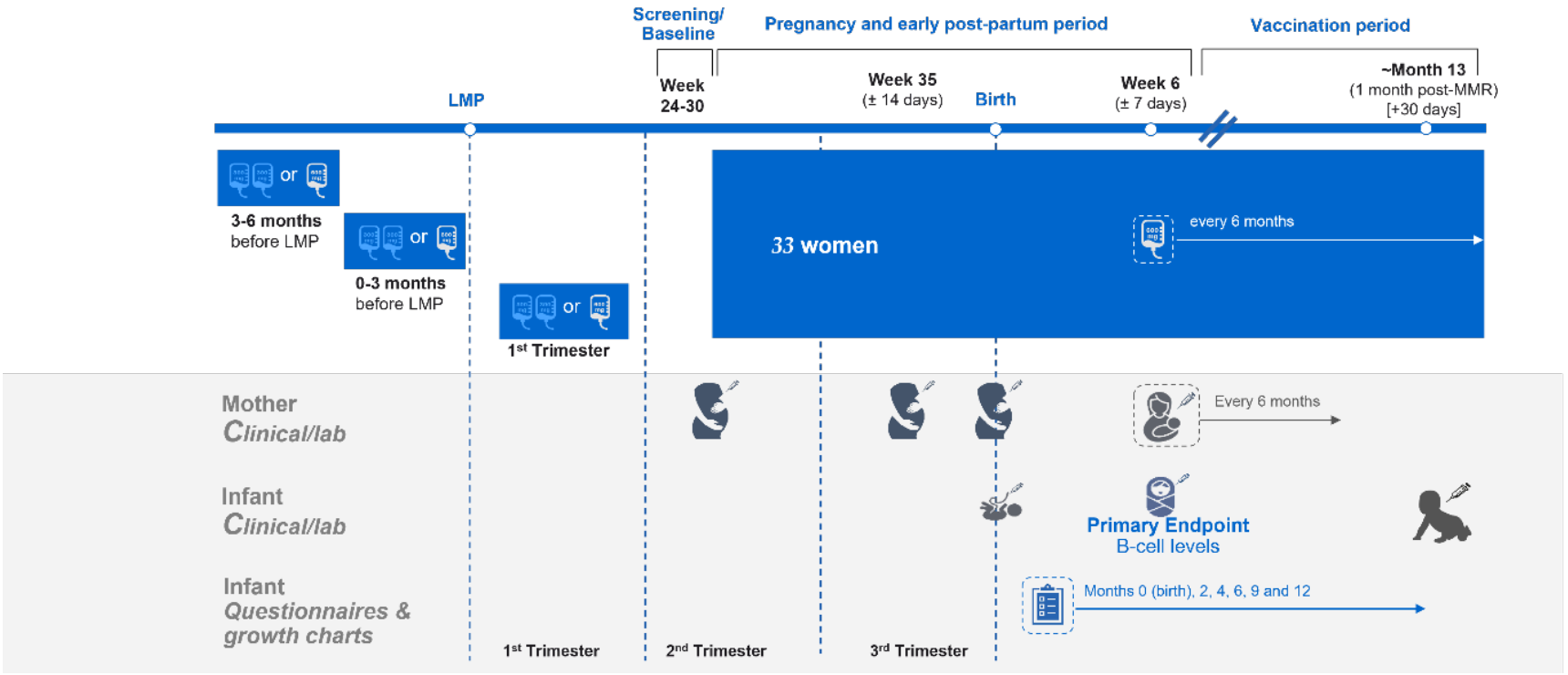
- Screening/baseline period (between gestational Week 24 and 30)
- Pregnancy and early postpartum period (up to Week 6 of life)

- Vaccination period (after Week 6 of life and up to 1 month [+30 days] after the first or second dose of the measles, mumps, and rubella [MMR] vaccine, or Month 13 of age [+30 days] if MMR vaccine is not planned to be administered)
- Follow-up visit after early discontinuation

### 3.1.1 Overview of Study Design

Figure 1 presents an overview of the study design. A Schedule of Assessments is provided in Appendix 1.

## Figure 1 Overview of Study Design




LMP = last menstrual period; MMR = measles, mumps, and rubella.

**Study description:** In this prospective, multicenter, open-label study, women with CIS or MS (in line with the locally approved indications) receiving commercial ocrelizumab up to 6 months before the LMP or during the first trimester of pregnancy will enter a screening/baseline period between gestational Weeks 24 and 30. Women fulfilling the selection criteria with accidental ocrelizumab exposure or in whom a decision to treat with ocrelizumab was taken as part of routine clinical practice, will be enrolled; *some* of the women should have potential fetal exposure (i.e., received their last dose of ocrelizumab < 3 months before the LMP or during the first trimester [up to gestational Week 13]). The baseline visit will be combined with the screening visit. To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. In the pregnancy and early postpartum period (up to Week 6 of life), laboratory, and clinical assessments will be performed during the third trimester (gestational Week 35 [± 14 days]), whenever possible in

accordance with planned prenatal care visits (samples at this visit may be collected by home nurse visit). To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. At delivery, blood samples from the mother and from the umbilical cord will be collected. An infant blood sample for measurement of B-cell levels (primary endpoint) will be collected at Week 6 of life (±7 days); or equivalent for preterm infants, i.e., gestational week at birth <37 weeks) during a site visit or by home nurse visit. Treatment with commercial ocrelizumab may be resumed at any time after birth for women who decide not to breastfeed. Some women may decide to resume treatment with ocrelizumab whilst breastfeeding; for those women, treatment with ocrelizumab should be restarted after collection of the infant blood sample at Week 6 of life (±7 days) if possible; but the decision is left to the discretion of the woman and the investigator. If the woman switches to another DMT postpartum, the infant blood sample at Week 6 of life (±7 days) will only be collected if the woman is not breastfeeding. In the vaccination period (after Week 6 of life [±7 days] and up to 1 month (+30 days) after the first/second dose of MMR vaccine, or Month 13 of age [+30 days] if the MMR vaccine is not planned to be administered), infants will receive vaccinations according to the local immunization schedule.

Antibody immune response(s) to common childhood vaccinations with full or partial doses given prior to 1 year will be measured 1 month (+30 days) after the first dose of MMR vaccine (if first dose is administered at 11 months of age or later) or 1 month (+30 days) after second dose of MMR vaccine (if first dose is administered before 11 months of age) or at Month 13 of chronological age (+30 days) in case MMR vaccine is not planned to be administered; and infants will be followed up for growth and developmental milestones up to 12 months of age using appropriate growth charts, absolute values, and the ASQ-3 questionnaire; other standard measurements recorded by e.g., the pediatrician as part of routine postnatal care may also be used. Postnatal timings of ocrelizumab infusions every 6 months and laboratory/clinical assessments in the mother may occur at different time points than infant assessments. A structured telephone interview will be conducted postpartum every 3 months (in-between ocrelizumab infusions), except in weeks in which an on-site visit is scheduled, for a general review, and to identify and collect information on any changes in the woman's or infant's health status (including the occurrence of MS relapses in the woman and use of new concomitant medications) and possible adverse events in both the woman and the infant (particularly infections); women will also be asked if the ASQ-3 form is being filled out. Women who decide to discontinue the study, or discontinue their infant's participation in the study, will be invited to attend an early study discontinuation visit as soon as possible (this visit may be conducted virtually or by telephone).

### 3.1.2 Screening/Baseline Period

After providing written informed consent, women will enter a screening period between gestational Weeks 24 and 30, after the morphological scan (usually done at gestational Week 18–20). Women fulfilling the inclusion/exclusion criteria with accidental ocrelizumab exposure, or in whom a decision to treat with ocrelizumab was taken as part of routine clinical practice, will be enrolled. *Some* of the*se* women should have potential fetal exposure (i.e., have received their last dose of ocrelizumab $<3$ months before the LMP or during the first trimester [up to gestational Week 13]). Exposure to ocrelizumab includes administration of an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days in women initiating treatment with ocrelizumab, or a single 600 mg infusion (in 500 mL 0.9%sodium chloride) in women already on treatment with ocrelizumab. The baseline visit will be combined with the screening visit. To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. The scheduled obstetric blood glucose test should preferably be conducted at the screening/baseline visit rather than at a separate visit.

### 3.1.3 Pregnancy and Early Postpartum Period

**Mother:**

- Pregnancy period: Laboratory and clinical assessments during the third trimester (gestational Week 35 [$\pm$14 days]) will be performed in accordance with planned prenatal care visits, whenever possible. To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. *All* visit samples may be collected by home nurse visit. Women may be given vaccines (e.g., for *Bordetella pertussis*) as part of routine obstetric care (note: live or live-attenuated vaccines are not recommended during ocrelizumab treatment and until B-cells return to normal level). Ocrelizumab must not be administered after the woman is enrolled in the study and until the infant's birth. Should this happen, the woman will be discontinued from the study.
- Early postpartum period: A blood sample will be collected from the mother within 24 hours after delivery for assessment of serum ocrelizumab concentration. Treatment with commercial ocrelizumab may be resumed at any time after birth for women who decide not to breastfeed. Some women may decide to resume treatment with ocrelizumab whilst breastfeeding. For those women, treatment with ocrelizumab should be restarted after collection of the infant blood sample at Week 6 of life ($\pm$7 days) if possible, but the decision is left to the discretion of the woman and the investigator. If the woman switches to another DMT postpartum, the infant blood sample at Week 6 of life ($\pm$7 days) will only be collected if the woman is not breastfeeding.

**Infant:**

At birth, a blood sample will be collected from the umbilical cord (only for live births; no collection should occur in the event of a pregnancy interruption [i.e., therapeutic abortion

or stillbirth]). The target time frame for collection will be within 1 hour after delivery; the actual time of collection after delivery will be recorded. At Week 6 (±7 days) of the infant's life, a blood sample will be collected from the infant (at an on-site visit, or by home nurse visit) for measurement of B-cell levels (the primary endpoint). For preterm infants, blood samples will be collected at the week of life equivalent to term infants (e.g., if birth occurred at gestational Week 35, blood sample would be collected at Week 8 of life).

*Note:* If the infant's B-cell levels are found to be below lower limit of normal (LLN), repeat analyses may be done at unscheduled visits at the discretion of the investigator (in consultation with the Sponsor).

### 3.1.4 Vaccination Period

Both the mother and the infant will enter an extension phase, which will continue approximately until the infant reaches 13 months of age. This is designed to evaluate whether infants potentially exposed to ocrelizumab during pregnancy are able to mount humoral immune responses to clinically relevant vaccines.

Infant laboratory assessments will be performed 1 month (+30 days) after the first dose of MMR vaccine (if first dose is administered at 11 months of age or later) or 1 month (+30 days) after second dose of MMR vaccine (if first dose is administered before 11 months of age), or at Month 13 of chronological age (+30 days), if MMR vaccine is not planned to be administered (as per local clinical practice, vaccinations may include diphtheria, tetanus, pertussis, Hemophilus influenzae type b [Hib], 13-valent pneumococcal conjugate vaccine [PCV-13], hepatitis B virus [HBV], and MMR). Additionally, infants will continue to be followed up for growth (age-adjusted body length, weight and head circumference) and developmental milestones up to 12 months of age. Growth charts following the World Health Organization (WHO) Child Growth Standards (WHO 2022), absolute values and the Ages and Stages Questionnaire, version 3 (ASQ-3) will be used; other standard measurements recorded by e.g., the pediatrician as part of routine postnatal care may also be used. The time windows for infant growth velocity and child developmental milestone assessments are given in Appendix 6. Post-natal timings of ocrelizumab infusions every 6 months and laboratory/clinical assessments in the mother may occur at different time points than infant assessments. In case the mother decides to switch to another DMT or to stop DMT after birth, no laboratory/clinical assessments will be performed for the mother. However, the infant blood sample 1 month (+30 days) after the first or second dose of MMR vaccine (or at Month 13 of age [+30 days]) will still be collected.

A structured telephone interview will be conducted by site personnel postpartum every 3 months (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's or infant's health status (including the occurrence of MS relapses in the woman and use of new concomitant medications) and possible adverse events in both the woman and the infant (particularly infections);

women will also be asked if the ASQ-3 form is being filled out. No telephone contact is needed in weeks where the woman is performing on-site visits.

### 3.1.5 Follow-Up Visit after Early Discontinuation

Women who decide to discontinue the study (this includes discontinuation of the mother, or discontinuation of the infant by the mother, or discontinuation at the investigator's discretion) are invited to attend an early study discontinuation visit (which may be conducted virtually or by telephone) as soon as possible. Depending on the timing of discontinuation, the following is recommended:

- **Discontinuation before birth:** Collection of pregnancy outcome and infant outcomes in the first year of life as per standard pharmacovigilance procedures.
- **Discontinuation after birth and before Week 6 of life of the infant:**
  - Collection of pregnancy outcome and infant outcomes in the first year of life as per standard pharmacovigilance procedures.
  - If the mother decides to stop participating at Week 6 of life (±7 days), attempts to collect the infant sample at Week 6 of life (±7 days) should be made before discontinuation.
  - If the mother switches to another DMT and is breastfeeding, the infant sample at Week 6 of life (±7 days) should not be collected.
- **Discontinuation after Week 6 of life of the infant:** Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures.

Further information is available in Appendix 1.

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date of the last assessment (vaccine response titers measured 1 month [+30 days] after the first or second dose of MMR vaccine, or at Month 13 of age (+30 days) if MMR is not planned to be administered for the last infant.

The total length of the study, from screening of the first woman to the end of the study, is expected to be approximately *33* months. This includes an enrollment period of approximately *16* months and subject participation period of approximately 17 months.

## 3.3 RATIONALE FOR STUDY DESIGN

This is a prospective, multicenter, open-label study evaluating placental transfer of ocrelizumab in women with CIS or MS receiving ocrelizumab up to 6 months before the LMP or during the first trimester of pregnancy (up to gestational Week 13).

Ocrelizumab targets CD19+ B-cells, and a rapid depletion of CD19+ B-cells in blood is the expected pharmacologic effect of ocrelizumab treatment. This occurs even at low doses (Food and Drug Administration [FDA] 2017), and is a biomarker for the pharmacodynamic effect of ocrelizumab. Therefore, CD19+ B-cell levels will be

measured as the primary endpoint, to evaluate the pharmacodynamic effect in infants following potential *in utero* exposure to ocrelizumab via the placenta. B-cell levels will be measured at 6 weeks of life (±7 days) rather than in the initial postpartum weeks because B-cell counts have been shown to be very low in the first few days of life of healthy neonates (Duchamp et al. 2014). Relative to total lymphocytes, B-cells also show a slightly delayed significant increase from the cord blood to the neonatal period and to the months 1 to 5 of life (Blanco et al. 2018), but ultimately most infants are reported to have B-cell levels above the LLN at a median age of 1.9 months (age range: 1–6 months; Duchamp et al. 2014). For any preterm births in our cohort, the sampling points will be adjusted using the corrected age (i.e., adding the difference between the full-term age of 37 weeks and the gestational age at birth). This approach is justified by data from a study of lymphocyte subsets in 338 term and preterm infants, where B-cell numbers increased at an approximately constant rate starting from gestational Week 22 (Amatuni et al. 2019).

In addition, serum concentrations of ocrelizumab will be measured in the umbilical cord blood at birth and in the infant at Week 6 of life (±7 days), to evaluate the infant's potential exposure to ocrelizumab via placental transfer.

A Phase IIIb study examining the effect of ocrelizumab treatment on the humoral responses in RMS patients found that patients who received ocrelizumab and were peripherally B-cell depleted were nevertheless able to mount humoral responses (though attenuated) to clinically relevant vaccines (tetanus toxoid, 23-valent pneumococcal polysaccharide vaccine, and influenza; Bar-Or et al. 2020). Vaccine-induced antibody titers will similarly be measured in this study to check whether infants potentially exposed to ocrelizumab during pregnancy can mount a protective immune response to clinically relevant vaccines.

Of note, the study will not be powered to investigate the effect of ocrelizumab on pregnancy/neonatal outcomes, however these will be captured as part of standard pharmacovigilance procedures. Additionally, infant health and development outcomes will be assessed using growth charts according to the WHO Child Growth Standards (WHO 2022; as well as using absolute values) and the ASQ-3, a widely accepted tool for measuring development in young children (Lipkin et al. 2020; American Association of Pediatrics Policy Statement, 2006). Other standard measurements recorded by e.g., the pediatrician as part of routine postnatal care may also be used.

Disease activity will be measured in women with MS using the standard assessments of Expanded Disability Status Scale (EDSS) and number of MS relapses, which are commonly used in clinical trials to assess treatment efficacy and disease progression. Serum neurofilament light chain (sNfL), a marker of neuroaxonal injury, will be measured during pregnancy, at delivery and the postpartum period to explore its utility as a surrogate for disease activity in this population. Several studies have demonstrated that sNfL is a sensitive and clinically meaningful blood biomarker to monitor tissue damage

and the effects of therapies in MS (Barro et al. 2018; Disanto et al. 2017), most recently also in pregnant women interrupting treatment for pregnancy (Yaldizli et al. 2020).

### 3.3.1 Rationale for Ocrelizumab Dose and Schedule

The dosing schedule of ocrelizumab during the postpartum period is at the discretion of the treating physicians, in accordance with local clinical practice and local labelling.

### 3.3.2 Rationale for Patient Population

As the aim of this study is to evaluate placental transfer of ocrelizumab and the corresponding pharmacodynamic effects, it will be conducted in women with CIS or MS (in line with the locally approved indications) aged 18–40 years who received ocrelizumab any time up to 6 months before the LMP or during the first trimester of pregnancy (up to gestational Week 13).

Based on the average terminal half-life of 26 days (Ocrelizumab USPI), ocrelizumab is expected to be eliminated from the body by approximately 4.5 months, with the longest terminal half-life recorded as 53 days in one woman. Considering the interpatient variability and the fact that ocrelizumab, as a fully humanized IgG1, is not expected to cross the placenta in the first trimester (Palmeira et al. 2012; Simister 2003), it is assumed that a potential fetal exposure is unlikely in women whose last ocrelizumab infusion was earlier than 3 months before conception. Therefore, women who received ocrelizumab 3–6 months before conception will represent the non-exposed group. Women who received ocrelizumab up to 3 months before conception or during the first trimester of pregnancy will represent groups with potential fetal exposure. Women who received ocrelizumab after the first trimester will be excluded since placental transfer of IgG is known to be significant after the first trimester (Palmeira et al. 2012; Simister 2003).

The maximum age is set at 40 years since only a minority of pregnancies occur after this age (e.g., only around 3% of births of first children in the EU in 2017 were to women aged 40 and over [Eurostat 2019] and in the United States, the birth rate in 2018 was the lowest for the 40-44 age group [CDC2019]). Additionally, advanced maternal age is associated with higher rates of maternal and fetal complications (Bouzaglou et al. 2020). Fetal complications, if they occur, may prevent the collection of the required sample or confound the interpretation of B-cell levels in the infants (the primary endpoint of the study).

To further minimize the impact of confounding factors on the primary endpoint being measured at Week 6 of life (±7 days), women with aneuploid or genetic disorders known to cause congenital malformations are excluded (women will be required to have a documented obstetric ultrasound from the first and second trimester). Similarly, women with other risk factors for adverse pregnancy outcomes which would limit the ability to collect B-cell levels in the infants (e.g., spontaneous abortion after the first trimester and history of stillbirth) are also excluded.

Women with current (positive hepatitis B surface antigen [HBsAg] results) or previous (positive hepatitis B core antibody [HBcAb] titers) hepatitis B infection are also excluded, as most guidelines recommend that patients treated with anti-CD20 therapies who have chronic hepatitis B should receive prophylactic treatment with appropriate antiviral drugs (EASL 2017; Terrault et al. 2018). Some of these drugs (e.g., entecavir) have been shown to have carcinogenic potential in animal studies (Aslam et al. 2018), and the general recommendation is that women who are or plan to become pregnant delay or stop treatment with prophylactic agents (EASL 2017; Terrault et al. 2018).

# 4. MATERIALS AND METHODS

## 4.1 STUDY PARTICIPANTS

This study will enroll approximately $33$ pregnant women with CIS or MS (in line with the locally approved indications).

### 4.1.1 Inclusion Criteria

Women must meet the following criteria for study entry:

- An Informed Consent Form (ICF) for participation of the maternal subject and her unborn (for collection of blood samples, infant demographics and adverse event data) is signed and dated by the subject. Where applicable, the written ICF with respect to the infant is also signed and dated by the holder of parental rights as designated by the maternal subject.
- Able and willing to comply with the study protocol, in the Investigator's judgment.
- Age 18–40 years, inclusive, at screening.
- Have a diagnosis of MS or CIS (in line with the locally approved indications).
- Currently pregnant with singleton pregnancy at gestational Week $\leq$30 at enrollment.

  *Note:* Gestational age will be determined by LMP and first trimester ultrasound so long as there is less than 1 week's difference in the projected due date. If there is over 1 week's difference, then the ultrasound alone will be used. For cases where the LMP is not known, then the earliest ultrasound will be used. For cases of in vitro fertilization (IVF), the projected dates from the IVF procedure will be preferentially used.
- Documentation that first (12-week) and second (18–20-week) obstetric ultrasound (prenatal screening) has been conducted before enrollment.
- Documentation that the last exposure to ocrelizumab occurred up to 6 months before the LMP before the woman became pregnant OR during the first trimester of pregnancy (up to gestational Week 13 inclusive).

  *Note:* Exposure to ocrelizumab includes administration of an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days for women initiating treatment with ocrelizumab, or a single 600 mg infusion (in 500 mL 0.9% sodium chloride) for women already on treatment with ocrelizumab.

### 4.1.2 Exclusion Criteria

Women who meet any of the following criteria will be excluded from study entry:

- Last exposure to ocrelizumab > 6 months before the woman's LMP or later than the first trimester of pregnancy (i.e., after gestational Week 13).
- Gestational age at enrollment > 30 weeks.
- Non-singleton pregnancy.
- Received the last dose of ocrelizumab at a different posology other than per the local prescribing information.
- Social circumstances (e.g., home relocation), that may preclude a woman from participating in the study.

#### Exclusions Related to Obstetric and Gynecological Health

- Lack of access to ultrasound prenatal care as part of standard clinical practice.
- Women in whom aneuploid disorders or genetic disorders that cause major congenital malformations have been detected during first trimester prenatal screening (e.g., ultrasound, amniocentesis, genetic testing, nuchal translucency screening, chorionic villus sampling), or in whom any fetal anomalies (i.e., fetal biometry, fetal anatomy) have been detected during the morphology scan at around or before gestational Week 18–20.
- Documented history of disorders associated with adverse pregnancy outcomes, including but not limited to, the following:
  - History of preterm birth (gestational age < 37 weeks) for any indication with or without fetal malformations.
  - History of spontaneous abortion (miscarriage) after the first trimester (i.e., after gestational Week 13).
  - History of stillbirth (defined as fetal loss at gestational age > 22 weeks).
  - History of pre-eclampsia/eclampsia.
  - History of a cervical pathology or intervention which may increase the risk of cervical incompetence (e.g., history of cervical cerclage, prior cervical conization or prior loop electrosurgical excision procedure [LEEP]).
- Prior or current history of any other gynecological or obstetric disease considered by the investigator to be associated with a high risk of adverse pregnancy outcomes in the current pregnancy.

#### Exclusions Related to General Health

- Lack of peripheral venous access.
- Pre-pregnancy body mass index (BMI) > 35 kg/$m^2$.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study.

- Prior or current history of primary or secondary immunodeficiency, or woman in an otherwise severely immunocompromised state. The woman may be re-screened and included if condition resolves.
- Significant and uncontrolled disease, such as cardiovascular (including cardiac arrhythmia and hypertension), pulmonary (including obstructive pulmonary disease), neurological, psychiatric (e.g., psychosis), renal, hepatic, endocrine (e.g., diabetes, thyroid disorders), or gastrointestinal or any other significant disease that may preclude a woman from participating in the study.
- Women with known active malignancies or being actively monitored for recurrence of malignancy including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin). Women with in situ carcinoma of the cervix of the uterus, even if excised and resolved with documented clean margins on pathology, are excluded from the study.
- Prior or current history of alcohol or drug abuse, or current use of tobacco.

## Exclusions Related to Laboratory Findings

- Any abnormal screening laboratory value that is clinically relevant will be retested only once in order to rule out any progressive or uncontrolled underlying condition. The last value before study entry must meet study criteria.
- Women with positive screening tests for hepatitis B, determined by a positive HBsAg result (current infection) or positive HBcAb titers (previous infection) will be excluded. Women with documented history of HBV vaccination or positive hepatitis B surface antibody (HBsAb) titers are eligible.

Note: based on local Ethics Committees (ECs) or National Competent Authority requirements, additional local diagnostic testing may be required for selected women or selected centers to exclude tuberculosis, Lyme disease, human T-lymphotropic virus 1 associated myelopathy (HAM), human immunodeficiency virus (HIV), hepatitis C virus infection (HCV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the investigator.

## Exclusions Related to Medications

### *Absolute Exclusions*

- Drugs known to have teratogenic effects including but not limited to certain anticonvulsants (even if used for pain management), antibiotics such as tetracyclines or fluoroquinolones. A more detailed, though not exclusive, list can be found in Appendix 2.
- Planned treatment with interferons, glatiramer acetate, or pulsed corticosteroids as a bridging therapy after the last ocrelizumab dose before enrollment and throughout pregnancy.

***Relative Exclusions*** *(according to medication washout period)*

- Treatment with one of the following agents prior to the last ocrelizumab dose or prior to the LMP, whichever occurred first:
  - Treatment with siponimod or ponesimod within 10 days
  - Treatment with mycophenolate within 6 weeks
  - Treatment with fingolimod within 2 months
  - Treatment with ozanimod within 3 months
  - Treatment with alemtuzumab within 4 months
  - Treatment with mitoxantrone, methotrexate, ofatumumab or cladribine within 6 months
  - Treatment with cyclophosphamide *or rituximab* within 12 months
- Treatment with natalizumab within 12 weeks prior to the LMP
- Treatment with teriflunomide within the last two years, unless measured plasma concentrations are less than 0.02 mg/L. If levels are above 0.02 mg/l or not known, an accelerated elimination procedure will be implemented before screening visit. One of the following elimination procedures can be used:
  - Cholestyramine 8 g administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated.
  - Alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days.
- Treatment with any investigational agent within 6 months or five half-lives of the investigational drug (whichever is longer) prior to the last ocrelizumab dose or prior to the LMP, whichever occurred first.

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study; therefore, no randomization or blinding is planned.

## 4.3 STUDY TREATMENT RELEVANT TO THE STUDY DESIGN

The study treatment is commercial ocrelizumab.

### 4.3.1 Study Treatment Formulation and Packaging

Information on formulation and packaging are available in the labeling (e.g., USPI [for United States] and SmPC [for EU]).

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labelling (USPI; SmPC). No measures of treatment compliance are planned.

#### 4.3.2.1 Study Treatment

Ocrelizumab must not be administered post-baseline and until the infant's birth. Treatment with commercial ocrelizumab may be resumed at any time after birth for women who decide not to breastfeed. Some women may decide to resume treatment with ocrelizumab whilst breastfeeding. For those women, treatment with ocrelizumab should be restarted after collection of the infant blood sample at Week 6 of life (±7 days) if possible, but the decision is left to the discretion of the woman and the investigator. If the woman switches to another DMT postpartum, the infant blood sample at Week 6 of life (±7 days) will only be collected if the woman is not breastfeeding.

#### 4.3.2.2 Premedication

According to the label, 100 mg IV methylprednisolone (or an equivalent) and an antihistamine must be administered prior to administration of each ocrelizumab infusion to reduce the frequency and severity of infusion-related reactions (IRRs). Premedication with an antipyretic (e.g., paracetamol) may also be considered prior to each ocrelizumab infusion.

### 4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to the study treatment. All such medications taken within 6 weeks prior to the screening/baseline visit and throughout the study should be reported to the investigator and recorded on the Concomitant Medications electronic case report form (eCRF). Folic acid (recommended daily intake 400 micrograms per day, or as per local practice) prescribed and administered up to the first trimester of pregnancy (up to gestational Week 13) will be documented.

#### 4.4.1 Prohibited Therapy

Drugs known to have teratogenic effects including but not limited to anticonvulsants (even if used for pain management), antibiotics such as tetracyclines or fluoroquinolones are not permitted. A more detailed, though not exclusive, list can be found in Appendix 2.

Planned treatment with interferons, glatiramer acetate or pulsed corticosteroids as a bridging therapy are not permitted after the last ocrelizumab dose before enrollment and throughout pregnancy.

No formal drug-drug interaction studies have been conducted with ocrelizumab, as no drug-drug interactions are expected via the cytochromes P450, other metabolizing enzymes or transporters.

Ocrelizumab is a monotherapy and has not been studied in combination with other DMTs. As with other immunomodulatory therapies, exercise caution when initiating ocrelizumab after an immunosuppressive therapy, and when initiating another therapy

after ocrelizumab, taking into consideration the potential for overlapping pharmacodynamic effects.

More information is available in Section 4.1.2 and the ocrelizumab labeling (SmPC; USPI).

## 4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each mother and infant.

### 4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). ICFs for enrolled women and her unborn and for women who are not subsequently enrolled will be maintained at the study site. Where applicable, the written ICF with respect to the infant is also signed and dated by the holder of parental rights as designated by the maternal subject.

All screening evaluations must be completed and reviewed to confirm that women meet the eligibility criteria before enrollment. The investigator will maintain a detailed record of all participants screened and document eligibility or record reasons for screening failure, as applicable. Reasons for screening failure will also be captured by the sites in the eCRF.

### 4.5.2 Mother's Assessments

#### 4.5.2.1 Demographics, Medical and MS History

Women's demographics (age, self-reported ethnicity and education level) and relevant medical history, including clinically significant diseases, surgeries/procedures, smoking history and alcohol intake, will be recorded during the screening period. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the woman within 6 weeks prior to screening/baseline and throughout the study will be recorded.

Obstetric and Gynecological History:

- Date of LMP, documentation of obstetric ultrasounds (prenatal screening), gestational age at enrollment

  *Note:* Gestational age will be determined by LMP and first trimester ultrasound so long as there is less than 1 week's difference in the projected due date. If there is over 1 week's difference, then the ultrasound alone will be used. For cases where the LMP is not known, then the earliest ultrasound will be used. For cases of IVF, the projected dates from the IVF procedure will be preferentially used.
- History of previous pregnancies (number, outcome, date), and clinically significant gynecological diseases

MS Disease History:

- Date of MS symptom onset and MS diagnosis
- Disease status (as available): EDSS and number of relapses up to 1 year before LMP
- History of previous DMTs: number of DMTs ever used, last DMT before ocrelizumab
- Treatment history with ocrelizumab: including start of therapy, date and dose of last infusion prior to enrollment

#### 4.5.2.2 Physical and Obstetric Examinations

A complete physical examination in women should include measurement of height and weight, an evaluation of head, eye, ear, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems, as well as vital signs (see following section). To reduce the burden of visits on the mothers, results from physical examinations done as part of routine care may be used. The following assessments will also be conducted: neurological examination (see Section 4.5.2.4), relapse description, and EDSS (see Section 4.5.2.6). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF. Height will be measured at screening only.

An obstetric examination will be performed as per local clinical practice, at visits indicated in Appendix 1 (Schedule of Assessments). To reduce the burden of visits on the mothers, results from obstetric examinations done as part of routine care may be used.

See Appendix 1 (Schedule of Assessments) for the timing of all assessments.

#### 4.5.2.3 Vital Signs

Vital signs may be measured, in particular throughout the infusion procedure as per the Label and may include measurements of heart rate, systolic and diastolic blood pressures, and temperature. If those measurements are performed as per clinical practice and are available, record any abnormalities observed on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event section of the eCRF (as presented in Section 5.1.2).

#### 4.5.2.4 Neurological Examination

A neurological examination will be performed at every planned visit and at unscheduled visit if applicable. To reduce the burden of visits on the mothers, results from neurological examinations done as part of routine care may be used. For women referred to the investigator, results from routine visits at the woman's neurologist may be

used. In the presence of newly identified or worsening neurological symptoms at any given time in the study, a neurological evaluation should be scheduled promptly.

As infection is a potentially serious complication of B-cell-depleting therapy, investigators will also screen women for signs and symptoms of any CNS infections, and specifically progressive multifocal leukoencephalopathy (PML), by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Women with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A woman with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (SAE; with all available information) with immediate notification of the Medical Monitor. Refer to Appendix 3 for guidance for diagnosis of PML.

#### 4.5.2.5 Assessment of Relapses

Potential relapses should be recorded throughout the study period after screening. See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

All new or worsening neurological events consistent with MS representing a “clinical relapse” are to be reported on the dedicated “MS relapse” form. A clinical relapse is defined as a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or sub-acutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection (Thompson et al. 2018). Multiple sclerosis relapses should not be reported as an AE, unless they are serious.

It is recommended that women with new neurological symptoms suggestive of a relapse have an EDSS/Functional Systems Scores (FSS) assessment performed as soon as possible, ideally within 7 days of the onset of symptoms. However, it is not mandatory to perform an EDSS assessment in case of a suspected relapse.

#### 4.5.2.6 Assessment of Disability

Disability in MS will be measured by the EDSS. See Appendix 1 (Schedule of Assessments) for the timing of assessments.

The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental], plus “other”) rated and scored as FSSs. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death) (see Appendix 4). *The EDSS*

*assessment may also be performed by the investigator via telephone, using a specific licensed questionnaire (see Appendix A4–2).*

#### 4.5.2.7 Laboratory, Biomarker, and Other Biological Samples

Routine laboratory assessments (performed in the central laboratory, except for urinalysis) are listed in the following sections. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. For details, refer to Schedule of Assessments, Appendix 1.

**At Screening/Baseline (Gestational Weeks 24–30)**

- **Hematology** (hemoglobin, hematocrit, quantitative platelet count, RBC count, WBC count, absolute or/and differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).
- **Serum chemistries** (AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin, creatinine, random glucose, potassium, sodium, chloride). The scheduled obstetric blood glucose test should preferably be conducted at the screening/baseline visit (Week 24–30) rather than at a separate visit.
- **Urinalysis:** using urine dipstick at site (may include pH, specific gravity, glucose, protein, ketones, blood), and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) at the discretion of the investigator.
- **Hepatitis B virus serology:** Women with positive screening tests for HBV, determined by a positive HBsAg result (current infection) or positive HBcAb titers (previous infection) will be excluded. Women with documented history of HBV vaccination or positive HBsAb titers are eligible.
- **Lymphocyte subtypes:** Blood samples will be collected to measure B-cell counts (CD19+ *and B-cell subsets [Table 2]),* T-cell counts (CD3+, CD4+, CD8+*), and natural killer (NK) cell counts (CD16+CD56+).*
- **Serum immunoglobulin concentration.**
- **Ocrelizumab concentration:** serum samples will be collected for determination of ocrelizumab concentration.
- **sNfL:** samples will be collected for determination of sNfL.

**During Third Trimester (Gestational Week 35±14 days)**

*Note:* Samples may be collected by home nurse visit.

- **Hematology** (hemoglobin, hematocrit, quantitative platelet count, RBC count, WBC count, absolute or/and differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).
- **Serum chemistries** (AST, ALT, GGT, total bilirubin, creatinine, random glucose, potassium, sodium, chloride).
- **Urinalysis**: using urine dipstick at site (may include pH, specific gravity, glucose, protein, ketones, and blood), and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) at the discretion of the investigator.

- **Lymphocyte subtypes**: Blood samples will be collected to measure B-cell counts (CD19+ *and B-cell subsets [Table 2]),* T-cell counts (CD3+, CD4+, CD8+*), and NK cell counts (CD16+CD56+).*
- **Serum antibody (IgG) titers to immunizations:** for measles, mumps, rubella, *tetanus*, diphtheria, pertussis, varicella zoster, Streptococcus pneumoniae, HBV and SARS-CoV-2 (along with nucleocapsid and spike protein titers; only for those mothers who have received the vaccine, as per local clinical practice) will be performed. Any vaccinations received by mothers during the study will be recorded as concomitant medications.
- **Ocrelizumab concentration:** serum samples will be collected for determination of ocrelizumab concentration.
- **Serum immunoglobulin concentration.**
- **sNfL:** samples will be collected for determination of sNfL.

**At Delivery (within 24 hours after delivery, only for live births)**

- **Ocrelizumab concentration:** serum samples will be collected for determination of ocrelizumab concentration.
- **Serum immunoglobulin concentration.**
- **sNfL:** samples will be collected for determination of sNfL.

**During the Vaccination Period (at Infusion 1 and Infusion 2)**

- **Hematology** (hemoglobin, hematocrit, quantitative platelet count, RBC count, WBC count, absolute or/and differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).
- **Serum chemistries** (AST, ALT, GGT, total bilirubin, creatinine, random glucose, potassium, sodium, chloride).
- **Urinalysis:** using urine dipstick at site (may include pH, specific gravity, glucose, protein, ketones, and blood), and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) at the discretion of the investigator.
- **Lymphocyte subtypes:** Blood samples will be collected to measure B-cell counts (CD19+ *and B-cell subsets [Table 2]),* T-cell counts (CD3 +, CD4 +, CD8+*), and NK cell counts (CD16+CD56+).* Samples will be collected prior to the ocrelizumab infusion.
- **Ocrelizumab concentration:** serum samples will be collected (before ocrelizumab administration) for determination of ocrelizumab concentration
- **Serum immunoglobulin concentration**
- **sNfL:** On the day of the infusion, samples should be collected 5–30 minutes prior to the methylprednisolone infusion as it has been shown to reduce antibody reactivity (Quintana et al. 2012).
- Any vaccinations received by mothers during the study will be recorded as concomitant medications.

*The B-cell subsets that will be analyzed are described in the table below.*

***Table 2 B-Cell Subsets***

- *Naive B-cells: CD45+, CD19+, IgD+, CD27−, CD38dim/−*
- *Memory B-cells: CD45+, CD19+, CD27+*
- *Unswitched memory B-cells: CD45+, CD19+, IgD+, CD27+*
- *Switched memory B-cells: CD45+, CD19+, IgD−, CD27+*
- *Double-negative B-cells: CD45+, CD19+, IgD−, CD27−*
- *IgD transitional B-cells: CD45+, CD19+, IgD+, CD27−, CD38 $^{bright}$*
- *Plasmablasts or plasma cells: CD45+, CD19+, CD27+, CD38 $^{bright}$*

### 4.5.3 Infant's Assessments

#### 4.5.3.1 Pregnancy Outcome and Infant Characteristics

**At birth:**

- Pregnancy and infant outcome
- Mode of delivery (vaginal delivery, instrumental delivery, scheduled or urgent cesarean section)
- Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score (1 min, 5 min, 10 min)
- Gestational age at birth
- Infant vital biometrics (weight, length, head circumference)
- Congenital malformations

**Week 6 of Life (±7 days)**

- Weight measurement for safety
- Feeding status: Mothers should record feeding status of the infant, i.e., whether exclusive breastfeeding, mixed feeding (partial breastfeeding along with infant formula and/or baby food), exclusive infant formula feeding, or fully weaned
- Changes to concomitant medications given to the infant should be recorded throughout the study. For administered vaccinations, see Section 4.5.4.

**Months 2, 4, 6, 9, and 12:**

- Growth velocity (weight, length and head circumference), using growth charts according to the WHO Child Growth Standards (WHO 2022); as well as absolute values (other standard measurements recorded by e.g., the pediatrician as part of routine postnatal care may also be used).
- Child developmental milestones in the domains of communication, gross motor, fine motor, problem solving, and personal-social, using ASQ-3.
- Feeding status: Mothers should record feeding status of the infant, i.e., whether exclusive breastfeeding, mixed feeding (partial breastfeeding along with infant formula and/or baby food), exclusive infant formula feeding, or fully weaned.

- Changes to concomitant medications given to the infant should be recorded throughout the study. For administered vaccinations, see Section 4.5.4.

See Appendix 6 for time windows for infant growth velocity and child developmental milestone assessments.

**One month (+30 days) after first dose of MMR vaccine (if first dose is administered at 11 months of age or later) OR 1 month (+30 days) after second dose of MMR vaccine (if first dose is administered before 11 months of age) OR at Month 13 of chronological age (+30 days) if MMR vaccine is not planned to be administered**

- Weight measurement for safety
- Changes to concomitant medications given to the infant should be recorded and throughout the study. For administered vaccinations, see Section 4.5.4.

#### 4.5.3.2 Laboratory, Biomarker, and Other Biological Samples

**Umbilical cord blood assessments (target collection time within one hour of birth; only for live births; no collection should occur in the event of a pregnancy interruption [i.e., therapeutic abortion or stillbirth])**

- **Ocrelizumab concentration**: a serum sample will be collected for determination of ocrelizumab concentration

**Week 6 of Life (±7 days)**

- **Lymphocyte subtypes:** A blood sample will be collected to measure B-cell counts (CD19+), T-cell counts (CD3+, CD4+, CD8+), *and NK cell counts (CD16+CD56+).*
- **Ocrelizumab concentration:** a serum sample will be collected for determination of ocrelizumab concentration.

  ***Note:*** If the infant's B-cell levels are below LLN, repeat analyses may be done at unscheduled visits at the discretion of the investigator (in consultation with the Sponsor).

  Infant samples will be collected by venipuncture. As per the recommendation of the European Commission ad hoc group (2008) the total blood volume to be collected from an infant in a clinical study should not exceed 0.8–0.9 mL/kg at any time point, or 2.4 mL/kg over any 4-week period throughout the study. If the blood volume collected for an infant (as a result of these limits) is insufficient to carry out all planned assessments, Table 3 shows the order of priority for assessments.

**Table 3 Prioritization Order for Infant Blood Sample Assessments at Week 6 of Life (±7 days)**

| Order of Priority | Assessment |
|---|---|
| 1 | Any safety laboratory samples (scheduled or unscheduled and performed at the discretion of the Investigator) |
| 2 | Lymphocyte subtypes blood sample [a] |
| 3 | Serum ocrelizumab concentration |

*NK = natural killer.*

[a] Blood samples will be collected to measure B-cell counts (CD19+), T-cell counts (CD3+, CD4+, and CD8+), *and NK cell counts (CD16+CD56+).*

**One month (+30 days) after first dose of MMR vaccine (if first dose is administered at 11 months of age or later) OR 1 month (+30 days) after second dose of MMR vaccine (if first dose is administered before 11 months of age) OR at Month 13 of chronological age (+30 days) if MMR vaccine is not planned to be administered**

- Lymphocyte subtypes: A blood sample will be collected to measure B-cell counts (CD19+), T-cell counts (CD3+, CD4+, CD8+) *and NK cell counts (CD16+CD56+).*

  ***Note:*** If the infant's B-cell levels are below LLN, repeat analyses may be done at unscheduled visits at the discretion of the investigator (in consultation with the Sponsor).

- *Serum antibody titers to vaccines administered as per local practice (e.g., diphtheria, tetanus, pertussis, Hib, PCV-13, HBV, and MMR)*

  ***Note****: While vaccination schedules are not exactly the same from country to country, all participating countries are expected to provide the specific vaccines for the planned titer assessments*

  Infant samples will be collected by venipuncture. As per the recommendation of the European Commission ad hoc group (2008) the total blood volume to be collected from an infant in a clinical study should not exceed 0.8–0.9 mL/kg at any time point, or 2.4 mL/kg over any 4-week period throughout the study. If the blood volume collected for an infant (as a result of these limits) is insufficient to carry out all planned assessments, Table 4 shows the order of priority for assessments.

**Table 4 Prioritization Order for Infant Blood Sample Assessments 1 Month (+30 days) after First/Second Dose of MMR Vaccine OR at Month 13 of Age (+30 Days)**

| Order of Priority | Assessment |
|---|---|
| 1 | Any safety laboratory samples (scheduled or unscheduled and performed at the discretion of the Investigator) |
| 2 | Serum titers of antibody responses to vaccines [a] |
| 3 | Lymphocyte subtypes blood sample [b] |

*Ab = antibody; IgG = immunoglobulin G;* MMR=measles, mumps, and rubella*; NK = natural killer;* PCV-13=13-valent pneumococcal conjugate vaccine.

[a] Titers of responses to vaccines administered as per local practice *may include the following: anti-measles Ab IgG, anti-rubella Ab IgG, anti-mumps Ab IgG, PCV-13 Ab (all serotypes), anti-tetanus toxoid IgG, anti-diphtheria IgG, Bordetella pertussis Ab IgG, hepatitis B surface Ab, and Hemophilus influenzae B IgG.*

[b] Blood samples will be collected to measure B-cell counts (CD19+), T-cell counts (CD3+, CD4+, and CD8+), *and NK cell counts (CD16+CD56+).*

### 4.5.4 Infant Vaccination Schedule

Infants will receive vaccinations according to the immunization schedule recommended in each participating country. The safety and timing of vaccination of the infant should still be discussed with the mother, in particular the vaccination with live-attenuated vaccines (e.g., MMR) for which the results on B-cell levels at Week 6 of life may be informative. Vaccines administered from birth throughout the end of the study, should be recorded at Months 2, 4, 6, 9, and 12 as well as at 1 month (+30 days) after first or second MMR dose/Month 13 of age (+30 days) and may include *diphtheria, tetanus, pertussis*, Hib, PCV-13, HBV, and MMR.

## 4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Study Treatment Discontinuation

The decision to discontinue a woman from treatment lies with the treating physician, in agreement with the woman's wishes, and is not regulated by this protocol.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF page. In case the woman switches to another treatment for MS, the DMT should also be documented on the appropriate eCRF page.

### 4.6.2 Discontinuation from the Study

Women and their unborns/infants have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a woman from the study at any time. Women who decide to discontinue the study (this includes discontinuation of either the mother or the infant) are invited to attend an early study discontinuation visit (which may be conducted virtually or by telephone) as soon as possible (further details in Section 3.1.5).

Reasons for woman discontinuation from the study may include, but are not limited to, the following:

- Woman withdrawal of consent.
- Study termination or site closure.
- Adverse event.
- Loss to follow-up.
- Any medical condition that the investigator or Sponsor determines may jeopardize the safety of the woman, unborn or infant if he or she continues in the study.
- Woman's non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor.

Every effort should be made to obtain a reason for woman discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF (see Section 3.1.5). Women who withdraw from the study will not be replaced.

### 4.6.3 Study Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to women in the study.
- Enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

### 4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for GCP.
- No study activity (i.e., all women and their infants have completed the study and all obligations have been fulfilled).

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

### 5.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to ocrelizumab and any other treatments used as co-administered products (i.e., premedication), according to the label. For a list of products, see Section 4.3.

For safety reporting requirements for non-studied medicinal products, see Section 5.2.

Safety assessments will consist of monitoring and recording serious adverse events and non-serious adverse events (including adverse events of special interest), performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice.

#### 5.1.1.1 Adverse Events

According to the ICH, an adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event 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 5.
- 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., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

Adverse events and serious adverse events related to MS are not considered for recording in the eCRF, unless they meet specific criteria. For more details, refer to Section 5.1.1.2.

#### 5.1.1.2 Assessment of Serious Adverse Events and Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor) and Other Non-Serious Adverse Events

**Serious Adverse Events**

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event 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.
- Results in persistent or significant disability/incapacity (i.e., the adverse event 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).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Appendix 5); 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 adverse event recorded on the eCRF (for detailed instructions, see Appendix 5).

### Non-Serious Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for this study include the following:

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 5).
- Suspected transmission of an infectious agent by the study medicine, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.

#### A. Non-Serious Adverse Events other than Adverse Events of Special Interest

All non-serious adverse events (in addition to adverse events of special interest) must be collected for this study, and coded according to the appropriate level of Medical Dictionary for Regulatory Activities (MedDRA) classification.

***B. Specific Adverse Events that are exempt from collection***

Adverse events and serious adverse events related to MS are not considered for recording in the eCRF. Medical occurrences or symptoms of deterioration that are anticipated as part of MS or which are expected in the patient population studied should be recorded as an adverse event only if judged by the physician to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study.

Following the above rationale, the following events will not be considered as adverse events for this study:

1. MS relapses.
2. Disability progression (increase in EDSS or other scales performed by the physician).
3. MRI activity (new/enlarged T2 or T1 gadolinium-enhancing lesion in spinal or brain MRI), **unless** the activity is suggestive of a serious adverse event such as PML. In this case, information should be recorded in the section "PML" of the eCRF.
4. MS signs and symptoms.

Although these adverse events are not being actively solicited, the investigator/patients are reminded of the possibility to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to the Sponsor of the suspected medicinal product, or to the concerned competent authorities via the national spontaneous reporting system.

### 5.1.2 Methods and Timing for Capturing/Assessing Safety Parameters

The investigator is accountable for ensuring that all adverse events collected as per protocol (see Section 5.1.1 for definition) are recorded in the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.1.3.

For each adverse event recorded in the adverse event section of the eCRF, the investigator will make an assessment of seriousness (see Section 5.1.1.2), severity (see Appendix 5), and causality (see Appendix 5).

#### 5.1.2.1 Adverse Event Reporting Period

Investigator will seek information on adverse events at each patient contact. All adverse events subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and in the Adverse Event eCRF.

Adverse events will be reported throughout the study and until the last study visit for both mother and infant. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment. Adverse events that

occur in a pregnant woman pre- and post- study should be reported to the marketing authorization holder (MAH), as a follow up spontaneous pregnancy report to the initially spontaneously reported pregnancy, by following the standard pharmacovigilance reporting process for post-marketing pregnancy cases.

#### 5.1.2.2 Procedures for Recording Adverse Events

Investigator should use correct medical terminology/concepts when recording adverse events in the Adverse Event eCRF. Colloquialisms and abbreviations should be avoided.

Only one adverse event term should be recorded in the event field of the eCRF.

See Appendix 5 for further specific instructions regarding:

- IRRs
- Diagnosis versus signs and symptoms
- Adverse events occurring secondary to other adverse events
- Persistent or recurrent adverse events
- Abnormal laboratory values
- Abnormal vital sign values
- Abnormal liver function tests
- Deaths
  - All events with an outcome or consequence of death should be classified as serious adverse events and reported to the Sponsor immediately. In certain circumstances, however, suspected adverse reactions with fatal outcome may not be subject to expedited reporting (see Section 5.4). All deaths that occur during the protocol-specified adverse event reporting period, regardless of relationship to study medicine, must be recorded in the Adverse Event eCRF and immediately reported to the Sponsor.
- Worsening of pre-existing medical conditions
- Lack of therapeutic efficacy
- Hospitalization or prolonged hospitalization
- Overdoses, misuses, abuses, off-label use, occupational exposure, or medication error
- Quality defects, falsified medicinal products and product complaints
- Drug interactions

### 5.1.3 Reporting Requirements from HCP to Sponsor

#### 5.1.3.1 Immediate Reporting Requirements from HCP to Sponsor

Certain events require immediate reporting to allow the Sponsor and the regulatory authorities to take appropriate measures to address potential new risks associated with

the use of the medicine. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study medicine:

- Serious adverse events
- Non-serious adverse events of special interest
- Accidental pregnancy occurred during the study (for additional information see Section 5.1.3.5)

The investigator must report new significant follow-up information for these events to the Sponsor 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 serious adverse events and non-serious adverse events of special interest, including follow-up, investigator should record all case details that can be gathered immediately (i.e., within 24 hours) in the Adverse Event eCRF and submit the report via the electronic data capture (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, refer to Section 5.1.3.4.

Investigator must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

#### 5.1.3.2 *Medical Monitors and Emergency Medical Contacts*

*To ensure the safety of study participants, access to the Medical Monitor is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. Details will be provided separately. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.*

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

For all non-serious adverse events, including follow-up reports, the investigator must record all case details that can be gathered within 30 calendar days of learning of the event on the adverse event section of the eCRF.

#### 5.1.3.4 If EDC System Is Temporarily Unavailable

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 calendar days for non-serious adverse events if not adverse events of special interest, using the fax number or email address provided to investigator.

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

#### 5.1.3.5 Reporting Requirements for Pregnancies, Abortions/Congenital Anomalies/Birth Defects

**Pregnancies**

All pregnancies in women enrolled in this study should have been previously reported to the Sponsor as spontaneous pregnancy reports by following the standard pharmacovigilance reporting process for post-marketing pregnancy cases. This should be done by a neurologist at the time of learning of the patient's pregnancy. In case a pregnant woman enrolled in the study becomes accidentally pregnant again during the study, she will remain on study and discontinue treatment with commercial ocrelizumab until pregnancy completion. She and her subject infant should continue with all study assessments. The investigator should complete the Global Clinical Trial Pregnancy Form and submit it to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the accidental pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator will submit to the Sponsor a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.
Any serious adverse events associated with the accidental pregnancy during the study (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event section of the eCRF.

**Abortions**

Pregnant women who experienced a spontaneous abortion will be excluded from the study at enrollment, scheduled at gestational Week 24–30; see Section 4.1.2, exclusions related to obstetric and gynecological health. Thus, the reporting of spontaneous abortion as serious adverse event is exempted in this study, while it should be reported as medical history on the study eCRF Medical History page, if a spontaneous abortion occurred in previous pregnancy.

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.1.3.1). A therapeutic or elective

abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an AE.

In addition, therapeutic or elective abortion should be reported as pregnancy outcomes on the study eCRF Pregnancy page and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.1.3.1).

### Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the medicine should be classified as a serious adverse event, recorded in the adverse event section of the eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.1.3.1).

## 5.1.4 Follow-Up of Patients after Adverse Events

### 5.1.4.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to studied medicinal product until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented in the adverse event section of the eCRF and in the patient's medical record to facilitate source data verification.

### 5.1.4.2 Sponsor Follow-Up

For all adverse events, the Sponsor or a designee may follow up by telephone, fax, electronic 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. Adverse event follow-up should be documented in the adverse event section of the eCRF.

## 5.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED MEDICINAL PRODUCTS

Although adverse event information is not being actively solicited for non-studied medicinal products, the investigator/patients are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to the MAH of the suspected medicinal 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 medicinal product, even in the absence of an adverse event:

- Pregnancy

- 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 physician/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

## 5.3 REPORTING OF PRODUCT COMPLAINTS WITHOUT ADVERSE EVENTS

Report Roche product complaints without adverse events, where a 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.

## 5.4 EXPEDITED REPORTING TO HEALTH AUTHORITIES, PHYSICIANS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Local prescribing information for ocrelizumab (SmPC).

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the physician’s assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of this open-label study will be primarily based on descriptive statistical methods. Unless otherwise specified, no statistical tests are planned. Corresponding 95%CIs will be presented as appropriate.

The primary analysis will be performed after the last blood draw at Week 6 to examine B-cell levels in infants. The full analysis, including the analysis of growth velocity of the infants in the first year, will be conducted at the end of the study.

Full details of all statistical aspects and planned statistical analyses will be specified in a separate statistical analysis plan (SAP), which will be finalized prior to the locking of the study database and may include further exploratory analyses not explicitly described in this section.

## Analysis Populations

Full analysis set (FAS)

Two separate FAS populations will be considered:

- Women's FAS: this will include all pregnant women defined through the inclusion and exclusion criteria in the study who were exposed to ocrelizumab either 0–6 months before the last menstrual period or in the first trimester of pregnancy (i.e., up to gestational Week 13 [inclusive]).
- Infants′ FAS: includes all infants born to women in the FAS who were potentially exposed to ocrelizumab during pregnancy.

Safety Population

The safety population for the women is the same as the FAS. The safety population for infants will include all infants of mothers in the FAS population.

## 6.1 DETERMINATION OF SAMPLE SIZE

The study will include approximately $33$ pregnant women.

There is no formal sample size calculation, as no confirmatory hypothesis testing is planned. The primary analysis will be descriptive. Considering a 10% dropout rate, $approximately\ 30$ evaluable infants are expected. A further investigation will be performed on the subgroup of infants whose mothers received the last dose of ocrelizumab 0–3 months before the LMP or during the first trimester.

The precisions (width of the two-sided 95% CIs based on normal approximation) for different event rates (an "event" is defined as B-cell levels below LLN) are shown in the following table. If no event is observed from the $30$ infants during the study, there is a 95% confidence that the event rate is below $0.114$.

**Table 5 Precision at Different Event Rates**

| *Sample Size* | *Number of Events* | *Event Rate* | *Precision* |
|---|---|---|---|
| *30* | *1* | *0.033* | *0.165* |
| *30* | *2* | *0.067* | *0.195* |
| *30* | *3* | *0.100* | *0.222* |
| *30* | *4* | *0.133* | *0.244* |
| *30* | *5* | *0.167* | *0.262* |

## 6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, screening failures, ocrelizumab administration, and discontinuations from the study will be summarized using descriptive statistics (frequency tables for categorical endpoints and mean, median, range, SD, and 25th–75th quartiles for the continuous endpoints). Subject disposition and the incidence of treatment discontinuation for different reasons will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized. All analyses will be performed for overall population.

## 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

For women, demographics (age, self-reported ethnicity and educational level), medical history, and neurological examination will be summarized. The following will also be summarized: MS disease history (duration since first MS symptoms, duration of MS since diagnosis, relapses in the past year), baseline measures of EDSS and other important variables.

Characteristics of infants at birth will also be summarized (gender, weight, gestational age at birth and other endpoints collected).

## 6.4 PRIMARY ANALYSES

### 6.4.1 Primary Endpoint

The primary analysis will occur once the last infant enrolled has completed the Week 6 of life visit (or equivalent if preterm birth) for B-cell measurement. A sensitivity analysis may be performed; details will be specified in the SAP.

The B-cell levels at Week 6 of life will be analyzed using descriptive statistics. Mean, corresponding 95% CI, SD, and other statistics will be presented. Stillbirths and abortions of any type will not be included in the primary B-cell analysis.

The primary estimand is defined as follows:

- Population: *Infants exposed to ocrelizumab up to 6 months before the mother's LMP or during the first trimester (up to gestational Week 13) of pregnancy and not exposed after the first trimester (Infants' FAS).*

- Variable: Binary endpoint if the B-cell level is below LLN.

  *Note: B-cell reference ranges by week of life (absolute and percentage counts) can be found in Appendix 7.*

- *Intercurrent events:*
  - *Withdrawal from the study prior to infant's Week 6 visit – missing data will not be imputed*
  - *Interrupted pregnancy (elective or* therapeutic abortion or stillbirth) – missing data will not be imputed
  - Fetal complications, or other issues, that render the sample not suitable for measurement of B-*cell levels at Week 6 of life:* missing data will not be imputed
  - Breastfeeding before sample at *Week 6 is taken:*
    - *No DMT postpartum while breastfeeding: B-cell data will be included*
    - *Received any DMT postpartum whilst breastfeeding: B-cell data will be excluded because sample will not be collected*
    - *Resume OCR postpartum while breastfeeding: B-cell data will be included*
  - *Infants that were born preterm and whose intervals of assessment were not adjusted (i.e., a baby was born at Week 35, the blood sample needs to be taken at Week 8 (*±14 weeks), gestational weeks that would sum up to a full-term baby): B-*cell data will be included.*
- Population-level summary: Proportion of infants with B-cell below LLN and the two-sided 95% CI will be reported; no formal statistical testing will be done.
- Handling of missing data: No data will be imputed. Every effort will be made to ensure all samples with all supporting information are collected for B-cell measurement.

### 6.4.2 Secondary Endpoints

Serum concentration of ocrelizumab in the pregnant women/mothers during pregnancy and at delivery, and the serum concentration of ocrelizumab in infants at birth (umbilical cord blood) and at Week 6 of life (or equivalent if preterm birth) will be summarized descriptively.

Mean titers of antibody immune response(s) to vaccinations will be summarized descriptively. The proportion of infants with a positive response (seroprotective titers; as defined for the individual vaccine) to different vaccinations will be calculated and the corresponding two-sided Clopper-Pearson 95% CIs will be presented overall.

Continuous variables at each visit, as well as change from baseline (if applicable) will be analyzed primarily using descriptive statistics. Mean, corresponding 95% CIs, SD, and other statistics will be presented.

### 6.4.3 Exploratory Endpoints

The exploratory endpoints listed in Section 2 will be summarized descriptively. Full details of the derivations and analyses of exploratory endpoints will be provided in the SAP.

### 6.4.4 Subgroup Analyses

The subgroup of infants with potential fetal exposure (infants of mothers with ocrelizumab exposure 0-3 months before the LMP or first trimester exposure) will be analyzed.

The following subgroups, based on timing of ocrelizumab exposure relative to the LMP, may be analyzed, depending on how many women/infants are enrolled in each group: (1) exposure to ocrelizumab 3–6 months prior to the LMP; (2) exposure to ocrelizumab in the 3 months prior to the LMP; (3) exposure to ocrelizumab during the first trimester of pregnancy (up to gestational Week 13).

## 6.5 SAFETY ANALYSES

The safety analyses will be performed on the safety populations for the women and for the infants separately. The analyses will be conducted on data collected from enrollment until the end of the study.

The safety outcome measures will comprise the following: incidence and nature of all adverse events, including findings on vital sign measurements, neurological examinations, clinical laboratory tests, locally-reviewed MRIs conducted for safety reasons (non-MS CNS pathology), and concomitant medications.

Safety will be assessed through summaries of adverse events (including rates/incidence rates and corresponding 95% CIs) and clinical laboratory abnormalities.

All adverse events will be summarized by mapped term, appropriate thesaurus level and toxicity grade, and tabulated by MedDRA system organ class (SOC) and preferred term for individual adverse events within each SOC. Grade 3–5 adverse events, serious adverse event, adverse events leading to treatment discontinuation, and time to withdrawal from the study due to an adverse event will be summarized. In addition, all serious adverse events and deaths will be listed.

Associated laboratory parameters, such as hepatic function, renal function, and hematology values will be grouped and presented together.

The proportion of pregnancy outcomes including live births (term and preterm), therapeutic abortions and stillbirths will be calculated, and the corresponding two-sided Clopper-Pearson 95% CIs will be presented overall.

Concomitant medications recorded during the study will be summarized using frequency tables.

## 6.6 INTERIM ANALYSIS

No formal effectiveness and safety interim analyses are planned. Interim analyses for administrative or scientific purposes may be conducted during the course of the study.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

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 EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

The eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

## 7.2 ELECTRONIC CASE REPORT FORMS

The eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

## 7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site 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, patient-reported outcomes, 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 trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

## 7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of investigational medicinal product (IMP), including eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation 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 Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the US or under a US Investigational New Drug (IND). Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU or European Economic Area will comply with the EU Clinical Trial*s* Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

## 8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs such as a Mobile Nursing ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the ICF will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each woman the objectives, methods, and potential risks associated with each optional procedure. Women will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a woman's agreement to participate in optional procedures. Women who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the woman or the woman's legally authorized representative before her participation in the study. Where applicable, the written ICF with respect to the infant will also be signed and dated by the holder of parental rights as designated by the maternal subject. The case history or clinical records for each woman shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the

woman to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a woman is participating in the study, the woman or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each woman shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the woman or the woman's legally authorized representative. All signed and dated Consent Forms must remain in each woman's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, 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 (HIPAA) of 1996. If the site 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 study site policies.

## 8.3 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 Principal Investigator 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.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

## 8.4 CONFIDENTIALITY

*Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.*

The Sponsor 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 data sets that are transmitted to any Sponsor 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.

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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

# 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

## 9.1 STUDY DOCUMENTATION

The investigator 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, ICFs, and documentation of IRB/EC and governmental approval.
In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

## 9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

## 9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) prior to study initiation. Due to the small sample size and the lack of reference quality tolerance limits (QTLs), no QTLs will be established or monitored. A Quality Tolerance Limit Management Plan is therefore not applicable to the study.

## 9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

## 9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Roche and will be managed by Roche and CROs.
The CROs will provide clinical operations management, data management, and biostatistics.

Patient data will be recorded via an EDC system using eCRFs.

## 9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to HCPs and to the public, at scientific congresses*, in clinical trial registries* and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and*/or* other *summaries of clinical study results may be available in health authority databases for public assess, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

*https://www.roche.com/innovation/process/clinical-trials/data-sharing/*

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator 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 Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor 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 Sponsor, except where agreed otherwise.

## 9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/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 necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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# Appendix 1
# Schedule of Assessments: Screening through the End of Treatment Period

| Visit | | Screening/ Baseline [a] | Pregnancy and Early Postpartum Period [b] | | | | | Vaccination Period [b] | | | Early Discontinuation [c] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | | 4 | – | – | 5 | 6 | 7 | Woman | Child |
| | | Gestational Weeks 24–30 | Gestational Week 35 (± 14 days) | At Delivery | At Birth [d] (cord blood) | Week 6 of life (± 7 days) | Months 2, 4, 6, 9, and 12 | | Infusion 1 Any Time after Birth [e, f, g] | Infusion 2 6 Months after Visit 5 [e, f] | Month 13 of Age (+ 3 days) [h] | | |
| **Patient population and ICF** | Diagnosis confirmation [i] | x | | | | | | | | | | | |
| | Informed consent [j] | x | | | | | | | | | | | |
| | Review inclusion/exclusion criteria | x | | | | | | | | | | | |
| **General medical history and demographics [k]** | Demographics (age, ethnicity, educational level) | x | | | | | | | | | | | |
| | Clinically significant diseases and surgery/procedures | x | x | x | | | | | x | x | | x | |
| | Smoking history and alcohol intake | x | | | | | | | | | | | |
| | Vaccination history | x | | | | | | | | | | | |
| | Height | x | | | | | | | | | | | |
| | Weight | x | x | | | | | | | | | | |
| | Previous and concomitant medication [l] | x | x | | | | | | x | x | | x | |
| **MS disease history** | Date of MS onset and diagnosis | x | | | | | | | | | | | |
| | Disease status (EDSS and number of relapses up to 1 year before the LMP) | x | | | | | | | | | | | |

## Appendix 1: Schedule of Assessments: Screening Through the End of Treatment Period

| Visit | | Screening/ Baseline [a] | Pregnancy and Early Postpartum Period [b] | | | | | Vaccination Period [b] | | | Early Discontinuation [c] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | | 4 | – | 5 | 6 | 7 | Woman | Child |
| | | Gestational Weeks 24–30 | Gestational Week 35 (± 14 days) | At Delivery | At Birth [d] (cord blood) | Week 6 of life (± 7 days) | Months 2, 4, 6, 9, and 12 | Infusion 1 Any Time after Birth [e, f, g] | Infusion 2 6 Months after Visit 5 [e, f] | Month 13 of Age (+ 3 days) [h] | | |
| | History of previous DMTs | x | | | | | | | | | | |
| | Treatment history with ocrelizumab (OCREVUS) [m] | x | | | | | | | | | | |
| **Obstetric and Gynecological history** | Date of LMP | x | | | | | | | | | | |
| | Gestational age [n] | x | | | | | | | | | | |
| | History of previous pregnancies (number, outcome, date) [o] | x | | | | | | | | | | |
| | Clinically significant gynecological diseases [p] | x | | | | | | | | | | |
| | Obstetric ultrasounds (prenatal screening) [n, q] | x | (x) | | | | | | | | | |
| **Maternal physical assessments and procedures** | General physical/obstetric examination [r] | x | x | | | | | x | x | | x | |
| | Neurological examination [s] | x | x | | | | | x | x | | x | |
| | Recording of potential relapses | x | x | | | | | x | x | | x | |
| | EDSS score | x | x | | | | | x | x | | x | |
| | Vaccination (e.g., *Bordetella* | (x) | (x) | | | | | (x) | (x) | | (x) | |

## Appendix 1: Schedule of Assessments: Screening Through the End of Treatment Period

| Visit | | Screening/ Baseline [a] | Pregnancy and Early Postpartum Period [b] | | | | | Vaccination Period [b] | | | Early Discontinuation [c] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | | 4 | – | – | 5 | 6 | 7 | Woman | Child |
| | | Gestational Weeks 24–30 | Gestational Week 35 (± 14 days) | At Delivery | At Birth [d] (cord blood) | Week 6 of life (± 7 days) | Months 2, 4, 6, 9, and 12 | | Infusion 1 Any Time after Birth [e, f, g] | Infusion 2 6 Months after Visit 5 [e, f] | Month 13 of Age (+ 3 days) [h] | | |
| | *pertussis* vaccination) [t] | | | | | | | | | | | | |
| **Maternal laboratory assessments [u]** | Hematology, chemistry, urinalysis [v] | x | x | | | | | | x | x | | x | |
| | HBV screening [w] | x | | | | | | | | | | | |
| | Whole blood sample for lymphocyte subtypes [x] | x | x | | | | | | x | x | | | |
| | Serum ocrelizumab concentration [y] | x | x | x | | | | | x | x | | | |
| | Serum immunoglobulin concentration [y] | x | x | x | | | | | x | x | | | |
| | Serum titers (IgG) of antibody immune responses titers to vaccinations [z] | | x | | | | | | | | | | |
| | sNfL levels [y] | x | x | x | | | | | x | x | | | |
| **Ocrelizumab infusion** | Ocrelizumab administration [e] | | | | | | | | (x) | (x) | | | |
| | Methylprednisolone and antihistamine premedication [f] | | | | | | | | (x) | (x) | | | |
| | Body weight for safety | | | | | x | | | | | x | | |

## Appendix 1: Schedule of Assessments: Screening Through the End of Treatment Period

| Visit | | Screening/ Baseline [a] | Pregnancy and Early Postpartum Period [b] | | | | | Vaccination Period [b] | | | Early Discontinuation [c] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | | 4 | – | – | 5 | 6 | 7 | Woman | Child |
| | | Gestational Weeks 24–30 | Gestational Week 35 (± 14 days) | At Delivery | At Birth [d] (cord blood) | Week 6 of life (± 7 days) | Months 2, 4, 6, 9, and 12 | | Infusion 1 Any Time after Birth [e, f, g] | Infusion 2 6 Months after Visit 5 [e, f] | Month 13 of Age (+ 3 days) [h] | | |
| **Infant physical assessments and procedures** | Pregnancy and Infant outcomes [aa] | | | | x | | | | | | | | |
| | Feeding status [bb] | | | | | x | x | | | | | | x |
| | Documentation of infant growth velocity (weight, length, head circumference) [cc] | | | | x | | x | | | | | | x |
| | ASQ-3 [dd] | | | | | | x | | | | | | x |
| | Concomitant medications [ee] | | | | | x | x | | | | x | | x |
| | Documentation of vaccination of the infant as part of routine care [ff] | | | | | | x | | | | x | | x |
| **Infant laboratory assessments [gg, hh]** | Whole blood for lymphocytes subtypes sample [ii] | | | | | x [hh, kk] | | | | | x | | |
| | Serum ocrelizumab concentration | | | | x [jj] | x [hh, kk] | | | | | | | |
| | Serum titers (IgG) of antibody immune response(s) to vaccinations [ll, mm] | | | | | | | | | | x | | |
| **Telephone interview** every 3 months | General review of mother and infant [nn] | | | | | (x) | (x) | | (x) | (x) | (x) | (x) | (x) |
| **Safety** | Adverse event assessment [oo] | x | x | x | x | x | x | | x | x | x | x | x |

## Appendix 1: Schedule of Assessments: Screening Through the End of Treatment Period

**Appendix 1: Schedule of Assessments: Screening Through the End of Treatment Period**

APGAR = Appearance, Pulse, Grimace, Activity, and Respiration; ASQ-3 = Ages and Stages Questionnaire version 3; CIS = Clinically isolated syndrome; DMT = Disease-modifying therapy; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; GGT = Gamma-glutamyl transpeptidase; HBcAb = Hepatitis B core antibody; *HBsAb* = Hepatitis B surface antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; Hib = *Hemophilus influenzae* type b; ICF = Informed consent form; IVF = in vitro fertilization; LEEP = loop electrosurgical excision procedure; LLN = Lower limit of normal; *LMP = last menstrual period;* MMR = Measles, mumps, and rubella; MS = Multiple sclerosis; *NK = natural killer*; PCV-13 = 13-pneumococcal conjugate vaccine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; *SmPC = Summary of Product Characteristics; sNfL = serum neurofilament light chain; USPI = U.S. Prescribing Information;* WHO = World Health Organization.

Note: 'x' indicates an assessment or procedure is to be done at that visit, and '(x)' indicates that depending on the situation, the assessment or procedure may or may not be done at that visit (e.g., the pertussis vaccine would not be administered if the mother has already received it, and the telephone interview will not be conducted in a week where there will be an on-site visit).

[a] The length of the screening/baseline period between gestational Week 24 and 30 is variable and depends on local timings for performing some of the eligibility assessments and associated preterm screenings performed during the first and second trimester. The baseline and screening visits will be combined.

[b] Depending on the timing of postpartum ocrelizumab infusion, postnatal assessments in the infant and the mother may occur at different time points. Visit 4 and 7 timings are related to infant assessments, and Visits 5 and 6 to the mother's ocrelizumab infusion and assessments.

[c] Women who decide to discontinue the study (this includes discontinuation of the mother or discontinuation of the infant by the mother, or discontinuation at the investigator's discretion) will be invited to attend an early study discontinuation visit (which may be conducted virtually or by telephone) as soon as possible.

[d] For the umbilical cord sample, the target time of collection is within 1 hour after birth. The actual time of collection after delivery should be recorded. The umbilical cord blood sample should only be collected if the mother delivered a live birth; no collection should occur in the event of a pregnancy interruption (i.e., therapeutic abortion or stillbirth).

[e] Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labelling (USPI; SmPC). The first postpartum ocrelizumab dose can also be administered as $2 \times 300$ mg infusions separated by 14 days. However, all clinical and laboratory assessments related to Visit 5 (except for documentation of ocrelizumab and premedication administration) will occur only at the first 300 mg infusion.

[f] All women must receive prophylactic treatment with 100 mg methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes prior to each ocrelizumab infusion and an antihistamine by oral or IV route, to be completed approximately 30–60 minutes prior to each infusion of ocrelizumab. The antihistamine should be the first premedication to be administered. The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered approximately 30–60 minutes prior to each infusion of ocrelizumab.

[g] Treatment with ocrelizumab may be resumed at any time after birth in women who decide not to breastfeed. Some women may decide to resume ocrelizumab whilst breastfeeding; in those women, treatment with ocrelizumab should be restarted after collection of the infant blood sample at Week 6 of life (±7 days) if possible (however, the decision is left to the discretion of the woman and the investigator). If the woman switches to another DMT postpartum, the infant blood sample at Week 6 of life (±7 days) will only be collected if the woman is not breastfeeding.

[h] Samples at this visit will be collected 1 month (+30 days) after the first dose of MMR vaccine (if first dose is administered at 11 months of age or later) OR 1 month (+30 days) after the second dose of MMR vaccine (if first dose is administered before 11 months of age) OR at Month 13 of chronological age (+30 days) if MMR vaccine is not planned to be administered.

[i] The following diagnoses are accepted: MS or CIS (in line with the locally approved indications).

[j] Written informed consent will be obtained from all women at screening in order to be eligible for the study. Where applicable, the written ICF with respect to the infant is also signed and dated by the holder of parental rights as designated by the maternal subject.

[k] Medical history includes clinically significant diseases, surgeries/procedures, smoking history, alcohol intake and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the woman within 6 weeks prior to the screening/baseline visit. Demographic data will include age, educational level and self-reported ethnicity. Clinically significant diseases and/or surgeries/procedures, and concomitant medication should also be recorded throughout the study.

[l] Documentation whether folic acid (recommended daily intake 400 micrograms per day, or as per local practice) was prescribed and administered up to the first trimester of pregnancy (up to gestational Week 13).

[m] Documentation of start of ocrelizumab therapy and date and dose of last ocrelizumab infusion prior to enrollment.

[n] Gestational age will be determined by LMP and first trimester ultrasound so long as there is less than 1 week's difference in the projected due date. If there is over 1 week's difference, then the ultrasound alone will be used. For cases where the LMP is not known, then the earliest ultrasound will be used. For cases of IVF, the projected dates from the IVF procedure will be preferentially used.

[o] History of previous pregnancy outcomes and disorders associated with adverse pregnancy outcomes includes, but is not limited to history of the following: preterm birth (gestational age $<$37 weeks) for any indication with or without fetal malformations; spontaneous abortion (miscarriage) after the first trimester (i.e., after gestational Week 13); stillbirth (defined as fetal loss at gestational age $>$22 weeks); pre-eclampsia/eclampsia; and cervical pathology or intervention which may increase the risk of cervical incompetence (e.g., history of cervical cerclage, prior cervical conization or prior LEEP).

[p] Prior or current history of any other gynecological disease considered by the investigator to be associated with a high risk of adverse pregnancy outcomes in the current pregnancy.

[q] The first (12-week) and second (18–20-week) obstetric ultrasounds have to be documented and should confirm the absence of abnormalities described in the exclusion criteria. The third trimester ultrasound may be performed in countries where this is part of routine obstetric care.

[r] A complete physical examination should be performed at the screening/baseline visit and at all subsequent visits (results from examinations done as part of routine care may be used). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF. An obstetric examination will also be performed as per local clinical practice.

[s] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the study period after screening. To reduce the burden of visits to mothers, results from neurological examinations done as part of routine care may be used. For patients referred to the investigator, results from routine visits at the woman's neurologist may be used.

[t] In women who undergo vaccination as part of routine care. Information on vaccinations administered during the study will be collected under concomitant medications.

[u] Samples at third trimester (Week 35 [±14 days]) may be collected by home nurse visit.

[v] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute or/and differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), and quantitative platelet count. Chemistry will include AST, ALT, GGT, creatinine, total bilirubin, random glucose, potassium, sodium, chloride. The scheduled obstetric blood glucose test should preferably be conducted at the screening/baseline visit rather than at a separate visit. Urine dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) will be done at site locally at the discretion of the investigator.

[w] Women with positive screening tests for HBV, determined by a positive HBsAg result (current infection) or positive HBcAb titers (previous infection) will be excluded. Women with documented history of HBV vaccination or positive HBsAb titers are eligible.

[x] Postpartum, lymphocyte subtype samples should be collected (fresh whole blood) prior to ocrelizumab infusion to screen for B-cell counts (CD19+ *and B-cell subsets [Table 2]),* T-cell counts (CD3+, CD4+, CD8+*), and NK cell counts (CD16+CD56+)* analysis by flow cytometry.

[y] At delivery, the serum sample should be collected within 24 hours after delivery. Postpartum, serum samples should be collected 5–30 minutes prior to the methylprednisolone infusion on the day of sampling. The maternal blood sample at delivery should only be collected if the mother delivered a live birth; no collection should occur in the event of a pregnancy interruption (i.e., therapeutic abortion or stillbirth).

[z] Serum titers of antibody responses to vaccinations for measles, mumps, rubella, tetanus toxoid, diphtheria, pertussis, varicella zoster, *Streptococcus pneumoniae*, HBV, and SARS-CoV-2 (along with nucleocapsid and spike protein titers; only for those mothers who have received the vaccine, as per local clinical practice) will be performed during the third trimester (Week 35±14 days).

[aa] These will include: mode of delivery (vaginal delivery, instrumental delivery, scheduled or urgent cesarean section); APGAR score (1 min, 5 min, 30 min); gestational age at birth; infant's measurements (weight, length, head circumference); and congenital malformations.

[bb] Mothers should record feeding status of the infant, i.e., whether exclusive breastfeeding, mixed feeding (partial breastfeeding

along with infant formula and/or baby food), exclusive infant formula feeding, or fully weaned.

[cc] Growth charts (according to the WHO Child Growth Standards [WHO 2022]) as well as other standard questionnaires may be used. In addition, absolute values will be recorded (measurements recorded by e.g., the pediatrician as part of routine postnatal care may be used. Infant growth will be captured at Months 2, 4, 6, 9, and 12 (see Appendix 6 for time windows for infant growth velocity and child developmental milestone assessments).

[dd] Assessment of child developmental milestones in the domains of communication, gross motor, fine motor, problem solving, and personal-social will be captured at Months 2, 4, 6, 9, and 12 using the ASQ-3 (see Appendix 6 for time windows for infant growth velocity and child developmental milestone assessments).

[ee] Changes to concomitant medication given to the infant should be recorded throughout the study.

[ff] Vaccines administered from birth throughout the end of the study should be recorded at Months 2, 4, 6, 9, and 12 as well as at Month 13 of age (+30 days)/1 month (+30 days) after first or second MMR dose.

[gg] As per the recommendation of the EC ad hoc group (2008) the total blood volume to be collected from an infant in a clinical study should not exceed 0.8–0.9 mL/kg at any timepoint, or 2.4 mL/kg over any 4 week period throughout the study. If the blood volume collected for an infant (as a result of these limits) is insufficient to carry out all planned assessments, the order of priority for assessments is as follows: *for the Week 6 sample,* (1) safety laboratory samples [scheduled or unscheduled and performed at the discretion of the Investigator] (2) lymphocyte subtypes sample for B-cell counts (CD19+), T-cell counts (CD3+, CD4+, and CD8+), *and NK cell counts (CD16+CD56+)* (3) serum ocrelizumab concentration; for the Month 13 of age (+30 days)/1 month (+30 days) after first or second MMR vaccine dose sample, (1) safety laboratory samples [scheduled or unscheduled and performed at the discretion of the Investigator] (2) serum titers of antibody response to immunizations (3) lymphocyte subtypes sample for B-cell counts (CD19+), T-cell counts (CD3+, CD4+, and CD8+), *and NK cell counts (CD16+CD56+).*

[hh] For preterm infants (gestational age <37 weeks), blood samples will be collected at the week of life equivalent to term infants (e.g., if birth occurred at gestational Week 35, blood sample would be collected at Week 8 of life).

[ii] If the infant's B-cell levels are below LLN, repeat analyses may be done at unscheduled visits, at the discretion of the investigator (in consultation with the Sponsor).

[jj] Note that this sample will be taken from umbilical cord blood.

[kk] Infant samples at Week 6 of life (±7 days) may be collected during a site visit, or by home nurse visit.

[ll] For Month 13 of age (+30 days)/1 month (+30 days) after the first or second dose of MMR: all efforts will be made to collect samples. However, if they cannot be collected, this will not be considered a protocol deviation.

[mm] Vaccinations may include the following, in line with clinical practice: *diphtheria, tetanus, pertussis*, Hib, PCV-13, HBV, and MMR. Antibody responses to vaccinations will be measured 1 month (+30 days) after the first dose of MMR vaccine (if first dose is administered at 11 months of age or later), or 1 month (+30 days) after second dose of MMR vaccine (if first dose is administered before 11 months of age), or at Month 13 of chronological age (+30 days) if MMR vaccine is not planned to be administered.

[nn] A structured telephone interview will be conducted by site personnel postpartum every 3 months (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's or infant's health status (including the occurrence of MS relapses in the woman and use of new concomitant medications) and possible adverse events in both the woman and the infant (particularly infections); women will also be asked if the ASQ-3 form is being filled out. No telephone contact is needed in weeks where the woman is performing on-site visits.

[oo] Adverse events in both the mother and the infant will be reported throughout the study as per standard pharmacovigilance procedures.

# Appendix 2
# Potentially Teratogenic Drugs

## Table A2-1 List of Potentially Teratogenic Drugs [a]

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| Anti-infective and Anti-parasitic agents | Albendazole | P02CA03 | D | n.a. | C |
| | Amikacin | J01GB06 | D | D | D |
| | Artemether | P01BE52 | D | n.a. | C |
| | Artemether | P01BE02 | D | n.a. | C |
| | Chloroquine | P01BA01 | D | B3 | n.a. |
| | Cidofovir | J05AB12 | D | D | C |
| | Demeclocycline | J01AA01 | D | n.a. | D |
| | Doxycycline | A01AB22 | D | n.a. | D |
| | Doxycycline | J01AA02 | D | D | D |
| | Efavirenz | J05AG03 | D | D | D |
| | Fluconazole | J02AC01 | D | B3 | C |
| | Ganciclovir | J05AB06 | D | D | C |
| | Gentamicine | J01GB03 | D | D | D |
| | Hydroxychloroquine | P01BA02 | D | B3 | n.a. |
| | Minocycline | J01AA08 | D | n.a. | D |
| | Netilmicin | J01GB07 | D | D | D |
| | Oxytetracycline | J01AA06 | D | D | n.a. |
| | Primaquine | P01BA03 | D | n.a. | n.a. |
| | Quinine | P01BC01 | D | D | C |
| | Ribavirin | J05AB04 | D | D | X |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Streptomycine | J01GA01 | n.a. | n.a. | D |
| | Tetracycline | A01AB13 | D | n.a. | D |
| | Tetracycline | J01AA07 | D | D | D |
| | Tigecycline | J01AA12 | D | D | D |
| | Tobramycin | J01GB01 | D | B3 | D |
| | Valganciclovir | J05AB14 | D | D | C |
| | Zalcitabine | J05AF03 | D | n.a. | C |
| Agents acting on the renin-angiotensin system | Benazepril | C09AA07 | n.a. | n.a. | D |
| | Candesartan | C09CA06 | D | D | D |
| | Captopril | C09AA01 | D | D | D |
| | Cilazapril | C09AA08 | D | n.a. | n.a. |
| | Enalapril | C09AA02 | D | D | D |
| | Eprosartan | C09CA02 | D | D | D |
| | Exforge | C09DB01 | D | D | D |
| | Fosinopril | C09AA09 | D | n.a. | C |
| | Irbesartan | C09CA04 | D | D | C |
| | Lisinopril | C09AA03 | D | D | D |
| | Losartan | C09CA01 | D | D | C |
| | Olmesartan | C09CA08 | D | n.a. | C |
| | Perindopril | C09AA04 | D | D | D |
| | Quinapril | C09AA06 | D | D | D |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Ramipril | C09AA05 | D | D | D |
| | Telmisartan | C09CA07 | D | D | C |
| | Trandolapril | C09AA10 | D | n.a. | C |
| | Valsartan | C09CA03 | D | D | D |
| Anti-thrombotic agents | Acenocoumarol | B01AA07 | n.a. | n.a. | n.a. |
| | Fenprocoumon | B01AA04 | n.a. | n.a. | n.a. |
| | Warfarin | B01AA03 | D | D | X |
| Statins | Atorvastatin | C10AA05 | D | D | X |
| | Fluvastatin | C10AA04 | D | B3 | X |
| | Pravastatin | C10AA03 | D | B3 | X |
| | Rosuvastatin | C10AA07 | D | D | X |
| | Simvastatin | C10AA01 | D | B3 | X |
| Dermatologicals | Aciretin | D05BB02 | X | D | X |
| | Adapalene | D10AD03 | D | B3 | C |
| | Finasteride | D11AX10 | X | D | X |
| | Isotretinoin | D10BA01 | X | n.a. | X |
| | Tazaroteen | D05AX05 | D | n.a. | X |
| | Tetracycline | D06AA04 | D | n.a. | B |
| | Tretinoin | D10AD01 | D | B3 | C |
| Pituitary, hypothalamic and sex hormones | Carboprost | G02AD04 | D | n.a. | C |
| | Cetrorelix | H01CC02 | D | C | X |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Danazol | G03XA01 | D | n.a. | X |
| | Dutasteride | G04CB02 | D | n.a. | X |
| | Dydrogesteron | G03DB01 | D | n.a. | n.a. |
| | Estrogens, esterified | G03CA57 | D | n.a. | X |
| | Finasteride | G04CB01 | D | D | X |
| | Follitropin alpha | G03GA05 | D | B1 | n.a. |
| | Ganirelix | H01CC01 | D | C | X |
| | Gestrinon | G03XA02 | D | n.a. | n.a. |
| | Levonorgestrel | G02AC03 | B3 | n.a. | X |
| | Lynestrenol | G03DC03 | D | D | n.a. |
| | Medrogestron – IM | G03DA02 | D | D | n.a. |
| | Medroxyprogesterone and estrogen | G03FA12 | D | B3 | X |
| | Medroxyprogesterone and estrogen | G03FB06 | D | B3 | X |
| | Mesterolon | G03BB01 | D | n.a. | n.a. |
| | Nafarelin | H01CA02 | D | B3 | X |
| | Nomegestrol | G03DB04 | D | n.a. | n.a. |
| | Norethisterone | G03DC02 | D | D | X |
| | Progesterone | G03DA04 | D | n.a. | n.a. |
| | Raloxifene | G03XC01 | D | D | X |
| | Testosterone | G03BA03 | D | D | X |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Tetracosactide | H01AA02 | D | C | n.a. |
| | Tibolon | G03CX01 | D | B3 | n.a. |
| Anti-neoplastic agents | Alitretinoin | L01XX22 | n.a. | n.a. | D |
| | Altretamine | L01XX03 | D | n.a. | D |
| | Amsacrine | L01XX01 | D | D | n.a. |
| | Bevacizumab | L01XC07 | D | D | C |
| | Bleomycin | L01DC01 | D | D | n.a. |
| | Bortezomib | L01XX32 | C | D | D |
| | Busulfan | L01AB01 | D | D | D |
| | Capecitabine | L01BC06 | D | D | D |
| | Carboplatin | L01XA02 | D | D | D |
| | Carmustine | L01AD01 | D | n.a. | D |
| | Cetuximab | L01XC06 | D | B2 | C |
| | Chlorambucil | L01AA02 | D | D | D |
| | Cisplatin | L01XA01 | D | D | D |
| | Cladribine | L01BB04 | D | D | D |
| | Clofarabine | L01BB06 | n.a. | D | D |
| | Cyclophosphamide | L01AA01 | D | D | D |
| | Cytarabine | L01BC01 | D | D | D |
| | Dacarbazine | L01AX04 | D | D | C |
| | Dactinomycin | L01DA01 | D | n.a. | C |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Dasatinib | L01XE06 | D | B3 | D |
| | Daunorubicin | L01DB02 | D | D | D |
| | Docetaxel | L01CD02 | D | D | D |
| | Doxorubicin | L01DB01 | D | D | D |
| | Epirubicin | L01DB03 | D | D | D |
| | Erlotinib | L01XE03 | C | B3 | D |
| | Estramustine | L01XX11 | D | n.a. | n.a. |
| | Etoposide | L01CB01 | D | D | D |
| | Fludarabine | L01BB05 | D | D | D |
| | Fluorouracil | L01BC02 | D | D | D |
| | Gemcitabine | L01BC05 | D | D | D |
| | Hydroxycarbamide | L01XX05 | n.a. | D | n.a. |
| | Idarubicin | L01DB06 | D | D | D |
| | Ifosfamide | L01AA06 | D | D | D |
| | Imatinib | L01XE01 | D | B3 | D |
| | Irinotecan | L01XX19 | D | B3 | D |
| | Lapatinib | L01XE07 | n.a. | B3 | D |
| | Lomustine | L01AD02 | D | D | D |
| | Melphalan | L01AA03 | D | D | D |
| | Mercaptopurine | L01BB02 | D | D | D |
| | Methotrexate | L01BA01 | D | D | X |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Mitomycine | L01DC03 | D | D | D |
| | Mitoxantrone | L01DB07 | D | D | D |
| | Nelaribine | L01BB07 | n.a. | D | D |
| | Oxaliplatin | L01XA03 | D | D | D |
| | Paclitaxel | L01CD01 | D | D | D |
| | Pemetrexed | L01BA04 | D | D | D |
| | Pentostatin | L01XX08 | n.a. | n.a. | D |
| | Procarbazine | L01XB01 | D | n.a. | D |
| | Raltitrexed | L01BA03 | D | n.a. | n.a. |
| | Sorafenib | L01XE05 | D | C | D |
| | Streptozocine | L01AD04 | n.a. | n.a. | D |
| | Sunitinib | L01XE04 | D | B3 | D |
| | Tegafur | L01BC03 | D | n.a. | n.a. |
| | Temozolomide | L01AX03 | D | D | D |
| | Teniposide | L01CB02 | D | n.a. | D |
| | Thioguanine | L01BB03 | D | D | D |
| | Thiotepa | L01AC01 | D | n.a. | D |
| | Topotecan | L01XX17 | D | D | D |
| | Tretinoin | L01XX14 | X | n.a. | D |
| | Vinblastine | L01CA01 | D | D | D |
| | Vincristine | L01CA02 | D | D | D |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Vindesine | L01CA03 | D | D | n.a. |
| | Vinorelbine | L01CA04 | D | D | D |
| Immunomodulating agents | Aminoglutethimide | L02BG01 | D | n.a. | D |
| | Azathioprine | L04AX01 | D | D | D |
| | Basiliximab | L04AC02 | D | B2 | B |
| | Daclizumab | L04AC01 | D | n.a. | C |
| | Fulvestrant | L02BA03 | D | D | D |
| | Goserelin | L02AE03 | D | D | D |
| | Interferon Beta 1a | L03AB07 | D | D | C |
| | Interferon Beta 1b | L03AB08 | D | D | C |
| | Leflunomide | L04AA13 | D | D | X |
| | Lenalilomide | L04AX04 | n.a. | D | X |
| | Letrozole | L02BG04 | D | B3 | D |
| | Leuprorelin | L02AE02 | D | C | n.a. |
| | Medrogestron IM | L02AB02 | D | D | n.a. |
| | Megestrol | L02AB01 | D | B3 | X |
| | Mycophenolic acid | L04AA06 | D | D | D |
| | Penicillamine | M01CC01 | D | n.a. | D |
| | Tamoxifen | L02BA01 | B3 | D | D |
| | Tasonermine | L03AX11 | D | B2 | n.a. |
| | Thalidomide | L04AX02 | D | D | X |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Toremifene | L02BA02 | B3 | B3 | D |
| | Triptorelin | L02AE04 | D | B3 | X |
| Anti-epileptic agents | Carbamazepine | N03AF01 | D | D | C |
| | Ethosuximide | N03AD01 | D | D | n.a. |
| | Lamotrigine | N03AX09 | D | B3 | C |
| | Methylfenobarbital | N03AA01 | D | n.a. | n.a. |
| | Oxcarbazepine | N03AF02 | D | D | C |
| | Phenobarbital | N03AA02 | D | D | D |
| | Phenytoin | N03AB02 | D | D | n.a. |
| | Primidone | N03AA03 | D | n.a. | n.a. |
| | Sultiam | N03AX03 | D | n.a. | n.a. |
| | Valproic acid | N03AG01 | D | D | D |
| | Vigabatrin | N03AG04 | D | D | C |
| Psycholeptic and psychoanaleptic agents | Amobarbital | N05CA02 | n.a. | n.a. | D |
| | Butabarbital | N05CA03 | n.a. | n.a. | D |
| | Lithium | N05AN01 | D | n.a. | n.a. |
| | Paroxetine | N06AB05 | D | C | D |
| | Pentobarbital | N05CA01 | n.a. | n.a. | D |
| | Secobarbital | N05CA06 | n.a. | n.a. | D |
| Miscellaneous agents | Acetohydroxac acid | G04BX03 | n.a. | n.a. | X |
| | Ambrisentan | C02KX02 | X | D | X |

**Appendix 2: Potentially Teratogenic Drug**

| Group | Name | ATC-Code | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|---|---|
| | Bosentan | C02KX01 | D | D | X |
| | Deferipron | V03AC02 | D | n.a. | n.a. |
| | Dihydroergotamine | N02CA01 | C | C | X |
| | Ergotamine | N02CA02 | C | n.a. | X |
| | Hydrokinine | M09AA01 | D | n.a. | n.a. |
| | Ivrabradine | C01EB17 | D | D | n.a. |
| | Misoprostol | A02BB01 | X | D | X |
| | Nandrolone | A14AB01 | D | n.a. | X |
| | Nicotine | N07BA01 | D | C | C |
| | Oxandrolone | A14AA08 | D | n.a. | X |
| | Prasteron | A14AA07 | D | n.a. | n.a. |
| | Retinol | A11CA01 | D | n.a. | n.a. |
| | Tretinoin | A01AD11 | D | n.a. | D |

ADEC = Australian Drug Evaluation Committee; ATC = anatomical therapeutic chemical; FASS = Swedish catalogue of approved drugs; FDA = Food and Drug Authority.

[a] See definitions of the pregnancy classifications in the following table.

Source: Zomerdijk et al. 2015.

**Table A2-2 Overview of the Definitions of the Pregnancy Classifications of the ADEC, FASS, and FDA**

| Category | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|
| **A** | Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. | Medicinal products which may be assumed to have been used by a large number of pregnant women and women of childbearing age without any identified disturbance in the reproductive process, e.g., an increased incidence of malformations or other direct or indirect harmful effect on the fetus. | Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). |
| **B** | Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. **B1** Studies in animals have not shown evidence of an increased occurrence of fetal damage.<br>**B2** Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.<br>**B3** Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. | Medicinal products which may be assumed to have been used by only a limited number of pregnant women and women of childbearing age, without any identified disturbance in the reproductive process having been noted so far, e.g., an increased incidence of malformations or other direct or indirect harmful effect on the fetus. **B1** reproduction toxicity studies have not given evidence of an increased incidence of fetal damage or other deleterious effects on the reproductive process.<br>**B2** reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of fetal damage or other deleterious effects on the reproductive process.<br>**B3** reproduction toxicity studies in animals have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in man. | Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal reproduction studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters) |

**Appendix 2: Potentially Teratogenic Drug**

| Category | The Former ADEC | The FASS | Pregnancy Classification of the FDA |
|---|---|---|---|
| **C** | Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations.<br>These effects may be reversible. Accompanying texts should be consulted for further details. | Medicinal products which by their pharmacological effects have caused, or must be suspected of causing, disturbances in the reproductive process that may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other injurious effects on the reproductive process of uncertain significance in humans, these findings are to be stated in this category. | Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risk. |
| **D** | Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. | Medicinal products which have caused an increased incidence of fetal malformations or other permanent damage in man or which, on the basis of e.g., reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects. If the product also has pharmacological effects that may directly or indirectly have a harmful effect on the fetus, this must also be stated. | There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective). |
| **X** | Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy. | Not applicable | Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks of the use of the drug in pregnant women clearly outweighs any |

ADEC = Australian Drug Evaluation Committee; FASS = Swedish catalogue of approved drugs; FDA = Food and Drug Authority.

Source: Zomerdijk et al. 2015.

# Appendix 3
# Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare infection of the CNS caused by reactivation of a latent JC virus (JCV), and develops almost exclusively in patients with a compromised immune system (i.e., opportunistic). It is pathologically characterized by lytic infection of oligodendrocytes and astrocytes by the JCV. [1,2]

Most confirmed cases of PML in patients with MS have been associated with and described in those treated with natalizumab, but cases associated with fingolimod and dimethyl fumarate have also been reported.[3]

## A3–1 CLINICAL PRESENTATION

Cognitive changes are the most common clinical feature of PML, but presentation is often heterogeneous with neurobehavioral, motor, language, and visual symptoms, as well as other clinical signs and symptoms that often resemble those observed with an MS relapse (see Table A3-1). However, in PML these tend to follow a slow and persistently progressive course.[1,2,4] No distinguishing clinical features appear to exist between PML associated with natalizumab, fingolimod, or DMF.[3,5]

Acute or subacute cognitive changes, language disturbances, and seizures should serve as “red flags” for the possibility of PML, whereas optic neuritis and myelopathy should be considered as unlikely clinical manifestations of PML.

### Table A3-1 Clinical Features of MS and PML

| Parameters | MS | PML |
|---|---|---|
| Onset | Acute | Subacute |
| | Hours to days | Over weeks |
| Evolution | Normally stabilize. May resolve spontaneously even without therapy | Progressive |
| Clinical Presentation | Diplopia<br>*Paranesthesia*<br>Paraparesis<br>Optic neuritis<br>Myelopathy | Aphasia<br>Behavioral/neuropsychiatric changes<br>Hemiparesis<br>Retrochiasmal visual changes (e.g., hemianopia)<br>Seizures |

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

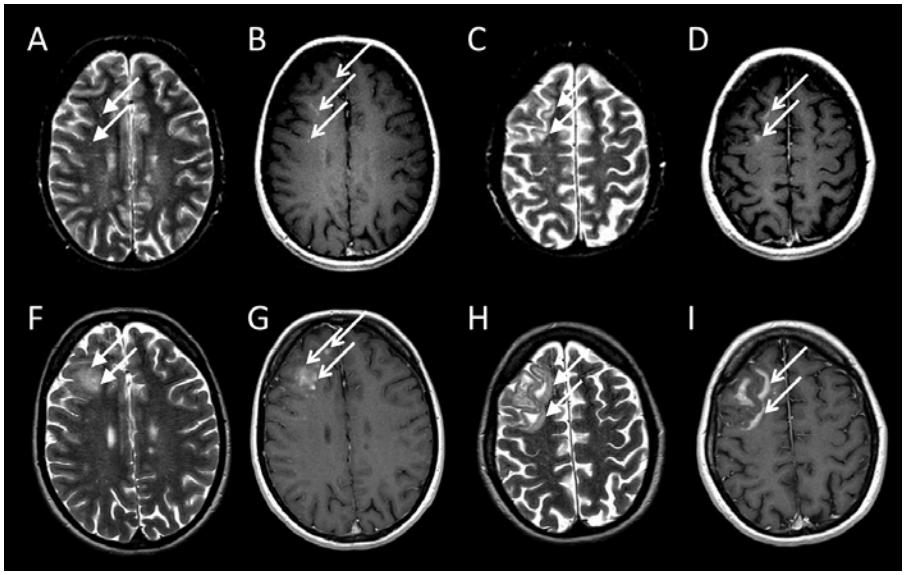
## A3–2 MRI PRESENTATION

MRI scans offer a sensitive tool in the diagnosis of PML but detection, particularly of pre-symptomatic PML, can be difficult owing to the overlap of imaging findings with MS lesions. However, the four most distinguishing imaging features of a PML lesion are (Figure A3-1 and Figure A3-2):

- Subcortical location (involvement of U-fibers)
- T1 hypointensity
- Diffusion weighted imaging hyperintensity
- Presence of punctate T2-hyperintense lesions (Table A3-2) [2]

No unique or pathognomonic radiographic features appear to exist for NTZ-, fingolimod- or DMF-associated PML.[3,5]

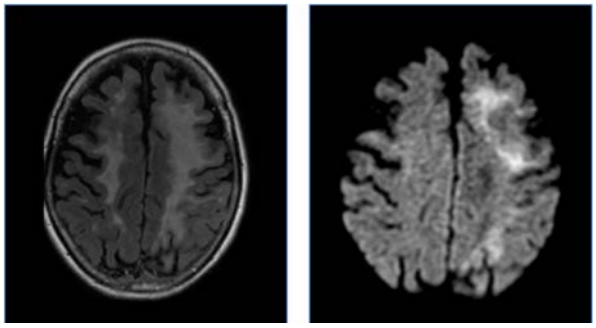
### Figure A3-1 Imaging characteristics of MS and PML




IRIS = immune reconstitution inflammatory syndrome; MS = multiple sclerosis; PMS = progressive multifocal leukoencephalopathy.

T2- and T1-weighted images (with contrast administration) at the time of PML diagnosis (top row) and at the time of PML-IRIS stage (bottom row). The images at diagnosis ('inflammatory PML') show a subcortical lesion and multiple cortical lesions in the right frontal lobe showing contrast enhancement **(C and D)** in addition to punctuate T2 lesions following a perivascular distribution that also enhance on T1 after contrast administration **(A and B)**. These inflammatory PML lesions show different enhancement pattern such as punctuate **(B)** and patchy **(D).** At the time of PML-IRIS manifestation, the PML lesions have increased in size, and the contrast enhancement of the main PML lesion **(H and I)** as well as in and around the perivascular T2 lesions **(F and G)** has also markedly increased. In addition, there are now signs of edema with mass effect around the PML lesions **(F and H)**. Adapted Wattjes 2018.[8]

## Figure A3-2 Imaging Characteristics of MS and PML



DWI = diffusion weighted imaging; FLAIR = fluid attenuated inversion recovery; MS = multiple sclerosis; PMS = progressive multifocal leukoencephalopathy.

FLAIR (left) and DWI (right) images. DWI can help determine new lesions (hyperintense) on a background of older diffuse MS lesions (right). Adapted from MS-PML.org.

## Table A3-2 Imaging Characteristics of MS and PML[1,6,7]

| Parameters | MS | PML |
|---|---|---|
| Location | • Unilateral or bilateral | • Often bilateral |
| | • Mostly located in periventricular, deep white matter, cerebellum, spinal cord areas | • [a] Subcortical frontal (+++), parietal (++), occipital (+) white matter (involving U-fibers) is the prime site |
| | • Also cortical and deep grey matter | • Cortex and basal ganglia are often involved |
| | • U-fibers may be involved | • Can involve corpus callosum but unusual; rarely brainstem and posterior fossa |
| Appearance and Borders | • Focal (mostly) | • Multifocal |
| | • Well-defined lesions with sharp edges; mostly round or finger-like in shape (especially periventricular lesions) | • Ill-defined lesions with sharp border towards grey matter, and ill-defined border towards white matter |
| Size | • Usually < 3cm | • Usually > 3cm |
| Mode of extension | • Initially focal, lesions enlarge within days or weeks and later decrease in size within months | • Lesions increase in size and new lesions appear |
| | | • Confluence with other lesions is common |

## Table A3-2 Imaging Characteristics of MS and PML[1,6,7] (cont.)

| Parameters | MS | PML |
|---|---|---|
| Mass effect | Acute lesions, in particular large lesions, show some mass effect | Not typical in neither small nor large lesions. PML-IRIS may show mass effect |
| T2W | Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure<br>Subacute and chronic lesions: hyperintense, with no ring structure | Always hyperintense<br>[a] Small, punctate T2-hyperintense lesions in the immediate vicinity of the main lesion are often present |
| FLAIR | Hyperintense equal to T2; sharply delineated | Always hyperintense (better appreciated than on T2W images making it more sensitive for detection of PML in subcortical structures) |
| T1W | Isointense or hypointense | [a] Typically hypointense; no reversion of signal intensity (hyperintensity suggestive of PML-IRIS) |
| DWI | It can be hyperintense or non-hyperintense | [a] Always hyperintense; in larger lesions there is a hyperintense rim at the lesion's edge [b] |
| Contrast enhancement | Acute lesions enhance—nodular or incomplete ring | 40%–50% enhancement–linear, nodular, punctate or peripheral pattern (variable) |
| Atrophy | Focal atrophy possible, due to focal degeneration | No atrophy in the early phase |

DWI = diffusion weighted imaging; FLAIR = fluid attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; T1W = T1-weighted; T2W = T2-weighted.

[a] Features especially helpful in the identification of small PML lesions.

[b] In the early stages of disease, DWI shows high signal owing to swollen and dying oligodendrocytes. Treatment commencement results in the lesion rim losing its DWI hyperintensity, and over time the lesion becomes hypointense owing to tissue destruction. Apparent diffusion coefficient values rise with progressive white matter injury, in keeping with more irreversible damage. This evolution of DWI signal changes is essential in monitoring disease progression and treatment response.

## A3–3 PML DIAGNOSIS

American Academy of Neurology consensus statements mandate that diagnosis is made from brain biopsy, or more commonly from clinical findings combined with JCV DNA in CSF, typically supported by typical imaging findings.[9]

Verification of a PML diagnosis without symptoms is challenging. **At a very early stage, CSF viral load might be low or undetectable and the dynamic nature of PML cannot be confirmed by a single MRI scan.** PML lesions usually evolve on repeated

imaging, either because the JCV-induced disease progresses or because the inflammatory response (IRIS) controlling the infection results in evolution of the image characteristics. Thus, stable appearances on repeated MRI may help to rule out PML, whereas evolving lesions are consistent with a PML diagnosis.[2]

## PML BRAIN MRI PROTOCOL:

Although recommendations on specific protocols are provided by different groups (e.g., MAGNIMS, CMSC), an optimal protocol would include the following sequences:

- FLAIR
- T2-weighted
- T1-weighted with and without gadolinium
- DWI (diffusion weighted imaging)

### Table A3-3 Establishing the diagnosis with Clinical, Radiographic and Laboratory Data (Modified from AAN Criteria[9])

| Certainty of PML Diagnosis | Compatible Clinical Features | Compatible Imaging Findings | CSF PCR for JC Virus |
|---|---|---|---|
| Definite | + | + | + |
| Probable | + | – | + |
| | – | + | + |
| | + | + | –/ND |
| Possible | – | – | + |
| | – | (+) [a] | – |
| Not PML | + | – | – |
| | – | – | – |

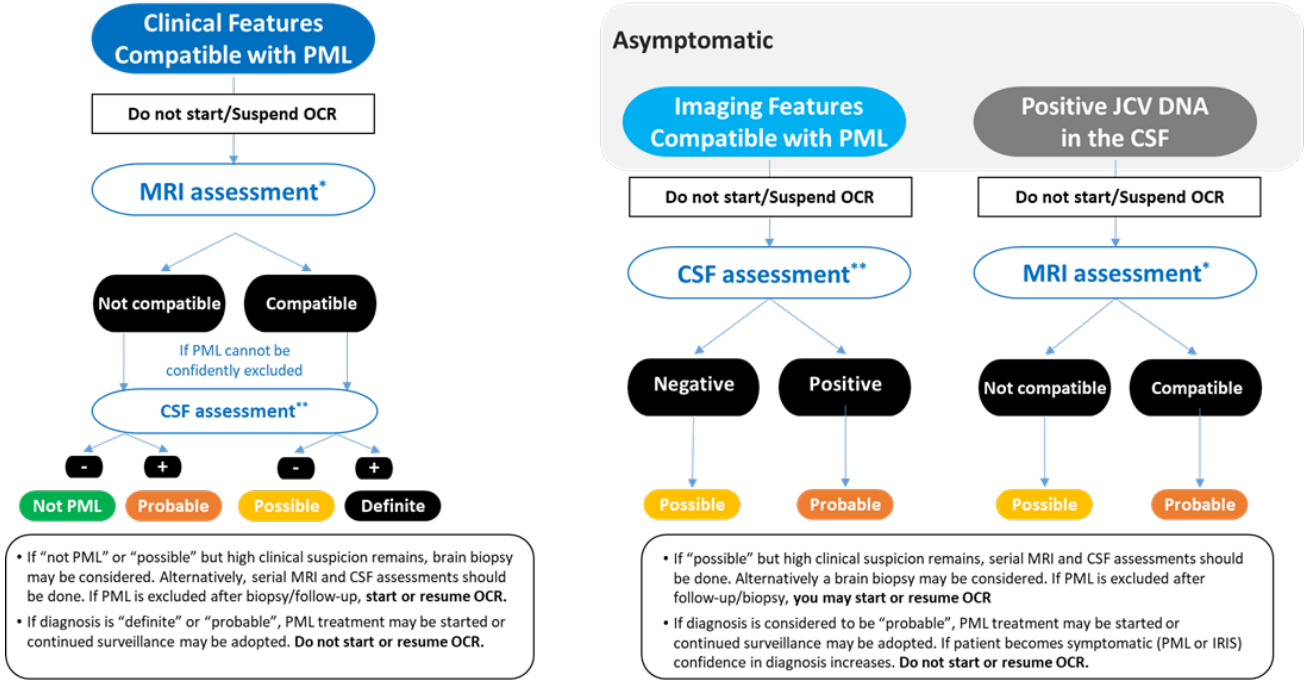
AAN = American Academy of Neurology; JCV = John Cunningham virus; MRI = magnetic resonance imaging; ND = not done or equivocal result; NTZ = natalizumab; PML = progressive multifocal leukoencephalopathy; + = positive; – = negative.

[a] Note: according to current AAN criteria, no diagnosis of PML can be made if only compatible imaging findings are present. However, recent evidence has shown that asymptomatic patients treated with NTZ, who have negative CSF JCV PCR results but PML compatible MRI changes, may later develop symptoms or have JCV detected in the CSF.[10]

## A3–3.1 ACTION STEPS IF PML IS SUSPECTED (CLINICAL, IMAGING OR CSF SUSPICION):

- If the patient has clinical features that are suggestive of PML (see Table A3-1), further investigations should include brain MRI with a specific protocol, and/or CSF analysis for JCV DNA (using a validated ultrasensitive PCR assay).
- If the patient is asymptomatic but has imaging features that are suggestive of PML (see Table A3-2), further investigations should include CSF analysis for JCV DNA (using a validated ultrasensitive PCR assay).
- If the patient is asymptomatic but has detectable copies of JCV DNA in the CSF using a validated and ultrasensitive PCR assay (in cases where this method is used for PML surveillance), further investigations should include brain MRI with specific protocol.

**Figure A3-3 Suggested Algorithm for Diagnosis of Progressive Multifocal Leukoencephalopathy**




CSF = cerebrospinal fluid; DWI = diffusion weighted imaging; FLAIR = fluid attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; JCV = John Cunningham virus; LLOQ = lower limit of quantification; MRI = magnetic resonance imaging; MS = multiple sclerosis; PMS = progressive multifocal leukoencephalopathy; RT = reverse transcription; T1W = T1-weighted; T2W = T2-weighted.

* Optimal MRI assessment would include the following sequences: FLAIR, T2W, T1W with and without gadolinium, DWI.

** An ultrasensitive RT-PCR assay with a LLOQ of 10 genome copies/mL is recommended (further details on UNILABS assay https://stratifyjcv.unilabsweb.com/csfjcvdnatest.aspx or QUEST assay https://testdirectory.questdiagnostics.com/test/test-detail/18939/?cc=SJC)

## A3–4 TREATMENT SWITCHING CONSIDERATIONS

Treatment with natalizumab is associated with the highest risk of PML in anti-JCV antibody positive patients (risk further varies with anti-JCV antibody index levels in serum) and treatment duration >2 years (class I according to a recent classification), while dimethyl fumarate (DMF) and fingolimod are deemed as class II agents with a low, but real, risk of PML.[3]

### NATALIZUMAB (NTZ)

- Natalizumab has pharmacodynamic effects for approximately 12 weeks following the last dose, but the risk of PML persists for 6 months after discontinuing treatment with natalizumab, and has been reported in patients who did not have findings suggestive of PML at the time of discontinuation. Physicians should therefore remain vigilant for clinical and radiological features of PML for approximately 6 months after NTZ discontinuation (Natalizumab USPI and SmPC)
- It is important to follow the natalizumab prescribing information which outlines the need for continued monitoring of natalizumab patients following discontinuation of the drug and potential switch to another treatment. The following recommendations apply to patients treated with natalizumab who are being considered for switching to ocrelizumab:
    1. To determine the optimal washout period when switching from natalizumab to ocrelizumab, physicians should consider balancing the risk of return of MS disease activity with possible additive immunosuppressive effects of each drug
    2. In patients with new or recent worsening of neurological signs/symptoms and/or a new or evolving lesion on brain MRI, PML must be ruled out (see suggested algorithm in Figure A3-3)
    3. In asymptomatic patients who carry a higher risk of PML as per established risk stratification factors according to natalizumab labels, rule out PML as far as possible, by excluding new or evolving lesions on brain MRI. A repeat MRI assessment that includes at least FLAIR/T2 and DWI sequences is recommended 3 and 6 months after discontinuing natalizumab in patients at high risk of PML who initiated ocrelizumab.[2]

### FINGOLIMOD (FNG) AND DIMETHYL FUMARATE (DMF)

- **For patients switching from fingolimod to ocrelizumab**, there is no definite risk-mitigation strategy. Based on available data, there appear to be no clinically or radiographically unique features of FNG-associated PML. In these patients there appears to be no correlation with profound lymphopenia and lymphocyte subsets (CD4, CD8, and CD4/8 ratios), and this is not believed to be informative of PML risk.[5]

- **For patients switching from DMF to ocrelizumab**, there is no definite risk-mitigation strategy. Prolonged lymphopenia with absolute lymphocyte counts of less than 750 lymphocytes/mL accounts for most cases of DMF-associated PML, although the risk might reside particularly in the loss of CD8+ cells that are crucial to control of JCV.[2]
- In patients switching from fingolimod or dimethyl fumarate with new or recent worsening of neurological signs/symptoms and/or a new or evolving lesion on brain MRI suggestive of PML, PML must be ruled out (see Figure A3-3)

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# Appendix 4
# Expanded Disability Status Scale (EDSS)

## A4–1 EDSS STEPS

| | |
|---|---|
| **0** | Normal neurological exam (all FS Grade 0) |
| **1.0** | No disability, minimal signs in one FS (one FS Grade 1) |
| **1.5** | No disability, minimal signs in more than one FS (more than one FS Grade 1) |
| **2.0** | Minimal disability in one FS (one FS Grade 2, others 0 or 1) |
| **2.5** | Minimal disability in two FS (two FS Grade 2, others 0 or 1) |
| **3.0** | Fully ambulatory but with moderate disability in one FS (one FS Grade 3, others 0 or 1) **OR**<br>Fully ambulatory but with mild disability in three or four FS (three/four FS Grade 2, others 0 or 1) |
| **3.5** | Fully ambulatory but with moderate disability in one FS (one FS Grade 3) and mild disability in one or two FS (one / two FS Grade 2) and others 0 or 1; **OR**<br>Fully ambulatory with two FS Grade 3 (others 0 or 1); **OR**<br>Fully ambulatory with five FS Grade 2 (others 0 or 1) |
| **4.0** | **Fully ambulatory for ≥ 500 meters without aid or rest**; up and about some 12 hours a day characterized by relatively severe disability consisting of one FS Grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps |
| **4.5** | **Ambulatory for 300–500 meters without aid or rest**; up and about much of the day, characterized by relatively severe disability usually consisting of one FS Grade 4 and combination of lesser grades exceeding limits of previous steps |
| **5.0** | **Ambulatory for 200–300 meters without aid or rest** (usual FS equivalents include at least one FS Grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5) |
| **5.5** | **Ambulatory for 100–200 meters without aid or rest** |
| **6.0** | **Ambulatory for at least 100 meters with intermittent or constant unilateral assistance** (cane or crutch) with or without rest **OR**<br>Ambulatory < 100 meters without help or assistance **OR**<br>Ambulatory ≥ 50 meters with unilateral assistance **OR**<br>Ambulatory ≥ 120 meters with bilateral assistance |
| **6.5** | **Ambulatory for at least 20 meters with constant bilateral assistance (canes or crutches)** without rest **OR**<br>Ambulatory for < 50 meters with unilateral assistance (cane or crutch) **OR**<br>Ambulatory 5 to 120 meters with constant bilateral assistance (canes or crutches) |
| **7.0** | **Unable to walk 5 meters even with aid, essentially restricted to wheelchair**; wheels self and transfers alone; up and about in wheelchair some 12 hours a day |
| **7.5** | **Unable to take more than a few steps; restricted to wheelchair**; may need some help in transferring and in wheeling self |
| **8.0** | **Essentially restricted to bed or chair or perambulated in wheelchair**, but out of bed most of day; retains many self-care functions; generally has effective use of arms |
| **8.5** | **Essentially restricted to bed much of the day**; has some effective use of arm(s); retains some self-care functions |

| | |
|---|---|
| **9.0** | Helpless bed patient; can communicate and eat |
| **9.5** | Totally helpless bed patient; unable to communicate effectively or eat/swallow |
| **10** | Death due to MS |

Standardized Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983:33,1444–52.


## FUNCTIONAL SYSTEM SCORES

### 1. VISUAL FSS

| | |
|---|---|
| **0** | normal |
| **1** | disc pallor and/or small scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67) |
| **2** | worse eye with maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34) |
| **3** | worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.21) |
| **4** | worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.2–0.1); Grade 3 plus maximal acuity of better eye of 20/60 (0.33) or less |
| **5** | worse eye with maximal visual acuity (corrected) less than 20/200 (0.1); Grade 4 plus maximal acuity of better eye of 20/60 (0.33) or less |
| **6** | Grade 5 plus maximal visual acuity of better eye of 20/60 (0.33) or less |

### 2. BRAINSTEM FSS

| | |
|---|---|
| **0** | normal |
| **1** | signs only |
| **2** | moderate nystagmus and/or moderate EOM impairment and/or other mild disability |
| **3** | severe nystagmus and/or marked EOM impairment and/or moderate disability of other cranial nerves |
| **4** | marked dysarthria and/or other marked disability |
| **5** | inability to swallow or speak |

## 3. PYRAMIDAL FSS

| | |
|---|---|
| **0** | normal |
| **1** | abnormal signs without disability |
| **2** | minimal disability: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance Grade 1) and/or BMRC Grade 4 in one or two muscle groups |
| **3** | mild to moderate paraparesis or hemiparesis: BMRC Grade 4 in > two muscle groups; and/or<br>BMRC Grade 3 in one or two muscle groups (movements against gravity are possible); and/or<br>Severe monoparesis: BMRC Grade 2 or less in one muscle group |
| **4** | marked paraparesis or hemiparesis: usually BMRC Grade 2 in two limbs and/or<br>monoplegia: BMRC Grade 0 or 1 in one limb; and/or<br>moderate tetraparesis: BMRC Grade 3 in ≥ three limbs |
| **5** | paraplegia: BMRC Grade 0 or 1 in all muscle groups of the lower limbs; and/or<br>marked tetraparesis: BMRC Grade 2 or less in ≥ three limbs; and/or<br>hemiplegia |
| **6** | tetraplegia: BMRC Grade 0 or 1 in all muscle groups of the upper and lower limbs |

## 4. CEREBELLAR FSS

| | |
|---|---|
| **0** | normal |
| **1** | abnormal signs without disability |
| **2** | mild ataxia and/or moderate station ataxia (Romberg) and/or tandem walking not possible |
| **3** | moderate limb ataxia and/or moderate or severe gait/truncal ataxia |
| **4** | severe gait/truncal ataxia and severe ataxia in three or four limbs |
| **5** | unable to perform coordinated movements due to ataxia |
| **X** | pyramidal weakness (BMRC Grade ≤3) or sensory deficits interfere with cerebellar testing |

## 5. SENSORY FSS

| | |
|---|---|
| **0** | normal |
| **1** | mild vibration or figure-writing or temperature decrease only in 1 or 2 limbs |
| **2** | mild decrease in touch / pain / position sense or moderate decrease in vibration in 1 or 2 limbs<br>and/or<br>mild vibration or figure-writing or temperature decrease alone in more than 2 limbs |
| **3** | moderate decrease in touch / pain / position sense or marked reduction in vibration in 1 or 2 limbs<br>and/or<br>mild decrease in touch or pain or moderate decrease in all proprioceptive tests in > 2 limbs |

| | |
|---|---|
| **4** | marked decrease in touch or pain in 1 or 2 limbs<br>and/or<br>moderate decrease in touch or pain and/or marked reduction of proprioception > 2 limbs |
| **5** | loss (essentially) of sensation in one or two limbs<br>and/or<br>moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head |
| **6** | sensation essentially lost below the head |

## 6. BOWEL/BLADDER FSS

| | |
|---|---|
| **0** | normal |
| **1** | mild urinary hesitancy, urgency **and/or** constipation |
| **2** | moderate urinary hesitancy/retention **and/or** moderate urinary urgency/incontinence **and/or** moderate bowel dysfunction |
| **3** | frequent urinary incontinence or intermittent self-catheterization; needs enema or manual measures to evacuate bowels |
| **4** | in need of almost constant catheterization |
| **5** | loss of bladder or bowel function; external or indwelling catheter |
| **6** | loss of bowel and bladder function |

## 7. CEREBRAL FSS

| | |
|---|---|
| **0** | normal |
| **1** | signs only in decrease in mentation; mild fatigue |
| **2** | mild decrease in mentation; moderate or severe fatigue |
| **3** | moderate decrease in mentation |
| **4** | marked decrease in mentation |
| **6** | dementia |

## 8. AMBULATION SCORE

| | |
|---|---|
| **0** | unrestricted |
| **1** | Fully ambulatory ≥ 500 meters without help or assistance but not unrestricted (pyramidal or cerebellar FS ≥ 2) |
| **2** | Ambulatory ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0, defined by FSS) |
| **3** | Ambulatory ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0) |
| **4** | Ambulatory ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5) |

**Appendix 4: Expanded Disability Status Scale (EDSS)**

| | |
|---|---|
| **5** | Ambulatory $<$ 100 meters without help or assistance (EDSS 6.0) |
| **6** | Ambulatory $\geq$ 50 meters with unilateral assistance (EDSS 6.0) |
| **7** | Ambulatory $\geq$ 120 meters with bilateral assistance (EDSS 6.0) |
| **8** | Ambulatory $<$ 50 meters with unilateral assistance (EDSS 6.5) |
| **9** | Ambulatory $\geq$ 5 meters, but $<$ 120 meters with bilateral assistance, (EDSS 6.5) |
| **10** | Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0) |
| **11** | Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5) |
| **12** | essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0) |

Standardized Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983:33,1444–52.

## *A4–2 EDSS BY TELEPHONE*

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### EDSS BY PHONE

The purpose of this interview is to obtain the best possible estimate of the Expanded Disability Status Scale (EDSS) score of patients who exceptionally cannot come to the study centre and be examined by a neurologist. The current version is using the Neurostatus definitions version 04/10.2 but is fully compatible with previous versions. Ideally the same EDSS physician who assessed the patient at the last visit should do the standardized interview for EDSS by phone. The interview should be done with the patient himself. If the patient cannot be interviewed due his health condition, the interview may be done with a caregiver or his or her physician.

Question the patient about the current status (or a specified time period in the past) until the EDSS score becomes clear. Some questions may have to be modified according to the patient's last disability status since the answer may be known before asking, e.g. if the patient is wheel-chair bound, the question „do you have any disability" may be superfluous and may sound offending to some patients. Generally, the questions exploring disability scores lower than the last known EDSS score may be superfluous.

The functional system (FS) and EDSS scores should reflect MS related deficits only. In case of doubt the examining physician should assume a relation to MS. Temporary signs or symptoms that are not due to multiple sclerosis, e.g. temporal immobilisation after fracture of one limb, as well as permanent signs or symptoms that are not due to multiple sclerosis, e.g. leg amputation after accident, will not be taken into consideration when assessing the FS scores and EDSS steps, but need to be noted in the questionnaire. A “P” next to the respective entry indicates permanent non MS related deficits, a “T” temporary non MS related deficits.

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## Standardized Telephone Interview to document EDSS

***Please do refer to the Neurostatus definition booklet, version 04/10.2 for the correct definitions of FS and walking distance and EDSS***

**1 Is the interview done with**

*(If the interview is done with a caregiver or physician, please adapt questions as needed!)*

❑ patient

❑ caregiver

*please note relationship:* .....

❑ physician

*please note specialization (neurologist, general practitioner, ...) :* .....

**2 As compared to now, did you observe in the last months, years or since your last visit to the centre any change in the complaints related to your disease?**

❑ improved much
❑ improved a little
❑ remained unchanged
❑ got a little worse
❑ got much worse

**3 Are you able to walk without aid?**

| | |
|---|---|
| ❑ yes | continue → question 3a |
| ❑ no | continue → question 4 |

**3a How far can you walk without any aid or rest?**

*Please refer to known distances (post office, shop, church etc.) and crosscheck with time estimates (1km equals 15 min) as well as comparison with the previous assessment.*

| | |
|---|---|
| ❑ unrestricted (not less than healthy peers, see Chapter 8 "Ambulation") | (EDSS 0 up to 5.0) |
| ❑ fully ambulatory (less than healthy peers but at least 500m, see Chapter 8 "Ambulation") | (EDSS 2 up to 5.0) |

If one of these 2 boxes is ticked, EDSS will be determined by the FS scores directly

| | |
|---|---|
| ❑ more than 300m but less than 500m | (EDSS 4.5) |
| ❑ more than 200m but less than 300m | (EDSS 5.0) |
| ❑ more than 100m but less than 200m | (EDSS 5.5) |

| | |
|---|---|
| ❑ less than 100m but no assistance used | continue → question 4 |
| ❑ between 100m and 300m but no reliable data | continue → question 3b |

**3b Are you able to do your normal daily work?**

*This question is only used if no reliable information about walking distance between 100m and 300m can be obtained, but note that incapacity for work is confounded by many subjective and social factors other than MS.*

| | |
|---|---|
| ❑ yes, no limitation (but walking distance was less than 300m) | (EDSS 4.5) |
| ❑ no, unable to work a full day without special provision | (EDSS 5.0) |
| ❑ no, normal daily activities are not possible | (EDSS 5.5) |

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**4 Are you able *to walk with unilateral or bilateral assistance*?**

| | |
|---|---|
| ❑ needs only unilateral assistance | continue → question 4a |
| ❑ needs bilateral assistance or help by other person | continue → question 4b |
| ❑ not able to walk more than a few steps with bilateral assistance | continue → question 5 |

**4a How many meters can you walk without rest, using constant or intermittent unilateral assistance?**

*Please refer to known distances (post office, shop, church etc.) and crosscheck with time estimates (1km equals 15 min) as well as comparison with the previous assessment.*

| | |
|---|---|
| ❑ more than 50m | (EDSS 6.0) |
| ❑ less than 50m | (EDSS ≥ 6.0) continue → question 4b |

**4b How many meters can you walk without rest, using constant or intermittent bilateral assistance?**

| | |
|---|---|
| ❑ more than 120m | (EDSS 6.0) |
| ❑ more than 5m but less than 120m | (EDSS 6.5) |
| ❑ less than 5m | (EDSS ≥ 7.0) continue → question 5 |

**5 Do you need a wheelchair?**

❑ no (EDSS ≤ 6.5) re-evaluate and use therefore again questions 3 and 4!
❑ yes (EDSS ≥ 7.0) continue → questions 5a-c

**5a Can you handle a standard wheelchair alone?**

❑ yes
❑ no

**5b Can you transfer yourself alone (e.g. from wheelchair to bed or toilet)?**

❑ yes (EDSS ≥ 7.0)
❑ no (EDSS ≥ 7.5)

**5c Do you stay for more than 8 hours per day in your wheelchair?**

❑ yes
❑ no

| | | |
|---|---|---|
| ***summary of 5a-c:*** | all no | (EDSS ≥ 7.5) continue → question 6 |
| | one or two no | (EDSS 7.5) |
| | all yes | (EDSS 7.0) |

**6 Are you restricted to bed for great part of the day?**

| | |
|---|---|
| ❑ no (EDSS 7.5) | |
| ❑ yes (EDSS ≥ 8.0) | continue → question 7a-c |

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**7a Can you use your arms for eating?**

- ❑ yes
- ❑ no

**7b Can you wash your face?**

- ❑ yes
- ❑ no

**7c Can you brush your teeth?**

- ❑ yes
- ❑ no

| | | |
|---|---|---|
| ***summary of 7a-c:*** | all no | (EDSS 9.0) |
| | two no | (EDSS 8.5) |
| | all yes | (EDSS 8.0) |

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## 8 Assigning the FS Scores

*Please use the Definition-Manual Version 04/10.2 to calculate the correct EDSS. The Visual FS and the Bowel & Bladder FS are already converted within the given answers. Since for this part of the questionnaire the walking distance must be at least 500m, the FS-combination will directly define the EDSS.*

### Visual FS

Do you have any problems with your vision? (despite optical correction like glasses or contact lenses)

0 = no
1 = slightly reduced visual acuity with one eye, glasses do not help (the other eye is much better)
2 = obvious vision problems with one eye, glasses do not help (the other eye is much better)
3 = obvious vision problems even when using both eyes, but can read with a magnifying glass or read large print
4 = vision is almost lost even when using both eyes and even when using a magnifying glass

***Visual-FS =***

### Brainstem FS

Do you have double vision when looking at something?

0 = no
2 = yes, when looking in some directions but does not affect my quality of life
3 = yes, almost always, one eye has to be covered, it does affect my quality of life,
4 = yes, complete loss of movement in more than one direction of gaze in either eye

When touching your face, has your sensation changed recently?

0 = no, normal sensation
2 = yes, numbness when touching some parts of the face
3 = yes, clearly decreased sensation in parts of the face, or pain attacks in the face
4 = yes, touch is not felt at all, in the complete left face, right face or both sides

When laughing or frowning your eyebrows, is your face symmetric and could you close both eyes completely?

0 = yes
2 = no, slight asymmetric only when laughing or frowning eyebrows
3 = no, asymmetric face also at rest, closure of one eye slightly impaired
4 = no, lid closure of one or both eyes impossible, difficulty with liquids

Do you have problems with hearing?

0 = no
2 = yes, slightly decreased hearing on one side
3 = yes, does not hear finger rub in one or both ears
4 = yes, deaf

Can you speak clearly?

0 = yes
2 = no, some difficulties in speaking, realized by others when talking with the patient
3 = no, dysarthria impairs conversation
4 = no, incomprehensible speech
5 = no, inability to speak

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Do you have difficulties with swallowing?

0 = no
2 = yes, difficulty with thin liquids
3 = yes, difficulty with thin liquids and solid food
4 = yes, requires pureed diet
5 = yes, inability to swallow

***Please take the worse single score to define the FS!***

***Brainstem-FS =***

**Pyramidal FS**

Do you have had problems moving one or both arms? (no problems with your legs)

0 = no
2 = yes, one arm cannot be elevated above horizontal
3 = yes, almost no function of one arm
4 = yes, complete loss of function of one arm

Do you have problems moving one or both of your legs? (no problems with your arms)

0 = no
2 = yes, one leg cannot be elevated when in supine position
3 = yes, almost no function of one leg or mild to moderate paraparesis
4 = yes, complete loss of function of one leg or marked parapareris
5 = yes, paraplegia

Do you have problems moving your legs as well as your arms?

0 = no
3 = yes, mild weakness of one body half
4 = yes, almost no function of one body half (arm and leg) or moderate quadriparesis
5 = yes, complete loss of function of one body half (arm and leg) or marked quadriparesis)
6 = yes, quadriplegia

***Please take the worse single score to define the FS!***

***Pyramidal-FS =***

**Cerebellar FS**

Do you have any tremor or clumsy movements?

0 = no
2 = yes, tremor or clumsy movements seen easily, but adequate movements (like handwriting, closing buttons) possible
3 = yes, tremor or clumsy movements interfere with adequate movements (like handwriting, closing buttons)
4 = yes, most functions are very difficult due to tremor or clumsy movements
5 = yes, no coordinated movements possible

Do you have problems with your balance when walking? When sitting?

0 = no
2 = yes, lose balance when walking on heels or toes, or walking on a line
3 = yes, lose balance on ordinary walking or when sitting
4 = yes, unable to walk, or require support by another person or assisting device because of ataxia
5 = yes, unable to sit or walk even with assistance

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***Please take the worse single score to define the FS!***

***Cerebellar-FS =***

**Sensory FS**

When touching your body, is the sensation normal?

0 = yes
2 = no, numbness when touching of 1 or 2 limbs
3 = no, clearly decreased sensation in 1 or 2 limbs or numbness in many parts of the body below the head
4 = no, even forced touching is not felt at all in 1 or 2 limbs or just clearly decreased sensation in more than 2 limbs
5 = no, sensation essentially lost in 1 or 2 limbs or moderate decrease of sensation for most of the body below the head
6 = no, sensation essentially lost below the head

***Sensory FS =***

**Bowel & Bladder FS**

Do you have any problems urinating or with bowel movements?

0 = no
2 = yes, moderate hesitancy, urgency; or retention; or rare (up to once a week) urinary or faecal incontinence; or severe constipation
3 = yes, frequent urinary or faecal incontinence, but spontaneous voiding generally possible; needs enemata or manual measures to evacuate bowels; in need of almost constant catheterization
4 = yes, loss of bladder function, permanent catheterization necessary; or loss of bowel function
5 = yes, loss of bowel and bladder function

***Bowel & Bladder FS =***

**Cerebral FS**

Do you have any concentration or memory problems?

0 = no
2 = yes, concentration and memory problems, decreased ambition, problems to cope with stress but able to handle the daily routine not apparent while taking the interview
3 = yes, definite abnormalities apparent while taking the interview but still oriented to person, place and time
4 = yes, marked decrease in mentation apparent while taking the interview not oriented in one or two spheres
5 = yes, meaningful conversation not possible due to confusion and/or disorientation

**Cerebral-FS =**

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# Appendix 5
# Methods for Assessing and Recording Adverse Events

## A5–1 ASSESSMENT OF SEVERITY OF ADVERSE EVENTS

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The table below will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

### Table A5-1 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 adverse event [d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v5.0), 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 a serious adverse event (see Section 5.1.1.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.1.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.1.1.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.1.

## A5–2 ASSESSMENT OF CAUSALITY OF ADVERSE EVENTS

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

Physicians 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 adverse event 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

## A5–3 PROCEDURES FOR RECORDING ADVERSE EVENTS

### A5–3.1 INFUSION-RELATED REACTIONS

Adverse events that occur during or within 24 hours after study medicine administration and are judged to be related to studied medicinal product infusion should be captured as a diagnosis (e.g., "infusion-related reaction [IRR]") in the adverse event section of the eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated IRR section of the eCRF. If a patient experiences both a local and systemic reaction to the same dose of studied medicinal product, each reaction should be recorded separately in the adverse event section of the eCRF, with signs and symptoms also recorded separately on the dedicated IRR section of the eCRF.

### A5–3.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For adverse events other than IRR (see Section A5–3.1 above), a diagnosis (if known) should be recorded in the adverse event 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 adverse event section of the CRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

### A5–3.3 ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events 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 adverse event

that is separated in time from the initiating event should be recorded as an independent event in the adverse event section of the CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF.
- If vomiting results in severe dehydration, both events should be reported separately on the CRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the CRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the CRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the CRF.

All adverse events should be recorded separately in the adverse event section of the eCRF if it is unclear as to whether the events are associated.

## A5–3.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once in the adverse event 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 adverse event becomes more severe, the most extreme severity should also be recorded in the adverse event section of the CRF. If the event becomes serious, it should be reported to the marketing authorization holder (MAH) immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.1.3.1 for reporting instructions). The adverse event 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 serious adverse events.

A recurrent adverse event is one that resolves between patient's evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately in the adverse event section of the CRF.

## A5–3.5 ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the adverse event section of the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the adverse event section of the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkaliemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the adverse event section of the eCRF (see Section A5–3.4 for details on recording persistent adverse events).

## A5–3.6 ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the adverse event section of the eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the adverse event section of the eCRF (see Section A5–3.4 for details on recording persistent adverse events).

## A5–3.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ the baseline value) in combination with either an elevated total bilirubin ($>2\times$ the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, physicians must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ the baseline value in combination with total bilirubin $>2\times$ the ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ the baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the adverse event section of the CRF (see Section A5–3.5) and reported to the MAH immediately (i.e., no more than 24 hours after learning of the event) either as a serious adverse event or a non-serious AESI (see Section 5.1.3.1).

## A5–3.8 DEATHS

All events with an outcome or consequence of death should be classified as serious adverse events 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 A5–3.10).

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.1.2.1), regardless of relationship to study medicine, must be recorded in the adverse event section of the eCRF and immediately reported to the MAH (see Section 5.1.3.1).

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 adverse event section of the eCRF. 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 pre-existing 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 adverse event 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.

## A5–3.9 PRE-EXISTING MEDICAL CONDITIONS

A pre-existing medical condition is one that is present at the baseline visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions in the eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events in the adverse event section of the eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

## A5–3.10 LACK OF THERAPEUTIC EFFICACY

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on EDSS score. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

## A5–3.11 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.1.1), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for giving birth
- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours
- Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones, and diagnostic testing. Such events should still be recorded as medical procedures in the concomitant procedures/treatments eCRF
- Hospitalization to receive trial medication such as infusions of ocrelizumab unless this is prolonged (more than 24 hours)

- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone

## A5–3.12 OVERDOSES, MISUSES, ABUSES, OFF-LABEL USE, OCCUPATIONAL EXPOSURE, OR MEDICATION ERROR

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the eCRF. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error (including intercepted or potential), or occupational exposure reports must be forwarded to the MAH with or without an AE.

Reports with or without an adverse event should be forwarded to the MAH as per non-serious timelines. If the associated adverse event fulfils the seriousness criteria, the event should be reported to the MAH immediately (i.e., no more than 24 hours after learning of the event, see Section 5.1.3.1).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

## A5–3.13 QUALITY DEFECTS, FALSIFIED PRODUCTS AND PRODUCT COMPLAINTS

Reports of suspected or confirmed falsified product or quality defect of a product, with or without an associated AE, should be forwarded to the MAH as per non-serious timelines. If the associated adverse event fulfils the seriousness criteria, the event should be reported to the MAH immediately (i.e., no more than 24 hours after learning of the event, see Section 5.1.3.1).

## A5–3.14 DRUG INTERACTIONS

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol, should be forwarded to the MAH as per non-serious timelines. If the associated adverse event fulfils the seriousness criteria, the event should be reported to MAH immediately (i.e., no more than 24 hours after learning of the event, see Section 5.1.3.1).

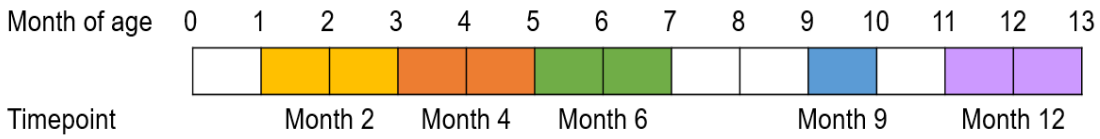
# Appendix 6
# Time Windows for Infant Growth Velocity and Child Developmental Milestone Assessments

The following time windows must be applied for the assessment of growth velocity and child developmental milestones at Months 2, 4, 6, 9, and 12:

| Timepoint | Associated time window |
|---|---|
| Month 2[a] | 1 month 0 days through 2 months 30 days |
| Month 4 | 3 months 0 days through 4 months 30 days |
| Month 6 | 5 months 0 days through 6 months 30 days |
| Month 9 | 9 months 0 days through 9 months 30 days |
| Month 12 | 11 months 0 days through 12 months 30 days |

[a] Where possible, the month 2 assessment can be combined with Visit 4 (Week 6 of life [±7 days]).

The following visualization depicts the timepoints and corresponding time windows based on the infant's month of age:




To calculate whether the infant falls under the respective assessment window based on its date of birth and weeks premature, the ASQ-3 age calculator can be used: https://agesandstages.com/free-resources/asq-calculator/. Note that an adjustment for premature birth will need to be made either manually or by using the calculator.

Assessment of growth velocity at Months 2, 4, 6, 9, and 12 must fall under the corresponding time windows of the ASQ-3; however, the date of assessment or data collection does not need to correspond to the same date of ASQ-3 assessment. Whenever possible, assessment of growth velocity may be collected as part of the infant's routine postnatal care visits performed by e.g., the pediatrician.

# Appendix 7
## *B-cell Reference Ranges by Week of Life: Absolute and Percentage Counts*

**TABLE III.** B-cell reference ranges by week of life: Absolute and percentage counts

| | Absolute B-cell count (cells/μL) | | | Percentage B-cell count (%) | | |
|---|---|---|---|---|---|---|
| Week | Mean | LLN* | ULN† | Mean | LLN* | ULN† |
| 1 | 452 | 127 | 1165 | 11.3 | 4.6 | 23.1 |
| 2 | 513 | 144 | 1322 | 12.1 | 5.0 | 24.9 |
| 3 | 577 | 163 | 1489 | 13.1 | 5.4 | 26.8 |
| 4 | 645 | 182 | 1664 | 14.0 | 5.8 | 28.7 |
| 5 | 716 | 202 | 1846 | 14.9 | 6.1 | 30.5 |
| 6 | 788 | 222 | 2033 | 15.8 | 6.5 | 32.4 |
| 7 | 863 | 243 | 2225 | 16.7 | 6.9 | 34.3 |
| 8 | 937 | 264 | 2418 | 17.6 | 7.2 | 36.1 |
| 9 | 1012 | 285 | 2612 | 18.4 | 7.6 | 37.8 |
| 10 | 1087 | 306 | 2803 | 19.3 | 7.9 | 39.5 |
| 11 | 1159 | 327 | 2991 | 20.0 | 8.3 | 41.1 |
| 12 | 1230 | 346 | 3172 | 20.8 | 8.6 | 42.7 |
| 13 | 1297 | 365 | 3346 | 21.5 | 8.9 | 44.1 |
| 14 | 1361 | 383 | 3511 | 22.2 | 9.1 | 45.5 |
| 15 | 1420 | 400 | 3665 | 22.8 | 9.4 | 46.8 |
| 16 | 1475 | 416 | 3807 | 23.4 | 9.6 | 47.9 |
| 17 | 1525 | 430 | 3935 | 23.9 | 9.8 | 49.0 |
| 18 | 1570 | 442 | 4050 | 24.3 | 10.0 | 49.9 |
| 19 | 1609 | 453 | 4151 | 24.7 | 10.2 | 50.7 |
| 20 | 1642 | 463 | 4237 | 25.1 | 10.3 | 51.5 |
| 21 | 1670 | 470 | 4308 | 25.4 | 10.5 | 52.1 |
| 22 | 1692 | 477 | 4364 | 25.6 | 10.6 | 52.5 |
| 23 | 1708 | 481 | 4406 | 25.8 | 10.6 | 52.9 |
| 24 | 1719 | 484 | 4435 | 25.9 | 10.7 | 53.2 |
| 25 | 1725 | 486 | 4450 | 26.0 | 10.7 | 53.4 |
| 26 | 1726 | 486 | 4453 | 26.1 | 10.7 | 53.5 |
| 27 | 1723 | 485 | 4445 | 26.1 | 10.8 | 53.5 |
| 28 | 1716 | 483 | 4426 | 26.1 | 10.7 | 53.5 |
| 29 | 1705 | 480 | 4398 | 26.0 | 10.7 | 53.3 |
| 30 | 1691 | 476 | 4362 | 25.9 | 10.7 | 53.2 |
| 31 | 1675 | 472 | 4319 | 25.8 | 10.6 | 52.9 |
| 32 | 1656 | 466 | 4270 | 25.6 | 10.6 | 52.6 |
| 33 | 1635 | 460 | 4216 | 25.5 | 10.5 | 52.3 |
| 34 | 1613 | 454 | 4159 | 25.3 | 10.4 | 51.9 |
| 35 | 1589 | 448 | 4099 | 25.1 | 10.3 | 51.5 |
| 36 | 1566 | 441 | 4037 | 24.9 | 10.3 | 51.0 |
| 37 | 1541 | 434 | 3975 | 24.7 | 10.2 | 50.6 |
| 38 | 1517 | 427 | 3912 | 24.4 | 10.1 | 50.1 |
| 39 | 1494 | 421 | 3851 | 24.2 | 10.0 | 49.7 |
| 40 | 1471 | 414 | 3792 | 24.0 | 9.9 | 49.2 |
| 41 | 1449 | 408 | 3735 | 23.8 | 9.8 | 48.8 |
| 42 | 1428 | 402 | 3682 | 23.6 | 9.7 | 48.4 |
| 43 | 1409 | 397 | 3632 | 23.4 | 9.6 | 48.0 |
| 44 | 1391 | 392 | 3588 | 23.2 | 9.6 | 47.6 |
| 45 | 1376 | 388 | 3548 | 23.0 | 9.5 | 47.3 |
| 46 | 1363 | 384 | 3515 | 22.9 | 9.4 | 47.0 |
| 47 | 1352 | 381 | 3488 | 22.8 | 9.4 | 46.7 |
| 48 | 1345 | 379 | 3468 | 22.7 | 9.3 | 46.5 |
| 49 | 1340 | 377 | 3456 | 22.6 | 9.3 | 46.3 |
| 50 | 1339 | 377 | 3452 | 22.5 | 9.3 | 46.2 |
| 51 | 1341 | 378 | 3458 | 22.5 | 9.3 | 46.2 |
| 52 | 1347 | 379 | 3475 | 22.5 | 9.3 | 46.3 |

*LLN*, Lower limit of normal; *ULN*, Upper limit of normal.
*Defined as the 2.5th percentile of B-cell count.
†Defined as the 97.5th percentile of B-cell count.

### *REFERENCE*

*Borriello F, Pasquarelli N, Law L, et al. Normal B-cell ranges in infants: a systematic review and meta-analysis. J Allergy Clin Immunol. 2022; 150:1216–24.*

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|---|---|
| Approval Task | Yusuf Tanrikulu (tanrikuy)<br>Deputy EU QPPV<br>05-Jun-2023 08:55:19 GMT+0000 |

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