Official Title: A Phase IV, Multicenter, Open-Label Study Evaluating B-Cell Levels in Infants of Lactating Women with CIS or MS Receiving Ocrelizumab – The Sopranino Study

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PROTOCOL

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PROTOCOL NUMBER:	MN42989
VERSION NUMBER:	4 (United States)
EUDRACT NUMBER:	2021-000063-79
IND NUMBER:	100593
NCT NUMBER:	NCT04998851
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.*

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PROTOCOL HISTORY

Protocol			Associated Parent Protocol	
Country or Region	**Version**	**Date Final**	**Version**	**Date Final**
United States	4	See electronic date stamp on final page of this document	3	5 June 2023
			2	1 April 2022
		-	1	15 March 2021

PROTOCOL AMENDMENT, VERSION 4 (United States): RATIONALE

Protocol MN42989 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 infant postpartum exposure to ocrelizumab via breastmilk has been updated to present data from an analysis performed with a cut-off date of 31 March 2022, replacing data from an analysis performed up to 31 March 2021 (Section 1.3).
- The secondary objectives have been amended to include the evaluation of the relative exposure to ocrelizumab in infants of lactating women with clinically isolated syndrome (CIS) or multiple sclerosis (MS) receiving ocrelizumab postpartum. The average relative infant dose will be assessed over 60 days, calculated as the average oral daily infant dosage (mg/kg/day) divided by the maternal dosage (mg/kg/day), multiplied by 100 (Sections 2 [Table 1] and 6.5.2).
- In the endpoint for the exploratory objective "to evaluate the evolution of B-cell levels over the first year of life in infants of lactating women with CIS or MS receiving ocrelizumab postpartum", language has been clarified that trajectory (absolute and percentage changes) of B-cells (CD19+ cell) in the infant will be measured from Day 30 after the mother's first ocrelizumab postpartum infusion to 1 month after the first or second dose of 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 sample size has been reduced from at least 20 to at least 10 women with CIS or MS. Given that women with CIS or MS are not routinely treated with ocrelizumab during breastfeeding 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 6.2).
- The telephone interview has been further expanded to include that women using the lactational amenorrhea method as contraception will be asked whether the three necessary criteria outlined in Section 4.1.1 to ensure adequate protection from an unplanned pregnancy are applied (Figure 1 [footnotes]; Sections 3.1.3, 3.1.4, and 4.1.1, and Appendix 1 [footnote "bb"]).
- Additional guidance on infant B-cell monitoring in case levels are found to be below the lower limit of normal (LLN) has been added (Sections 3.1.3 and 4.5.3.3, and Appendix 1 [footnote "y"]).
- It has been clarified throughout the protocol that dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (U.S. Prescribing Information and the Summary of Product Characteristics) (Section 3.1.3; Appendix 1).

- The total length of the study has been increased from approximately 2 years to approximately 3 years, due to the extension of the enrolment period from approximately 8 months to approximately 21 months (Section 3.2).
- Language has been added to clarify that, based on the ocrelizumab average terminal half-life of 26 days, it is assumed that a potential fetal exposure is unlikely in women whose last ocrelizumab infusion was earlier than 3 months before last menstrual period (Section 3.3.2).
- To reduce the burden of visits on the mothers, it has been detailed that 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 (Section 4.5.2.4; Appendix 1 [footnote "i"]).
- 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 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 4.5.2.7 and 4.5.3.3 [Tables 3 and 4]; Appendix 1).
- 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 provide further details on how infant's non-laboratory assessments are to be collected (Sections 4.5.3.1 and 4.5.3.2).
- It has been clarified that all laboratory samples for the infant within one visit are to be collected at one timepoint (Section 4.5.3.3).
- 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 4.5.3.3).
- The list of antibody (Ab) titers of responses to vaccines administered as per local practice, has been updated to detail that the following will be included: anti-measles Ab IgG, anti-rubella Ab IgG, anti-mumps Ab IgG, 13-pneumococcal conjugate vaccine (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 4.5.3.3 [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).
- The full analysis set (FAS) population of infants has been amended to remove the requirement to only include infants of the FAS population of women whose B-cell level data at Day 30 post-infusion 1 are available; the FAS population of infants will include all the infants of the FAS population of women (Section 6.1).

- Due to a reduction in sample size, the precision (width of the two-sided 95% CIs) for event rates (an event is defined as B-cells below the LLN) have been amended (Section 6.2).
- A reference to Appendix 7 (B-cell reference ranges by week of life [absolute and percentage counts]) has been added (Section 6.5.1).
- The handling of intercurrent events of the estimand of the proportion of infants with B-cell levels below the LLN (Section 6.5.1) have been amended to include the following:
  - If an infant does not receive any breastmilk before B-cell measurement during the entire 30-day period after the mother's first ocrelizumab postpartum infusion, B-cell data will be excluded from the analysis.
  - If an infant's blood sample is collected before the assessment window (i.e., before Day 28), the data will be excluded from the analysis.
  - If an infant's blood sample is collected while the infant has an illness, the B-cell data will be excluded on a case-by-case basis if the illness is likely to confound the B-cell data.
- Further details on the statistical considerations for the PCV-13 serotypes have been added (Section 6.5.2).
- 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 following changes have been made to the Schedule of Assessments (Appendix 1):
  - The requirement to measure breastmilk ocrelizumab concentration at screening has been removed.
  - The requirement to collect documentation of collection of second postpartum ocrelizumab administration at Visit 7 has been included, with a corresponding footnote (footnote "dd") detailing that documentation of premedication is not required.
  - The corresponding footnote to the assessment "Whole blood sample for lymphocyte subtype sample" in infant laboratory assessments has been corrected to footnote "x".
  - It has been clarified that breastmilk samples that are to be collected on Day 0 (baseline) should be taken before the infusion (footnote "j").
- 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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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IV, MULTICENTER, OPEN-LABEL STUDY EVALUATING B-CELL LEVELS IN INFANTS OF LACTATING WOMEN WITH CIS OR MS RECEIVING OCRELIZUMAB – *THE SOPRANINO STUDY***
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TEST PRODUCT:	Ocrelizumab (RO4964913)
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 OF LACTATING WOMEN WITH CIS OR MS RECEIVING OCRELIZUMAB – *THE SOPRANINO STUDY***
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IND NUMBER:	100593
NCT NUMBER:	NCT04998851
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IV
INDICATION:	Multiple Sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics of ocrelizumab in the breastmilk of lactating women with clinically isolated syndrome (CIS) or multiple sclerosis (MS) [in line with the locally approved indications] treated with ocrelizumab, by assessing the concentration of ocrelizumab in mature breastmilk, as well as the corresponding exposure and pharmacodynamic effects (blood B-cell levels) in the infants. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Co-Primary Outcome Measure	
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum present with B-cell depletion	• Proportion of infants with B-cell levels (CD19+ cells, absolute counts in blood) below the LLN, measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate the exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated ADID, calculated as the ocrelizumab average milk concentration over 60 days post-ocrelizumab infusion 1 multiplied by an estimated infant milk intake of 150 mL/kg/day
Secondary Outcome Measures	
• To evaluate B-cell levels in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• B-cell levels (CD19+ cells, absolute counts and percentage of lymphocytes) measured at Day 30 after the mother's first ocrelizumab postpartum infusion

Objectives	Corresponding Endpoints
Secondary Outcome Measures (cont.)	
• To evaluate transfer of ocrelizumab into breastmilk of lactating women with CIS or MS receiving ocrelizumab postpartum	• AUC of ocrelizumab in mature breastmilk (i.e., milk produced after Day 14 postpartum) over 60 days after the first postpartum ocrelizumab infusion using the following time points: – If receiving 1×600 mg: before infusion and at 24 hours (Day 1), Day 7, Day 30 and Day 60 post-infusion – If receiving 2×300 mg: before infusion 1 and at 24 hours (Day 1), Day 7, Day 14, Day 15 (24 hours after infusion 2), Day 21, Day 30, and Day 60 post-infusion 1 • Average and peak ocrelizumab milk concentration as well as time to reach peak milk concentration, measured over 60 days after the mother's first postpartum ocrelizumab infusion
• To evaluate the *relative and* maximum exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated MDID calculated as the peak ocrelizumab milk concentration multiplied by an estimated infant milk intake of 150 mL/kg/day measured over 60 days after the mother's first postpartum ocrelizumab infusion • *Average RID over 60 days, calculated as the ADID (mg/kg/day) divided by the maternal dosage (mg/kg/day) multiplied by 100* *Note:* Other pharmacokinetic and exposure parameters may be calculated as appropriate, based on the data obtained
• To evaluate whether there is transfer of ocrelizumab from the mother to the infant via breastmilk	• Serum concentration of ocrelizumab in the infant measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum 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 MMR, diphtheria, tetanus, pertussis, Hib, HBV, and PCV-13 • Proportion of infants with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines
Safety Objectives	
• To evaluate the safety of ocrelizumab in lactating women with CIS or MS receiving ocrelizumab postpartum and in their respective infants	• Rate and nature of adverse events in the mother throughout the study, including changes in clinical and laboratory results • Rate and nature of adverse events in the infant throughout the study, including infections and hospitalizations

Objectives	Corresponding Endpoints
Exploratory Objectives	
• To evaluate infant's growth velocity and developmental milestones in the first year of life	• Assessment of growth velocity based on age-adjusted length, weight, head circumference, using monthly growth charts according to the WHO Child Growth Standards, as well as absolute values at Months 2, 4, 6, 9, and 12 • 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 measure disease activity in lactating women with CIS or MS receiving ocrelizumab postpartum	• Number of MS relapses during the postpartum period (clinical relapses) • Mean change in the EDSS score from last pre-baseline measurement (up to 1 year before LMP) to baseline
• To evaluate the evolution of B-cell levels over the first year of life in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Trajectory (absolute and percentage changes) of B-cells (CD19+ cells) *in the infant from* Day 30 after the mother's first ocrelizumab postpartum infusion *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

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; *RID = relative infant dose;* WHO = World Health Organization.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a prospective, multicenter, open-label study in lactating women with CIS or MS (in line with the locally approved indications) who decided together with their treating physician to continue on, or start treatment with, OCREVUS™ (ocrelizumab) postpartum despite ocrelizumab currently not being recommended during lactation.

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 at least *10* women with CIS or MS who are breastfeeding or planning to breastfeed.

The study will consist of the following periods:

- Screening period: After providing written informed consent, women will enter a screening period for eligibility assessments. Considering that decisions on initiating or resuming treatment with a disease-modifying therapy (DMT) in the postpartum period are usually taken before or during pregnancy, screening may be conducted at any time from the third trimester until 24 weeks postpartum. Final inclusion will only take place for women who have delivered a healthy term infant and have made a decision to breastfeed their infant despite ongoing ocrelizumab treatment. General health and medical history of the infant will also be reviewed for eligibility.

  Women resuming treatment with ocrelizumab postpartum will be included only if the last exposure to ocrelizumab occurred more than 3 months before the last menstrual period (LMP) (i.e., women without potential fetal exposure) to exclude any interference between fetal exposure and exposure via lactation.

- Treatment and sampling period: Women fulfilling the inclusion/exclusion criteria will receive the ocrelizumab dose regimen as per the locally approved label. The first dose of ocrelizumab may be administered at any point between Week 2 and Week 24 postpartum, as an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days or as a single 600 mg infusion (in 500 mL 0.9% sodium chloride) according to the local prescribing information. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. *Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (U.S. Prescribing Information [USPI]; Summary of Product Characteristics [SmPC]).* If women did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses (Summary of Product Characteristics [SmPC], United States Prescribing Information [USPI]). Women referred by healthcare professionals (HCPs) to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

  Maternal breastmilk samples will be collected over several time points up to 60 (± 2) days after the first postpartum ocrelizumab infusion at approximately the same time of day, although flexibility is allowed on collection timings to accommodate the mother and infant feeding schedule. The only exception is the first (Day 1) post-infusion breastmilk sample and, in women who received a 2×300 mg dose, the second (Day 15) post-infusion breastmilk sample, which should be collected 24 hours after the midpoint of the infusion. On days of collection, milk should be expressed from both breasts until completely emptied using an electric breast pump. The milk from each breast is then mixed and a sample (volume = 5 mL) is removed for analysis. The infant can be bottle-fed the remaining expressed milk. If the infant is not usually fed using a bottle, milk may be expressed from one breast only. If the mother presents with unilateral mastitis, milk should only be expressed from the unaffected breast, until the infection resolves. If mastitis presents bilaterally (rare), breastmilk collection should be stopped until the infection resolves.

  The infant blood sample will be collected at Day 30 (± 2 days) of lactation after the first ocrelizumab infusion administered postpartum, i.e., regardless of whether women receive a 600 mg or a 2×300 mg dose. Blood samples may be collected at home by a visiting nurse, or at the hospital as part of study visits. *Note:* If the infant's B-cell levels are found to be below lower limit of normal (LLN), *analyses of B-, T-, and natural killer cells will be repeated every 4 weeks until B-cell levels are found to be above the age-adequate LLN (in consultation with the Sponsor). The first repeat analysis will also include a complete blood count and immunoglobulin levels.*

  A structured telephone interview will be conducted by site personnel every 2 weeks in the treatment and sampling period, for a general review, and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother and use of and 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 using the lactational amenorrhea method as contraception will also be asked whether the three necessary criteria to ensure*

adequate protection from an unplanned pregnancy are applied. No telephone contact is needed in weeks where the woman is performing on-site visits.

- Vaccination period: After the 60-day (±2 days) treatment and sampling period, infants will continue to be followed-up for growth (age-adjusted length, weight, head circumference) and developmental milestones up to 12 months of age. Growth charts (following the World Health Organization 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 post-natal care, may also be used.

  Infant laboratory assessments will be performed 1 month (+30 days) after the first or second dose of measles, mumps, and rubella (MMR) vaccine, or at Month 13 of age (+30 days), in case MMR vaccine is not planned to be administered, to evaluate whether infants are able to mount humoral immune responses to clinically relevant vaccines, and for measurement of B-cell levels. In case the mother decides to switch to another DMT or to stop DMT after the 60-day treatment and sampling period, the infant blood sample will still be collected.

  A structured telephone interview will be conducted by site personnel postpartum every 3 months in the vaccination period (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother and use of and 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 using the lactational amenorrhea method as contraception will also be asked whether the three necessary criteria to ensure adequate protection from an unplanned pregnancy are applied.* No telephone contact is needed in weeks where the woman is performing on-site visit.
- Discontinuation: Women who decide to discontinue the study (this includes discontinuation of either the mother or the infant; this does not apply to treatment discontinuation) will be invited to attend an early study discontinuation visit (which may be conducted remotely, i.e., virtually or by telephone) as soon as possible. Depending on the timing of discontinuation, the following is recommended:

  Discontinuation before the infant blood draw at 30 (±2) days post-infusion 1: Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures

  - If the mother remains on treatment with ocrelizumab and decides to stop participating at 30 (±2) days after the first postpartum ocrelizumab infusion, attempts to collect the infant sample at 30 (±2) days should be made before discontinuation.
  - If the mother switches to another DMT, the infant sample at 30 (±2) days should not be collected.

  Discontinuation after the infant blood draw at 30 (±2) days post-infusion 1: Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures.

NUMBER OF WOMEN

This study will enroll at least *10* women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

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.
The primary analysis will be conducted at the end of the Treatment and Sampling Period (Day 60 [±2 days]).

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 *3* years. This includes an enrolment period of approximately *21* months and a woman's participation period of 16 months.

TARGET POPULATION

INCLUSION CRITERIA

The following criteria must be met for study entry:

- An Informed Consent Form (ICF) for participation of the maternal subject and her infant (for collection of blood, infant demographic 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
- Woman is able and willing to comply with the study protocol, according to the judgment of the investigator, in particular:
  - Woman is willing to breastfeed (either exclusively, or with formula supplementation) for at least 60 days after the first postpartum ocrelizumab infusion (this decision is to be taken prior to and independent from study participation)
  - Woman is willing to provide breastmilk samples before and after their first and, if applicable, second postpartum ocrelizumab infusion

    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.
- Woman is between 18 and 40 years of age at screening
- Woman has a diagnosis of MS or CIS (in line with the locally approved indications)
- Woman has delivered a healthy term singleton infant ($\geq$ 37 weeks gestation)
- Infant is between 2–24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- For women who received commercial ocrelizumab (OCREVUS) before enrolment: documentation that last exposure to ocrelizumab occurred more than 3 months before the LMP (i.e., excluded a potential fetal exposure) and was given at the approved dose of 2×300 mg or 1×600 mg
- Woman agrees to use acceptable contraceptive methods or alternative methods during the study as described below and, if applicable, upon study treatment discontinuation, as defined by the local prescribing information
  - The following contraceptive methods are considered acceptable (failure rate $>$ 1% [Clinical Trial Facilitation Group (CTFG)]): progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide; combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

  Birth control methods that are highly effective (i.e., failure rate $<$ 1% [CTFG]) may also be used but are not required, and include: oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation [unless not recommended or contraindicated during breastfeeding]; oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence.

  Note: lactational amenorrhea method can be used to ensure adequate protection from an unplanned pregnancy, and the following three criteria must be met: 1) amenorrhea; 2) fully or nearly fully breastfeeding (no interval of $>$ 4–6 hours between breastfeeds); and 3) $<$ 6 months postpartum. If any of the three listed criteria change at any stage during the study, an alternative or additional method of acceptable contraception is required. *During the structured telephone interview, occurring every 2 weeks during the treatment and sampling period and every 3 months during the vaccination period, women will also be asked whether the three criteria are applied.*

EXCLUSION CRITERIA

Mothers/infants who meet any of the following criteria will be excluded from study entry:

Exclusions related to the mother

- Hypersensitivity to ocrelizumab or to any of its excipients
- Woman received last dose of ocrelizumab <3 months before the LMP or during pregnancy (i.e., there was a potential fetal exposure to ocrelizumab)
- Active infections (note: the woman may be included once the infection is treated and is resolved; women with bilateral mastitis infection should not have samples collected until the infection is completely resolved)
- Prior or current history of primary or secondary immunodeficiency, or woman in an otherwise severely immunocompromised state. Woman may be re-screened and included if condition resolves
- Woman 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 high risk of breast malignancies undergoing prophylactic treatment with drugs such as tamoxifen are excluded
- Woman has history of breast implants, breast augmentation, breast reduction surgery or mastectomy
- Woman has prior or current history of chronic alcohol abuse or drug abuse
- Woman has any medical, obstetrical or psychiatric condition that, in the opinion of the investigator, would compromise the woman's ability to participate in this study
- Treatment with a DMT for CIS or MS during pregnancy and/or first weeks postpartum, with the exception of formulations of interferon-beta, glatiramer acetate or pulsed corticosteroids
- Drugs known to transfer to the breastmilk and with established or potential deleterious effects for the infant, including but not limited to aspirin (risk of Reye's syndrome), tetracyclines or fluoroquinolones
- Treatment with any investigational agent within 6 months or five half-lives of the investigational drug (whichever is longer) prior to the LMP, unless the investigational agent is ocrelizumab administered >3 months prior to the LMP in the context of a study or registry sponsored by Roche

Exclusions related to the infant

- Infant is >24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- Infant has any abnormality that may interfere with breastfeeding or milk absorption, including but not limited to cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia
- Infant has an active infection. Infant may be included once the infection resolves
- Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's ability to participate in this study, including interference with the interpretation of study results
- Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's ability to participate in this study, including interference with the interpretation of study results
- Infant has at least one documented brief resolved unexplained event (BRUE), as defined by the 2016 Guidelines of the American Academy of Pediatrics

Exclusions related to laboratory findings

- Mother with any abnormal screening laboratory value that is clinically relevant should 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.

- Mother 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 (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.

STUDY TREATMENT

The study treatment is commercial ocrelizumab.

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 IRRs. Premedication with an antipyretic (e.g., paracetamol) may also be considered prior to each ocrelizumab infusion

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary analysis will be conducted on the full analysis set (all women who meet the eligibility criteria and received any postpartum dose of ocrelizumab) and infants of women in the full analysis set. The analysis will be performed after the last breastmilk sample collection at the end of the 60-day treatment and sampling period.

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 estimated average oral daily infant dosage will be analyzed using descriptive statistics. Mean, corresponding 95% CI, standard deviation, and other statistics will be presented.

More details about missing data handling, as well as sensitivity analyses based on alternative imputation approaches, will be specified in the statistical analysis plan.

DETERMINATION OF SAMPLE SIZE

The study will include at least 10 women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

With 10 infants, a precision (width of the two-sided 95% CI) of 0.443 is expected if one event is observed (defined as B-cells below the LLN) and a precision of 0.531 if two events are observed in the study. If no event is observed during the study, there is a 95% confidence that the event rate is below 0.31.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	definition
ADID	average (oral) daily infant dosage
AE	adverse event
AESI	adverse events of special interest
ASQ-3	Ages And Stages Questionnaire, version 3
AUC	area under the milk concentration-time curve
BRUE	brief resolved unexplained event
CBC	*complete blood count*
CIS	clinically isolated syndrome
CRO	contract research organization
CTFG	clinical trial facilitation group
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	Food and Drug Administration
FSS	functional systems score
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
HCV	hepatitis c virus infection
Hib	*Hemophilus influenzae* type b
HIPAA	health insurance portability and accountability act
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	definition
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
IRR	infusion-related reaction
LLN	lower limit of normal
LMP	last menstrual period
mAb	monoclonal antibody
MAH	marketing authorization holder
MDID	maximum (oral) daily infant dosage
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-pneumococcal conjugate vaccine
PML	progressive multifocal leukoencephalopathy
PPMS	primary-progressive multiple sclerosis
QTL	quality tolerance limit
RID	relative infant dose
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
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). Multiple sclerosis 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 multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary-progressive multiple sclerosis (PPMS; Lublin et al. 2014). Relapsing-remitting multiple sclerosis 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, Zhao, and Devonshire 2008; Weinshenker et al. 1989). Primary-progressive multiple sclerosis 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 (for example, magnetic resonance imaging [MRI], lumbar puncture, evoked potentials) evidence (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 (mAb) 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-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). The appropriate treatment strategy during pregnancy and after birth remains uncertain, since none of the many DMTs available for MS are recommended during pregnancy or breastfeeding (LaHue et al. 2019). There is no consensus on how soon after birth may DMTs be safely resumed. Women often have to choose between breastfeeding and early resumption of a disease-modifying therapy (DMT) postpartum. This can have a significant impact on disease management since the risk of postpartum relapse is high. About 30% of women experience a relapse in the first 3 months postpartum (Vukusic et al. 2004). Such relapses may in turn worsen disability (Portaccio et al. 2014).

The general benefits of breastfeeding are well established, both for mothers as well as for infants. Infants who are exclusively breastfed have a lower risk of gastrointestinal as well as respiratory infections (Kramer and Kakuma 2012), and mothers who breastfeed have a reduced risk of breast, ovarian, and endometrial cancer (Ip et al. 2007; Kramer and Kakuma 2012; Jordan et al. 2017; Collaborative Group on Hormonal Factors in Breast Cancer, 2002). In addition, there is good evidence that exclusive breastfeeding may reduce the risk of postpartum relapses. A systematic literature review/meta-analysis of 24 studies exploring the association between breastfeeding and MS relapse reported a pooled adjusted hazard ratio (HR) for the association of breastfeeding and postpartum relapses of 0.57 (95% CI: 0.38 to 0.85; $p = 0.006$) vs. non-breastfeeding (Krysko et al. 2020); and a study of a cohort of 466 pregnancies in

375 women with MS (based on electronic health records) found that exclusive breastfeeding reduced the risk of early postpartum relapses (adjusted HR = 0.37, p = 0.009; Langer-Gould et al. 2020). Despite reduction in postpartum relapses with breastfeeding, annual relapse rates remain fairly high after birth, highlighting the need for additional strategies to prevent such relapses (Krysko et al. 2020). An efficacious mAb therapy that could safely be resumed soon after birth would significantly reduce the risk of postpartum relapses (LaHue et al. 2020).

Available Evidence

In a pre- and post-natal development study in cynomolgus monkeys, administration of ocrelizumab from gestation day 20 to approximately 5 weeks postpartum was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. There were two cases of moribundity, one attributed to weakness due to premature birth accompanied by opportunistic infection and the other to an infective meningoencephalitis involving the cerebellum of the neonate from a maternal dam with an active infection (mastitis). The course of both neonatal infections could have potentially been impacted by B-cell depletion. Newborn offspring of maternal animals exposed to ocrelizumab were noted to have depleted B-cell populations during the post-natal phase. Measurable levels of ocrelizumab were detected in milk (approximated 0.2% of steady state through serum levels) during the lactation period. Overall, it has to be taken into account that ocrelizumab was administered as 15/20 and 75/100 mg/kg loading/study doses, which correspond to human equivalent doses of approximately 3000 mg (approximately 5 × clinical dose) and 15,000 mg (approximately 25 × clinical dose), respectively. Maternal doses administered in this study resulted in mean maximum serum concentrations (C_{max}) that were 4.5- and 21-fold above those anticipated in the clinical setting. Moreover, preclinical studies studying ocrelizumab exposure through lactation only (i.e., administering ocrelizumab only postpartum) have not been conducted.

Clinical studies of the effects on infants associated with the use of ocrelizumab during lactation have not been performed. A few cases of exposure through breastmilk have been reported. Reduced B-cell levels at birth were reported in an infant born to a mother exposed to ocrelizumab during the second trimester of pregnancy (following relapse activity post-alemtuzumab), who also received a single 300-mg dose postpartum. Two months after this dose, the infant's B-cell levels were normal. The authors also reported an infant who was exposed through breastmilk to a single 600-mg dose postpartum, in whom B-cell levels were normal 39 days afterwards. Neither infant had hospitalizations or infections requiring antibiotic or hospitalization, during the period of exposure through breastfeeding (Ciplea et al. 2020).

As of 31 March *2022*, *40* cases of infant postpartum exposure to ocrelizumab via breastmilk have been reported in the Roche global safety database (*Oreja-Guevara et al. 2022). Thirty-three* infants were exposed to ocrelizumab postpartum via breast milk; *7* infants had in utero and postpartum ocrelizumab exposure. *Fifteen* infants

experienced no adverse events; *6* infants experienced adverse events (sleepiness potentially due to diphenhydramine hydrochloride exposure; excessive vomiting and swelling due to potential dairy allergies; conjunctivitis and otitis media, treated with unspecific antibiotics*; life-threatening breathing disorder and mild neurodermatitis; pelvic inflammation and nephritis; conjunctivitis*) and *19* infants had no reported adverse event information. B-cell levels available for 5 infants were in line within reported age-specific reference ranges.

Supporting Evidence from Other Anti-CD20 Therapies

In a study in 9 women with MS treated with rituximab (another anti-CD20 mAb), the median average rituximab concentration in mature breastmilk was low, at 0.063 µg/mL (range 0.046–0.097) in the 4 patients with serial breastmilk collection; with an estimated median absolute infant dose of 0.0094 mg/kg/d and a relative infant dose (RID) of 0.08% (range 0.06%–0.10%). Rituximab was virtually undetectable in milk by 90 days post-infusion (Krysko et al. 2019). In another study in 23 patients from the German Multiple Sclerosis and Pregnancy Registry who received the mAbs natalizumab (n = 17), rituximab (n = 3), ocrelizumab (n = 2) or rituximab + ocrelizumab (n = 1) during lactation, no negative impact on infant health and development attributable to drug exposure through breastmilk was seen after a median follow-up of 1 year. The concentration of natalizumab was low in breastmilk and in the serum of infants, and B-cell levels were normal in breastfed infants whose mothers received the anti-CD20 mAb rituximab; Ciplea et al. 2020).

Uncertainties and Need for Additional Evidence

Data on ocrelizumab kinetics in human milk and on the effects of ocrelizumab on breastfed infants are sparse and, as stated, no clinical studies have been performed evaluating the benefit-risk of ocrelizumab during breastfeeding. Given that IgG-based mAbs have large molecular sizes and limited transport mechanisms, the expected transfer into breastmilk is low (Hurley and Theil 2011). Additionally, most Igs have low oral bioavailability, which further reduces the likelihood of absorption by breastfeeding infants (Jasion et al. 2015). However, it has been shown that in women with MS minimal transfer of other anti-CD20 mAbs (rituximab) into breastmilk occurs, while the effects on the immune system and developmental milestones of potentially exposed infants remain unknown.

Given the unmet need for women with MS who may wish to breastfeed but are at high risk of postpartum relapses, and given the available evidence of minimal transfer of rituximab into breastmilk, a dedicated prospective interventional study to specifically evaluate the transfer of ocrelizumab into breastmilk and the corresponding pharmacodynamic effects in infants is therefore required, and justified. This study 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 pharmacokinetics of ocrelizumab in the breastmilk of lactating women with CIS or MS (in line with the locally approved indications) treated with ocrelizumab, by assessing the concentration of ocrelizumab in mature breastmilk, as well as the corresponding exposure and pharmacodynamic effects (blood 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
Co-Primary Outcome Measure	
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum present with B-cell depletion	• Proportion of infants with B-cell levels (CD19+cells, absolute counts in blood) below the LLN, measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate the exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated ADID, calculated as the ocrelizumab average milk concentration over 60 days post-ocrelizumab infusion 1 multiplied by an estimated infant milk intake of 150 mL/kg/day
Secondary Outcome Measures	
• To evaluate B-cell levels in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• B-cell levels (CD19+ cells, absolute counts and percentage of lymphocytes) measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate transfer of ocrelizumab into breastmilk of lactating women with CIS or MS receiving ocrelizumab postpartum	• AUC of ocrelizumab in mature breastmilk (i.e., milk produced after Day 14 postpartum) over 60 days after the first postpartum ocrelizumab infusion using the following time points: – If receiving 1×600 mg: before infusion and at 24 hours (Day 1), Day 7, Day 30 and Day 60 post-infusion – If receiving 2×300 mg: before infusion 1 and at 24 hours (Day 1), Day 7, Day 14, Day 15 (24 hours after infusion 2), Day 21, Day 30, and Day 60 post-infusion 1 • Average and peak ocrelizumab milk concentration as well as time to reach peak milk concentration, measured over 60 days after the mother's first postpartum ocrelizumab infusion

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire, version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; RID = relative infant dose; WHO = World Health Organization.

Table 1 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Secondary Outcome Measures (cont.)	
• To evaluate the *relative and* maximum exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated MDID calculated as the peak ocrelizumab milk concentration multiplied by an estimated infant milk intake of 150 mL/kg/day measured over 60 days after the mother's first postpartum ocrelizumab infusion • *Average RID over 60 days, calculated as the ADID (mg/kg/day) divided by the maternal dosage (mg/kg/day) multiplied by 100* *Note:* Other pharmacokinetic and exposure parameters may be calculated as appropriate, based on the data obtained.
• To evaluate whether there is transfer of ocrelizumab from the mother to the infant via breastmilk	• Serum concentration of ocrelizumab in the infant measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum 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 MMR, *diphtheria, tetanus, pertussis*, Hib, HBV, and PCV-13 • Proportion of infants with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines
Safety Objectives	
• To evaluate the safety of ocrelizumab in lactating women with CIS or MS receiving ocrelizumab postpartum and in their respective infants	• Rate and nature of adverse events in the mother throughout the study, including changes in clinical and laboratory results • Rate and nature of adverse events in the infant throughout the study, including infections and hospitalizations

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire, version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; RID = relative infant dose; WHO = World Health Organization.

Table 1 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Exploratory Objectives	
• To evaluate infant's growth velocity and developmental milestones in the first year of life	• Assessment of growth velocity based on age-adjusted length, weight, head circumference, using monthly growth charts according to the WHO Child Growth Standards, as well as absolute values at Months 2, 4, 6, 9, and 12 • 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 measure disease activity in lactating women with CIS or MS receiving ocrelizumab postpartum	• Number of MS relapses during the postpartum period (clinical relapses) • Mean change in the EDSS score from last pre-baseline measurement (up to 1 year before LMP) to baseline
• To evaluate the evolution of B-cell levels over the first year of life in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Trajectory (absolute and percentage changes) of B-cells (CD19+ cells) *in the infant from* Day 30 after the mother's first ocrelizumab postpartum infusion *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

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire, version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; *RID = relative infant dose;* WHO = World Health Organization.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a prospective, multicenter, open-label study in lactating women with CIS or MS (in line with the locally approved indications) who decided together with their treating physician to continue on, or start treatment with, OCREVUS™ (ocrelizumab) postpartum despite ocrelizumab currently not being recommended during lactation.

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 at least 10 women with CIS or MS who are breastfeeding or planning to breastfeed. Laboratory and clinical assessments will be performed as described in the Schedule of Assessments presented in Appendix 1.

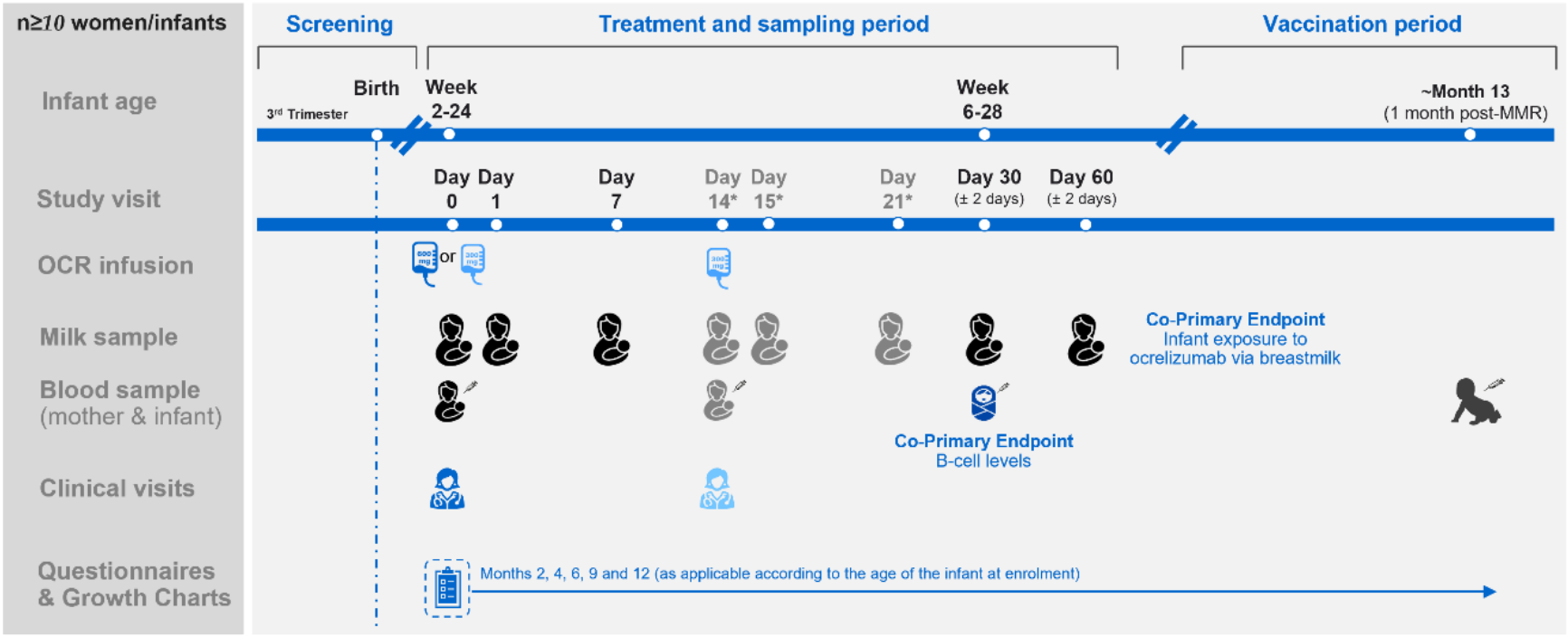
The study will consist of the following periods:

- Screening period
- Treatment and sampling period
- Vaccination period

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



* Samples and visits at Day 14, 15 and 21 apply only to patients initiating treatment with ocrelizumab as 2x300mg separated by a 14-day interval.

ASQ-3 = Ages and Stages Questionnaire, version 3; LMP = last menstrual period; MMR = measles, mumps, and rubella; OCR = ocrelizumab.

Study description: In this prospective, multicenter, open-label study, lactating women with CIS or MS (in line with the locally approved indications) who decided together with their treating physician to continue on, or start treatment with, commercial ocrelizumab postpartum will enter a **screening period**, which may be started during the third trimester of pregnancy and continue until 24 weeks postpartum. Women who have delivered a healthy term infant and made a decision to breastfeed their infant will be enrolled if they and their infants fulfil the respective eligibility criteria. Women resuming treatment with ocrelizumab postpartum will be included only if the last exposure to ocrelizumab occurred more than 3 months before the LMP (i.e., women without potential fetal exposure). In the **60-day (±2 days) treatment and sampling period**, women will receive the ocrelizumab dose regimen as per the locally-approved label, at any point between Week 2 and Week 24 postpartum. The first dose of ocrelizumab may be administered as two 300 mg infusions separated by 14 days (for those initiating ocrelizumab) or as a single 600 mg infusion (for those resuming ocrelizumab). For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. Women referred by healthcare professionals to participate in the trial may receive ocrelizumab treatment

at their neurologist's site as part of their standard of care treatment. Laboratory and clinical assessments will be performed at the designated visits.

Women will collect their breastmilk samples over several time points up to 60 (±2) days after the first postpartum ocrelizumab infusion, reserving 5 mL at each sampling point for analysis of ocrelizumab concentrations. Infant blood samples will be collected at Day 30 (±2 days) after the first postpartum ocrelizumab infusion (regardless of whether women receive a 600 mg or a 2×300 mg dose). Infant blood samples may be collected at home by a visiting nurse, if not collected at the clinical site during a study visit. In **the vaccination period,** infants will continue to 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 for example, the pediatrician as part of routine postnatal care, may also be used). 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, to evaluate whether infants are able to mount humoral immune responses to clinically relevant vaccines, and for measurement of B-cell levels. 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 mother 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 using the lactational amenorrhea method as contraception will also be asked whether the three necessary criteria outlined in Section 4.1.1 to ensure adequate protection from an unplanned pregnancy are applied.* No telephone contact is needed in weeks where the woman is performing on-site visits. Women who decide to discontinue the study (this includes discontinuation of either the mother or the infant) 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 Period

After providing written informed consent, women will enter a screening period for eligibility assessments. Considering that decisions on initiating or resuming treatment with a DMT in the postpartum period are usually taken before or during pregnancy, screening may be conducted at any time from the third trimester until 24 weeks postpartum. Final inclusion will only take place for women who have delivered a healthy term infant and have made a decision to breastfeed their infant despite ongoing ocrelizumab. General health and medical history of the infant will be reviewed for eligibility.

Women resuming treatment with ocrelizumab postpartum will be included only if the last exposure to ocrelizumab occurred more than 3 months before the last menstrual period (LMP), i.e., if they have no potential fetal exposure; to exclude any interference between fetal exposure and exposure via lactation.

3.1.3 Treatment and Sampling Period

Women fulfilling the inclusion/exclusion criteria will receive the ocrelizumab dose regimen as per the locally approved label. The first dose of ocrelizumab may be administered at any point between Week 2 and Week 24 postpartum, as an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days or as a single 600 mg infusion (in 500 mL 0.9% sodium chloride), according to the local prescribing information. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. *Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (U.S. Prescribing Information [USPI]; Summary of Product Characteristics [SmPC]).* If women did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses (SmPC, USP). Women referred by healthcare professionals (HCPs) to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

Maternal breastmilk samples will be collected over several time points up to 60 (± 2) days after the first postpartum ocrelizumab infusion at approximately the same time of day, although flexibility is allowed on collection timings to accommodate the mother and infant feeding schedule. The only exception is the first (Day 1) post-infusion breastmilk sample, and in women who received a 2×300 mg dose, the second (Day 15) post-infusion breastmilk sample, which should be collected 24 hours after the midpoint of the infusion. On days of collection, milk should be expressed from both breasts until completely emptied using an electric breast pump. The milk from each breast is then mixed and a sample (volume $= 5$ mL) is removed for analysis. The infant can be bottle-fed the remaining expressed milk. If the infant is not usually fed using a bottle, milk may be expressed from one breast only. If the mother presents with unilateral

mastitis, milk should only be expressed from the unaffected breast, until the infection resolves. If mastitis presents bilaterally (rare), breastmilk collection should be stopped until the infection resolves.

The infant blood sample will be collected at Day 30 (±2 days) of lactation after the first ocrelizumab infusion administered postpartum, i.e., regardless of whether women receive a 600 mg or a 2×300 mg dose. The corresponding breastmilk sample should be collected on the same day as the infant blood sample. Blood samples may be collected at home by a visiting nurse, or at the hospital as part of study visits (see Appendix 1, Schedule of Assessments).

Note: If the infant's B-cell levels are found to be below lower limit of normal (LLN), *analyses of B-, T-, and natural killer (NK) cells will be repeated every 4 weeks until B-cell levels are found to be above the age-adequate LLN as per Appendix 7 (in consultation with the Sponsor). The first repeat analysis will also include a complete blood count (CBC) and immunoglobulin levels.*

A structured telephone interview will be conducted by site personnel every 2 weeks in the treatment and sampling period, for a general review and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother 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 using the lactational amenorrhea method as contraception will also be asked whether the three necessary criteria outlined in Section 4.1.1 to ensure adequate protection from an unplanned pregnancy are applied.* No telephone contact is needed in weeks where the woman is performing on-site visits.

3.1.4 Vaccination Period

After the 60-day (±2 days) treatment and sampling period, infants will continue to be followed-up for growth (age-adjusted length, weight, 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) questionnaires 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.

Infant laboratory assessments will be performed 1 month (+30 days) after the first or second dose of measles, mumps, and rubella (MMR) vaccine, or at Month 13 of age (+30 days), if MMR vaccine is not planned to be administered, to evaluate whether infants are able to mount humoral immune responses to clinically relevant vaccines, as well as to measure their B-cell levels. In case the mother decides to switch to another

DMT or to stop DMT after the 60-day treatment and sampling period, the infant blood sample will still be collected.

A structured telephone interview will be conducted by site personnel postpartum every 3 months in the vaccination period (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother 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 using the lactational amenorrhea method as contraception will also be asked whether the three necessary criteria outlined in Section 4.1.1 to ensure adequate protection from an unplanned pregnancy are applied.* No telephone contact is needed in weeks where the woman is performing on-site visits.

3.1.5 Discontinuation

Women who decide to discontinue the study (this includes discontinuation of either the mother or the infant; this does not apply to treatment discontinuation as described in Section 3.1.4) will be invited to attend an early study discontinuation visit (which may be conducted remotely, i.e., virtually or by telephone) as soon as possible. Depending on the timing of discontinuation, the following is recommended:

- **Discontinuation before the infant blood draw at 30 (±2) days post-infusion 1:**
  - Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures
  - If the mother remains on treatment with ocrelizumab and decides to stop participating at 30 (±2) days after the first postpartum ocrelizumab infusion, attempts to collect the infant sample at 30 (±2) days should be made before discontinuation
  - If the mother switches to another DMT, the infant sample at 30 (±2) days should not be collected.
- **Discontinuation after the infant blood draw at 30 (±2) days post-infusion 1:** Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures.

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 vaccine is not planned to be administered) for the last infant. The primary analysis will be conducted at the end of the Treatment and Sampling Period (Day 60 [+2 days]).

The total length of the study, from screening of the first woman to the end of the study, is expected to be approximately *3* years. This includes an enrolment period of approximately *21* months and a woman's participation period of 16 months.

3.3 RATIONALE FOR STUDY DESIGN

This is a prospective, multicenter, open-label study evaluating the transfer of ocrelizumab into breastmilk of lactating women with CIS or MS treated with ocrelizumab postpartum. Ocrelizumab targets B-cells, and a rapid depletion of CD19+ B-cells in blood is the expected pharmacologic effect of ocrelizumab treatment (and hence, is a biomarker for pharmacodynamic effect). This depletion occurs briefly even at low doses such as 2×10 mg (FDA 2017). Therefore, CD19+ B-cell levels will be measured as a co-primary endpoint (specifically, the proportion of infants with B-cells below the LLN at Day 30 [±2 days] post-infusion).

To evaluate the amount of drug that may be transferred from mother to infant through breastmilk, the co-primary endpoint is the average (oral) daily infant dosage (ADID), which expresses the average amount of ocrelizumab in breastmilk (and available to the infant) as an infant dose, over the observed period of 60 days (±2 days) post-infusion. The excretion in breastmilk is expected to be highest during the first 60 days after the ocrelizumab infusion, declining thereafter over the 6-monthly dosing interval. Breastmilk samples will be collected before the infusion, and at days 1, 7, 30 (±2) and 60 (±2) (with additional timepoints for mothers who are receiving a split dose, i.e., 2×300 mg), to cover two average half-lives of ocrelizumab in serum (26 days [USPI]) and the expected time window of greatest breastmilk transfer for anti-CD20 monoclonal antibodies (Krysko et al. 2019). Samples will be taken only after the development of mature milk (i.e., milk produced after Day 14 postpartum) to avoid the collection of colostrum, which may contain a high concentration of antibody because of a more porous mammary epithelium (FDA 2019). In addition, mothers will be instructed to completely empty both breasts with an electric pump, and mix milk from both breasts before removing the amount required for the sample. If the infant is not usually fed using a bottle, milk may be expressed from one breast only. This will reduce variability across the study, as for example foremilk and hindmilk (milk expressed at the start and end of feeding, respectively) have different compositions, which can influence the amount of drug available in the sample (Hebert 2016). To account for differences in exclusive breastfeeding versus supplementation with formula, a feeding schedule diary completed by the women will record the number of breastmilk feeds and/or feed with formula milk (supplementation) on the day of the sample collection and the previous and following day, as recommended by the FDA (Food and Drug Administration; FDA 2019). For mothers presenting with mastitis during the sampling period, sample collections from the infected breast(s) will be interrupted, given that clinical and subclinical mastitis are associated with increased milk concentrations of serum-derived immune factors such as IgG (Filteau 2003).

To further understand the extent of ocrelizumab transfer through breastmilk and the exposure in infants, secondary endpoints will include the area under the milk concentration-time curve (AUC) of ocrelizumab in breastmilk over 60 days post-ocrelizumab infusion, average concentration, peak concentration, time to peak

concentration and the maximum (oral) daily infant dosage (MDID), as recommended by the FDA (FDA 2019). To evaluate potential adverse impact on the infants, infant health and development outcomes will be assessed using growth charts according to the WHO Child Growth Standards (WHO 2022) 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).

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 of lactating women with CIS or MS receiving ocrelizumab postpartum can mount a protective immune response to clinically relevant vaccines.

As exploratory endpoints, disease activity will be measured in the mothers using standard assessments such as Expanded Disability Status Scale (EDSS) and number of MS relapses. These endpoints are commonly used in MS clinical trials to assess treatment efficacy and disease progression.

As recommended (FDA 2019), this study is designed to minimize burden on the mother and disruption to the infant's feeding schedule. For example, at sample collection time (when the infant would be fed the remainder of the collected milk through a bottle), mothers may instead collect the sample from only one breast if the infant is not normally fed using a bottle. Further, the infant blood sample on Day 30 ($\pm$2 days) post-infusion and at 1 month ($+$30 days) after the first or second dose of MMR vaccine/Month 13 of age ($+$30 days) may be collected at home by a visiting nurse, or at the hospital as part of study visits.

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 labeling *(USPI; SmPC)*. As per the dosing regimen approved in the labeling, 600 mg ocrelizumab is to be given as IV infusion every 6 months. The first dose is given as two 300 mg IV infusions two weeks apart; and subsequent doses are given as single 600 mg IV infusions. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. If women did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses (Ocrelizumab SmPC, Ocrelizumab USPI).

3.3.2 Rationale for Subject Population

As the aim of this study is to evaluate breastmilk transfer of ocrelizumab and the corresponding pharmacodynamic effects in the infant, it will be conducted in women with CIS or MS (in line with the locally approved indications) aged 18–40 years who have planned to start or resume ocrelizumab after delivery, while breastfeeding for a minimum of 60 days.

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 1 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 (Simister 2003; Palmeira et al. 2012), it is assumed that a potential fetal exposure is unlikely in women whose last ocrelizumab infusion was earlier than 3 months before LMP. Women who were exposed to ocrelizumab within 3 months of their LMP, or during pregnancy, will *therefore* be excluded to eliminate cases of potential fetal exposure to ocrelizumab that could confound the results of B-cell levels in the infant or the presence of ocrelizumab in breastmilk.

Women who have given birth to more than one baby (i.e., have had non-singleton births) are excluded, because such mothers might find it difficult to comply with study requirements, and might find it more difficult to reserve the amount of breastmilk needed for the sample. Therefore, their infants might receive a different amount of breastmilk, potentially confounding the B-cell level results.

Infants who are >24 weeks of age at the mother's first postpartum dose of ocrelizumab will be excluded. Although the WHO recommends exclusive breastfeeding up to 6 months with continued breastfeeding along with appropriate complementary foods up to 2 years of age or older (WHO 2020a), these recommendations are not followed in most countries. Recent findings from the National Immunization Survey 2018–2019 in the United States show that the percentage of infants who are breastfed decreases from 58.3% at 6 months to 35.3% at 1 year (Centers for Disease Control and Prevention 2020a). The maximum maternal age is set at 40 years, as mothers in late childbearing age of ≥ 35 years (in particular primiparous mothers) have been shown to have the greatest risk of non-initiation of exclusive breastfeeding both at discharge and at 1 month postpartum, even though they had the antenatal intention to exclusively breastfeed (Kitano et al. 2016).

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. 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), and all antiviral drug labels do not recommend breastfeeding when taking the drugs.

In addition, infants with any abnormality that may interfere with breastfeeding or milk absorption, such as cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia are excluded, given that the co-primary aim of this study is to evaluate the corresponding pharmacodynamic effects of potential ocrelizumab exposure through breastmilk. Infants who have had at least one documented brief resolved unexplained event (BRUE), are also excluded, because these potentially life-threatening events have an unknown impact on infant physiology and development, and may confound the interpretation of infant's growth velocity and development milestones in the first year. The term BRUE is defined by the American Academy of Pediatrics as an event occurring in an infant younger than 1 year when the observer reports a sudden, brief, and now resolved episode of ≥ 1 of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hyper- or hypotonia); and (4) altered level of responsiveness (Tieder et al. 2016).

4. MATERIALS AND METHODS

4.1 STUDY PARTICIPANTS

This study will enroll at least 10 women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

4.1.1 Inclusion Criteria

The following criteria must be met for study entry:

- An Informed Consent Form (ICF) for participation of the maternal subject and her infant (for collection of blood, infant demographic 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
- Woman is able and willing to comply with the study protocol, according to the judgment of the investigator, in particular:
  - Woman is willing to breastfeed (either exclusively, or with formula supplementation) for at least 60 days after the first postpartum ocrelizumab infusion (this decision is to be taken prior to and independent from study participation)
  - Woman is willing to provide breastmilk samples before and after their first and, if applicable, second postpartum ocrelizumab infusion

    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.
- Woman is between 18 and 40 years of age at screening
- Woman has a diagnosis of MS or CIS (in line with the locally approved indications)

- Woman has delivered a healthy term singleton infant (≥37 weeks gestation)
- Infant is between 2–24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- For women who received commercial ocrelizumab (OCREVUS) before enrolment: documentation that last exposure ocrelizumab occurred more than 3 months before the LMP (i.e., excluded a potential fetal exposure) and was given at the approved dose of 2×300 mg or 1×600 mg
- Woman agrees to use acceptable contraceptive methods or alternative methods during the study as described below and, if applicable, upon study treatment discontinuation, as defined by the local prescribing information (see Section 4.6.1).
  - The following contraceptive methods are considered acceptable (failure rate >1% [Clinical Trial Facilitation Group (CTFG)]): progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide; combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

  Birth control methods that are highly effective (i.e., failure rate <1% [CTFG]) may also be used but are not required, and include: oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation [unless not recommended or contraindicated during breastfeeding, see Table A2-1]; oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence.

  Note: lactational amenorrhea method can be used to ensure adequate protection from an unplanned pregnancy, and the following three criteria must be met: 1) amenorrhea; 2) fully or nearly fully breastfeeding (no interval of >4–6 hours between breastfeeds); and 3) <6 months postpartum. If any of the three listed criteria change at any stage during the study, an alternative or additional method of acceptable contraception is required. *During the structured telephone interview, occurring every 2 weeks during the treatment and sampling period and every 3 months during the vaccination period, women will also be asked whether the three criteria are applied.*

4.1.2 Exclusion Criteria

Mothers or infants who meet any of the following criteria will be excluded from study entry:

Exclusions related to the mother

- Hypersensitivity to ocrelizumab or to any of its excipients
- Woman received last dose of ocrelizumab <3 months before the LMP or during pregnancy (i.e., there was a potential fetal exposure to ocrelizumab)

- Active infections (note: the woman may be included once the infection is treated and is resolved; women with bilateral mastitis infection should not have samples collected until the infection is completely resolved)
- Prior or current history of primary or secondary immunodeficiency, or woman in an otherwise severely immunocompromised state. Woman may be re-screened and included if condition resolves
- Woman 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 high risk of breast malignancies undergoing prophylactic treatment with drugs such as tamoxifen are excluded
- Woman has history of breast implants, breast augmentation, breast reduction surgery or mastectomy
- Woman has prior or current history of chronic alcohol abuse or drug abuse
- Woman has any medical, obstetrical or psychiatric condition that, in the opinion of the investigator, would compromise the woman's ability to participate in this study
- Treatment with a DMT for CIS or MS during pregnancy and/or first weeks postpartum, with the exception of formulations of interferon-beta, glatiramer acetate or pulsed corticosteroids
- Drugs known to transfer to the breastmilk and with established or potential deleterious effects for the infant, including but not limited to aspirin (risk of Reye's syndrome), tetracyclines or fluoroquinolones. A more detailed, though not comprehensive, list can be found in Appendix 2
- Treatment with any investigational agent within 6 months or five half-lives of the investigational drug (whichever is longer) prior to the LMP, unless the investigational agent is ocrelizumab administered >3 months prior to the LMP in the context of a study or registry sponsored by Roche

<u>Exclusions related to the infant</u>

- Infant is >24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- Infant has any abnormality that may interfere with breastfeeding or milk absorption, including but not limited to cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia
- Infant has an active infection. Infant may be included once the infection resolves
- Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's ability to participate in this study, including interference with the interpretation of study results
- Infant has at least one documented BRUE, as defined by the 2016 Guidelines of the American Academy of Pediatrics

Exclusions Related to Laboratory Findings

- Mother with any abnormal screening laboratory value that is clinically relevant should 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.
- Mother 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 hepatitis B virus (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.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. No randomization, treatment assignment or blinding is planned.

4.3 STUDY TREATMENT AND OTHER TREATMENTS 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 the United States] and SmPC [for the 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 labeling (USPI; SmPC). No measures of treatment compliance are planned.

4.3.2.1 Study Treatment

As per the labeling, 600 mg ocrelizumab is to be given as IV infusion every 6 months. The first dose of ocrelizumab may be administered at any point between Week 2 and Week 24 postpartum as two 300-mg IV infusions two weeks apart (in 250 mL 0.9% sodium chloride) or as a single 600-mg IV infusion (in 500 mL 0.9% sodium chloride); and subsequent doses given according to the local prescribing information. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. If women did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for

subsequent 600 mg doses (SmPC, USPI). Women referred by HCPs to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

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 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 woman participating in the study, in addition to the study treatment. All such medications taken within 6 weeks prior to the baseline visit and throughout the study should be reported to the investigator and recorded on the Concomitant Medications electronic case report form (eCRF).

4.4.1 Prohibited Therapy

Drugs known to transfer to the breastmilk and with established or potential deleterious effects for the infant, including but not limited to aspirin (risk of Reye's syndrome), tetracyclines or fluoroquinolones are not permitted. A more detailed, though not comprehensive, list can be found in Appendix 2.

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.

Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers should NOT be administered while the woman is B-cell depleted.

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

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 or 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 their infants 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 enrolment. 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, and Disease Characteristics

Women's demographics (age, self-reported ethnicity, and level of education) and relevant medical history, including clinically significant diseases, surgeries/procedures, vaccination history, 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 the baseline visit will be recorded. Clinically significant diseases and/or surgeries and concomitant medication should also be recorded throughout the study if available.

Obstetric history:

- History of previous pregnancies

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 the LMP
- History of previous DMTs (prior to and during pregnancy): number of DMTs ever used, last DMT before ocrelizumab
- Treatment history with ocrelizumab (to be collected only in women who received commercial ocrelizumab prior to enrolment): Documentation of start of ocrelizumab therapy and date and dose of last ocrelizumab infusion prior to enrolment.

4.5.2.2 Physical Examinations and Related Assessments

A complete physical examination in participating women should include 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 at the woman's HCP (obstetrician/gynecologist, pediatrician and/or neurologist of referred woman) 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. Height will be recorded at screening only.

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).

See Appendix 1 (Schedule of Assessments) for the timing of 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 these measurements are performed as per clinical practice and are available, any abnormalities should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded on the Adverse Event section of the eCRF (as presented in Section 5.1.2).

4.5.2.4 Neurological Examinations

A neurological examination will be performed at baseline, early study discontinuation as well as at unscheduled visits if applicable, to distinguish relapse in MS from another neurological (non-MS) disorder. *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 (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 treatment period. 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 hours, with or without recovery, and in the absence of fever or infection (Thompson et al. 2018). MS relapses should not be reported as an adverse event, unless they are serious.

It is recommended that women with new neurological symptoms suggestive of a relapse have an EDSS/Functional Systems Score (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 paragraphs. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. For more details, refer to Schedule of Assessments (see Appendix 1).

- **Hematology** (hemoglobin, hematocrit, quantitative platelet count, red blood cell [RBC] count, white blood cell [WBC] absolute or/and differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).
- **Serum chemistry** (potassium, sodium, chloride, random glucose, AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin and creatinine).
- **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.
- **Serum Ig concentration:** Quantitative measurement for IgG, IgM and IgA levels.
- **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+).*
- **Ocrelizumab concentration in breastmilk:** Breastmilk samples throughout the study will be collected for determination of ocrelizumab concentration. Women should record the volume of pumped breastmilk and indicate date and time for collection as well as whether breastmilk was pumped from one or both breasts. At each sampling point, 5 mL of breastmilk should be saved (as directed by the site staff) to send to the central laboratory. The 24-hour (Day 1, as well as Day 15 for women who received the 2×300 mg regimen) post-infusion samples are collected based on the midpoint of infusion. For example, if the infusion began at 8 a.m. and ended at 10 a.m., the 24-hour sample collection would occur at 9 a.m. on the day before and after the infusion. For details, refer to Schedule of Assessments (see Appendix 1).

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 Medical History, Biometrics and Concomitant Medications

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

- Previous and concomitant medication given to the infant should be recorded at screening and throughout the study. For administered vaccinations, refer to Section 4.5.3.2.

Note: *these standard-of-care data may be collected by the investigator as reported by the mother and/or via direct contact with the pediatrician.*

4.5.3.2 Physical Examinations and Related Assessments

- Body weight (measured at every visit where a blood sample will be taken, i.e., at Day 30 [±2 days] post-infusion 1, and 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). *Infant weight will be collected by a mobile nurse during home visits or by qualified site staff if the visit occurs at the site.*
- Feeding schedule diary (during the treatment and sampling period): Women should record the number of breastmilk feeds and/or feed with formula milk (supplementation) on the day of the sample collection and the previous and following day, i.e., day of collection ±1 day. *The mother's record of the feeding schedule diary will be collected by study personnel at the site or by a mobile nurse during visits to the mother.*
- Feeding status (during the vaccination period): Women 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, at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment. *The mother's record of feeding status will be collected by study personnel at the site or by a mobile nurse during visits to the mother.*
- ASQ-3 at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment.
- 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) at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment.
- Documentation of vaccinations: 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 30 days after the first postpartum ocrelizumab infusion 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 Month 13/1 month after first or second MMR dose, and may include diphtheria, tetanus, and pertussis, Hemophilus influenzae type b (Hib), 13-pneumococcal conjugate vaccine (PCV-13), HBV and MMR. *Documentation of vaccinations will be collected by the investigator via interview and documentation provided by the mother (e.g., vaccine card) or via direct contact with the pediatrician.*

See Appendix 1 (Schedule of Assessments) for the timing of assessments and Appendix 6 for the time windows for infant growth velocity and child developmental milestone assessments.

4.5.3.3 Laboratory, Biomarker, and Other Biological Samples

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

Day 30 (±2 days) post-infusion 1

- **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** in serum

Note: If the infant's B-cell levels are found to be below LLN at any visit, *analyses of B-, T-, and NK cells will be repeated every 4 weeks until B-cell levels are found to be above the age-adequate LLN as per Appendix 7 (in consultation with the Sponsor). The first repeat analysis will also include CBC and immunoglobulin levels.*

Infant samples will be collected by venipuncture *at one timepoint*. As per the recommendations 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 Day 30 (±2 days) Post-Infusion 1

Order of Priority	Assessment
1	Any *necessary* 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] The same sample will be used to measure B-cell counts (CD19+), T-cell counts (CD3+, CD4+, 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 is not planned to be administered

- **Mean titers (IgG) of antibody immune response(s) to common childhood vaccinations** with full or partial doses given prior to 1 year will be measured (which include responses to MMR, *diphtheria, tetanus, pertussis*, Hib, HBV, and PCV-13). Titers will be measured at 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.

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.

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

Note: If the infant's B-cell levels are found to be below LLN at any visit, *analyses of B-, T-, and NK cells will be repeated every 4 weeks until B-cell levels are found to be above the age-adequate LLN as per Appendix 7 (in consultation with the Sponsor). The first repeat analysis will also include a CBC and immunoglobulin levels.*

Infant samples will be collected by venipuncture *at one timepoint*. As per the recommendations 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 the First/Second Dose of MMR Vaccine or at Month 13 of Age (+30 Days) if MMR Vaccine Is Not Planned to Be Administered

Order of Priority	Assessment
1	Any *necessary* safety laboratory samples (scheduled or unscheduled and performed at the discretion of the investigator)
2	Mean titers (IgG) of antibody immune response(s) to vaccinations [a]
3	Lymphocyte subtypes blood sample [b]

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

[a] *The following antibody titers will be measured: 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] *The* same sample will be used to measure B-cell counts (CD19+*),* T-cell counts (CD3+, CD4+, CD8+*), and NK cell counts (CD16+CD56+).*

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 (with the exception of an accidental pregnancy, as described below). 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.

In case a woman enrolled in the study becomes accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until the pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection). The investigator should complete the Global Clinical Trial Pregnancy Form and submit to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the 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.

4.6.2 Discontinuation from the Study

Women and their 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; this does not apply to treatment discontinuation as described in Section 3.1.4) will be invited to attend an early study discontinuation visit as soon as possible (further details in Section 3.1.5).

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

- Woman's withdrawal of consent
- Study termination or site closure
- AE
- Loss to follow-up
- Any medical condition that the investigator or Sponsor determines may jeopardize the woman's or infant's safety 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 the woman's 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.
- Enrolment 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 subject 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

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 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.

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.

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 and Assessing Safety Parameters

The investigator is accountable for ensuring that all adverse events collected as per protocol (see Section 5.1.1.1 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

The 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 occurring in a pregnant woman pre- and post- study period should be reported to the marketing authorization holder (MAH), as a follow-up spontaneous pregnancy report to 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 instruction regarding:

- IRRs
- Diagnosis versus signs and symptoms
- Adverse events occurring secondary to other adverse events
- Persistent or recurrent AEs
- 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 Investigator to Sponsor

5.1.3.1 Immediate Reporting Requirements from Investigator 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:

- SAEs
- Non-serious adverse events of special interest
- Pregnancy occurred during breastfeeding (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 Institutional Review Board (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, 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 Electronic Data Capture 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 woman enrolled in the study becomes accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection). 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 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 breastfeeding (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

The study enrolls postpartum women breastfeeding their infants following the first postpartum ocrelizumab dose. In case a woman enrolled in the study becomes accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection).

In case of a spontaneous abortion in an accidental pregnancy during breastfeeding, the spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), 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).

If a therapeutic or elective abortion was performed in an accidental pregnancy during breastfeeding because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as an serious adverse event, 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.

All abortions that occur in an accidental pregnancy during breastfeeding should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

Congenital Anomalies/Birth Defects

The study enrolls women postpartum who delivered a healthy term infant and who plan to breastfeed their infants following the first postpartum ocrelizumab dose. In case a woman enrolled in the study becomes accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection).

Any congenital anomaly/birth defect in a child born to a woman who became accidentally pregnant during breastfeeding and was exposed to the medicinal product should be

classified as an 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 (see also Section 5.1.3.5)
- 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 (e.g., SmPC for the EU).

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 conducted after the last breastmilk sample collection at the end of the 60-day treatment and sampling period. Full analysis, including analysis of the vaccination response in infants, 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.

6.1 ANALYSIS POPULATIONS

Full Analysis Set

The full analysis set (FAS) population of women will include all women who meet the eligibility criteria and receive any postpartum dose of ocrelizumab.

The FAS population of infants will include all the infants of the FAS population of women.

Safety Population

The safety population will be the same as the FAS. The safety population of infants will include all infants of women in the FAS population.

6.2 DETERMINATION OF SAMPLE SIZE

There is no formal sample size calculation, as no confirmatory hypothesis testing is planned. The primary analysis will be descriptive. The study will include at least 10 women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

With 10 infants, a precision (width of the two-sided 95% CI) of 0.443 is expected if one event is observed (defined as B-cells below the LLN) and a precision of 0.531 if two events are observed in the study. If no event is observed during the study, there is a 95% confidence that the event rate is below 0.31.

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrolment, 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 will be tabulated, with treatment discontinuations summarized by reason for discontinuation. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized. Women and infants enrolled but excluded from the FAS will be listed.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

For women, demographics (age and self-reported race), 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), and other important variables.

Characteristics of infants at birth will also be summarized (gender, weight, gestational age at birth and other endpoints collected). Values at the mother's first ocrelizumab

infusion visit (which may take place any time between Week 2 and Week 24 postpartum) will be considered as baseline.

6.5 PRIMARY ANALYSES

6.5.1 Primary Endpoint

The primary analysis will be conducted on the FAS (defined earlier). The analysis will be performed after the last breastmilk sample collection at the end of the 60-day treatment and sampling period.

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 estimated ADID will be analyzed using descriptive statistics. Mean, corresponding 95% CI, SD, and other statistics will be presented.

The estimand of the proportion of infants with B-cell levels below the LLN is defined as below:

- Population: all infants of women in the FAS population who have B-cell levels measured at Day 30 after the mother's first ocrelizumab postpartum infusion.
- 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 will be handled as follows:
  - Incomplete dosing, including delayed second (300 mg) ocrelizumab infusion: all the B-cell data will be included in the analysis.
  - Infant did not receive any breastmilk *before B-cell measurement during the entire 30-day period* after the mother's first ocrelizumab postpartum infusion: B-cell data will be excluded from the analysis.
  - Mother used other DMT during breastfeeding before B-cell measurement on Day 30 post-ocrelizumab infusion 1: B-cell data will be excluded from the analysis.
  - Mother used other medication before B-cell measurement on Day 30 post-ocrelizumab infusion 1 that is not allowed by protocol during breastfeeding: B-cell data will be excluded from the analysis.
  - *Infant's blood sample collected before assessment window (i.e., before Day 28): Data will be excluded from the analysis.*
  - Infant's blood sample collected beyond the assessment window: B-cell data might be included or excluded depending on the cause of the delay (rules will be specified in the SAP) and schedule of delayed visit.
  - *Infant's blood sample collected while infant has an illness: B-cell data will be excluded on a case-by-case basis if there is a strong biological rationale that the illness may confound the B-cell data.*

- Population-level summary: The proportion of infants with B-cell levels below LLN will be reported with the two-sided 95% CI; 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.

The estimand of the ADID in breastmilk is defined as below:

- Population: all women in the FAS population who provide any breastmilk samples (primary analysis set of mother)
- Variable: ADID
- Intercurrent events will be handled as follows:
  - Incomplete dosing, including delayed second (300 mg) ocrelizumab infusion: all the ADID data will be collected and included in the analysis. No adjustments based on actual dose will be made.
  - Mother used other DMT during breastfeeding: ADID data will be included.
  - Mother used other medication not allowed by protocol during breastfeeding: ADID data will be included in the analysis.
  - Mother has mastitis infection during the sample collection period: ADID data will be included from milk samples obtained from the non-infected breast (in case of bilateral mastitis, breastmilk sampling will be interrupted until the infection resolves).
- Population-level summary: The summary statistics together with 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 milk samples with all supporting information are collected.

More details about missing data handling, as well as sensitivity analyses based on alternative imputation approaches, will be specified in the SAP.

6.5.2 Secondary Endpoints

The ocrelizumab concentration in mature breastmilk at each time point, MDID, *RID,* and AUC will be summarized descriptively. Continuous variables at each month *(*e.g., length and weight of infants*)*, as well change from baseline (if applicable) will be analyzed primarily using descriptive statistics.

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 for the overall population. *For PCV-13, positive humoral responses (as defined by antibody concentrations ≥0.35 μg/mL) will be described for all pneumococcal vaccine serotypes individually.*

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

6.5.3 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.

6.6 SAFETY ANALYSES

6.6.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Signs Data

The safety outcome measures 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.

All safety analyses will be conducted on data collected from the first postpartum ocrelizumab infusion until the end of the study. The safety analysis will be performed on the safety populations of women and infants separately. 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 events, 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.

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

6.7 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 United States or under a U.S. 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 Trials 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 patient the objectives, methods, and potential risks associated with each optional procedure. Patients 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 patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient'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 patient 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 patient 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 patient is participating in the study, the patient 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 patient 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 patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the 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 Informed Consent Form (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. 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 healthcare professionals 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 access, 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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7		
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Patient population and ICF	Diagnosis confirmation [d]	x												
	Informed consent [e]	x												
	Review inclusion/ exclusion criteria	x	x											
Maternal general medical history and demographics [f]	Demographics (age, ethnicity, level of education)	x												
	Clinically significant diseases and surgery/ procedures	x	x			x							x	
	Smoking history and alcohol intake	x												
	Vaccination history	x												
	Height	x												
	Weight	x	x			x								
	Previous and concomitant medication	x	x			x							x	

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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		**1**	**2**	**3**	**4**	**2a [a]**	**3a [a]**	**4a [a]**	**5**	**6**	**–**	**7**		
Day of visit		**(Variable)**	**0 (baseline)**	**1**	**7**	**14**	**15**	**21**	**30 (± 2 days)**	**60 (± 2 days)**	**Months 2, 4, 6, 9, and 12**	**Month 13 of Age (+ 30 days) [c]**	**Woman**	**Child**
Maternal MS disease history	Date of MS onset and diagnosis	x												
Maternal MS disease history (cont.)	Disease status (EDSS and relapses up to 1 year before the LMP)	x												
	History of previous DMTs (prior and/or during pregnancy)	x												
	Treatment history with ocrelizumab (OCREVUS) [g]	x												
Maternal obstetric history	Previous pregnancies	x												
Maternal physical assessments	General physical examination [h]	x	x			x							x	
	Neurological examination [i]		x										x	
	Recording of potential relapses		x			x							x	
	EDSS score		x										x	

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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7		
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Maternal laboratory assessments	Breastmilk ocrelizumab concentration [j]		x	x	x	x	x	x	x	x				
	Hematology, chemistry, urinalysis [k]	x	x			x							x	
	Hepatitis B virus (HBV) screening [l]	x												
	Whole blood sample for lymphocyte subtypes [m]	x												
	Serum Ig concentration	x												
Ocrelizumab infusion	Methyl-prednisolone and antihistamine premedication [n]		x			x								
	Ocrelizumab administration [o]		x			x								
	Documentation of collection of second postpartum ocrelizumab administration [dd]											*x*		

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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7		
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Infant physical assessments and procedures	General health and medical history [p]	x												
	Body weight for safety								x			x		
	Pregnancy and infant outcomes [q]	x												
	Feeding schedule diary and status [r]		x	x	x	x	x	x	x	x	x			
	ASQ-3 [s]										x			x
	Documentation of infant growth velocity (weight, length, head circumference) [t]										x			x
	Previous and concomitant medications [u]	x							x		x	x		x
	Documentation of vaccination of the infant as part of routine care [v]										x	x		x

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

		Screening [b]	Treatment and Sampling Period [a]							Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7	
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Infant laboratory assessments [w, x]	Whole blood sample for lymphocytes subtypes sample [x, y]								x			x[z]		
	Serum titers (IgG) of antibody immune responses to vaccinations [aa]											x[z]		
	Serum ocrelizumab concentration								x					
Telephone interview	General review of mother and infant [bb]			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Safety	Adverse event assessment [cc]	x	x	x	x	x	x	x	x	x	x	x	x	x

Mother's assessments Infant's assessments

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; BRUE = brief resolved unexplained event; 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; HCPs = Healthcare professionals; Hib = *Hemophilus influenzae* type b; ICF = Informed Consent Form; *IRR = infusion-related reaction;* 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; *SmPC = Summary of Product Characteristics; 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 telephone interview will not be conducted in a week where there will be an on-site visit).

[a] Visits 2a, 3a and 4a are only applicable for women who will be receiving the first ocrelizumab dose as two 300 mg infusions.

[b] The length of the screening period is variable and depends on local timings for performing some of the eligibility assessments. It is possible that visit 1 (screening) is completed in one day or over several days/weeks. Screening may be started during the third trimester of pregnancy and continue until 24 weeks postpartum.

[c] Samples 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 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.

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

[e] 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.

[f] 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 baseline visit. Demographic data will include age, self-reported race/ethnicity, and level of education. Clinically significant diseases and/or surgeries and concomitant medication should also be recorded throughout the study. Information on vaccinations administered to the mother during the study will be collected under concomitant medications.

[g] Documentation of start of ocrelizumab (OCREVUS) therapy and date and dose of last ocrelizumab infusion prior to enrolment. Ocrelizumab-related information to be collected only in women who received commercial ocrelizumab prior to enrolment.

[h] A complete physical examination should be performed at the screening and baseline visits and at all visits during the treatment period (results from examinations done as part of routine care at subject's HCPs [obstetrician/gynecologist, pediatrician, neurologist of referred subjects] 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.

[i] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. *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.*

[j] Women should record the volume of pumped breastmilk and indicate date and time for collection as well as whether breastmilk was pumped from one or both breasts. *For sampling on Day 0 (baseline), the sample should be taken before the infusion.* For 24 hours post-infusion (Day 1 and Day 15), samples are collected based on the midpoint of infusion. For example, if the infusion began at 8 am and ended at 10 a.m., the 24-hour sample collection would occur at 9 a.m. on the day after the infusion. With the exception of the 24-hour (Day 1; and [for women who received a 2 × 300 mg dose] Day 15) post-infusion breastmilk collection time points, flexibility is allowed on collection timing to accommodate the mother and the infant feeding schedule. If the mother presents with unilateral mastitis, milk should only be expressed from the unaffected breast, until the infection resolves. If mastitis presents bilaterally (rare), breastmilk collection should be stopped until the infection resolves.

[k] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute or/and differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), and quantitative platelet count. Chemistry will include potassium, sodium, chloride, random glucose, AST, ALT, GGT, creatinine, total bilirubin. 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.

[l] 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.

[m] Blood samples will be collected to measure B-cell counts (CD19+ *and B-cell subsets [Table 2*]),T-cell counts (CD3+, CD4+, and CD8+*), and NK cell counts (CD16+CD56+).*

[n] 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.

[o] In line with the dose regimen in the local label, the first dose of ocrelizumab may be administered as an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days, or as a single 600 mg infusion (in 500 mL 0.9% sodium chloride), at any point between Week 2 and 24 postpartum. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. *Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (USPI; SmPC).* If women did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses. Women referred by HCPs to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

[p] General health and medical history for infants includes screening for the following (infants should be excluded from the study if any are present): age >24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab; any abnormality that may interfere with breastfeeding or milk absorption, including but not limited to cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia; an active infection (the infant may be included once the infection resolves); at least one documented BRUE, as defined by the 2016 Guidelines of the American Academy of Pediatrics.

[q] These will include: mode of delivery (vaginal delivery, instrumental delivery, scheduled or urgent cesarean section); APGAR score (1 min, 5 min, 10 min); gestational age at birth; infant's measurements (weight, length, head circumference); and congenital malformations.

[r] During the treatment and sampling period, women should record the number of breastmilk feeds and/or feeds with formula milk (supplementation) on the day of the sample collection and the previous and following day, i.e., day of collection ±1 day. During the vaccination period, women 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, at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment.

[s] 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 as applicable and depending on the infant's age at enrolment (see Appendix 6 for details of time windows of infant growth velocity and child developmental milestone assessments).

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

[u] Including documentation of past or current medications as well as clinically significant pediatric disease/abnormality. Changes to concomitant medication given to the infant should be recorded throughout the study.

[v] *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 13/1 month after first or second MMR dose.*

[w] Infant sampling at Day 30 (±2 days) post-infusion 1 and at 1 month (+30 days) after first or second dose of MMR*, or* Month 13 of age *in case MMR vaccine is not planned to be administered* (+30 days) may be conducted via in-home nurse visits or at the hospital as part of study visits. CD19+ B-cell level at Day 30 (±2 days) post-infusion 1 represents the co-primary endpoint measurement.

[x] 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 sample at Day 30 (±2 days) post-infusion 1, (1) safety laboratory samples [scheduled or unscheduled and performed at the discretion of the investigator] (2) lymphocyte subtypes sample for B-cell counts (CD19+) and T-cell counts (CD3+, CD4+, and CD8+*), and NK cell counts (CD16+CD56+)*. (3) serum ocrelizumab concentration; for the Month 13 of age/1 month after first/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+) and T-cell counts (CD3+, CD4+, and CD8+*), and NK cell counts (CD16+CD56+)*.

[y] *If the infant's B-cell levels are found to be below LLN, analyses of B-, T-, and NK cells will be repeated every 4 weeks until B-cell levels are found to be above the age-adequate LLN as per Appendix 7 (in consultation with the Sponsor). The first repeat analysis will also include a complete blood count and immunoglobulin levels.*

[z] For 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, all efforts will be made to collect samples. However, if they cannot be collected, it will not be considered a protocol deviation.

[aa] Serum anti-vaccine antibody (IgG) titers will be measured to vaccines administered as per local practice over the first year of life (which include MMR, *diphtheria, tetanus, pertussis*, Hib, HBV and PCV-13); 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.

[bb] A structured telephone interview will be conducted by site personnel postpartum every 2 weeks during the treatment and sampling period and every 3 months during the vaccination period (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother 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 using the lactational amenorrhea method as contraception will also be asked whether the three necessary criteria outlined in Section 4.1.1 to ensure adequate protection from an unplanned pregnancy are applied.* No telephone contact is needed in weeks where the woman is performing on-site visits.

[cc] Adverse events in both mother and infant will be reported throughout the study as per standard pharmacovigilance procedures. Adverse events will also be captured at screening for women who received ocrelizumab before pregnancy.

[dd] *Documentation of premedication is not required.*

Appendix 2
Compatibility of Common Medications with Breastfeeding

The following information is compiled from guidance provided by the New Zealand Medicines and Medical Devices Safety Authority (Medsafe), available at https://www.medsafe.govt.nz/profs/puarticles/June2015/June2015Lactation.htm and https://www.medsafe.govt.nz/profs/puarticles/lactation.htm.

An up-to-date database of medicine levels in breastmilk and infant blood and possible adverse reactions in the nursing infant is available at LactMed (https://www.ncbi.nlm.nih.gov/books/NBK501922/). The WHO has also produced a classification guide for medicines use in breastfeeding based on the WHO list of essential drugs (www.who.int/maternal_child_adolescent/documents/55732/en/).

Medicines with inherent toxicity or those with high infant exposure and therefore potential for significant toxicity are contraindicated during breastfeeding, and include:

- Cytotoxic agents
- Immunosuppressive agents
- Amiodarone
- Lithium
- Ergotamine
- Gold salts
- Isotretinoin

Radiopharmaceutical administration also requires temporary cessation of breastfeeding.

There are a range of health issues that affect women who are breastfeeding. These most commonly include infection, depressive disorders, pain, contraception, low milk supply and atopic conditions. Table A2-1 provides information on the compatibility of medicines used in the treatment of these conditions with breastfeeding.

Table A2-1 Compatibility of Commonly Used Medicines with Breastfeeding

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Infection	*Antibiotics*		
	β-lactams (e.g., amoxicillin)	Compatible	Gastrointestinal flora changes possible; monitor infant for diarrhea, vomiting, thrush
	Macrolides (e.g., erythromycin)	Compatible	Single dose of azithromycin considered safe
	Cephalosporins (e.g., cephalexin)	Compatible	May also affect infant gut flora (third generation more likely)
	Fluoroquinolones (e.g., ciprofloxacin)	Avoid if possible	Potential risk of arthropathies
	Trimethoprim	Compatible	
	Nitrofurantoin	Compatible	Avoid nitrofurantoin if infant less than 1 month old or premature
	Metronidazole	Avoid if possible	If single 2 g metronidazole dose given, discontinue breastfeeding for 12 hours
	Antifungals		
	Azoles (e.g., fluconazole)	Compatible	If applying miconazole oral gel to nipples, apply after breastfeeding
	Nystatin	Compatible	
	Antivirals		
	Acyclovir	Compatible	
Depressive disorders	*Antidepressants*		
	SSRIs (e.g., paroxetine)	Compatible	Paroxetine and sertraline preferred due to shorter half-lives

Appendix 2: Compatibility of Common Medications with Breastfeeding

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Pain	TCAs (e.g., amitriptyline)	Less preferred due to potential toxicity	Amitriptyline compatible in doses up to 150 mg/day
	Anxiolytics		
	Benzodiazepines (e.g., temazepam)	Compatible in a single dose; avoid repeated doses	Short-acting benzodiazepines preferred as accumulation may occur Monitor infant for drowsiness
	Analgesics		
	Paracetamol	Compatible	Paracetamol analgesic of choice
	NSAIDs (e.g., ibuprofen)	Compatible	Avoid breastfeeding with long-term acetylsalicylic acid treatment
	Opiates (e.g., codeine)	Compatible in occasional doses	Monitor infant for drowsiness, apnea, bradycardia and cyanosis Use codeine with caution in rapid metabolizers
	Tramadol	Compatible	
Contraception	*Hormonal methods*		
	Progesterone	Compatible	See data sheet
	Estrogen	Avoid if possible	May inhibit lactation
Allergies and hay fever	*Antihistamines*		
	Sedating (e.g., promethazine)	Probably compatible	Occasional use probably safe Monitor for sedation in mother and infant
	Non-sedating (e.g., loratadine)	Compatible	
	Topical		
	Corticosteroids (e.g., hydrocortisone)	Compatible	If applying to breasts apply after feeding

Appendix 2: Compatibility of Common Medications with Breastfeeding

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Asthma	β2- adrenergic (e.g., salbutamol)	Compatible	
	Corticosteroids (e.g., budesonide)	Compatible	
Other	Warfarin	Compatible	
	Metformin	Compatible	

NSAIDs = non-steroidal anti-inflammatory drugs; SSRIs = Selective serotonin reuptake inhibitors; TCAs = Tricyclic antidepressants.

Source: Medsafe. URL: https://www.medsafe.govt.nz/profs/puarticles/June2015/June2015Lactation.htm. (Accessed 17 December 2020).

TABULATED SUMMARY OF DRUG DISTRIBUTION INTO BREASTMILK

Table A2-2 shows published milk/plasma (M/P) ratios from the literature and provides an estimate of the weight-adjusted infant dose. Interpretation of these requires an understanding of the limitations associated with published data, such as the availability of only single pairs of plasma and milk concentrations. Infant clearance (related to post-conceptual age) should always be considered.

Table A2-2 Summary of Distribution of Drugs into Breastmilk

Drug	M/P_{AUC}	% Maternal Dose	Comments
Acid-suppressants:			
Cimetidine	1.7-5.8	5.4–6.7	Avoid in favor of safer alternatives with lower potential for side effects. May accumulate in milk due to active transport.
Famotidine	1.5	1.6	Probably safe.
Ranitidine	2.8	5.0–7.8	Probably safe when restricted to sporadic doses or a single dose at night-time. May accumulate in milk due to active transport.
Analgesics:			
Aspirin	0.06	3.2	Avoid due to possible association with Reye's syndrome.
Codeine	2.16	6.8	Considered safe.
Ibuprofen	0	<0.6	Considered safe. Not detected in milk.
Indomethacin	0.37	<1.0	Considered safe. One case of seizures (causality questionable).
Mefenamic acid	ID	0.3	Probably safe.
Methadone	0.47	2.2	Considered safe in methadone maintenance as 60% of infants born to mothers in maintenance programs develop symptoms of withdrawal.
Morphine	2.46	0.4	Considered safe.
Naproxen	ID	1.1	Probably safe.
Nefopam	ID	0.4	Probably safe.
Piroxicam	ID	5–10	Use a NSAID with a shorter half-life where possible.
Paracetamol	0.8	2.9–7.9	Considered safe.
Sumatriptan	4.1–5.7	0.3–6.7	Exposure limited by low oral availability in term infants. Expressing for 8 hours post-dose will almost completely avoid exposure.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Antibiotics:			
Aminoglycosides			
Gentamicin	0.17	2.2	Considered compatible with breastfeeding due to low transfer and low oral availability.
Cephalosporins			
Cefaclor	ID	0.7	Considered safe. Low transfer into milk. Third generation cephalosporins have greater potential to alter bowel flora.
Cefalexin	0.09	0.5–1.2	
Cefotaxime	ID	0.3	
Ceftriaxone	0.04	0.7–4.7	
Fluoroquinolones			
Ciprofloxacin	2.17	4.8	Avoid fluoroquinolones due to theoretical risk of arthropathies.
Macrolides			
Clarithromycin	0.25	1.8	Considered safe. May alter bowel flora.
Erythromycin	0.41	2.1	
Penicillins			
Amoxicillin	ID	0.7	Considered safe. Note: although amoxicillin/clavulanic acid combination is used extensively in lactation, there are no published data on the safety of clavulanic acid.
Benzylpenicillin	0.37	0.8	
Phenoxymethyl-penicillin	ID	0.25	
Tetracyclines			
Minocycline	ID	3.6	Avoid tetracyclines where feasible due to the possible risks of dental staining and adverse effects on bone development.
Tetracycline	0.58	4.8	
Others			

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Acyclovir	ID	1.1–1.2	Considered safe. No adverse effects noted in breastfed infants.
Fluconazole	0.75	11	Potential for accumulation particularly in premature infants.
Metronidazole	0.9–1.1	0.1–36.0	Controversial as exposure may be high. With high doses consider expressing and discarding milk.
Nitrofurantoin	ID	0.6–6.0	Avoid in G6PD-deficient infants (due to the risk of hemolysis).
Sulphamethoxazole and Trimethoprim (i.e., co-trimoxazole)	0.1 1.26	2–2.5 3.8–5.5	Avoid suphaemethoxazole in infants with hyperbilirubinemia and G6PD deficiency.
Anticoagulants			
Warfarin	0	<4.4	Probably safe. No changes in prothrombin times detected in breastfeeding infants. Monitor prothrombin time.
Anticonvulsants:			
Carbamazepine	0.36–0.39	2.8–7.3	Considered safe. Monitor for sedation, poor suckling.
Lamotrigine	ID	10–22	Concentrations in breastfed infants have been consistent with those expected to produce clinical effect. Best to avoid.
Phenobarbitone	ID	23–156	Avoid due to high infant exposure.
Phenytoin	0.13–0.18	3.0–7.2	Considered safe. Observe for sedation, poor suckling. One report of methemoglobinemia, poor suckling and sedation.
Sodium valproate	0.05	1.8	Considered safe at low doses. High doses may increase the risk of hepatitis.
Vigabatrin	ID	<1%	Avoid until further data are available.
Antidepressants:			
Tricyclics:			
Amitriptyline	0.83	0.6–0.9	Probably safe. Negligible or no concentrations detected in breastfed infants.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Desipramine	ID	0.5–1.0	
Dothiepin	0.8–1.6	0.2-1.5	
Doxepin	ID	0.01	
Imipramine	ID	0.13	
Nortriptyline	ID	0.53	
Others			
Moclobemide	0.72	1.6	Probably safe.
Antiemetics:			
Domperidone	ID	0.05	Probably safe. May increase milk secretion.
Metoclopramide	ID	4.7–11.3	Low dose or sporadic use probably safe. May increase milk secretion.
Antihistamines:			
Loratadine	1.2	0.7	Probably safe. No adverse effects reported in infants.
Triprolidine	0.53	0.9	Considered safe.
Antipsychotics:			
Chlorpromazine	ID	0.2	
Flupenthixol	ID	0.5–0.8	Probably safe. May increase milk secretion. Monitor infant for sedation, irritability etc.
Haloperidol	ID	0.15–2.0	
Cardiovascular:			
Amiodarone	ID	37	Avoid in breastfeeding.
Atenolol	2.3–4.5	5.7–19.2	Avoid in favor of antihypertensives with lower infant exposure.
Captopril	0.03	0.014	Considered safe.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Digoxin	0.6–0.9	2.3–5.6	Considered safe.
Diltiazem	0.98	0.9	Unlikely to be problematical in breastfeeding.
Enalapril	0.02	<0.1	Considered safe.
Metoprolol	2.8-3.6	1.7–3.3	Probably safe.
Nadolol	4.6	5.1	Consider choosing a beta-blocker with a lower infant dose, if feasible.
Propranolol	0.32–0.76	0.2–0.9	Probably safe.
Quinapril	0.12	1.6	Considered safe.
Verapamil	0.6	0.14–0.84	Considered safe.
Sedatives/hypnotics:			
Clonazepam	ID	1.5–3.0	Short-term use of low doses is probably safe.
Diazepam	0.16	2.0–2.3	Reasonable to breastfeed after a low single dose but potential for accumulation with prolonged use. Sedation has been reported in breastfed infants.
Lorazepam	ID	2.2	Short-term use of low doses is probably safe.
Midazolam	0.16	0.7	Short-term use of low doses is probably safe.
Nitrazepam	ID	ID	Short-term use of low doses is probably safe. Potential for accumulation with prolonged administration.
Zopiclone	0.5	4.1	Short-term use of low doses is probably safe.
Social Drugs:			
Cannabis (THC)	ID	ID	Avoid as long-term effects are unknown.
Caffeine	0.5–0.8	0.6–21.0	Low intake probably safe. Restlessness and irritability documented. Prolonged half-life (80–100 hours) in neonates.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Ethanol	0.9	3-4	Occasional low usage probably safe. Chronic intake may be associated with impairment of psychomotor development. Consider withholding breastfeeding for 1–2 hours per standard drink.
Nicotine	2.92	ID	Cigarette smoking should be avoided due to health hazards associated with smoking. Use of nicotine patches may be considered compatible with breastfeeding and is favored over smoking.
Miscellaneous:			
Ethinyloestradiol	ID	0.3	May suppress lactation.
Levonorgestrel	ID	1.1	Considered safe.
Medroxyprogesterone	ID–0.72	3.4–5.0	Considered safe.
Norethisterone	ID–0.26	0.02-1.9	Considered safe.
Prednisone	ID	0.26	Short courses of low doses (≤20 mg daily) are probably safe. Note: there are insufficient data on other systemic corticosteroids (e.g., betamethasone, dexamethasone).
Pseudoephedrine	2.5	4.0	Low doses or sporadic use probably safe.
Sulphasalazine	ID	1.2–7.0	Avoid in infants with hyperbilirubinemia or G6PD deficiency.

AUC = area under the concentration-time curves; G6PD = glucose-6-phosphate dehydrogenase; ID = insufficient data; M/P_{AUC} = AUC of the drug in maternal milk and plasma; NSAID = nonsteroidal anti-inflammatory drug; THC = Tetrahydrocannabinol.

Source: Medsafe. URL: https://www.medsafe.govt.nz/profs/puarticles/lactation.htm.

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 John Cunningham 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
Evolution	Hours to days	Over weeks
	Normally stabilize. May resolve spontaneously even without therapy	Progressive
Clinical Presentation	Diplopia *Paranesthesia* Paraparesis Optic neuritis Myelopathy	Aphasia Behavioral/neuropsychiatric changes Hemiparesis Retrochiasmal visual changes (e.g., hemianopia) Seizures

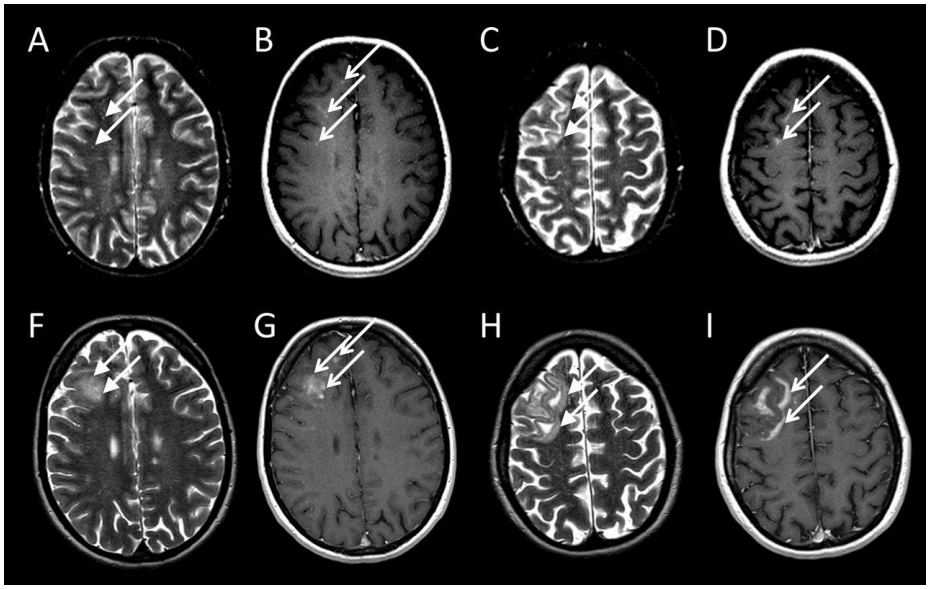
A3–2 MRI PRESENTATION

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 (see 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]

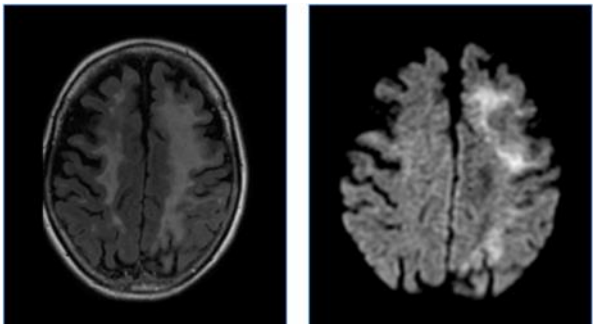
Figure A3-1 Imaging Characteristics of MS and PML



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 from 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 • Mostly located in periventricular, deep white matter, cerebellum, spinal cord areas • Also cortical and deep grey matter • U-fibers may be involved	• Often bilateral • [a] Subcortical frontal (+++), parietal (++), occipital (+) white matter (involving U-fibers) is the prime site • Cortex and basal ganglia are often involved • Can involve corpus callosum but unusual; rarely brainstem and posterior fossa
Appearance and Borders	• Focal (mostly) • Well-defined lesions with sharp edges; mostly round or finger-like in shape (especially periventricular lesions)	• Multifocal • 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
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

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

Parameters	MS	PML
T2W	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure Subacute and chronic lesions: hyperintense, with no ring structure	Always hyperintense [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; 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]

A3–3.1 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	+	–	+
	–	+	+
Possible	+	+	–/ND
	–	–	+
	–	(+) [a]	–
Not PML	+	–	–
	–	–	–

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

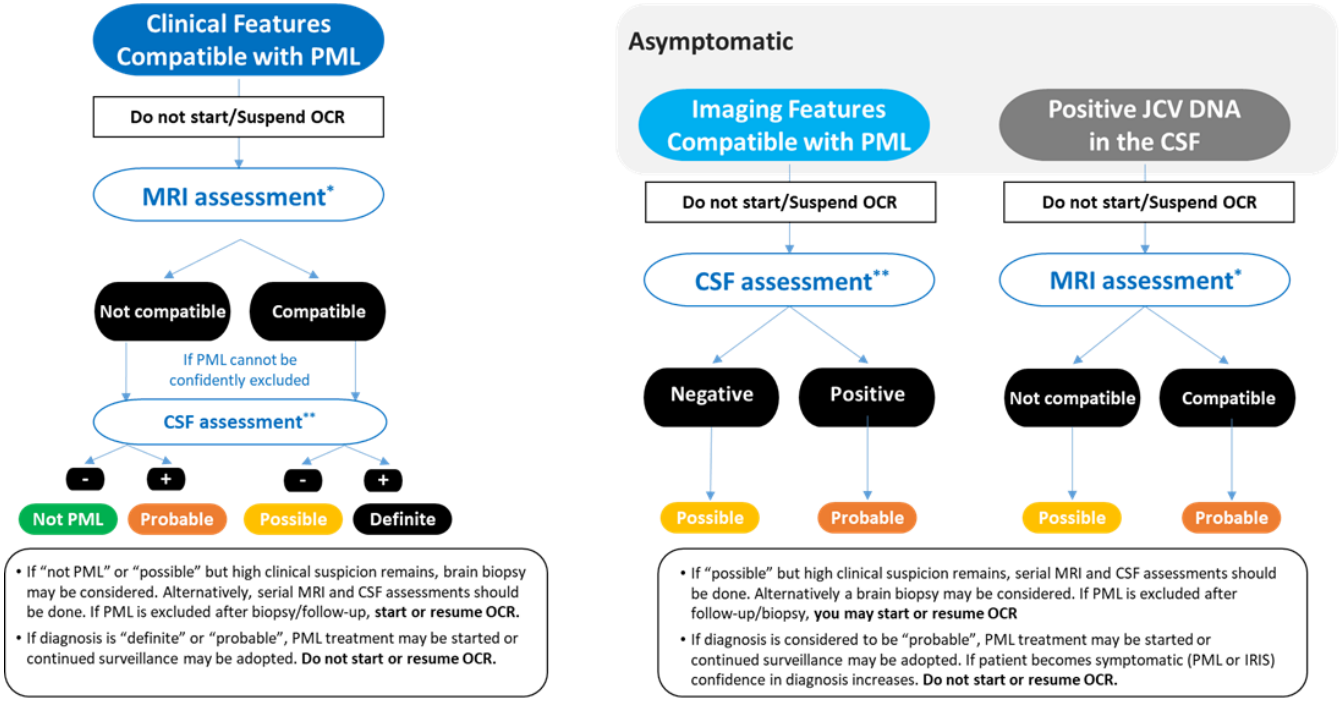
[a] **Note:** according to current AAN criteria, no diagnosis of PML can be made if only compatible imaging findings are present. However, recent evidence has shown that asymptomatic patients treated with NTZ, who have negative CSF JCV PCR results but PML-compatible MRI changes, may later develop symptoms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

A3–3.2 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 wash-out 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** 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** Fully ambulatory with two FS Grade 3 (others 0 or 1); **OR** 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** Ambulatory <100 meters without help or assistance **OR** Ambulatory ≥50 meters with unilateral assistance **OR** Ambulatory ≥120 meters with bilateral assistance
6.5	**Ambulatory for at least 20 meters with constant bilateral assistance (canes or crutches)** without rest **OR** Ambulatory for <50 meters with unilateral assistance (cane or crutch) **OR** Ambulatory 5–120 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. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).Neurology 1983:33,1444–52.

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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 **BMRC Grade 3 in one or two muscle groups** (movements against gravity are possible); and/or **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 **monoplegia:** BMRC Grade 0 or 1 in one limb; and/or **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 **marked tetraparesis:** BMRC Grade 2 or less in ≥ three limbs; and/or **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 and/or 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 and/or 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 and/or moderate decrease in touch or pain and/or marked reduction of proprioception >2 limbs
5	loss (essentially) of sensation in one or two limbs and/or 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)

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. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).Neurology 1983:33,1444–52.

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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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 5.0) 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 (version 5.0), 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 "hyperkalemia."

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 AEs).

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 AEs).

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 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 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).

A5–3.14 DRUG INTERACTIONS

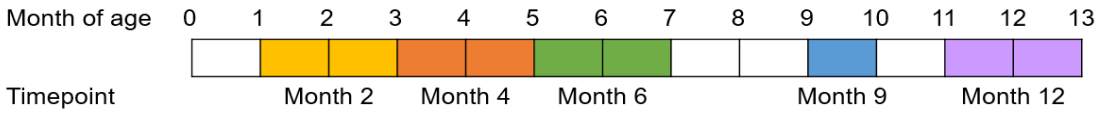
Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol, should be forwarded to the MAH as per non-serious timelines. If the associated adverse event fulfils the seriousness criteria, the event should be reported to MAH immediately (i.e., no more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

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, the Ages and Stages Questionnaire, version 3 (ASQ-3) age calculator2 can be used: https://agesandstages.com/free-resources/asq-calculator/.

Assessment of growth velocity at Months 2, 4, 6, 9, and 12 (as applicable and depending on the infant's age at enrolment) 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 post-natal 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	[redacted] Deputy EU QPPV 19-Dec-2023 08:04:45 GMT+0000

Approval Task	[redacted] Company Signatory 20-Dec-2023 17:12:29 GMT+0000

PROTOCOL

TITLE:	**A PHASE IV, MULTICENTER, OPEN-LABEL STUDY EVALUATING B-CELL LEVELS IN INFANTS OF LACTATING WOMEN WITH CIS OR MS RECEIVING OCRELIZUMAB – *THE SOPRANINO STUDY***
PROTOCOL NUMBER:	MN42989
VERSION NUMBER:	3
EUDRACT NUMBER:	2021-000063-79
IND NUMBER:	100593
NCT NUMBER:	NCT04998851
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.*

CONFIDENTIAL

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	See electronic date stamp on the final page of this document.
2	1 April 2022
1	15 March 2021

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol MN42989 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 infant postpartum exposure to ocrelizumab via breastmilk has been updated to present data from an analysis performed with a cut-off date of 31 March 2022, replacing data from an analysis performed up to 31 March 2021 (Section 1.3).
- The secondary objectives have been amended to include the evaluation of the relative exposure to ocrelizumab in infants of lactating women with clinically isolated syndrome (CIS) or multiple sclerosis (MS) receiving ocrelizumab postpartum. The average relative infant dose will be assessed over 60 days, calculated as the average oral daily infant dosage (mg/kg/day) divided by the maternal dosage (mg/kg/day), multiplied by 100 (Sections 2 [Table 1] and 6.5.2).
- In the endpoint for the exploratory objective "to evaluate the evolution of B-cell levels over the first year of life in infants of lactating women with CIS or MS receiving ocrelizumab postpartum", language has been clarified that trajectory (absolute and percentage changes) of B-cells (CD19+ cell) in the infant will be measured from Day 30 after the mother's first ocrelizumab postpartum infusion to 1 month after the first or second dose of 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 sample size has been reduced from at least 20 to at least 10 women with CIS or MS. Given that women with CIS or MS are not routinely treated with ocrelizumab during breastfeeding 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 6.2).
- It has been clarified throughout the protocol that dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (U.S. Prescribing Information and the Summary of Product Characteristics) (Section 3.1.3; Appendix 1).
- The total length of the study has been increased from approximately 2 years to approximately 3 years, due to the extension of the enrolment period from approximately 8 months to approximately 21 months (Section 3.2).
- Language has been added to clarify that, based on the ocrelizumab average terminal half-life of 26 days, it is assumed that a potential fetal exposure is unlikely in women whose last ocrelizumab infusion was earlier than 3 months before last menstrual period (Section 3.3.2).
- To reduce the burden of visits on the mothers, it has been detailed that 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 (Section 4.5.2.4; Appendix 1 [footnote "i"]).

- 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 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 4.5.2.7 and 4.5.3.3 [Tables 3 and 4]; Appendix 1).
- 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 4.5.3.3).
- The list of antibody (Ab) titers of responses to vaccines administered as per local practice, has been updated to detail that the following will be included: 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, *Hemophilus influenza* B IgG (Section 4.5.3.3 [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).
- The full analysis set (FAS) population of infants has been amended to remove the requirement to only include infants of the FAS population of women whose B-cell level data at Day 30 post-infusion 1 are available; the FAS population of infants will include all the infants of the FAS population of women (Section 6.1).
- Due to a reduction in sample size, the precision (width of the two-sided 95% CIs) for event rates (an event is defined as B-cells below the lower limit of normal [LLN]) have been amended (Section 6.2).
- A reference to Appendix 7 (B-cell reference ranges by week of life [absolute and percentage counts]) has been added (Section 6.5.1).
- The handling of intercurrent events of the estimand of the proportion of infants with B-cell levels below the LLN (Section 6.5.1) have been amended to include the following:
  - If an infant does not receive any breastmilk before B-cell measurement during the entire 30-day period after the mother's first ocrelizumab postpartum infusion, B-cell data will be excluded from the analysis.
  - If an infant's blood sample is collected before the assessment window (i.e., before Day 28), the data will be excluded from the analysis.

  - If an infant's blood sample is collected while the infant has an illness, the B-cell data will be excluded on a case-by-case basis if the illness is likely to confound the B-cell data.
- 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 following changes have been made to the Schedule of Assessments (Appendix 1):
  - The requirement to measure breastmilk ocrelizumab concentration at screening has been removed.
  - The requirement to collect documentation of collection of second postpartum ocrelizumab administration at Visit 7 has been included, with a corresponding footnote (footnote "ee") detailing that documentation of premedication is not required.
  - The corresponding footnote to the assessment "Whole blood sample for lymphocyte subtype sample" in infant laboratory assessments has been corrected to footnote "y".
  - It has been clarified that breastmilk samples that are to be collected on Day 0 (baseline) should be taken before the infusion (footnote "j").
- 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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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IV, MULTICENTER, OPEN-LABEL STUDY EVALUATING B-CELL LEVELS IN INFANTS OF LACTATING WOMEN WITH CIS OR MS RECEIVING OCRELIZUMAB – *THE SOPRANINO STUDY***
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TEST PRODUCT:	Ocrelizumab (RO4964913)
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 OF LACTATING WOMEN WITH CIS OR MS RECEIVING OCRELIZUMAB – *THE SOPRANINO STUDY***
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IND NUMBER:	100593
NCT NUMBER:	NCT04998851
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IV
INDICATION:	Multiple Sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics of ocrelizumab in the breastmilk of lactating women with clinically isolated syndrome (CIS) or multiple sclerosis (MS) [in line with the locally approved indications] treated with ocrelizumab, by assessing the concentration of ocrelizumab in mature breastmilk, as well as the corresponding exposure and pharmacodynamic effects (blood B-cell levels) in the infants. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Co-Primary Outcome Measure	
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum present with B-cell depletion	• Proportion of infants with B-cell levels (CD19+ cells, absolute counts in blood) below the LLN, measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate the exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated ADID, calculated as the ocrelizumab average milk concentration over 60 days post-ocrelizumab infusion 1 multiplied by an estimated infant milk intake of 150 mL/kg/day
Secondary Outcome Measures	
• To evaluate B-cell levels in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• B-cell levels (CD19+ cells, absolute counts and percentage of lymphocytes) measured at Day 30 after the mother's first ocrelizumab postpartum infusion

Objectives	Corresponding Endpoints
Objectives	Corresponding Endpoints
Secondary Outcome Measures (cont.)	
• To evaluate transfer of ocrelizumab into breastmilk of lactating women with CIS or MS receiving ocrelizumab postpartum	• AUC of ocrelizumab in mature breastmilk (i.e., milk produced after Day 14 postpartum) over 60 days after the first postpartum ocrelizumab infusion using the following time points: – If receiving 1 × 600 mg: before infusion and at 24 hours (Day 1), Day 7, Day 30 and Day 60 post-infusion – If receiving 2 × 300 mg: before infusion 1 and at 24 hours (Day 1), Day 7, Day 14, Day 15 (24 hours after infusion 2), Day 21, Day 30, and Day 60 post-infusion 1 • Average and peak ocrelizumab milk concentration as well as time to reach peak milk concentration, measured over 60 days after the mother's first postpartum ocrelizumab infusion
• To evaluate the *relative and* maximum exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated MDID calculated as the peak ocrelizumab milk concentration multiplied by an estimated infant milk intake of 150 mL/kg/day measured over 60 days after the mother's first postpartum ocrelizumab infusion • *Average RID over 60 days, calculated as the ADID (mg/kg/day) divided by the maternal dosage (mg/kg/day) multiplied by 100* *Note:* Other pharmacokinetic and exposure parameters may be calculated as appropriate, based on the data obtained
• To evaluate whether there is transfer of ocrelizumab from the mother to the infant via breastmilk	• Serum concentration of ocrelizumab in the infant measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum 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 MMR, diphtheria, tetanus, pertussis, Hib, HBV, and PCV-13 • Proportion of infants with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines
Safety Objectives	
• To evaluate the safety of ocrelizumab in lactating women with CIS or MS receiving ocrelizumab postpartum and in their respective infants	• Rate and nature of adverse events in the mother throughout the study, including changes in clinical and laboratory results • Rate and nature of adverse events in the infant throughout the study, including infections and hospitalizations

Objectives	Corresponding Endpoints
Exploratory Objectives	
• To evaluate infant's growth velocity and developmental milestones in the first year of life	• Assessment of growth velocity based on age-adjusted length, weight, head circumference, using monthly growth charts according to the WHO Child Growth Standards, as well as absolute values at Months 2, 4, 6, 9, and 12 • 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 measure disease activity in lactating women with CIS or MS receiving ocrelizumab postpartum	• Number of MS relapses during the postpartum period (clinical relapses) • Mean change in the EDSS score from last pre-baseline measurement (up to 1 year before LMP) to baseline
• To evaluate the evolution of B-cell levels over the first year of life in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Trajectory (absolute and percentage changes) of B-cells (CD19+ cells) *in the infant from* Day 30 after the mother's first ocrelizumab postpartum infusion *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

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; *RID = relative infant dose;* WHO = World Health Organization.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a prospective, multicenter, open-label study in lactating women with CIS or MS (in line with the locally approved indications) who decided together with their treating physician to continue on, or start treatment with, OCREVUS™ (ocrelizumab) postpartum despite ocrelizumab currently not being recommended during lactation.

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 at least *10* women with CIS or MS who are breastfeeding or planning to breastfeed.

The study will consist of the following periods:

- Screening period: After providing written informed consent, women will enter a screening period for eligibility assessments. Considering that decisions on initiating or resuming treatment with a disease-modifying therapy (DMT) in the postpartum period are usually taken before or during pregnancy, screening may be conducted at any time from the third trimester until 24 weeks postpartum. Final inclusion will only take place for women who have delivered a healthy term infant and have made a decision to breastfeed their infant despite ongoing ocrelizumab treatment. General health and medical history of the infant will also be reviewed for eligibility.

  Women resuming treatment with ocrelizumab postpartum will be included only if the last exposure to ocrelizumab occurred more than 3 months before the last menstrual period (LMP) (i.e., women without potential fetal exposure) to exclude any interference between fetal exposure and exposure via lactation.

- Treatment and sampling period: Women fulfilling the inclusion/exclusion criteria will receive the ocrelizumab dose regimen as per the locally approved label. The first dose of ocrelizumab may be administered at any point between Week 2 and Week 24 postpartum, as an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days or as a single 600 mg infusion (in 500 mL 0.9% sodium chloride) according to the local prescribing information. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. *Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (U.S. Prescribing Information [USPI]; Summary of Product Characteristics [SmPC]).* If women did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses (Summary of Product Characteristics [SmPC], United States Prescribing Information [USPI]). Women referred by healthcare professionals (HCPs) to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

  Maternal breastmilk samples will be collected over several time points up to 60 (± 2) days after the first postpartum ocrelizumab infusion at approximately the same time of day, although flexibility is allowed on collection timings to accommodate the mother and infant feeding schedule. The only exception is the first (Day 1) post-infusion breastmilk sample and, in women who received a 2×300 mg dose, the second (Day 15) post-infusion breastmilk sample, which should be collected 24 hours after the midpoint of the infusion. On days of collection, milk should be expressed from both breasts until completely emptied using an electric breast pump. The milk from each breast is then mixed and a sample (volume = 5 mL) is removed for analysis. The infant can be bottle-fed the remaining expressed milk. If the infant is not usually fed using a bottle, milk may be expressed from one breast only. If the mother presents with unilateral mastitis, milk should only be expressed from the unaffected breast, until the infection resolves. If mastitis presents bilaterally (rare), breastmilk collection should be stopped until the infection resolves.

  The infant blood sample will be collected at Day 30 (± 2 days) of lactation after the first ocrelizumab infusion administered postpartum, i.e., regardless of whether women receive a 600 mg or a 2×300 mg dose. Blood samples may be collected at home by a visiting nurse, or at the hospital as part of study visits. *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).

  A structured telephone interview will be conducted by site personnel every 2 weeks in the treatment and sampling period, for a general review, and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother and use of and 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.

- Vaccination period: After the 60-day (±2 days) treatment and sampling period, infants will continue to be followed-up for growth (age-adjusted length, weight, head circumference) and developmental milestones up to 12 months of age. Growth charts (following the World Health Organization 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 post-natal care, may also be used.

  Infant laboratory assessments will be performed 1 month (+30 days) after the first or second dose of measles, mumps, and rubella (MMR) vaccine, or at Month 13 of age (+30 days), in case MMR vaccine is not planned to be administered, to evaluate whether infants are able to mount humoral immune responses to clinically relevant vaccines, and for measurement of B-cell levels. In case the mother decides to switch to another DMT or to stop DMT after the 60-day treatment and sampling period, the infant blood sample will still be collected.

  A structured telephone interview will be conducted by site personnel postpartum every 3 months in the vaccination period (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother and use of and 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 visit.
- Discontinuation: Women who decide to discontinue the study (this includes discontinuation of either the mother or the infant; this does not apply to treatment discontinuation) will be invited to attend an early study discontinuation visit (which may be conducted remotely, i.e., virtually or by telephone) as soon as possible. Depending on the timing of discontinuation, the following is recommended:

  Discontinuation before the infant blood draw at 30 (±2) days post-infusion 1: Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures

  - If the mother remains on treatment with ocrelizumab and decides to stop participating at 30 (±2) days after the first postpartum ocrelizumab infusion, attempts to collect the infant sample at 30 (±2) days should be made before discontinuation.
  - If the mother switches to another DMT, the infant sample at 30 (±2) days should not be collected.

  Discontinuation after the infant blood draw at 30 (±2) days post-infusion 1: Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures.

NUMBER OF WOMEN

This study will enroll at least *10* women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

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. The primary analysis will be conducted at the end of the Treatment and Sampling Period (Day 60 [±2 days]).

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 *3* years. This includes an enrolment period of approximately *21* months and a woman's participation period of 16 months.

TARGET POPULATION

INCLUSION CRITERIA

The following criteria must be met for study entry:

- An Informed Consent Form (ICF) for participation of the maternal subject and her infant (for collection of blood, infant demographic 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
- Woman is able and willing to comply with the study protocol, according to the judgment of the investigator, in particular:
  - Woman is willing to breastfeed (either exclusively, or with formula supplementation) for at least 60 days after the first postpartum ocrelizumab infusion (this decision is to be taken prior to and independent from study participation)
  - Woman is willing to provide breastmilk samples before and after their first and, if applicable, second postpartum ocrelizumab infusion

    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.
- Woman is between 18 and 40 years of age at screening
- Woman has a diagnosis of MS or CIS (in line with the locally approved indications)
- Woman has delivered a healthy term singleton infant ($\geq$37 weeks gestation)
- Infant is between 2–24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- For women who received commercial ocrelizumab (OCREVUS) before enrolment: documentation that last exposure to ocrelizumab occurred more than 3 months before the LMP (i.e., excluded a potential fetal exposure) and was given at the approved dose of 2×300 mg or 1×600 mg
- Woman agrees to use acceptable contraceptive methods or alternative methods during the study as described below and, if applicable, upon study treatment discontinuation, as defined by the local prescribing information
  - The following contraceptive methods are considered acceptable (failure rate $>1\%$ [Clinical Trial Facilitation Group (CTFG)]): progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide; combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

  Birth control methods that are highly effective (i.e., failure rate $<1\%$ [CTFG]) may also be used but are not required, and include: oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation [unless not recommended or contraindicated during breastfeeding]; oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence.

  Note: lactational amenorrhea method can be used to ensure adequate protection from an unplanned pregnancy, and the following three criteria must be met: 1) amenorrhea; 2) fully or nearly fully breastfeeding (no interval of >4–6 hours between breastfeeds); and 3) <6 months postpartum. If any of the three listed criteria change at any stage during the study, an alternative or additional method of acceptable contraception is required.

EXCLUSION CRITERIA

Mothers/infants who meet any of the following criteria will be excluded from study entry:

Exclusions related to the mother

- Hypersensitivity to ocrelizumab or to any of its excipients
- Woman received last dose of ocrelizumab <3 months before the LMP or during pregnancy (i.e., there was a potential fetal exposure to ocrelizumab)
- Active infections (note: the woman may be included once the infection is treated and is resolved; women with bilateral mastitis infection should not have samples collected until the infection is completely resolved)
- Prior or current history of primary or secondary immunodeficiency, or woman in an otherwise severely immunocompromised state. Woman may be re-screened and included if condition resolves
- Woman 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 high risk of breast malignancies undergoing prophylactic treatment with drugs such as tamoxifen are excluded
- Woman has history of breast implants, breast augmentation, breast reduction surgery or mastectomy
- Woman has prior or current history of chronic alcohol abuse or drug abuse
- Woman has any medical, obstetrical or psychiatric condition that, in the opinion of the investigator, would compromise the woman's ability to participate in this study
- Treatment with a DMT for CIS or MS during pregnancy and/or first weeks postpartum, with the exception of formulations of interferon-beta, glatiramer acetate or pulsed corticosteroids
- Drugs known to transfer to the breastmilk and with established or potential deleterious effects for the infant, including but not limited to aspirin (risk of Reye's syndrome), tetracyclines or fluoroquinolones
- Treatment with any investigational agent within 6 months or five half-lives of the investigational drug (whichever is longer) prior to the LMP, unless the investigational agent is ocrelizumab administered >3 months prior to the LMP in the context of a study or registry sponsored by Roche

Exclusions related to the infant

- Infant is >24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- Infant has any abnormality that may interfere with breastfeeding or milk absorption, including but not limited to cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia
- Infant has an active infection. Infant may be included once the infection resolves
- Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's ability to participate in this study, including interference with the interpretation of study results
- Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's ability to participate in this study, including interference with the interpretation of study results
- Infant has at least one documented brief resolved unexplained event (BRUE), as defined by the 2016 Guidelines of the American Academy of Pediatrics

Exclusions related to laboratory findings

- Mother with any abnormal screening laboratory value that is clinically relevant should 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.

- Mother 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 (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.

STUDY TREATMENT

The study treatment is commercial ocrelizumab.

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 IRRs. Premedication with an antipyretic (e.g., paracetamol) may also be considered prior to each ocrelizumab infusion

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary analysis will be conducted on the full analysis set (all women who meet the eligibility criteria and received any postpartum dose of ocrelizumab) and infants of women in the full analysis set. The analysis will be performed after the last breastmilk sample collection at the end of the 60-day treatment and sampling period.

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 estimated average oral daily infant dosage will be analyzed using descriptive statistics. Mean, corresponding 95% CI, standard deviation, and other statistics will be presented.

More details about missing data handling, as well as sensitivity analyses based on alternative imputation approaches, will be specified in the statistical analysis plan.

DETERMINATION OF SAMPLE SIZE

The study will include at least 10 women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

With 10 infants, a precision (width of the two-sided 95% CI) of 0.443 is expected if one event is observed (defined as B-cells below the LLN) and a precision of 0.531 if two events are observed in the study. If no event is observed during the study, there is a 95% confidence that the event rate is below 0.31.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	definition
ADID	average (oral) daily infant dosage
AE	adverse event
AESI	adverse events of special interest
ASQ-3	Ages And Stages Questionnaire, version 3
AUC	area under the milk concentration-time curve
BRUE	brief resolved unexplained event
CIS	clinically isolated syndrome
CRO	contract research organization
CTFG	clinical trial facilitation group
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	Food and Drug Administration
FSS	functional systems score
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
HCV	hepatitis c virus infection
Hib	*Hemophilus influenzae* type b
HIPAA	health insurance portability and accountability act
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	investigational medicinal product

Abbreviation	definition
IND	investigational new drug
IRB	Institutional Review Board
IRR	infusion-related reaction
LLN	lower limit of normal
LMP	last menstrual period
mAb	monoclonal antibody
MAH	marketing authorization holder
MDID	maximum (oral) daily infant dosage
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-pneumococcal conjugate vaccine
PML	progressive multifocal leukoencephalopathy
PPMS	primary-progressive multiple sclerosis
QTL	quality tolerance limit
RID	relative infant dose
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
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). Multiple sclerosis 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 multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary-progressive multiple sclerosis (PPMS; Lublin et al. 2014). Relapsing-remitting multiple sclerosis 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, Zhao, and Devonshire 2008; Weinshenker et al. 1989). Primary-progressive multiple sclerosis 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 (for example, magnetic resonance imaging [MRI], lumbar puncture, evoked potentials) evidence (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 (mAb) 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-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). The appropriate treatment strategy during pregnancy and after birth remains uncertain, since none of the many DMTs available for MS are recommended during pregnancy or breastfeeding (LaHue et al. 2019). There is no consensus on how soon after birth may DMTs be safely resumed. Women often have to choose between breastfeeding and early resumption of a disease-modifying therapy (DMT) postpartum. This can have a significant impact on disease management since the risk of postpartum relapse is high. About 30% of women experience a relapse in the first 3 months postpartum (Vukusic et al. 2004). Such relapses may in turn worsen disability (Portaccio et al. 2014).

The general benefits of breastfeeding are well established, both for mothers as well as for infants. Infants who are exclusively breastfed have a lower risk of gastrointestinal as well as respiratory infections (Kramer and Kakuma 2012), and mothers who breastfeed have a reduced risk of breast, ovarian, and endometrial cancer (Ip et al. 2007; Kramer and Kakuma 2012; Jordan et al. 2017; Collaborative Group on Hormonal Factors in Breast Cancer, 2002). In addition, there is good evidence that exclusive breastfeeding may reduce the risk of postpartum relapses. A systematic literature review/meta-analysis of 24 studies exploring the association between breastfeeding and MS relapse reported a pooled adjusted hazard ratio (HR) for the association of breastfeeding and postpartum relapses of 0.57 (95% CI: 0.38 to 0.85; $p = 0.006$) vs. non-breastfeeding (Krysko et al. 2020); and a study of a cohort of 466 pregnancies in

375 women with MS (based on electronic health records) found that exclusive breastfeeding reduced the risk of early postpartum relapses (adjusted HR = 0.37, p = 0.009; Langer-Gould et al. 2020). Despite reduction in postpartum relapses with breastfeeding, annual relapse rates remain fairly high after birth, highlighting the need for additional strategies to prevent such relapses (Krysko et al. 2020). An efficacious mAb therapy that could safely be resumed soon after birth would significantly reduce the risk of postpartum relapses (LaHue et al. 2020).

Available Evidence

In a pre- and post-natal development study in cynomolgus monkeys, administration of ocrelizumab from gestation day 20 to approximately 5 weeks postpartum was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. There were two cases of moribundity, one attributed to weakness due to premature birth accompanied by opportunistic infection and the other to an infective meningoencephalitis involving the cerebellum of the neonate from a maternal dam with an active infection (mastitis). The course of both neonatal infections could have potentially been impacted by B-cell depletion. Newborn offspring of maternal animals exposed to ocrelizumab were noted to have depleted B-cell populations during the post-natal phase. Measurable levels of ocrelizumab were detected in milk (approximated 0.2% of steady state through serum levels) during the lactation period. Overall, it has to be taken into account that ocrelizumab was administered as 15/20 and 75/100 mg/kg loading/study doses, which correspond to human equivalent doses of approximately 3000 mg (approximately 5 × clinical dose) and 15,000 mg (approximately 25 × clinical dose), respectively. Maternal doses administered in this study resulted in mean maximum serum concentrations (C_{max}) that were 4.5- and 21-fold above those anticipated in the clinical setting. Moreover, preclinical studies studying ocrelizumab exposure through lactation only (i.e., administering ocrelizumab only postpartum) have not been conducted.

Clinical studies of the effects on infants associated with the use of ocrelizumab during lactation have not been performed. A few cases of exposure through breastmilk have been reported. Reduced B-cell levels at birth were reported in an infant born to a mother exposed to ocrelizumab during the second trimester of pregnancy (following relapse activity post-alemtuzumab), who also received a single 300-mg dose postpartum. Two months after this dose, the infant's B-cell levels were normal. The authors also reported an infant who was exposed through breastmilk to a single 600-mg dose postpartum, in whom B-cell levels were normal 39 days afterwards. Neither infant had hospitalizations or infections requiring antibiotic or hospitalization, during the period of exposure through breastfeeding (Ciplea et al. 2020).

As of 31 March *2022*, *40* cases of infant postpartum exposure to ocrelizumab via breastmilk have been reported in the Roche global safety database (*Oreja-Guevara et al. 2022). Thirty-three* infants were exposed to ocrelizumab postpartum via breast milk; *7* infants had in utero and postpartum ocrelizumab exposure. *Fifteen* infants

experienced no adverse events; *6* infants experienced adverse events (sleepiness potentially due to diphenhydramine hydrochloride exposure; excessive vomiting and swelling due to potential dairy allergies; conjunctivitis and otitis media, treated with unspecific antibiotics*; life-threatening breathing disorder and mild neurodermatitis; pelvic inflammation and nephritis; conjunctivitis*) and *19* infants had no reported adverse event information. B-cell levels available for 5 infants were in line within reported age-specific reference ranges.

Supporting Evidence from Other Anti-CD20 Therapies

In a study in 9 women with MS treated with rituximab (another anti-CD20 mAb), the median average rituximab concentration in mature breastmilk was low, at 0.063 µg/mL (range 0.046–0.097) in the 4 patients with serial breastmilk collection; with an estimated median absolute infant dose of 0.0094 mg/kg/d and a relative infant dose (RID) of 0.08% (range 0.06%–0.10%). Rituximab was virtually undetectable in milk by 90 days post-infusion (Krysko et al. 2019). In another study in 23 patients from the German Multiple Sclerosis and Pregnancy Registry who received the mAbs natalizumab (n = 17), rituximab (n = 3), ocrelizumab (n = 2) or rituximab + ocrelizumab (n = 1) during lactation, no negative impact on infant health and development attributable to drug exposure through breastmilk was seen after a median follow-up of 1 year. The concentration of natalizumab was low in breastmilk and in the serum of infants, and B-cell levels were normal in breastfed infants whose mothers received the anti-CD20 mAb rituximab; Ciplea et al. 2020).

Uncertainties and Need for Additional Evidence

Data on ocrelizumab kinetics in human milk and on the effects of ocrelizumab on breastfed infants are sparse and, as stated, no clinical studies have been performed evaluating the benefit-risk of ocrelizumab during breastfeeding. Given that IgG-based mAbs have large molecular sizes and limited transport mechanisms, the expected transfer into breastmilk is low (Hurley and Theil 2011). Additionally, most Igs have low oral bioavailability, which further reduces the likelihood of absorption by breastfeeding infants (Jasion et al. 2015). However, it has been shown that in women with MS minimal transfer of other anti-CD20 mAbs (rituximab) into breastmilk occurs, while the effects on the immune system and developmental milestones of potentially exposed infants remain unknown.

Given the unmet need for women with MS who may wish to breastfeed but are at high risk of postpartum relapses, and given the available evidence of minimal transfer of rituximab into breastmilk, a dedicated prospective interventional study to specifically evaluate the transfer of ocrelizumab into breastmilk and the corresponding pharmacodynamic effects in infants is therefore required, and justified. This study 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 pharmacokinetics of ocrelizumab in the breastmilk of lactating women with CIS or MS (in line with the locally approved indications) treated with ocrelizumab, by assessing the concentration of ocrelizumab in mature breastmilk, as well as the corresponding exposure and pharmacodynamic effects (blood 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
Co-Primary Outcome Measure	
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum present with B-cell depletion	• Proportion of infants with B-cell levels (CD19+cells, absolute counts in blood) below the LLN, measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate the exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated ADID, calculated as the ocrelizumab average milk concentration over 60 days post-ocrelizumab infusion 1 multiplied by an estimated infant milk intake of 150 mL/kg/day
Secondary Outcome Measures	
• To evaluate B-cell levels in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• B-cell levels (CD19+ cells, absolute counts and percentage of lymphocytes) measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate transfer of ocrelizumab into breastmilk of lactating women with CIS or MS receiving ocrelizumab postpartum	• AUC of ocrelizumab in mature breastmilk (i.e., milk produced after Day 14 postpartum) over 60 days after the first postpartum ocrelizumab infusion using the following time points: – If receiving 1×600 mg: before infusion and at 24 hours (Day 1), Day 7, Day 30 and Day 60 post-infusion – If receiving 2×300 mg: before infusion 1 and at 24 hours (Day 1), Day 7, Day 14, Day 15 (24 hours after infusion 2), Day 21, Day 30, and Day 60 post-infusion 1 • Average and peak ocrelizumab milk concentration as well as time to reach peak milk concentration, measured over 60 days after the mother's first postpartum ocrelizumab infusion

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire, version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; RID = relative infant dose; WHO = World Health Organization.

Table 1 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Secondary Outcome Measures (cont.)	
• To evaluate the *relative and* maximum exposure to ocrelizumab in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Estimated MDID calculated as the peak ocrelizumab milk concentration multiplied by an estimated infant milk intake of 150 mL/kg/day measured over 60 days after the mother's first postpartum ocrelizumab infusion • *Average RID over 60 days, calculated as the ADID (mg/kg/day) divided by the maternal dosage (mg/kg/day) multiplied by 100* *Note:* Other pharmacokinetic and exposure parameters may be calculated as appropriate, based on the data obtained.
• To evaluate whether there is transfer of ocrelizumab from the mother to the infant via breastmilk	• Serum concentration of ocrelizumab in the infant measured at Day 30 after the mother's first ocrelizumab postpartum infusion
• To evaluate whether infants of lactating women with CIS or MS receiving ocrelizumab postpartum 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 MMR, *diphtheria, tetanus, pertussis*, Hib, HBV, and PCV-13 • Proportion of infants with positive humoral response (seroprotective titers; as defined for the individual vaccine) to vaccines
Safety Objectives	
• To evaluate the safety of ocrelizumab in lactating women with CIS or MS receiving ocrelizumab postpartum and in their respective infants	• Rate and nature of adverse events in the mother throughout the study, including changes in clinical and laboratory results • Rate and nature of adverse events in the infant throughout the study, including infections and hospitalizations

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire, version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; RID = relative infant dose; WHO = World Health Organization.

Table 1 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Exploratory Objectives	
• To evaluate infant's growth velocity and developmental milestones in the first year of life	• Assessment of growth velocity based on age-adjusted length, weight, head circumference, using monthly growth charts according to the WHO Child Growth Standards, as well as absolute values at Months 2, 4, 6, 9, and 12 • 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 measure disease activity in lactating women with CIS or MS receiving ocrelizumab postpartum	• Number of MS relapses during the postpartum period (clinical relapses) • Mean change in the EDSS score from last pre-baseline measurement (up to 1 year before LMP) to baseline
• To evaluate the evolution of B-cell levels over the first year of life in infants of lactating women with CIS or MS receiving ocrelizumab postpartum	• Trajectory (absolute and percentage changes) of B-cells (CD19+ cells) *in the infant from* Day 30 after the mother's first ocrelizumab postpartum infusion *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

ADID = average oral daily infant dosage; ASQ-3 = Ages and Stages Questionnaire, version 3; AUC = area under the milk concentration-time curve; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Hib = Hemophilus influenzae type b; LLN = lower limit of normal; LMP = last menstrual period; MDID = maximum oral daily infant dosage; MMR = measles, mumps, and rubella MS = multiple sclerosis; PCV-13 = 13-pneumococcal conjugate vaccine; *RID = relative infant dose;* WHO = World Health Organization.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a prospective, multicenter, open-label study in lactating women with CIS or MS (in line with the locally approved indications) who decided together with their treating physician to continue on, or start treatment with, OCREVUS™ (ocrelizumab) postpartum despite ocrelizumab currently not being recommended during lactation.

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 at least 10 women with CIS or MS who are breastfeeding or planning to breastfeed. Laboratory and clinical assessments will be performed as described in the Schedule of Assessments presented in Appendix 1.

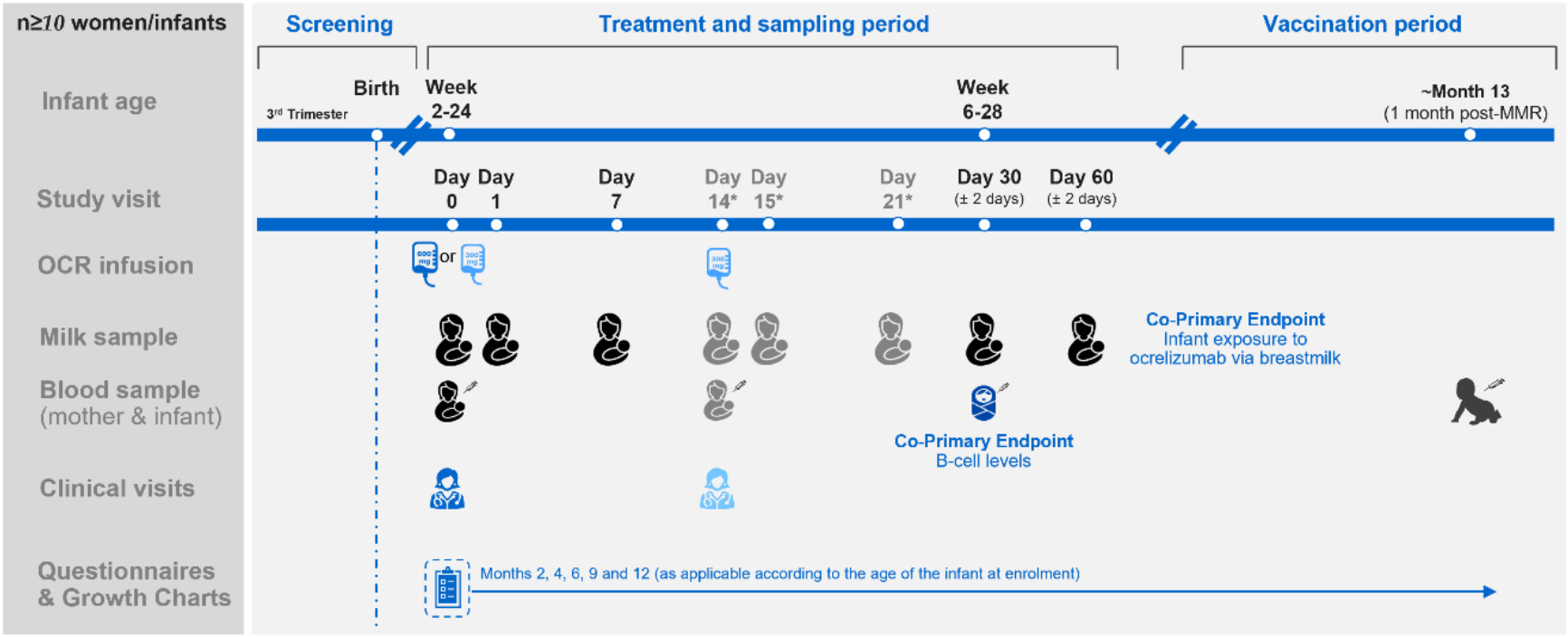
The study will consist of the following periods:

- Screening period
- Treatment and sampling period
- Vaccination period

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



* Samples and visits at Day 14, 15 and 21 apply only to patients initiating treatment with ocrelizumab as 2x300mg separated by a 14-day interval.

ASQ-3 = Ages and Stages Questionnaire, version 3; LMP = last menstrual period; MMR = measles, mumps, and rubella; OCR = ocrelizumab.

Study description: In this prospective, multicenter, open-label study, lactating women with CIS or MS (in line with the locally approved indications) who decided together with their treating physician to continue on, or start treatment with, commercial ocrelizumab postpartum will enter a **screening period**, which may be started during the third trimester of pregnancy and continue until 24 weeks postpartum. Women who have delivered a healthy term infant and made a decision to breastfeed their infant will be enrolled if they and their infants fulfil the respective eligibility criteria. Women resuming treatment with ocrelizumab postpartum will be included only if the last exposure to ocrelizumab occurred more than 3 months before the LMP (i.e., women without potential fetal exposure). In the **60-day (±2 days) treatment and sampling period**, women will receive the ocrelizumab dose regimen as per the locally-approved label, at any point between Week 2 and Week 24 postpartum. The first dose of ocrelizumab may be administered as two 300 mg infusions separated by 14 days (for those initiating ocrelizumab) or as a single 600 mg infusion (for those resuming ocrelizumab). For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. Women referred by healthcare professionals to participate in the trial may receive ocrelizumab treatment

at their neurologist's site as part of their standard of care treatment. Laboratory and clinical assessments will be performed at the designated visits.

Women will collect their breastmilk samples over several time points up to 60 (±2) days after the first postpartum ocrelizumab infusion, reserving 5 mL at each sampling point for analysis of ocrelizumab concentrations. Infant blood samples will be collected at Day 30 (±2 days) after the first postpartum ocrelizumab infusion (regardless of whether women receive a 600 mg or a 2×300 mg dose). Infant blood samples may be collected at home by a visiting nurse, if not collected at the clinical site during a study visit. In **the vaccination period,** infants will continue to 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 for example, the pediatrician as part of routine postnatal care, may also be used). 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, to evaluate whether infants are able to mount humoral immune responses to clinically relevant vaccines, and for measurement of B-cell levels. 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 mother 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. Women who decide to discontinue the study (this includes discontinuation of either the mother or the infant) 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 Period

After providing written informed consent, women will enter a screening period for eligibility assessments. Considering that decisions on initiating or resuming treatment with a DMT in the postpartum period are usually taken before or during pregnancy, screening may be conducted at any time from the third trimester until 24 weeks postpartum. Final inclusion will only take place for women who have delivered a healthy term infant and have made a decision to breastfeed their infant despite ongoing ocrelizumab. General health and medical history of the infant will be reviewed for eligibility.

Women resuming treatment with ocrelizumab postpartum will be included only if the last exposure to ocrelizumab occurred more than 3 months before the last menstrual period (LMP), i.e., if they have no potential fetal exposure; to exclude any interference between fetal exposure and exposure via lactation.

3.1.3 Treatment and Sampling Period

Women fulfilling the inclusion/exclusion criteria will receive the ocrelizumab dose regimen as per the locally approved label. The first dose of ocrelizumab may be administered at any point between Week 2 and Week 24 postpartum, as an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days or as a single 600 mg infusion (in 500 mL 0.9% sodium chloride), according to the local prescribing information. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. *Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (U.S. Prescribing Information [USPI]; Summary of Product Characteristics [SmPC]).* If women did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses (SmPC, USP). Women referred by healthcare professionals (HCPs) to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

Maternal breastmilk samples will be collected over several time points up to 60 (± 2) days after the first postpartum ocrelizumab infusion at approximately the same time of day, although flexibility is allowed on collection timings to accommodate the mother and infant feeding schedule. The only exception is the first (Day 1) post-infusion breastmilk sample, and in women who received a 2×300 mg dose, the second (Day 15) post-infusion breastmilk sample, which should be collected 24 hours after the midpoint of the infusion. On days of collection, milk should be expressed from both breasts until completely emptied using an electric breast pump. The milk from each breast is then mixed and a sample (volume $= 5$ mL) is removed for analysis. The infant can be bottle-fed the remaining expressed milk. If the infant is not usually fed using a bottle, milk may be expressed from one breast only. If the mother presents with unilateral

mastitis, milk should only be expressed from the unaffected breast, until the infection resolves. If mastitis presents bilaterally (rare), breastmilk collection should be stopped until the infection resolves.

The infant blood sample will be collected at Day 30 (±2 days) of lactation after the first ocrelizumab infusion administered postpartum, i.e., regardless of whether women receive a 600 mg or a 2×300 mg dose. The corresponding breastmilk sample should be collected on the same day as the infant blood sample. Blood samples may be collected at home by a visiting nurse, or at the hospital as part of study visits (see Appendix 1, Schedule of Assessments).

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).

A structured telephone interview will be conducted by site personnel every 2 weeks in the treatment and sampling period, for a general review and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother 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.

3.1.4 Vaccination Period

After the 60-day (±2 days) treatment and sampling period, infants will continue to be followed-up for growth (age-adjusted length, weight, 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) questionnaires 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.

Infant laboratory assessments will be performed 1 month (+30 days) after the first or second dose of measles, mumps, and rubella (MMR) vaccine, or at Month 13 of age (+30 days), if MMR vaccine is not planned to be administered, to evaluate whether infants are able to mount humoral immune responses to clinically relevant vaccines, as well as to measure their B-cell levels. In case the mother decides to switch to another DMT or to stop DMT after the 60-day treatment and sampling period, the infant blood sample will still be collected.

A structured telephone interview will be conducted by site personnel postpartum every 3 months in the vaccination period (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's and

infant's health status (including the occurrence of MS relapses in the mother 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 Discontinuation

Women who decide to discontinue the study (this includes discontinuation of either the mother or the infant; this does not apply to treatment discontinuation as described in Section 3.1.4) will be invited to attend an early study discontinuation visit (which may be conducted remotely, i.e., virtually or by telephone) as soon as possible. Depending on the timing of discontinuation, the following is recommended:

- **Discontinuation before the infant blood draw at 30 (±2) days post-infusion 1:**
  - Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures
  - If the mother remains on treatment with ocrelizumab and decides to stop participating at 30 (±2) days after the first postpartum ocrelizumab infusion, attempts to collect the infant sample at 30 (±2) days should be made before discontinuation
  - If the mother switches to another DMT, the infant sample at 30 (±2) days should not be collected.
- **Discontinuation after the infant blood draw at 30 (±2) days post-infusion 1:** Collection of infant outcomes in the first year of life as per standard pharmacovigilance procedures.

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 vaccine is not planned to be administered) for the last infant. The primary analysis will be conducted at the end of the Treatment and Sampling Period (Day 60 [+2 days]).

The total length of the study, from screening of the first woman to the end of the study, is expected to be approximately 3 years. This includes an enrolment period of approximately 21 months and a woman's participation period of 16 months.

3.3 RATIONALE FOR STUDY DESIGN

This is a prospective, multicenter, open-label study evaluating the transfer of ocrelizumab into breastmilk of lactating women with CIS or MS treated with ocrelizumab postpartum. Ocrelizumab targets B-cells, and a rapid depletion of CD19+ B-cells in blood is the expected pharmacologic effect of ocrelizumab treatment (and hence, is a biomarker for pharmacodynamic effect). This depletion occurs briefly even at low doses

such as 2 × 10 mg (FDA 2017). Therefore, CD19+ B-cell levels will be measured as a co-primary endpoint (specifically, the proportion of infants with B-cells below the LLN at Day 30 [±2 days] post-infusion).

To evaluate the amount of drug that may be transferred from mother to infant through breastmilk, the co-primary endpoint is the average (oral) daily infant dosage (ADID), which expresses the average amount of ocrelizumab in breastmilk (and available to the infant) as an infant dose, over the observed period of 60 days (±2 days) post-infusion. The excretion in breastmilk is expected to be highest during the first 60 days after the ocrelizumab infusion, declining thereafter over the 6-monthly dosing interval. Breastmilk samples will be collected before the infusion, and at days 1, 7, 30 (±2) and 60 (±2) (with additional timepoints for mothers who are receiving a split dose, i.e., 2 × 300 mg), to cover two average half-lives of ocrelizumab in serum (26 days [USPI]) and the expected time window of greatest breastmilk transfer for anti-CD20 monoclonal antibodies (Krysko et al. 2019). Samples will be taken only after the development of mature milk (i.e., milk produced after Day 14 postpartum) to avoid the collection of colostrum, which may contain a high concentration of antibody because of a more porous mammary epithelium (FDA 2019). In addition, mothers will be instructed to completely empty both breasts with an electric pump, and mix milk from both breasts before removing the amount required for the sample. If the infant is not usually fed using a bottle, milk may be expressed from one breast only. This will reduce variability across the study, as for example foremilk and hindmilk (milk expressed at the start and end of feeding, respectively) have different compositions, which can influence the amount of drug available in the sample (Hebert 2016). To account for differences in exclusive breastfeeding versus supplementation with formula, a feeding schedule diary completed by the women will record the number of breastmilk feeds and/or feed with formula milk (supplementation) on the day of the sample collection and the previous and following day, as recommended by the FDA (Food and Drug Administration; FDA 2019). For mothers presenting with mastitis during the sampling period, sample collections from the infected breast(s) will be interrupted, given that clinical and subclinical mastitis are associated with increased milk concentrations of serum-derived immune factors such as IgG (Filteau 2003).

To further understand the extent of ocrelizumab transfer through breastmilk and the exposure in infants, secondary endpoints will include the area under the milk concentration-time curve (AUC) of ocrelizumab in breastmilk over 60 days post-ocrelizumab infusion, average concentration, peak concentration, time to peak concentration and the maximum (oral) daily infant dosage (MDID), as recommended by the FDA (FDA 2019). To evaluate potential adverse impact on the infants, infant health and development outcomes will be assessed using growth charts according to the WHO Child Growth Standards (WHO 2022) 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).

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 of lactating women with CIS or MS receiving ocrelizumab postpartum can mount a protective immune response to clinically relevant vaccines.

As exploratory endpoints, disease activity will be measured in the mothers using standard assessments such as Expanded Disability Status Scale (EDSS) and number of MS relapses. These endpoints are commonly used in MS clinical trials to assess treatment efficacy and disease progression.

As recommended (FDA 2019), this study is designed to minimize burden on the mother and disruption to the infant's feeding schedule. For example, at sample collection time (when the infant would be fed the remainder of the collected milk through a bottle), mothers may instead collect the sample from only one breast if the infant is not normally fed using a bottle. Further, the infant blood sample on Day 30 ($\pm$2 days) post-infusion and at 1 month ($+$30 days) after the first or second dose of MMR vaccine/Month 13 of age ($+$30 days) may be collected at home by a visiting nurse, or at the hospital as part of study visits.

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 labeling *(USPI; SmPC)*. As per the dosing regimen approved in the labeling, 600 mg ocrelizumab is to be given as IV infusion every 6 months. The first dose is given as two 300 mg IV infusions two weeks apart; and subsequent doses are given as single 600 mg IV infusions. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. If women did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses (Ocrelizumab SmPC, Ocrelizumab USPI).

3.3.2 Rationale for Subject Population

As the aim of this study is to evaluate breastmilk transfer of ocrelizumab and the corresponding pharmacodynamic effects in the infant, it will be conducted in women with CIS or MS (in line with the locally approved indications) aged 18–40 years who have planned to start or resume ocrelizumab after delivery, while breastfeeding for a minimum of 60 days.

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 1 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 (Simister 2003; Palmeira et al. 2012), it is assumed that a potential fetal exposure is unlikely in women whose last ocrelizumab infusion was earlier than 3 months before LMP. Women who were exposed to ocrelizumab within 3 months of their LMP, or during pregnancy, will *therefore* be excluded to eliminate cases of potential fetal exposure to ocrelizumab that could confound the results of B-cell levels in the infant or the presence of ocrelizumab in breastmilk.

Women who have given birth to more than one baby (i.e., have had non-singleton births) are excluded, because such mothers might find it difficult to comply with study requirements, and might find it more difficult to reserve the amount of breastmilk needed for the sample. Therefore, their infants might receive a different amount of breastmilk, potentially confounding the B-cell level results.

Infants who are $>$24 weeks of age at the mother's first postpartum dose of ocrelizumab will be excluded. Although the WHO recommends exclusive breastfeeding up to 6 months with continued breastfeeding along with appropriate complementary foods up to 2 years of age or older (WHO 2020a), these recommendations are not followed in most countries. Recent findings from the National Immunization Survey 2018–2019 in the United States show that the percentage of infants who are breastfed decreases from 58.3% at 6 months to 35.3% at 1 year (Centers for Disease Control and Prevention 2020a). The maximum maternal age is set at 40 years, as mothers in late childbearing age of $\geq$35 years (in particular primiparous mothers) have been shown to have the greatest risk of non-initiation of exclusive breastfeeding both at discharge and at 1 month postpartum, even though they had the antenatal intention to exclusively breastfeed (Kitano et al. 2016).

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. 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), and all antiviral drug labels do not recommend breastfeeding when taking the drugs.

In addition, infants with any abnormality that may interfere with breastfeeding or milk absorption, such as cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia are excluded, given that the co-primary aim of this study is to evaluate the corresponding pharmacodynamic effects of potential ocrelizumab exposure through breastmilk. Infants who have had at least one documented brief resolved unexplained event (BRUE), are also excluded, because these potentially life-threatening events have an unknown impact on infant physiology and development, and may confound the interpretation of infant's growth velocity and development milestones in the

first year. The term BRUE is defined by the American Academy of Pediatrics as an event occurring in an infant younger than 1 year when the observer reports a sudden, brief, and now resolved episode of ≥ 1 of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hyper- or hypotonia); and (4) altered level of responsiveness (Tieder et al. 2016).

4. MATERIALS AND METHODS

4.1 STUDY PARTICIPANTS

This study will enroll at least 10 women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

4.1.1 Inclusion Criteria

The following criteria must be met for study entry:

- An Informed Consent Form (ICF) for participation of the maternal subject and her infant (for collection of blood, infant demographic 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
- Woman is able and willing to comply with the study protocol, according to the judgment of the investigator, in particular:
  - Woman is willing to breastfeed (either exclusively, or with formula supplementation) for at least 60 days after the first postpartum ocrelizumab infusion (this decision is to be taken prior to and independent from study participation)
  - Woman is willing to provide breastmilk samples before and after their first and, if applicable, second postpartum ocrelizumab infusion

    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.
- Woman is between 18 and 40 years of age at screening
- Woman has a diagnosis of MS or CIS (in line with the locally approved indications)
- Woman has delivered a healthy term singleton infant (≥ 37 weeks gestation)
- Infant is between 2–24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- For women who received commercial ocrelizumab (OCREVUS) before enrolment: documentation that last exposure ocrelizumab occurred more than 3 months before the LMP (i.e., excluded a potential fetal exposure) and was given at the approved dose of 2×300 mg or 1×600 mg

- Woman agrees to use acceptable contraceptive methods or alternative methods during the study as described below and, if applicable, upon study treatment discontinuation, as defined by the local prescribing information (see Section 4.6.1).
  - The following contraceptive methods are considered acceptable (failure rate >1% [Clinical Trial Facilitation Group (CTFG)]): progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide; combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

  Birth control methods that are highly effective (i.e., failure rate <1% [CTFG]) may also be used but are not required, and include: oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation [unless not recommended or contraindicated during breastfeeding, see Table A2-1]; oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence.

  Note: lactational amenorrhea method can be used to ensure adequate protection from an unplanned pregnancy, and the following three criteria must be met: 1) amenorrhea; 2) fully or nearly fully breastfeeding (no interval of >4–6 hours between breastfeeds); and 3) <6 months postpartum. If any of the three listed criteria change at any stage during the study, an alternative or additional method of acceptable contraception is required.

4.1.2 Exclusion Criteria

Mothers or infants who meet any of the following criteria will be excluded from study entry:

Exclusions related to the mother

- Hypersensitivity to ocrelizumab or to any of its excipients
- Woman received last dose of ocrelizumab <3 months before the LMP or during pregnancy (i.e., there was a potential fetal exposure to ocrelizumab)
- Active infections (note: the woman may be included once the infection is treated and is resolved; women with bilateral mastitis infection should not have samples collected until the infection is completely resolved)
- Prior or current history of primary or secondary immunodeficiency, or woman in an otherwise severely immunocompromised state. Woman may be re-screened and included if condition resolves
- Woman 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 high risk of breast malignancies undergoing prophylactic treatment with drugs such as tamoxifen are excluded

- Woman has history of breast implants, breast augmentation, breast reduction surgery or mastectomy
- Woman has prior or current history of chronic alcohol abuse or drug abuse
- Woman has any medical, obstetrical or psychiatric condition that, in the opinion of the investigator, would compromise the woman's ability to participate in this study
- Treatment with a DMT for CIS or MS during pregnancy and/or first weeks postpartum, with the exception of formulations of interferon-beta, glatiramer acetate or pulsed corticosteroids
- Drugs known to transfer to the breastmilk and with established or potential deleterious effects for the infant, including but not limited to aspirin (risk of Reye's syndrome), tetracyclines or fluoroquinolones. A more detailed, though not comprehensive, list can be found in Appendix 2
- Treatment with any investigational agent within 6 months or five half-lives of the investigational drug (whichever is longer) prior to the LMP, unless the investigational agent is ocrelizumab administered >3 months prior to the LMP in the context of a study or registry sponsored by Roche

Exclusions related to the infant

- Infant is >24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab
- Infant has any abnormality that may interfere with breastfeeding or milk absorption, including but not limited to cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia
- Infant has an active infection. Infant may be included once the infection resolves
- Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's ability to participate in this study, including interference with the interpretation of study results
- Infant has at least one documented BRUE, as defined by the 2016 Guidelines of the American Academy of Pediatrics

Exclusions Related to Laboratory Findings

- Mother with any abnormal screening laboratory value that is clinically relevant should 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.
- Mother 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 hepatitis B virus (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.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. No randomization, treatment assignment or blinding is planned.

4.3 STUDY TREATMENT AND OTHER TREATMENTS 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 the United States] and SmPC [for the 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 labeling (USPI; SmPC). No measures of treatment compliance are planned.

4.3.2.1 Study Treatment

As per the labeling, 600 mg ocrelizumab is to be given as IV infusion every 6 months. The first dose of ocrelizumab may be administered at any point between Week 2 and Week 24 postpartum as two 300-mg IV infusions two weeks apart (in 250 mL 0.9% sodium chloride) or as a single 600-mg IV infusion (in 500 mL 0.9% sodium chloride); and subsequent doses given according to the local prescribing information. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. If women did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses (SmPC, USPI). Women referred by HCPs to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

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 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 woman participating in the study, in addition to the study treatment. All such medications taken within 6 weeks prior to the baseline visit and throughout the study should be reported to the investigator and recorded on the Concomitant Medications electronic case report form (eCRF).

4.4.1 Prohibited Therapy

Drugs known to transfer to the breastmilk and with established or potential deleterious effects for the infant, including but not limited to aspirin (risk of Reye's syndrome), tetracyclines or fluoroquinolones are not permitted. A more detailed, though not comprehensive, list can be found in Appendix 2.

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.

Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers should NOT be administered while the woman is B-cell depleted.

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

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 or 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 their infants 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 enrolment. 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, and Disease Characteristics

Women's demographics (age, self-reported ethnicity, and level of education) and relevant medical history, including clinically significant diseases, surgeries/procedures, vaccination history, 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 the baseline visit will be recorded. Clinically significant diseases and/or surgeries and concomitant medication should also be recorded throughout the study if available.

Obstetric history:

- History of previous pregnancies

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 the LMP
- History of previous DMTs (prior to and during pregnancy): number of DMTs ever used, last DMT before ocrelizumab
- Treatment history with ocrelizumab (to be collected only in women who received commercial ocrelizumab prior to enrolment): Documentation of start of ocrelizumab therapy and date and dose of last ocrelizumab infusion prior to enrolment.

4.5.2.2 Physical Examinations and Related Assessments

A complete physical examination in participating women should include 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 at the woman's HCP (obstetrician/gynecologist, pediatrician and/or neurologist of referred woman) 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. Height will be recorded at screening only.

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).

See Appendix 1 (Schedule of Assessments) for the timing of 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 these measurements are performed as per clinical practice and are available, any abnormalities should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded on the Adverse Event section of the eCRF (as presented in Section 5.1.2).

4.5.2.4 Neurological Examinations

A neurological examination will be performed at baseline, early study discontinuation as well as at unscheduled visits if applicable, to distinguish relapse in MS from another neurological (non-MS) disorder. *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 (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 treatment period. 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 hours, with or without recovery, and in the absence of fever or infection (Thompson et al. 2018).
MS relapses should not be reported as an adverse event, unless they are serious.

It is recommended that women with new neurological symptoms suggestive of a relapse have an EDSS/Functional Systems Score (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 paragraphs. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. For more details, refer to Schedule of Assessments (see Appendix 1).

- **Hematology** (hemoglobin, hematocrit, quantitative platelet count, red blood cell [RBC] count, white blood cell [WBC] absolute or/and differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).
- **Serum chemistry** (potassium, sodium, chloride, random glucose, AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin and creatinine).
- **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.
- **Serum Ig concentration:** Quantitative measurement for IgG, IgM and IgA levels.
- **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+).*
- **Ocrelizumab concentration in breastmilk:** Breastmilk samples throughout the study will be collected for determination of ocrelizumab concentration. Women

should record the volume of pumped breastmilk and indicate date and time for collection as well as whether breastmilk was pumped from one or both breasts. At each sampling point, 5 mL of breastmilk should be saved (as directed by the site staff) to send to the central laboratory. The 24-hour (Day 1, as well as Day 15 for women who received the 2×300 mg regimen) post-infusion samples are collected based on the midpoint of infusion. For example, if the infusion began at 8 a.m. and ended at 10 a.m., the 24-hour sample collection would occur at 9 a.m. on the day before and after the infusion. For details, refer to Schedule of Assessments (see Appendix 1).

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 Medical History, Biometrics and Concomitant Medications

- General health and medical history
- Gestational age at birth
- Congenital malformations
- Mode of delivery (vaginal delivery, instrumental delivery, scheduled or urgent cesarean section)
- Appearance, Pulse, Grimace, Activity, and Respiration score (1 min, 5 min, 10 min)
- Infant vital biometrics (head circumference, weight, length) at birth
- Previous and concomitant medication given to the infant should be recorded at screening and throughout the study. For administered vaccinations, refer to Section 4.5.3.2.

4.5.3.2 Physical Examinations and Related Assessments

- Body weight (measured at every visit where a blood sample will be taken, i.e., at Day 30 [±2 days] post-infusion 1, and 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).
- Feeding schedule diary (during the treatment and sampling period): Women should record the number of breastmilk feeds and/or feed with formula milk (supplementation) on the day of the sample collection and the previous and following day, i.e., day of collection ±1 day.

- Feeding status (during the vaccination period): Women 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, at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment.
- ASQ-3 at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment.
- 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) at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment.
- Documentation of vaccinations: 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 30 days after the first postpartum ocrelizumab infusion 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 Month 13/1 month after first or second MMR dose, and may include diphtheria, tetanus, and pertussis, Hemophilus influenzae type b (Hib), 13-pneumococcal conjugate vaccine (PCV-13), HBV and MMR.

See Appendix 1 (Schedule of Assessments) for the timing of assessments and Appendix 6 for the time windows for infant growth velocity and child developmental milestone assessments.

4.5.3.3 Laboratory, Biomarker, and Other Biological Samples

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

Day 30 (±2 days) post-infusion 1

- **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** in serum

Note: If the infant's B-cell levels are found to be below LLN at any visit, 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 recommendations 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 Day 30 (±2 days) Post-Infusion 1

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] The same sample will be used to measure B-cell counts (CD19+), T-cell counts (CD3+, CD4+, 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 is not planned to be administered

- **Mean titers (IgG) of antibody immune response(s) to common childhood vaccinations** with full or partial doses given prior to 1 year will be measured (which include responses to MMR, *diphtheria, tetanus, pertussis*, Hib, HBV, and PCV-13). Titers will be measured at 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.

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.

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

Note: If the infant's B-cell levels are found to be below LLN at any visit, 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 recommendations 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 the First/Second Dose of MMR Vaccine or at Month 13 of Age (+30 Days) if MMR Vaccine Is Not Planned to Be Administered

Order of Priority	Assessment
1	Any safety laboratory samples (scheduled or unscheduled and performed at the discretion of the investigator)
2	Mean titers (IgG) of antibody immune response(s) to vaccinations [a]
3	Lymphocyte subtypes blood sample [b]

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

[a] *The following antibody titers will be measured: 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] *The* same sample will be used to measure B-cell counts (CD19+), T-cell counts (CD3+, CD4+, CD8+), *and NK cell counts (CD16+CD56+).*

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 (with the exception of an accidental pregnancy, as described below). 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.

In case a woman enrolled in the study becomes accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until the pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection). The investigator should complete the Global Clinical Trial Pregnancy Form and submit to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the 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.

4.6.2 Discontinuation from the Study

Women and their 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; this does not apply to treatment discontinuation as described in Section 3.1.4) will be invited to attend an early study discontinuation visit as soon as possible (further details in Section 3.1.5).

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

- Woman's withdrawal of consent
- Study termination or site closure
- AE
- Loss to follow-up
- Any medical condition that the investigator or Sponsor determines may jeopardize the woman's or infant's safety 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 the woman's 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.
- Enrolment 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 subject 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

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 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.

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.

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 and Assessing Safety Parameters

The investigator is accountable for ensuring that all adverse events collected as per protocol (see Section 5.1.1.1 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

The 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 occurring in a pregnant woman pre- and post- study period should be reported to the marketing authorization holder (MAH), as a follow-up spontaneous pregnancy report to 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 instruction regarding:

- IRRs
- Diagnosis versus signs and symptoms
- Adverse events occurring secondary to other adverse events
- Persistent or recurrent AEs
- 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 Investigator to Sponsor

5.1.3.1 Immediate Reporting Requirements from Investigator 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:

- SAEs
- Non-serious adverse events of special interest
- Pregnancy occurred during breastfeeding (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 Institutional Review Board (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, 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 Electronic Data Capture 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 woman enrolled in the study becomes accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection). 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 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 breastfeeding (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

The study enrolls postpartum women breastfeeding their infants following the first postpartum ocrelizumab dose. In case a woman enrolled in the study becomes

accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection).

In case of a spontaneous abortion in an accidental pregnancy during breastfeeding, the spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), 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).

If a therapeutic or elective abortion was performed in an accidental pregnancy during breastfeeding because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as an serious adverse event, 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.

All abortions that occur in an accidental pregnancy during breastfeeding should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

Congenital Anomalies/Birth Defects

The study enrolls women postpartum who delivered a healthy term infant and who plan to breastfeed their infants following the first postpartum ocrelizumab dose. In case a woman enrolled in the study becomes accidentally pregnant again during breastfeeding, she will remain on study and discontinue treatment with commercial ocrelizumab until pregnancy completion. She and her infant should continue with all study assessments (including breastmilk sample collection).

Any congenital anomaly/birth defect in a child born to a woman who became accidentally pregnant during breastfeeding and was exposed to the medicinal product should be classified as an 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 (see also Section 5.1.3.5)
- 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 (e.g., SmPC for the EU).

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 conducted after the last breastmilk sample collection at the end of the 60-day treatment and sampling period. Full analysis, including analysis of the vaccination response in infants, 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.

6.1 ANALYSIS POPULATIONS

Full Analysis Set

The full analysis set (FAS) population of women will include all women who meet the eligibility criteria and receive any postpartum dose of ocrelizumab.

The FAS population of infants will include all the infants of the FAS population of women.

Safety Population

The safety population will be the same as the FAS. The safety population of infants will include all infants of women in the FAS population.

6.2 DETERMINATION OF SAMPLE SIZE

There is no formal sample size calculation, as no confirmatory hypothesis testing is planned. The primary analysis will be descriptive. The study will include at least 10 women with CIS or MS (in line with the locally approved indications) who are breastfeeding or planning to breastfeed.

With 10 infants, a precision (width of the two-sided 95% CI) of 0.443 is expected if one event is observed (defined as B-cells below the LLN) and a precision of 0.531 if two events are observed in the study. If no event is observed during the study, there is a 95% confidence that the event rate is below 0.31.

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrolment, 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 will be tabulated, with treatment discontinuations summarized by reason for discontinuation. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized. Women and infants enrolled but excluded from the FAS will be listed.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

For women, demographics (age and self-reported race), 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), and other important variables.

Characteristics of infants at birth will also be summarized (gender, weight, gestational age at birth and other endpoints collected). Values at the mother's first ocrelizumab infusion visit (which may take place any time between Week 2 and Week 24 postpartum) will be considered as baseline.

6.5 PRIMARY ANALYSES

6.5.1 Primary Endpoint

The primary analysis will be conducted on the FAS (defined earlier). The analysis will be performed after the last breastmilk sample collection at the end of the 60-day treatment and sampling period.

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 estimated ADID will be analyzed using descriptive statistics. Mean, corresponding 95% CI, SD, and other statistics will be presented.

The estimand of the proportion of infants with B-cell levels below the LLN is defined as below:

- Population: all infants of women in the FAS population who have B-cell levels measured at Day 30 after the mother's first ocrelizumab postpartum infusion.
- 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 will be handled as follows:
  - Incomplete dosing, including delayed second (300 mg) ocrelizumab infusion: all the B-cell data will be included in the analysis.
  - Infant did not receive any breastmilk *before B-cell measurement during the entire 30-day period* after the mother's first ocrelizumab postpartum infusion: B-cell data will be excluded from the analysis.
  - Mother used other DMT during breastfeeding before B-cell measurement on Day 30 post-ocrelizumab infusion 1: B-cell data will be excluded from the analysis.
  - Mother used other medication before B-cell measurement on Day 30 post-ocrelizumab infusion 1 that is not allowed by protocol during breastfeeding: B-cell data will be excluded from the analysis.
  - *Infant's blood sample collected before assessment window (i.e., before Day 28): Data will be excluded from the analysis.*
  - Infant's blood sample collected beyond the assessment window: B-cell data might be included or excluded depending on the cause of the delay (rules will be specified in the SAP) and schedule of delayed visit.
  - *Infant's blood sample collected while infant has an illness: B-cell data will be excluded on a case-by-case basis if there is a strong biological rationale that the illness may confound the B-cell data.*
- Population-level summary: The proportion of infants with B-cell levels below LLN will be reported with the two-sided 95% CI; 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.

The estimand of the ADID in breastmilk is defined as below:

- Population: all women in the FAS population who provide any breastmilk samples (primary analysis set of mother)

- Variable: ADID
- Intercurrent events will be handled as follows:
  - Incomplete dosing, including delayed second (300 mg) ocrelizumab infusion: all the ADID data will be collected and included in the analysis. No adjustments based on actual dose will be made.
  - Mother used other DMT during breastfeeding: ADID data will be included.
  - Mother used other medication not allowed by protocol during breastfeeding: ADID data will be included in the analysis.
  - Mother has mastitis infection during the sample collection period: ADID data will be included from milk samples obtained from the non-infected breast (in case of bilateral mastitis, breastmilk sampling will be interrupted until the infection resolves).
- Population-level summary: The summary statistics together with 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 milk samples with all supporting information are collected.

More details about missing data handling, as well as sensitivity analyses based on alternative imputation approaches, will be specified in the SAP.

6.5.2 Secondary Endpoints

The ocrelizumab concentration in mature breastmilk at each time point, MDID, *RID,* and AUC will be summarized descriptively. Continuous variables at each month (e.g., length and weight of infants), as well change from baseline (if applicable) will be analyzed primarily using descriptive statistics.

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 for the overall population.

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

6.5.3 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.

6.6 SAFETY ANALYSES

6.6.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Signs Data

The safety outcome measures 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.

All safety analyses will be conducted on data collected from the first postpartum ocrelizumab infusion until the end of the study. The safety analysis will be performed on the safety populations of women and infants separately. 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 events, 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.

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

6.7 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 United States or under a U.S. 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 patient the objectives, methods, and potential risks associated with each optional procedure. Patients 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 patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient'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 patient 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 patient 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 patient is participating in the study, the patient 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 patient 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 patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the 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 Informed Consent Form (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. 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 healthcare professionals 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 access, 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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7		
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Patient population and ICF	Diagnosis confirmation [d]	x												
	Informed consent [e]	x												
	Review inclusion/ exclusion criteria	x	x											
Maternal general medical history and demographics [f]	Demographics (age, ethnicity, level of education)	x												
	Clinically significant diseases and surgery/ procedures	x	x			x							x	
	Smoking history and alcohol intake	x												
	Vaccination history	x												
	Height	x												
	Weight	x	x			x								
	Previous and concomitant medication	x	x			x							x	

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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7		
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Maternal MS disease history	Date of MS onset and diagnosis	x												
Maternal MS disease history (cont.)	Disease status (EDSS and relapses up to 1 year before the LMP)	x												
	History of previous DMTs (prior and/or during pregnancy)	x												
	Treatment history with ocrelizumab (OCREVUS) [g]	x												
Maternal obstetric history	Previous pregnancies	x												
Maternal physical assessments	General physical examination [h]	x	x			x							x	
	Neurological examination [i]		x										x	
	Recording of potential relapses		x			x							x	
	EDSS score		x										x	

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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7		
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Maternal laboratory assessments	Breastmilk ocrelizumab concentration [j]		x	x	x	x	x	x	x	x				
	Hematology, chemistry, urinalysis [k]	x	x			x							x	
	Hepatitis B virus (HBV) screening [l]	x												
	Whole blood sample for lymphocyte subtypes [m]	x												
	Serum Ig concentration	x												
Ocrelizumab infusion	Methyl-prednisolone and antihistamine premedication [n]		x			x								
	Ocrelizumab administration [o]		x			x								
	Documentation of collection of second postpartum ocrelizumab administration [ee]											*x*		

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

		Screening [b]	Treatment and Sampling Period [a]								Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7		
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Infant physical assessments and procedures	General health and medical history [p]	x												
	Body weight for safety								x			x		
	Pregnancy and infant outcomes [q]	x												
	Feeding schedule diary and status [r]		x	x	x	x	x	x	x	x	x			
	ASQ-3 [s]										x			x
	Documentation of infant growth velocity (weight, length, head circumference) [t]										x			x
	Previous and concomitant medications [u]	x							x		x	x		x
	Documentation of vaccination of the infant as part of routine care [v]										x	x		x

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

		Screening [b]	Treatment and Sampling Period [a]							Vaccination Period		Early Study Discontinuation Evaluation	
Visit [a]		1	2	3	4	2a [a]	3a [a]	4a [a]	5	6	–	7	
Day of visit		(Variable)	0 (baseline)	1	7	14	15	21	30 (± 2 days)	60 (± 2 days)	Months 2, 4, 6, 9, and 12	Month 13 of Age (+ 30 days) [c]	Woman	Child
Infant laboratory assessments [w, x,y]	Whole blood sample for lymphocytes subtypes sample [y, z]								x			x		
	Serum titers (IgG) of antibody immune responses to vaccinations [z, aa, bb]											x		
	Serum ocrelizumab concentration								x					
Telephone interview	General review of mother and infant [cc]			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Safety	Adverse event assessment [dd]	x	x	x	x	x	x	x	x	x	x	x	x	x

Mother's assessments Infant's assessments

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; BRUE = brief resolved unexplained event; 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; HCPs = Healthcare professionals; Hib = *Hemophilus influenzae* type b; ICF = Informed Consent Form; *IRR = infusion-related reaction;* 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; *SmPC = Summary of Product Characteristics; 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 telephone interview will not be conducted in a week where there will be an on-site visit).

[a] Visits 2a, 3a and 4a are only applicable for women who will be receiving the first ocrelizumab dose as two 300 mg infusions.

[b] The length of the screening period is variable and depends on local timings for performing some of the eligibility assessments. It is possible that visit 1 (screening) is completed in one day or over several days/weeks. Screening may be started during the third trimester of pregnancy and continue until 24 weeks postpartum.

[c] Samples 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 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.

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

[e] 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.

[f] 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 baseline visit. Demographic data will include age, self-reported race/ethnicity, and level of education. Clinically significant diseases and/or surgeries and concomitant medication should also be recorded throughout the study. Information on vaccinations administered to the mother during the study will be collected under concomitant medications.

[g] Documentation of start of ocrelizumab (OCREVUS) therapy and date and dose of last ocrelizumab infusion prior to enrolment. Ocrelizumab-related information to be collected only in women who received commercial ocrelizumab prior to enrolment.

[h] A complete physical examination should be performed at the screening and baseline visits and at all visits during the treatment period (results from examinations done as part of routine care at subject's HCPs [obstetrician/gynecologist, pediatrician, neurologist of referred subjects] 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.

[i] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. *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.*

[j] Women should record the volume of pumped breastmilk and indicate date and time for collection as well as whether breastmilk was pumped from one or both breasts. *For sampling on Day 0 (baseline), the sample should be taken before the infusion.* For 24 hours post-infusion (Day 1 and Day 15), samples are collected based on the midpoint of infusion. For example, if the infusion began at 8 am and ended at 10 a.m., the 24-hour sample collection would occur at 9 a.m. on the day after the infusion. With the exception of the 24-hour (Day 1; and [for women who received a 2 × 300 mg dose] Day 15) post-infusion breastmilk collection time points, flexibility is allowed on collection timing to accommodate the mother and the infant feeding schedule. If the mother presents with unilateral mastitis, milk should only be expressed from the unaffected breast, until the infection resolves. If mastitis presents bilaterally (rare), breastmilk collection should be stopped until the infection resolves.

[k] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute or/and differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), and quantitative platelet count. Chemistry will include potassium, sodium, chloride, random glucose, AST, ALT, GGT, creatinine, total bilirubin. 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.

[l] 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.

[m] Blood samples will be collected to measure B-cell counts (CD19+ *and B-cell subsets [Table 2*]), T-cell counts (CD3+, CD4+, and CD8+*), and NK cell counts (CD16+CD56+).*

[n] 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.

[o] In line with the dose regimen in the local label, the first dose of ocrelizumab may be administered as an initial split dose of two 300 mg infusions (in 250 mL 0.9% sodium chloride) separated by 14 days, or as a single 600 mg infusion (in 500 mL 0.9% sodium chloride), at any point between Week 2 and 24 postpartum. For women where a decision not to administer a second 300 mg infusion is taken after enrolment, continuation in the study will be allowed. *Dosing and treatment duration are at the discretion of the physicians, in accordance with local clinical practice and local labeling (USPI; SmPC).* If women did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent 600 mg doses. Women referred by HCPs to participate in the trial may receive ocrelizumab treatment at their neurologist's site as part of their standard of care treatment.

[p] General health and medical history for infants includes screening for the following (infants should be excluded from the study if any are present): age >24 weeks of age at the time of the mother's first postpartum dose of ocrelizumab; any abnormality that may interfere with breastfeeding or milk absorption, including but not limited to cleft palate and/or lip, congenital diaphragmatic hernia and esophageal atresia; an active infection (the infant may be included once the infection resolves); at least one documented BRUE, as defined by the 2016 Guidelines of the American Academy of Pediatrics.

[q] These will include: mode of delivery (vaginal delivery, instrumental delivery, scheduled or urgent cesarean section); APGAR score (1 min, 5 min, 10 min); gestational age at birth; infant's measurements (weight, length, head circumference); and congenital malformations.

[r] During the treatment and sampling period, women should record the number of breastmilk feeds and/or feeds with formula milk (supplementation) on the day of the sample collection and the previous and following day, i.e., day of collection ±1 day. During the vaccination period, women 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, at Months 2, 4, 6, 9, and 12, as applicable and depending on the infant's age at enrolment.

[s] 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 as applicable and depending on the infant's age at enrolment (see Appendix 6 for details of time windows of infant growth velocity and child developmental milestone assessments).

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

[u] Including documentation of past or current medications as well as clinically significant pediatric disease/abnormality. Changes to concomitant medication given to the infant should be recorded throughout the study.

[v] Documentation of vaccinations administered to the infant will be collected throughout the study.

[w] Infant sampling at Day 30 (±2 days) post-infusion 1 and at 1 month (+30 days) after first or second dose of MMR*, or* Month 13 of age *in case MMR vaccine is not planned to be administered* (+30 days) may be conducted via in-home nurse visits or at the hospital as part of study visits. CD19+ B-cell level at Day 30 (±2 days) post-infusion 1 represents the co-primary endpoint measurement.

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

[y] 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 sample at Day 30 (±2 days) post-infusion 1, (1) safety laboratory samples [scheduled or unscheduled and performed at the discretion of the investigator] (2) lymphocyte subtypes sample for B-cell counts (CD19+) and T-cell counts (CD3+, CD4+, and CD8+*), and NK cell counts (CD16+CD56+).* (3) serum ocrelizumab concentration; for the Month 13 of age/1 month after first/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+) and T-cell counts (CD3+, CD4+, and CD8+*), and NK cell counts (CD16+CD56+).*

[z] For 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, all efforts will be made to collect samples. However, if they cannot be collected, it will not be considered a protocol deviation.

[aa] Serum anti-vaccine antibody (IgG) titers will be measured to vaccines administered as per local practice over the first year of life (which include MMR, *diphtheria, tetanus, pertussis*, Hib, HBV and PCV-13); 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.

[bb] 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 13/1 month after first or second MMR dose.

[cc] A structured telephone interview will be conducted by site personnel postpartum every 2 weeks during the treatment and sampling period and every 3 months during the vaccination period (in-between ocrelizumab infusions) for a general review, and to identify and collect information on any changes in the woman's and infant's health status (including the occurrence of MS relapses in the mother 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.

[dd] Adverse events in both mother and infant will be reported throughout the study as per standard pharmacovigilance procedures. Adverse events will also be captured at screening for women who received ocrelizumab before pregnancy.

[ee] *Documentation of premedication is not required.*

Appendix 2
Compatibility of Common Medications with Breastfeeding

The following information is compiled from guidance provided by the New Zealand Medicines and Medical Devices Safety Authority (Medsafe), available at https://www.medsafe.govt.nz/profs/puarticles/June2015/June2015Lactation.htm and https://www.medsafe.govt.nz/profs/puarticles/lactation.htm.

An up-to-date database of medicine levels in breastmilk and infant blood and possible adverse reactions in the nursing infant is available at LactMed (https://www.ncbi.nlm.nih.gov/books/NBK501922/). The WHO has also produced a classification guide for medicines use in breastfeeding based on the WHO list of essential drugs (www.who.int/maternal_child_adolescent/documents/55732/en/).

Medicines with inherent toxicity or those with high infant exposure and therefore potential for significant toxicity are contraindicated during breastfeeding, and include:

- Cytotoxic agents
- Immunosuppressive agents
- Amiodarone
- Lithium
- Ergotamine
- Gold salts
- Isotretinoin

Radiopharmaceutical administration also requires temporary cessation of breastfeeding.

There are a range of health issues that affect women who are breastfeeding. These most commonly include infection, depressive disorders, pain, contraception, low milk supply and atopic conditions. Table A2-1 provides information on the compatibility of medicines used in the treatment of these conditions with breastfeeding.

Table A2-1 Compatibility of Commonly Used Medicines with Breastfeeding

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Infection	*Antibiotics*		
	β-lactams (e.g., amoxicillin)	Compatible	Gastrointestinal flora changes possible; monitor infant for diarrhea, vomiting, thrush
	Macrolides (e.g., erythromycin)	Compatible	Single dose of azithromycin considered safe
	Cephalosporins (e.g., cephalexin)	Compatible	May also affect infant gut flora (third generation more likely)
	Fluoroquinolones (e.g., ciprofloxacin)	Avoid if possible	Potential risk of arthropathies
	Trimethoprim	Compatible	
	Nitrofurantoin	Compatible	Avoid nitrofurantoin if infant less than 1 month old or premature
	Metronidazole	Avoid if possible	If single 2 g metronidazole dose given, discontinue breastfeeding for 12 hours
	Antifungals		
	Azoles (e.g., fluconazole)	Compatible	If applying miconazole oral gel to nipples, apply after breastfeeding
	Nystatin	Compatible	
	Antivirals		
	Acyclovir	Compatible	
Depressive disorders	*Antidepressants*		
	SSRIs (e.g., paroxetine)	Compatible	Paroxetine and sertraline preferred due to shorter half-lives

Appendix 2: Compatibility of Common Medications with Breastfeeding

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Pain	TCAs (e.g., amitriptyline)	Less preferred due to potential toxicity	Amitriptyline compatible in doses up to 150 mg/day
	Anxiolytics		
	Benzodiazepines (e.g., temazepam)	Compatible in a single dose; avoid repeated doses	Short-acting benzodiazepines preferred as accumulation may occur Monitor infant for drowsiness
	Analgesics		
	Paracetamol	Compatible	Paracetamol analgesic of choice
	NSAIDs (e.g., ibuprofen)	Compatible	Avoid breastfeeding with long-term acetylsalicylic acid treatment
	Opiates (e.g., codeine)	Compatible in occasional doses	Monitor infant for drowsiness, apnea, bradycardia and cyanosis Use codeine with caution in rapid metabolizers
	Tramadol	Compatible	
Contraception	*Hormonal methods*		
	Progesterone	Compatible	See data sheet
	Estrogen	Avoid if possible	May inhibit lactation
Allergies and hay fever	*Antihistamines*		
	Sedating (e.g., promethazine)	Probably compatible	Occasional use probably safe Monitor for sedation in mother and infant
	Non-sedating (e.g., loratadine)	Compatible	
	Topical		
	Corticosteroids (e.g., hydrocortisone)	Compatible	If applying to breasts apply after feeding

Appendix 2: Compatibility of Common Medications with Breastfeeding

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Asthma	β2- adrenergic (e.g., salbutamol)	Compatible	
	Corticosteroids (e.g., budesonide)	Compatible	
Other	Warfarin	Compatible	
	Metformin	Compatible	

NSAIDs = non-steroidal anti-inflammatory drugs; SSRIs = Selective serotonin reuptake inhibitors; TCAs = Tricyclic antidepressants.

Source: Medsafe. URL: https://www.medsafe.govt.nz/profs/puarticles/June2015/June2015Lactation.htm. (Accessed 17 December 2020).

TABULATED SUMMARY OF DRUG DISTRIBUTION INTO BREASTMILK

Table A2-2 shows published milk/plasma (M/P) ratios from the literature and provides an estimate of the weight-adjusted infant dose. Interpretation of these requires an understanding of the limitations associated with published data, such as the availability of only single pairs of plasma and milk concentrations. Infant clearance (related to post-conceptual age) should always be considered.

Table A2-2 Summary of Distribution of Drugs into Breastmilk

Drug	M/P_{AUC}	% Maternal Dose	Comments
Acid-suppressants:			
Cimetidine	1.7-5.8	5.4–6.7	Avoid in favor of safer alternatives with lower potential for side effects. May accumulate in milk due to active transport.
Famotidine	1.5	1.6	Probably safe.
Ranitidine	2.8	5.0–7.8	Probably safe when restricted to sporadic doses or a single dose at night-time. May accumulate in milk due to active transport.
Analgesics:			
Aspirin	0.06	3.2	Avoid due to possible association with Reye's syndrome.
Codeine	2.16	6.8	Considered safe.
Ibuprofen	0	<0.6	Considered safe. Not detected in milk.
Indomethacin	0.37	<1.0	Considered safe. One case of seizures (causality questionable).
Mefenamic acid	ID	0.3	Probably safe.
Methadone	0.47	2.2	Considered safe in methadone maintenance as 60% of infants born to mothers in maintenance programs develop symptoms of withdrawal.
Morphine	2.46	0.4	Considered safe.
Naproxen	ID	1.1	Probably safe.
Nefopam	ID	0.4	Probably safe.
Piroxicam	ID	5–10	Use a NSAID with a shorter half-life where possible.
Paracetamol	0.8	2.9–7.9	Considered safe.
Sumatriptan	4.1–5.7	0.3–6.7	Exposure limited by low oral availability in term infants. Expressing for 8 hours post-dose will almost completely avoid exposure.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Antibiotics:			
Aminoglycosides			
Gentamicin	0.17	2.2	Considered compatible with breastfeeding due to low transfer and low oral availability.
Cephalosporins			
Cefaclor	ID	0.7	Considered safe. Low transfer into milk. Third generation cephalosporins have greater potential to alter bowel flora.
Cefalexin	0.09	0.5–1.2	
Cefotaxime	ID	0.3	
Ceftriaxone	0.04	0.7–4.7	
Fluoroquinolones			
Ciprofloxacin	2.17	4.8	Avoid fluoroquinolones due to theoretical risk of arthropathies.
Macrolides			
Clarithromycin	0.25	1.8	Considered safe. May alter bowel flora.
Erythromycin	0.41	2.1	
Penicillins			
Amoxicillin	ID	0.7	Considered safe. Note: although amoxicillin/clavulanic acid combination is used extensively in lactation, there are no published data on the safety of clavulanic acid.
Benzylpenicillin	0.37	0.8	
Phenoxymethyl-penicillin	ID	0.25	
Tetracyclines			
Minocycline	ID	3.6	Avoid tetracyclines where feasible due to the possible risks of dental staining and adverse effects on bone development.
Tetracycline	0.58	4.8	
Others			

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Acyclovir	ID	1.1–1.2	Considered safe. No adverse effects noted in breastfed infants.
Fluconazole	0.75	11	Potential for accumulation particularly in premature infants.
Metronidazole	0.9–1.1	0.1–36.0	Controversial as exposure may be high. With high doses consider expressing and discarding milk.
Nitrofurantoin	ID	0.6–6.0	Avoid in G6PD-deficient infants (due to the risk of hemolysis).
Sulphamethoxazole and Trimethoprim (i.e., co-trimoxazole)	0.1 1.26	2–2.5 3.8–5.5	Avoid suphaemethoxazole in infants with hyperbilirubinemia and G6PD deficiency.
Anticoagulants			
Warfarin	0	<4.4	Probably safe. No changes in prothrombin times detected in breastfeeding infants. Monitor prothrombin time.
Anticonvulsants:			
Carbamazepine	0.36–0.39	2.8–7.3	Considered safe. Monitor for sedation, poor suckling.
Lamotrigine	ID	10–22	Concentrations in breastfed infants have been consistent with those expected to produce clinical effect. Best to avoid.
Phenobarbitone	ID	23–156	Avoid due to high infant exposure.
Phenytoin	0.13–0.18	3.0–7.2	Considered safe. Observe for sedation, poor suckling. One report of methemoglobinemia, poor suckling and sedation.
Sodium valproate	0.05	1.8	Considered safe at low doses. High doses may increase the risk of hepatitis.
Vigabatrin	ID	<1%	Avoid until further data are available.
Antidepressants:			
Tricyclics:			
Amitriptyline	0.83	0.6–0.9	Probably safe. Negligible or no concentrations detected in breastfed infants.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Desipramine	ID	0.5–1.0	
Dothiepin	0.8–1.6	0.2-1.5	
Doxepin	ID	0.01	
Imipramine	ID	0.13	
Nortriptyline	ID	0.53	
Others			
Moclobemide	0.72	1.6	Probably safe.
Antiemetics:			
Domperidone	ID	0.05	Probably safe. May increase milk secretion.
Metoclopramide	ID	4.7–11.3	Low dose or sporadic use probably safe. May increase milk secretion.
Antihistamines:			
Loratadine	1.2	0.7	Probably safe. No adverse effects reported in infants.
Triprolidine	0.53	0.9	Considered safe.
Antipsychotics:			
Chlorpromazine	ID	0.2	
Flupenthixol	ID	0.5–0.8	Probably safe. May increase milk secretion. Monitor infant for sedation, irritability etc.
Haloperidol	ID	0.15–2.0	
Cardiovascular:			
Amiodarone	ID	37	Avoid in breastfeeding.
Atenolol	2.3–4.5	5.7–19.2	Avoid in favor of antihypertensives with lower infant exposure.
Captopril	0.03	0.014	Considered safe.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Digoxin	0.6–0.9	2.3–5.6	Considered safe.
Diltiazem	0.98	0.9	Unlikely to be problematical in breastfeeding.
Enalapril	0.02	<0.1	Considered safe.
Metoprolol	2.8-3.6	1.7–3.3	Probably safe.
Nadolol	4.6	5.1	Consider choosing a beta-blocker with a lower infant dose, if feasible.
Propranolol	0.32–0.76	0.2–0.9	Probably safe.
Quinapril	0.12	1.6	Considered safe.
Verapamil	0.6	0.14–0.84	Considered safe.
Sedatives/hypnotics:			
Clonazepam	ID	1.5–3.0	Short-term use of low doses is probably safe.
Diazepam	0.16	2.0–2.3	Reasonable to breastfeed after a low single dose but potential for accumulation with prolonged use. Sedation has been reported in breastfed infants.
Lorazepam	ID	2.2	Short-term use of low doses is probably safe.
Midazolam	0.16	0.7	Short-term use of low doses is probably safe.
Nitrazepam	ID	ID	Short-term use of low doses is probably safe. Potential for accumulation with prolonged administration.
Zopiclone	0.5	4.1	Short-term use of low doses is probably safe.
Social Drugs:			
Cannabis (THC)	ID	ID	Avoid as long-term effects are unknown.
Caffeine	0.5–0.8	0.6–21.0	Low intake probably safe. Restlessness and irritability documented. Prolonged half-life (80–100 hours) in neonates.

Appendix 2: Compatibility of Common Medications with Breastfeeding

Drug	M/P_{AUC}	% Maternal Dose	Comments
Ethanol	0.9	3-4	Occasional low usage probably safe. Chronic intake may be associated with impairment of psychomotor development. Consider withholding breastfeeding for 1–2 hours per standard drink.
Nicotine	2.92	ID	Cigarette smoking should be avoided due to health hazards associated with smoking. Use of nicotine patches may be considered compatible with breastfeeding and is favored over smoking.
Miscellaneous:			
Ethinyloestradiol	ID	0.3	May suppress lactation.
Levonorgestrel	ID	1.1	Considered safe.
Medroxyprogesterone	ID–0.72	3.4–5.0	Considered safe.
Norethisterone	ID–0.26	0.02-1.9	Considered safe.
Prednisone	ID	0.26	Short courses of low doses (≤20 mg daily) are probably safe. Note: there are insufficient data on other systemic corticosteroids (e.g., betamethasone, dexamethasone).
Pseudoephedrine	2.5	4.0	Low doses or sporadic use probably safe.
Sulphasalazine	ID	1.2–7.0	Avoid in infants with hyperbilirubinemia or G6PD deficiency.

AUC = area under the concentration-time curves; G6PD = glucose-6-phosphate dehydrogenase; ID = insufficient data; M/P_{AUC} = AUC of the drug in maternal milk and plasma; NSAID = nonsteroidal anti-inflammatory drug; THC = Tetrahydrocannabinol.

Source: Medsafe. URL: https://www.medsafe.govt.nz/profs/puarticles/lactation.htm.

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 John Cunningham 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
Evolution	Hours to days	Over weeks
	Normally stabilize. May resolve spontaneously even without therapy	Progressive
Clinical Presentation	Diplopia *Paranesthesia* Paraparesis Optic neuritis Myelopathy	Aphasia Behavioral/neuropsychiatric changes Hemiparesis Retrochiasmal visual changes (e.g., hemianopia) Seizures

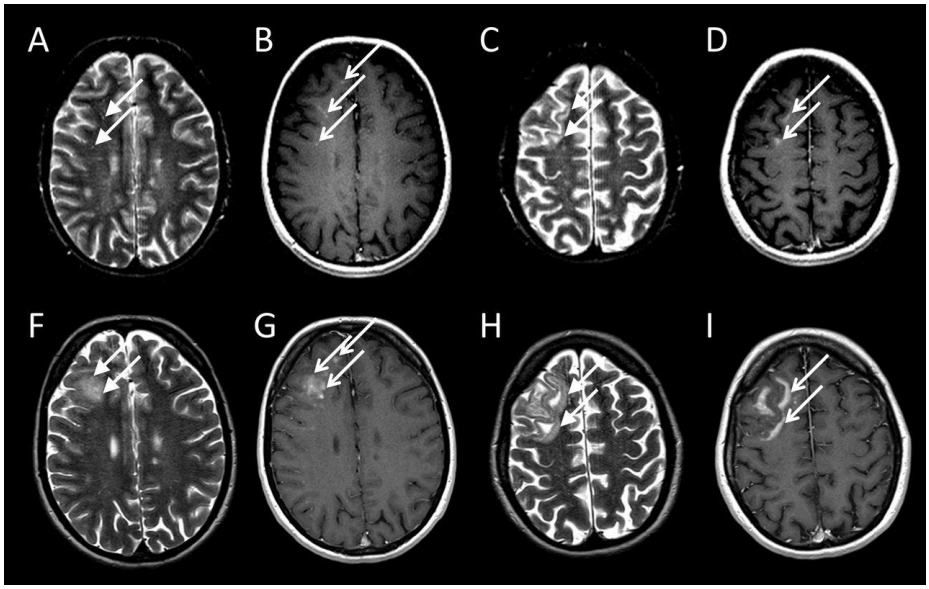
A3–2 MRI PRESENTATION

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 (see 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]

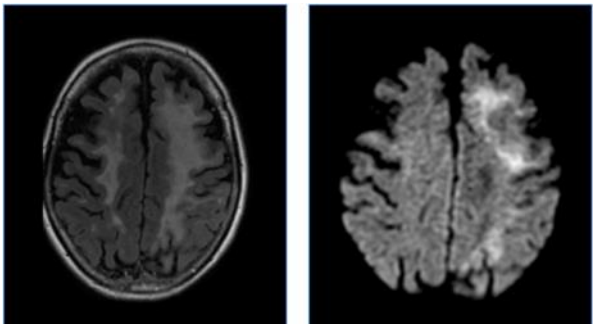
Figure A3-1 Imaging Characteristics of MS and PML



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 from 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 • Mostly located in periventricular, deep white matter, cerebellum, spinal cord areas • Also cortical and deep grey matter • U-fibers may be involved	• Often bilateral • [a] Subcortical frontal (+++), parietal (++), occipital (+) white matter (involving U-fibers) is the prime site • Cortex and basal ganglia are often involved • Can involve corpus callosum but unusual; rarely brainstem and posterior fossa
Appearance and Borders	• Focal (mostly) • Well-defined lesions with sharp edges; mostly round or finger-like in shape (especially periventricular lesions)	• Multifocal • 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
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

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

Parameters	MS	PML
T2W	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure Subacute and chronic lesions: hyperintense, with no ring structure	Always hyperintense [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; 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]

A3–3.1 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	+	–	+
	–	+	+
Possible	+	+	–/ND
	–	–	+
	–	(+) [a]	–
Not PML	+	–	–
	–	–	–

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

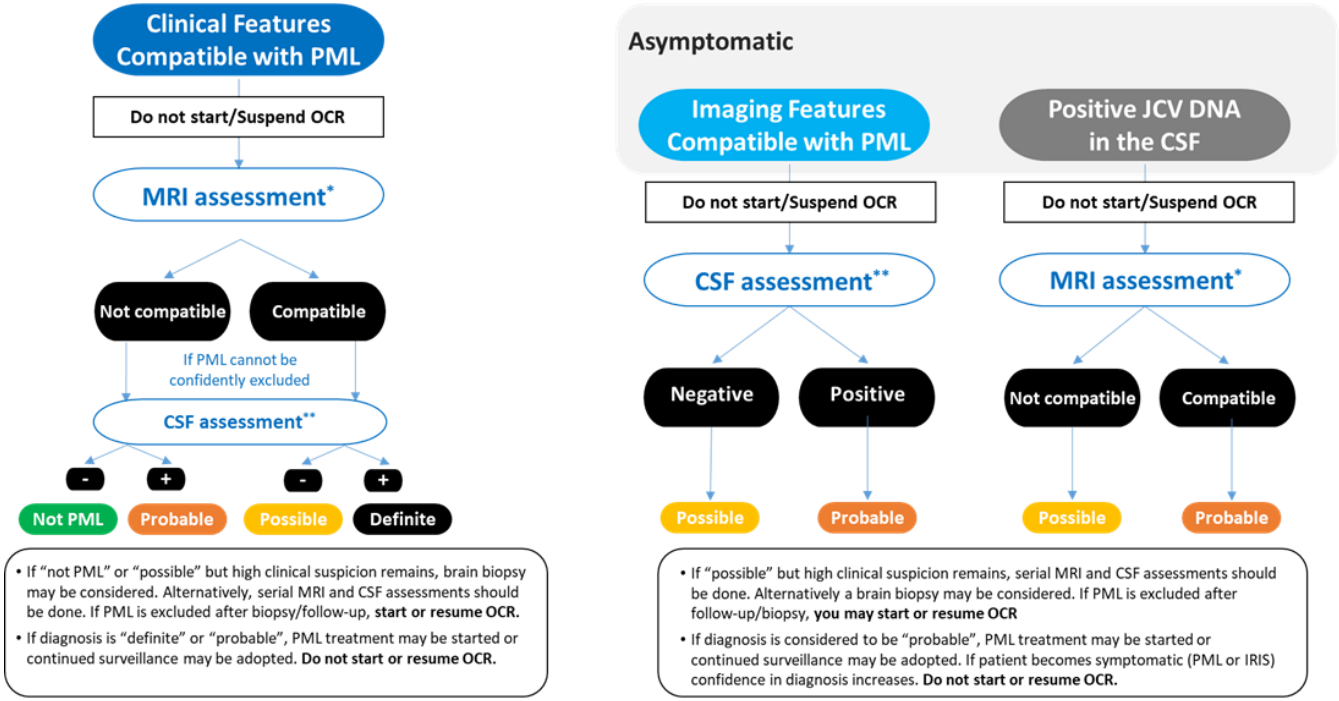
[a] **Note:** according to current AAN criteria, no diagnosis of PML can be made if only compatible imaging findings are present. However, recent evidence has shown that asymptomatic patients treated with NTZ, who have negative CSF JCV PCR results but PML-compatible MRI changes, may later develop symptoms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

A3–3.2 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 wash-out 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** 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** Fully ambulatory with two FS Grade 3 (others 0 or 1); **OR** 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** Ambulatory <100 meters without help or assistance **OR** Ambulatory ≥50 meters with unilateral assistance **OR** Ambulatory ≥120 meters with bilateral assistance
6.5	**Ambulatory for at least 20 meters with constant bilateral assistance (canes or crutches)** without rest **OR** Ambulatory for <50 meters with unilateral assistance (cane or crutch) **OR** Ambulatory 5–120 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. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).Neurology 1983:33,1444–52.

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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 **BMRC Grade 3 in one or two muscle groups** (movements against gravity are possible); and/or **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 **monoplegia:** BMRC Grade 0 or 1 in one limb; and/or **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 **marked tetraparesis:** BMRC Grade 2 or less in ≥ three limbs; and/or **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 and/or 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 and/or 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 and/or moderate decrease in touch or pain and/or marked reduction of proprioception >2 limbs
5	loss (essentially) of sensation in one or two limbs and/or 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)

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. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).Neurology 1983:33,1444–52.

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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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 5.0) 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 (version 5.0), 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 "hyperkalemia."

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 AEs).

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 AEs).

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 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 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).

A5–3.14 DRUG INTERACTIONS

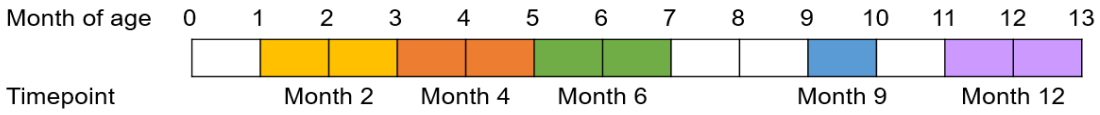
Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol, should be forwarded to the MAH as per non-serious timelines. If the associated adverse event fulfils the seriousness criteria, the event should be reported to MAH immediately (i.e., no more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

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, the Ages and Stages Questionnaire, version 3 (ASQ-3) age calculator2 can be used: https://agesandstages.com/free-resources/asq-calculator/.

Assessment of growth velocity at Months 2, 4, 6, 9, and 12 (as applicable and depending on the infant's age at enrolment) 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 post-natal 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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