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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE IV MULTICENTER, OPEN-LABEL STUDY EVALUATING B CELL LEVELS IN INFANTS POTENTIALLY EXPOSED TO OCRELIZUMAB DURING PREGNANCY – THE MINORE STUDY**

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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONs OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special interest
AIRI	Analysis Set of Infants
ALT	Alanine Aminotransferase
ASQ-3	Ages and Stages Questionnaire version 3
AST	Aspartate Aminotransferase
ATC	Atomic Therapeutic Chemical
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
COVID-19	coronavirus disease of 2019
DMT	Disease Modifying Therapy
DTaP	Diphtheria, Tetanus, And Pertussis
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
FAS	Full Analysis Set
FASI	Full Analysis Set Of Infants
FASW	Full Analysis Set Of Women
GGT	Gamma-Glutamyl Transpeptidase
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B Surface antigen
HBV	Hepatitis B Virus
Hib	Hemophilus Influenzae Type B
ICE	Intercurrent Event
IgG	Immunoglobulin
IRR	Infusion-Related Reaction
LLN	Lower Limit Of Normal
LMP	Last Menstrual Period
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
MMR	Measles, Mumps, and Rubella
MS	Multiple Sclerosis
NfL	Neurofilament Light Chain
NK	Natural Killer
OCR	Ocrelizumab
PASI	Pharmacokinetic Analysis Set Infants
PCV-13	13-Valent Pneumococcltal Conjugate Vaccine

PPMS	Primary Progressive Multiple Sclerosis
PT	Preferred Term
RBC	Red Blood Cell
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAFI	Safety Analysis Of Infants
SAFW	Safety Analysis Of Women
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard Deviation
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
US	United States
WBC	White Blood Cell
WHO	World Health Organization

1. BACKGROUND

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and degenerative disease of the central nervous system (CNS) that affects approximately 1 million people in the United States (US) and 2.8 million worldwide.

Ocrelizumab is a recombinant humanized monoclonal antibody (mAb) that selectively targets and eliminates CD20-expressing B cells, 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.

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

2. STUDY DESIGN

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

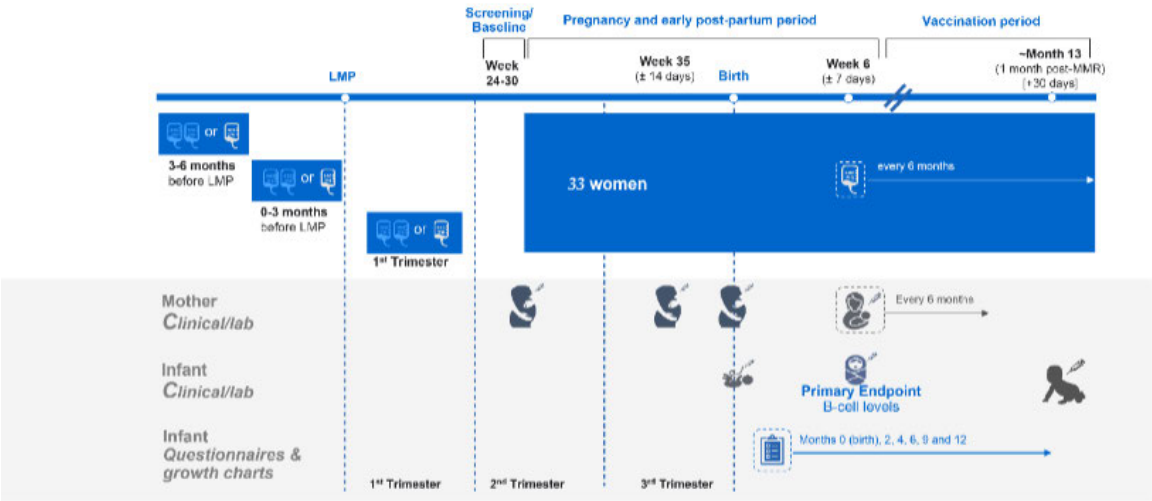
This study will enroll approximately 33 pregnant women with CIS or MS, some of whom should have potential fetal exposure (i.e., received their last dose of ocrelizumab <3 months before the LMP or during the first trimester [up to gestational Week 13]). Laboratory and clinical assessments will be performed as described in the Schedule of Assessments presented in Appendix 2.

The study will consist of the following periods:

- Screening/baseline period (between gestational Week 24 and 30)
- Pregnancy and early postpartum period (up to Week 6 of life)
- Vaccination period (after Week 6 of life and up to 1 month [+30 days] after the first or second dose of measles, mumps, and rubella (MMR) vaccine, or Month 13 of age [+30 days] if MMR vaccine is not planned to be administered)
- Follow-up visit after early discontinuation

Figure 1 presents an overview of the study design. The schedule of assessments is provided in Appendix 2.

Figure 1 Overview of Study Design



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

Study description: In this prospective, multicenter, open-label study, women with CIS or MS (in line with the locally approved indications) receiving commercial ocrelizumab up to 6 months before the LMP or during the first trimester of pregnancy will enter a screening/baseline period between gestational Weeks 24 and 30. Women fulfilling the selection criteria with accidental ocrelizumab exposure or in whom a decision to treat with ocrelizumab was taken as part of routine clinical practice, will be enrolled; some of the women should have potential fetal exposure (i.e., received their last dose of ocrelizumab < 3 months before the LMP or during the first trimester [up to gestational Week 13]). The baseline visit will be combined with the screening visit. To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. In the pregnancy and early postpartum period (up to Week 6 of life), laboratory and clinical assessments will be performed during the third trimester (gestational Week 35 [± 14 days]), whenever possible in accordance with planned prenatal care visits (samples at this visit may be collected by home nurse visit). To reduce the burden of visits on the mothers, results from physical and obstetric examinations, as well as neurological examinations, done as part of routine care may be used. At delivery, blood samples from the mother and from the umbilical cord will be collected. An infant blood sample for measurement of B-cell levels (primary endpoint) will be collected at Week 6 of life (± 7 days); or equivalent for preterm infants, i.e., gestational week at birth < 37 weeks) during a site visit or by home nurse visit. Treatment with commercial ocrelizumab may be resumed at any time after birth for women who decide not to breastfeed. Some women may decide to resume treatment with ocrelizumab whilst breastfeeding; for those women, treatment with ocrelizumab should be restarted after collection of the infant blood sample at Week 6 of life (± 7 days) if possible; but the

decision is left to the discretion of the woman and the investigator. If the woman switches to another disease modifying therapy (DMT) postpartum, the infant blood sample at Week 6 of life (± 7 days) will only be collected if the woman is not breastfeeding. In the vaccination period (after Week 6 of life [± 7 days] and up to 1 month (+ 30 days) after the first/second dose of MMR vaccine, or Month 13 of age [+ 30 days] if the MMR vaccine is not planned to be administered), infants will receive vaccinations according to the local immunization schedule.

Further details of the procedures during each period can be found in the protocol.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1 – please refer here for the list of objectives and corresponding endpoints. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 DETERMINATION OF SAMPLE SIZE

The study will include approximately 33 pregnant women.

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

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

Table 1 Sample Size Precision at Different Event Rates

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

2.3 ANALYSIS TIMING

The primary analysis will be conducted when the last infant finishes the Week 6 of life measurement.

The full analysis, including the analysis of growth velocity of the infants in the first year, will be conducted at the end of the study. 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 Month 13 of age [+ 30 days] for the last infant.

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.

3. STUDY CONDUCT

3.1 RANDOMIZATION

No randomization, treatment assignment or blinding is planned.

3.2 INDEPENDENT REVIEW FACILITY

Not applicable to this study.

3.3 DATA MONITORING

There is no Independent Data Monitoring Committee (IDMC) planned for this study.

4. STATISTICAL METHODS

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.

For continuous variables, descriptive statistics (e.g., number of patients [n], mean, standard deviation [SD], median, 25th and 75th percentiles, minimum, maximum) will be calculated and summarized.

For categorical variables, the number and percentage in each category will be displayed.

The analyses outlined in this Statistical Analysis Plan (SAP) supersede those specified in the protocol.

4.1 ANALYSIS SETS

4.1.1 Full Analysis Set (Women)

The full analysis set of women (FASW) will include all enrolled pregnant who were exposed to ocrelizumab either 0-6 months before the LMP or in the first-trimester of pregnancy (i.e., up to gestational Week 13 [inclusive]). This corresponds to 13*7+6, 97 days, as the last day of the first trimester.

4.1.2 Full Analysis Set (Infants)

The full analysis set of infants (FASI) will include all infants born to women in the FASW who were potentially exposed to ocrelizumab during pregnancy.

4.1.3 Safety Analysis Set (Women)

The safety analysis set of women (SAFW) will be the same as the FASW.

4.1.4 Safety Analysis Set (Infants)

The safety analysis set of infants (SAFI) will be the same as the FASI.

4.1.5 Antibody Immune Response Analysis Set (Infants)

The antibody immune response analysis set of infants (AIRI) will include all infants in the SAFI for whom any serum titers of antibody immune response to vaccinations are available. This analysis set will be used to analyze humoral immune responses to common childhood immunizations.

4.1.6 Pharmacokinetic-Analysis Set (Infants)

The pharmacokinetic analysis set of infants (PASI) will include all infants in the FASI with a serum sample and umbilical cord (all available data) to allow measurement of ocrelizumab concentration. This analysis set will be used to estimate the serum concentration of ocrelizumab in the infant due to ocrelizumab transfer from the mother to the infant via the umbilical cord blood at birth.

4.2 ANALYSIS OF STUDY CONDUCT

Patient disposition information will be summarized separately for the mother and infant as: the reason and number of screen failures (women only), the number enrolled, in the respective full analysis set (FAS) population, in the respective safety analysis set (SAF) population, completed each study period, discontinued from each study period and the reasons for discontinuation.

Major protocol deviations, including deviations of inclusion/exclusion criteria, will also be summarized and listed.

Mothers and infants enrolled but excluded from the respective FAS will be listed.

4.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

4.3.1 Women

The following demographic, MS history, baseline disease characteristics of women will be summarized and listed for the FASW, unless otherwise stated:

Demographic

- Age (years) as continuous and categorical (18–29, 30–40, >40)
- Self-reported race and ethnicity
- Education level
- Height (cm), weight (kg), and Body Mass Index (BMI: kg/m²)

- Smoking history (never, former)
- If previous smoker, time (years) since last use
- Alcohol use history (never, former)
- If previous user of alcohol, time (years) since last use

Multiple Sclerosis History

- Type of MS (relapsing-remitting multiple sclerosis [RRMS], secondary progressive multiple sclerosis [SPMS], primary progressive multiple sclerosis [PPMS], CIS)
- Duration (years) since onset of MS symptoms and its category ($\leq$3 years, $>$3 to $\leq$5 years, $>$5 years to $\leq$10 years, >10 years to $\leq$15 years, $>$15 years)
- Duration (years) since MS diagnosis and its category ($\leq$3 years, >3 to $\leq$5 years, $>$5 years to $\leq$10 years, >10 years to $\leq$15 years, $>$15 years)
- Expanded disability status scale (EDSS)
  - Change in EDSS score from last pre-baseline measurement (up to 1 year before LMP) to baseline
  - EDSS score:
    - Most recent prior to LMP: continuous and categorical (<2 vs $\geq$2)
    - Last score prior to enrollment : continuous and categorical (<2 vs $\geq$2)
- Relapses
  - Women with relapses up to 1 year prior to the LMP (yes, no)
  - Duration (Weeks) of most recent relapse and enrollment and its category (≤4 weeks, >4 and ≤8 weeks, >8 and ≤12 weeks, >12 and ≤16 weeks, >16 weeks)
  - Duration (months) between last onset of MS relapse up to one year prior to LMP and LMP and its category (≤6 months, >6 and ≤12 months)
  - Duration (months) between last onset of MS relapse after LMP prior to enrollment and enrollment and its category ($\leq$6 months, >6 months)

If the date of the relapse is completely missing the relapse will be excluded from the analysis as appropriate. If only the year is available, it will be imputed to the first day of the year. If the day is missing, it will be imputed to the first day of the month.

Prior DMT Use

- Number of DMTs used prior to screening (1, 2, 3 and >3)
- Type of DMTs used prior to screening
- Number of women by the most recent DMT
- Reason for discontinuing most recent DMT

- Duration of the most recent DMT as continuous and categorical (≤6 months, >6 and ≤12 months, >12 and ≤24 months, >24 months)
- Time (months) from last DMT to first ocrelizumab infusion before enrollment
- Time (months) from last DMT to LMP

Prior Ocrelizumab Use

- Number and percentage of women received ocrelizumab in 3-month interval of before/during pregnancy (3-6 prior LMP, 0-3 month prior to LMP, 1st trimester)
- Time (months) between last ocrelizumab before LMP and LMP
- Time (months) between LMP and last ocrelizumab after LMP
- Received ocrelizumab after LMP (yes, no)
- Duration (months) of ocrelizumab therapy prior to enrolment
- Duration of ocrelizumab therapy prior to enrolment (≤6 months, >6 and ≤12 months, >12 and ≤24 months, >24 months)

Prior Medications

Prior medication (defined as treatment ended before LMP) and concurrent medications (defined as treatment started on or after the LMP) will be summarized, by frequency tables according to the Anatomic Therapeutic Chemical (ATC) classification system using the WHO Drug dictionary.

Baseline Disease Characteristics

- Baseline EDSS continuous and categorical (<2.5 vs ≥2.5)
- Baseline EDSS distribution: count and percent of patients corresponding to each observed score of EDSS at baseline
- Presence of any clinically significant abnormalities from the neurological examination (Yes, No)
- Type of neurological abnormality (disability progression independent of relapse, MS relapse, signs or symptoms suggestive of Progressive Multifocal Leukoencephalopathy, Other)

Obstetric and Gynecological History

- History of previous pregnancies (Yes/No)
- Number of previous pregnancies (1, 2, 3, 4, >4)
- Previous pregnancy outcome (Full term live birth, preterm live birth, spontaneous abortion, still birth, therapeutic abortion, elective abortion, ectopic pregnancy, unknown)

- Gestational Age (Weeks) as continuous and categorical (<23, 23-27, 28-32, 33-36, ≥37)
- History of adverse pregnancy outcomes (Yes/No)
- History of obstetrical complications during previous pregnancies (Yes/No)
- Type of obstetrical complication during previous pregnancies
- Reason for termination (if terminated)

Medical History

Medical history of the women will be summarized in SAFW by System Organ Class (SOC) and Preferred Term (PT). For each previous and concurrent medical history recorded medical history (MH), the term entered by the investigator describing the event (the "reported term") will be assigned a standardized term (the "Preferred Term" [PT]) and assigned to a superclass term (the "System Organ Class" [SOC]) on the basis of the Medical Dictionary for Regulatory Activities (MedDRA) World Health Organization (WHO) dictionary of terms.

Previous and concurrent medical history will be also listed.

Vaccination History

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination history will be summarized in the SAFW overall and split by the period prior to infant's birth and before/after LMP and after infant's birth. Non-SARS-CoV-2 vaccination history will be summarized by pathogen (Appendix 5) in SAFW overall and split by the period prior to infant's birth and before/after LMP and after infant's birth. Where time period can't be determined due to completely or partially missing date, it will be imputed to before infant's birth.

SARS-CoV-2 vaccination history will also be listed in the SAFW, including the following:

- Manufacturer name (first, second and, if applicable, third dose and any booster dose[s]) (Pfizer/Biontech coronavirus disease of 2019 [COVID -19] vaccine, Moderna COVID -19 vaccine, Astra Zeneca COVID -19 vaccine, Johnson and Johnson Covid-19 vaccine, Other)
    - Type of vaccine for each dose (mRNA vaccine, Viral Vector Vaccine, Inactivated Vaccine, Other)
    - Timepoint of last COVID-19 vaccination prior to LMP (>6months before LMP, 3-6 months before LMP, <3 months before LMP, 1st trimester, 2nd trimester, 3rd trimester, ≤6 months postpartum, >6 months postpartum).

Other Vaccinations history (vaccines other than SARS-CoV-2) will also be listed in the SAFW.

4.3.2 Infants

The following baseline characteristics of infants will be summarized and listed in the FASI:

Characteristics at Birth

- Details of birth (vaginal delivery, vaginal delivery - forceps/vacuum instrumental, cesarean – scheduled, cesarean – emergency)
- Gestational age (weeks)
- Gestational age category (pre-term, full-term)
- Sex (male, female)
- Weight (kg)
- Length (cm)
- Head circumference (cm)
- Apgar score – 1 minute
- Apgar score – 5 minute
- Apgar score – 10 minute
- Congenital anomalies

The listing of characteristics at birth will also include congenital anomalies.

Infant feeding

- Feeding status (Breast Milk, Infant Formula, Partial Breast Milk/infant formula, Other) at Months 2, 4, 6, 9, and 12 by no switch of DMT, switch to another DMT regardless of timing and overall.
- Number of weeks exclusively breastfed by visit.

4.4 PRIMARY ENDPOINT ANALYSIS

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

4.4.1 Primary Endpoint

The primary endpoint is binary, defined as the proportion in infants with B cell levels (CD19+ cells, absolute counts) below the LN), measured at Week 6 of life (Yes/No).

The primary estimand is defined as follows:

- Population: Infants exposed to commercial ocrelizumab up to 6 months before the woman's LMP or during the first trimester (up to gestational Week 13) of pregnancy and not exposed after the first trimester (FASI)
- Variable: Binary endpoint, based on whether the B cell level is below the age adjusted LLN.

- Treatment: Commercial ocrelizumab (potential exposure during pregnancy).
- Intercurrent events:
  - Withdrawal from the study prior to infant's Week 6 visit – missing data will not be imputed
  - Interrupted pregnancy (elective/therapeutic abortion or stillbirth) – missing data will not be imputed
  - Fetal complications, or other issues, that render the sample not suitable for measurement of B cell levels at week 6 of life. – missing data will not be imputed
  - Breastfeeding before sample at week 6 is taken:
    - No DMT postpartum whilst breastfeeding: B cell will be included
    - Received any DMT postpartum whilst breastfeeding: B cell will be excluded since sample will not be collected.
    - Resume OCR postpartum whilst breastfeeding: B cell will be included.
  - Infants that were born pre-term and whose interval of assessment was not adjusted (i.e. a baby was born at week 35, the blood sample needs to be taken at week 8 ($\pm$14 days), gestational weeks that would sum up to a full term baby): B cell will be included.
- Population-level summary: Proportion of infants with B cell below LLN and the two-sided 95% CI will be reported; no formal statistical testing will be done.

B-cell reference ranges by week of life (absolute and percentage counts) are defined by Borriello et al. 2022 (Appendix 4). B cell data being confounded with illness will be determined by clinical team in a blinded manner before conducting the primary analysis.

4.4.2 Analytical Approach for Primary Endpoint

The proportion of infants with B cell levels at Week 6 of life below the LLN will be analyzed using descriptive statistics. The event rate and corresponding Clopper Pearson 95% CI will be presented. A corresponding listing will be presented for B cell levels (absolute count), including whether any intercurrent events (ICEs) led to exclusion of infant data from the analysis.

4.4.3 Handling of Missing Data

No data will be imputed unless otherwise stated. Every effort will be made to ensure all samples with all supporting information are collected for B cell measurement.

4.4.4 Sensitivity Analysis for Primary Endpoint

The following sensitivity analyses may be performed on the primary endpoint if more than 20% of infants are impacted. Infant with any of the following condition will be considered as being impacted:

- infants blood samples collected outside the Week 6±7 days visit window.
- gestational age is less than 37 weeks, but interval of assessment is not adjusted.
- resume OCR postpartum whilst breastfeeding before sample at Week 6 is taken.

A sensitivity analysis may be conducted substituting any B Cell values with missing data.

4.4.5 Subgroup Analyses for Primary Endpoint

To assess the impact of fetal exposure during pregnancy, a subgroup analysis will be performed of infants based on maternal OCR exposure prior to the study as list below:

- in 3-month interval of before/during pregnancy (3-6 months before the LMP, <3 months before the LMP, during the first trimester [up to gestational Week 13]
- ≥3 months before the LMP vs <3 months before the LMP and/or during pregnancy.

The analysis will be presented in the same way as for the primary endpoint

4.5 SECONDARY ENDPOINTS

4.5.1 Infant B Cell Levels at 6 Weeks of Life

Infant B cell levels (CD19+ cells, absolute counts and percentage of lymphocytes) measured at Week 6 of life will be summarized descriptively in the FASI, irrespective of the occurrence of any ICEs identified for the primary endpoint.

4.5.2 Infant Serum Concentration of Ocrelizumab

To evaluate whether there is placental transfer of ocrelizumab from the mother to the infant, serum ocrelizumab concentrations are measured in the umbilical cord blood at birth (within 1 hour after delivery) and at 6 weeks of life. Summary statistics for the serum concentration of ocrelizumab in the umbilical cord and in the infant at Week 6 will be presented (including breastfeed prior to sample taken) in the FASI, and a corresponding listing produced.

Correlation between maternal OCR concentration and OCR concentration in infant will be explored in order to characterize the exposure and transfer relationship.

Serum ocrelizumab concentration reported as below limit of quantification (BLQ) will be imputed to zero for the calculation of summary statistics.

4.5.3 Infant Absolute Antibody Immune Response

The infant's antibody (Immunoglobulin [Ig]G) immune response to common childhood immunizations with full or partial doses given prior to 1 year may include (but is not limited to) responses to MMR, diphtheria, tetanus, and pertussis (DTaP), Hemophilus influenzae type b (Hib), hepatitis B virus (HBV) and 13-valent pneumococcal conjugate vaccine (PCV-13), measured 1 month after the first or second dose of MMR vaccine or at Month 13 of age (+30 days) in case MMR vaccine is not planned to be administered.

Summary statistics for each serum IgG antibody titer will be presented in the AIRI and a corresponding listing produced. Results for MMR titers will be summarized together irrespective of whether or not the infant received MMR vaccine. Analysis will be presented for the following subgroups:

- Maternal OCR exposure prior to the study in 3-month interval of before/during pregnancy (3-6 prior LMP, 0-3 month prior to LMP, 1st trimester)
- Type of feed: exclusive breast milk from birth to Month 6 vs others (including complementary feeding [breastmilk + formula milk, in various proportions] and formula feeding [no breast milk])
- Women with/without receiving postpartum ocrelizumab

A listing with all immune responses will be produce.

4.5.3.1 Infant Positive Antibody Immune Response

The proportion of infants with positive humoral response (seroprotective titers as defined for the individual vaccine) will be presented for each individual IgG antibody titer in infants in the AIRI population. Analysis will be presented for all infants as well as by subgroups defined in Section 4.5.3.

A corresponding listing will be produced.

Seroprotective titers are defined for each vaccine in the table below:

Vaccine test	Seroprotective Titer
Bordetella pertussis antibodies, IgG	> 1.04 COI
Haemophilus influenzae B, IgG	≥ 0.15 µg/mL
Anti-Diphtheria IgG(-70)CL	≥ 0.01 IU/mL
Anti-Tetanus Toxoid IgG(-70)RUO	≥ 0.01 IU/mL
13 Valent anti-pneumococcal antibody panel	≥ 0.35 µg/mL
Anti-Measles Vir IgG(-70)CL	≥ 120 mIU/mL
Anti-MumpsAT Vir iGG(-70)CL	≥ 17 U/mL
Anti-Rub Vir IgG(-70)RUOCL	≥ 10 IU/mL
anti-HBs	≥ 10 mIU/mL

COI=Cut-off Index; IU=International Unit IgG=immunoglobulin G.

Source: Storsaeter et al. 1998; European Medicines Agency 2015

For Tetanus and Diphtheria, a sensitivity analysis will be conducted using a seroprotective threshold of ≥ 0.1 IU/mL for infants receiving a 4th dose at least one month prior to the titer assessment. The ≥ 0.01 IU/mL threshold will still be used for those only receiving 3 doses.

4.5.4 Women's Ocrelizumab Levels during Pregnancy

To evaluate the levels of ocrelizumab in the mother during pregnancy, serum levels of ocrelizumab are measured during pregnancy (Week 24-30 and Week 35) and at delivery (within 24 hours after delivery). Summary statistics for the serum concentration of ocrelizumab in the women will be presented in the FASW. Analysis will also be presented for subgroups based on OCR exposure prior to the study as list below:

- In 3-month interval of before/during pregnancy (3-6 months before LMP, 0-3 months before to LMP, during the 1st trimester)
- ≥3 months before to LMP vs <3 months prior to LMP and/or during pregnancy

Serum concentration of ocrelizumab reported as BLQ will be imputed to zero for the calculation of summary statistics.

4.6 EXPLORATORY ENDPOINTS

All exploratory analyses will be conducted using the SAFW or SAFI population as appropriate, unless otherwise specified.

4.6.1 Infants Growth Velocity

Infant growth velocity will be assessed by recording the infant's weight (kg), height (cm) and head circumference (cm) at birth, and Months 2, 4, 6, 9 and 12. The visit label will be derived based on infants actual age at the time of assessment: Month 2 (31-91 days), Month 4 (92-152 days), Month 6 (153-227 days), Month 9 (228-318 days), Month 12 (319-409 days), Month 13 (≥410 days).

Analysis will be based on the SAFI and includes:

- Actual values and change from baseline (defined as at birth) for weight, length/height, head circumference, and growth velocity (defined as the change from baseline divided by the number of months since baseline) will be summarized at each age time-point (birth, Months 2, 4, 6, 9, and 12).
- The weight-for-age and length/height-for-age percentiles and change from baseline percentiles at each time-point will be summarized.
- The number and percentage of infants in the 3rd, 5th, 10th, 25th, 50th, and >50th percentile of the WHO growth charts will be presented for weight-for-age and length/height-for-age percentile at each time point. The number and percentage of infants within 10th-90th percentile, and 3rd-97th percentile of the WHO growth charts will also be presented.

- Shift tables will be presented for each parameter to compare the change from infant's percentile at baseline (≤3rd, >3rd - ≤5th, >5th - ≤10th, >10th - ≤25th, >25th -≤50th, >50th) to each time-point (WHO 2006; WHO 2007; WHO 2017).
- Mean percentiles for weight-for age and length/height-for-age and corresponding 90% CIs will be plotted over time.
- Individual growth charts will be presented for each infant. This chart will present the weight and length/height for the infant over time, including reference lines for the 3rd, 25th, 50th, 75th, 90th and 97th percentiles for weight-for-age and length/height-for-age from WHO growth charts. Separate plots will be produces for each infant. Combined plots will also be produced for males and females separately, to show the trajectories of each infant on the same page.

All observed assessments will be included in the analysis; no imputation for missing assessments will be performed. The analysis will be based on the SAFI. Analysis will also be presented for the following subgroups:

- Type of feed: exclusive breast milk from birth to Month 6 vs others (including complementary feeding [breastmilk + formula milk, in various proportions] and formula feeding [no breast milk]).
- Maternal OCR exposure prior to the study in 3-month interval of before/during pregnancy (3-6 prior LMP, 0-3 month prior to LMP, 1st trimester)

All infant growth velocity data will be listed.

4.6.2 Infants Childhood Developmental Milestones

The infant's developmental milestones will be assessed using the Ages and Stages Questionnaire version 3 (ASQ-3), in the domains of communication, gross motor, fine motor, problem solving, and personal-social at Week 6 and Months 2, 4, 6, 9, and 12.

The total score for each domain will be summarized by visit using continuous statistics in the SAFI. In addition, the number and percentage of infants with abnormal scores (Yes/No) will be presented in the SAFI, as per cut-offs below transcribed from the ASQ-3 User's guide.

ASQ-3 questionnaire	Area				
	Communication	Gross Motor	Fine Motor	Problem Solving	Personal Social
Month 2	22.77	41.84	30.16	24.62	33.71
Month 4	34.60	38.41	29.62	34.98	33.16
Month 6	29.65	22.25	25.14	27.72	25.34
Month 9	13.97	17.82	31.32	28.72	18.91
Month 12	15.64	21.49	34.50	27.32	21.73

ASQ-3 = Ages and Stages Questionnaire version 3.

Values below the respective cut-off will be classified as abnormal (i.e., further assessment with a professional may be needed).

A corresponding listing will be produced.

Only questionnaires assigned to the correct time point will be included in the main analysis. If the wrong questionnaire is used for some time points in >20% infants, a sensitivity analysis will be performed with these data included.

4.6.3 Women's Immunity During Pregnancy

To evaluate humoral immunity to clinically relevant pathogens in mothers during pregnancy. Serum antibody (IgG) titers to immunizations: for measles, mumps, rubella, TT, diphtheria, pertussis, varicella zoster, Streptococcus pneumoniae, HBV and SARS-CoV-2 (along with nucleocapsid and spike protein titers; only for those mothers who have received the vaccine, as per local clinical practice) will be collected in the third trimester (Week 35). This will be presented in the same way as for infant immune response in Section 4.5.3 but for the SAFW population.

A listing with all immune response will be produce.

4.6.4 Women's Disease Activity

To assess disease activity and progression in women, the potential relapse is recorded and EDSS, a neurological examination is performed during pregnancy (Week 24-30 and Week 35), at infusion (if applicable), at early discontinuation and unscheduled visit if applicable. This will be summarized as follows in the FASW:

- Clinical Relapse:
  - Number of relapses before, during pregnancy (defined by LMP) and after pregnancy (defined as after birth) will be summarized in 3-month interval respectively.
  - Number and percentage of women in each category (0, 1, 2, 3 and $\geq$4) in 3-month intervals of before/during/after pregnancy.
  - Number of relapses after first OCR and up to 1 year before pregnancy, during pregnancy, up to 1 year after delivery will be presented. Annualized relapse

rate and 95% CI may also be presented if warranted by the number of data points.

- Mean EDSS score in 3-month interval of before/during/after pregnancy. In case of multiple EDSS score at the same visit, the median will be used.
- Change from baseline in EDSS by visit.
- Presence of any clinically significant abnormalities from the neurological examination (Yes, No) by visit
- Type of neurological abnormality (disability progression independent of relapse, MS relapse, signs or symptoms suggestive of Progressive Multifocal Leukoencephalopathy, Other) by visit

MS relapses, EDSS and neurological examination findings will also be listed. Analysis will also be presented for subgroups based on OCR exposure prior to the study as list in Section 4.5.4.

4.6.5 Women's Neuroaxonal Damage

To detect presence of neuroaxonal damage in the mother during pregnancy and postpartum, serum neurofilament light chain (sNfL) levels are measured at baseline (gestational age Week 24-30), gestational age Week 35, at delivery and postpartum (in line with ocrelizumab administration timepoints). Absolute sNfL levels will be log (base 10) transformed. The geometric mean with corresponding 95% CI and change from baseline will be back transformed and presented. Absolute sNfL levels as well as change from baseline based on log back transformed may also be displayed graphically over time, as appropriate.

4.6.6 Infant Evolution of B Cell Levels

To evaluate the evolution of B cell levels between birth and the first year of life, B cell (CD19+ cell, absolute counts and percentage of lymphocytes levels are collected in the infant from week 6 of life to 1 month after the first or second dose of MMR vaccine or Month 13 of age in case MMR vaccine is not planned to be administered.

Summary statistics for the mean absolute values and percentage change from Week 6 will be presented at each visit (Week 6 of life, 1 month after month after the first or second dose of MMR vaccine, Month 13 of age in case MMR vaccine isn't administered) for absolute CD19+ cell counts and percentage of lymphocytes based on the FASI, irrespective of the occurrence of any ICEs identified for the primary endpoint.

Subject profile plots (one line per infant) will be used to display the trajectory of CD19+ cell levels (absolute counts and percentage of lymphocytes) over time in the FASI. The Y axis will be the absolute cell count or percentage of lymphocytes, and the X axis will be age in weeks. Lines will be plotted based on the actual age (i.e., not pooled into age categories). The age-specific LLN and ULN (see Appendix 4) for CD19+ cell counts and percentage of lymphocytes will be overlayed.

All B cell data collected will be listed.

4.7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Pharmacokinetic and pharmacodynamic (B cells) analyses for ocrelizumab in the umbilical cord blood at birth and serum are described elsewhere for the secondary endpoint.

4.8 SAFETY ANALYSES

The safety outcome measures comprise the following: incidence and nature of all adverse events (AEs), including findings on vital sign measurements, clinical laboratory tests, and concomitant medications.

The safety analysis will be performed on the safety populations of women (SAFW) and infants (SAFI) separately.

4.8.1 Exposure of Study Medication

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

Definitions

Dose: Ocrelizumab dose is given as one infusion or two infusions administered 2 weeks apart. Women will be considered to have received a dose of treatment if at least part of one infusion of that Dose (either Day 1 or Day 15 for dual infusions) was given.

Treatment duration (in weeks) for woman received OCR will be calculated as follows:

[(Date of last contact* - Date of first postpartum dose) + 1] / 7

*Earliest 1) date of last OCR dose plus risk window of 6 months (182 days)
2) date of death
3) Clinical Cut-off Date

Exposure Analysis

The following measures of exposure of ocrelizumab will be summarized in the SAFW using descriptive statistics:

- Number of patients completing each dose type (Dose 1, full dose; Dose 1 split dose #1; Dose 1, split dose #2, Dose 2, full dose; Dose 3, full dose)
- Treatment duration (weeks)
- Number of doses received (Day 1 and Day 15 infusions are considered as one dose)

- Total cumulative dose (mg)

A corresponding listing will be produced.

MS treatment postpartum

- Type of DMT including ocrelizumab use postpartum
- Time (months) between delivery and first postpartum ocrelizumab as continuous and categorical (0-3 months, >3 and ≤6 months, >6 months)
- Number of women who received ocrelizumab dose postpartum
- Number of ocrelizumab doses postpartum
- Time (months) between first and second postpartum ocrelizumab dose

4.8.2 Adverse Events

All summaries of AEs will be presented separately for women and infants based on the respective Safety population. Adverse events will be presented overall and by timepoint (defined below). AEs will also be presented for subgroups based on OCR exposure prior to the study as list below, for infants and women separately:

- In 3-month interval of before/during pregnancy (3-6 months before LMP, 0-3 months before to LMP, during the 1st trimester)
- ≥3 months before to LMP vs <3 months prior to LMP and/or during pregnancy

For each recorded adverse event (AE), the term entered by the investigator describing the event (the "reported term") will be assigned a standardized term (the "Preferred Term" [PT]) and assigned to a superclass term (the "System Organ Class" [SOC]) on the basis of the MedDRA WHO dictionary of terms version 26.1.

Definitions

Infant AE timepoints:

Neonatal (<28 days): AEs with an observed or imputed date of onset before the first 28 days of life.

Infant (≥28days): AEs with an observed or imputed date of onset on or after the 28 days of life.

Women AE timepoints:

Pregnancy: AEs with an observed or imputed date of onset before the infants' birth, i.e. during pregnancy. An AE with a completely missing, non-imputed start date will be assumed to be a pregnancy AE.

Pre-ocrelizumab postpartum: AEs with an observed or imputed date of onset on or after the infants' birth but before the start date of the first postpartum ocrelizumab infusion.

Post-ocrelizumab postpartum: AEs with an observed or imputed date of onset on or after the start date of the first postpartum ocrelizumab infusion.

Imputation of incomplete date: incomplete dates will be imputed as follows:

- If the start date is incomplete:
  - If the day is missing, impute to 01.
  - If the month is missing, impute to January.
  - If the date is completely missing, then the date will remain missing
- If the end date is incomplete:
  - If the day is missing, impute to the last day of the month
  - If the month is missing, impute to December
  - If the date is completely missing, then the date will be missing

Serious Adverse Events (SAEs): all SAEs including serious MS relapses and serious Infusion Related Reactions (IRRs).

Output Conventions

All analyses of AE data will be performed using the PTs unless otherwise specified.

For all summary tables, the AEs will be sorted by SOC (in decreasing order of overall incidence) and then by PT (in decreasing order of overall incidence). At each level of summarization (at least one event, SOC and PT), subjects reporting more than one AE will be counted only once. For AEs by grade (intensity), the highest grade will be reported.

The following summary tables will be generated for mothers and infants separately:

- Overview summary table of AEs, including: total number of subjects with at least one AE, total number of AEs, total number of deaths, total number withdrawn from study due to an AE, and total number of subjects with at least one:
  - AE with fatal outcome
  - SAE
  - SAE leading to withdrawal from treatment in the mother ("Drug Withdrawn" for the "Action taken with ocrelizumab due to SAE/AE" field in the "Adverse Event/IRR" electronic Case Report Form [eCRF] form)
  - SAE leading to dose modification/interruption in the mother.
  - Related SAE

  - AE leading to withdrawal from treatment in the mother.
  - Time to withdrawal from the study due to an AE from enrollment (in women)
  - Time to withdrawal from the study due to an AE from birth (in infants)
  - AE leading to dose modification/interruption in the mother.
  - Related AE
  - Related AE leading to withdrawal from treatment in the mother.
  - Related AE leading to dose modification/interruption in the mother.
  - AE of Grade ≥ 3
  - Infusion related reaction (IRR) in the mother
  - Serious IRR in the mother
  - Infections (using the MedDRA SOC of 'Infections and Infestations')
  - Serious infections
  - Serious infections leading to withdrawal from treatment in the mother.
- Adverse Events of Special Interest (AESI):
  - Cases of potential medicine-induced liver injury include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law and in the protocol.
  - Suspected transmission of an infectious agent by the study medicine, as defined in the protocol.

All SAEs, AESIs, AEs leading to withdrawal and deaths occurring during the study will be listed.

4.8.3 Laboratory Data

Laboratory assessments (performed in central laboratory, except for urinalysis) will include the following:

- **Haematology (Women)**: 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 (Women):** potassium, sodium, chloride, random glucose, AST, LT, gamma-glutamyl transpeptidase (GGT), total bilirubin and creatinine.
- **Urinalysis (Women):** 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):** Women with positive screening tests for HBV, 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 HBV vaccination or positive HBsAb titers are eligible.

- **Serum immunoglobulin (Ig) concentration (Women)**
- **Serum antibody (IgG) titers to immunizations (Women)** for measles, mumps, rubella, TT, diphtheria, pertussis, varicella zoster, Streptococcus pneumoniae, HBV and SARS-CoV-2 (along with nucleocapsid and spike protein titers; only for those mothers who have received the vaccine, as per local clinical practice) will be performed.
- **Serum antibody (IgG) titers to immunizations (Infant):** May include but not be limited to MMR, DTaP, Hib, PCV-13, and HBV; 1 month after the first dose of MMR vaccine, or at month 13 (±30 days) if MMR vaccine is not planned to be administered.
- **Lymphocyte subtypes (Women and Infant):** Blood samples will be collected to measure B-cell counts (CD19+) and B-cell subsets (Appendix 3), T-cell counts (CD3+, CD4+, CD8+) and natural killer NK cell counts (CD16+, CD56+).
- **Ocrelizumab concentration (Women and Infant):** serum samples will be collected for determination of ocrelizumab concentration.
- **sNfL (Women)**: samples will be collected for determination of sNfL, as described in Section 4.6.5.

4.8.3.1 General laboratory evaluation

All laboratory assessments in the women (hematology, serum chemistry, urinalysis, HBV serology and serum immunoglobulin concentration) will be summarized in the SAFW or listed when applicable.

Absolute values and change from baseline at each visit will be summarized using standard unit. The baseline value for laboratory assessments summarized in women will be the last value prior to the first dose of study medication. When laboratory data are presented over time, these laboratory values will be time-windowed into a common visit structure. If multiple values of the same laboratory parameter occur within the same time window, the worst value for that parameter will be presented in the summary table.

Unless specified otherwise, any laboratory parameters which are BLQ will be listed, for summaries a value of the LLQ/2 will be imputed. Values above the upper limit of quantification will be summarized at the upper limit of quantification.

For hematology and serum chemistry, the number and percentage of patients with normal/abnormal laboratory outcomes based on normal laboratory ranges will be summarized for each parameter and visit. For urinalysis, the number and percentage with each test result category will be reported for each parameter and visit.

Corresponding patient-level listings will be produced for the following in the SAFW: haematology, serum immunoglobin concentration, laboratory abnormalities for

haematology, laboratory abnormalities for serum chemistry, laboratory abnormalities for uinalysis.

4.8.3.2 Lymphocytes evaluation

All lymphocytes parameters (including markers of lymphocyte subtypes [T-, B-, and NK-cells]) but not be limited to CD19+, CD3+, CD4+, CD8+) will be summarized using absolute counts at each visit.

Corresponding listings will also be produced for lymphocyte parameters in infants and women.

Parameters may also be displayed graphically over time, as appropriate.

The primary endpoint analysis of the proportion of infants with B cell levels below the LLN is described in Section 4.4.1.

4.8.3.3 Serum antibody titers evaluation of infant

The secondary endpoint analysis of serum antibody (IgG) titers to immunization in the infant is described in Section 4.4.2.

4.8.4 Vital Signs

The actual value at each visit will be summarized for the following vital signs parameters in women: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min), temperature (ºC).

4.8.5 Neurological Examination

Neurological examination findings will be listed.

4.8.6 Pregnancy outcomes

The pregnancy outcomes including live births (term and preterm), therapeutic abortions and stillbirths will be calculated as follows:

- Pregnancy Interrupted (Yes/No)
- Type of pregnancy outcome (elective abortion, therapeutic abortion, stillbirth, live birth, not applicable)
- Details of interrupted pregnancy (Elective abortion, therapeutic abortion, stillbirth) If termination: reason for termination (prenatal testing finding, maternal health, psychosocial/nonmedical reasons, other)
- Details of non-interrupted live births (vaginal delivery (term), vaginal delivery (pre-term), virginal delivery (forceps/vacuum – instrumental), cesarean (scheduled), cesarean (emergency)
- Gestational age at enrollment
- Gestational age at pregnancy termination
- Gestational age at live birth (absolute values as well as pre/full term)

- Sex
- Singleton pregnancy
- Ultrasound abnormalities detected by trimester
- Presence of congenital anomalies

All pregnancy outcome details will be listed.

4.8.7 Concomitant Medications

Concomitant medications (defined as treatment started after baseline visit) will be summarized, for women and infants separately, by frequency tables according to the ATC classification system using the WHO Drug dictionary during pregnancy and during breastfeeding separately.

4.9 MISSING DATA

All methods for handling missing data and associated sensitivity analyses are described above, section by section, for each endpoint. If not otherwise specified, missing values are not imputed.

4.10 INTERIM ANALYSES

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.

5. REFERENCES

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Appendix 1 Protocol Synopsis

TITLE:	**A PHASE IV, MULTICENTER, OPEN-LABEL STUDY EVALUATING B-CELL LEVELS IN INFANTS POTENTIALLY EXPOSED TO OCRELIZUMAB DURING PREGNANCY – *THE MINORE STUDY***
PROTOCOL NUMBER:	MN42988
VERSION NUMBER:	3
EUDRACT NUMBER:	2021-000062-14
IND NUMBER:	100593
NCT NUMBER:	NCT04998812
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IV
INDICATION:	Multiple Sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Background

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

Objectives and Endpoints

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

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

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

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

STUDY DESIGN

DESCRIPTION OF STUDY

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

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

The study will consist of the following periods.

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

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

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

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

Number of Women

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

End of Study

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

Length of Study

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

Target Population

Inclusion Criteria

Women must meet the following criteria for study entry:

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

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

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

Exclusion Criteria

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

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

Exclusions related to obstetric and gynecological health

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

Exclusions related to general health

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

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

Exclusions related to laboratory findings

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

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

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

Exclusions related to medications

Absolute exclusions

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

Relative exclusions (according to medication washout period)

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

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

STUDIED MEDICINAL PRODUCTS

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

Statistical Methods

Primary Analysis

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

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

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

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

Determination of Sample Size

The study will include approximately *33* pregnant women.

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

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

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

Appendix 2 Schedule of Assessments: Screening Through the End of Treatment Period

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

Appendix 2: Schedule of Assessments: Screening Through the End of Treatment Period

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

Appendix 2: Schedule of Assessments: Screening Through the End of Treatment Period

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

Appendix 2: Schedule of Assessments: Screening Through the End of Treatment Period

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

Mother's assessments Infant's assessments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 3 B-Cell Subsets

- *Naïve 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/Plasma cells: CD45+, CD19+, CD27+, CD38 bright*

Appendix 4 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.

Adapted from: Borriello et al. 2022.

Appendix 5 Non-SARS-CoV-2 Vaccination by Pathogen

Vaccination against	Hepatitis A virus	Hepatitis B virus	Tuberculosis	Tick-borne encephalitis	Typhus	Influenza	Measles	Mumps	Rubella	Varicella zoster	SARS-CoV-2	Diphtheria	Tetanus	B. Pertussis	Polio	Human papillomavirus	Pneumococcus	Meningococcus	Haemophilus influenzae B	Rabies
Labcorp test		anti-HBs					Anti-Measles Vir IgG(-70)CL	Anti-MumpsAT Vir IGG(-70)CL	Anti-Rub Vir IgG(-70)RUOCL	Anti-VZV VirusIgG(-70)RUOCL	SARS-CoV-2	Anti-Diphtheria IgG(-70)CL	Anti-Tetanus Toxoid IgG(-70)RUO	Bordetella pertussis antibodies, IgG			13 Valent anti-pneumococcal antibody panel		Haemophilus influenzae B, IgG	
HEPATITIS B (HEPB)		x																		
INFLUENZA (IIV, IIV3, IIV4, LAIV, LAIV4, RIV3)						x														
MEASLES, MUMPS, AND RUBELLA (MMR)							x	x	x											
MRNA VACCINE											x									
DIPHTHERIA AND TETANUS TOXOIDS, ACELLULAR PERTUSSIS, AND INACTIVATED POLIOVIRUS (DTAP-IPV)												x	x	x	x					
TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID, AND ACELLULAR PERTUSSIS (TDAP)												x	x	x						
DIPTHERIA, TETANUS TOXOID, AND ACELLULAR PERTUSSIS (DTAP)												x	x	x						
DIPTHERIA AND TETANUS TOXOID (DT)												x	x							
PNEUMOCOCCAL 13-VALENT (PCV13)																	x			
HUMAN PAPILLOMAVIRUS (HPV)																x				
PNEUMOCOCCAL 23-VALENT (PPSV23)																	x			
POLIOMYELITIS (IPV)															x					
MENINGOCOCCAL (MENACWY, MENB, MENC, MPSV4)																		x		
HAEMOPHILUS INFLUENZAE TYPE B (HIB)																			x	
HEPATITIS A (HEPA)	x																			
VARICELLA (VAR)										x										
DIPHTHERIA AND TETANUS TOXOIDS, ACELLULAR PERTUSSIS, INACTIVATED POLIOVIRUS, AND HAEMOPHILUS												x	x	x	x				x	
HEPATITIS A AND HEPATITIS B (HEPA-HEPB)	x	x																		
PERTUSSIS ACELLULAR (AP)														x						
DIPHTHERIA AND TETANUS TOXOIDS, ACELLULAR PERTUSSIS, HEPATITIS B, AND INACTIVATED POLIOVIRUS (DTAP-HEPB-IPV)		x										x	x	x	x					
MEASLES AND MUMPS							x	x												
DIPHTHERIA AND TETANUS TOXOIDS, INACTIVATED POLIOVIRUS												x	x		x					
PNEUMOCOCCAL 7-VALENT (PCV7, PCV)																	x			
RUBELLA (RUBE)									x											
TETANUS TOXOID (TT)													x							
TYPHOID					x															
TYPHIM VI VACCINE					x															
TUBERCULOSIS VACCINE			x																	
TUBERCULOSIS			x																	
TICK-BORNE ENCEPHALITIS				x																
TETANUS AND DIPHTHERIA TOXOID (TD)												x	x							
FSME: TICK-BORNE ENCEPHALITIS (TBE)				x																
SHINGRIX										x										
RABIES																				x
BCG VACCINE (TUBERCULOSIS)			x																	
DIPHTERIA, TETANUS, POLIOVIRUS												x	x		x					
DIPHTHERIA, TETANUS, POLIOMYELITIS												x	x		x					
FSME				x																

Appendix 5 Non-SARS-CoV-2 Vaccination by Pathogen (cont.)

Vaccination against	Hepatitis A virus	Hepatitis B virus	Tuberculosis	Tick-borne encephalitis	Typhus	Influenza	Measles	Mumps	Rubella	Varicella zoster	SARS-CoV-2	Diphtheria	Tetanus	B. Pertussis	Polio	Human papillomavirus	Pneumococcus	Meningococcus	Haemophilus influenzae B	Rabies
Labcorp test		anti-HBs					Anti-Measles Vir IgG(-70)CL	Anti-MumpsAT Vir IGG(-70)CL	Anti-Rub Vir IgG(-70)RUOCL	Anti-VZV VirusIgG(-70)RUOCL	SARS-CoV-2	Anti-Diphtheria IgG(-70)CL	Anti-Tetanus Toxoid IgG(-70)RUO	Bordetella pertussis antibodies, IgG			13 Valent anti-pneumococcal antibody panel		Haemophilus influenzae B, IgG	
PFIZER COVID-19 VACCINE											x									
ENCEPUR N : TICK-BORNE ENCEPHALITIS				x																
PFIZER COVID VACCINE											x									
FLU						x														
DT-IPV REVAXIS												x	x		x					
ORAL POLIO VACCINE (OPV)															x					
DIPHTERIA, TETANUS TOXOID, INACTIVED POLIOVIRUS												x	x		x					
DITE POLIO : REVAXIS												x	x		x					
MENINGOCOCCAL SEROGROUP C VACCINE: NEISVAC C																		x		
FSME-IMMUN CC BAXTER				x																
DIPHTHERIA, TETANUS, POLIOVIRUS												x	x		x					
GARDASIL HPV9 NONVALENT																x				
MEASLES, RUBELLA							x		x											
DIPTHERIA, TETANUS TOXOID, POLIOMYELITIS AND ACELLULAR PERTUSSIS (DTAP)												x	x	x	x					
MEASLES, MUMPS, RUBELLA, AND VARICELLA (MMRV)							x	x	x	x										
DIPHTHERIA AND TETANUS TOXOIDS, ACELLULAR PERTUSSIS AND HAEMOPHILUS INFLUENZAE TYPE B (DTAP-												x	x	x	x				x	
DIPTHERIA, TETANUS TOXOID, AND ACELLULAR PERTUSSIS (DTAP)15												x	x	x						
MEASLES, MUMPS, RUBELLA (MMR)							x	x	x											
DIPTHERIA AND TETANUS TOXOID (DT) AND AND INACTIVATED POLIOVIRUS												x	x		x					
ACTIVATED POLIOVIRUS (OPV)															x					
BACILLUS CALMETTE–GUÉRIN			x																	
DIPHTERIA, TETANUS TOXOID, INACTIVE POLIOVIRUS												x	x		x					
MEASLES (MEAS)							x													
DIPTHERIA AND TETANUS TOXOID (DT) AND POLIOMYELITIS												x	x		x					

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