# TITLE PAGE

# STUDY REPORT NO. 1140626

## PASS INFORMATION

| | |
|---|---|
| **TITLE:** | **OCRELIZUMAB PREGNANCY REGISTRY** |
| **PROTOCOL NUMBER (VERSION):** | WA40063 (v2.0) |
| **VERSION NUMBER:** | 1.0 |
| **U.S. POST-MARKETING REQUIREMENT (PMR) NUMBER** | PMR 3194-3 |
| **EMA RWD Catalog (EU PAS REGISTER NUMBER):** | EUPAS31342 |
| **LINK TO STUDY RECORD IN EMA RWD Catalog (EU PAS REGISTER):** | https://catalogues.ema.europa.eu/node/2269/administrative-details |
| **STUDIED MEDICINAL PRODUCT:** | OCREVUS® |
| **AUTHORS:** | F. Hoffmann-La Roche, IQVIA |
| **DATE FINAL:** | See electronic date stamp below |

| Date and Time(UTC) | Reason for Signing | Name |
|---|---|---|
| 23-May-2025 09:56:10 | Company Signatory | [redacted] |
| 23-May-2025 10:17:18 | Company Signatory | [redacted] |

| | |
|---|---|
| **ACTIVE SUBSTANCE** | L04AG08: ocrelizumab |
| **PRODUCT REFERENCE NUMBER:** | RO4964913 |
| **PROCEDURE NUMBER:** | IND 100593; BLA 761053 |
| **JOINT PASS:** | No |
| **RESEARCH QUESTION AND OBJECTIVES:** | To assess and characterize the frequency of maternal, fetal, and infant outcomes among women with multiple sclerosis (MS) exposed to ocrelizumab during the 6 months before the estimated date of last menstrual period (LMP) or at any time during pregnancy.<br><br>The objectives for this study were as follows:<br><br>• To estimate the frequency of selected adverse pregnancy outcomes (i.e., spontaneous abortions, stillbirths, elective or therapeutic terminations, and preterm births) in subjects with MS exposed to ocrelizumab during the defined exposure window.<br><br>• To estimate the frequency of selected adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age (GA), post-natal growth and development, and outcomes related to immune suppression) at birth and through at least the first year of life of infants from pregnancies in subjects with MS exposed to ocrelizumab during the defined exposure window.<br><br>• To compare the maternal, fetal, and infant outcomes of subjects with MS exposed to ocrelizumab with two unexposed control populations: one consisting of subjects with MS who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of subjects without MS. |
| **COUNTRIES OF STUDY POPULATION:** | United States and Germany |

## MARKETING AUTORISATION HOLDER(S)

| | |
|---|---|
| **MARKETING AUTHORIZATION HOLDER (MAH):** | Roche Registration GmbH (RRG)<br>Emil-Barell-Strasse 1<br>D-79639 Grenzach-Wyhlen<br>Germany |
| **MAH CONTACT PERSON:** | [redacted]<br>Genentech, Inc.<br>1 DNA Way<br>South San Francisco, USA, 94080 |

**TABLE OF CONTENTS:**

# 1. SYNOPSIS/ABSTRACT

## TITLE

OCRELIZUMAB PREGNANCY REGISTRY

## KEYWORDS

Multiple sclerosis (MS), ocrelizumab, humanized monoclonal antibody, postmarketing safety, pregnancy.

## RATIONALE AND BACKGROUND

OCREVUS® (ocrelizumab) was approved by the United States Food and Drug Administration (FDA) on 28 March 2017, for the treatment of adult subjects with relapsing forms of MS or primary progressive MS (PPMS). Subsequently, OCREVUS was approved in the European Union (including Germany). Based on pathophysiologic considerations at the time the registry was planned, ocrelizumab was hypothesized to affect pregnancy outcomes and infant outcomes in the following ways:

- By direct exposure of the fetus to ocrelizumab, which is assumed to occur after the 16th week of gestation as receptor-mediated transplacental transfer of immunoglobulin G-1; this is minimal during the first trimester of pregnancy
- Indirectly due to known or unknown infections or infectious complications in the mother exposed to ocrelizumab during pregnancy, which may affect the offspring, where the infection may be associated with ocrelizumab exposure
- Indirectly due to effects of ocrelizumab on the placenta

## RESEARCH QUESTION AND OBJECTIVES

This study aimed to assess and characterize the frequency of maternal, fetal, and infant outcomes among subjects with MS exposed to ocrelizumab during the 6 months before the estimated date of last menstrual period (LMP) or at any time during pregnancy.

## AMENDMENT AND UPDATES TO PROTOCOL

Following the FDA-agreed final Protocol WA40063 (version 1.0, 15 April 2019, IND 100593, SN 0903) to fulfill postmarketing requirement (PMR) 3194-3, Protocol WA40063 (v2.0, 19 January 2020, IND 100593, SN 0942) was amended primarily to clarify that the study will not enroll subjects younger than 18 years old, in accordance with the OCREVUS U.S. Prescribing Information and Summary of Product Characteristics, and to update the study start date and end date.

## STUDY DESIGN

This was a prospective observational study that collected primary data from pregnant subjects with MS from the United States and Germany, who were administered ocrelizumab during the 6 months prior to their LMP or at any time during pregnancy. The internal comparator group consisted of subjects with MS who were pregnant at the time of study entry and who were not exposed to any MS disease-modifying therapies (DMTs) during the 6 months prior to their LMP or at any time during pregnancy (apart from glatiramer acetate [e.g., Copaxone®] exposure through the first trimester).

## SETTING

This study was conducted in Germany and the United States.

## SUBJECT AND STUDY SIZE (INCLUDING DROPOUTS)

In total, there were 455 pregnancies included in the full analysis set in this study, including 226 in the ocrelizumab-exposed group and 229 in the internal comparator group. Among these 455 pregnancies, subjects in 27 pregnancies in the ocrelizumab-exposed group and subjects in 9 pregnancies in the internal comparator group withdrew or were lost to follow-up before the outcome of their pregnancy was observed. As a result, 419 documented pregnancy outcomes were observed, including 199 documented pregnancy outcomes in the ocrelizumab-exposed group and 220 documented pregnancy outcomes in the internal comparator group. The prevalence of major congenital malformations was evaluated among the live-born infants and the fetal deaths from the pregnancies with a documented outcome, including 191 live-born infants and 0 fetal deaths in the ocrelizumab-exposed group and 220 live-born infants and 3 fetal deaths in the internal comparator group.

See Figure 1 in Section 10.1 for full details on attrition from the analytic sets.

## VARIABLES AND DATA SOURCES

Data were obtained from the subjects' or their health-care providers (HCPs) (neurologist, obstetrician, and infant's HCPs [live birth only]).

## RESULTS

### Baseline Characteristics of Subjects with Pregnancies in Ocrelizumab-exposed Group

The mean (SD) age at enrollment was 32.4 years (3.97) among subjects in the 226 pregnancies in the ocrelizumab-exposed group. Among the subjects in 204 pregnancies with documentation of MS type, 198 (97.1%) had a relapsing form of MS. At enrollment, subjects in 20 (8.8% [20/226]) pregnancies had been exposed to prior MS treatments. The majority of subjects (65.0% [147/226]) enrolled during the first trimester of pregnancy; subjects in 140 (61.9% [140/226]) pregnancies had their initial ocrelizumab administration 3 months pre-LMP to first trimester, with a mean (SD) dose of 579.5 mg (76.05).

### Major Congenital Malformations

Using the European Surveillance of Congenital Anomalies (EUROCAT) classification system, the prevalence of major congenital malformations among the 191 live-born infants (no fetal deaths) from pregnancies in the ocrelizumab-exposed group was 6.3% (95% CI: 3.3% to 10.7%). When using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification system the prevalence was 8.4% (95% CI: 4.9% to 13.2%). Details on all major congenital malformations in the ocrelizumab-exposed group can be found in Annex 1, Case Narratives.

### Pregnancy Outcomes

Among the 199 pregnancies in the ocrelizumab-exposed group with a documented outcome, there were 185 (93.0%) live births, 13 (6.5%) spontaneous abortions, and 1 (0.5%) elective or therapeutic termination. Of the 185 live births, 20 (10.8%) were preterm. The 1 elective or therapeutic termination was due to a reason other than a prenatal testing finding. None of the pregnancies with a documented pregnancy outcome resulted in a stillbirth. There were no ectopic or molar pregnancies observed in this study. There were also no maternal deaths or pregnancy-related serious adverse events (SAEs) that resulted in serious disability among subjects with pregnancies in the ocrelizumab-exposed group. None of the pregnancy-related SAEs

observed were related to ocrelizumab exposure according to the reporter. Details on all pregnancy outcomes and pregnancy-related SAEs among pregnancies in the ocrelizumab-exposed group can be found in Annex 1, Case Narratives.

**Infant Outcomes**

Among the 191 live-born infants in the ocrelizumab-exposed group, there were no neonatal, perinatal, or infant deaths observed in this study. Among the 187 infants with documented weight for gestational age (GA), 32 (17.1% [32/187]) were born small for GA. There were 5 (2.7% [5/191]) infants with events reported as adverse infant and childhood outcomes related to immune suppression. Additionally, 39 infants (20.4% [39/191]) experienced serious and severe infections and hospitalizations. None of the infant SAEs were related to ocrelizumab exposure according to the reporter. Details on all infant outcomes, infant SAEs, and infant non-serious adverse events (AEs) among infants from pregnancies in the ocrelizumab-exposed group can be found in Annex 1, Case Narratives.

**Baseline Characteristics of Subjects with Pregnancies in Internal Comparator Group**

The mean (SD) age at enrollment was 32.7 years (3.68) among subjects in the 229 pregnancies in the internal comparator group. At enrollment, subjects in 98 (42.8% [98/229]) pregnancies had been exposed to prior MS treatment. Among the subjects in 227 pregnancies with documentation of MS type, 217 (95.6%) had a relapsing form of MS. The majority of subjects (53.7% [123/229]) enrolled during the first trimester of pregnancy.

**Comparison of Maternal, Fetal, and Infant Outcomes to Comparator Populations**

There were few major congenital malformations among both the ocrelizumab-exposed group (n=12) and the internal comparator group (n=11). The adjusted risk ratio (RR) comparing the prevalence of major congenital malformations among the ocrelizumab-exposed group to the internal comparator group was 1.26 (95% CI: 0.53 to 2.99). The prevalence ratio (PR) comparing the prevalence of major congenital malformations among live births and fetal deaths in the ocrelizumab-exposed group to the EUROCAT external comparator group, was 3.32 (95% CI: 2.16 to 3.32). The PR comparing the prevalence of major congenital malformations among live births in the ocrelizumab-exposed group to the MACDP external comparator group was 3.36 (95% CI: 2.18 to 3.36).

The frequency of spontaneous abortion was higher among pregnancies from the ocrelizumab-exposed group compared to those from the internal comparator group (RR: 3.74; 95% CI: 1.04 to 13.51). No increased frequency in elective or therapeutic termination was observed among pregnancies in the ocrelizumab-exposed group compared to the internal comparator group (RR: 0.26; 95% CI: 0.03 to 2.48).

No increased frequency in adverse infant outcomes was observed among infants in the ocrelizumab-exposed group compared to the internal comparator. The adjusted ratio comparing the frequency of preterm birth among infants from pregnancies in the ocrelizumab-exposed group to the frequency among infants from pregnancies in the overall internal comparator group was 0.97 (95% CI: 0.69 to 1.37). The adjusted ratio comparing the frequency of serious and/or severe infection and hospitalization among infants from pregnancies in the ocrelizumab-exposed group to the frequency among

infants from pregnancies in the overall internal comparator group was 0.93 (95% CI: 0.62 to 1.39).

Details on all pregnancy outcomes, pregnancy-related SAEs, infant outcomes, infant SAEs, and infant non-serious AEs among pregnancies and infants from the internal comparator group can be found in Annex 1, Case Narratives.

## DISCUSSION

Among pregnancies with exposure to ocrelizumab—including those with the initial administration in the 3 months pre-LMP to the end of the first trimester—the frequency of the pregnancy and infant outcomes of interest was low. The majority of pregnancies with a documented outcome (93.0% [185/199]) ended in a live birth. Spontaneous abortions occurred in 6.5% (13/199) of pregnancies. There was 1 elective or therapeutic termination and no fetal deaths/stillbirths, ectopic pregnancies, molar pregnancies, or maternal deaths. Using the EUROCAT classification, the prevalence of major congenital malformations was 6.3% (95% CI: 3.3% to 10.7%) in the ocrelizumab-exposed group overall. At birth, 11.8% (22/187) of infants were low birth weight and 17.1% (32/187) were small for GA. Over the first year of life, 2.6% (5/191) of infants experienced events reported as adverse infant and childhood outcomes potentially related to immune suppression and 1.6% (3/191) had a developmental delay. There were no growth delays or neonatal, perinatal, or infant deaths.

The prevalence of major congenital malformations was higher among pregnancies-exposed to ocrelizumab than those from the general population without MS in the EUROCAT and MACDP external comparator groups. The prevalence of major congenital malformations, however, was not different between pregnancies in the ocrelizumab-exposed group and those in the internal comparator group, suggesting no increased frequency due to ocrelizumab-exposure among subjects with MS.

With the exception of spontaneous abortion, no increased frequency of any of the adverse pregnancy or infant outcomes was observed among ocrelizumab-exposed pregnancies compared to pregnancies in the internal comparator group. The observed increased frequency of spontaneous abortion may be subject to selection bias. Because the majority of spontaneous abortions occur early in pregnancy, and subjects in the ocrelizumab-exposed group tended to enroll in this study earlier in pregnancy than subjects in the internal comparator group, higher likelihood to report spontaneous abortions among the ocrelizumab-exposed group than the internal comparator group.

This was an observational study and, as such, it may be subject to bias. Data of interest may be missing due to lack of capture in routine clinical care or early discontinuation of subjects from the study. The majority of data was obtained directly from subjects and was not clinically validated and may be subject to misclassification. Additionally, subjects with pregnancies that experienced spontaneous, elective, or therapeutic terminations before enrollment were not eligible to participate, which may have resulted in an underestimation of these outcomes. As pregnant subjects in the ocrelizumab-exposed group tended to enroll earlier in pregnancy than those in the internal comparator group, this may have resulted in differential likelihood/opportunity for reporting of the outcomes between the groups.

The estimated risk ratios comparing the outcomes of interest between the ocrelizumab-exposed group and the internal comparator group may be subject to residual confounding. The propensity score model used to estimate the inverse probability of treatment weights (IPTWs) had to be adapted in the final analysis from what was

originally planned due to limitations of the observed data. Specifically, race, ethnicity, and Expanded Disability Status Scale (EDSS) score were excluded from the model because differences in data collection between countries with respect to these variables resulted in substantial missingness and differences in the distribution of available data by country of enrollment, which caused positivity issues and inflated standard errors. Additionally, several prognostic variables were either excluded from the models or combined into a single variable (risk factors) due to sparse data. Finally, the variable for country of enrollment was also excluded from the propensity score model due to the unequal distribution of pregnancies in the internal comparator group by country of enrollment. This unequal distribution caused inflated standard errors in the propensity score model.

The comparison of the prevalence of major congenital malformations between the ocrelizumab-exposed group and the external comparator groups may be subject to confounding as no adjustment was made for differences in population characteristics and risk factors for major congenital malformations between these populations. Comparisons to the Roche MS Study BA39732 MELODIC were not possible as that study was ongoing at the time of this report.

## CONCLUSION

This study fulfilled PMR 3194-3 by conducting a prospective pregnancy registry that compared maternal, fetal and infant outcomes among pregnancies exposed to ocrelizumab with two unexposed control populations of subjects with MS who were not exposed to DMTs and to subjects without MS. With the exception of a low imbalanced frequency of spontaneous abortions, which may be due to selection bias, no increased frequency of adverse pregnancy outcomes was observed. Additionally, no increased frequency of major congenital malformations, minor congenital malformations, and adverse infant outcomes were observed relative to the internal comparator group.

## MARKETING AUTHORISATION HOLDER(S)

Roche Registration GmbH (RRG)
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

## NAMES AND AFFILIATIONS OF PRINCIPAL INVESTIGATORS

Dr. Joan Largent
IQVIA
4820 Emperor Blvd.
Durham, NC 27703
U.S.A.

Site: 325273

Dr. Maria Houtchens
Brigham and Women's Hospital
Partners Multiple Sclerosis Center
60 Fenwood Road, Suite 4084
Boston, MA 02115
U.S.A.

Site: 325274

Prof. Dr. Kerstin Hellwig
Katholisches Klinikum gGmbH
NEUROLOGISCHE Universitätsklinik
St. Josef Hospital, Gudrunstrasse 56, 44791 Bochum
Germany

Site: 325272