Design of a Multi-Source Post-Marketing Study to Evaluate Pregnancy and Infant Outcomes in Women With Multiple Sclerosis Who Were Exposed to Ocrelizumab During, or Within 6 Months Before, Pregnancy

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BACKGROUND

- Ocrelizumab (OCR) is a recombinant, humanized, monoclonal immunoglobulin G1 antibody that selectively targets CD20⁺ B cells
- Immunoglobulins such as OCR do not cross the placenta during the first trimester of pregnancy, but transfer of OCR can occur thereafter¹
- The safety profile of OCR has been investigated in multiple clinical trials and although the use of effective contraception was mandatory, 25 pregnancies have been reported in women with multiple sclerosis (MS) receiving OCR during these trials up to the end of January 2017; in 14 of these 25 pregnancies, the fetuses were considered to have been exposed to OCR²
- The small number of pregnancies and pregnancy outcomes² that have been reported from clinical trials means the safety profile of
- OCR in pregnancy and fetal outcomes has yet to be established Therefore, and as part of post-marketing activities, this study has been designed to provide a greater degree of information to patients and clinicians
- OCR has an average terminal half-life of 26 days,³ and based on the estimated elimination rates after the last administration, the current European and FDA label information states "Women of child bearing potential should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab"³ and "You should use birth control (contraception) during treatment with ocrelizumab and for 6 months after your last infusion of ocrelizumab",⁴ respectively

OBJECTIVE

• To assess the pregnancy and infant safety of OCR after maternal use in the 6 months before or during pregnancy in the setting of routine healthcare

METHODS

Study Objectives

- To characterize pregnancy and infant outcomes of women with MS exposed to OCR during the 6 months before the estimated date of conception or at any time during pregnancy, including:^a
- —The frequency of selected adverse pregnancy outcomes (e.g. spontaneous abortions, stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections)
- The frequency of selected adverse fetal/neonatal/infant outcomes (e.g. major congenital malformations, small for gestational age, adverse effects on immune system development [adverse effects on immune system development] include hospitalizations due to infectious diseases, cancer, and vaccinepreventable diseases and vaccine-associated poliomyelitis]) at birth and through at least the first year of life of infants
- This study will compare the frequency of each safety event of interest between OCR-exposed pregnant women with MS and two comparison cohorts

^aProtocol number BA39732. The final study design may be amended based on any further discussions with the regulatory authorities.

Study Design

- The study will be conducted in existing population-based healthcare databases and registries (Figure 1)
- The study cohorts will include (**Table 1 and Figure 2**):
- OCR-exposed pregnancies in women with MS
- Pregnancies not exposed to OCR in women with MS
- Pregnancies not exposed to OCR in women without MS

DISCLOSURES

AV Margulis, E Andrews and E Rivero-Ferrer work for RTI Health Solutions, a business unit of RTI International is an independent, nonprofit research organization that conducts work for government, public and private organizations, including 1. Kane SV, Acquah LA. Am J Gastroenterol 2009;104:228–233; 2. Vukusic S, et al. ECTRIMS/ACTRIMS 2017; Poster presentation P710; 3. EMEA. Ocrevus (ocrelizumab). Summary of Product Characteristics. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/ pharmaceutical companies. Our organization (RTI Health Solutions) received contract funding from Roche, with retention of independent publication rights. S Hernandez-Diaz reports funding from Pfizer, GSK and Lilly. M Magyari has served on scientific advisory boards for Biogen, Sanofi, Teva, Roche, medicines/004043/human med 002187.jsp&mid=WC0b01ac058001d124; 4. FDA. OCREVUS[™] (ocrelizumab). Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda docs/nda/2017/761053Orig1s000Lbl.pdf; 5. Data from Optum DAPI provided by Optum; Novartis, Merck, has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, Teva, Roche. S Bader-Weder is an employee and shareholder of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche 6. FDA. Establishing Pregnancy Exposure Registries. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071639.pdf; 7. CDC. MMWR Morb Mortal Wkly Rep. 2008;57:1–5; 8. MacDorman MF, Gregory EC. Natl Vital Stat Rep. 2015;64:1–24; 9. CDC. Products Ltd and shareholder of F. Hoffmann-La Roche Ltd. M Garas is an employee and shareholder of F. Hoffmann-La Roche Ltd. Q Wang is an employee of F. Hoffmann-La Roche Ltd. D Wormser is an employee and shareholder of F. Hoffmann-La Roche Ltd. Available at: https://www.cdc.gov/ncbddd/heartdefects/data.html; 10. CDC. Available at: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm; 11. Rothman KJ. Episheet. Available at: http://www.krothman.org/episheet.xls; 12. Wormser D, et al. AAN 2018 Abstract P4.367.





Table 1. Description of study cohorts Secondary comparison cohort **Exposed cohort Primary comparison cohort** mother and infants is required Comparison subcohort 1b subcohort 1a Target study size (n) 300 900 300 Cohort Pregnancies in women without MS or OCR use Pregnancies in women at 1 year of age with MS exposed to non- with MS not exposed to definition with MS and exposure OCR DMTs approved for DMTs approved for the to OCR treatment of MS **MS diagnosis** Required Absence of diagnosis Required Required pregnancy, infections requiring hospitalization in pregnancy) No use of OCR in Use of MS o use of DMTs the 6 months before the 6 months before therapies in the 6 months before the 6 months before pregnancy or any tim during pregnancy Table 2. Relative risk of major malformations excluded under two pregnancy or any time pregnancy or any time pregnancy or any time during pregnancy during pregnancy during pregnancy assumptions of pregnancies ending in live births No use of OCR in he 6 months befor DMT, disease-modifying therapy; MS, multiple sclerosis; OCR, ocrelizuma

Figure 1. Healthcare databases and registries included in the study



Figure 2. Study flow **C-section** gnancy outcomes Elective termination (linkage to infants Urinary tract infection^a not required) **Pregnancies in women with MS** Fetal death/stillbirth and exposure to OCR ections requiring hospitalizatio **Preterm birth** Pregnancies in women with MS exposed to non-OCR DMTs MCMs Pregnancies in women without MS Infant growth^c Specific categories of MCN Infant outcomes linkage to infants Infant development Minor malformation Adverse effects on the immune system^d Small for gestational age linkage

^aDuring pregnancy; ^be.g. cardiovascular. Additionally, specific malformations will be explored depending on the number of events observed (e.g. hypospadias, cleft lip with or without cleft palate, and cardiac malformations [or subtypes]). MCMs are not expected through direct effects of the drug, as transplacental transfer of IgG1 is minimal before the 16th week of gestation; Length, weight, and head circumference including measurements at birth and during follow-up, will be explored where ations due to infectious diseases, stratified by neonatal infections (within 28 days of birth) and later infections. The rationale for this stratification is that fever in neonates generally triggers a much more intensive sepsis workup; dany cancer, including leukemia; vaccine-preventable diseases and vaccine-associated poliomyelitis in the first year of life. An event will be considered to be a study outcome only if diagnosed between first immunization and 1 year of age. DMT, disease-modifying therapy; IgG, immunoglobulin; MCM, major congenital malformation; MS, multiple sclerosis; OCR, ocrelizumab.

Eligibility Criteria

- The study population includes women from the three study cohorts and their children born during the study period (Figure 3)
- —Women with continuous enrollment with pharmacy benefits in the 6 months before the estimated beginning of pregnancy and throughout pregnancy — Children with continuous enrollment covering outpatient care and hospitalizations during follow-up

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- For pregnancy outcomes, linkage to infants is not required (i.e. pregnancies) Study Size not linked to infants will be retained); for infant outcomes, linkage between the The target for this study will be approximately 300 pregnancies exposed to OCR and 900 pregnancies in each of the two comparator cohorts
- Based on this target, **Table 2** outlines the relative risks that can be excluded Follow-up of women will start at the estimated beginning of pregnancy and will for major malformations combined under two assumptions of the number of finish at the end of pregnancy; follow-up of infants will start at birth and finish pregnancies ending in live birth estimates
- For each outcome of interest that can occur multiple times, follow-up for that outcome will stop at its first occurrence (e.g. urinary tract infections in

	Estimated pregnancies ending in live birth 83.6% ⁵		Estimated pregnancies ending in live birth 62% ⁶	
Cohort (target number of pregnancies)	OCR exposed (300)	Comparator (900)	OCR exposed (300)	Comparator (900)
Number of live births accrued (% of target)	250 (83%)	750 (83%)	186 (62%)	558 (62%)
Estimated number of linked records ^a (% of target)	215 (72%)	645 (72%)	160 (53%)	480 (53%)
Exclusion of RR if true RR is 1	≥3.5 ^b		≥4.3 ^b	

^aIt is expected that 86% of live births will be linked to infant records:⁵ ^bBased on a baseline prevalence of major malformations combined of approximatel 3% of live births.7 OCR. ocrelizumab: RR. relative risk.

Table 3. Study size required to have 80% probability that the upper limit of the 95% CIs will be below selected thresholds

Outcome	Prevalence of outcome in background population	Upper limit of 95% CI for RR will be less than:	Exposed/unexposed pregnancies needed
Stillbirth	6 per 1,000 ⁸	11 8 5	300:900 400:1,200
		5 3	1,440:4,320
Cardiac congenital malformations	1% ⁹	12.8	160:480
		9.0	215:645
		6.5	300:900
		5	400:1,200
		4	540:1,620
Major congenital malformations (combined)	3%7	5	130:390
		4.3	160:480
		4	177:531
		3.5	215:645
		3	280:840
		2.9	300:900
		2.5	405:1,215
		2	705:2,115
Preterm birth	10% ¹⁰	5	37:111
		4	50:150
		3	80:240
		2.2	160:480
		2.0	215:645
		1.9	250:750
		1.8	300:900
		1.5	575:1,725

Note: Assumptions underlying these calculations No difference in risk between the exposed and unexposed (i.e. risk ratio = 1), regardless of comparison cohort (women with MS without OCR exposure,

women without MS)

Matching ratio of exposed to unexposed was 1:3

Probability that the upper limit of 95% CI will be as stated = 0.8

 Calculations were done using the "Study Size" tool in Episheet.¹ MS, multiple sclerosis; OCR, ocrelizumab; RR, relative risk

REFERENCES



• For outcomes that are more common than 3%, such as preterm birth or spontaneous abortions (for which linkage to infant records is not needed), the study will be able to exclude lower levels of increased risk, assuming the true relative risk is 1; estimations for less common outcomes are provided in **Table 3**

Data Analysis

- Results will be presented separately for each data source
- Overall results (e.g. odds ratios for major congenital malformations) will be summarized using meta-analytic techniques
- Data analysis will be performed by data custodians at their sites and behind firewalls, and individual-level data will not be available for data integration

RESULTS

- The study period will start from the first dispensing/prescription of OCR in the participating data sources (approved in the US in 2017 and in Denmark in 2018; **Figure 3**)
- The number of OCR-exposed pregnancies and live births will be monitored yearly to inform the study size, and data extraction from the first data source is anticipated in Q1 2022, a minimum of 4 years after data accrual in the first data source • The planned end of study date is Q1 2023, following which, results will be prepared for dissemination to the MS community

Figure 3. Study timelines



OCR, ocrelizumat

CONCLUSIONS

- This study will complement the planned Ocrelizumab Pregnancy Registry (see Poster 367)¹² and address some known limitations of registries (e.g. slow enrollment, loss to follow-up), while generating important information on pregnancy and fetal outcomes following exposure to ocrelizumab
- This information will be useful in guiding discussions between healthcare providers and women who may have been exposed to ocrelizumab before or during pregnancy

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