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

AV Margulis,[1] EB Andrews,[2] S Hernandez-Diaz,[3] M Magyari,[4] E Rivero-Ferrer,[1] S Bader-Weder,[5] J Evershed,[6] M Garas,[5] Q Wang,[5] D Wormser[5]

[1]RTI Health Solutions, Barcelona, Spain; [2]RTI Health Solutions, Research Triangle Park, NC, USA; [3]Harvard University, Boston, MA, USA; [4]Danish Multiple Sclerosis Center, Copenhagen University Hospital, Copenhagen, Denmark; [5]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [6]Roche Products Ltd, Welwyn Garden City, UK

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 thereafter[1]
- 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 OCR[2]
- The small number of pregnancies and pregnancy outcomes[2] 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

[2]Vukusic S, et al
ECTRIMS 2017

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 vaccine-preventable 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

[a]Protocol 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

Table 1. Description of study cohorts

	Exposed cohort	Primary comparison cohort		Secondary comparison cohort
		Comparison subcohort 1a	Comparison subcohort 1b	
Target study size (n)	300	900		300
Cohort definition	Pregnancies in women with MS and exposure to OCR	Pregnancies in women with MS exposed to non-OCR DMTs approved for the treatment of MS	Pregnancies in women with MS not exposed to DMTs approved for the treatment of MS	Pregnancies in women without MS or OCR use
MS diagnosis	Required	Required	Required	Absence of diagnosis required
Use of MS therapies	Required: use of OCR in the 6 months before pregnancy or any time during pregnancy	Required: use of DMTs in the 6 months before pregnancy or any time during pregnancy No use of OCR in the 6 months before pregnancy or any time during pregnancy	No use of DMTs in the 6 months before pregnancy or any time during pregnancy	No use of OCR in the 6 months before pregnancy or any time during pregnancy

DMT, disease-modifying therapy; MS, multiple sclerosis; OCR, ocrelizumab.

Figure 1. Healthcare databases and registries included in the study

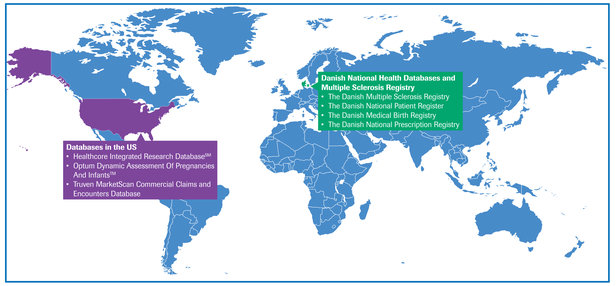
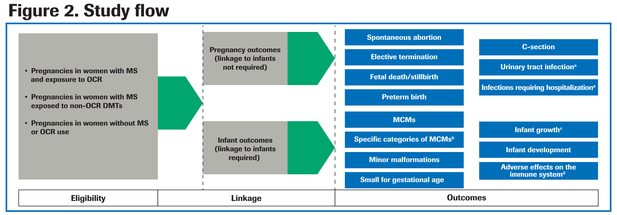


Figure 2. Study flow



[a]During pregnancy; [b]e.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; [c]Length, weight, and head circumference including measurements at birth and during follow-up, will be explored where available; [d]Hospitalizations due to infectious diseases, stratified by neonatal infections (within 28 days of birth) and later infections. The rationale for this stratification is that fewer in neonates generally triggers a much more intensive sepsis workup; [e]any 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
- For pregnancy outcomes, linkage to infants is not required (i.e. pregnancies not linked to infants will be retained); for infant outcomes, linkage between the mother and infants is required
- Follow-up of women will start at the estimated beginning of pregnancy and will finish at the end of pregnancy; follow-up of infants will start at birth and finish at 1 year of age
- 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 pregnancy, infections requiring hospitalization in pregnancy)

Table 2. Relative risk of major malformations excluded under two assumptions of pregnancies ending in live births

	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]	

[a]It is expected that 86% of live births will be linked to infant records;[5] [b]Based on a baseline prevalence of major malformations combined of approximately 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	300:900
		8	400:1,200
		5	675:2,025
		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.[11]

MS, multiple sclerosis; OCR, ocrelizumab; RR, relative risk.

Study Size

- 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 for major malformations combined under two assumptions of the number of pregnancies ending in live birth estimates
- 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**

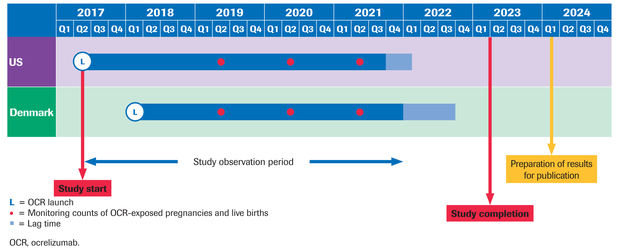
Data Analysis

- 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, ocrelizumab.

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

ACKNOWLEDGMENTS

We would like to thank John Seeger and Anita Loughlin from Optum, Mette Nørgaard from Aarhus University, and Daina Esposito and Vibha Desai from HealthCore for their contributions to the design of this study. This research is being funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing and editorial assistance for this presentation was provided by Articulate Science, UK, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

DISCLOSURES

AV Margulis, E Andrews and E Rivero-Ferrer work for RTI Health Solutions, a business unit of RTI International, which has been compensated for this research. RTI International is an independent, nonprofit research organization that conducts work for government, public and private organizations, including 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, Novartis, Merck, has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, has received support for congress participation from Biogen, Genzyme, Teva, Roche. S Bader-Weder is an employee and shareholder of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche 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.

REFERENCES

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/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; 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. 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.