OCREVUS® (Ocrelizumab)
Konzentrat zur Herstellung einer Infusionslösung, 300mg/10ml
Zul.-Nr. 66185
Injektionslösung zur subkutanen Anwendung, 920mg/23ml
Zul.-Nr. 68988

Public Risk Management Plan (RMP) Summary

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Ocrevus” is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Ocrevus” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Roche Pharma (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ocrevus.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR OCREVUS (OCRELIZUMAB)

This is a summary of the risk management plan for ocrelizumab. The risk management plan details important risks of ocrelizumab, how these risks can be minimized, and how more information will be obtained about ocrelizumab risks and uncertainties (missing information).

Ocrelizumab summary of product characteristics and its package leaflet give essential information to healthcare professionals and patients on how ocrelizumab should be used.

This summary of the risk management plan for ocrelizumab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of the ocrelizumab risk management plan.

I. THE MEDICINE AND WHAT IT IS USED FOR

Ocrelizumab is authorized for the treatment of relapsing and primary progressive forms of multiple sclerosis (see EU Summary of Product Characteristics for the full indication). It contains ocrelizumab as the active substance and it is given by intravenous or subcutaneous route.

Further information about the evaluation of ocrelizumab benefits can be found in ocrelizumab European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/ocrevus

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ocrelizumab, together with measures to minimize such risks and the proposed studies for learning more about ocrelizumab risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and summary of product characteristics addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ocrelizumab is not yet available, it is listed under 'missing Information' below.

II.A List of Important Risks and Missing Information

Important risks of ocrelizumab are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ocrelizumab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation) • Infections
Important potential risks	• Malignancies including breast cancer • Progressive multifocal leukoencephalopathy
Missing information	• Safety in pregnancy and lactation • Long-term safety of ocrelizumab treatment • Safety in pediatric population

IV = intravenous; SC = subcutaneous.

II.B Summary of Important Risks

Important identified risk: Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, MA30143 substudy, CN41144, and CN42097.
Risk factors and risk groups	Symptoms of injection reactions have been more frequently reported with the first injection. Reactions related to infusion of ocrelizumab occur most often at the first infusion in patients who have not had this type of infusion before. In patients who receive ocrelizumab, the risk of infusion-related reactions was reduced by 2-fold or more when both oral antihistamine and methylprednisolone were administered before the infusion, compared with methylprednisolone alone (with the exception of Dose 1, infusion 2). Adding analgesics/antipyretics to oral histamines did not appear to have additional benefit. Dosing intervals other than every 6 months have not been systematically studied in multiple sclerosis patients and it is not known whether delaying dosing beyond the 6-month dosing schedule would be associated with an increased likelihood of infusion-related reactions beyond what was observed with the first infusion. The low number of patients with treatment-induced anti-drug antibodies did not allow for an evaluation of the impact of anti-drug antibodies on rate and intensity of infusion-related reactions.
Risk minimization measures	**Routine risk communication:** Section Posology and method of administration, Section Warnings and precautions and Section Undesirable effects in the Swiss Product Information includes more detailed information. **Routine risk minimization activities recommending specific clinical measures to address the risk:** **Injection reactions (observed with SC formulation)** • Shortly before injection, patients should receive premedication to reduce the potential for occurrence of injection reactions. • Physicians should alert patients that injection reactions can occur within 24 hours of injection. • Patients should be observed for at least one hour after the initial dose of the medicinal product for any symptom of severe injection reactions. • Appropriate resources for the management of severe reactions of severe injection reactions, hypersensitivity reactions and/or anaphylactic reactions should be available for the initial dose of the medicinal product.

Important identified risk: Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	
	Infusion-related reactions (observed with the IV formulation • Withholding of medicines for high blood pressure should be considered for 12 hours prior to and throughout each ocrelizumab infusion. • Treatment with other medicines such as corticosteroid and antihistamine to prevent or reduce possible side effects such as infusion-related reactions are required before each infusion; you may also receive medicines used to reduce fever. • Appropriate resources should be available for the management of severe reactions such as serious infusion-related reactions, or allergic reactions to ocrelizumab or any of the other ingredients of this medicine. • Patients should be observed for at least one hour after the completion of the ocrelizumab infusion for any symptom of infusion-related reaction. Physicians should alert patients that an infusion-related reaction can occur within 24 hours of infusion. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** **SC formulation**: Treatment with ocrelizumab should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions. **IV formulation**: Treatment with ocrelizumab should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions. Ocrelizumab is a medicinal product subject to restricted medical prescription that applies to IV and SC formulation.
	Additional risk minimization measures: • Healthcare Provider Brochure • Patient Brochure
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

IV = intravenous; SC = subcutaneous.

Important identified risk: Infections	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, ML29966,

Important identified risk: Infections	
	MN39158, MA30143, CN41144, and CN42097.
Risk factors and risk groups	Previous or concomitant medicines that affect the immune system such as chemotherapy, immunosuppressants or other medicines used to treat multiple sclerosis can be important contributing factors. Exploratory analyses were carried out in order to identify prognostic and treatment-emergent risk factors for infections and serious infections. Risk factors for serious infections were only explored for rheumatoid arthritis because event numbers were too low in the multiple sclerosis studies. Data from the rheumatoid arthritis cohort indicated that ocrelizumab treatment might increase the risk of serious infections for patients from Asia on long term steroid treatment, notably on the ocrelizumab 1000 mg dose. However, these observations do not reach statistical significance and are confounded with Asian region, which cannot be correlated with Asian ethnicity, lower body weight, as well as increased treatment with the drug. In the multiple sclerosis population, where patients were treated with ocrelizumab as monotherapy, there was no imbalance in serious infections observed. Of note, in the multiple sclerosis clinical program, the population only received intermittently corticosteroids for symptomatic treatment of relapse, and included a very low number of Asian patients, with no clinical sites in Asia. In the multiple sclerosis studies, mean and median levels of neutrophils (a type of white blood cell) did not change during treatment with ocrelizumab. Most events were of Grade 1 (mild) and 2 (moderate) neutropenia (low numbers of neutrophils) without any temporal pattern associated with infections. Anti-CD20 antibody therapy may trigger Hepatitis B virus reactivation in patients with a history of Hepatitis B virus infection. However, no such reports in multiple sclerosis patients treated with ocrelizumab were reported. Similarly, immunomodulatory therapy may trigger reactivation of hidden herpes virus in patients who had a herpes infection in the past.
Risk minimization measures	**Routine risk communication:** Section 4.3 of the European Union Summary of Product Characteristics – Contraindications Section 4.4 of the European Union Summary of Product Characteristics – Special warnings and precautions for use Section 4.8 of the European Union Summary of Product Characteristics – Undesirable effects Section 2 and 4 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • An active infection must be excluded prior to ocrelizumab administration because the infusion must be delayed in patients with an active infection until the infection is resolved. • It is recommended to verify the patient's immune status before dosing since patients with a severely weakened immune system should not be treated.

Important identified risk: Infections	
	• Physicians should take prompt action for patients presenting with pneumonia (lung infection) because there may be an increased risk of aspiration pneumonia (a type of lung inflammation that is due to material from the stomach or mouth entering the lungs) and severe pneumonia in patients treated with ocrelizumab. • Hepatitis B virus screening should be performed before initiation of treatment with ocrelizumab as per local guidelines because patients with active Hepatitis B virus infection should not be treated with ocrelizumab. Patients with positive serology (blood serum diagnostic); carriers of Hepatitis B virus should be referred to a liver disease expert before start of treatment and should be monitored and managed following local medical standards to prevent Hepatitis B reactivation. • For progressive multifocal leukoencephalopathy (a rare and life-threatening brain infection), see under respective risk. Section 4.3 of the European Union Summary of Product Characteristics – (Contraindications) and Section 4.4 (Special warnings and precautions for use) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730, Study WA40404 See section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk: Malignancies including breast cancer	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, MA30143, MN39158, MN39159, ML29966, CN41144, and CN42097.
Risk factors and risk groups	In nonclinical safety studies (animal studies) with ocrelizumab, no risk factors that are considered predictive of cancer (e.g., chronic inflammation, unusual cell proliferation, or dysplasia) were identified. No risk factors for cancers, including breast cancer, specific to the multiple sclerosis population have been identified in clinical studies with ocrelizumab. There is no evidence that switching from other disease-modifying therapies increases the risk for cancer.

Important potential risk: Malignancies including breast cancer	
Risk minimization measures	**Routine risk communication:** Section 4.3 of the European Union Summary of Product Characteristics – Contraindications Section 4.4 of the European Union Summary of Product Characteristics – Special warnings and precautions for use Section 5.3 of the European Union Summary of Product Characteristics – Preclinical safety data Section 2 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Patients should be asked whether they have an active cancer, are actively being monitored for a cancer, or have known risk factor for cancer, because patients with a known active cancer should not be treated with ocrelizumab, and individual benefit risk should be considered in patients with known risk factors for cancers and in patients who are being actively monitored for recurrence of cancer. Patients should be instructed to follow standard breast cancer screening per local guidelines. Section 4.3 of the European Union Summary of Product Characteristics – (Contraindications) and Section 4.4 (Special warnings and precautions for use) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730, Study WA40404 See section II. C of this summary for an overview of the post-authorization development plan.

Important potential risk: Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, ML29966, MN39158, MN39159, MA30143, CN41144, and CN42097.

Important potential risk: Progressive multifocal leukoencephalopathy	
Risk factors and risk groups	Primary infection with or reactivation of the JC-Virus, a polyoma virus that resides in hidden form in approximately 50% of patients with multiple sclerosis, can lead to a rare and life-threatening viral brain infection called progressive multifocal leukoencephalopathy (PML). PML has been observed very rarely in patients treated with anti-CD20 antibodies, including ocrelizumab, and has mostly been associated with the presence of risk factors (patient population e.g., lymphopenia, advanced age or polytherapy with immunosuppressants). To date, no specific risk factors associated with anti-CD20 monoclonal antibodies have been identified (e.g., prolonged exposure) beside the known risk factors. The main risk factor for PML in patients with multiple sclerosis is previous exposure to natalizumab. The risk of PML is lowest among patients negative for anti-JC-Virus antibodies, and highest in patients positive for anti-JC-Virus antibodies, who had taken immunosuppressants before commencing natalizumab treatment, and who had received 25 to 48 months of natalizumab therapy. The risk of PML increases with the number of natalizumab infusions given. Natalizumab-treated patients with prior hematopoietic stem cell transplantation (a procedure in which a person receives blood-forming stem cells [cells from which all blood cells develop] from a genetically similar, but not identical, donor) may also be at an increased risk. The European Medicines Agency recommendations to minimize the risk of PML with natalizumab outline that in patients who have not been treated with immunosuppressants before starting natalizumab, the level of anti-JC virus antibodies relates to the level of risk for PML. The patients with a high antibody level who have not used immunosuppressants before natalizumab and have been treated with natalizumab for more than 2 years are considered at higher risk of PML. The mechanisms by which natalizumab increases the risk of PML are unknown but may involve an altered trafficking of lymphoid cells harboring latent JC-Virus, decreased immune surveillance, or a combination of these processes. A PML risk has also been associated with other multiple sclerosis disease-modifying therapies, including fingolimod and dimethyl fumarate.
Risk minimization measures	**Routine risk communication**: Section 4.4 of the European Union Summary of Product Characteristics – Special warnings and precautions for use Section 2 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Physicians should be alert for the early signs and symptoms of PML (a rare and life-threatening viral brain infection) which can include any new onset, or worsening of neurological signs or symptoms (such as memory lapses, trouble thinking, difficulty walking, sight loss, changes in the way of talking). If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including magnetic resonance imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebrospinal fluid testing for JC Viral Deoxyribonucleic

Important potential risk: Progressive multifocal leukoencephalopathy	
	acid presence, and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently. As for any other active infection, current PML is a contraindication for treatment with ocrelizumab. Section 4.3 of the European Union Summary of Product Characteristics – (Contraindications) and Section 4.4 (Special warnings and precautions for use) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status***: Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730 See section II.C of this summary for an overview of the post-authorization development plan.

CD20 = cluster of differentiation 20; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Important potential risk: Hepatitis B Reactivation*	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, MA30143 substudy, CN41144, and CN42097
Risk factors and risk groups	Reactivation of hepatitis B refers to the abrupt increase in hepatitis B virus (HBV) replication in a patient with inactive or resolved hepatitis B. Reactivation can occur spontaneously, but more typically is triggered by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation. Hepatitis B virus (HBV) reactivation has been reported in ocrelizumab post-marketing treatment experience. Fulminant hepatitis, hepatic failure and death, has been reported in patients treated with other anti-CD20 antibodies. The majority of patients received Rituximab in combination with chemotherapy.

Important potential risk: Hepatitis B Reactivation*	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, MA30143 substudy, CN41144, and CN42097
Risk minimization measures	**Routine risk communication:** Section Posology and method of administration, Section Warnings and precautions and Section Undesirable effects in the Swiss Product Information includes more detailed information **Routine risk minimization activities recommending specific clinical measures to address the risk:** • An active infection must be excluded prior to ocrelizumab administration because the infusion must be delayed in patients with an active infection until the infection is resolved. • It is recommended to verify the patient's immune status before dosing since severely immunocompromised patients should not be treated. • HBV screening should be performed before initiation of treatment with ocrelizumab as per local guidelines because patients with active HBV infection should not be treated with ocrelizumab. Patients with positive serology; carriers of HBV should be referred to a liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Ocrelizumab is a medicinal product subject to restricted medical prescription that applies to IV and SC formulation. **Additional risk minimization measures:** • Healthcare Provider Brochure • Patient Brochure
Additional pharmacovigilance activities	Study BA39730 Study WA40404

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Missing information: Safety in pregnancy and lactation	
Risk minimization measures	**Routine risk communication:** Section 4.4 of the European Union Summary of Product Characteristics - Special warnings and precautions for use Section 4.6 of the European Union Summary of Product Characteristics - Section 4.6 Fertility, pregnancy and lactation Section 5.3 of the European Union Summary of Product Characteristics - Preclinical safety data Section 2 of the European Union Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Women of childbearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab. • For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunisation response. • Women should be advised to discontinue breast-feeding during ocrelizumab therapy. Section 4.4 of the European Union Summary of Product Characteristics (Special warnings and precautions for use) and Section 4.6 (Fertility, pregnancy and lactation) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status***: Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39732 See section II. C of this summary for an overview of the post-authorization development plan.

Missing information: Long-term safety of ocrelizumab treatment	
Risk minimization measures	**Routine risk communication:** Section 3 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730, Study WA40404 See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Safety in pediatric population	
Risk minimization measures	**Routine risk communication:** Section 4.2 of the European Union Summary of Product Characteristics Posology and method of administration Section 2 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

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II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of ocrelizumab.

II.C.2 Other studies in post-authorization development plan

Study short name: BA39730- A long-term surveillance of ocrelizumab-treated patients with multiple sclerosis

Purpose of the study:

The primary objective is:

- To estimate (overall and by multiple sclerosis [MS] type) the event rates of serious adverse events, including malignancy and serious infections, following ocrelizumab treatment in patients with MS.

The secondary objective is:

- To compare the incidence of each serious safety event between ocrelizumab-exposed patients with relapsing forms of multiple sclerosis (RMS) and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source.

If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with primary progressive multiple sclerosis (PPMS) exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.

Study short name: BA39732 - A multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis.

Purpose of the study:

The objectives are as follows:

- To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, fetal death/stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy)
- To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab—i.e., major congenital malformations, small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life)

- To compare the frequency of each safety event of interest between ocrelizumab-exposed pregnant women with MS and two comparison cohorts:

– (1) primary comparison cohort—pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to any non-ocrelizumab DMTs approved for the treatment of MS or any new DMT approved during the study period [subcohort 1a], and pregnancies not exposed to these DMTs [subcohort 1b])

– (2) secondary comparison cohort—pregnancies in women without MS who have not been exposed to ocrelizumab.

Study short name: WA40404 A Phase IIIb multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis.

Purpose of the study:

To evaluate the safety and efficacy of ocrelizumab compared with placebo in patients (with Expanded Disability Status Scale score 3 to 8) using the 9-Hole Peg Test as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint.

Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gadolinium-enhancing magnetic resonance imaging lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles.