OCREVUS® 920 MG SC

Ocrelizumab
Solution for injection

NAME OF THE MEDICINAL PRODUCT
OCREVUS 920 MG SC

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 920 mg of ocrelizumab in 23 mL at a concentration of 40 mg/mL.

Ocrelizumab is a recombinant humanised anti-human CD20 monoclonal antibody produced in Chinese Hamster Ovary cell lines by recombinant DNA technology.

For the full list of excipients, see section 11.

PHARMACEUTICAL FORM
Solution for injection.

Clear to slightly opalescent, and colourless to pale brown solution.

CLINICAL PARTICULARS

1 INDICATIONS AND USAGE

OCREVUS 920 MG SC is indicated for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

OCREVUS 920 MG SC is for subcutaneous use in the abdomen only.

OCREVUS 920 MG SC has different dosage and administration instructions than intravenous ocrelizumab.

OCREVUS 920 MG SC should be administered via subcutaneous injection by a healthcare professional.

2.2 Assessments Prior to First Dose of OCREVUS 920 MG SC

Hepatitis B Virus Screening

Prior to initiating ocrelizumab treatment, perform Hepatitis B virus (HBV) screening. OCREVUS 920 MG SC is contraindicated in patients with active HBV confirmed by positive results for HBsAg and anti-HBV tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment *[see Warnings and Precautions (5.2)]*.

Serum Immunoglobulins

Prior to initiating ocrelizumab treatment, perform testing for quantitative serum immunoglobulins *[see Warnings and Precautions (5.4)]*. For patients with low serum immunoglobulins, consult immunology experts before initiating treatment with ocrelizumab.

Vaccinations

Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ocrelizumab treatment for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ocrelizumab treatment for non-live vaccines *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

2.3 Assessments and Premedication Prior to Every Dose

Infection Assessment

Prior to every dose of OCREVUS 920 MG SC, determine whether there is an active infection. In case of active infection, delay administration of OCREVUS 920 MG SC until the infection resolves *[see Warnings and Precautions (5.2)]*.

Recommended Premedication

Pre-medicate orally with 20 mg of dexamethasone (or an equivalent corticosteroid) and an antihistamine (e.g., desloratadine) administered at least 30 minutes prior to each OCREVUS 920 MG SC administration to reduce the risk of local and systemic injection reactions *[see Warnings and Precautions (5.1)]*.

The addition of an antipyretic (e.g., acetaminophen) may also be considered.

2.4 Recommended Dosage

The recommended dosage of OCREVUS 920 MG SC is 920 mg/23,000 units (920 mg ocrelizumab and 23,000 units of hyaluronidase) administered as a single 23 mL subcutaneous injection in the abdomen over approximately 10 minutes every 6 months.

Monitor the patient closely during injections, with access to appropriate medical support to manage severe injection reactions. For the initial dose, monitor the patient for at least one hour post-injection. For subsequent doses, monitor the patient for at least 15 minutes post-injection *[see Warnings and Precautions (5.1)]*.

2.5 Delayed or Missed Doses

If a planned injection of OCREVUS 920 MG SC is missed, administer OCREVUS 920 MG SC as soon as possible; do not wait until the next scheduled dose. Reset the dose schedule to administer the next sequential dose 6 months after the missed dose is administered. Doses of OCREVUS 920 MG SC must be separated by at least 5 months *[see Dosage and Administration (2.4)]*.

2.6 Preparation and Administration

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is OCREVUS 920 MG SC and not intravenous ocrelizumab.

Visually inspect the vial for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the vial if particulates or discoloration are present. Do not shake. Discard any unused portion remaining in the vial.

OCREVUS 920 MG SC is compatible with polypropylene (PP), polycarbonate (PC), polyethylene (PE), stainless steel (SS), polyvinylchloride (PVC), and polyurethane (PUR).

Preparation of the Syringe

OCREVUS 920 MG SC should be prepared by a healthcare professional.

- Immediate use is recommended, as OCREVUS 920 MG SC does not contain any antimicrobial preservative. If the dose is not administered immediately, refer to "Storage of the Syringe" below.
- Remove the vial from refrigerated storage and allow the solution to acclimate to room temperature at or below 25°C.
- Withdraw the entire contents of OCREVUS 920 MG SC solution from the vial with a syringe and transfer needle (21G needle recommended).
- Do not dilute.
- Remove the transfer needle from the syringe and replace with a subcutaneous infusion set (e.g., winged/butterfly) containing a 24G-26G needle for injection. Use a subcutaneous infusion set with a priming volume NOT to exceed 0.8 mL for administration.
- Prime the subcutaneous infusion line with the drug product solution to eliminate the air in the infusion line and stop before the fluid reaches the needle.
- Ensure the syringe contains exactly 23 mL of drug product solution after priming and expelling any excess volume from the syringe.
- Administer immediately to avoid needle clogging. DO NOT store the prepared syringe that has been attached to the already primed subcutaneous infusion set.

Administration

- Administer 23 mL of OCREVUS 920 MG SC subcutaneously in the abdomen over approximately 10 minutes. DO NOT administer the remaining priming volume in the subcutaneous infusion set to the patient.
- The recommended injection site is the abdomen, except for 2 inches (5 cm) around the navel. Do not administer OCREVUS 920 MG SC injections into areas where the skin is red, bruised, tender, or hard, or areas where there are moles or scars.

Storage of the Syringe

- If the dose is not to be administered immediately, use aseptic technique to withdraw the entire OCREVUS 920 MG SC contents from the vial into the syringe to account for the dose volume (23 mL) plus the priming volume for the subcutaneous infusion set. Replace the transfer needle with a syringe closing cap. DO NOT attach a subcutaneous infusion set.
- If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and normally not longer than 24 hours at 2°C to 8°C, unless the preparation has taken place in controlled and validated aseptic conditions. For storage conditions of the prepared syringe refer to "shelf life of the prepared syringe" [see HOW SUPPLIED/STORAGE AND HANDLING (16)].
- If the prepared syringe was stored at 2°C to 8°C, allow the syringe to acclimate to room temperature prior to administration.

3 DOSAGE FORMS AND STRENGTHS

OCREVUS 920 MG SC Injection: 920 mg ocrelizumab and 23,000 units hyaluronidase per 23 mL (40 mg and 1,000 units per mL) clear to slightly opalescent, and colorless to pale brown solution in a single-dose vial.

4 CONTRAINDICATIONS

OCREVUS 920 MG SC is contraindicated in patients with:

- A history of hypersensitivity to ocrelizumab, hyaluronidase, or any component of OCREVUS 920 MG SC listed in section 11 *[see Warnings and Precautions (5.1)]*.
- Active HBV infection *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*
- A history of life-threatening administration reaction to ocrelizumab *[see Warnings and Precautions (5.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Injection Reactions

OCREVUS 920 MG SC can cause injection reactions, which can be local or systemic. Common symptoms of local injection reactions reported by patients treated with OCREVUS 920 MG SC in multiple sclerosis (MS) clinical trials included erythema, pain, swelling, and pruritus. Common symptoms of systemic injection reactions reported by patients included headache and nausea. In an open-label, active-controlled trial, injection reactions were more frequently reported with the first injection; 49% of patients experienced an injection reaction with the first injection *[see Adverse Reactions (6.1)]*.

In MS clinical trials where ocrelizumab was administered intravenously, the incidence of infusion reactions in patients [who received methylprednisolone (or an equivalent steroid) and possibly other premedication to reduce the risk of infusion reactions prior to infusion] was 34% to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of intravenous ocrelizumab-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization. Symptoms of infusion reactions can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis.

Monitor patients during and after injections *[see Dosage and Administration (2.4)]*. Inform patients that injection reactions can occur during or within 24 hours of the injection.

Reducing the Risk of Injection Reactions and Managing Injection Reactions

Administer oral premedication (e.g., dexamethasone or an equivalent corticosteroid, and an antihistamine) at least 30 minutes prior to each OCREVUS 920 MG SC injection to reduce the risk of injection reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered *[see Dosage and Administration (2.3)]*.

Management recommendations for injection reactions depend on the type and severity of the reaction. For life-threatening injection reactions, immediately and permanently stop OCREVUS 920 MG SC and administer appropriate supportive treatment. For less severe injection reactions, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed at the healthcare provider's discretion and only after all symptoms have resolved.

5.2 Infections

Serious, including life-threatening or fatal, bacterial, viral, parasitic, and fungal infections have been reported in patients receiving ocrelizumab. An increased risk of infections (including serious and fatal bacterial, fungal, and new or reactivated viral infections) has been observed in patients during and following completion of treatment with anti-CD20 B-cell depleting therapies.

A higher proportion of intravenous ocrelizumab-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of intravenous ocrelizumab-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of intravenous ocrelizumab-treated patients experienced one or more infections compared to 68% of patients on placebo.

Intravenous ocrelizumab was not associated with an increased risk of serious infections in MS patients in controlled trials.

Ocrelizumab increases the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections *[see Adverse Reactions (6.1)]*.

Delay OCREVUS 920 MG SC administration in patients with an active infection until the infection is resolved.

Respiratory Tract Infections

A higher proportion of intravenous ocrelizumab-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of patients treated with intravenous ocrelizumab experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of patients treated with intravenous ocrelizumab experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of patients treated with intravenous ocrelizumab experienced upper respiratory tract infections compared to 43% of patients on placebo, and 10% of patients treated with intravenous ocrelizumab experienced lower respiratory tract infections compared to 9% of patients on placebo. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and bronchitis.

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in patients treated with intravenous ocrelizumab than in REBIF-treated patients, including herpes zoster (2.1% vs. 1.0%), herpes simplex (0.7% vs. 0.1%), oral herpes (3.0% vs. 2.2%), genital herpes (0.1% vs. 0%), and herpes virus infection (0.1% vs. 0%). Infections were predominantly mild to moderate in severity.

In the placebo-controlled (PPMS) clinical trial, oral herpes was reported more frequently in the patients treated with intravenous ocrelizumab than in the patients on placebo (2.7% vs. 0.8%).

Serious cases of infections caused by herpes simplex virus and varicella zoster virus, including central nervous system infections (encephalitis and meningitis), intraocular infections, and disseminated skin and soft tissue infections, have been reported in the postmarketing setting in multiple sclerosis patients receiving ocrelizumab. Some cases were life-threatening. Serious herpes virus infections may occur at any time during treatment with OCREVUS 920 MG SC.

If serious herpes infections occur, OCREVUS 920 MG SC should be discontinued or withheld until the infection has resolved, and appropriate treatment should be administered.

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation has been reported in MS patients treated with ocrelizumab in the postmarketing setting. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with ocrelizumab. Do not administer OCREVUS 920 MG SC to patients with active HBV confirmed by positive results for HBsAg and anti-HB tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment.

Possible Increased Risk of Immunosuppressant Effects With Other Immunosuppressants

When initiating OCREVUS 920 MG SC after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS 920 MG SC, consider the potential for increased immunosuppressive effects *[see Drug Interactions (7.1) and Clinical Pharmacology (12.1, 12.2)]*. OCREVUS 920 MG SC has not been studied in combination with other MS therapies.

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ocrelizumab treatment for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ocrelizumab for non-live vaccines.

OCREVUS 920 MG SC may interfere with the effectiveness of non-live vaccines *[see Drug Interactions (7.2)]*.

The safety of immunization with live or live-attenuated vaccines following OCREVUS 920 MG SC therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion *[see Clinical Pharmacology (12.2)]*.

Vaccination of *Infants Born to Mothers Treated with OCREVUS 920 MG SC During Pregnancy*

In infants of mothers exposed to OCREVUS 920 MG SC during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts as measured by $CD19^+$ B-cells. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

You may administer non-live vaccines, as indicated, prior to recovery from B-cell depletion, but should consider assessing vaccine immune responses, including consultation with a qualified specialist, to assess whether a protective immune response was mounted *[see Use in Specific Populations (8.1)]*.

5.3 Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with ocrelizumab in the postmarketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in ocrelizumab-treated patients who had not been treated previously with natalizumab (which has a known association with PML), were not taking any immunosuppressive or immunomodulatory medications associated with the risk of PML prior to or concomitantly with ocrelizumab, and did not have any known ongoing systemic medical conditions resulting in compromised immune system function.

JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies.

At the first sign or symptom suggestive of PML, withhold OCREVUS 920 MG SC and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Following discontinuation of another MS medication associated with PML, lower PML-related mortality and morbidity have been reported in patients who were initially asymptomatic at diagnosis compared to patients who had characteristic clinical signs and symptoms at diagnosis.

It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

If PML is confirmed, treatment with OCREVUS 920 MG SC should be discontinued.

5.4 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with ocrelizumab treatment. The pooled data of intravenous ocrelizumab clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of immunoglobulin G (IgG<LLN) and increased rates of serious infections. Monitor the levels of quantitative serum immunoglobulins during OCREVUS 920 MG SC treatment and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Consider discontinuing OCREVUS 920 MG SC therapy in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins *[see Adverse Reactions (6.1)]*.

5.5 Malignancies

An increased risk of malignancy with OCREVUS 920 MG SC may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in patients treated with intravenous ocrelizumab. Breast cancer occurred in 6 of 781 females treated with intravenous ocrelizumab and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

5.6 Immune-Mediated Colitis

Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving ocrelizumab in the postmarketing setting. Some cases of colitis were serious, requiring hospitalization, with a few patients requiring surgical intervention. Systemic corticosteroids were required in many of these patients. The time from treatment initiation to onset of symptoms in these cases ranged from a few weeks to years. Monitor patients for immune-mediated colitis during OCREVUS 920 MG SC treatment, and evaluate promptly if signs and symptoms that may indicate immune-mediated colitis, such as new or persistent diarrhea or other gastrointestinal signs and symptoms, occur.

5.7 Effects on Ability to Drive and Use Machines

OCREVUS 920 MG SC has no or negligible influence on the ability to drive and use machines.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Injection Reactions *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.3)]*
- Reduction in Immunoglobulins *[see Warnings and Precautions (5.4)]*
- Malignancies *[see Warnings and Precautions (5.5)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ocrelizumab has been evaluated in active-controlled clinical trials of ocrelizumab administered intravenously in patients with relapsing forms of MS (RMS) (Study 1 and Study 2) *[see Clinical Studies (14.1)]* and primary progressive MS (PPMS) (Study 3) *[see Clinical Studies (14.2)]*, and in an open-label, active-

controlled trial of OCREVUS 920 MG SC administered subcutaneously in patients with RMS and PPMS (Study 4) *[see Clinical Studies (14.3)]*.

Adverse Reactions With Ocrelizumab Intravenous in Patients With RMS and PPMS

The safety of intravenous ocrelizumab has been evaluated in 1311 patients across the MS clinical studies, which included 825 patients in active-controlled clinical trials in patients with RMS and 486 patients in a placebo-controlled study in patients with PPMS.

RMS

In active-controlled intravenous ocrelizumab clinical trials (Study 1 and Study 2), 825 patients with RMS received ocrelizumab 600 mg intravenously every 24 weeks (initial treatment was given as two separate 300 mg infusions at Weeks 0 and 2) *[see Clinical Studies (14.1)]*. The overall exposure in the 96-week controlled treatment periods was 1448 patient-years.

The most common adverse reactions in RMS trials (incidence ≥ 10%) were upper respiratory tract infections and infusion reactions. Table 1 summarizes the adverse reactions that occurred in active-controlled intravenous ocrelizumab RMS trials (Study 1 and Study 2).

Table 1 Adverse Reactions in Adult Patients With RMS With an Incidence of at least 5% for Intravenous Ocrelizumab and Higher than REBIF

Adverse Reactions	**Studies 1 and 2**	
	Ocrelizumab 600 mg IV Every 24 Weeks[1] (n=825) %	**REBIF 44 mcg SQ 3 Times per Week (n=826) %**
Upper respiratory tract infections	40	33
Infusion reactions	34	10
Depression	8	7
Lower respiratory tract infections	8	5
Back pain	6	5
Herpes virus- associated infections	6	4
Pain in extremity	5	4

[1] The first dose was given as two separate 300 mg infusions at Weeks 0 and 2.

PPMS

In a placebo-controlled intravenous ocrelizumab clinical trial (Study 3), a total of 486 patients with PPMS received one course of ocrelizumab (600 mg of ocrelizumab administered as two 300 mg infusions two weeks apart) given intravenously every 24 weeks and 239 patients received placebo intravenously *[see Clinical Studies (14.2)]*. The overall exposure in the controlled treatment period was 1416 patient-years, with median treatment duration of 3 years.

The most common adverse reactions in the PPMS trial (incidence ≥ 10%) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections. Table 2 summarizes the adverse reactions that occurred in the placebo-controlled intravenous ocrelizumab PPMS trial (Study 3).

Table 2 Adverse Reactions in Adult Patients With PPMS With an Incidence of at Least 5% for Intravenous Ocrelizumab and Higher Than Placebo

Adverse Reactions	Study 3	
	Ocrelizumab 600 mg IV Every 24 Weeks[1] (n=486) %	Placebo (n=239) %
Upper respiratory tract infections	49	43
Infusion reactions	40	26
Skin infections	14	11
Lower respiratory tract infections	10	9
Cough	7	3
Diarrhea	6	5
Edema peripheral	6	5
Herpes virus associated infections	5	4

[1] One dose of intravenous ocrelizumab (600 mg administered as two 300 mg infusions two weeks apart)

Laboratory Abnormalities

Decreased Immunoglobulins

Ocrelizumab decreased total immunoglobulins, with the greatest decline seen in IgM levels; however, a decrease in IgG levels was associated with an increased rate of serious infections.

In the active-controlled (RMS) trials (Study 1 and Study 2), the proportion of patients at baseline reporting IgG, IgA, and IgM below the lower limit of normal (LLN) in patients treated with intravenous ocrelizumab was 0.5%, 1.5%, and 0.1%, respectively. Following treatment, the proportion of patients treated with intravenous ocrelizumab reporting IgG, IgA, and IgM below the LLN at 96 weeks was 1.5%, 2.4%, and 16.5%, respectively.

In the placebo-controlled (PPMS) trial (Study 3), the proportion of patients at baseline reporting IgG, IgA, and IgM below the LLN in patients treated with intravenous ocrelizumab was 0.0%, 0.2%, and 0.2%, respectively. Following treatment, the proportion of patients treated with intravenous ocrelizumab reporting IgG, IgA, and IgM below the LLN at 120 weeks was 1.1%, 0.5%, and 15.5%, respectively.

The pooled data of intravenous ocrelizumab clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of IgG and increased rates of serious infections. The type, severity, latency, duration, and outcome of serious infections observed during episodes of immunoglobulins below LLN were consistent with the overall serious infections observed in patients treated with intravenous ocrelizumab .

Decreased Neutrophil Levels

In the PPMS clinical trial (Study 3), decreased neutrophil counts occurred in 13% of patients treated with intravenous ocrelizumab compared to 10% in placebo patients. The majority of the decreased neutrophil counts were only observed once for a given patient treated with intravenous ocrelizumab and were between the LLN and 1.0 x 10^9/L. Overall, 1% of the patients in the intravenous ocrelizumab group had neutrophil counts less than 1.0 x 10^9/L and these were not associated with an infection.

Adverse Reactions With OCREVUS 920 MG SC in Patients With RMS and PPMS

The safety of OCREVUS 920 MG SC was evaluated in Study 4, an active-controlled, open-label, randomized study in ocrelizumab-naïve patients with RMS or PPMS *[see Clinical Studies (14.3)]*. One hundred eighteen

patients received OCREVUS 920 MG SC as their first dose and 118 patients received intravenous ocrelizumab for their first dose (two separate 300 mg infusions at Weeks 0 and 2).

The most common adverse reactions (reported in at least 10% of OCREVUS 920 MG SC-treated patients) were injection reactions.

In Study 4, injection reactions occurred in 49% (58/118) of patients after the first injection of OCREVUS 920 MG SC. Of these 118 patients, 47% and 11% experienced at least one local injection reaction and one systemic injection reaction, respectively. The most common symptoms reported by patients with local and systemic injection reactions included: injection site erythema, injection site pain, injection site swelling, injection site pruritus, headache, and nausea. Among the patients experiencing an injection reaction, the majority of patients (83%) had injection reactions occur within 24 hours after the end of the injection, as opposed to during the injection (19%). All injection reactions were of mild (73%) or moderate (27%) severity. The median duration of symptoms was 3 days for systemic injection reactions and 3.5 days for local injection reactions. All patients recovered from injection reactions, of which 26% required symptomatic treatment.

For subsequent injections, among the 118 patients who received OCREVUS 920 MG SC only throughout the study, the frequency of local injection reactions ranged from 31% to 43% and the frequency of systemic injection reactions ranged from 3% to 7% from Injection 2 to Injection 4. All injection reactions were of mild or moderate severity.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ocrelizumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Immune-mediated colitis *[see Warnings and Precautions (5.6)]*

Hepatobiliary Disorders: Liver injury *[see Warnings and Precautions (5.7)]*

Infections and Infestations: Serious herpes infections *[see Warnings and Precautions (5.2)]*, progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.3)]*, and babesiosis

Skin: Pyoderma gangrenosum

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

The concomitant use of OCREVUS 920 MG SC and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with OCREVUS 920 MG SC. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating OCREVUS 920 MG SC *[see Warnings and Precautions (5.2)]*.

7.2 Vaccinations

A Phase 3b randomized, open-label study examined the concomitant use of intravenous ocrelizumab and several non-live vaccines in adults 18-55 years of age with relapsing forms of MS (68 subjects undergoing treatment with intravenous ocrelizumab at the time of vaccination and 34 subjects not undergoing treatment with intravenous ocrelizumab at the time of vaccination). Concomitant exposure to intravenous ocrelizumab attenuated antibody responses to tetanus toxoid-containing vaccine, pneumococcal polysaccharide, pneumococcal conjugate vaccines, and seasonal inactivated influenza vaccines. The impact of the observed attenuation on vaccine effectiveness in this patient population is unknown. The safety and effectiveness of live or live-attenuated vaccines administered concomitantly with ocrelizumab have not been assessed *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

OCREVUS 920 MG SC is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. There are no adequate data on the developmental risk associated with use of OCREVUS 920 MG SC or ocrelizumab-containing products in pregnant women. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to OCREVUS 920 MG SC or ocrelizumab-containing products have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown *[see Warnings and Precautions (5.2)]*.

Following administration of ocrelizumab to pregnant monkeys at doses similar to or greater than those used clinically, increased perinatal mortality, depletion of B-cell populations, and renal, bone marrow, and testicular toxicity were observed in the offspring in the absence of maternal toxicity *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

OCREVUS 920 MG SC for subcutaneous injection contains ocrelizumab and hyaluronidase *[see Description (11)]*.

Ocrelizumab:

- Following intravenous administration of ocrelizumab to monkeys during organogenesis (loading doses of 15 or 75 mg/kg on gestation days 20, 21, and 22, followed by weekly doses of 20 or 100 mg/kg), depletion of B-lymphocytes in lymphoid tissue (spleen and lymph nodes) was observed in fetuses at both doses.
- Intravenous administration of ocrelizumab (three daily loading doses of 15 or 75 mg/kg, followed by weekly doses of 20 or 100 mg/kg) to pregnant monkeys throughout the period of organogenesis and continuing through the neonatal period resulted in perinatal deaths (some associated with bacterial infections), renal toxicity (glomerulopathy and inflammation), lymphoid follicle formation in the bone marrow, and severe decreases in circulating B-lymphocytes in neonates. The cause of the neonatal deaths is uncertain; however, both affected neonates were found to have bacterial infections. Reduced testicular weight was observed in neonates at the high dose.

- A no-effect dose for adverse developmental effects was not identified; the doses tested in monkey are 2 and 10 times the recommended human dose of 600 mg intravenous ocrelizumab, on a mg/kg basis.

Hyaluronidase:

- In an embryo-fetal study, mice were dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (human recombinant) at dose levels up to 2,200,000 U/kg, which is > 5,700 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is > 940 times higher than the human dose.
- In a pre-and postnatal development study, mice have been dosed daily by subcutaneous injection, with hyaluronidase (human recombinant) from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is > 2,800 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory, or fertility of the offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of ocrelizumab or hyaluronidase, from administration of OCREVUS 920 MG SC, in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OCREVUS 920 MG SC and any potential adverse effects on the breastfed infant from OCREVUS 920 MG SC or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Women of childbearing potential should use effective contraception while receiving OCREVUS 920 MG SC and for 6 months after the last dose of OCREVUS 920 MG SC *[see Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

Safety and effectiveness of OCREVUS 920 MG SC in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of OCREVUS 920 MG SC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Ocrelizumab is a recombinant humanized monoclonal antibody directed against CD20-expressing B-cells. Ocrelizumab is a glycosylated immunoglobulin G1 (IgG1) with a molecular mass of approximately 145 kDa.

Hyaluronidase (human recombinant) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is a glycosylated single-chain protein produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (human recombinant) has a molecular weight of approximately 61 kDa.

OCREVUS 920 MG SC (ocrelizumab and hyaluronidase) injection for subcutaneous use is a sterile, preservative-free, clear to slightly opalescent, and colorless to pale brown solution supplied in single-dose vials. Each 23 mL of solution contains 920 mg ocrelizumab, 23,000 units of rHuPH20 [hyaluronidase (human recombinant)], α-α-trehalose dihydrate, sodium acetate trihydrate, L-methionine, polysorbate 20, glacial acetic acid, and water for injection at pH 5.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which ocrelizumab exerts its therapeutic effects in multiple sclerosis is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase in OCREVUS 920 MG SC acts transiently and locally. The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

12.2 Pharmacodynamics

For B-cell counts, assays for $CD19^+$ B-cells are used because the presence of ocrelizumab interferes with the CD20 assay. In clinical studies with OCREVUS 920 MG SC and intravenous ocrelizumab, $CD19^+$ B-cell counts in blood were reduced by 14 days after administration. In clinical studies with intravenous ocrelizumab, B-cell counts rose to above the lower limit of normal (LLN) or above baseline counts between infusions of ocrelizumab at least one time in 0.3% to 4.1% of patients. In a clinical study of 51 patients treated with intravenous ocrelizumab, the median time for B-cell counts to return to either baseline or LLN was 72 weeks (range 27-175 weeks) after the last ocrelizumab infusion. Within 2.5 years after the last infusion, B-cell counts rose to either baseline or LLN in 90% of patients.

12.3 Pharmacokinetics

After subcutaneous administration of 920 mg ocrelizumab, the estimated mean exposure (AUC over the 24-week dosing interval) was 3730 µg/mL•day. The mean C_{max} was 132 µg/mL and t_{max} was reached after approximately 4 days (range 2 – 13 days). The estimated absolute bioavailability following subcutaneous administration was 81%.

In Study 4, the differences in pharmacokinetic exposures following the administration of OCREVUS 920 MG SC subcutaneously at 920 mg/23,000 units and ocrelizumab intravenously at 600 mg in MS patients were not clinically significant.

Pharmacokinetics (PK) of ocrelizumab in MS clinical studies fit a two-compartment model with time-dependent clearance.

Distribution

The population PK estimate of the central volume of distribution was 2.78 L. Peripheral volume and inter-compartment clearance were estimated at 2.68 L and 0.55 L/day, respectively.

Elimination

Constant clearance was estimated at 0.17 L/day, and initial time-dependent clearance at 0.05 L/day, which declined with a half-life of 33 weeks. The terminal elimination half-life was 20 days.

Metabolism

The metabolism of OCREVUS 920 MG SC has not been directly studied because antibodies are cleared principally by catabolism.

Specific Populations

Renal Impairment

Patients with mild renal impairment were included in clinical trials. No significant change in the pharmacokinetics of ocrelizumab was observed in those patients.

Hepatic Impairment

Patients with mild hepatic impairment were included in clinical trials. No significant change in the pharmacokinetics of ocrelizumab was observed in those patients.

12.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. Therefore, comparison of the incidence of antibodies to OCREVUS 920 MG SC with the incidence of antibodies to other products may be misleading.

In Study 4, no patients tested positive for ocrelizumab anti-drug antibodies (ADAs) or anti-rHuPH20 (hyaluronidase [human recombinant]) antibodies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

OCREVUS 920 MG SC contains ocrelizumab and hyaluronidase.

No carcinogenicity studies have been performed to assess the carcinogenic potential of ocrelizumab.

No studies have been performed to assess the mutagenic potential of ocrelizumab . As an antibody, ocrelizumab is not expected to interact directly with DNA.

No effects on reproductive organs were observed in male monkeys administered ocrelizumab by intravenous injection (three loading doses of 15 or 75 mg/kg, followed by weekly doses of 20 or 100 mg/kg) for 8 weeks. There were also no effects on estrus cycle in female monkeys administered ocrelizumab over three menstrual cycles using the same dosing regimen. The doses tested in monkey are 2 and 10 times the recommended human dose of 600 mg intravenous ocrelizumab, on a mg/kg basis.

Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. In addition, when subcutaneous hyaluronidase (recombinant human) was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is > 570 times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

14 CLINICAL STUDIES

Studies 1-3 (described below), which established the effectiveness of ocrelizumab for the treatment of RMS and PPMS in adults, were conducted with intravenously-administered ocrelizumab. Study 4 demonstrated comparable exposure of OCREVUS 920 MG SC relative to the ocrelizumab intravenous formulation, which established the efficacy of OCREVUS 920 MG SC *[see Clinical Pharmacology (12.3)]*.

14.1 Intravenous Ocrelizumab in Patients With Relapsing Forms of Multiple Sclerosis

The efficacy of intravenous ocrelizumab was demonstrated in two randomized, double-blind, double-dummy, active comparator-controlled clinical trials of identical design, in patients with relapsing forms of multiple

sclerosis (RMS) treated for 96 weeks (Study 1; NCT01247324 and Study 2; NCT01412333). The dose of intravenous ocrelizumab was 600 mg every 24 weeks (initial treatment was given as two 300 mg IV infusions administered 2 weeks apart, and subsequent doses were administered as a single 600 mg IV infusion) and placebo subcutaneous injections were given 3 times per week. The dose of REBIF, the active comparator, was 44 mcg given as subcutaneous injections 3 times per week and placebo IV infusions were given every 24 weeks. Both studies included patients who had experienced at least one relapse within the prior year, or two relapses within the prior two years, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Patients with primary progressive forms of multiple sclerosis (MS) were excluded. Neurological evaluations were performed every 12 weeks and at the time of a suspected relapse. Brain MRIs were performed at baseline and at Weeks 24, 48, and 96.

The primary outcome of both Study 1 and Study 2 was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the mean number of MRI T1 gadolinium (Gd)-enhancing lesions at Weeks 24, 48, and 96, and new or enlarging MRI T2 hyperintense lesions. Progression of disability was defined as an increase of 1 point or more from the baseline EDSS score attributable to MS when the baseline EDSS score was 5.5 or less, or 0.5 points or more when the baseline EDSS score was above 5.5. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit 12 weeks after the initial documentation of neurological worsening. The primary population for analysis of confirmed disability progression was the pooled population from Studies 1 and 2.

In Study 1, 410 patients were randomized to intravenous ocrelizumab and 411 to REBIF; 11% of intravenous ocrelizumab-treated patients and 17% of REBIF-treated patients did not complete the 96-week double-blind treatment period. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 37 years; 66% were female. The mean time from MS diagnosis to randomization was 3.8 years, the mean number of relapses in the previous year was 1.3, and the mean EDSS score was 2.8; 74% of patients had not been treated with a non-steroid therapy for MS in the 2 years prior to the study. At baseline, 40% of patients had one or more T1 Gd-enhancing lesions (mean 1.8).

In Study 2, 417 patients were randomized to intravenous ocrelizumab and 418 to REBIF; 14% of intravenous ocrelizumab-treated patients and 23% of REBIF-treated patients did not complete the 96-week double-blind treatment period. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 37 years; 66% were female. The mean time from MS diagnosis to randomization was 4.1 years, the mean number of relapses in the previous year was 1.3, and the mean EDSS score was 2.8; 74% of patients had not been treated with a non-steroid therapy for MS in the 2 years prior to the study. At baseline, 40% of intravenous ocrelizumab-treated patients had one or more T1 Gd-enhancing lesions (mean 1.9).

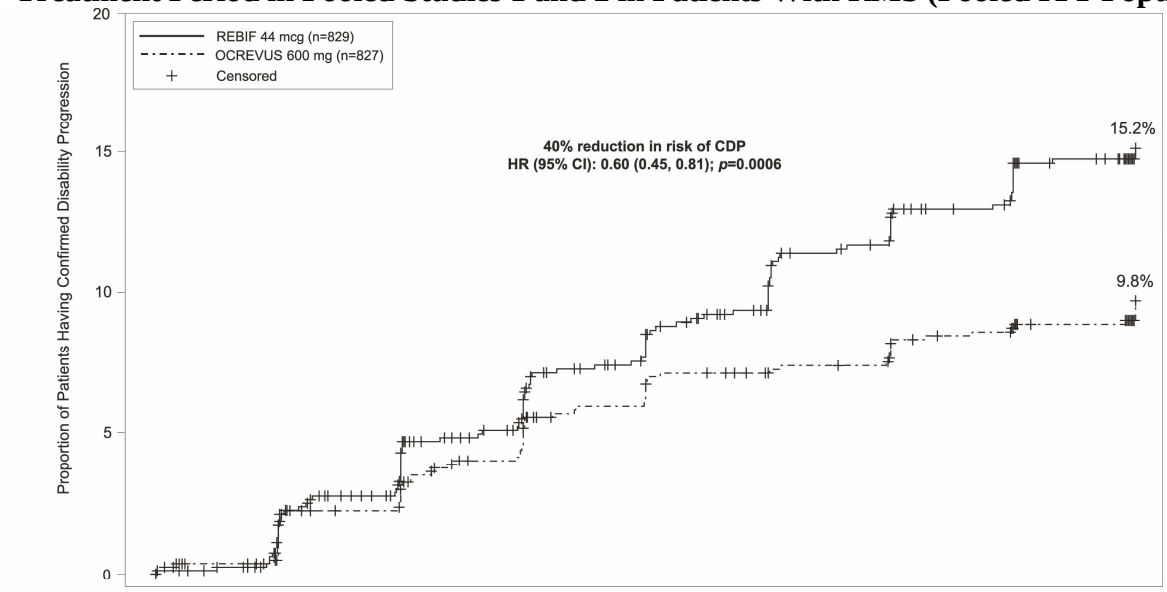
In Study 1 and Study 2, intravenous ocrelizumab significantly lowered the annualized relapse rate and the proportion of patients with disability progression confirmed at 12 weeks after onset compared to REBIF. Results for Study 1 and Study 2 are presented in Table 3 and Figure 1.

Table 3 Key Clinical and MRI Endpoints in RMS Patients From Study 1 and Study 2

Endpoints	Study 1		Study 2	
	Intravenous Ocrelizumab 600 mg every 24 weeks N=410	REBIF 44 mcg three times a week N=411	Intravenous Ocrelizumab 600 mg every 24 weeks N=417	REBIF 44 mcg three times a week N=418
Clinical Endpoints				
Annualized Relapse Rate (Primary Endpoint)	0.156	0.292	0.155	0.290
Relative Reduction	46% (p<0.0001)		47% (p<0.0001)	
Proportion Relapse-free	83%	71%	82%	72%
Proportion of Patients with 12-week Confirmed Disability Progression[1]	9.8% Intravenous Ocrelizumab vs 15.2% REBIF			
Risk Reduction (Pooled Analysis[2])	40%; p=0.0006			
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI	0.016	0.286	0.021	0.416
Relative Reduction	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI	0.323	1.413	0.325	1.904
Relative Reduction	77% (p<0.0001)		83% (p<0.0001)	

[1] Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5, Kaplan-Meier estimates at Week 96.
[2] Data prospectively pooled from Study 1 and Study 2.

Figure 1 Kaplan-Meier Plot* of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks With the Initial Event of Neurological Worsening Occurring During the Double-Blind Treatment Period in Pooled Studies 1 and 2 in Patients With RMS (Pooled ITT Population)



No. of Patients at Risk

	Baseline	12	24	36	48	60	72	84	96
REBIF 44 mcg	828	784	741	696	665	632	608	583	449
OCREVUS 600 mg	827	795	765	737	716	702	688	672	526

*Pre-specified pooled analysis of Study 1 and 2

In exploratory subgroup analyses of Study 1 and Study 2, the effect of intravenous ocrelizumab on annualized relapse rate and disability progression was similar in male and female patients.

14.2 Intravenous Ocrelizumab in Patients With Primary Progressive Multiple Sclerosis

Study 3 was a randomized, double-blind, placebo-controlled clinical trial in patients with primary progressive multiple sclerosis (PPMS) (NCT01194570). Patients were randomized 2:1 to receive either intravenous ocrelizumab 600 mg or placebo as two 300 mg intravenous infusions 2 weeks apart every 24 weeks for at least 120 weeks. Selection criteria required a baseline EDSS of 3 to 6.5 and a score of 2 or greater for the EDSS pyramidal functional system due to lower extremity findings. Neurological assessments were conducted every 12 weeks. An MRI scan was obtained at baseline and at Weeks 24, 48, and 120.

In Study 3, the primary outcome was the time to onset of disability progression attributable to MS confirmed to be present at the next neurological assessment at least 12 weeks later. Disability progression occurred when the EDSS score increased by 1 point or more from the baseline EDSS if the baseline EDSS was 5.5 points or less, or by 0.5 points or more if the baseline EDSS was more than 5.5 points. In Study 3, confirmed disability progression also was deemed to have occurred if patients who had onset of disability progression discontinued participation in the study before the next assessment. Additional outcome measures included timed 25-foot walk, and percentage change in T2 hyperintense lesion volume.

Study 3 randomized 488 patients to intravenous ocrelizumab and 244 to placebo; 21% of intravenous ocrelizumab-treated patients and 34% of placebo-treated patients did not complete the trial. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 45; 49% were female. The mean time since symptom onset was 6.7 years, the mean EDSS score was 4.7, and 26% had one or more T1 Gd-enhancing lesions at baseline; 88% of patients had not been treated previously with a non-steroid treatment for MS. The time to onset of disability progression confirmed at

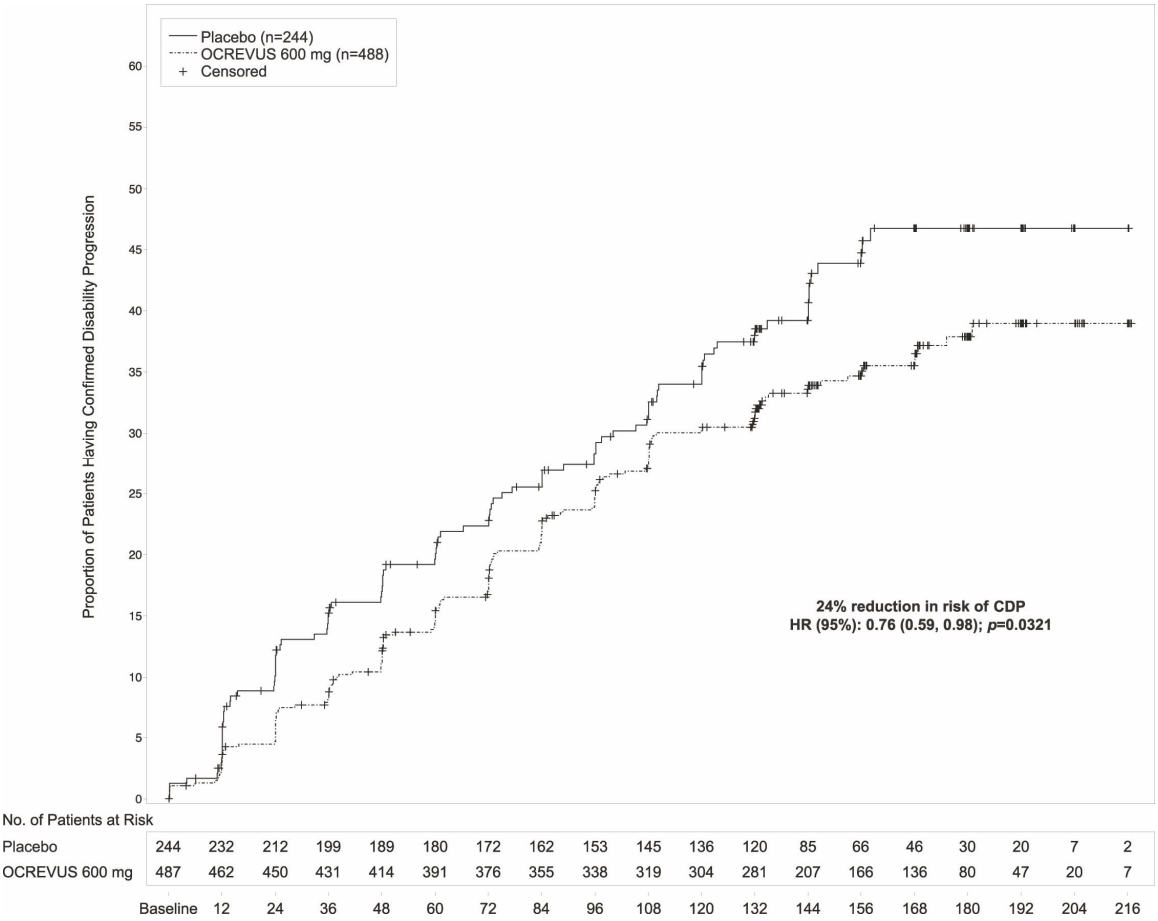
12 weeks after onset was significantly longer for intravenous ocrelizumab-treated patients than for placebo-treated patients (see Figure 2). Results for Study 3 are presented in Table 4 and Figure 2.

Table 4 Key Clinical and MRI Endpoints in PPMS Patients for Study 3

Endpoints	**Study 3**	
	Intravenous Ocrelizumab 600 mg (two 300 mg infusions two weeks apart every 24 weeks) N=488	Placebo N=244
Clinical Outcomes		
Proportion of patients with 12-week Confirmed Disability Progression[1]	32.9%	39.3%
Risk reduction	24%; p=0.0321	
MRI Endpoints		
Mean change in volume of T2 lesions, from baseline to Week 120 (cm^3)	-0.39	0.79
	p<0.0001	

[1] Defined as an increase of 1.0 point or more from the baseline EDSS score for patients with baseline score of 5.5 or less, or an increase of 0.5 or more when the baseline score is more than 5.5.

Figure 2 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks With the Initial Event of Neurological Worsening Occurring During the Double-Blind Treatment Period in Study 3*



No. of Patients at Risk

Placebo	244	232	212	199	189	180	172	162	153	145	136	120	85	66	46	30	20	7	2
OCREVUS 600 mg	487	462	450	431	414	391	376	355	338	319	304	281	207	166	136	80	47	20	7
Baseline	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216	

*All patients in this analysis had a minimum of 120 weeks of follow-up. The primary analysis is based on all disability progression events accrued including 21 without confirmatory EDSS at 12 weeks.

In the overall population in Study 3, the proportion of patients with 20 percent worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in intravenous ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).

In exploratory subgroup analyses of Study 3, the proportion of female patients with disability progression confirmed at 12 weeks after onset was similar in intravenous ocrelizumab-treated patients and placebo-treated patients (approximately 36% in each group). In male patients, the proportion of patients with disability progression confirmed at 12 weeks after onset was approximately 30% in intravenous ocrelizumab-treated patients and 43% in placebo-treated patients. Clinical and MRI endpoints that generally favored intravenous ocrelizumab numerically in the overall population, and that showed similar trends in both male and female patients, included annualized relapse rate, change in T2 lesion volume, and number of new or enlarging T2 lesions.

14.3 OCREVUS 920 MG SC in Patients With RMS or PPMS

Study 4 was a multicenter, randomized, open-label, parallel arm trial conducted to evaluate the comparative bioavailability, pharmacokinetics, pharmacodynamics, safety, and immunogenicity of OCREVUS 920 MG SC compared with intravenous ocrelizumab in patients with either RMS or PPMS (NCT05232825).

Study 4 enrolled 236 patients (213 with RMS, 23 with PPMS), 18-65 years of age with an EDSS between 0 to 6.5 at screening. The demographics were similar and baseline characteristics were balanced across the two treatment groups. The mean age was 40 years in both groups. In the OCREVUS 920 MG SC group, 35% of patients were male and the mean/median duration since MS diagnosis was 5.7/3.1 years, compared to 41% male and 4.8/2.4 years in the ocrelizumab IV group.

16 HOW SUPPLIED/STORAGE AND HANDLING

OCREVUS 920 MG SC (ocrelizumab and hyaluronidase) injection for subcutaneous use is a sterile, preservative-free, clear to slightly opalescent, and colorless to pale brown solution supplied as a carton containing one 920 mg and 23,000 units/23 mL (40 mg and 1,000 units/mL) single-dose vial.

Store OCREVUS 920 MG SC vials refrigerated at 2°C to 8°C. Keep the vial in the original carton in order to protect from light. Do not freeze or shake.

If necessary, the unopened vial may be stored outside the refrigerator at temperatures ≤25°C for up to 12 hours.

The vials can be removed and placed back into the refrigerator so that the total combined time out of the refrigerator of the unopened vial may not exceed 12 hours at ≤25°C.

For storage conditions after preparation of the syringe, see section Shelf-life.

Shelf-life:

Unopened vial
The expiry date of the product is indicated on the packaging materials.

Prepared syringe

- Chemical and physical in-use stability has been demonstrated for 30 days at 2°C to 8°C and additionally for 8 hours unprotected from light at ≤30°C.
- From a microbiological point of view, the product should be used immediately once transferred from the vial to the syringe. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and normally not longer than 24 hours at 2°C to 8°C, unless the preparation has taken place in controlled and validated aseptic conditions.

17 MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

18 MARKETING AUTHORISATION NUMBER(S):

180-44-38420-00

19 MANUFACTURER

Hoffmann-La Roche Ltd., Basel, Switzerland

Approved in Septmeber 2025.