PACK INSERT FOR MALAYSIA

OCREVUS 920 MG/23 ML

Concentrate for Solution for Injection
Ocrelizumab

1. NAME OF THE MEDICINAL PRODUCT

Ocrevus 920 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 920 mg of ocrelizumab in 23 mL (40 mg/mL).

Ocrelizumab is a humanised monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1).

Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions. The first administration should be under clinical observation with appropriate medical support to manage severe reactions such as severe injection reactions, hypersensitivity reactions and/or anaphylactic reactions (see section 4.4).

Premedication for injection reactions

The following two premedications are to be administered shortly before each ocrelizumab injection to reduce the risk of local and systemic injection reactions (IRs):

- 20 mg oral dexamethasone (or equivalent)
- Oral antihistamine (e.g., desloratadine or equivalent)

In addition, premedication with an antipyretic (e.g., paracetamol) may also be considered shortly before each administration.

Posology

The recommended dose is 920 mg administered every 6 months.
No division of the initial dose or subsequent doses into separate administrations is required.
A minimum interval of 5 months should be maintained between each dose of ocrelizumab.

Injection or treatment discontinuation in case of IRs

Life-threatening IRs

If there are signs of a life-threatening IR, the injection should be stopped immediately, and the patient should receive appropriate treatment. Treatment must be permanently discontinued in these patients (see section 4.3).

Severe IRs

If a patient experiences a severe IR, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed only after all symptoms have resolved (see section 4.4).

Delayed or missed doses

If an injection is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval of 6 months (with a minimum of 5 months) should be maintained between doses.

Special populations

Adults over 55 years old

Based on the limited data available for intravenous ocrelizumab (see sections 5.1 and 5.2), no posology adjustment is needed in patients over 55 years of age. Patients enrolled in the ongoing clinical trials continue to be dosed with 600 mg intravenous ocrelizumab every six months after they become older than 55 years old. The use of subcutaneous ocrelizumab was not studied in patients over 65 years of age.

Renal impairment

The safety and efficacy of ocrelizumab in patients with renal impairment has not been formally studied. Patients with mild renal impairment were included in clinical trials. There is no experience in patients with moderate and severe renal impairment. Ocrelizumab is a monoclonal antibody and cleared via catabolism (i.e. breakdown into peptides and amino acids), and a dose adjustment is not expected to be required for patients with renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of ocrelizumab in patients with hepatic impairment has not been formally studied. Patients with mild hepatic impairment were included in clinical trials. There is no experience in patients with moderate and severe hepatic impairment. Ocrelizumab is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a dose adjustment is not expected to be required for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of ocrelizumab in children and adolescents aged 0 to 18 years has not yet been established. No data are available.

Method of administration

Ocrevus 920 mg solution for injection is not intended for intravenous administration and should always be administered as a subcutaneous injection by a healthcare professional.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient by the correct route, as prescribed.

Patients may start treatment using intravenous or subcutaneous ocrelizumab and patients currently receiving intravenous ocrelizumab may continue treatment with intravenous ocrelizumab or transition to Ocrevus 920 mg solution for injection.

The 920 mg dose should be administered as a subcutaneous injection in the abdomen in approximately 10 minutes. Use of a subcutaneous infusion set (e.g., winged/butterfly) is recommended. Any residual hold-up volume remaining in the subcutaneous infusion set should not be administered to the patient.

The injection site should be the abdomen, except for 5 cm around the navel. Injections should never be given into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.

Ocrevus solution for injection should always be administered by a healthcare professional. For the initial dose, post-injection monitoring with access to appropriate medical support to manage severe reactions such as IRs, for at least one hour after injection is recommended. For subsequent doses, the need for post-injection monitoring is at the treating physician's discretion (see section 4.4).

For instructions on use and handling of the medicinal product prior to administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Current active infection (see section 4.4).
- Patients in a severely immunocompromised state (see section 4.4).
- Known active malignancies (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Injection reactions (IRs)

Treatment with subcutaneous ocrelizumab is associated with IRs, which may be related to cytokine release and/or other chemical mediators. Physicians should alert patients that IRs can occur during or within 24 hours of administration. Symptoms of IRs have been more frequently reported with the first injection. IRs can be local IRs or systemic IRs. Common symptoms of local IRs at the injection site include erythema, pain, swelling and pruritus. Common symptoms of systemic IRs include headache and nausea (see section 4.8).

Shortly before injection, patients should receive premedication to reduce the risk of IRs (see section 4.2). Patients should be observed for at least one hour after the initial dose of the medicinal product for any symptom of severe IR. Appropriate resources for the management of severe IRs, hypersensitivity reactions and/or anaphylactic reactions should be available for the initial dose of the medicinal product. For subsequent doses, the need for post-injection monitoring is at the treating physician's discretion. IRs can be managed with symptomatic treatment, should they occur.

If there are signs of a life-threatening IR, the injection should be stopped immediately, and the patient should receive appropriate treatment. Ocrelizumab treatment must be permanently discontinued in these patients. If a patient experiences a severe IR, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed only after all symptoms have resolved.

Intravenous ocrelizumab is associated with infusion-related reactions (IRRs), which may also be related to cytokine release and/or other chemical mediators. IRRs may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis. Serious IRRs, some requiring hospitalisation, have been reported with the use of intravenous ocrelizumab.

Hypersensitivity may be clinically indistinguishable from an IR or an IRR in terms of symptoms. If a hypersensitivity reaction is suspected, the injection must be stopped immediately and permanently (see 'Hypersensitivity reactions' below).

Hypersensitivity reactions

A hypersensitivity reaction could also occur (acute allergic reaction to medicinal product). Type 1 acute hypersensitivity reactions (IgE-mediated) may be clinically indistinguishable from IR symptoms.

A hypersensitivity reaction may present during any administration, although typically would not present during the first administration. For subsequent administrations, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. Patients with known IgE-mediated hypersensitivity to ocrelizumab or any of the excipients must not be treated (see section 4.3).

Infection

Administration of ocrelizumab 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 (e.g., with lymphopenia, neutropenia, hypogammaglobulinemia) should not be treated (see sections 4.3 and 4.8).

The overall proportion of patients experiencing a serious infection (SI) was similar to comparators (see section 4.8) in studies with intravenous ocrelizumab. The frequency of grade 4 (life-threatening) and grade 5 (fatal) infections was low in all treatment groups, but in PPMS it was higher with intravenous ocrelizumab compared with placebo for life-threatening (1.6% vs 0.4%) and fatal (0.6% vs 0%) infections. All life-threatening infections resolved without discontinuing ocrelizumab.

In PPMS, patients with swallowing difficulties are at a higher risk of aspiration pneumonia. Treatment with ocrelizumab may further increase the risk of severe pneumonia in these patients. Physicians should take prompt action for patients presenting with pneumonia.

Progressive multifocal leukoencephalopathy (PML)

John Cunningham virus (JCV) infection resulting in PML has been observed very rarely in patients treated with anti-CD20 antibodies, including ocrelizumab, and mostly associated with risk factors (patient population e.g., lymphopenia, advanced age, polytherapy with immunosuppressants).

Physicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms, as these can be similar to MS disease.

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 cerebro-spinal fluid (CSF) testing for JCV Deoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has been reported in patients treated with anti-CD20 antibodies.

HBV screening should be performed in all patients before initiation of treatment as per local guidelines. Patients with active HBV (i.e. an active infection confirmed by positive results for HBsAg and anti HB testing) should not be treated with ocrelizumab (see section 4.3). Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody (HBcAb +); carriers of HBV (positive for surface antigen, HBsAg+) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Late neutropenia

Cases of late onset of neutropenia have been reported at least 4 weeks after the latest intravenous ocrelizumab infusion (see section 4.8). Although some cases were Grade 3 or 4, the majority of the cases were Grade 1 or 2. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended.

Malignancies

An increased number of malignancies (including breast cancers) have been observed in the controlled period of the pivotal clinical trials in patients treated with intravenous ocrelizumab, compared to control groups. The incidence was within the background rate expected for an MS population. After approximately 10 years of continuous ocrelizumab treatment over the controlled period and Open-Label Extension (OLE) phase of the pivotal clinical trials, the incidence of malignancies remained within the background rate expected for an MS population. Patients with a known active malignancy should not be treated with ocrelizumab (see section 4.3). Individual benefit risk should be considered in patients with known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy. Patients should follow standard breast cancer screening per local guidelines.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves (see section 4.3).

In other auto-immune conditions, use of ocrelizumab concomitantly with immunosuppressants (e.g., chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increase of SIs, including opportunistic infections. Infections included and were not limited to atypical pneumonia and *pneumocystis jirovecii* pneumonia, varicella pneumonia, tuberculosis, histoplasmosis. In rare cases, some of these infections were fatal. An exploratory analysis identified the following factors associated with risk of SIs: higher doses of ocrelizumab than recommended in MS, other comorbidities, and chronic use of immunosuppressants/corticosteroids.

It is not recommended to use other immunosuppressives concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses. Knowledge is limited as to whether concomitant steroid use for symptomatic treatment of relapses is associated with an increased risk of infections in

clinical practice. In the intravenous ocrelizumab MS pivotal studies, the administration of corticosteroids for the treatment of relapse was not associated with an increased risk of SI.

When initiating ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab, the potential for overlapping pharmacodynamic effects should be taken into consideration (see section 5.1). Caution should be exercised when prescribing ocrelizumab taking into consideration the pharmacodynamics of other disease modifying MS therapies.

Vaccinations

The safety of immunisation with live or live-attenuated vaccines, following ocrelizumab therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended during treatment and not until B-cell repletion. In clinical trials, the median time for B-cell repletion was 72 weeks (see section 5.1).

In a randomised open-label study, RMS patients treated with intravenous ocrelizumab were able to mount humoral responses, although decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide with or without a booster vaccine, keyhole limpet haemocyanin neoantigen, and seasonal influenza vaccines (see section 4.5 and 5.1).

It is recommended to vaccinate patients treated with ocrelizumab with seasonal influenza vaccines that are inactivated.

Physicians should review the immunisation status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete their immunisation at least 6 weeks prior to initiation of ocrelizumab treatment.

Exposure in utero to ocrelizumab and vaccination of neonates and infants with live or live attenuated vaccines

Due to the potential depletion of B cells in infants of mothers who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered; therefore, measuring CD19-positive B-cell levels in neonates and infants prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunisation schedule and measurement of vaccine-induced response titres should be considered to check whether individuals have mounted a protective immune response because the efficacy of the vaccination may be decreased.

The safety and timing of vaccination should be discussed with the infant's physician (see section 4.6).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed, as no interactions are expected via cytochrome P450 enzymes, other metabolising enzymes or transporters.

Vaccinations

The safety of immunisation with live or live-attenuated vaccines, following ocrelizumab therapy has not been studied.

Data are available on the effects of tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet haemocyanin neoantigen, and seasonal influenza vaccines in patients receiving intravenous ocrelizumab (see section 4.4 and 5.1).

After treatment over 2 years with intravenous ocrelizumab, the proportion of patients with positive antibody titres against *S. pneumoniae*, mumps, rubella and varicella were generally similar to the proportions at baseline.

Immunosuppressants

It is not recommended to use other immunosuppressive therapies concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use contraception while receiving ocrelizumab and for 4 months after the last administered dose of ocrelizumab.

Pregnancy

There is a limited amount of data from the use of ocrelizumab in pregnant women. Ocrelizumab is an immunoglobulin G (IgG). IgG is known to cross the placental barrier. Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to ocrelizumab *in utero*. No B cell count data have been collected in neonates and infants exposed to ocrelizumab and the potential duration of B-cell depletion in neonates and infants is unknown (see section 4.4).

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 depletion *in utero* was also detected in animal studies.

Animal studies (embryo-foetal toxicity) do not indicate teratogenic effects. Reproductive toxicity was observed in pre- and post-natal development studies (see section 5.3).

Ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

Human IgGs are known to be excreted in breastmilk the first few days after birth (colostrum period), which decreases to low concentrations soon afterwards.

In a prospective, multicenter, open label study MN42989 (SOPRANINO), 13 lactating women received ocrelizumab at a median of 2.0 months postpartum (range 0.5-5.0 months). Low concentrations of ocrelizumab were detected in the breastmilk over 60 days following the mother's first postpartum infusion (median relative infant dose of 0.27% [range 0.0-1.8 %]), indicating minimal transfer of ocrelizumab to breastmilk. At 30 days after the mother's first postpartum infusion, ocrelizumab was undetectable in all available serum samples of breastfed infants (n=9), and infant B-cell levels were within normal range in all available blood samples (n=10). No effects of ocrelizumab on health, growth and development were observed in breastfed infants over a follow-up period of 44.6 weeks (range 8.6-62.7 weeks).

While no clinical data on infants potentially exposed to ocrelizumab via breastmilk receiving live or live-attenuated vaccines are available, no risks are expected due to normal B-cell levels and undetectable serum ocrelizumab levels observed in those infants.

In a separate prospective clinical study, low ocrelizumab concentrations in breastmilk (median relative infant dose of 0.1% [range 0.07-0.7%]) over 90 days after the mother's first postpartum infusion were observed in 29 lactating women who received ocrelizumab at a median of 4.3 months postpartum (range 0.1-36 months). Follow-up of 21 infants breastfed for at least 2 weeks showed normal growth and development up to 1 year.

Ocrelizumab can be used during breastfeeding starting a few days after birth.

Fertility

Preclinical data reveal no special hazards for humans based on studies of male and female fertility in cynomolgus monkeys exposed to ocrelizumab.

4.7 Effects on ability to drive and use machines

Ocrevus has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In the controlled period of the pivotal clinical trials, the most important and frequently reported adverse reactions were IRRs (34.3%, 40.1% in RMS and PPMS, respectively) and infections (58.5%, 72.2% in RMS and PPMS, respectively) (see section 4.4).

A total of 2,376 patients were included in the controlled period of the pivotal clinical trials; of these patients, 1,852 entered the OLE phase. All patients switched to ocrelizumab treatment during the OLE phase. 1,155 patients completed the OLE phase, resulting in approximately 10 years of continuous ocrelizumab treatment (15,515 patient-years of exposure) across the controlled period and OLE phase. The overall safety profile observed during the controlled period and OLE phase remains consistent with that observed during the controlled period.

The safety profile of Ocrevus solution for injection was consistent with the known safety profile of intravenous ocrelizumab below in Table 1 except for the very common adverse reaction of IRs.

Tabulated list of adverse reactions

Adverse reactions reported in the controlled period of the pivotal clinical trials with intravenous ocrelizumab and derived from spontaneous reporting are listed below in Table 1. The adverse reactions are listed by MedDRA system organ class and categories of frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each System Organ Class, the adverse reactions are presented in order of decreasing frequency.

Table 1 Adverse reactions

MedDRA System Organ Class (SOC)	Very common	Common	Not Known
Infections and infestations	Upper respiratory tract infection, nasopharyngitis, influenza	Sinusitis, bronchitis, oral herpes, gastroenteritis, respiratory tract infection, viral infection, herpes zoster, conjunctivitis, cellulitis	
Blood and lymphatic system disorders		Neutropenia	Late onset of Neutropenia[3]
Respiratory, thoracic and mediastinal disorders		Cough, catarrh	
Investigations	Blood immunoglobulin M decreased	Blood immunoglobulin G decreased	
Injury, poisoning and procedural complications	Infusion-related reactions[1], injection reaction[2,3]		

[1] Observed only in the pooled intravenous ocrelizumab dataset

[2] Observed in a study outside of the pooled intravenous ocrelizumab dataset (associated with subcutaneous administration).

[3] Observed in the postmarketing setting.

Description of selected adverse reactions

Injection reactions

Based on the observed symptoms, IRs are categorised into systemic IRs and local IRs.

In OCARINA II, 118 patients (ocrelizumab-naïve) received the first injection of the product. The most common symptoms reported with systemic IRs and local IRs included: headache (2.5%), nausea (1.7%), injection site erythema (29.7%), injection site pain (14.4%), injection site swelling (8.5%), and injection site pruritus (6.8%). IRs occurred in 48.3% of these patients after the first injection. Of the 118 patients, 11.0% and 45.8% of patients experienced at least one event of systemic IR and local IR, respectively. Among the patients with IR, the majority of patients (82.5%) had IRs occur within 24 hours after the end of injection as opposed to during the injection. All IRs were non serious and of mild (71.9%) or moderate (28.1%) severity. The median duration of IR was 3 days for systemic IRs and 4 days for local IRs. All patients recovered from IRs, of which 26.3% required symptomatic treatment.

In OCARINA I, 125 patients received one or more subcutaneous injections of ocrelizumab 1200 mg. Of the 125 patients who received the first injection, 16.0% of patients experienced at least one event of systemic IR and 64.0% of patients experienced at least one event of local IR. Of the 104 patients who received the second injection, the incidence of systemic IR and local IR decreased to 7.7% and 37.5%,

respectively. All IRs were non serious and all except one IR were of mild or moderate severity for the first injection. All IRs were non serious and of mild or moderate severity for the second injection. 21.2% and 17.9% of patients experiencing IR required symptomatic treatment after the first and second injection, respectively.

Intravenous ocrelizumab is associated with infusion-related reactions (IRRs), which may also be related to cytokine release and/or other chemical mediators. IRRs may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis. Serious IRRs, some requiring hospitalisation, have been reported with the use of intravenous ocrelizumab.

Infection

In the active-controlled studies in RMS, infections occurred in 58.5% of patients receiving intravenous ocrelizumab vs 52.5% of patients receiving interferon beta 1a. SIs occurred in 1.3% of patients receiving intravenous ocrelizumab vs 2.9% of patients receiving interferon beta 1a. In the placebo-controlled study in PPMS, infections occurred in 72.2% of patients receiving intravenous ocrelizumab vs 69.9% of patients receiving placebo. SIs occurred in 6.2% of patients receiving intravenous ocrelizumab vs 6.7% of patients receiving placebo.

All patients switched to intravenous ocrelizumab during the OLE phase in both RMS and PPMS pivotal intravenous ocrelizumab studies. Over the OLE phase in RMS and PPMS patients, the overall risk of SIs did not increase from that observed during the controlled period. As observed during the controlled period, the rate of SIs in PPMS patients remained higher than that observed in RMS patients.

In line with the previous analysis of risk factors for SIs in auto immune conditions other than MS (see section 4.4), a multivariate analysis of risk factors for SIs was conducted in the approximately 10 years of cumulative exposure data from the controlled period and OLE phase of the pivotal clinical trials. Risk factors for SIs in RMS patients include having at least 1 comorbidity, recent clinical relapse, and Expanded Disability Status Scale (EDSS) ≥ 6.0. Risk factors for SIs in PPMS patients include body mass index greater than 25 kg/m^2, having at least 2 comorbidities, EDSS ≥ 6.0, and IgM < lower limit of normal (LLN). Comorbidities included, but were not limited to, cardiovascular, renal and urinary tract conditions, previous infections, and depression.

Respiratory tract infections

The proportion of respiratory tract infections was higher in intravenous ocrelizumab treated patients compared to interferon beta-1-a and placebo.
In the RMS clinical trials, 39.9% of intravenous ocrelizumab treated patients and 33.2% interferon beta-1-a treated patients experienced an upper respiratory tract infection and 7.5% of intravenous ocrelizumab treated patients and 5.2% of interferon beta-1-a treated patients experienced a lower respiratory tract infection.
In the PPMS clinical trial, 48.8% of intravenous ocrelizumab treated patients and 42.7% of patients who received placebo experienced an upper respiratory tract infection, and 9.9% of intravenous ocrelizumab treated patients and 9.2% of patients who received placebo experienced a lower respiratory tract infection.
The respiratory tract infections reported in patients treated with intravenous ocrelizumab were predominately mild to moderate (80 – 90 %).

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in intravenous ocrelizumab treated patients than in interferon-beta-1a 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%). All infections were mild to moderate in severity, except one Grade 3 event, and patients recovered with treatment by standard therapies.

In the placebo-controlled (PPMS) clinical trial, a higher proportion of patients with oral herpes (2.7% vs 0.8%) were observed in the intravenous ocrelizumab treatment arm.

Laboratory abnormalities

Immunoglobulins

Ocrelizumab treatment resulted in a decrease in total immunoglobulins over the controlled period of the pivotal clinical intravenous ocrelizumab trials, mainly driven by reduction in IgM.

Clinical trial data from the controlled period and OLE phase of the pivotal clinical trials have shown an association between decreased levels of IgG (and less so for IgM or IgA) and increased rate of SIs. 2.1% of RMS patients had a SI during a period with IgG < LLN and in 2.3% of PPMS patients had a SI during a period with IgG < LLN. The difference in rate of SIs between patients with IgG < LLN compared to patients with IgG ≥ LLN did not increase over time. The type, severity, latency, duration, and outcome of SIs observed during episodes of immunoglobulins below LLN were consistent with the overall SIs observed in patients treated with ocrelizumab during the controlled period and OLE phase. Throughout the 10 years of continuous ocrelizumab treatment, mean IgG levels of RMS and PPMS patients remained above LLN.

Lymphocytes

In RMS, a decrease in lymphocyte < LLN was observed in 20.7% of patients treated with intravenous ocrelizumab compared with 32.6% of patients treated with interferon beta-1a. In PPMS, a decrease in lymphocytes <LLN was observed in 26.3% of intravenous ocrelizumab treated patients vs 11.7% of placebo-treated patients.

The majority of these decreases reported in intravenous ocrelizumab treated patients were Grade 1 (<LLN – 800 cells/mm^3) and 2 (between 500 and 800 cells/mm^3) in severity. Approximately 1% of the patients in the intravenous ocrelizumab group had a Grade 3 lymphopenia (between 200 and 500 cells/mm^3). None of the patients was reported with Grade 4 lymphopenia (< 200 cells/mm^3).

An increased rate of SIs was observed during episodes of confirmed total lymphocytes counts decrease in intravenous ocrelizumab treated patients. The number of SIs was too low to draw definitive conclusions.

Neutrophils

In the active-controlled (RMS) treatment period, a decrease in neutrophils < LNN was observed in 14.7% of patients treated with intravenous ocrelizumab compared with 40.9% of patients treated with interferon beta-1a. In the placebo-controlled (PPMS) clinical trial, the proportion of intravenous ocrelizumab patients presenting decreased neutrophils was higher (12.9 %) than placebo patients (10.0 %); among these a higher percentage of patients (4.3%) in the intravenous ocrelizumab group had Grade 2 or above neutropenia vs 1.3% in the placebo group; approximately 1% of the patients in the intravenous ocrelizumab group had Grade 4 neutropenia vs 0% in the placebo group.

The majority of the neutrophil decreases were transient (only observed once for a given patient treated with ocrelizumab) and were Grade 1 (between <LLN and 1500 cells/mm^3) and 2 (between 1000 and 1500 cells/mm^3) in severity. Overall, approximately 1% of the patients in the intravenous ocrelizumab group had Grade 3 or 4 neutropenia. One patient with Grade 3 (between 500 and 1000 cells/mm^3) and one patient with Grade 4 (< 500 cells/mm^3) neutropenia required specific treatment with granulocyte-colony stimulating factor, and remained on ocrelizumab after the episode. Neutropenia can occur several months after the administration of ocrelizumab (see section 4.4).

Other

One patient, who received 2000 mg of intravenous ocrelizumab, died of systemic inflammatory response syndrome (SIRS) of unknown aetiology, following a magnetic resonance imaging (MRI) examination 12 weeks after the last infusion; an anaphylactoid reaction to the MRI gadolinium-contrast agent could have contributed to the SIRS.

4.9 Overdose

There is limited clinical trial experience with doses higher than the approved dose of ocrelizumab. The highest dose tested to date in MS patients is 2000 mg, administered as two 1000 mg intravenous infusions separated by 2 weeks (Phase II dose finding study in RRMS) and 1200 mg, administered as a subcutaneous injection (Phase Ib dose finding study). The adverse reactions were consistent with the safety profile in the pivotal clinical studies.

There is no specific antidote in the event of an overdose; interrupt the injection immediately and observe the patient for IRs (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG08.

Mechanism of action

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B cells.

CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells.

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS is not fully elucidated but is presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. The capacity of B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

Subcutaneous ocrelizumab contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated active substances when administered subcutaneously.

Pharmacodynamic effects

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post treatment (first time-point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period with intravenous ocrelizumab. For the B-cell counts, CD19 is used, as the presence of ocrelizumab interferes with the recognition of CD20 by the assay.

In the Phase III studies, between each dose of intravenous ocrelizumab, up to 5% of patients showed B-cell repletion (> LLN or baseline) at least at one time point. The extent and duration of B-cell depletion was consistent in the PPMS and RMS trials.

The longest follow up time after the last intravenous infusion (Phase II study WA21493, N=51) indicates that the median time to B-cell repletion (return to baseline/LLN whichever occurred first) was 72 weeks (range 27 - 175 weeks). 90% of all patients had their B-cells repleted to LLN or baseline by approximately two and a half years after the last infusion.

Clinical efficacy and safety

Subcutaneous formulation

OCARINA II
Study CN42097 (OCARINA II) was a multi-center, randomised, open-label, parallel arm trial conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological and clinical effects of subcutaneous ocrelizumab compared with intravenous ocrelizumab in patients with either RMS or PPMS. OCARINA II was designed to demonstrate non-inferiority of treatment with subcutaneous ocrelizumab versus intravenous ocrelizumab based on the primary PK endpoint of area under the concentration time curve (AUC) up to week 12 post-injection/infusion (AUC_{w1-12}).

A total of 236 patients with RMS or PPMS (213 patients with RMS, 23 patients with PPMS) were randomised in a 1:1 ratio to the subcutaneous arm or intravenous arm. During the controlled period (Day 0 to Week 24), patients received either a single 920 mg subcutaneous injection at study Day 1 or two 300 mg intravenous infusions at study Day 1 and 14. After the controlled period, all patients had the opportunity to receive further subcutaneous injections of 920 mg ocrelizumab at Weeks 24 and 48 (Dose 2 and 3, respectively). Patients were excluded if they had previous treatment with anti-CD20 antibodies within the last 24 months, including ocrelizumab.

Patients were aged 18-65 years with an EDSS between 0 to 6.5 at screening. The demographics were similar and baseline characteristics were well balanced across the two treatment groups. The mean age was 39.9 years in the subcutaneous arm and 40.0 years in the intravenous arm. 34.7% of patients were male in the subcutaneous arm and 40.7% of patients were male in the intravenous arm. The mean/median duration since MS diagnosis was 5.70/3.10 years in the subcutaneous arm and 4.78/2.35 years in the intravenous arm.

Non-inferiority of the ocrelizumab exposure after administration of 920 mg subcutaneous ocrelizumab compared to 600 mg intravenous ocrelizumab was demonstrated based on the PK primary endpoint, AUC up to week 12 (AUC_{w1-12}) post-injection (see section 5.2).

Intravenous formulation

Relapsing forms of multiple sclerosis (RMS)

Efficacy and safety of ocrelizumab were evaluated in two randomised, double-blind, double-dummy, active comparator-controlled clinical trials (WA21092 and WA21093), with identical design, in patients with relapsing forms of MS (in accordance with McDonald criteria 2010) and evidence of disease activity (as defined by clinical or imaging features) within the previous two years. Study design and baseline characteristics of the study population are summarised in Table 2.

Demographic and baseline characteristics were well balanced across the two treatment groups. Patients receiving ocrelizumab (Group A) were given 600 mg every 6 months (Dose 1 as 2 x 300 mg intravenous infusions, administered 2 weeks apart, and subsequent doses were administered as a single 600 mg intravenous infusion). Patients in Group B were administered Interferon beta-1a 44 mcg via subcutaneous injection 3 times per week.

Table 2 Study design, demographic and baseline characteristics

	Study 1	**Study 2**

Study name	**WA21092 (OPERA I) (n=821)**		**WA21093 (OPERA II) (n=835)**	
Study design				
Study population	Patients with relapsing forms of MS			
Disease history at screening	At least two relapses within the prior two years or one relapse within the prior year; EDSS* between 0 and 5.5, inclusive			
Study duration	2 years			
Treatment groups	Group A: Ocrelizumab 600 mg Group B: interferon beta-1a 44 mcg S.C. (IFN)			
Baseline characteristics	Ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrelizumab 600 mg (n=417)	IFN 44 mcg (n=418)
Mean age (years)	37.1	36.9	37.2	37.4
Age range (years) at inclusion	18 - 56	18 - 55	18 - 55	18 - 55
Gender distribution (% male/% female)	34.1/65.9	33.8/66.2	35.0/65.0	33.0/67.0
Mean/Median disease duration since diagnosis (years)	3.82/1.53	3.71/1.57	4.15/2.10	4.13/1.84
Patients naive to previous DMT (%)**	73.4	71.0	72.7	74.9
Mean number of relapses in the last year	1.31	1.33	1.32	1.34
Proportion of patients with Gd enhancing T1 lesions	42.5	38.1	39.0	41.4
Mean EDSS*	2.82	2.71	2.73	2.79

* Expanded Disability Status Scale

** Patients who had not been treated with a disease-modifying therapy (DMT) in the 2 years prior to randomisation.

Key clinical and MRI efficacy results are presented in Table 3 and Figure 1.

The results of these studies show that ocrelizumab significantly suppressed relapses, sub-clinical disease activity measured by MRI, and disease progression compared with interferon beta-1a 44 mcg subcutaneous.

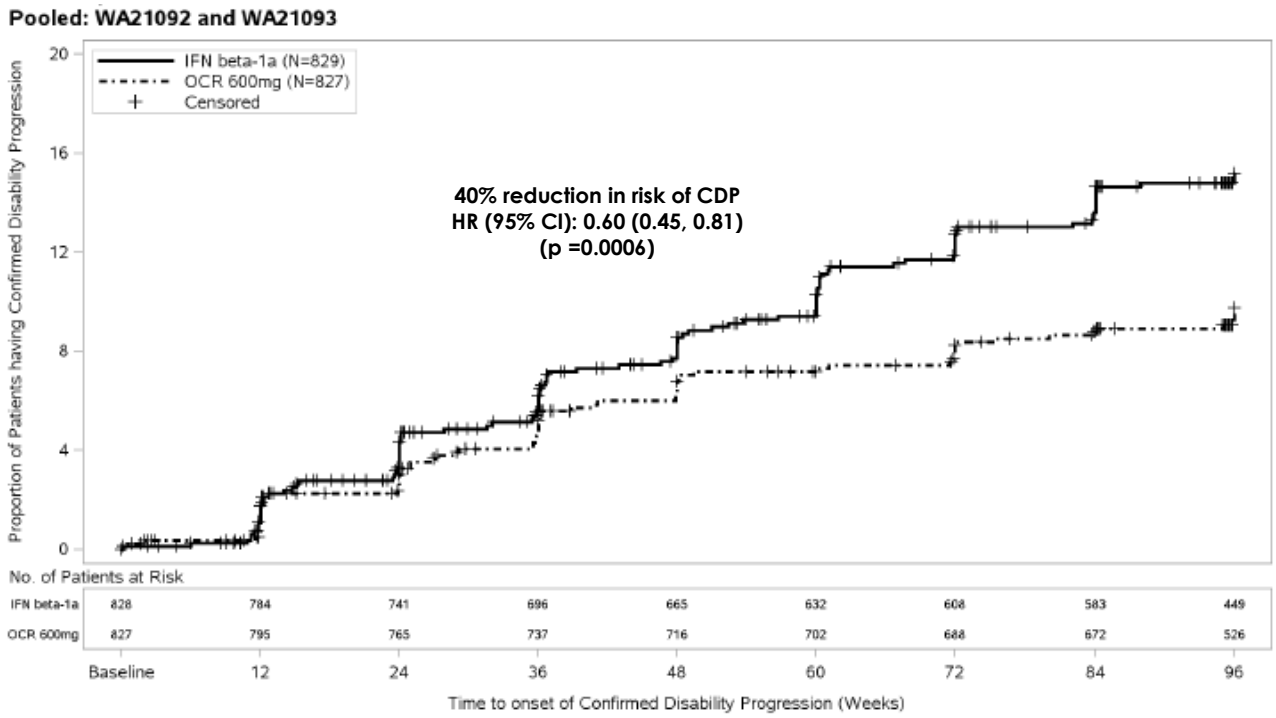
Table 3 Key clinical and MRI endpoints from Studies WA21092 and WA21093 (RMS)

Endpoints	**Study 1: WA21092 (OPERA I)**		**Study 2: WA21093 (OPERA II)**	
	Ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrelizumab 600 mg (n=417)	IFN 44 mcg (n=418)
Clinical Endpoints				
Annualised Relapse Rate (ARR) (primary endpoint)[8]	0.156	0.292	0.155	0.290
Relative Reduction	46 % (p<0.0001)		47 % (p<0.0001)	
Proportion of patients with 12 week Confirmed Disability Progression[3]	9.8% Ocrelizumab vs 15.2% IFN 40% (p=0.0006)[7]			

Risk Reduction (Pooled Analysis[1]) Risk Reduction (Individual Studies[2])	43 % (p=0.0139)[7]		37 % (p=0.0169)[7]	
Proportion of patients with 24 week Confirmed Disability Progression (CDP)[3]	7.6% Ocrelizumab vs 12.0% IFN 40% (p=0.0025)[7]			
Risk Reduction (Pooled Analysis[1]) Risk Reduction (Individual Studies[2])	43 % (p=0.0278)[7]		37 % (p=0.0370)[7]	
Proportion of patients with at least 12 weeks Confirmed Disability Improvement[4]	20.7% Ocrelizumab vs 15.6% IFN			
Relative Increase (Pooled Analysis[1])	33% (p=0.0194)			
Relative Increase (Individual Studies[2])	61% (p=0.0106)		14% (p=0.4019)	
Proportion of patients Relapse free at 96 weeks[2]	80.4%	66.7%	78.9%	64.3%
	(p<0.0001)		(p<0.0001)	
Proportion of patients with No Evidence of Disease Activity (NEDA)[5]	48%	29%	48%	25%
Relative Increase[2]	64% (p<0.0001)		89% (p<0.0001)	
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	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 scan	0.323	1.413	0.325	1.904
Relative reduction	77% (p<0.0001)		83% (p<0.0001)	
Percentage change in brain volume from Week 24 to week 96	-0.572	-0.741	-0.638	-0.750
Relative reduction in brain volume loss	22.8% (p=0.0042)[6]		14.9% (p=0.0900)	

[1] Data prospectively pooled from Study 1 and 2
[2] Non-confirmatory p-value analysis; not part of the pre-specified testing hierarchy
[3] CDP defined as an increase of ≥ 1.0 point from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5, Kaplan-Meier estimates at Week 96
[4] Defined as decrease of ≥ 1.0 point from the baseline EDSS score for patients with baseline EDSS score ≥ 2 and ≤ 5.5, or ≥0.5 when the baseline score is > 5.5. Patients with baseline score < 2 were not included in analysis.
[5] NEDA defined as absence of protocol defined relapses, 12-week CDP, and any MRI activity (either Gd-enhancing T1 lesions, or new or enlarging T2 lesions) during the whole 96-week treatment. Exploratory result based on complete ITT population.
[6] Non-confirmatory p-value; hierarchical testing procedure terminated before reaching endpoint.
[7] Log-rank test
[8] Confirmed relapses (accompanied by a clinically relevant change in EDSS).

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 (Pooled WA21092 and WA21093 ITT Population)*



*Pre-specified pooled analysis of WA21092 and WA21093.

Results of the pre-specified pooled analyses of time to CDP sustained for at least 12 weeks (40% risk reduction for ocrelizumab compared to interferon beta-1a (p=0.0006) were highly consistent with the results sustained for at least 24 weeks (40% risk reduction for ocrelizumab compared to interferon beta-1a, p=0.0025).

The studies enrolled patients with active disease. These included both active treatment naive and previously treated inadequate responders, as defined by clinical or imaging features. Analysis of patient populations with differing baseline levels of disease activity, including active and highly active disease, showed that the efficacy of ocrelizumab on ARR and 12 week CDP was consistent with the overall population.

Primary progressive multiple sclerosis (PPMS)

Efficacy and safety of ocrelizumab were also evaluated in a randomised, double-blind, placebo-controlled clinical trial in patients with primary progressive MS (Study WA25046) who were early in their disease course according to the main inclusion criteria, i.e.: ages 18-55 years, inclusive; EDSS at screening from 3.0 to 6.5 points; disease duration from the onset of MS symptoms less than 10 years in patients with an EDSS at screening ≤5.0 or less than 15 years in patients with an EDSS at screening >5.0. With regard to disease activity, features characteristic of inflammatory activity, even in progressive MS, can be imaging-related, (i.e. T1 Gd-enhancing lesions and/or active [new or enlarging] T2 lesions). MRI evidence should be used to confirm inflammatory activity in all patients. Patients over 55 years of age were not studied. Study design and baseline characteristics of the study population are presented in Table 4.

Demographic and baseline characteristics were well balanced across the two treatment groups. Cranial MRI showed imaging features characteristic of inflammatory activity either by T1 Gd enhancing lesions or T2 lesions.

During the Phase III PPMS study, patients received 600 mg ocrelizumab every 6 months as two 300 mg infusions, given two weeks apart, throughout the treatment period. The 600 mg infusions in RMS and the 2 x 300 mg infusions in PPMS demonstrated consistent PK/PD profiles. IRR profiles per infusion were also similar, independent of whether the 600 mg dose was administered as a single 600 mg infusion or as two 300 mg infusions separated by two weeks (see sections 4.8 and 5.2), but

due to overall more infusions with the 2 x 300 mg regimen, the total number of IRRs were higher. Therefore, after Dose 1 it is recommended to administer ocrelizumab in a 600 mg single infusion (see section 4.2) to reduce the total number of infusions (with concurrent exposure to prophylactic methylprednisolone and an antihistamine) and the related infusion reactions.

Table 4 Study design, demographics and baseline characteristics for Study WA25046

Study name	**Study WA25046 ORATORIO (n=732)**	
Study design		
Study population	Patients with primary progressive form of MS	
Study duration	Event-driven *(Minimum 120 weeks and 253 confirmed disability progression events)* *(Median follow-up time:* Ocrelizumab *3.0 years, Placebo 2.8 years*	
Disease history at screening	Age 18-55 years, EDSS of 3.0 to 6.5	
Treatment groups	Group A: Ocrelizumab 600 mg Group B: Placebo, in 2:1 randomisation	
Baseline characteristics	Ocrelizumab 600 mg (n=488)	Placebo (n=244)
Mean age (years)	44.7	44.4
Age range (years) at inclusion	20 - 56	18 - 56
Gender distribution (% male/% female)	51.4/48.6	49.2/50.8
Mean/Median disease duration since PPMS diagnosis (years)	2.9/1.6	2.8/1.3
Mean EDSS	4.7	4.7

Key clinical and MRI efficacy results are presented in Table 5 and Figure 2.

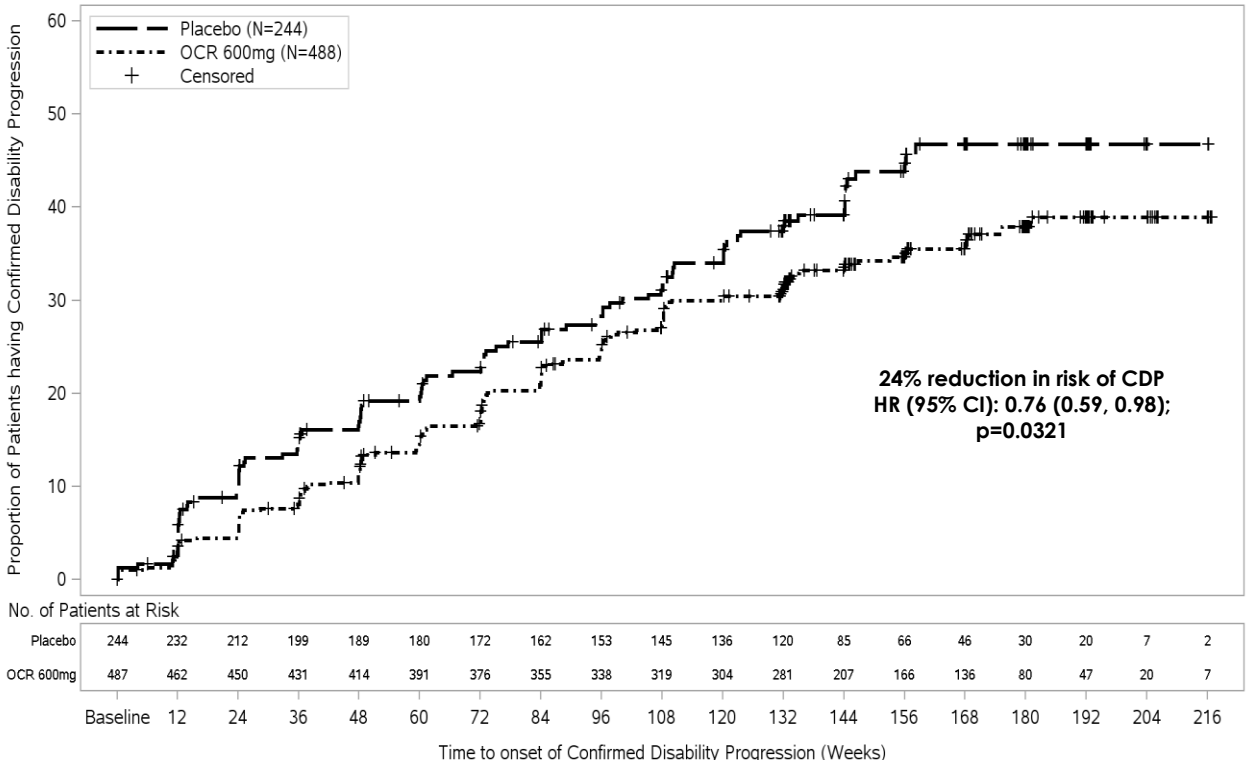
The results of this study show that ocrelizumab significantly delays disease progression and reduces deterioration in walking speed compared with placebo.

Table 5 Key clinical and MRI endpoints from Study WA25046 (PPMS)

	Study 3	
	WA25046 (Oratorio)	
Endpoints	Ocrelizumab 600 mg (n=488)	Placebo (n=244)
Clinical Endpoints		
Primary efficacy endpoint Proportion of patients with 12 weeks - Confirmed Disability Progression[1] (primary endpoint)	30.2%	34.0%
Risk reduction	24% (p=0.0321)	
Proportion of patients with 24 weeks - Confirmed Disability Progression[1]	28.3%	32.7%
Risk reduction	25% (p=0.0365)	
Percentage change in Timed 25-Foot Walk from baseline to Week 120	38.9	55.1
Relative reduction in progression rate of walking time	29.4% (p=0.0404)	
MRI Endpoints		
Percentage change in T2 hyperintense lesion volume, from baseline to Week 120	-3.4	7.4
	(p<0.0001)	
Percentage change in brain volume from Week 24 to Week 120	-0.902	-1.093
Relative reduction in rate of brain volume loss	17.5% (p=0.0206)	

[1] Defined as an increase of ≥ 1.0 point from the baseline EDSS score for patients with baseline score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5, Kaplan-Meier estimates at Week 120.

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 (WA25046 ITT Population)*



* All patients in this analysis had a minimum of 120 weeks of follow-up. The primary analysis is based on all events accrued.

Pre-specified non-powered subgroup analysis of the primary endpoint suggests that patients who are younger or those with T1 Gd-enhancing lesions at baseline receive a greater treatment benefit than patients who are older or without T1 Gd-enhancing lesions (≤ 45 years: HR 0.64 [0.45, 0.92], >45 years: HR 0.88 [0.62, 1.26]; with T1 Gd-enhancing lesions at baseline: HR 0.65 [0.40-1.06], without T1 Gd-enhancing lesions at baseline: HR 0.84 [0.62-1.13]).

Moreover, post-hoc analyses suggested that younger patients with T1 Gd-enhancing lesions at baseline have the better treatment effect (≤ 45 years: HR 0.52 [0.27-1.00]; ≤ 46 years [median age of the WA25046 study]; HR 0.48 [0.25-0.92]; <51 years: HR 0.53 [0.31-0.89]).

Post-hoc analyses were performed in the Extended Controlled Period (ECP), which includes double-blinded treatment and approximately 9 additional months of controlled follow-up before continuing into the Open-Label Extension (OLE) or until withdrawal from study treatment. The proportion of patients with 24 week Confirmed Disability Progression of EDSS≥7.0 (24W-CDP of EDSS≥7.0, time to wheelchair) was 9.1% in the placebo group compared to 4.8% in the ocrelizumab group at Week 144, resulting in a 47% risk reduction of the time to wheelchair (HR 0.53, [0.31, 0.92]) during the ECP. As these results were exploratory in nature and included data after unblinding, the results should be interpreted with caution.

Immunogenicity

Subcutaneous formulation

Across OCARINA I and OCARINA II, no patients had treatment-emergent anti-drug antibodies (ADAs) to ocrelizumab. Patients in OCARINA II were tested at baseline and every 6 months post treatment for the duration of the trial for ADAs. Transient ADAs may therefore not be detected between the assessed time points.

The incidence of treatment-emergent anti-rHuPH20 (hyaluronidase) antibodies in patients treated with subcutaneous ocrelizumab in OCARINA I was 2.3% (3/132). No patients from OCARINA II had treatment-emergent anti-rHuPH20 antibodies.

Intravenous formulation

Patients in MS trials (WA21092, WA21093 and WA25046) were tested at multiple time points (baseline and every 6 months post treatment for the duration of the trial) for ADAs. Out of 1311 patients treated with ocrelizumab, 12 (~1%) tested positive for treatment-emergent ADAs, of which 2 patients tested positive for neutralising antibodies. The impact of treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADA associated with ocrelizumab.

Immunisations

In a randomised open-label study in RMS patients (N=102), the percentage of patients with a positive response to tetanus vaccine at 8 weeks after vaccination was 23.9% in the intravenous ocrelizumab group compared to 54.5% in the control group (no disease-modifying therapy except interferon-beta). Geometric mean anti-tetanus toxoid specific antibody titres at 8 weeks were 3.74 and 9.81 IU/ml, respectively. Positive response to ≥5 serotypes in 23-PPV at 4 weeks after vaccination was 71.6% in the intravenous ocrelizumab group and 100% in the control group. In patients treated with intravenous ocrelizumab a booster vaccine (13-PCV) given 4 weeks after 23-PPV did not markedly enhance the response to 12 serotypes in common with 23-PPV. The percentage of patients with seroprotective titres against five influenza strains ranged from 20.0–60.0% and 16.7–43.8% pre-vaccination and at 4 weeks post vaccination from 55.6–80.0% in patients treated with intravenous ocrelizumab and 75.0–97.0% in the control group, respectively. See sections 4.4 and 4.5.

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics of ocrelizumab in the MS studies were described by a two compartment model with time-dependent clearance, and with PK parameters typical for an IgG1 monoclonal antibody.

After administration of 920 mg subcutaneous ocrelizumab, the predicted mean exposure (AUC over the 24 week dosing interval) was 3730 µg/mL•day. The primary PK endpoint in OCARINA II, AUC_{w1-12}, after 920 mg subcutaneous ocrelizumab was shown to be non-inferior to 600 mg intravenous ocrelizumab. The geometric mean ratio for AUC_{w1-12} was 1.29 (90% CI: 1.23–1.35).

Absorption

The estimated bioavailability after subcutaneous administration of 920 mg ocrelizumab was 81%. The mean C_{max} was 132 µg/mL and t_{max} was reached after approximately 4 days (range 2-13 days).

Distribution

The population pharmacokinetics estimate of the central volume of distribution was 2.78 L. Peripheral volume and inter-compartment clearance were estimated at 2.68 L and 0.294 L/day.

Biotransformation

The metabolism of ocrelizumab has not been directly studied, as antibodies are cleared principally by catabolism (i.e. breakdown into peptides and amino acids).

Elimination

Constant clearance was estimated at 0.17 L/day, and initial time-dependent clearance at 0.0489 L/day which declined with a half-life of 33 weeks. The terminal elimination half-life of ocrelizumab was 26 days.

Special populations

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of ocrelizumab in children and adolescents less than 18 years of age.

Elderly

There are no dedicated PK studies of ocrelizumab in patients ≥55 years due to limited clinical experience (see section 4.2).

Renal impairment

No formal pharmacokinetic study has been conducted. Patients with mild renal impairment were included in clinical trials and no change in the pharmacokinetics of ocrelizumab was observed in those patients. There is no PK information available in patients with moderate or severe renal impairment.

Hepatic impairment

No formal pharmacokinetic study has been conducted. Patients with mild hepatic impairment were included in clinical trials, and no change in the pharmacokinetics was observed in those patients. There is no PK information available in patients with moderate or severe hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and embryo-foetal development. Neither carcinogenicity nor mutagenicity studies have been conducted with ocrelizumab.

In two pre- and post-natal development studies in cynomolgus monkeys, administration of intravenous ocrelizumab from gestation day 20 to at least parturition was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. The maternal doses administered in these studies resulted in maximum mean serum concentrations (C_{max}) that were 4.5- to 21-fold above those anticipated in the clinical setting.

There were five cases of neonatal moribundities, one attributed to weakness due to premature birth accompanied by opportunistic bacterial infection, one due to an infective meningoencephalitis involving the cerebellum of the neonate from a maternal dam with an active bacterial infection (mastitis) and three with evidence of jaundice and hepatic damage, with a viral aetiology suspected, possibly a polyomavirus. The course of these five confirmed or suspected infections could have potentially been impacted by B-cell depletion. Newborn offspring of maternal animals exposed to ocrelizumab were noted to have depleted B cell populations during the post-natal phase.

Hyaluronidase

Non-clinical data for recombinant human hyaluronidase reveal no special hazard based on conventional studies of repeated dose toxicity including safety pharmacology endpoints.

Hyaluronidase (rHuPH20) is found in most tissues of the human body. Subcutaneous administration of ocrelizumab with hyaluronidase was well tolerated in rats and minipigs in local tolerance studies.

Reproductive toxicology studies with rHuPH20 revealed embryofetal toxicity in mice, with no effect level >1,100-fold higher than the suggested clinical dose, however, without evidence of teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
Sodium acetate trihydrate
Glacial acetic acid
α,α-trehalose dihydrate
Polysorbate 20
L-methionine
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

This medicine should not be used after the expiry date (EXP) shown on the pack.

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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze. Do not shake.
Keep the vials in the outer carton in order to protect from light.

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 6.3.

6.5 Nature and contents of container

23 mL of solution for injection in a vial (colourless Type I glass).
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

The medicinal product should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

The medicinal product is for single use only and should be prepared by a healthcare professional using aseptic technique.

No incompatibilities between this medicinal product and polypropylene (PP), polycarbonate (PC), polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) and stainless steel have been observed.

Preparation of the syringe

- Prior to use, the vial should be removed from the refrigerator to allow the solution to come to room temperature.
- Withdraw the entire contents of Ocrevus solution for injection from the vial with a syringe and transfer needle (21G recommended).
- Remove the transfer needle and attach a subcutaneous infusion set (e.g., winged/butterfly) containing a 24 – 26G needle for injection. Use a subcutaneous infusion set with residual hold-up volume NOT exceeding 0.8 mL for administration.
- Prime the subcutaneous infusion line with the solution for injection to eliminate the air in the infusion line and stop before the fluid reaches the needle.
- Ensure the syringe contains exactly 23 mL of the 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.

If the dose is not administered immediately, refer to “Storage of the syringe” below.

Storage of the syringe

- If the dose is not to be administered immediately, use aseptic technique to withdraw the entire contents of Ocrevus solution for injection from the vial into the syringe to account for the dose volume (23 mL) and priming volume for the subcutaneous infusion set. Replace the transfer needle with a syringe closing cap. Do not attach a subcutaneous infusion set for storage.
- If the syringe was stored in a refrigerator, allow the syringe to reach room temperature prior to adminsitration.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Medicine: keep out of reach of children

MYOcrevus20250909CDS15.0
Date of Revision: Sep 2025

Made for
F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Roche Diagnostics GmbH, Mannheim, Germany

Release of finished drug product:
by F. Hoffmann-La Roche Ltd, Kaiseraugst, Switzerland