

■ PROGRESSION IN MS STARTS EARLY¹⁻⁸

AT THE FIRST SIGN
OF DISEASE ACTIVITY
IN RMS AND PPMS*

START

NOW

WITH TWICE-YEARLY
OCREVUS[†]

#1 prescribed DMT for patients starting or switching to a new therapy[‡]

*RMS and PPMS diagnoses based on McDonald criteria.

[†]The first dose of OCREVUS is split between 2 treatments, for a total of 3 treatments in the first year.⁸

[‡]Symphony Health prescriber-based DMT data since July 2017.⁹

DMT=disease-modifying therapy.

150K+
PATIENTS
TREATED GLOBALLY

Indications

OCREVUS is indicated for the treatment of:

- Relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS (PPMS), in adults

Contraindications

OCREVUS is contraindicated in patients with active hepatitis B virus infection and in patients with a history of life-threatening infusion reaction to OCREVUS.

Important Safety Information

Warnings and Precautions

Infusion Reactions

OCREVUS can cause infusion reactions, which 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. In multiple sclerosis (MS) clinical trials, the incidence of infusion reactions in OCREVUS-treated patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to each infusion] was 34-40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of OCREVUS-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization.

For additional safety information, please see [page 10](#) and full

Prescribing Information and **Medication Guide**.

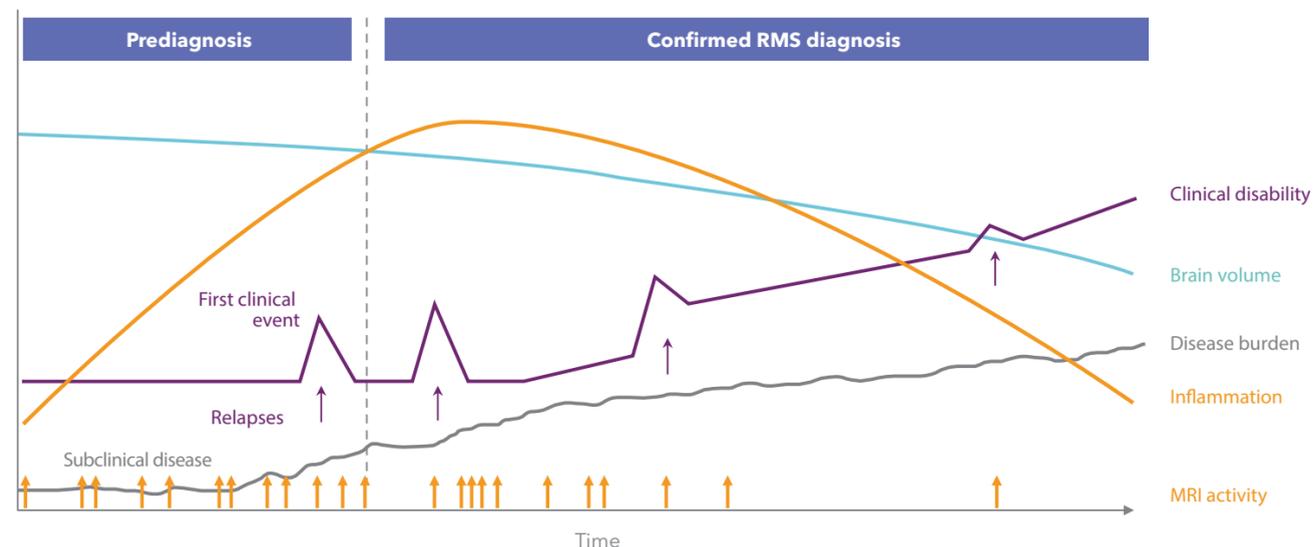
OCREVUS[®]
ocrelizumab 300MG/10ML
INJECTION FOR IV

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Progression in MS starts early, despite initial presentation¹⁻⁷

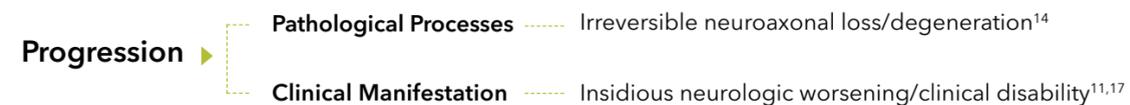
MS is characterized by acute and diffuse inflammation and chronic neurodegeneration^{2,4,10}



Adapted from Gavin Giovannoni based on Fox RJ, Cohen JA. *Cleve Clin J Med.* 2001;68:157-171.

Inflammation is an important driver of progression early in MS^{2,6,7,10-13}

- Inflammatory activity is thought to be highest early in MS and is associated with younger age, relapses, and new lesions^{2,5,14-16}
- These lesions contribute to axonal loss/degeneration, which is associated with disability progression^{11,13,14,17}

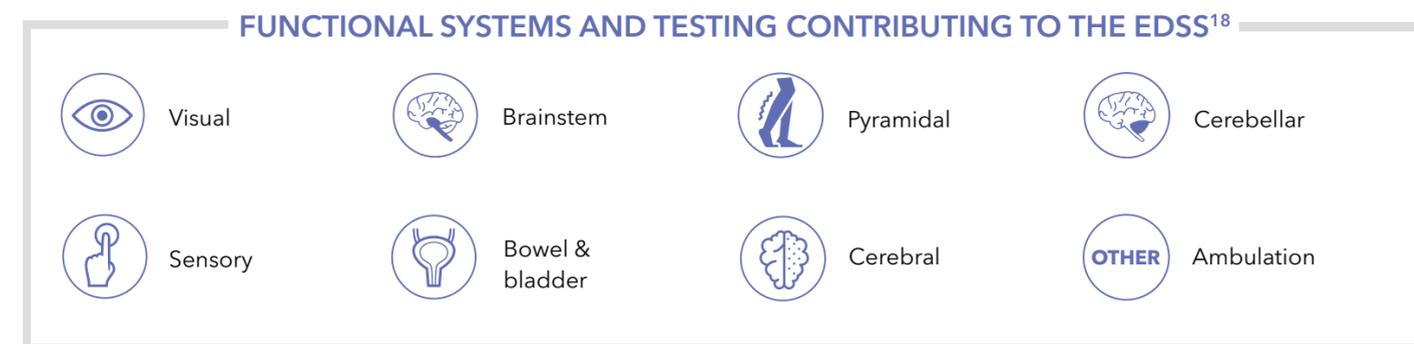


As functional reserve is lost, the ability to compensate for damage decreases and disability emerges.^{10,12}

Recognizing and managing progression early in RMS can be challenging⁵

Disability progression in MS patients goes beyond impact on ambulation¹⁸

- Early neurologic deficits can be difficult to evaluate on exam; even tools used in clinical trials, such as the EDSS, may not capture early signs of worsening¹⁹⁻²²
 - Additional assessments (eg, SDMT;BDI-II; HADS) may help with earlier identification of subtle changes in function
- Patients who are still ambulatory can accumulate moderate disability in any 1 of the functional systems or mild disability across several functional systems (which equates to an EDSS of 3.0 in clinical trials)¹⁸

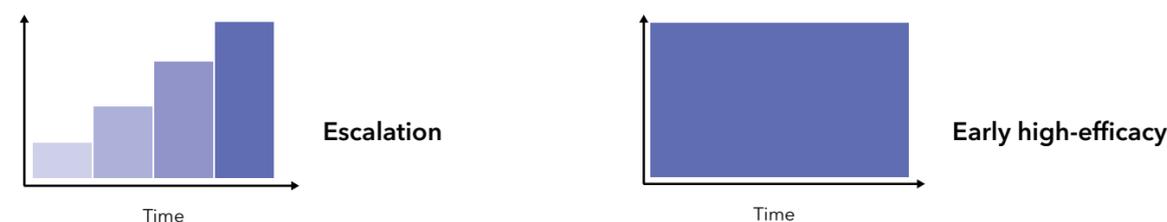


“Silent” progression can accrue unnoticed early in MS and have lasting consequences⁵

- While relapses can contribute to early neurologic changes in RMS, disability accumulation can often occur in the absence of relapse^{5,23}
- Once MS patients reach the need for walking assistance (EDSS ≥4.0), some may be at risk for more rapid accumulation of irreversible disability^{4,24,25}

Balancing the risk of disease against other factors is key to decision-making in MS^{26,27}

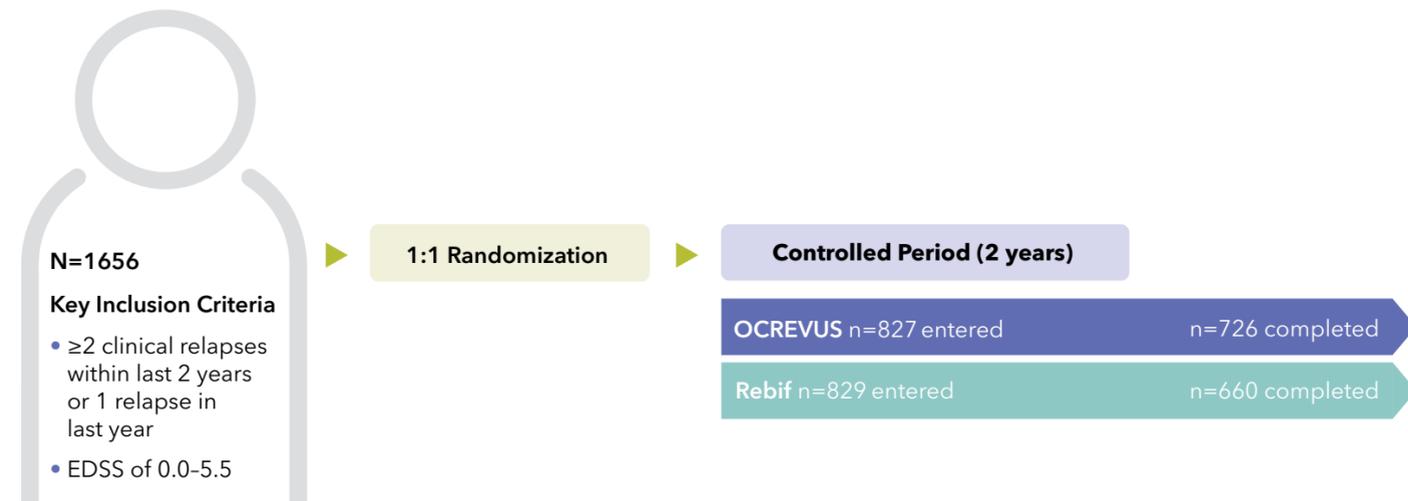
- There are 2 contemporary treatment paradigms in MS



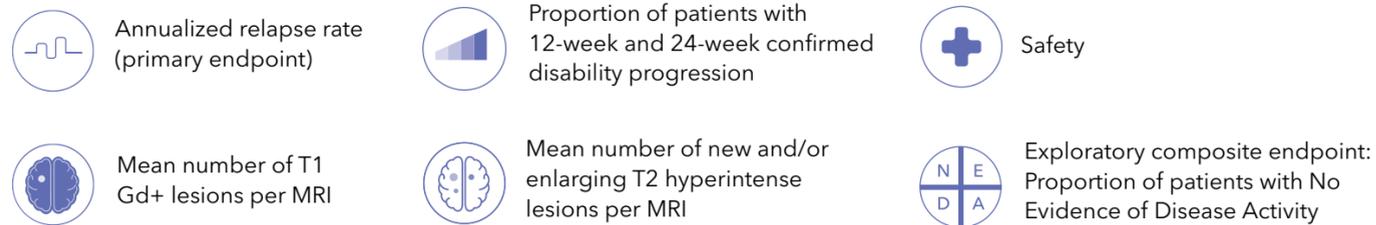
BDI-II=Beck Depression Inventory-II; EDSS=Expanded Disability Status Scale; HADS=Hospital Anxiety Depression Scale; SDMT=Symbol Digit Modalities Test.

OPERA I and II: Identical, head-to-head clinical trials vs Rebif over 2 years⁸

The efficacy and safety of OCREVUS in RMS were studied vs Rebif® (interferon β -1a) in 2 double-blind, double-dummy trials evaluating over 1600 patients for 2 years²⁸



ENDPOINTS STUDIED FOR 2 YEARS IN OPERA I AND II



- Patients receiving OCREVUS were given a 600 mg IV dose every 24 weeks (Dose 1 administered as two 300 mg IV infusions 2 weeks apart) and placebo subcutaneous injections 3 times a week²⁸
- Patients receiving Rebif were given 44 μ g subcutaneous injections 3 times per week and placebo IV infusions every 24 weeks²⁸
- Additional endpoints studied included proportion of patients with confirmed disability improvement and mean number of new T1 hypointense lesions (chronic black holes) per MRI²⁸

OCREVUS: OPERA I, n=410; OPERA II, n=417.

Rebif: OPERA I, n=411; OPERA II, n=418.

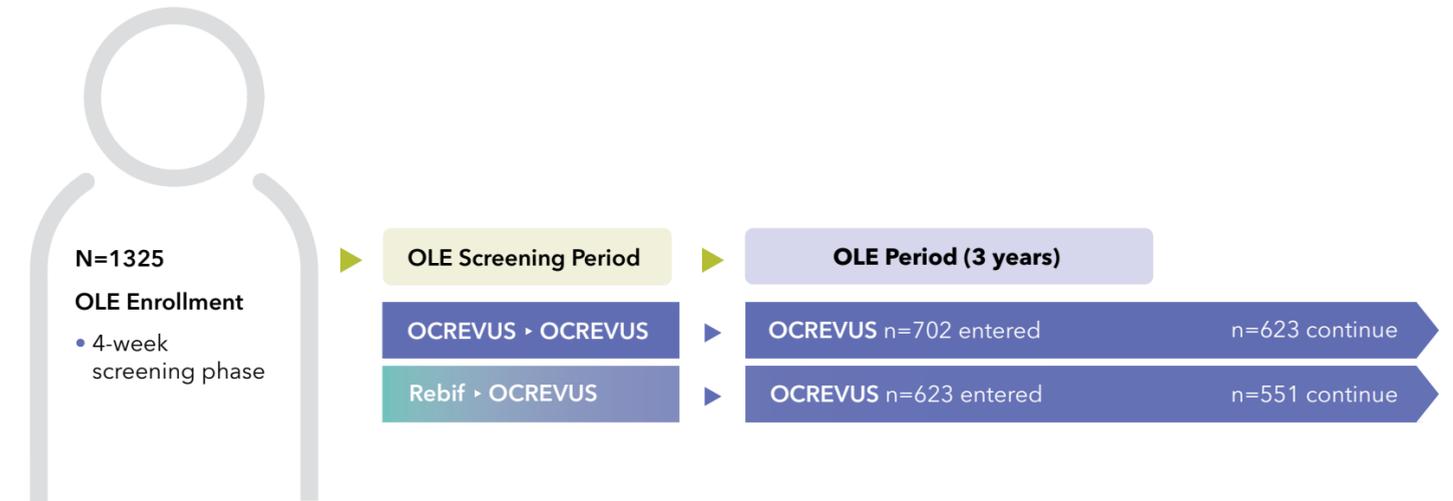
Important Safety Information

Infections

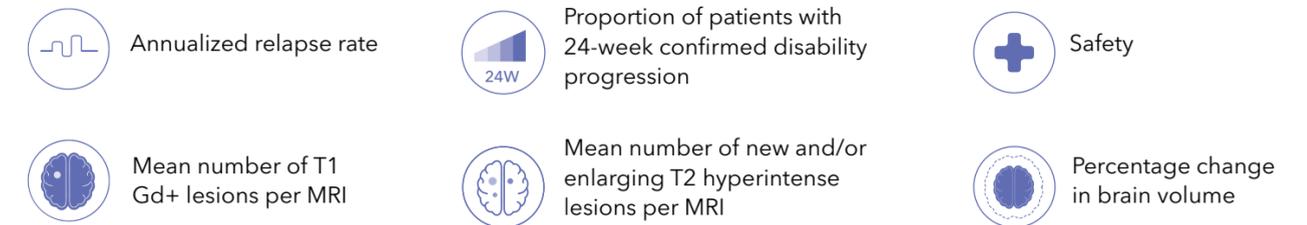
A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections. OCREVUS was not associated with an increased risk of serious infections in MS patients. Delay OCREVUS administration in patients with an active infection until the infection is resolved.

Three years of data in the OLE period²⁹

Over 90% of patients who completed the controlled period entered the OLE, and of those, $\approx 90\%$ completed Year 3 of the OLE



ENDPOINTS OBSERVED DURING THE OLE PERIOD³⁰



- Patients who received Rebif during the controlled period continued to receive Rebif during the OLE screening period until their first infusion of OCREVUS
- In the OLE phase, the first 600 mg dose of OCREVUS was administered as two 300 mg infusions given 2 weeks apart

Limitations of OLE Data

- The OLE is an open-label and uncontrolled study period
- Patients in the OLE period successfully completed the controlled period and are subject to continued dropout; they may represent an enriched population
- The endpoints measured were not prespecified nor powered to conclude statistical significance; they only convey numerical trends
- Conclusions regarding the treatment effect of OCREVUS cannot be drawn on the basis of OLE data

Gd+=gadolinium-enhancing; OLE=open-label extension.

For additional safety information, please see [page 10](#) and full [Prescribing Information](#) and [Medication Guide](#).



The OCREVUS relapsing MS patient^{8,28,29}



Average controlled period patient

- Age: **37**
- Mean EDSS: **2.8**
- Mean number of T1 Gd+ lesions: **1.8**
- Mean number of T2 lesions: **50.1**
- Untreated within 2 years: **74%**
- Mean time since diagnosis: **4 years**

Misti, an OCREVUS Patient Ambassador, for representative purposes only.



Average OLE period patient

- Age: **39**
- Mean EDSS: **2.6**
- Mean number of T1 Gd+ lesions: **0.02**
- Mean number of T2 lesions: **50.9**

Blair, an OCREVUS Patient Ambassador, for representative purposes only.



Controlled trial patients had to have an EDSS score between 0 and 5.5;
≈40% of all patients studied had baseline EDSS <2.5.³¹

Important Safety Information

Respiratory Tract Infections

A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients 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.

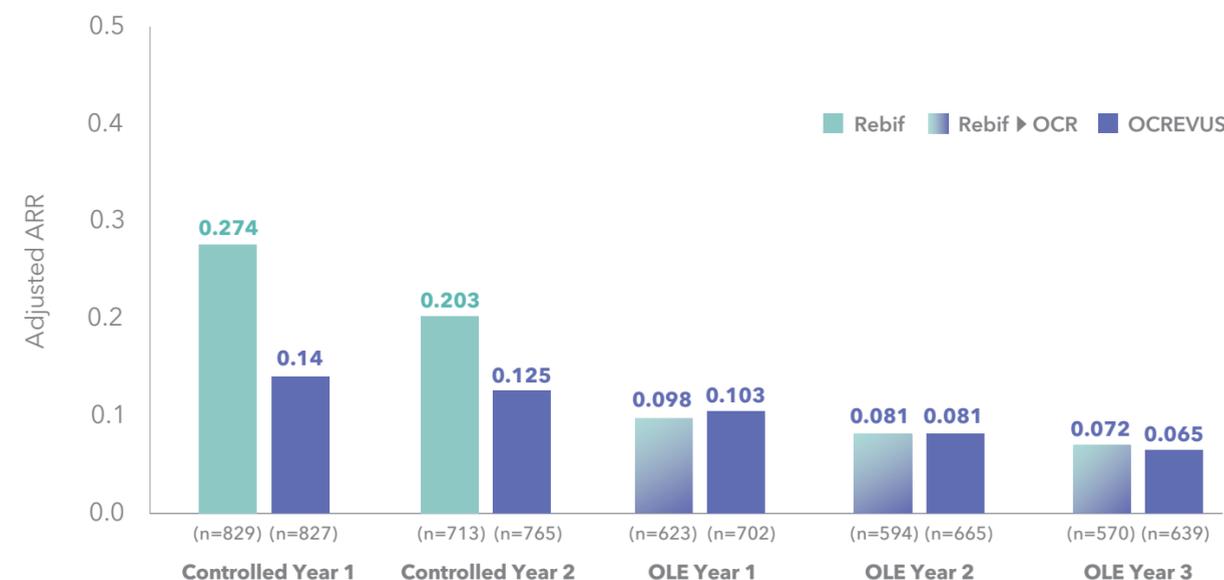
Reduced relapse rates by nearly half vs Rebif⁸

CONTROLLED PERIOD OCREVUS demonstrated superior relapse reductions vs Rebif at Year 2 of the controlled period⁸



The efficacy and safety of OCREVUS in RMS were studied vs Rebif in 2 double-blind, double-dummy trials evaluating over 1600 patients for 2 years.

CONTROLLED & OLE PERIODS Annualized relapse rates observed in the OLE were consistent with the controlled period²⁹



Relapses were defined as new or worsening neurologic symptoms that were attributable to multiple sclerosis, persisted for over 24 hours, were immediately preceded by a stable or improving neurological state for at least 30 days, and were accompanied by objective neurological worsening as defined in the study protocols.²⁸

Measurements performed at intermediate timepoints were not prespecified in the statistical testing hierarchy and reflect numerical trends only.

For additional safety information, please see [page 10](#) and full **Prescribing Information** and **Medication Guide**.



Near-complete suppression of T1 Gd+ lesions vs Rebif^{8,*}

CONTROLLED PERIOD

Superior reductions in mean number of T1 Gd+ lesions per MRI over 2 years; T1 Gd+ lesions are thought to represent acute inflammation

↓ **94%** | **95%**
 OPERA I | OPERA II
RELATIVE REDUCTIONS
 p<0.0001

Mean number of T1 Gd+ lesions with OCREVUS vs Rebif:
OPERA I: 0.016 vs 0.286 | **OPERA II: 0.021 vs 0.416**

*The precise mechanism by which OCREVUS exerts its therapeutic effects in MS is unknown.

CONTROLLED & OLE PERIODS

Mean number of T1 Gd+ lesions observed in the OLE were consistent with the controlled period³⁰



Relative reductions vs Rebif in T1 Gd+ lesions were observed in the controlled period at each of the intermediate timepoints, Weeks 24, 48, and 96. The measurements performed at these intermediate timepoints were not prespecified in the statistical testing hierarchy and reflect numerical trends only.²⁸

Unadjusted controlled and OLE data include the ITT population; clinical cutoff date: February 5, 2018. Number of T1 Gd+ lesions at each timepoint for all patients in the treatment group divided by the total number of brain MRI scans (performed at baseline and at Week 24, 48, 96) at this timepoint.³⁰

Gd+=gadolinium-enhancing; ITT=intent-to-treat; ROW=rest of world.

Important Safety Information

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in OCREVUS-treated patients 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 OCREVUS-treated patients than in the patients on placebo (2.7% vs 0.8%).

Superior reductions in T2 lesion activity vs Rebif⁸

CONTROLLED PERIOD

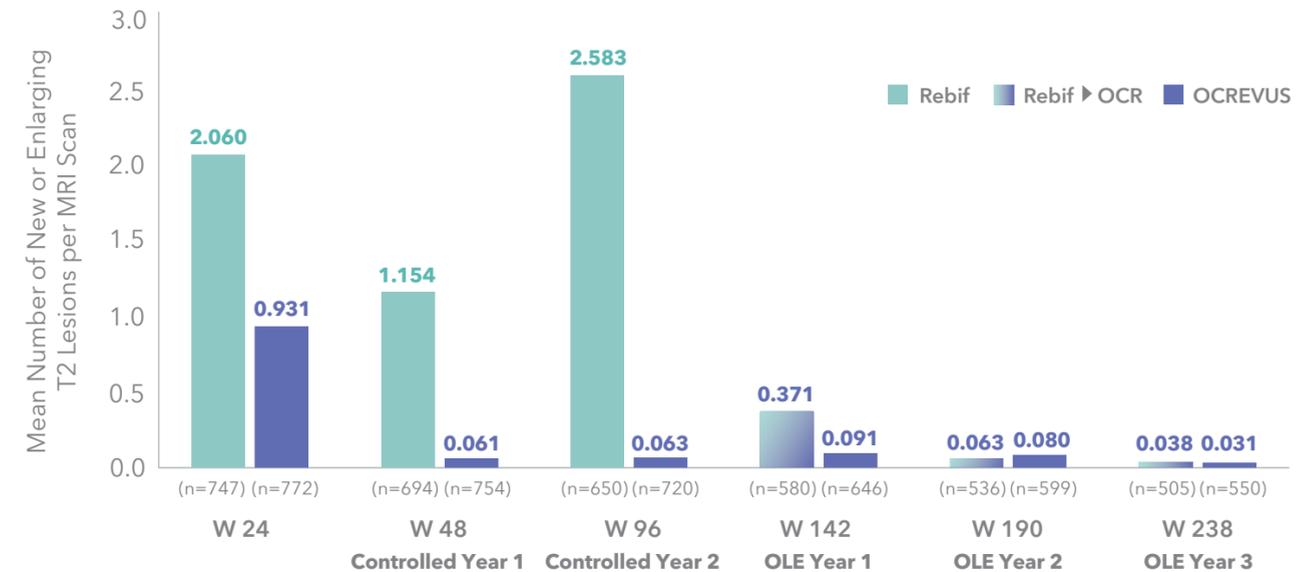
Significant relative reductions in mean number of new or enlarging T2 lesions per MRI over 2 years; T2 lesions are thought to represent cumulative disease burden

↓ **77%** | **83%**
 OPERA I | OPERA II
RELATIVE REDUCTIONS
 p<0.0001

Mean number of new or enlarging hyperintense T2 lesions with OCREVUS vs Rebif:
OPERA I: 0.323 vs 1.413 | **OPERA II: 0.325 vs 1.904**

CONTROLLED & OLE PERIODS

Mean number of new or enlarging T2 lesions observed in the OLE were consistent with the controlled period³⁰



Relative reductions in T2 lesions were observed in the controlled period at each of the intermediate timepoints, Weeks 24, 48, and 96. The measurements performed at these intermediate timepoints were not prespecified in the statistical testing hierarchy and reflect numerical trends only.²⁸

Unadjusted controlled and OLE data include the ITT population; clinical cutoff date: February 5, 2018. Number of new or enlarging T2 lesions relative to preceding scan for all patients in the treatment group at each timepoint for all patients in the treatment group divided by the total number of brain MRI scans (performed at baseline and at Week 24, 48, 96) at that timepoint.³⁰



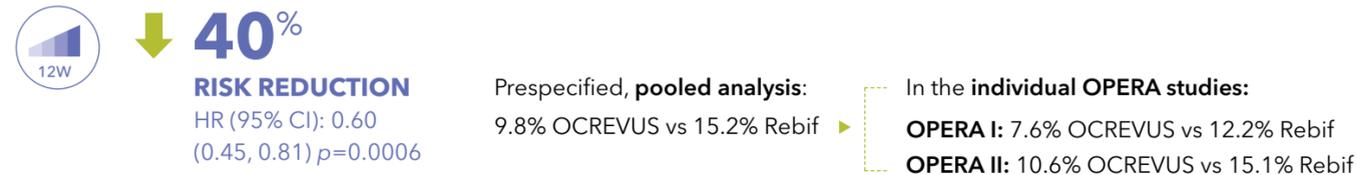
For additional safety information, please see page 10 and full **Prescribing Information** and **Medication Guide**.

Significantly impacted disability across a broad spectrum of RMS endpoints^{8,28}

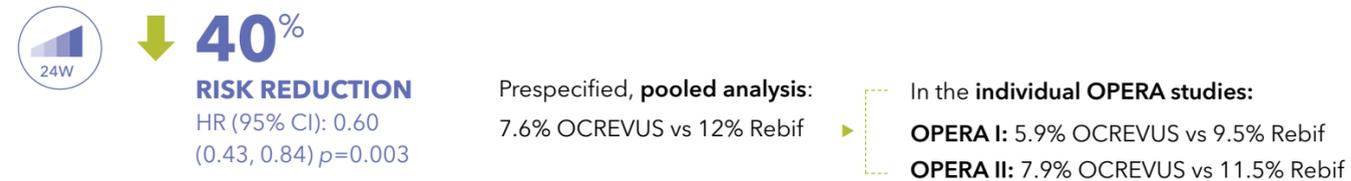
CONTROLLED PERIOD

OCREVUS consistently delayed disability progression and demonstrated confirmed disability improvement vs Rebif

12-week confirmed disability progression vs Rebif (proportion of patients)



24-week confirmed disability progression vs Rebif (proportion of patients)



Posthoc analysis: 48-week confirmed disability progression vs Rebif^{32,33}

- 57% risk reduction (proportion of patients: 3.2% OCREVUS vs 7.2% Rebif)
- Not prespecified to conclude statistical significance; these data only convey numerical trends

CONTROLLED PERIOD

12-week confirmed disability improvement vs Rebif²⁸



Confirmed disability progression was defined as patients with EDSS ≤ 5.5 who experienced an EDSS increase of ≥ 1.0 . For patients with EDSS > 5.5 , progression was an EDSS increase of ≥ 0.5 . Disability progression was categorized as confirmed if it was present at 12 or 24 weeks over the treatment period.²⁸

Confirmed disability improvement was defined as a reduction from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was > 5.5) that was sustained for at least 12 weeks in patients with a baseline EDSS score of at least 2.0.²⁸

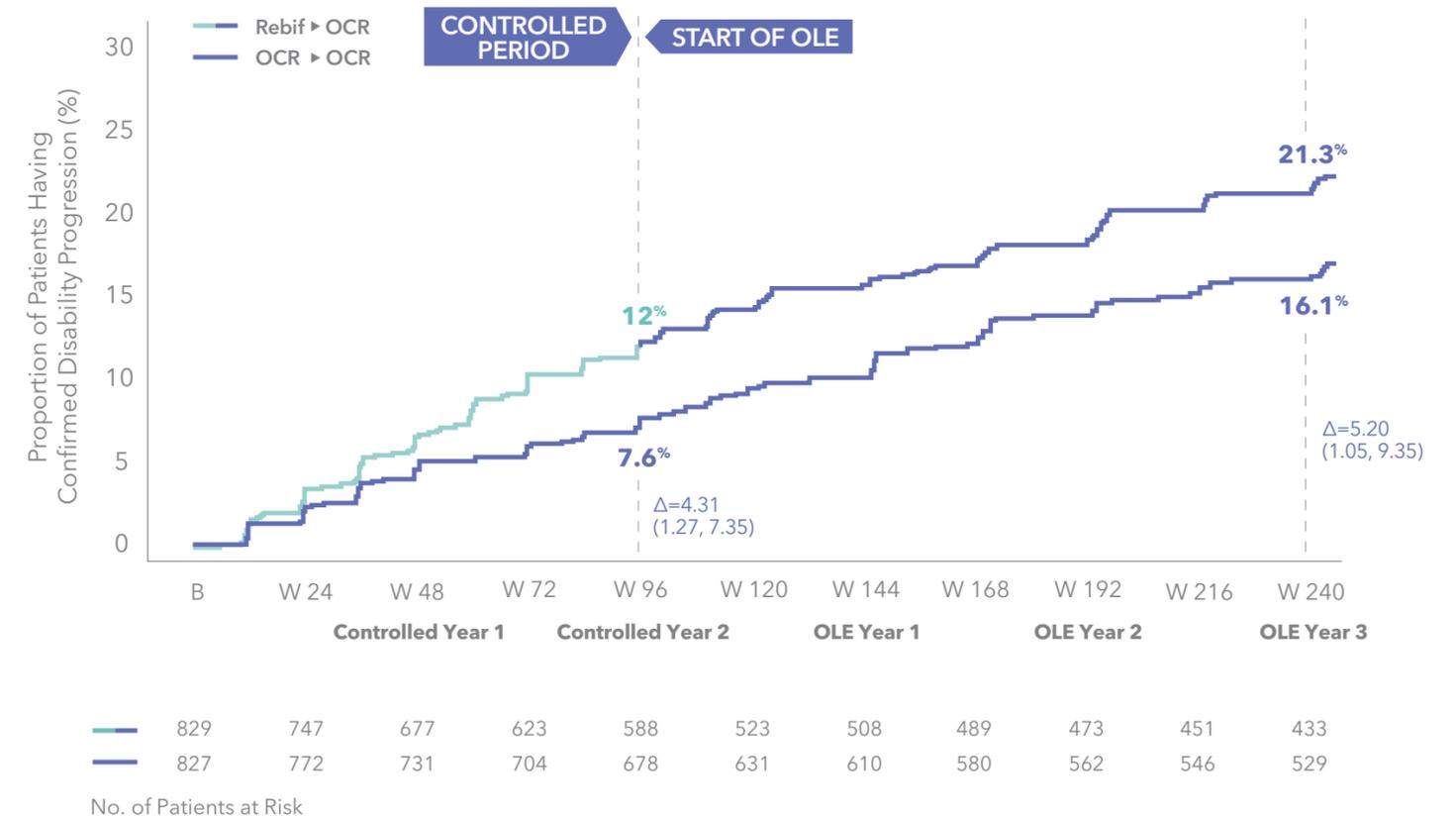
Important Safety Information

Progressive Multifocal Leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Although no cases of PML were identified in OCREVUS clinical trials, JC virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. 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 (per USPI).

Disability progression observed over 5 years^{8,28,29}

Time to onset of 24-week confirmed disability progression during controlled and OLE periods



In the controlled period, fewer OCREVUS patients experienced disability progression than those who started on Rebif.

For additional safety information, please see page 10 and full **Prescribing Information** and **Medication Guide**.



Over 6 years of safety experience^{8,34}

As of January 2019, 4611 patients have received OCREVUS in the all-exposure trial population, resulting in 14,329 patient-years of exposure

- In Phase III trials, the most common adverse events were infusion-related reactions and infections (mainly mild to moderate). Other common adverse event rates were similar among OCREVUS, placebo, and Rebif
- In the OCREVUS all-exposure population, reported rates of events continue to be consistent with those seen during the controlled RMS and PPMS trials
- There has been no change to the risk-benefit profile of OCREVUS since launch

Adverse events per 100 PY in OCREVUS trial population*

	OPERA (pooled) treatment period [†]		ORATORIO treatment period [†]		Phase II and III OLE population [†]	All-exposure population ^{†,‡}
	OCREVUS population n=825	Rebif population n=826	OCREVUS population n=486	Placebo population n=239	Mean number of doses: 9.6 N=2305	Mean number of doses: 6.3 N=4611
	PY=1448		PY=1416		PY=11,025	PY=14,329
Any adverse event	290	296	252	259	214	252
Adverse events leading to study treatment discontinuation	2.35	3.93	1.25	1.10	1.13	1.08
Infections	84.5	67.8	70.8	72.5	71.0	76.7
Urinary tract infection (UTI)	11.6	9.7	15.1	17.8	13.0	12.4
Nasopharyngitis	13.0	8.3	12.8	17.7	10.8	13.4
Upper respiratory tract infection	13.3	9.4	5.2	2.9	9.7	10.0
Infusion-related reactions (IRRs)	34.9	7.9	31.0	20.3	17.9	26.1
Malignancies [§]	0.28	0.14	0.93	0.27	0.51	0.46
Serious adverse events	5.39	6.29	10.15	12.07	7.84	7.33
Serious infections	0.83	1.79	2.74	3.02	2.21	1.99
No. of potential serious opportunistic infections	0	0	0	0	5	6
Fatalities	0.07	0.14	0.25	0.41	0.19	0.16

*Includes patients who received any dose of OCREVUS during the controlled treatment and associated open-label extension periods of the Phase II and Phase III studies; data from patients who were originally randomized to a comparator (Rebif or placebo) are included after the switch to open-label OCREVUS treatment.

[†]Multiple occurrences of the same adverse event (except for malignancies) in 1 patient are counted multiple times. Rate per 100 PY (95% CI) cutoff January 2019.

[‡]Includes patients who received any dose of OCREVUS during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, OBOE, and ENSEMBLE.

[§]Malignancies are identified using adverse events falling into the standard MedDRA query "Malignant tumours (narrow)." Reported as incidence rate per 100 PY of first malignancy.

^{||}Serious infections are defined using adverse events falling into the MedDRA SOC *Infections and Infestations*, and using "Is the event non-serious or serious?" from the adverse event case report form. Potential serious opportunistic infections were medically reviewed.

ORATORIO (PPMS): A randomized, double-blind, placebo-controlled clinical trial in 732 patients (OCREVUS, n=488; placebo, n=244) with PPMS treated for at least 120 weeks. Selection criteria included patients aged 18 to 55 and required a baseline EDSS of 3 to 6.5 and a score of 2 or greater for the EDSS pyramidal FSS due to lower extremity findings. Patients also had no history of RMS, SPMS, or PRMS.^{8,35}

FSS=functional systems score; MedDRA=Medical Dictionary for Regulatory Activities; PY=patient-years; SOC=system organ class.

Observed rates of infections

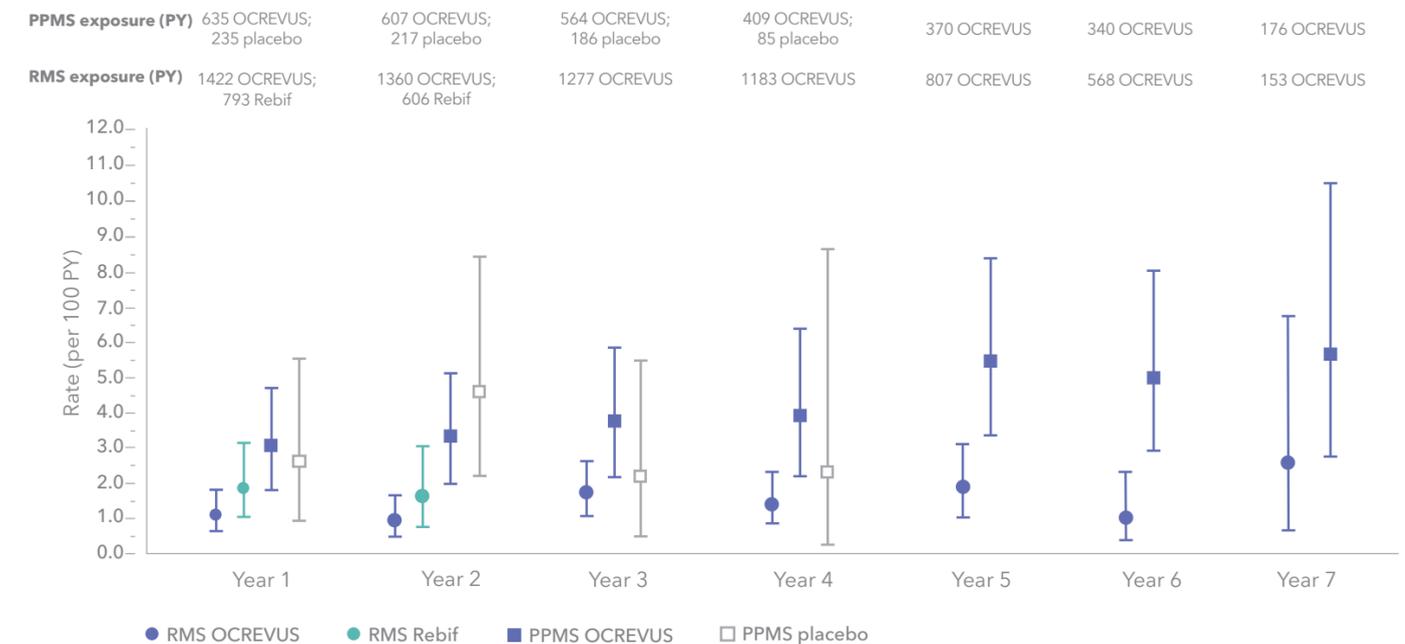
Patients who experienced 1 or more infections in the controlled period⁸

- These infections were mainly mild to moderate



- OCREVUS did not increase the risk of serious infections vs Rebif or placebo, though serious infections have occurred

Serious infection rates vs Rebif and placebo: Phase III Trials and OLE³⁴



- OCREVUS all-exposure population*:** the rate per 100 PY of serious infections as of January 2019 (1.99 [95% CI 1.77-2.23]) was similar to the rate observed at the primary analysis cut-off date
- The most common serious infections were UTIs and pneumonia

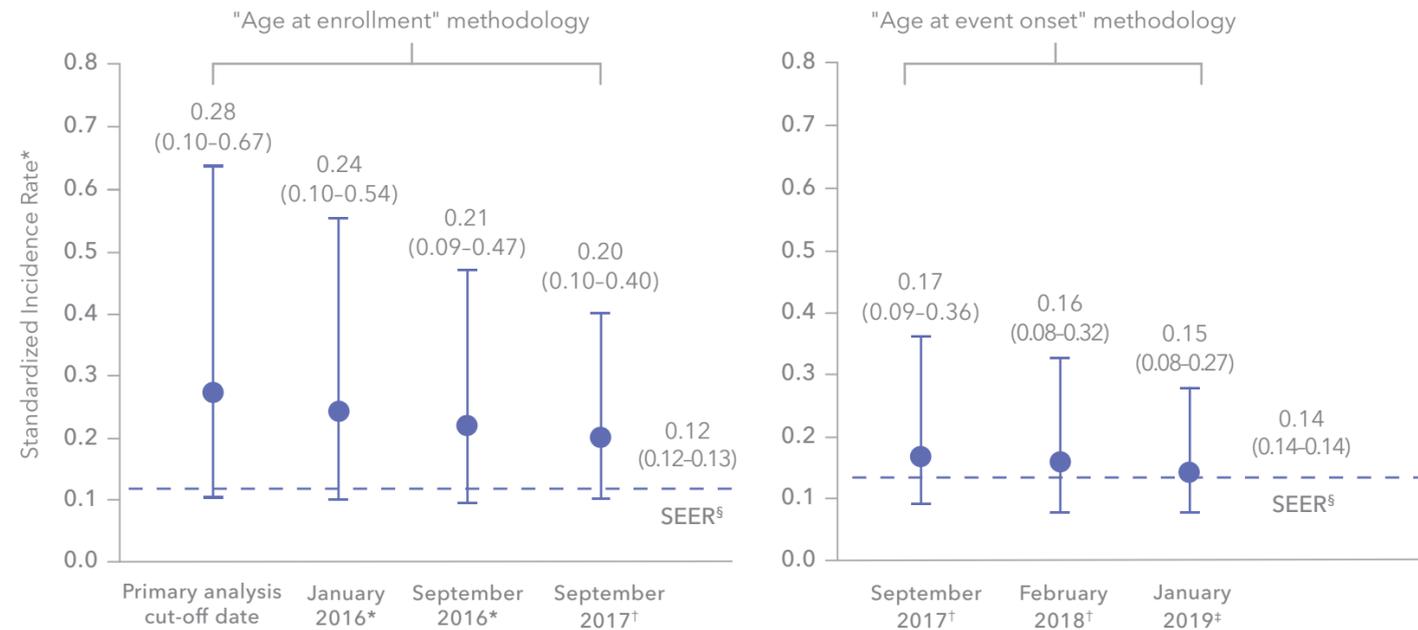
OCREVUS[®]
ocrelizumab 300MG/10ML INJECTION FOR IV

For additional safety information, please see [page 10](#) and full [Prescribing Information](#) and [Medication Guide](#).

Additional important safety information⁸

An increased risk of malignancy, including breast cancer, may exist in OCREVUS-treated patients

Age-standardized incidence rate of female breast cancer over OCREVUS studied populations and SEER population (per 100 PY)³⁴



Breast cancer was found in⁸:

6 OF 781 FEMALES ON OCREVUS **VS** **0** OF 668 FEMALES ON REBIF OR PLACEBO

in the OPERA and ORATORIO clinical trials.

Breast cancer was found in³⁴:

16 OF **2939** FEMALES ON OCREVUS (8446 PY)

in the all-exposure population of the clinical trials (data as of January 2019)

⁸"Age-at-enrollment" methodology only captures how old a patient was at the trial baseline, and not when the event occurred. However, as study follow-up continues and patients become older, the "age-at-event-onset" methodology, based on the age of the patient at the onset of malignancy, is a more precise method of calculating the standardized incidence rate.

*Includes patients who received any dose of OCREVUS during the controlled treatment and associated OLE periods of the Phase II and Phase III studies.

†Includes patients who received any dose of OCREVUS during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, and OBOE.

‡Includes patients who received any dose of OCREVUS during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE, and ENSEMBLE.

§SEER incidence calculated from 2000-2012 data.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative source of information reporting data on cancer incidence in ≈28% of the general US (non-MS specific) population. No comparisons should be made due to limitations which have not been fully accounted for, such as variations in patient populations, as well as differences in sample size, temporal changes, and other potential confounding factors.

Breast cancer screening recommendations

The FDA recommends that OCREVUS patients follow standard breast cancer screening guidelines⁸

Women with disabilities are **less likely** to have received a mammogram³⁶

39% OF WOMEN WITH DISABILITIES **VS** **25%** OF WOMEN WITHOUT DISABILITIES

DID NOT RECEIVE A MAMMOGRAM

during the previous 2 years of a CDC survey in 2010 of women 50 to 74 years of age.

The American Cancer Society recommendations³⁷

PREVENTATIVE SCREENING GUIDELINES FOR WOMEN			
Age <40	Age 40 to 44	Age 45 to 54	Age 55+
Those with risk factors for breast cancer (genetic or environmental) should ask their HCP whether mammograms are advisable and how often to have them	Should have the choice to start annual breast cancer screening with mammograms (x-rays of the breast) if it is the patient's desire	Should get mammograms every year	Can switch to mammograms every 2 years, or can continue annual screening

- The risks of and the potential benefits of mammograms should be considered, and discussed with the patient's HCP
- Breast MRI also has a role in screening for some patients (decision should be made in consultation with a breast cancer specialist)
- Screening should continue as long as a woman is in good health and is expected to live 10 more years or longer
- Other screening guidelines from federally recognized sources (eg, the US Preventive Services Task Force, the Centers for Disease Control and Prevention) may be used based on HCP preference and in consultation with their patient



For additional safety information, please see [page 10](#) and full [Prescribing Information](#) and [Medication Guide](#).

Dosing and administration with twice-yearly OCREVUS^{8,†}

Recommended dose and dose administration

- The initial 600 mg dose is administered as 2 separate intravenous infusions given over approximately 2.5 hours*: first as a 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion
- Subsequent doses are administered over approximately 3.5 hours* as a single 600 mg intravenous infusion every 24 weeks
- Observe the patient for at least 1 hour after the completion of the infusion

*Infusion time may take longer if the infusion is interrupted or slowed.

INITIAL DOSE

DAY 1 DAY 15



Infusion 1 Infusion 2

SUBSEQUENT DOSES

EVERY 24 WEEKS



Single infusion

Delayed or missed doses

- If a planned infusion of OCREVUS is missed, administer OCREVUS as soon as possible; do not wait until the next scheduled dose
- Reset the dose schedule to administer the next sequential dose 24 weeks after the missed dose is administered

[†]The first dose of OCREVUS is split between 2 treatments, for a total of 3 treatments in the first year.⁸

Hepatitis B Virus (HBV) Reactivation

There were no reports of hepatitis B reactivation in MS patients treated with OCREVUS. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with other anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS 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.

OCREVUS adherence and persistence data⁸

- Adherence and persistence are important considerations when it comes to your patient's dosing regimen. There are many reasons patients and providers choose to start or discontinue treatment, from adverse events to patient preference

In the OCREVUS RMS clinical trials, the percentage of patients who completed the clinical trials at year 2 were:



Results from a 1-year analysis of adherence and persistence with OCREVUS³³

- OCREVUS was studied using real-world claims data in a 1-year analysis assessing 1121 OCREVUS patients from March 28, 2017 to June 2018

ADHERENCE

Adherence is the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.

- This was calculated using the proportion of days covered (PDC) method, which calculates the number of days covered by the medication over a fixed length of time

92% remained adherent on OCREVUS vs 8% who did not.

PERSISTENCE

Persistence measures the duration of time from initiation to discontinuation of therapy.

- For OCREVUS, no evidence of Dose 2 within 60 days of a 26-week dosing interval (ie, no second dose prior to 34 weeks after the first infusion of OCREVUS), and no evidence of switching to another DMT

92% remained persistent on OCREVUS vs 8% who discontinued treatment.

Limitations of OCREVUS 1-year real-world analysis

- Claims data have inherent limitations:
 - Limited clinical information available may result in residual confounding (eg, MS subtype, line of therapy)
 - Lack of data on reason for discontinuation
 - Data may not be generalized to all patients, including those without insurance
- A subset of OCREVUS patients were identified by algorithm; a sensitivity analysis was performed on only confirmed OCREVUS patients, and showed similar results

For additional safety information, please see [page 10](#) and full [Prescribing Information](#) and [Medication Guide](#).



START NOW: OCREVUS CONNECTS®: The support your patients need, all in one place

OCREVUS CONNECTS® provides support to help patients start and stay on OCREVUS

OCREVUS CONNECTS® YOU AND YOUR PATIENTS TO



Live Support from dedicated OCREVUS Patient Navigators



Help getting **insurance approval**, including benefits investigations and prior authorization resources



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Indications

OCREVUS is indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults

Contraindications

OCREVUS is contraindicated in patients with active hepatitis B virus infection and in patients with a history of life-threatening infusion reaction to OCREVUS.

Important Safety Information

Warnings and Precautions

Infusion Reactions

OCREVUS can cause infusion reactions, which 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. In multiple sclerosis (MS) clinical trials, the incidence of infusion reactions in OCREVUS-treated patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to each infusion] was 34-40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of OCREVUS-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization.

Observe patients treated with OCREVUS for infusion reactions during the infusion and for at least one hour after completion of the infusion. Inform patients that infusion reactions can occur up to 24 hours after the infusion. Administer pre-medication (e.g., methylprednisolone or an equivalent corticosteroid, and an antihistamine) to reduce the frequency and severity of infusion reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered. For life-threatening infusion reactions, immediately and permanently stop OCREVUS and administer appropriate supportive treatment. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

Infections

A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections. OCREVUS was not associated with an increased risk of serious infections in MS patients. Delay OCREVUS administration in patients with an active infection until the infection is resolved.

Respiratory Tract Infections

A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients 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 OCREVUS-treated patients 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 OCREVUS-treated patients 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 OCREVUS. Serious herpes virus infections may occur at any time during treatment with OCREVUS. Some cases were life-threatening.

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

Progressive Multifocal Leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Although no cases of PML were identified in OCREVUS clinical trials, JC virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants).

At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. 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 (per USPI).

Hepatitis B Virus (HBV) Reactivation

There were no reports of hepatitis B reactivation in MS patients treated with OCREVUS. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with other anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS 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 after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, consider the potential for increased immunosuppressive effect. OCREVUS 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 OCREVUS for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of OCREVUS for non-live vaccines. OCREVUS may interfere with the effectiveness of non-live vaccines. The safety of immunization with live or live-attenuated vaccines following OCREVUS therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with OCREVUS During Pregnancy

In infants of mothers exposed to OCREVUS 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.

Malignancies

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

Use in Specific Populations

Pregnancy

There are no adequate data on the developmental risk associated with use of OCREVUS in pregnant women. There are no data on B-cell levels in human neonates following maternal exposure to OCREVUS. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. OCREVUS is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier.

Lactation

There are no data on the presence of ocrelizumab 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 and any potential adverse effects on the breastfed infant from OCREVUS or from the underlying maternal condition.

Females and Males of Reproductive Potential

Women of childbearing potential should use contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS.

Most Common Adverse Reactions

RMS: The most common adverse reactions in RMS trials (incidence \geq 10% and $>$ REBIF) were upper respiratory tract infections (40%) and infusion reactions (34%).

PPMS: The most common adverse reactions in PPMS trials (incidence \geq 10% and $>$ placebo) were upper respiratory tract infections (49%), infusion reactions (40%), skin infections (14%), and lower respiratory tract infections (10%).

Please see accompanying full **Prescribing Information** and **Medication Guide**.



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START NOW WITH TWICE-YEARLY OCREVUS IN FIRST-LINE PATIENTS*

How to start and manage patients on OCREVUS⁸

The **first and only DMT** proven to impact disease activity and disability progression in both RMS and PPMS

- **Prior to first dose:** perform Hepatitis B virus screening and complete necessary vaccinations (4 weeks prior for live or live-attenuated vaccines and, when possible, 2 weeks prior for non-live vaccines)
- **Before each infusion:** assess for active infection and administer premedications
- **After each infusion:** monitor patients for 1 hour for possible infusion-related reactions (IRRs)
- No ongoing mandatory laboratory monitoring is required

*The first dose of OCREVUS is split between 2 treatments, for a total of 3 infusions in the first year.⁸

More than 1 in 3 MS patients starting or switching to a new therapy start on OCREVUS.³³

Important Safety Information Most Common Adverse Reactions

RMS: The most common adverse reactions in RMS trials (incidence $\geq 10\%$ and $> \text{REBIF}$) were upper respiratory tract infections (40%) and infusion reactions (34%).

PPMS: The most common adverse reactions in PPMS trials (incidence $\geq 10\%$ and $> \text{placebo}$) were upper respiratory tract infections (49%), infusion reactions (40%), skin infections (14%), and lower respiratory tract infections (10%).

For additional safety information, please see [page 10](#) and full [Prescribing Information](#) and [Medication Guide](#).

OCREVUS[®]

ocrelizumab

300MG/10ML
INJECTION FOR IV

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OCREVUS safely and effectively. See full prescribing information for OCREVUS.

OCREVUS[®] (ocrelizumab) injection, for intravenous use
Initial U.S. Approval: 2017

----- RECENT MAJOR CHANGES -----	
Indications and Usage (1)	7/2019
Warnings and Precautions, Infusion Reactions (5.1)	11/2019
Warnings and Precautions, Infection (5.2)	5/2020

----- INDICATIONS AND USAGE -----

OCREVUS is a CD20-directed cytolytic antibody indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults (1)
- Primary progressive MS, in adults (1)

----- DOSAGE AND ADMINISTRATION -----

- Hepatitis B virus screening is required before the first dose (2.1)
- Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (e.g., diphenhydramine) prior to each infusion (2.2)
- Administer OCREVUS by intravenous infusion
 - Start dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion (2.3)
 - Subsequent doses: 600 mg intravenous infusion every 6 months (2.3)
- Must be diluted prior to administration (2.3, 2.6)
- Monitor patients closely during and for at least one hour after infusion (2.3, 2.5)

----- DOSAGE FORMS AND STRENGTHS -----

- Injection: 300 mg/10 mL (30 mg/mL) in a single-dose vial (3)

----- CONTRAINDICATIONS -----

- Active hepatitis B virus infection (4)
- History of life-threatening infusion reaction to OCREVUS (4)

----- WARNINGS AND PRECAUTIONS -----

- Infusion reactions: Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue OCREVUS if a life-threatening or disabling infusion reaction occurs (2.3, 5.1)
- Infections: Delay OCREVUS administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with OCREVUS and after discontinuation, until B-cell repletion (5.2)
- Malignancies: An increased risk of malignancy, including breast cancer, may exist with OCREVUS (5.3)

----- ADVERSE REACTIONS -----

The most common adverse reactions were:

- RMS (incidence ≥10% and > REBIF): upper respiratory tract infections and infusion reactions (6.1)
- PPMS (incidence ≥10% and > placebo): upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- USE IN SPECIFIC POPULATIONS -----

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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- DOSAGE AND ADMINISTRATION**
 - Assessments Prior to First Dose of OCREVUS
 - Preparation Before Every Infusion
 - Recommended Dosage and Dose Administration
 - Delayed or Missed Doses
 - Dose Modifications Because of Infusion Reactions
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OCREVUS[®] (ocrelizumab)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OCREVUS is indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of OCREVUS

Hepatitis B Virus Screening

Prior to initiating OCREVUS, perform Hepatitis B virus (HBV) screening. OCREVUS 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)].

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 OCREVUS for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of OCREVUS for non-live vaccines [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.2)].

2.2 Preparation Before Every Infusion

Infection Assessment

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

Recommended Premedication

Pre-medicate with 100 mg of methylprednisolone (or an equivalent corticosteroid) administered intravenously approximately 30 minutes prior to each OCREVUS infusion to reduce the frequency and severity of infusion reactions [see *Warnings and Precautions* (5.1)]. Pre-medicate with an antihistamine (e.g., diphenhydramine) approximately 30-60 minutes prior to each OCREVUS infusion to further reduce the frequency and severity of infusion reactions.

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

2.3 Recommended Dosage and Dose Administration

Administer OCREVUS under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions.

- Initial dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion.
- Subsequent doses: single 600 mg intravenous infusion every 6 months.
- Observe the patient for at least one hour after the completion of the infusion [see *Warnings and Precautions* (5.1)].

OCREVUS[®] (ocrelizumab)

		Amount and Volume¹	Infusion Rate and Duration³
Initial Dose (two infusions)	Infusion 1	300 mg in 250 mL	<ul style="list-style-type: none">Start at 30 mL per hourIncrease by 30 mL per hour every 30 minutesMaximum: 180 mL per hourDuration: 2.5 hours or longer
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (one infusion)	One infusion every 6 months ²	600 mg in 500 mL	<ul style="list-style-type: none">Start at 40 mL per hourIncrease by 40 mL per hour every 30 minutesMaximum: 200 mL per hourDuration: 3.5 hours or longer

¹Solutions of OCREVUS for intravenous infusion are prepared by dilution of the drug product into an infusion bag containing 0.9% Sodium Chloride Injection, to a final drug concentration of approximately 1.2 mg/mL.

²Administer the first Subsequent Dose 6 months after Infusion 1 of the Initial Dose.

³Infusion time may take longer if the infusion is interrupted or slowed [see *Dosage and Administration* (2.5)].

2.4 Delayed or Missed Doses

If a planned infusion of OCREVUS is missed, administer OCREVUS 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 must be separated by at least 5 months [see *Dosage and Administration* (2.3)].

2.5 Dose Modifications Because of Infusion Reactions

Dose modifications in response to infusion reactions depends on the severity.

Life-threatening Infusion Reactions

Immediately stop and permanently discontinue OCREVUS if there are signs of a life-threatening or disabling infusion reaction [see *Warnings and Precautions* (5.1)]. Provide appropriate supportive treatment.

Severe Infusion Reactions

Immediately interrupt the infusion and administer appropriate supportive treatment, as necessary [see *Warnings and Precautions* (5.1)]. Restart the infusion only after all symptoms have resolved. When restarting, begin at half of the infusion rate at the time of onset of the infusion reaction [see *Dosage and Administration* (2.2)]. If this rate is tolerated, increase the rate as described in Table 1. This change in rate will increase the total duration of the infusion but not the total dose.

Mild to Moderate Infusion Reactions

Reduce the infusion rate to half the rate at the onset of the infusion reaction and maintain the reduced rate for at least 30 minutes [see *Warnings and Precautions* (5.1)]. If this rate is tolerated, increase the rate as described in Table 1. This change in rate will increase the total duration of the infusion but not the total dose.

2.6 Preparation and Storage of the Dilute Solution for Infusion

Preparation

OCREVUS must be prepared by a healthcare professional using aseptic technique.

Visually inspect for particulate matter and discoloration prior to administration. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter. Do not shake.

Withdraw intended dose and further dilute into an infusion bag containing 0.9% Sodium Chloride Injection, to a final drug concentration of approximately 1.2 mg/mL.

- Withdraw 10 mL (300 mg) of OCREVUS and inject into 250 mL
- Withdraw 20 mL (600 mg) of OCREVUS and inject into 500 mL

Do not use other diluents to dilute OCREVUS since their use has not been tested. The product contains no preservative and is intended for single use only.

Storage of Infusion Solution

Prior to the start of the intravenous infusion, the content of the infusion bag should be at room temperature.

Use the prepared infusion solution immediately. If not used immediately, store up to 24 hours in the refrigerator at 2°C–8°C (36°F–46°F) and 8 hours at room temperature up to 25°C (77°F), which includes infusion time. In the event an intravenous infusion cannot be completed the same day, discard the remaining solution.

No incompatibilities between OCREVUS and polyvinyl chloride (PVC) or polyolefin (PO) bags and intravenous (IV) administration sets have been observed.

Administration

Administer the diluted infusion solution through a dedicated line using an infusion set with a 0.2 or 0.22 micron in-line filter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/10 mL (30 mg/mL) clear or slightly opalescent, and colorless to pale brown solution in a single-dose vial.

OCREVUS[®] (ocrelizumab)

4 CONTRAINDICATIONS

OCREVUS is contraindicated in patients with:

- Active HBV infection [see *Dosage and Administration* (2.6) and *Warnings and Precautions* (5.2)]
- A history of life-threatening infusion reaction to OCREVUS [see *Warnings and Precautions* (5.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

OCREVUS can cause infusion reactions, which 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. In multiple sclerosis (MS) clinical trials, the incidence of infusion reactions in OCREVUS-treated patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to each infusion] was 34 to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of OCREVUS-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization.

Observe patients treated with OCREVUS for infusion reactions during the infusion and for at least one hour after completion of the infusion. Inform patients that infusion reactions can occur up to 24 hours after the infusion.

Reducing the Risk of Infusion Reactions and Managing Infusion Reactions

Administer pre-medication (e.g., methylprednisolone or an equivalent corticosteroid, and an antihistamine) to reduce the frequency and severity of infusion reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered [see *Dosage and Administration* (2.3)].

Management recommendations for infusion reactions depend on the type and severity of the reaction [see *Dosage and Administration* (2.5)]. For life-threatening infusion reactions, immediately and permanently stop OCREVUS and administer appropriate supportive treatment. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

5.2 Infections

A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections [see *Adverse Reactions* (6.1)]. OCREVUS was not associated with an increased risk of serious infections in MS patients.

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

Respiratory Tract Infections

A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients 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 OCREVUS-treated patients 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 OCREVUS-treated patients 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 OCREVUS. Serious herpes virus infections may occur at any time during treatment with OCREVUS. Some cases were life-threatening.

If serious herpes infections occur, OCREVUS should be discontinued or withheld until the infection has resolved, and appropriate treatment should be administered [see *Patient Counseling Information* (17)].

Progressive Multifocal Leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Although no cases of PML were identified in OCREVUS clinical trials, JC virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. 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.

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Hepatitis B Virus (HBV) Reactivation

There were no reports of hepatitis B reactivation in MS patients treated with OCREVUS. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with other anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS 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 after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, consider the potential for increased immunosuppressive effects *[see Drug Interactions (7.1) and Clinical Pharmacology (12.1, 12.2)]*. OCREVUS 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 OCREVUS for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of OCREVUS for non-live vaccines.

OCREVUS 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 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 During Pregnancy

In infants of mothers exposed to OCREVUS 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 Malignancies

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

6 ADVERSE REACTIONS

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

- Infusion Reactions *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Malignancies *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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 OCREVUS has been evaluated in 1311 patients across MS clinical studies, which included 825 patients in active-controlled clinical trials in patients with relapsing forms of MS (RMS) and 486 patients in a placebo-controlled study in patients with primary progressive MS (PPMS).

Adverse Reactions in Patients with Relapsing Forms of MS

In active-controlled clinical trials (Study 1 and Study 2), 825 patients with RMS received OCREVUS 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 2 summarizes the adverse reactions that occurred in RMS trials (Study 1 and Study 2).

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Table 2 Adverse Reactions in Adult Patients with RMS with an Incidence of at least 5% for OCREVUS and Higher than REBIF

Adverse Reactions	Studies 1 and 2	
	OCREVUS 600 mg IV Every 24 Weeks' (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

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

Adverse Reactions in Patients with Primary Progressive MS

In a placebo-controlled clinical trial (Study 3), a total of 486 patients with PPMS received one course of OCREVUS (600 mg of OCREVUS 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 3 summarizes the adverse reactions that occurred in the PPMS trial (Study 3).

Table 3 Adverse Reactions in Adult Patients with PPMS with an Incidence of at least 5% for OCREVUS and Higher than Placebo

Adverse Reactions	Study 3	
	OCREVUS 600 mg IV Every 24 Weeks' (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

¹One dose of OCREVUS (600 mg administered as two 300 mg infusions two weeks apart)

Laboratory Abnormalities

Decreased Immunoglobulins

OCREVUS decreased total immunoglobulins with the greatest decline seen in IgM levels. In MS clinical trials, there was no apparent association between immunoglobulin decrease and risk for 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 OCREVUS-treated patients was 0.5%, 1.5%, and 0.1%, respectively. Following treatment, the proportion of OCREVUS-treated patients 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 OCREVUS-treated patients was 0.0%, 0.2%, and 0.2%, respectively. Following treatment, the proportion of OCREVUS-treated patients reporting IgG, IgA, and IgM below the LLN at 120 weeks was 1.1%, 0.5%, and 15.5%, respectively.

Decreased Neutrophil Levels

In the PPMS clinical trial (Study 3), decreased neutrophil counts occurred in 13% of OCREVUS-treated patients compared to 10% in placebo patients. The majority of the decreased neutrophil counts were only observed once for a given patient treated with OCREVUS and were between LLN - 1.5 x 10⁹/L and 1.0 x 10⁹/L. Overall, 1% of the patients in the OCREVUS group had neutrophil counts less than 1.0 x 10⁹/L and these were not associated with an infection.

6.2 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 with the incidence of antibodies to other products may be misleading.

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Patients in MS trials (Study 1, Study 2, and Study 3) were tested at multiple time points (baseline and every 6 months post-treatment for the duration of the trial) for anti-drug antibodies (ADAs). Out of 1311 patients treated with OCREVUS, 12 (~1%) tested positive for ADAs, of which 2 patients tested positive for neutralizing antibodies. These data are not adequate to assess the impact of ADAs on the safety and efficacy of OCREVUS.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OCREVUS. 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.

Serious herpes infections have been identified during postapproval use of OCREVUS *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

The concomitant use of OCREVUS 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. 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 *[see Warnings and Precautions (5.2)]*.

7.2 Vaccinations

A Phase 3b randomized, open-label study examined the concomitant use of OCREVUS and several non-live vaccines in adults 18-55 years of age with relapsing forms of MS (68 subjects undergoing treatment with OCREVUS at the time of vaccination and 34 subjects not undergoing treatment with OCREVUS at the time of vaccination). Concomitant exposure to OCREVUS 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 OCREVUS have not been assessed *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

OCREVUS 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 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 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, 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

Following intravenous administration of OCREVUS 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 OCREVUS (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, on a mg/kg basis.

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8.2 Lactation

Risk Summary

There are no data on the presence of ocrelizumab 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 and any potential adverse effects on the breastfed infant from OCREVUS or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of OCREVUS 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.

OCREVUS (ocrelizumab) Injection for intravenous infusion is a preservative-free, sterile, clear or slightly opalescent, and colorless to pale brown solution supplied in single-dose vials. Each mL of solution contains 30 mg ocrelizumab, glacial acetic acid (0.25 mg), polysorbate 20 (0.2 mg), sodium acetate trihydrate (2.14 mg), and trehalose dihydrate (40 mg) 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 cytotoxicity and complement-mediated lysis.

12.2 Pharmacodynamics

For B-cell counts, assays for CD19+ B-cells are used because the presence of OCREVUS interferes with the CD20 assay. Treatment with OCREVUS reduces CD19+ B-cell counts in blood by 14 days after infusion. In clinical studies, B-cell counts rose to above the lower limit of normal (LLN) or above baseline counts between infusions of OCREVUS at least one time in 0.3% to 4.1% of patients. In a clinical study of 51 patients, the median time for B-cell counts to return to either baseline or LLN was 72 weeks (range 27-175 weeks) after the last OCREVUS 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

Pharmacokinetics (PK) of OCREVUS in MS clinical studies fit a two compartment model with time-dependent clearance. The overall exposure at the steady-state (AUC over the 24 week dosing intervals) of OCREVUS was 3,510 mcg/mL per day. In clinical studies in MS patients, maintenance doses of ocrelizumab were either 600 mg every 6 months (RMS patients) or two 300 mg infusions separated by 14 days every 6 months (PPMS patients). The mean maximum concentration was 212 mcg/mL in patients with RMS (600 mg infusion) and 141 mcg/mL in patients with PPMS (two 300 mg infusions administered within two weeks). The pharmacokinetics of ocrelizumab was essentially linear and dose proportional between 400 mg and 2000 mg.

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 0.29 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 26 days.

Metabolism

The metabolism of OCREVUS 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 OCREVUS was observed in those patients.

Hepatic impairment

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

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

No studies have been performed to assess the mutagenic potential of OCREVUS. As an antibody, OCREVUS 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, on a mg/kg basis.

14 CLINICAL STUDIES

14.1 Relapsing Forms of Multiple Sclerosis (RMS)

The efficacy of OCREVUS was demonstrated in two randomized, double-blind, double-dummy, active comparator-controlled clinical trials of identical design, in patients with RMS treated for 96 weeks (Study 1 and Study 2). The dose of OCREVUS 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 OCREVUS and 411 to REBIF; 11% of OCREVUS-treated 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 OCREVUS and 418 to REBIF; 14% of OCREVUS-treated 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 OCREVUS-treated patients had one or more T1 Gd-enhancing lesions (mean 1.9).

In Study 1 and Study 2, OCREVUS 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 4 and Figure 1.

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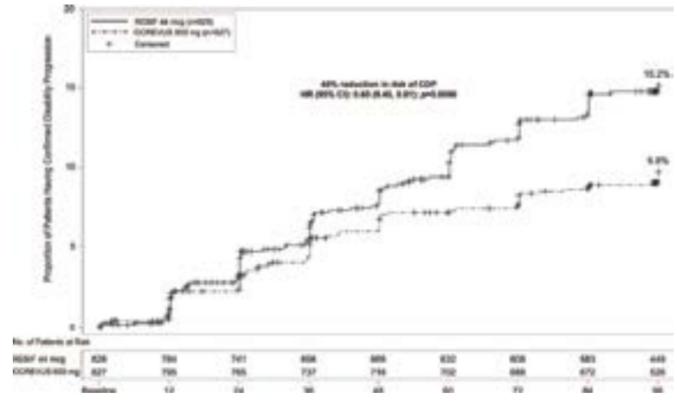
Table 4 Key Clinical and MRI Endpoints in RMS Patients from Study 1 and Study 2

Endpoints	Study 1		Study 2	
	OCREVUS 600 mg every 24 weeks N=410	REBIF 44 mcg three times a week N=411	OCREVUS 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% OCREVUS 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)



*Pre-specified pooled analysis of Study 1 and 2

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

14.2 Primary Progressive Multiple Sclerosis (PPMS)

Study 3 was a randomized, double-blind, placebo-controlled clinical trial in patients with PPMS. Patients were randomized 2:1 to receive either OCREVUS 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.

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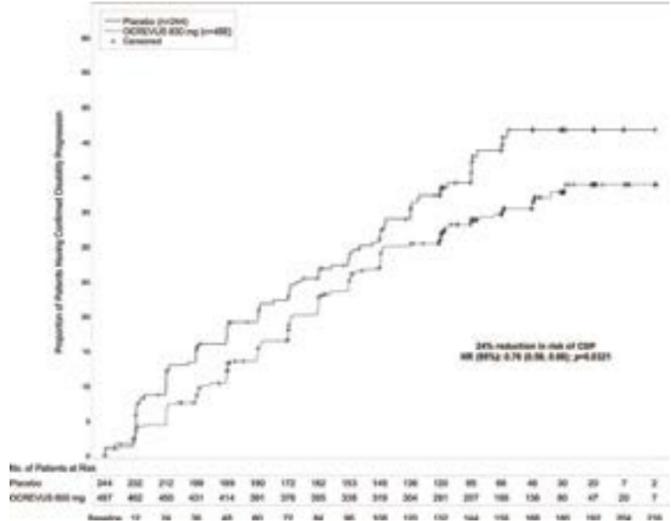
Study 3 randomized 488 patients to OCREVUS and 244 to placebo; 21% of OCREVUS-treated patients and 34% of placebo-treated patients did not complete the trial. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 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 OCREVUS-treated patients than for placebo-treated patients (see Figure 2). Results for Study 3 are presented in Table 5 and Figure 2.

Table 5 Key Clinical and MRI Endpoints in PPMS patients for Study 3

Endpoints	Study 3	
	OCREVUS 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*



*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 OCREVUS-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 OCREVUS-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 OCREVUS-treated patients and 43% in placebo-treated patients. Clinical and MRI endpoints that generally favored OCREVUS 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.

OCREVUS® (ocrelizumab)

16 HOW SUPPLIED/STORAGE AND HANDLING

OCREVUS (ocrelizumab) injection is a preservative-free, sterile, clear or slightly opalescent, and colorless to pale brown solution supplied as a carton containing one 300 mg/10 mL (30 mg/mL) single-dose vial (NDC 50242-150-01).

Store OCREVUS vials at 2°C–8°C (36°F–46°F) in the outer carton to protect from light. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Infusion Reactions

Inform patients about the signs and symptoms of infusion reactions, and that infusion reactions can occur up to 24 hours after infusion. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions [see *Warnings and Precautions* (5.1)].

Infection

Advise patients to contact their healthcare provider for any signs of infection during treatment or after the last dose [see *Clinical Pharmacology* (12.2)]. Signs include fever, chills, constant cough, or signs of herpes such as cold sore, shingles, or genital sores [see *Warnings and Precautions* (5.2)].

Advise patients that PML has happened with drugs that are similar to OCREVUS and may happen with OCREVUS. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that 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 [see *Warnings and Precautions* (5.2)].

Advise patients that OCREVUS may cause reactivation of hepatitis B infection and that monitoring will be required if they are at risk [see *Warnings and Precautions* (5.2)].

Advise patients that herpes infections, including serious herpes infections affecting the central nervous system, skin, and eyes, have occurred during treatment with OCREVUS. Advise patients to promptly contact their healthcare provider if they experience any signs or symptoms of herpes infections including oral or genital symptoms, fever, skin rash, pain, itching, decreased visual acuity, eye redness, eye pain, headache, neck stiffness, or change in mental status [see *Warnings and Precautions* (5.2)].

Vaccination

Advise patients to complete any required live or live-attenuated vaccinations at least 4 weeks and, whenever possible, non-live vaccinations at least 2 weeks prior to initiation of OCREVUS. Administration of live-attenuated or live vaccines is not recommended during OCREVUS treatment and until B-cell recovery [see *Warnings and Precautions* (5.2)].

Malignancies

Advise patients that an increased risk of malignancy, including breast cancer, may exist with OCREVUS. Advise patients that they should follow standard breast cancer screening guidelines [see *Warnings and Precautions* (5.3)].

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking OCREVUS they should inform their healthcare provider [see *Pregnancy* (8.1)].

OCREVUS® [ocrelizumab]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
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OCREVUS® (ocrelizumab)

MEDICATION GUIDE

OCREVUS® (oak-rev-us)
(ocrelizumab)
injection, for intravenous use

What is the most important information I should know about OCREVUS?

OCREVUS can cause serious side effects, including:

- **Infusion reactions:** OCREVUS can cause infusion reactions that can be serious and require you to be hospitalized. You will be monitored during your infusion and for at least 1 hour after each infusion of OCREVUS for signs and symptoms of an infusion reaction. Tell your healthcare provider or nurse if you get any of these symptoms:
 - itchy skin
 - rash
 - hives
 - tiredness
 - coughing or wheezing
 - trouble breathing
 - throat irritation or pain
 - feeling faint
 - fever
 - redness on your face (flushing)
 - nausea
 - headache
 - swelling of the throat
 - dizziness
 - shortness of breath
 - fatigue
 - fast heart beat

These infusion reactions can happen for up to 24 hours after your infusion. It is important that you call your healthcare provider right away if you get any of the signs or symptoms listed above after each infusion.

If you get infusion reactions, your healthcare provider may need to stop or slow down the rate of your infusion.

- **Infection:** OCREVUS increases your risk of getting upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes infections. Tell your healthcare provider if you have an infection or have any of the following signs of infection including fever, chills, or a cough that does not go away. Signs of herpes infection include cold sores, shingles, genital sores and, if more serious, a severe or persistent headache, confusion, change in vision, eye redness, or eye pain. These signs can happen during treatment or after you have received your last dose of OCREVUS. If you have an active infection, your healthcare provider should delay your treatment with OCREVUS until your infection is gone.
- **Progressive Multifocal Leukoencephalopathy (PML):** Although no cases have been seen with OCREVUS treatment in clinical trials, PML may happen with OCREVUS. PML is a rare brain infection that usually leads to death or severe disability. Tell your healthcare provider right away if you have any new or worsening neurologic signs or symptoms. These may include problems with thinking, balance, eyesight, weakness on 1 side of your body, strength, or using your arms or legs.

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- **Hepatitis B virus (HBV) reactivation:** Before starting treatment with OCREVUS, your healthcare provider will do blood tests to check for hepatitis B viral infection. If you have ever had hepatitis B virus infection, the hepatitis B virus may become active again during or after treatment with OCREVUS. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems including liver failure or death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop receiving OCREVUS.
- **Weakened immune system:** OCREVUS taken before or after other medicines that weaken the immune system could increase your risk of getting infections.

What is OCREVUS?

OCREVUS is a prescription medicine used to treat:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults.

It is not known if OCREVUS is safe or effective in children.

Who should not receive OCREVUS?

- **Do not** receive OCREVUS if you have an active hepatitis B virus (HBV) infection.
- **Do not** receive OCREVUS if you have had a life threatening allergic reaction to OCREVUS. Tell your healthcare provider if you have had an allergic reaction to OCREVUS or any of its ingredients in the past. See **“What are the ingredients in OCREVUS?”** for a complete list of ingredients in OCREVUS.

Before receiving OCREVUS, tell your healthcare provider about all of your medical conditions, including if you:

- have or think you have an infection. See **“What is the most important information I should know about OCREVUS?”**
- have ever taken, take, or plan to take medicines that affect your immune system, or other treatments for MS. These medicines could increase your risk of getting an infection.
- have ever had hepatitis B or are a carrier of the hepatitis B virus.
- have had a recent vaccination or are scheduled to receive any vaccinations.
 - **You should receive any required ‘live’ or ‘live-attenuated’ vaccines at least 4 weeks before you start treatment with OCREVUS.** You **should not receive** ‘live’ or ‘live-attenuated’ vaccines while you are being treated with OCREVUS and until your healthcare provider tells you that your immune system is no longer weakened.
 - **When possible, you should receive any ‘non-live’ vaccines at least 2 weeks before you start treatment with OCREVUS.** If you would like to receive any non-live (inactivated) vaccines, including the seasonal flu vaccine, while you are being treated with OCREVUS, talk to your healthcare provider.
 - If you are pregnant or planning to become pregnant talk to your doctor about vaccinations for your baby, as some precautions may be needed.
- are pregnant, think that you might be pregnant, or plan to become pregnant. It is not known if OCREVUS will harm your unborn baby. You should use birth control (contraception) during treatment with OCREVUS and for 6 months after your last infusion of OCREVUS.
- are breastfeeding or plan to breastfeed. It is not known if OCREVUS passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take OCREVUS.

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Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive OCREVUS?

- OCREVUS is given through a needle placed in your vein (intravenous infusion) in your arm.
- Before treatment with OCREVUS, your healthcare provider will give you a corticosteroid medicine and an antihistamine to help reduce infusion reactions (make them less frequent and less severe). You may also receive other medicines to help reduce infusion reactions. See **“What is the most important information I should know about OCREVUS?”**
- Your first full dose of OCREVUS will be given as 2 separate infusions, 2 weeks apart. Each infusion will last about 2 hours and 30 minutes.
- Your next doses of OCREVUS will be given as one infusion every 6 months. These infusions will last about 3 hours and 30 minutes.

What are the possible side effects of OCREVUS?

OCREVUS may cause serious side effects, including:

- See **“What is the most important information I should know about OCREVUS?”**
- **Risk of cancers (malignancies) including breast cancer.** Follow your healthcare provider’s instructions about standard screening guidelines for breast cancer.

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Most common side effects include infusion reactions and infections. See **“What is the most important information I should know about OCREVUS?”**

These are not all the possible side effects of OCREVUS.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OCREVUS.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OCREVUS for a condition for which it was not prescribed. Do not give OCREVUS to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about OCREVUS that is written for health professionals.

What are the ingredients in OCREVUS?

Active ingredient: ocrelizumab

Inactive ingredients: glacial acetic acid, polysorbate 20, sodium acetate trihydrate, trehalose dihydrate.

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For more information, go to www.OCREVUS.com or call 1-844-627-3887.

This Medication Guide has been approved by the U.S. Food and Drug Administration

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