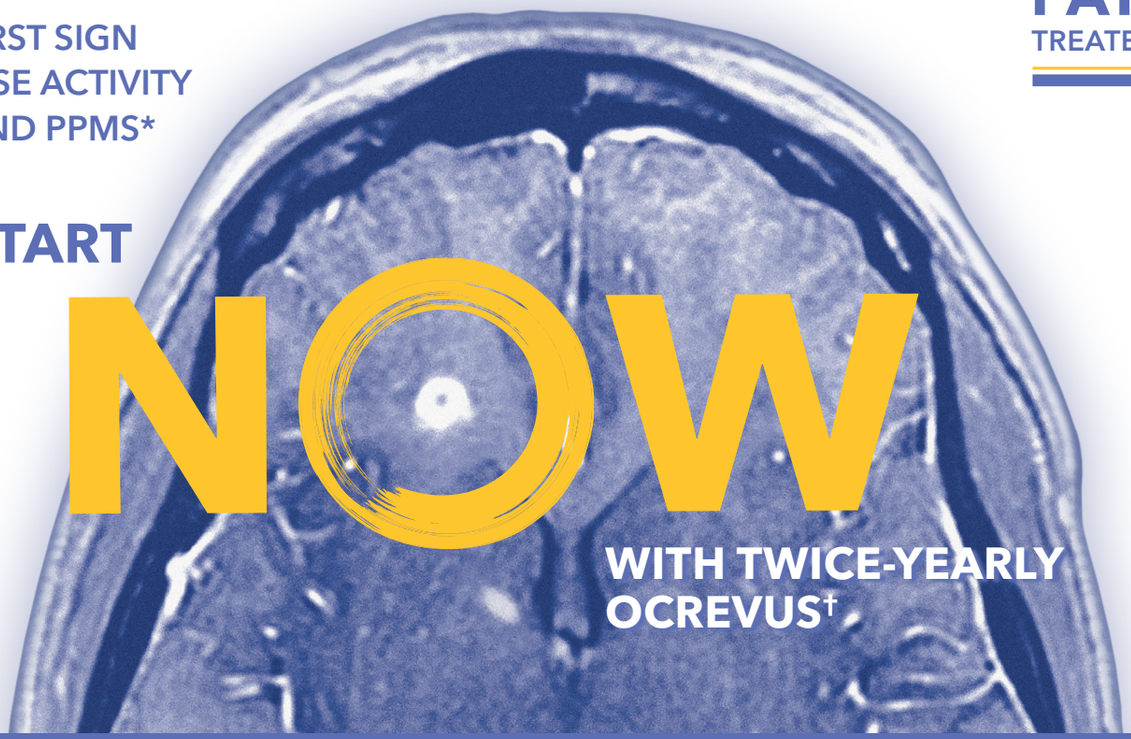
PROGRESSION IN MS STARTS EARLY[1-8]

150K+ PATIENTS TREATED GLOBALLY

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.

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 pages 18 and 19 and accompanying full **Prescribing Information** and **Medication Guide** in pocket.

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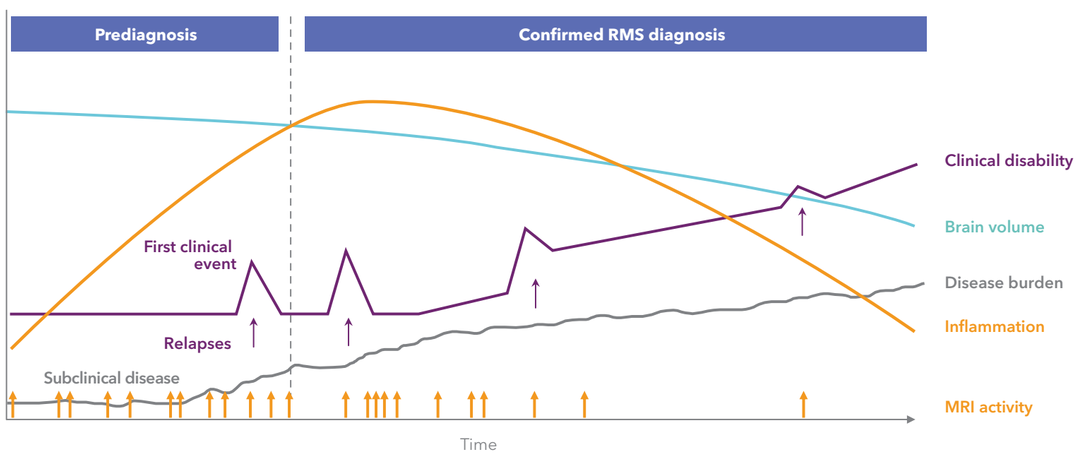
Progression in MS starts early, despite initial presentation[1-7]

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]

Progression

- **Pathological Processes** ------ Irreversible neuroaxonal loss/degeneration[14]
- **Clinical Manifestation** ------ Insidious neurologic worsening/clinical disability[11,17]

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 challenging[5]

Disability progression in MS patients goes beyond impact on ambulation[18]

- 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 worsening[19-22]
  - –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]

FUNCTIONAL SYSTEMS AND TESTING CONTRIBUTING TO THE EDSS[18]

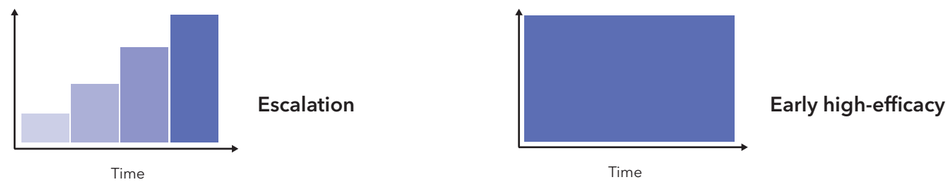
- Visual
- Brainstem
- Pyramidal
- Cerebellar
- Sensory
- Bowel & bladder
- Cerebral
- OTHER: Ambulation

"Silent" progression can accrue unnoticed early in MS and have lasting consequences[5]

- 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]

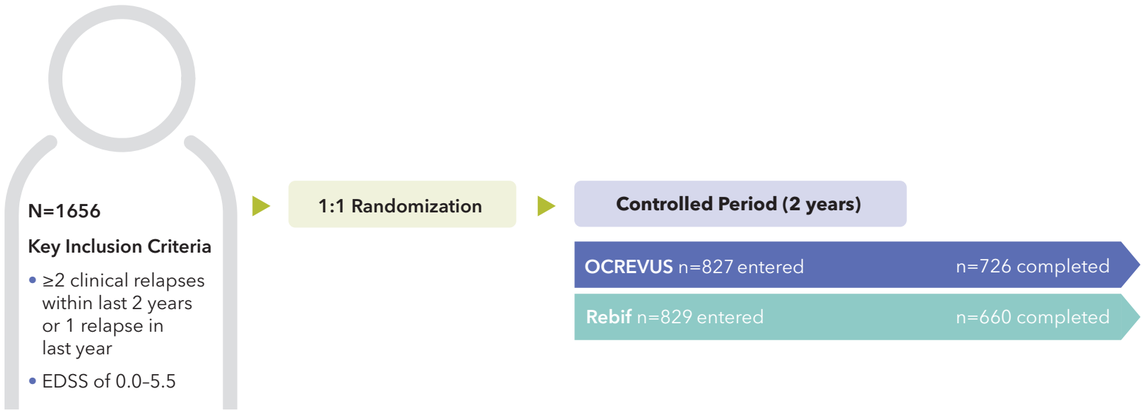
- There are 2 contemporary treatment paradigms in MS



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 years[8]

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 years[28]



ENDPOINTS STUDIED FOR 2 YEARS IN OPERA I AND II

- Annualized relapse rate (primary endpoint)
- Proportion of patients with 12-week and 24-week confirmed disability progression
- Safety
- Mean number of T1 Gd+ lesions per MRI
- Mean number of new and/or enlarging T2 hyperintense lesions per MRI
- Exploratory composite endpoint: Proportion of patients with No Evidence of Disease Activity

- 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 week[28]
- Patients receiving Rebif were given 44 µg subcutaneous injections 3 times per week and placebo IV infusions every 24 weeks[28]
- Additional endpoints studied included proportion of patients with confirmed disability improvement and mean number of new T1 hypointense lesions (chronic black holes) per MRI[28]

OCREVUS: OPERA I, n=410; OPERA II, n=417.
Rebif: OPERA I, n=411; OPERA II, n=418.

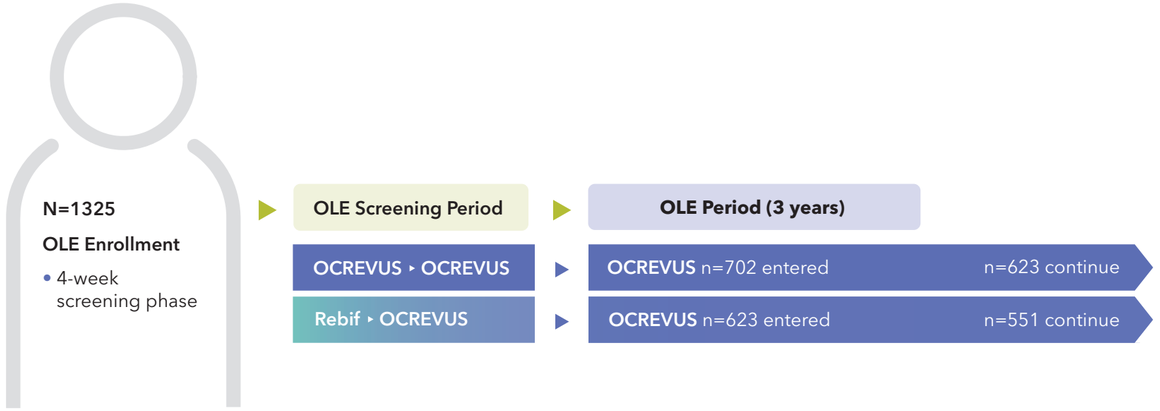
Important Safety Information

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 period[29]

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



ENDPOINTS OBSERVED DURING THE OLE PERIOD[30]

- Annualized relapse rate
- Proportion of patients with 24-week confirmed disability progression
- Safety
- Mean number of T1 Gd+ lesions per MRI
- Mean number of new and/or enlarging T2 hyperintense lesions per MRI
- Percentage change in brain volume

- 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 pages 18 and 19 and accompanying full **Prescribing Information** and **Medication Guide** in pocket.

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The OCREVUS relapsing MS patient[8,28,29]

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

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**

Blair, 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**

60% of patients studied were **under 40 years old**[31]

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 Rebif[8]

CONTROLLED PERIOD

OCREVUS demonstrated superior relapse reductions vs Rebif at Year 2 of the controlled period[8]

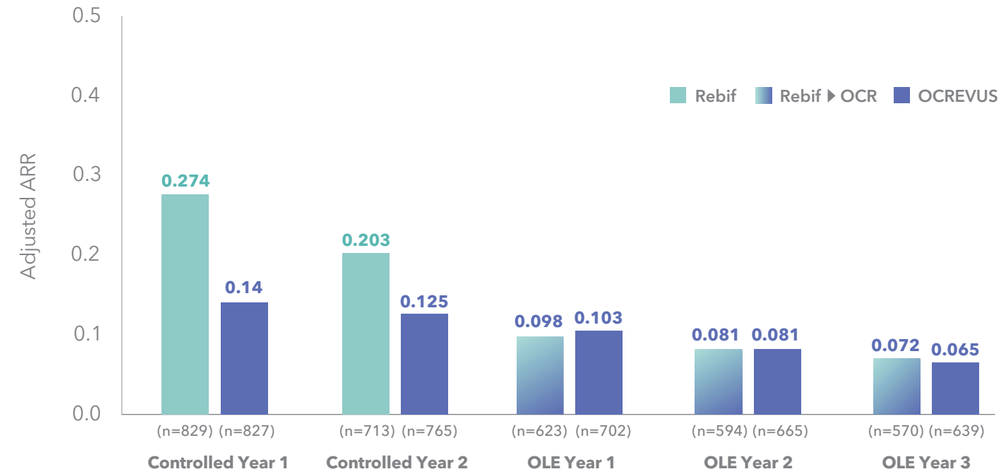
46% OPERA I | **47%** OPERA II
RELATIVE REDUCTIONS
$p<0.0001$

Annualized relapse rate with OCREVUS vs Rebif:
OPERA I: 0.156 vs 0.292 | OPERA II: 0.155 vs 0.290

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 period[29]



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.

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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

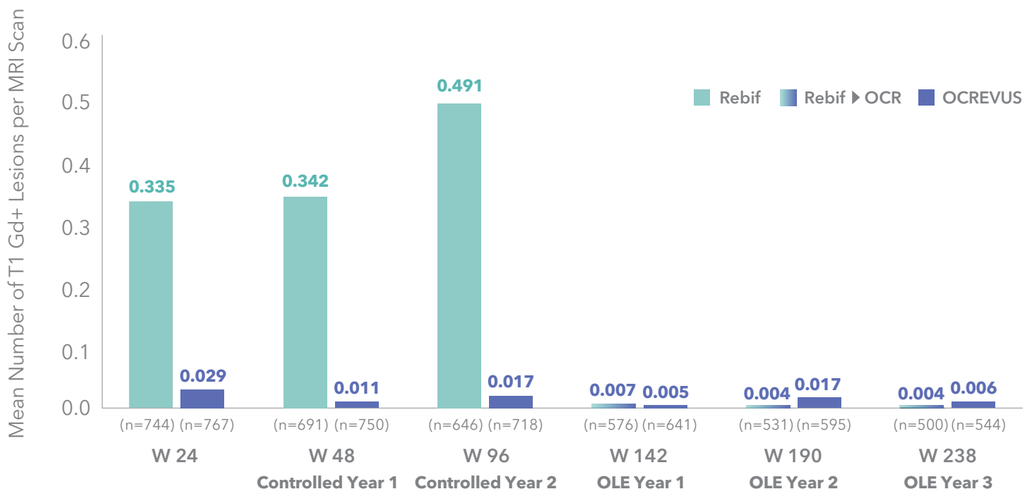
p<0.0001

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 period[30]



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 Rebif[8]

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

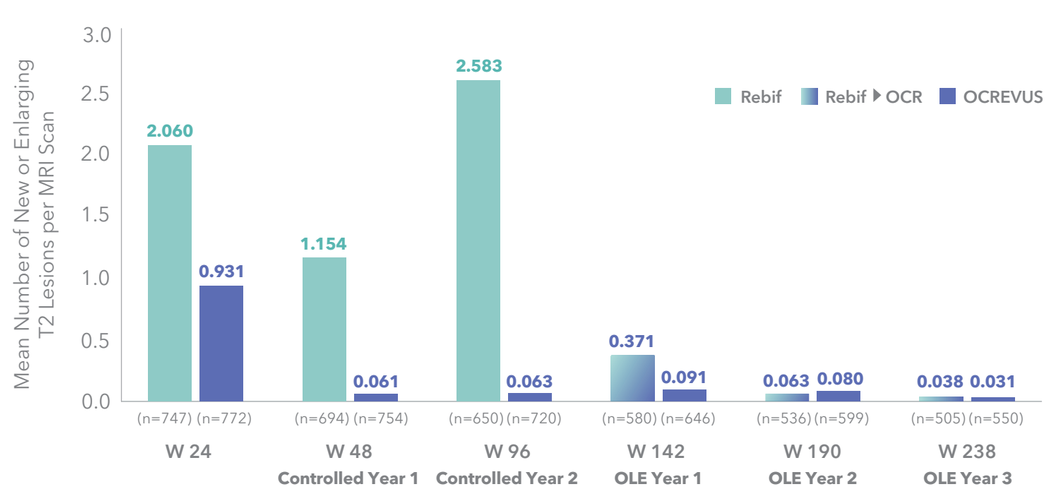
RELATIVE REDUCTIONS

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 period[30]



Relative reductions in T2 lesions were 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]

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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)

12W

40%
RISK REDUCTION
HR (95% CI): 0.60
(0.45, 0.81) *p*=0.0006

Prespecified, **pooled analysis**:
9.8% OCREVUS vs 15.2% Rebif

In the **individual OPERA studies:**
OPERA I: 7.6% OCREVUS vs 12.2% Rebif
OPERA II: 10.6% OCREVUS vs 15.1% Rebif

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

24W

40%
RISK REDUCTION
HR (95% CI): 0.60
(0.43, 0.84) *p*=0.003

Prespecified, **pooled analysis**:
7.6% OCREVUS vs 12% Rebif

In the **individual OPERA studies:**
OPERA I: 5.9% OCREVUS vs 9.5% Rebif
OPERA II: 7.9% OCREVUS vs 11.5% Rebif

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 Rebif[28]

12W

33%
DIFFERENCE
p=0.02

12-week confirmed disability improvement: 20.7% OCREVUS vs 15.6% Rebif

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]

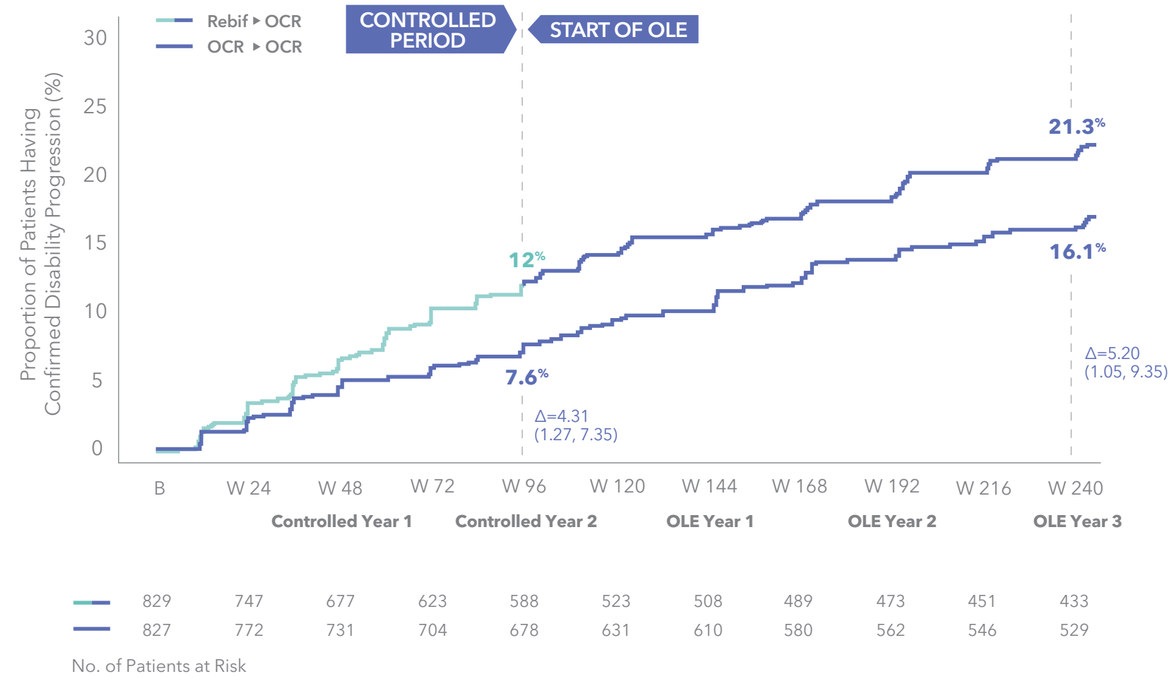
Confirmed disability improvement was defined as a reduction from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks in patients with a baseline EDSS score of at least 2.0.[28]

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.

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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	Rebif population	OCREVUS population	Placebo population	Mean number of doses: 9.6	Mean number of doses: 6.3
	n=825	n=826	n=486	n=239	N=2305	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 period[8]

- These infections were mainly mild to moderate

OPERA I AND II

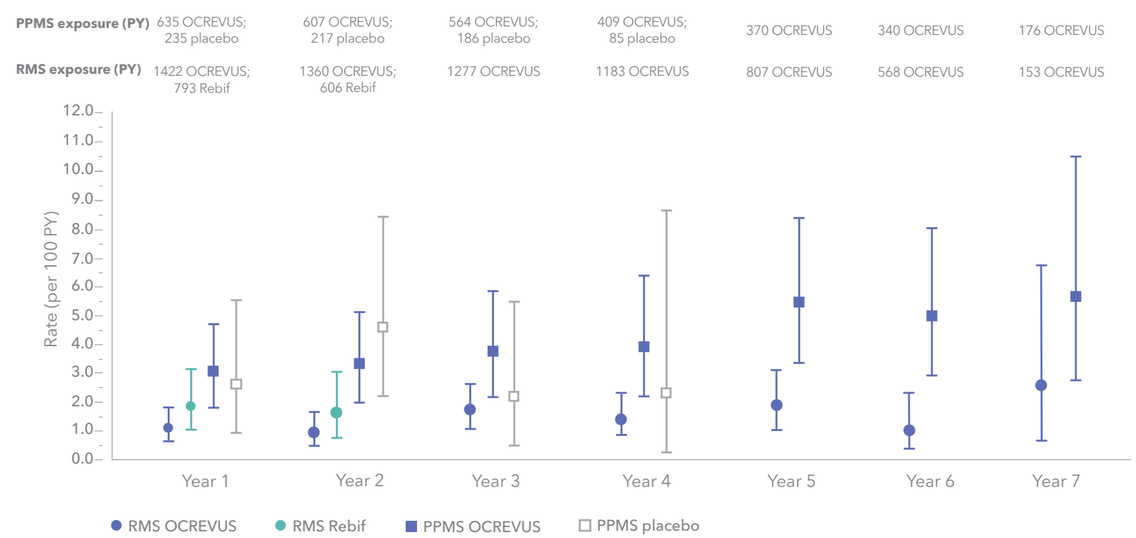
58% OCREVUS vs 52% Rebif

ORATORIO

70% OCREVUS vs 68% Placebo

- 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 OLE[34]



- **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

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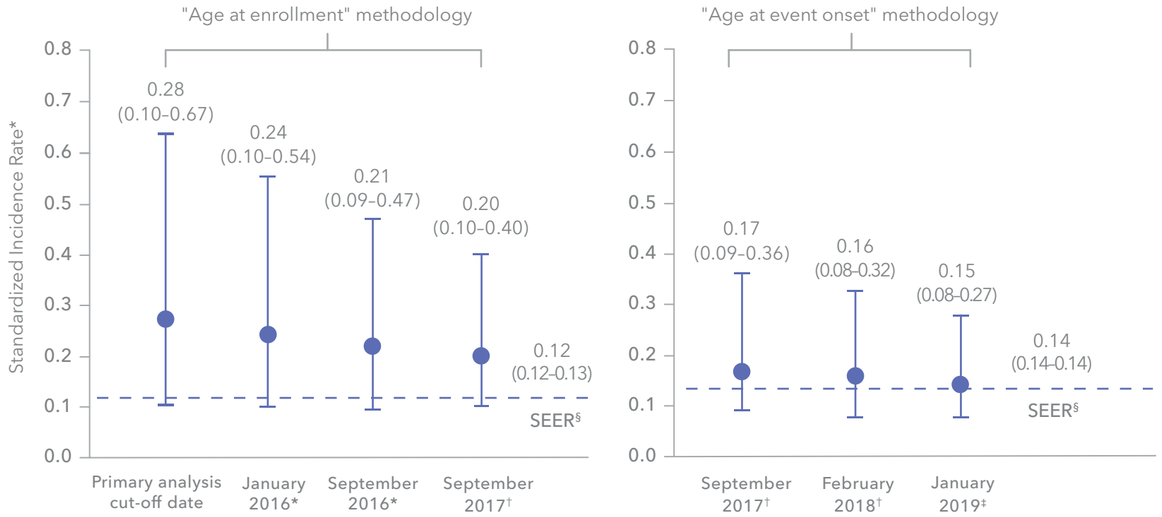
Additional important safety information[8]

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 in[8]:

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 in[34]:

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

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

"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 guidelines[8]

Women with disabilities are **less likely** to have received a mammogram[36]

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 recommendations[37]

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 pages 18 and 19 and accompanying full **Prescribing Information** and **Medication Guide** in pocket.

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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.

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]

<u>Hepatitis B Virus (HBV) Reactivation</u>
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 data[8]

- 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 OCREVUS[33]

- 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

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OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

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 ≥10% and >REBIF) were upper respiratory tract infections (40%) and infusion reactions (34%).

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

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Notes

Notes

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

How to start and manage patients on OCREVUS[8]

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 ≥10% and >REBIF) were upper respiratory tract infections (40%) and infusion reactions (34%).

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

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