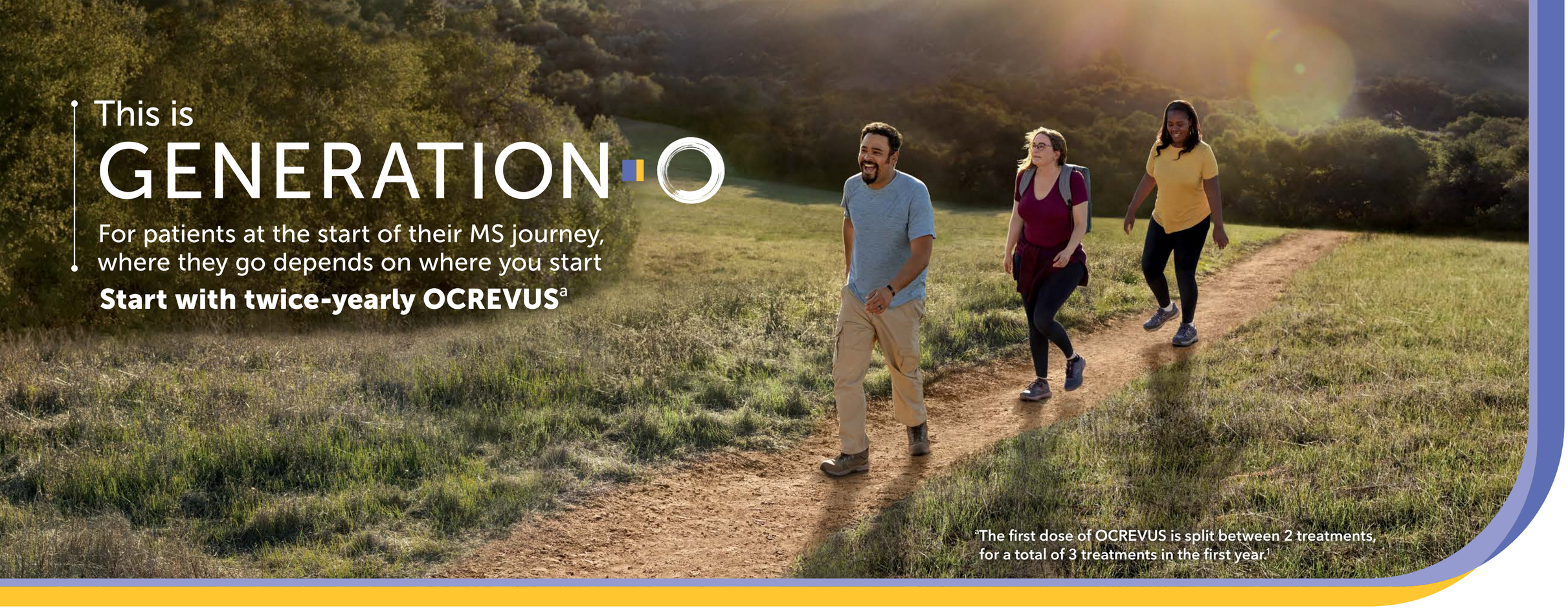

225,000+ patients treated globally and 8+ years of safety data[2,3]

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.

Select Important Safety Information

The warnings and precautions for OCREVUS are infusion reactions, and infections, which include respiratory tract infections, herpes, progressive multifocal leukoencephalopathy (PML), and hepatitis B virus (HBV) reactivation. Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, and malignancies.

For additional safety information, please see pages 25 and 26 and **click here** for full Prescribing Information and Medication Guide.

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PROGRESSION BEGINS EARLY IN MS[4-10]

MS is characterized by acute and diffuse inflammation and chronic neurodegeneration[5,7,11]

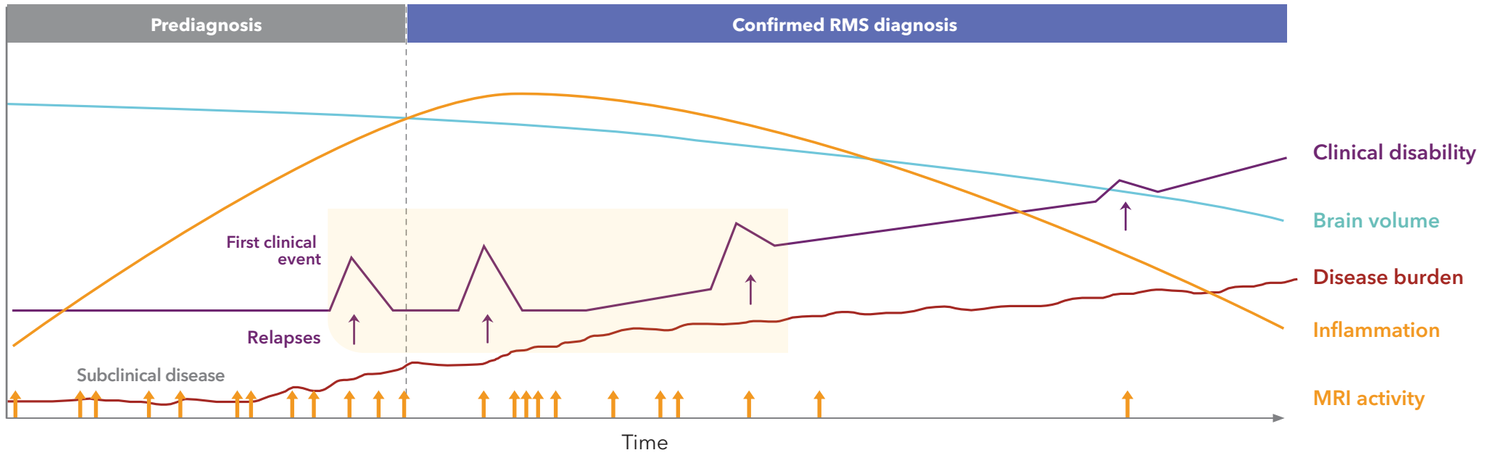
INFLAMMATORY ACTIVITY IS THOUGHT TO BE **HIGHEST EARLY IN MS** AND IS ASSOCIATED WITH[5]:

Younger age
The average age at diagnosis of MS is 32[12-14]

Lesions
Lesions can contribute to axonal loss/degeneration, which is associated with progression[8]

Relapses
Relapses are the acute clinical manifestation of neurologic damage early in MS[15,16]

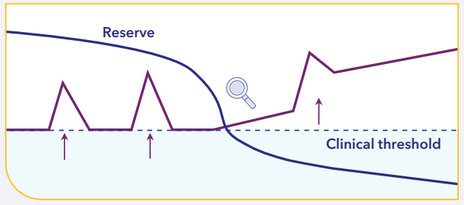
INFLAMMATION IS AN IMPORTANT DRIVER OF PROGRESSION EARLY IN MS[5,9-11,17-20]



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

THE BRAIN **MAY COMPENSATE FOR DAMAGE** EARLY IN MS VIA FUNCTIONAL RESERVE[8,11,17,21-23]

Progression can be associated with, or independent of, relapse.



As functional reserve is lost, the ability to compensate for damage decreases and disability emerges.

Disability can accumulate in the absence of relapse ("silent" progression)[8,23]

ADDRESSING PROGRESSION FROM THE START

Treatment considerations include the risk of progression in early MS along with other factors

AN EARLY **WINDOW OF OPPORTUNITY** TO IMPACT MS

Inflammatory activity **can occur in advance** of the first relapse[5,9]

Progression begins early in MS, despite initial presentation[8,11,17,21]

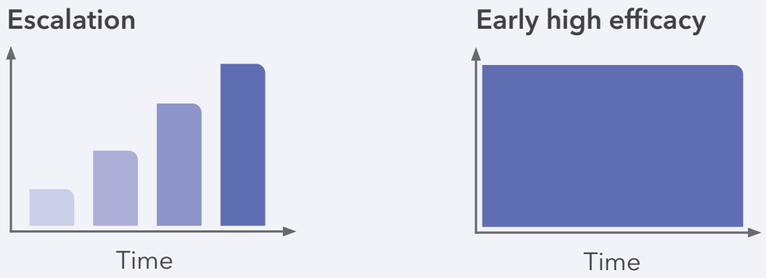
Disability can begin to accumulate early and **may become irreversible** over time[15,24]

Disability progression can be **difficult to detect early** in MS[25-27]

Progression goes beyond impact on ambulation and occurs across all functional domains[25]

- Functional systems assessed in clinical trials as part of Expanded Disability Status Scale (EDSS) include visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral, along with an ambulation test

CONTEMPORARY **TREATMENT PARADIGMS** IN MS[28]



Treatment considerations in MS are evolving—evaluation of these approaches is a robust area of research[29,30]

When selecting a strategy to manage MS, the early impact of progression should be considered along with factors such as treatment goals, patient preferences, age, and comorbidities[28]

GENERATION O IN OPERA I AND II

Select baseline characteristics of patients in OCREVUS trials for RMS

60%
of patients studied were **younger than 40 years of age**[31]

3/4
of all patients had no disease-modifying therapy (DMT) **within the previous 2 years**[1]

45%
of all patients were diagnosed within 2 years of screening and **treatment naive**[3,32]

37 years
mean age with approximately **4 years** from MS diagnosis to trial participation[1]

40%
of patients had an EDSS score of **<2.5**[1,31]

Patients in the controlled period had to have an EDSS score between 0 and 5.5.

40%
had ≥1 T1 Gd+ lesions, thought to represent **acute inflammation**[1]

AVERAGE PATIENT IN THE CONTROLLED PERIOD[1,33,34]

Age: **37**
Mean EDSS score: **2.8**

Mean number of T1 Gd+ lesions: **1.8**
Mean number of T2 lesions: **51.0**

Untreated within 2 years: **74%**
Mean time since diagnosis: **4 years**

Gd+=gadolinium-enhancing.

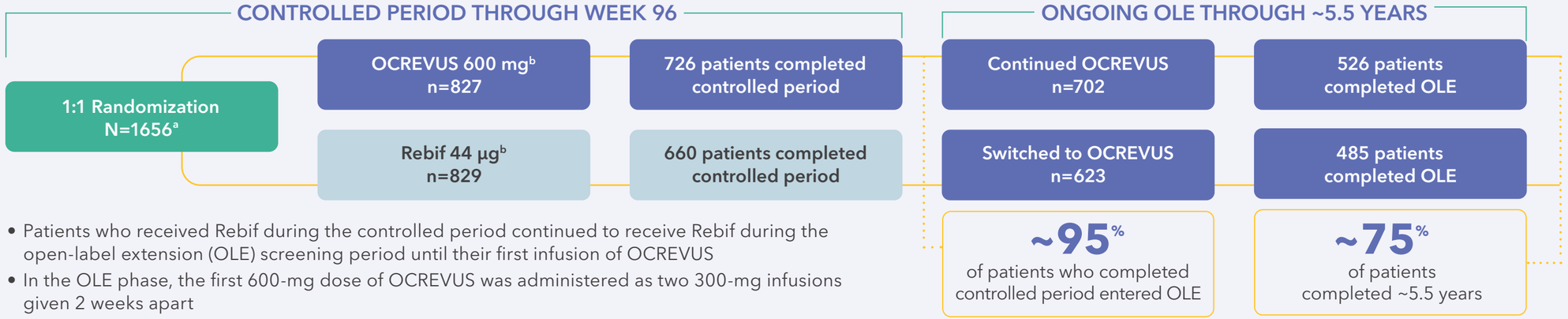
Select Important Safety Information

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.

7+ YEARS OF CLINICAL TRIAL EXPERIENCE

OPERA I and OPERA II were identical head-to-head clinical trials of OCREVUS vs Rebif® (interferon β-1a) in RMS[34]

OPERA I AND OPERA II POOLED ANALYSIS[2,35,36]



- Patients who received Rebif during the controlled period continued to receive Rebif during the open-label extension (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

KEY INCLUSION CRITERIA[34]

- ≥2 relapses within last 2 years
- ≥1 relapse in last year
- EDSS score from 0.0 to 5.5

CONTROLLED AND OLE **STUDY ENDPOINTS**[34,35]

- Annualized relapse rate (primary endpoint)
- 12-week and 24-week confirmed disability progression (CDP) in the controlled period and 24-week and 48-week CDP in the OLE period
- Confirmed disability improvement (CDI) at 12 weeks through 96 weeks
- Mean number of T1 Gd+ lesions and new or enlarging T2 hyperintense lesions per MRI at Week 96
- Exploratory composite endpoint: proportion of patients with No Evidence of Disease Activity (NEDA) in the controlled period
- Safety

Limitations of the open-label, 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 or 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.

[a]OCREVUS: OPERA I, n=410; OPERA II, n=417. Rebif: OPERA I, n=411; OPERA II, n=418.[34]

[b]OCREVUS arm: 600-mg intravenous (IV) dose every 24 weeks (first dose: two 300-mg IV infusions 2 weeks apart) or placebo as subcutaneous (SC) injections3 times/week; Rebif arm: 44-µg SC 3 times/week or placebo IV infusions every 24 weeks.[34]

Select Important Safety Information

The warnings and precautions for OCREVUS are infusion reactions, and infections, which include respiratory tract infections, herpes, progressive multifocal leukoencephalopathy (PML), and hepatitis B virus (HBV) reactivation. Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, and malignancies.

SUPERIOR RELAPSE REDUCTIONS VS REBIF AT YEAR 2

OCREVUS reduced relapse rates by nearly half[1]

SUPERIOR RELAPSE REDUCTIONS vs REBIF AT YEAR 2 (CONTROLLED PERIOD)[1]

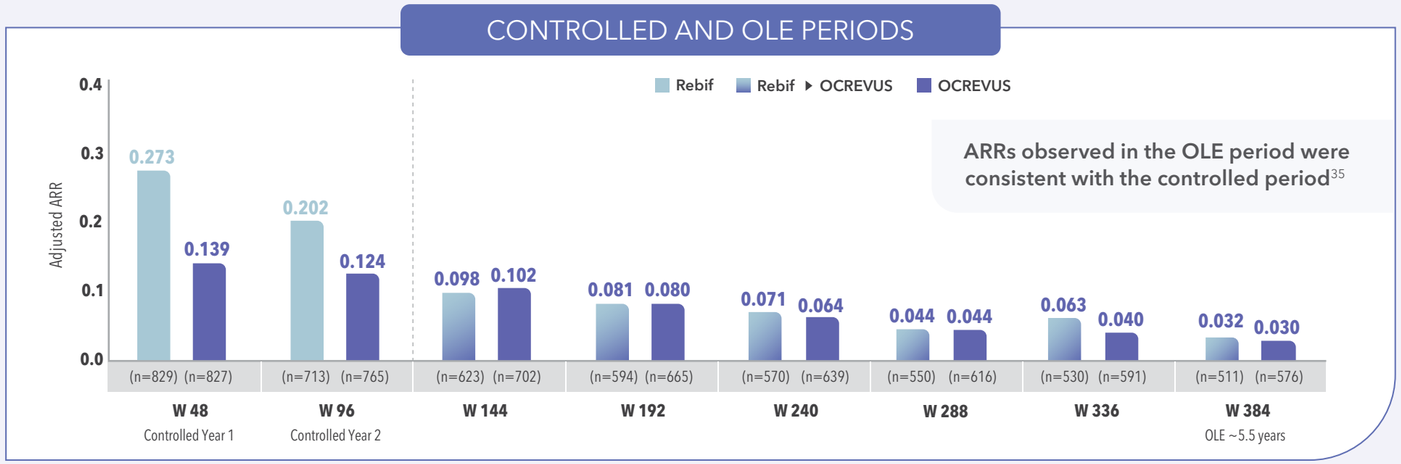
46% OPERA I | **47%** OPERA II

RELATIVE REDUCTIONS
p<0.0001

ARR with OCREVUS vs Rebif:
OPERA I: 0.156 vs 0.292
OPERA II: 0.155 vs 0.290

- **83%/82%** of patients treated with OCREVUS were relapse free at the end of the 2-year controlled period vs **71%/72%** with Rebif (OPERA I/OPERA II)

ANNUALIZED RELAPSE RATE (ARR) DATA THROUGH **7+ YEARS**[35]



Relapses were defined as new or worsening neurologic symptoms that were attributable to MS, persisted for more than 24 hours, were immediately preceded by a stable or improving neurologic state for at least 30 days, and were accompanied by objective neurologic worsening as defined in the study protocols.[34]

Measurements performed at intermediate timepoints were not prespecified in the statistical testing hierarchy and reflect numerical trends only.[34]

Select Important Safety Information

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.

IMPACT ON DISABILITY

Only OCREVUS significantly impacted disability in 3 endpoints across 2 identical RMS trials vs an active comparator[1,34]

SUPERIOR REDUCTION IN RISK OF CDP vs REBIF (CONTROLLED PERIOD)[1,34]

12-WEEK CDP

↓ 40%

RISK REDUCTION

HR (95% CI): 0.60 (0.45, 0.81)
p=0.0006

PROPORTION OF PATIENTS

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 CDP

↓ 40%

RISK REDUCTION

HR (95% CI): 0.60 (0.43, 0.84)
p=0.003

PROPORTION OF PATIENTS

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

48-WEEK CDP vs REBIF (CONTROLLED PERIOD, POST HOC ANALYSIS)[3,36]

- 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

SUPERIOR REDUCTION IN RISK OF CDP vs REBIF (CONTROLLED PERIOD)[1,34]

12-WEEK CDI
(proportion of patients)

↑ 33%

DIFFERENCE

p=0.02

Pooled analysis:
20.7% OCREVUS vs 15.6% Rebif

Confirmed disability progression (CDP) was defined as patients with EDSS score ≤5.5 who experienced an EDSS score increase of ≥1.0. For patients with EDSS score >5.5, progression was an EDSS score increase of ≥0.5. Disability progression was categorized as confirmed if it was present at 12 or 24 weeks over the treatment period.[34]

Confirmed disability improvement (CDI) 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.[34]

Select 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.

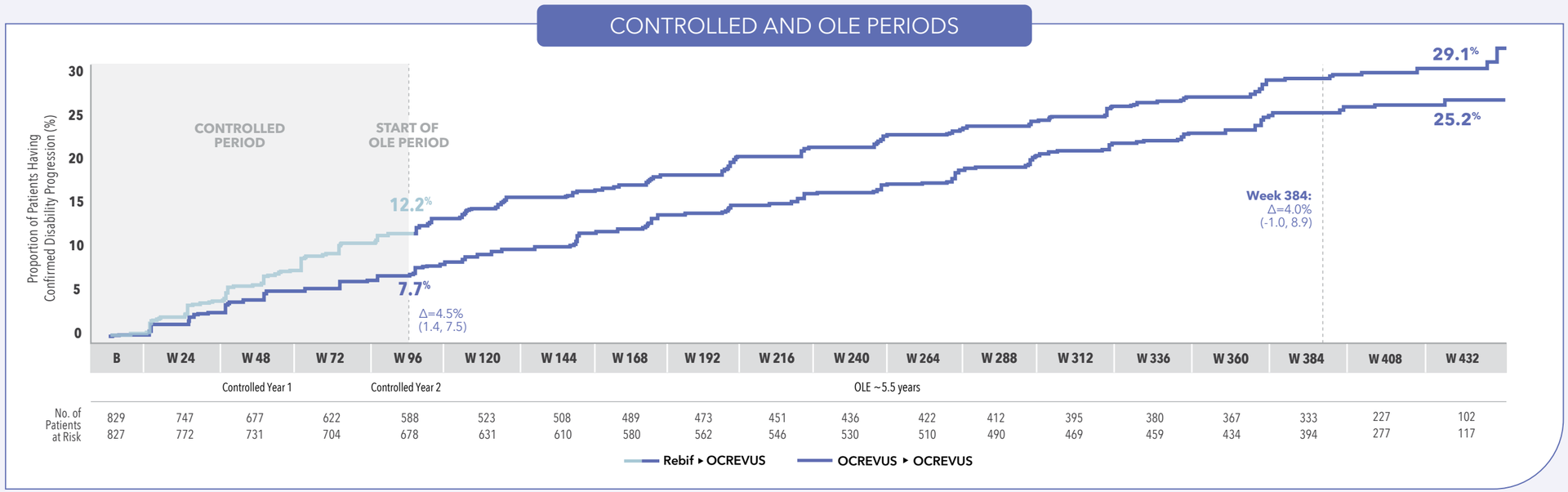
For additional safety information, please see pages 25 and 26 and **click here** for full Prescribing Information and Medication Guide.

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

DISABILITY DATA THROUGH 7+ YEARS

In the controlled period, fewer OCREVUS patients had experienced disability progression than those who started on Rebif[1,34]

TIME TO ONSET OF **24-WEEK CDP**[35]



- All patients in the OLE period have been treated with OCREVUS[35]

>90% of patients treated with OCREVUS showed no 12-week or 24-week confirmed disability progression in the controlled period[1,34]

Select Important Safety Information

Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with OCREVUS treatment. The pooled data of OCREVUS clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of immunoglobulin G (IgG<LLN) and increased rates of serious infections.

SUPERIOR REDUCTIONS IN MRI LESIONS VS REBIF

OCREVUS demonstrated superior reductions in mean number of T1 Gd+ lesions and T2 lesions over 2 years[1]

NEAR-COMPLETE SUPPRESSION OF T1 Gd+ LESIONS[1,a]

94% OPERA I | **45%** OPERA II

RELATIVE REDUCTIONS
$p<0.0001$

OCREVUS vs Rebif:
OPERA I: 0.016 vs 0.286
OPERA II: 0.021 vs 0.416

[a]The precise mechanism by which OCREVUS exerts its therapeutic effects in MS is unknown.

SUPERIOR REDUCTIONS IN MEAN NUMBER OF NEW OR ENLARGING T2 LESIONS[1]

77% OPERA I | **83%** OPERA II

RELATIVE REDUCTIONS
$p<0.0001$

OCREVUS vs Rebif:
OPERA I: 0.323 vs 1.413
OPERA II: 0.325 vs 1.904

Select Important Safety Information

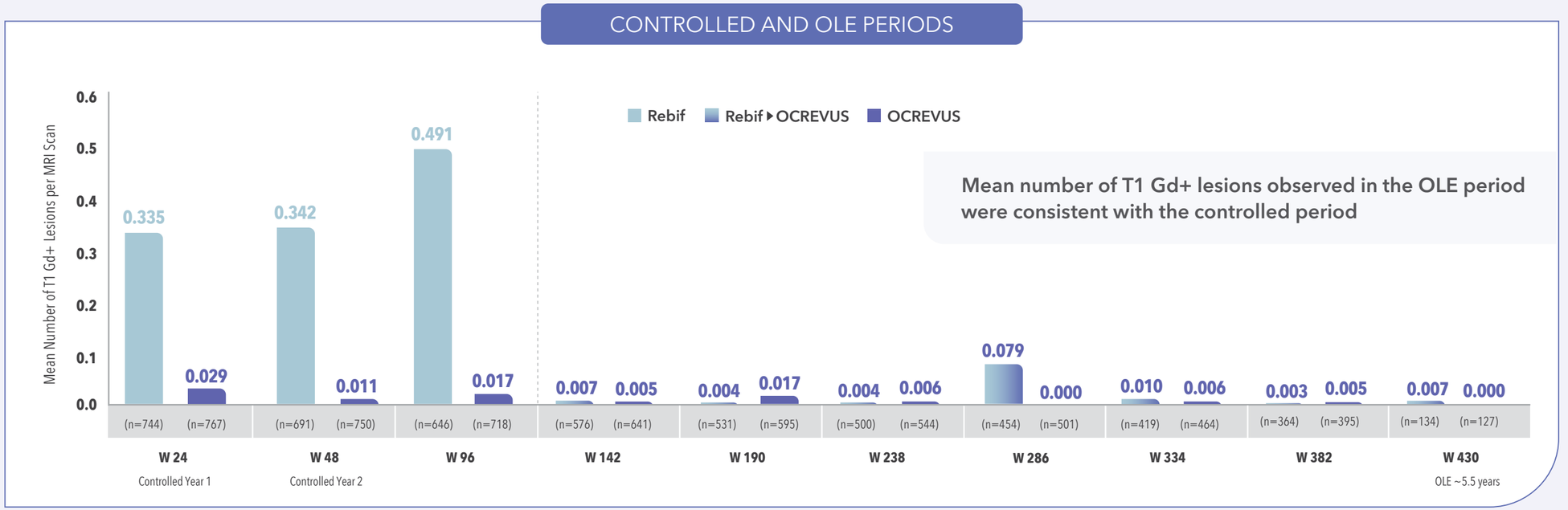
Malignancies
An increased risk of malignancy, including breast cancer, may exist with OCREVUS. In controlled trials, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients. Breast cancer occurred in 6 of 781 females treated with OCREVUS and none of 668 females treated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

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.

MRI DATA THROUGH 7+ YEARS

T1 Gd+ lesions in the controlled and OLE periods[35]

T1 Gd+ LESIONS[35]



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.[34]

Unadjusted controlled and OLE data include the ITT population; clinical cutoff date: November 2020. Number of T1 Gd+ lesions at each timepoint for all patients in the treatment group divided by the total number of brain MRI scans at that timepoint.[35]

ITT=intent-to-treat.

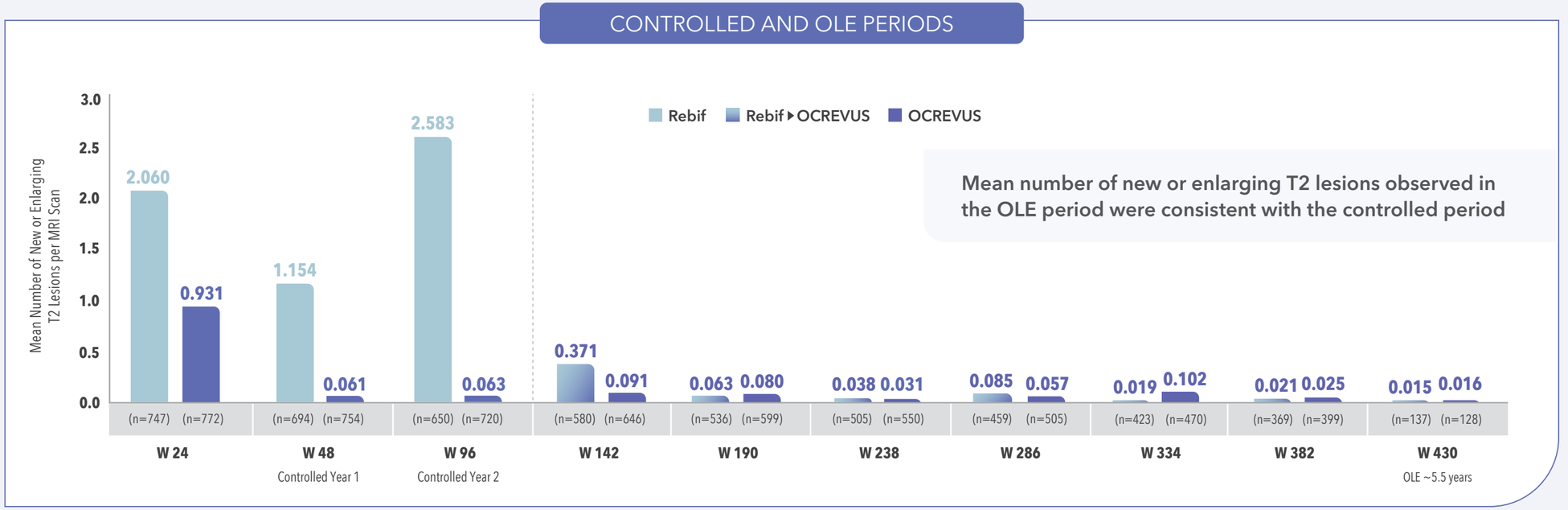
Select Important Safety Information

The warnings and precautions for OCREVUS are infusion reactions, and infections, which include respiratory tract infections, herpes, progressive multifocal leukoencephalopathy (PML), and hepatitis B virus (HBV) reactivation. Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, and malignancies.

MRI DATA THROUGH 7+ YEARS

New or Enlarging T2 lesions in the controlled and OLE periods[35]

NEW OR ENLARGING T2 LESIONS[35]



Relative reductions vs Rebif 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.[34]

Unadjusted controlled and OLE data include the ITT population; clinical cutoff date: November 2020. Number of new or enlarging T2 lesions at each timepoint for all patients in the treatment group divided by the total number of brain MRI scans at that timepoint.[35]

ITT=intent-to-treat.

Select Important Safety Information

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.

NEDA BY WEEK 96 (POST HOC ANALYSIS)

No evidence of disease activity (NEDA) in the controlled period including re-baselined analysis

NEDA IS THE PROPORTION OF RMS PATIENTS WITH[34]:

NO PROTOCOL-DEFINED RELAPSES ■ NO 3-MONTH CDP ■ NO T1 GD+ MRI ACTIVITY ■ NO NEW OR ENLARGING T2 LESIONS

Controlled Period NEDA[34]
Pooled Analysis

48% OCREVUS vs **27%** Rebif

Weeks 0-96

ASSESSMENT AND LIMITATIONS

- The predefined secondary endpoint of NEDA in the OPERA studies was not statistically significant, and it was considered nonconfirmatory because it fell below the break in the statistical hierarchy at change in Multiple Sclerosis Functional Composite Scale score from baseline to Week 96
- Exploratory result based on modified ITT population

Re-baselined NEDA[37]
Pooled Analysis

72% OCREVUS vs **42%** Rebif

Weeks 24-96
(re-baselined to 24 weeks)

82% OCREVUS vs **57%** Rebif

Weeks 48-96
(re-baselined to 48 weeks)

ASSESSMENT AND LIMITATIONS

- During Weeks 48 to 96, the lower frequency of MRI scans compared with other time periods may have influenced the proportions of patients maintaining NEDA
- Moving into the clinical practice setting, the optimal timing of re-baselining should reflect the anticipated timing for reaching complete DMT efficacy, to give a more reliable indication of subsequent drug failure
- Conclusions from cross-trial comparisons are limited because of differences including comparators, patient populations, MRI techniques, frequency of assessments, analysis methods, and definitions of NEDA

Why re-baseline NEDA data?

NEDA analyses are often re-baselined, or calculated at a later timepoint, in order to minimize any confounding impact of pretreatment disease activity and to better reflect the steady state of DMT impact on disability worsening and disease activity.[37]

Select 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.

8+ YEARS OF SAFETY EXPERIENCE

As of November 2020, 5688 patients have received OCREVUS in the all-exposure trial population, resulting in 21,675 PY of exposure[38]

In Phase III trials, the most common adverse events (AEs) were infusion reactions and infections (mainly mild to moderate)[1]

- Other common AE rates were similar with Rebif and placebo[1]
- In the OCREVUS all-exposure population, reported rates of AEs continue to be consistent with those seen during the controlled RMS and primary-progressive multiple sclerosis (PPMS) trials[38]

AEs PER 100 PATIENT-YEARS (PY) IN OCREVUS TRIAL POPULATION[38]

	OPERA (pooled) treatment period[a]		ORATORIO treatment period[a]		OCREVUS all-exposure population[b]
	OCREVUS n=825	Rebif n=826	OCREVUS n=486	Placebo n=239	Mean number of doses: 8.3 N=5688
	PY=1448	PY=1399	PY=1606	PY=729	PY=21,675
Any AE	290	296	252	259	238
AEs leading to discontinuation	2.35	3.93	1.25	1.10	0.96
Serious AEs	5.4	6.3	10.2	12.1	7.1
Infections	84.5	67.8	70.8	72.5	71.8
Serious infections[c]	0.83	1.79	2.74	3.02	2.00
Infusion reactions	34.9	7.9	31.0	20.3	24.5
Malignancies[d,e]	0.28	0.14	0.93	0.27	0.42
Deaths	0.07	0.14	0.25	0.41	0.15

- **Potential serious opportunistic infections in the OCREVUS all-exposure population:** 0.02 per 100 PY (95% CI: 0.01, 0.05) as of November 2020[38]

AEs were classified according to Medical Dictionary for Regulatory Activities (MedDRA) versions 18.0, 18.1, and 22.1. Multiple occurrences of the same AE in one patient are counted multiple times, except for malignancies.

[a]Data as of April–July 2015.

[b]Includes patients who received any dose of OCREVUS during the controlled period and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, and CONSONANCE, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCREVUS treatment (data as of November 2020).

[c]Serious infections are defined using AEs falling into the MedDRA system organ class "Infections and infestations," and using "Is the event nonserious or serious?" from the AE case report form.

[d]Malignancies are identified using AEs falling into the standard MedDRA query "Malignant tumours (narrow)."

[e]For malignancies, incidence rates are reported and exposure in PY was calculated from first treatment to onset of first malignancy.

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 score of 3.0 to 6.5 and a score of 2.0 or greater for the EDSS pyramidal functional systems score due to lower extremity findings. Patients also had no history of RMS, SPMS (secondary progressive multiple sclerosis), or PRMS (progressive relapsing multiple sclerosis).[1,39]

OBSERVED RATES OF INFECTION

Patients who experienced ≥1 infections in the controlled period[1]

INFECTIONS IN THE CONTROLLED PERIOD WERE MAINLY MILD TO MODERATE IN SEVERITY[1]

OPERA I AND II

58% OCREVUS vs **52%** Rebif

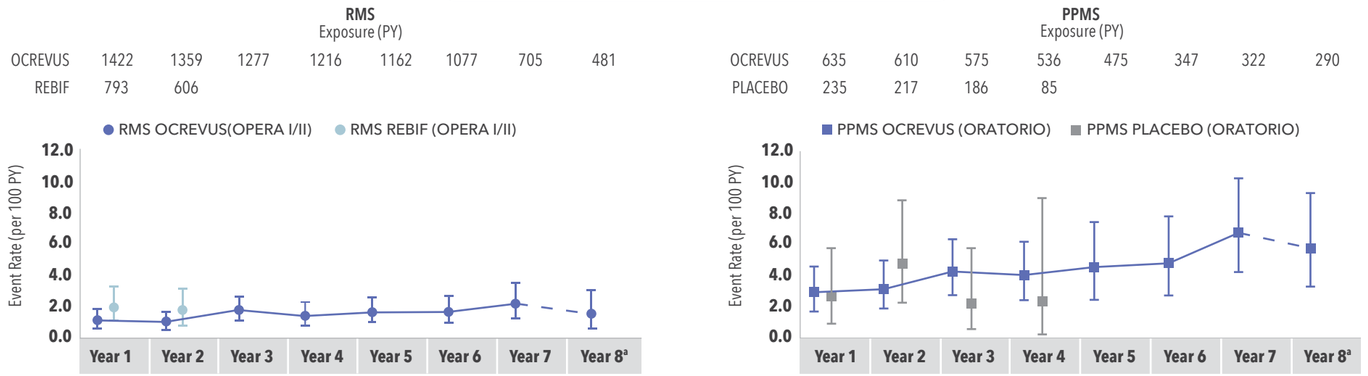
ORATORIO

70% OCREVUS vs **52%** Placebo

- OCREVUS did not increase the risk of serious infections vs Rebif or placebo, though serious infections have occurred[1]

RATE OF SERIOUS INFECTIONS OBSERVED FOR 8+ YEARS[2,38]

PHASE III TRIALS AND OLE



- **Serious infections in the OCREVUS all-exposure population:** 2.00 per 100 PY (95% CI: 1.82, 2.20) as of November 2020[38]
- The most common serious infections were urinary tract infections, pneumonia, and cellulitis[2]

[a]The exposure in PY during Year 8 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

SERIOUS INFECTIONS AND IgG LEVELS

There is an association between decreased levels of immunoglobulin (IgG) and serious infections[1]

- MOST PATIENTS TAKING OCREVUS REMAINED **AT OR ABOVE THE LOWER LIMIT OF NORMAL FOR IgG** (LLN; 5.65 g/L) (DATA AS OF JANUARY 2020)[2]

TOTAL PATIENTS TREATED WITH OCREVUS IN OPERA, ORATORIO, AND OLE
N=2092

90.5%
n=1894
Patients with IgG≥LLN

9.5%
n=198
Patients with IgG<LLN

Of 2092 patients treated with OCREVUS, 20 serious infections were observed in 15 patients during episodes of IgG<LLN (OPERA, ORATORIO, and OLE)

- RATE OF **SERIOUS INFECTIONS** (DATA AS OF JANUARY 2020)[2]

All-exposure population	Patients with IgG≥LLN	Patients with IgG<LLN
2.28 /100 PY	**2.16** /100 PY	**5.68** /100 PY

- Serious infections during episodes of IgG<LLN were consistent with overall serious infections observed in patients treated with OCREVUS in terms of type, severity, latency, duration, and outcome

Select Important Safety Information

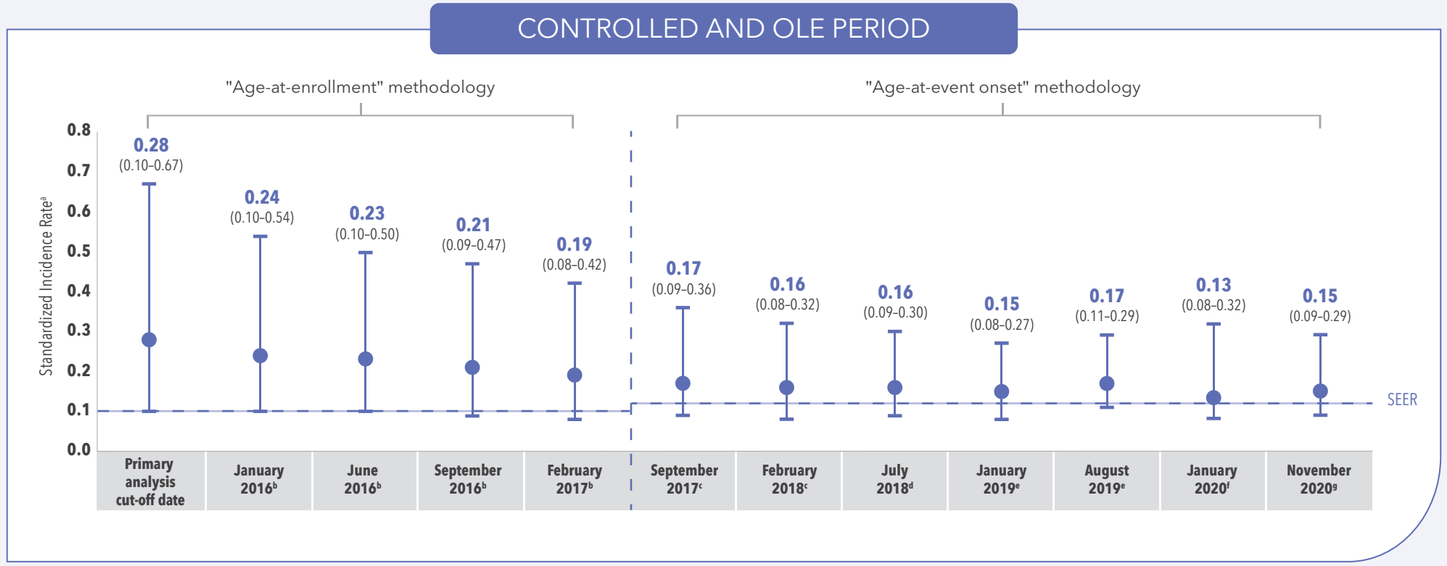
Reduction in Immunoglobulins

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

ADDITIONAL IMPORTANT SAFETY INFORMATION

An increased risk of malignancy, including breast cancer, may exist in OCREVUS-treated patients[1]

AGE-STANDARDIZED INCIDENCE RATE OF FEMALE BREAST CANCER OVER OCREVUS-STUDIED POPULATIONS AND SEER POPULATION (PER 100 PY)[38]



"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.

[a] Nonmelanoma Skin Cancer (NMSC) is not reported in the Surveillance, Epidemiology, and End Results (SEER) program.

[b] Includes patients who received any dose of OCREVUS during the controlled period, extended-controlled period, and associated OLE periods of the Phase II and Phase III studies, including patients originally randomized to comparator (Rebif or placebo) who switched to open-label OCREVUS treatment.

[c] Includes patients described in footnote b plus VELOCE, CHORDS, CASTING, and OBOE.

[d] Includes patients described in footnote c plus ENSEMBLE.

[e] Includes patients described in footnote d plus LIBERTO.

[f] Includes patients described in footnote d plus CONSONANCE.

[g] Includes patients who received any dose of OCREVUS during the controlled period, and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, and CONSONANCE, including patients originally randomized to comparator (Rebif or placebo) who switched to open-label OCREVUS treatment.

The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information reporting data on cancer incidence in 48% of the general US (non-MS specific) population. No comparisons should be made due to limitations that 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.[41]

Breast cancer was found in:

- 6/781 females treated with OCREVUS and 0/668 females treated with Rebif or placebo in the controlled period[1]
- 24/3557 females on OCREVUS (12,928 PY) in the all-exposure population as of November 2020[38]

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

The American Cancer Society recommends that patients age <40 with risk factors for breast cancer should ask their HCP whether mammograms are advisable and how often to have them. Patients age 45 to 54 should get mammograms every year.[1,40]

2x-YEARLY OCREVUS DOSING[a]

Shorter 2-hour infusion option after first dose[1,b]

TREATMENT **INITIATION**

INITIAL DOSE

DAY 1 — 300 MG — Infusion 1

DAY 15 — 300 MG — Infusion 2

≥2.5-HOUR DURATION

2-hour infusion is available for patients who have not experienced serious infusion reactions (IRs) with any previous OCREVUS infusion

2 HOURS if no serious IRs[c] have occurred

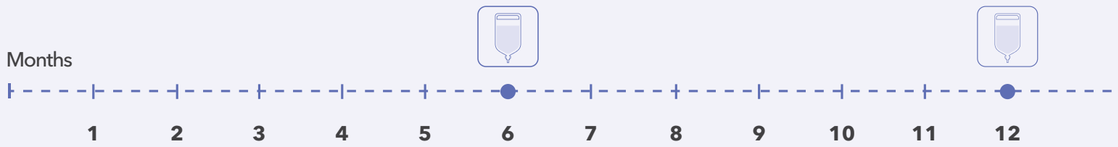
3.5 TO 4 HOURS

[a] Three treatments in the first year: first 600-mg dose administered as two 300-mg IV infusions over approximately 2.5 hours, separated by 2 weeks; subsequent doses administered as a single 600-mg IV infusion every 6 months.

[b] Infusion time may take longer if the infusion is interrupted or slowed. No change in premedication, dose, formulation, or posttreatment monitoring between infusion timing options.

[c] Per the study protocol, serious IRs included those that were fatal or life threatening, required or prolonged hospitalization, resulted in persistent or significant disability, or were deemed to be medically significant by the trial investigator.[3]

ONE 600-MG INFUSION EVERY 6 MONTHS BEYOND INITIAL TREATMENT[1]



Delayed or missed doses[1]:

If a planned infusion of OCREVUS is missed, administer it 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.

PREMEDICATION AND OBSERVATION[1]

Premedication	Infusion	Observation
30 to 60 minutes	2 hours or 3.5 to 4 hours	60 minutes

With the OCREVUS dosing schedule, patients only need 2 infusions every 12 months[1]

Select Important Safety Information

Malignancies

An increased risk of malignancy, including breast cancer, may exist with OCREVUS.

SHORTER 2-HOUR INFUSION

2-hour infusion is available for patients who have not experienced serious IRs with any previous OCREVUS infusion[1]

Per the ENSEMBLE protocol, serious IRs included those that were fatal or life threatening, required or prolonged hospitalization, resulted in persistent or significant disability, or were deemed to be medically significant by the trial investigator.[3]

NO LIFE-THREATENING, FATAL, OR SERIOUS IRs OCCURRED WITH OCREVUS IN THE ENSEMBLE PLUS STUDY[1,42]

The proportions of patients with IRs were similar between the 2 infusion protocols[1,42]

24.4%
2-HOUR INFUSION

23.3%
3.5- TO 4-HOUR INFUSION

- Overall, in all randomized doses, 27.1% of the patients in the 2-hour infusion group and 25.0% of the patients in the 3.5-hour infusion group reported mild or moderate infusion reactions; two infusion reactions were severe in intensity, with 1 severe infusion reaction (0.3%) reported in 1 patient in each group in this substudy.

ENSEMBLE PLUS evaluated the safety of OCREVUS 2-hour infusion[1]

A prospective, multicenter, randomized, double-blind, controlled, parallel-arm substudy of 580 patients with early RRMS. 81% (469/579) of treated patients received a single randomized infusion of OCREVUS for the primary analysis.

3.5- to 4-hour infusion of OCREVUS: 99.7% of infusions did not result in serious IRs in the OPERA and ORATORIO studies (controlled period)[1,43]

- IRs were highest with the first infusion. Of the IRs that occurred, most were mild to moderate in severity
- 0.3% of OCREVUS-treated MS patients experienced IRs that were serious, some requiring hospitalization

Select Important Safety Information

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.

PERSISTENCE AND ADHERENCE

Clinical trial completion rates and real-world persistence and adherence data

OCREVUS CLINICAL **TRIAL COMPLETION**[1]

Percentage of patients who completed the OCREVUS RMS clinical trials at Year 2:

OPERA I

89% OCREVUS vs **83%** Rebif

OPERA II

86% OCREVUS vs **77%** Rebif

OCREVUS REAL-WORLD **PERSISTENCE AND ADHERENCE**[3,44]

Study design for OCREVUS real-world analysis among patients with 2 years of follow-up[3,44]

OCREVUS was studied with other DMTs using real-world US commercial and Medicare claims data from IBM MarketScan®.

- Persistence and adherence over a 2-year period were evaluated in the IBM MarketScan® Commercial Claims and Medicare Supplemental Databases
- Inclusion criteria included: patients ≥18 years of age with a diagnosis of MS who initiated an FDA-approved DMT between April 2017 and December 2017 and with 2 years of follow-up data (n=1710)
- Exclusion criteria included: patients on alemtuzumab, mitoxantrone, and any off-label therapies; patients initiating multiple DMTs on index; and patients with any claims of index DMT in the prior 12 months

Persistence was defined as no evidence of switching to another DMT or no gap in index DMT coverage of ≥60 days at any time during the evaluation period.[a]

Adherence was calculated based on proportion of days covered (PDC), with ≥80% considered adherent to the DMT initiated.[a]

– PDC = number of days of supply or administration divided by 730 days

[a]For orals and self-injectables, if a patient received their prescription early, the patient was assumed to be persistent/adherent for the total number of days for which they possessed medication. For IV infusions, including OCREVUS, these overlapping days were not considered.

Select Important Safety Information

The warnings and precautions for OCREVUS are infusion reactions, and infections, which include respiratory tract infections, herpes, progressive multifocal leukoencephalopathy (PML), and hepatitis B virus (HBV) reactivation. Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, and malignancies.

OCREVUS REAL-WORLD ANALYSIS

Among patients with 2 years of follow-up concluding December 31, 2019[44]

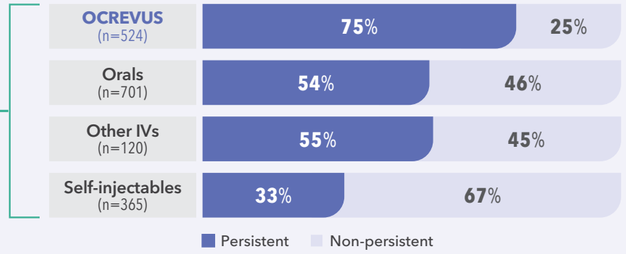
LIMITATIONS FOR OCREVUS REAL-WORLD ANALYSIS AMONG PATIENTS WITH 2 YEARS OF FOLLOW-UP[3,44]

- Potential for selection bias based on requirement that patients have continuous enrollment for 3 years, which may limit generalizability of the results
- Deviations from FDA-approved dosing schedule may cause persistence and adherence to be misclassified
- Caution should be exercised in making any direct comparisons due to differences in DMT dosing schedules and pharmacodynamics
- Claims data have inherent limitations:
  - –Unable to ascertain if patients on injectable and oral medications took DMT as prescribed
  - –ICD-10 codes do not identify patients by MS subtypes
  - –Limited clinical information available may impact interpretation of results (eg, MS disease duration, line of therapy)
  - –Lack of data on reason for discontinuation
  - –Possible coding errors and missing data

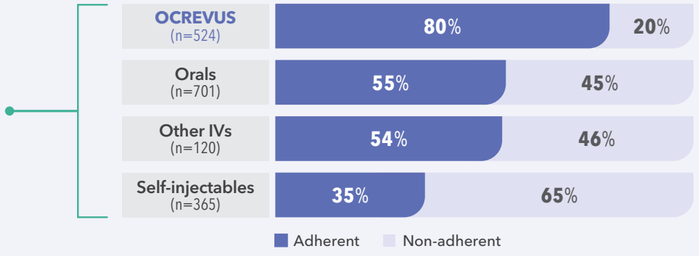
RESULTS FOR OCREVUS REAL-WORLD ANALYSIS INCLUDE ONLY DMTs THAT WERE FDA APPROVED AS OF 2017 AND EXCLUDE ALEMTUZUMAB AND MITOXANTRONE[3,44]

Real-world persistence and adherence rates should not be considered as a comparison of safety and efficacy[44]

PERSISTENCE AMONG PATIENTS WITH 2 YEARS OF FOLLOW-UP



ADHERENCE AMONG PATIENTS WITH 2 YEARS OF FOLLOW-UP



Select Important Safety Information

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.

ACCESS AND SUPPORT

The majority of patients with MS have unrestricted first-line access to OCREVUS[a]

DEDICATED TO ENSURING A **SMOOTH EXPERIENCE** FOR EVERY PATIENT PRESCRIBED OCREVUS

OCREVUS CONNECTS®

Call 1 (844) OCREVUS (1-844-627-3887)
Monday through Friday 9 AM–8 PM ET

Visit OCREVUS.COM for more information

- **Live Support** from dedicated OCREVUS Patient Navigators throughout the treatment journey
- **Help getting insurance approval**, including benefits investigations and prior authorization resources
- The ability to enroll in **My Patient Solutions**, an online tool for practices and infusion sites to manage OCREVUS patients
- Help with **coordinating infusions and locating infusion sites**, including infusion centers and hospitals, HCP offices, and home infusion providers
- Connections to **patient financial assistance**, including the OCREVUS Co-pay Program for drug and infusion costs and other options like the Genentech Patient Foundation or referrals to independent co-pay assistance foundations[b,c]

[a]As of February 2022, OCREVUS is available for first-line access in 68% of insured patients with published coverage for RMS.

[b]To be eligible for free Genentech medicine from the Genentech Patient Foundation, insured patients who have coverage for their medicine must have pursued all other forms of patient assistance and must meet certain income requirements. Uninsured patients and insured patients without coverage for their medicine must meet different income requirements.

[c]Eligibility criteria apply. Not valid for patients using federal or state government programs to pay for their medications. Patient must be taking the Genentech medication for an FDA-approved indication. See full terms and conditions at OCREVUS.com/Copay.

STARTING 2X-YEARLY OCREVUS[a]

How to start and manage patients on OCREVUS[1]

PRIOR TO FIRST DOSE

- Perform hepatitis B virus screening
- Test for quantitative serum immunoglobulins
- 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 reactions

Verifiable IV administration can facilitate monitoring of patient adherence[45,46]

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

Select 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.

Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with OCREVUS treatment. The pooled data of OCREVUS clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of immunoglobulin G (IgG<LLN) and increased rates of serious infections.

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.

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

Hepatitis B reactivation has been reported in MS patients treated with OCREVUS in the postmarketing setting. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with 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.

Reduction in Immunoglobulins

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

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

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to OCREVUS during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-872-4370 or visiting www.ocrevuspregnancyregistry.com.

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 effective 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%).

You may report side effects to the FDA at **(800) FDA-1088** or **www.fda.gov/medwatch**. You may also report side effects to Genentech at **(888) 835-2555**.

This is GENERATION O

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

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This is

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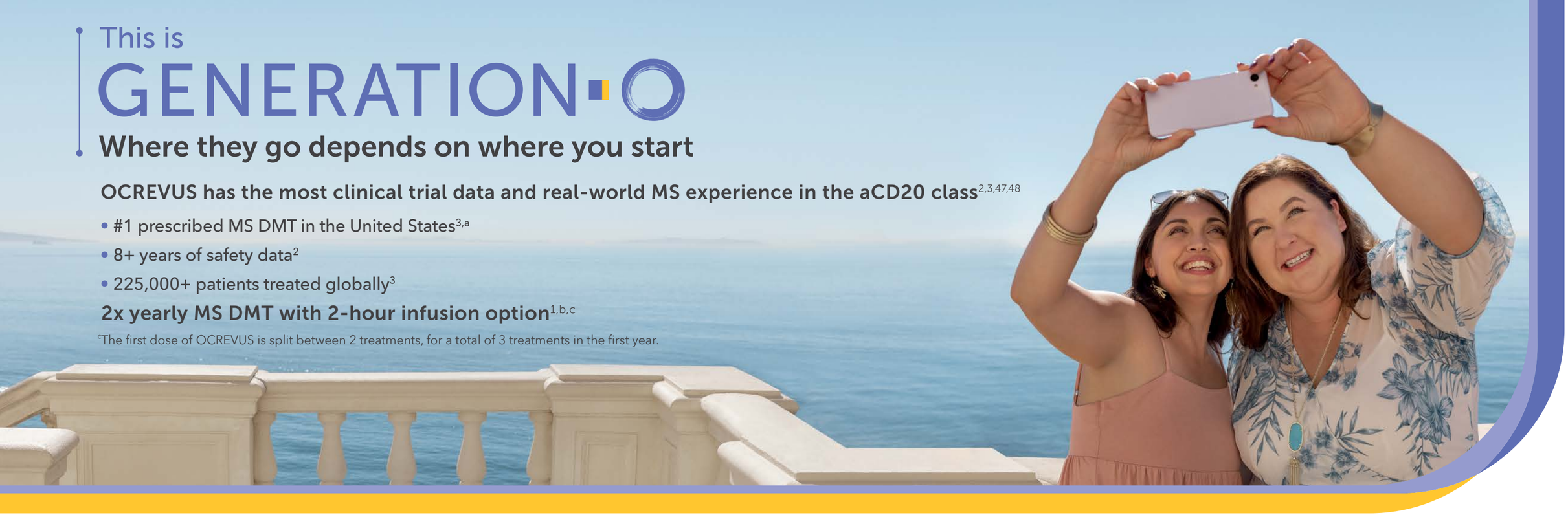
Where they go depends on where you start



OCREVUS has the most clinical trial data and real-world MS experience in the aCD20 class[2,3,47,48]

- #1 prescribed MS DMT in the United States[3,a]
- 8+ years of safety data[2]
- 225,000+ patients treated globally[3]

2x yearly MS DMT with 2-hour infusion option[1,b,c]

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

Choose OCREVUS for patients at the start of their MS journey

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

[a]From April 2019 to April 2021; IQVIA Claims & IQVIA NSP, rolling 3-month prescriber-based data; includes all patients with an OCREVUS prescription. Includes all patients with an ICD-10-CM of G35 (multiple sclerosis).

[b]2-hour infusion can be administered after the initial dose for patients who do not experience serious IRs with any previous OCREVUS infusion.

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.

Select Important Safety Information

The warnings and precautions for OCREVUS are infusion reactions, and infections, which include respiratory tract infections, herpes, progressive multifocal leukoencephalopathy (PML), and hepatitis B virus (HBV) reactivation. Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, and malignancies.

For additional safety information, please see pages 25 and 26 and **click here** for full Prescribing Information and Medication Guide.

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