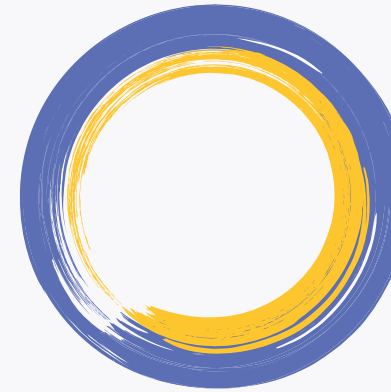


**OCREVUS**<sup>®</sup>  
ocrelizumab 300MG/10ML  
INJECTION FOR IV



## Breastfeeding Data With OCREVUS Exposure

### Key Considerations From the USPI

#### USPI INFORMATION REGARDING LACTATION USE IN SPECIFIC POPULATIONS RISK SUMMARY

##### Lactation

- 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.

**Safe use of OCREVUS during pregnancy, labor, delivery, or breastfeeding has not been established.**

### IMPORTANT SAFETY INFORMATION

#### 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, hepatitis B virus (HBV) reactivation, and a warning for progressive multifocal leukoencephalopathy (PML). Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, malignancies, immune-mediated colitis, and liver injury.

Please see additional safety information on [pages 4-5](#) and click here for full OCREVUS [Prescribing Information](#) and [Medication Guide](#).

# SAFETY PROFILE WITH 10+ YEARS OF CLINICAL TRIAL DATA

## 2-YEAR, DOUBLE-BLIND PERIOD AND 8+ YEARS OPEN-LABEL EXTENSION

**■ AEs PER 100 PATIENT-YEARS (PY) IN OCREVUS TRIAL POPULATION<sup>1</sup>**

	OPERA (pooled) treatment period*			ORATORIO treatment period*			OCREVUS all-exposure population <sup>†</sup>
	OCREVUS n=825 PY=1448	Rebif® n=826 PY=1399	All RMS <sup>‡</sup> n=4558 PY=21,080	OCREVUS n=486 PY=1606	Placebo n=239 PY=729	All PPMS <sup>§</sup> n=1597 PY=7190	Mean number of doses: 9.6 N=6155 PY=28,269
Any AE	290	296	227	252	259	215	224
AEs leading to discontinuation	2.4	3.9	1.0	1.2	1.1	1.0	1.0
Serious AEs	5.4	6.3	5.7	10.2	12.1	10.9	7.0
Infections	84.5	67.8	66.2	70.8	72.5	61.6	65.1
Serious infections <sup>¶</sup>	0.8	1.8	1.5	2.7	3.0	3.7	2.1
Infusion reactions	34.9	7.9	23.2	31.0	20.3	16.8	21.6
Malignancies <sup>¶¶</sup>	0.3	0.1	0.4	0.9	0.3	0.9	0.5
Deaths	0.1	0.1	0.1	0.3	0.4	0.4	0.2

**Pregnancy was an exclusion at the time of study enrollments. The studies were not designed to assess safety in pregnant and breastfeeding women.**

AEs were classified according to the MedDRA versions 18.0, 18.1, 22.1, and 24.1. Multiple occurrences of the same AE in one patient are counted multiple times, except for malignancies.

OPERA I and II (RMS): Two randomized, double-blind, double-dummy, active comparator-controlled clinical trials of identical design vs Rebif in 1656 patients (OCREVUS: OPERA I [n=410], OPERA II [n=417]; Rebif: OPERA I [n=411], OPERA II [n=418]) with RMS treated for 96 weeks. Both studies included patients who had experienced ≥1 relapse within the prior year or ≥2 relapses within the prior 2 years and had an EDSS score between 0 and 5.5.

\*Data as of April-July 2015.<sup>1</sup>

<sup>†</sup>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, CONSONANCE, CHIMES, and OLERO, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCREVUS treatment (data as of November 2022).<sup>1</sup>

<sup>‡</sup>Includes patients with PMS 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, CHIMES, and OLERO (data as of November 2022).<sup>1</sup>

<sup>§</sup>Includes patients with PPMS who received any dose of OCREVUS during the controlled period and associated OLE periods of OBOE, ORATORIO, CONSONANCE, and OLERO (data as of November 2022).<sup>1</sup>

<sup>¶</sup>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.

<sup>¶¶</sup>Malignancies are identified using AEs falling into the standard MedDRA query "Malignant tumors (narrow)."<sup>1</sup>

<sup>††</sup>For malignancies, incidence rates are reported and exposure in PYs was calculated from first treatment to onset of first malignancy.<sup>1</sup>

AE=adverse event; EDSS=Expanded Disability Status Scale; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis.

## SAFETY PROFILE WITH 10+ YEARS OF CLINICAL TRIAL DATA

AS OF NOVEMBER 2022, 6155 PATIENTS HAVE RECEIVED OCREVUS IN THE ALL-EXPOSURE TRIAL POPULATION, RESULTING IN 28,269 PYs OF EXPOSURE<sup>1</sup>

In Phase III trials, the most common adverse events were infusion reactions and infections (mainly mild to moderate in severity)<sup>2</sup>

- Other common adverse event rates were similar to Rebif and placebo
- In the OCREVUS all-exposure population, reported rates of AEs continue to be consistent with those seen during the controlled RMS and PPMS trials

Potentially serious opportunistic infections in the OCREVUS all-exposure population: 0.03 per 100 PYs (95% CI: 0.01, 0.06) as of November 2022<sup>1</sup>

### PIVOTAL STUDY DESIGN

#### OPERA I and II (RMS)<sup>2,3</sup>

Two randomized, double-blind, double-dummy, active-comparator, controlled clinical trials of identical design vs Rebif in 1656 patients (OCREVUS: OPERA I [n=410], OPERA II [n=417]; Rebif: OPERA I [n=411], OPERA II [n=418]) with RMS treated for 96 weeks. Both studies included patients who had experienced  $\geq 1$  relapse within the prior year, or 2 relapses within the prior 2 years, and had an Expanded Disability Status Scale score between 0 and 5.5. The primary outcome of both studies was the annualized relapse rate.

#### ORATORIO (PPMS)<sup>2,4</sup>

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 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).

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

AE=adverse event; OLE=open-label extension; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis.

# IMPORTANT SAFETY INFORMATION

## 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.

## 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

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

A higher proportion of 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 in controlled trials. 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.

### 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 you should consider assessing vaccine immune responses, including consultation with a qualified specialist, to assess whether a protective immune response was mounted.

# IMPORTANT SAFETY INFORMATION (cont.)

## Progressive Multifocal Leukoencephalopathy (PML)

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

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

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

Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms of PML. Monitoring with MRI for signs consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. If PML is confirmed, treatment with OCREVUS should be discontinued.

## 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.

## Immune-Mediated Colitis

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

## Liver Injury

Clinically significant liver injury, without findings of viral hepatitis, has been reported in the postmarketing setting in patients treated with anti-CD20 B-cell depleting therapies approved for the treatment of MS, including OCREVUS. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred from weeks to months after administration.

Patients treated with OCREVUS found to have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3x the upper limit of normal (ULN) with serum total bilirubin greater than 2x ULN are potentially at risk for severe drug-induced liver injury.

Obtain liver function tests prior to initiating treatment with OCREVUS, and monitor for signs and symptoms of any hepatic injury during treatment. Measure serum aminotransferases, alkaline phosphatase, and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice. If liver injury is present and an alternative etiology is not identified, discontinue OCREVUS.

## 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 effective contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS. Instruct patients that if they are pregnant or plan to become pregnant while taking OCREVUS, they should inform their healthcare provider.

## Most Common Adverse Reactions

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

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

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

# ONGOING COMMITMENT TO EVIDENCE GENERATION IN WOMEN'S HEALTH IN MS

## GENENTECH HAS AN ONGOING PROGRAM EVALUATING OCREVUS EXPOSURE IN THE PERIPARTUM PERIOD<sup>5</sup>

- Potential placental and breastmilk transfer of OCREVUS
- Evaluation of the impact of prenatal exposure to OCREVUS on infant B-cell levels
- Maternal and infant safety outcomes

## USPI INFORMATION REGARDING PREGNANCY AND LACTATION

### USE IN SPECIFIC POPULATIONS RISK SUMMARY

#### Pregnancy

- OCREVUS is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. There are no adequate data on the developmental risk associated with use of OCREVUS in pregnant women. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to OCREVUS have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown.
- Following administration of ocrelizumab to pregnant monkeys at doses similar to or greater than those used clinically, increased perinatal mortality, depletion of B-cell populations, renal, bone marrow, and testicular toxicity were observed in the offspring in the absence of maternal toxicity.
- In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

#### Contraception

- Females of childbearing potential should use effective contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS. Instruct patients that if they are pregnant or plan to become pregnant while taking OCREVUS, they should inform their healthcare provider.

#### 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.

MS=multiple sclerosis.

# SOPRANINO PROSPECTIVE PK/PD STUDY OF OCREVUS IN THE POSTPARTUM PERIOD<sup>5</sup>

## ASSESSING THE BIOLOGIC TRANSFER OF OCREVUS DURING BREASTFEEDING

A global, multicenter, open-label, Phase IV study in women with RMS cared for in tertiary MS centers

DESIGNED TO EVALUATE:

- B-cell levels in infants exposed to OCREVUS during breastfeeding
- Pharmacokinetic parameters of OCREVUS in breastmilk

### GENERAL LIMITATIONS:

- Definitive conclusions cannot be drawn based on these data
- Safe use of OCREVUS during pregnancy, labor, delivery, or breastfeeding has not been established
- No comparisons can be made to other DMTs, including other aCD20s, due to the single-arm study design

## DESIGNED TO STUDY EXPOSURE TO OCREVUS IN BREASTFEEDING WOMEN AND THEIR INFANTS<sup>5,6</sup>



### Co-primary endpoints:

- Estimated average daily infant dose of OCREVUS (ADID) >60 days after mother's first postpartum infusion (MFPPi)
- Proportion of infants with B-cell levels below LLN at 1 month after MFPPi
  - Day 30 was measured from the time of the first dose (either the 600-mg dose or the first 300-mg dose)

### Additional endpoint included:

- Serum concentration of OCREVUS in infant at Day 30 after MFPPi

## 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.

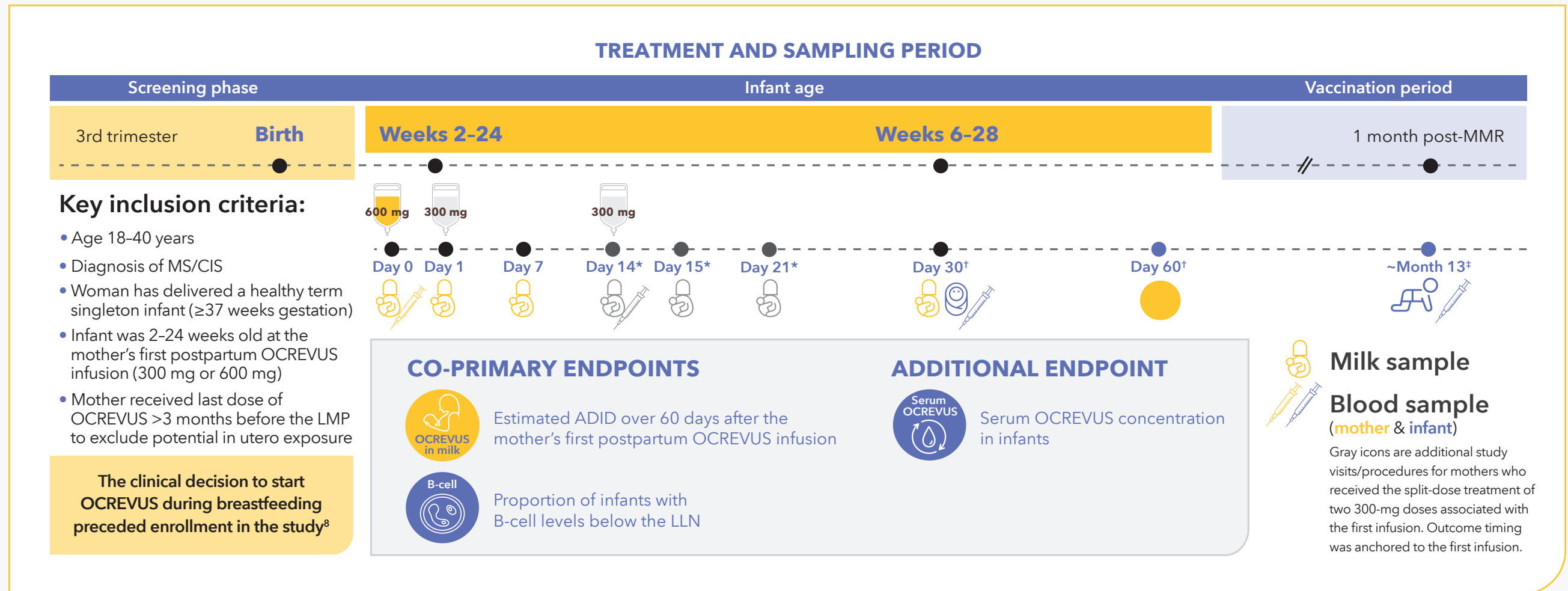
## Lactation

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.

aCD20=anti-CD20; ADID=average daily infant dose; DMT=disease-modifying therapy; LLN=lower limit of normal; PD=pharmacodynamics; PK=pharmacokinetics; RMS=relapsing multiple sclerosis.

# PROSPECTIVE PK/PD STUDY TO MEASURE B-CELL LEVELS IN BREASTFED INFANTS<sup>5,6</sup>

This is the primary analysis. The complete safety data and vaccination data are not yet available. The purpose of this study is to measure B-cell levels of infants (N=13) exposed to OCREVUS during breastfeeding and pharmacokinetic parameters in breastmilk.



Median (range) time in study for infant participants: 44.57 (8.6-62.7) weeks.<sup>7</sup>  
 Median (range) time in study for women participants: 44.57 (8.6-73.3) weeks.<sup>7</sup>  
 CCOD: March 29, 2024.

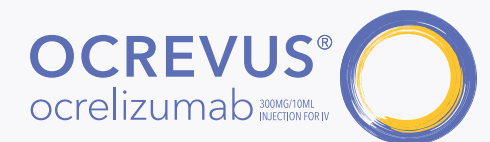
**LIMITATIONS:**

- Definitive conclusions cannot be drawn based on these data given the limited sample size
- Safe use of OCREVUS during pregnancy, labor, delivery, or breastfeeding has not been established
- No comparisons can be made to other DMTs, including other aCD20s, due to single-arm study design

\*Samples and visits at Days 14, 15, and 21 apply only to women initiating treatment with OCREVUS with the split-dose treatment of two 300-mg doses separated by a 14-day interval.  
<sup>†</sup>±2 days.<sup>6</sup>

<sup>‡</sup>One month (+30 days) after the first dose of MMR vaccine (if first dose is administered at 11 months of age or later) OR 1 month (+30 days) after the second dose of MMR vaccine (if first dose is administered before 11 months of age) OR at Month 13 of chronological age (+30 days) if MMR vaccine was not planned to be administered.<sup>6</sup>

ADID=average daily infant dose; CCOD=clinical cut-off date; CIS=clinically isolated syndrome; DMT=disease-modifying therapy; LLN=lower limit of normal; LMP=last menstrual period; MMR=measles, mumps, and rubella; MS=multiple sclerosis; PD=pharmacodynamics; PK=pharmacokinetics.



# CHARACTERISTICS OF MOTHERS WHO PARTICIPATED IN THE STUDY (N=13)<sup>6</sup>

## BASELINE CHARACTERISTICS: 13 WOMEN WITH RMS ENROLLED



At screening	Mothers (N=13)
Age, years	35.0 (30.0–40.0)
RMS, n (%)	13 (100)
Duration since MS symptom onset, years	5.2 (0.0–18.0)
EDSS score	2.0 (0.0–3.5)
Pregnancy history, n (%) ≥1 previous pregnancy*	11 (84.6)

Note: Displayed values are median (range) unless otherwise stated.<sup>6</sup>

Last OCREVUS infusion median range<sup>†</sup>  
5.0 months before LMP (3.0–8.5)

1st postpartum OCREVUS infusion median range<sup>‡</sup>  
2.0 months after birth (0.5–5.0)



**LIMITATION:**

- Definitive conclusions cannot be drawn based on these data given the limited sample size

\*Women with previous live birth 6/11 (54.5%).<sup>6</sup>

<sup>†</sup>A total of 8/13 (61.5%) mothers had been previously treated with OCREVUS for a median (range) of 31.9 months (13.2–58.6).<sup>6</sup>

<sup>‡</sup>First dose administered as a single 600-mg infusion in 8/13 mothers and as two 300-mg infusions in 5/13 (38.5%).<sup>6</sup>

EDSS=Expanded Disability Status Scale; LMP=last menstrual period; MS=multiple sclerosis; RMS=remitting multiple sclerosis.

# INFANT CHARACTERISTICS AT BIRTH (N=13)<sup>6</sup>

## SOPRANINO ENROLLED 13 FULL-TERM HEALTHY INFANTS

### Median head circumference

- 35.5 cm (33.5-38.0)
- 90% within 3rd-97th age percentiles

### Median length

- 50.4 cm (46.5-53.3)
- 90% within 3rd-97th age percentiles

### Median weight\*

- 3.4 kg (2.9-4.2)
- 100% within 3rd-97th age percentiles

At birth	Infants (N=13)
<b>Delivery, n (%)</b>	
Vaginal	8 (61.5)
Vaginal (forceps/vacuum; instrumental)	1 (7.7)
Caesarean (scheduled)	4 (30.8)
Caesarean (emergency)	0 (0.0)
<b>Gestational age (weeks)</b>	39.0 (37.0-41.0)
<b>Sex, n (%)</b>	
Male	7 (53.8)
Female	6 (46.2)
<b>Minor congenital anomalies,<sup>†</sup> n (%)</b>	1 (7.7)

### LIMITATION:

- Definitive conclusions cannot be drawn based on these data given the limited sample size

\*Participant number is 10/13.<sup>6</sup>

<sup>†</sup>Tethered oral tissue (mild; did not affect latch or breastfeeding) is classified as a minor congenital anomaly (ankyloglossia), per EUROCAT Guide 1.5. No major congenital anomalies occurred.<sup>6</sup>  
EUROCAT=European Surveillance of Congenital Anomalies.

## OCREVUS LEVELS IN BREASTMILK AND IN INFANT SERUM<sup>6</sup>

**CO-PRIMARY ENDPOINT:**  
MINIMAL TRANSFER AND LOW CONCENTRATIONS OF OCREVUS WERE DETECTED IN BREASTMILK (N=13)<sup>6</sup>

**ADID\*:** 45.1 ug

**Average RID<sup>†</sup>:** 0.3%

**Maximum RID:** 0.8%

Estimated ADID over 60 days after the mother's first postpartum OCR infusion<sup>1</sup>

**ADDITIONAL ENDPOINT:**  
OCREVUS CONCENTRATIONS WERE BELOW DETECTABLE LEVELS IN THE AVAILABLE INFANT SERUM SAMPLES (n=9)<sup>6‡§</sup>

9 out of 9 infants measured had serum concentrations of OCREVUS below LLQ=156 ng/mL

Results based on infant serum 30 days after their mothers' first postpartum infusion of OCREVUS

Lower limit of quantification (LLQ)=156 ng/mL

§OCREVUS could not be measured in 4/13 infants due to: Healthcare professional unable to draw blood (n=2), early discontinuation (n=1), and an accidentally discarded sample (n=1).

### LIMITATIONS:

- Definitive conclusions cannot be drawn based on these data given the duration of the follow-up
- The clinical meaningfulness of the data is unknown due to the variability of dosing, evaluations, or variance in infant age
- The partial use of infant formula along with breastmilk may confound the results

\*ADID is calculated as the arithmetic mean of the mother's daily OCREVUS milk concentration (µg/ml) over 60 days post OCREVUS infusion 1 multiplied by an estimated infant milk intake of 150 ml/kg/day and based on the weight (kg) recorded at the Day 30 visit.<sup>6</sup>

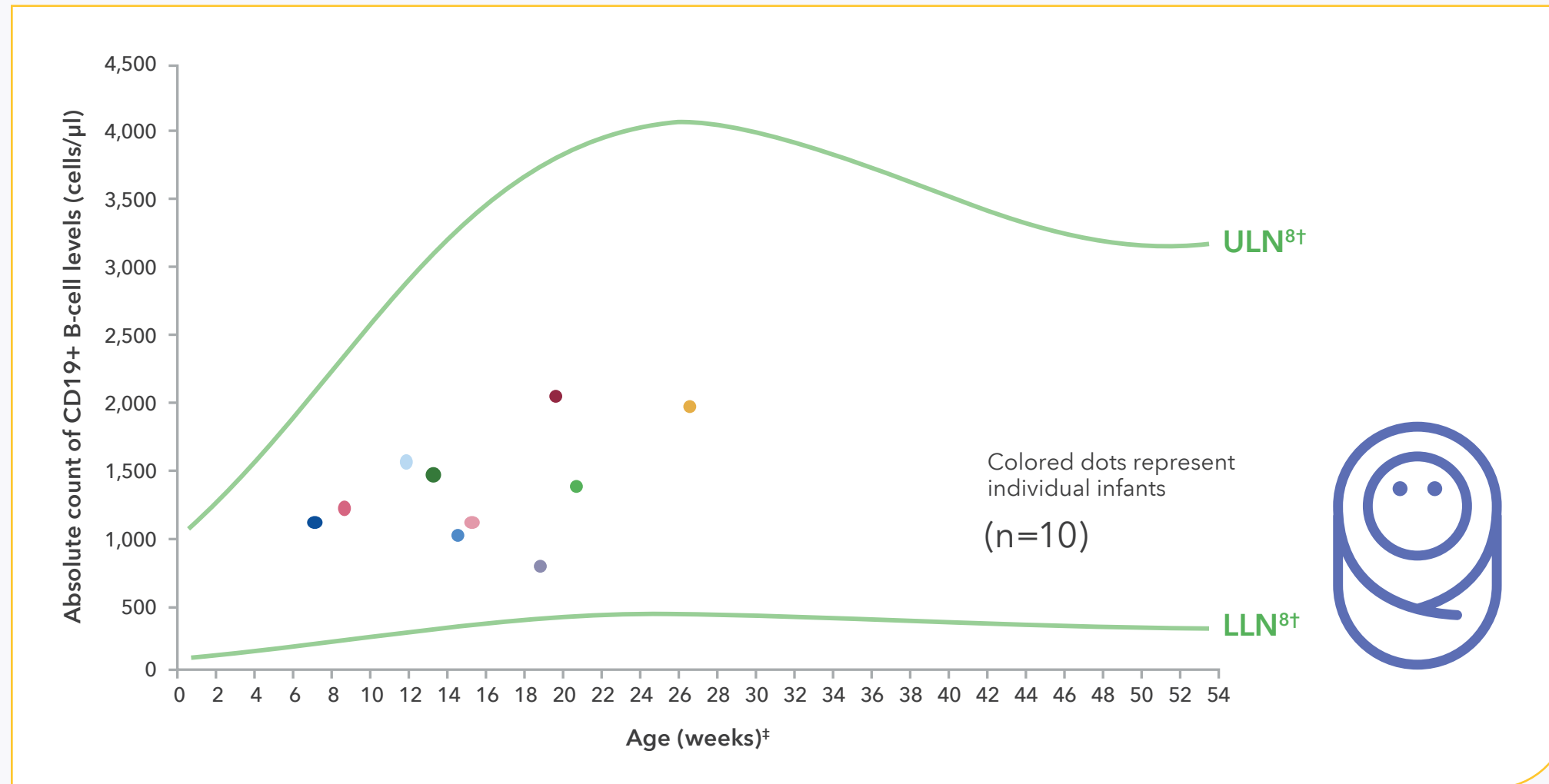
<sup>†</sup>The RID over 60 days is calculated as the ADID divided by the average maternal dosage over 60 days multiplied by 100.<sup>6</sup>

<sup>‡</sup>Based on serum OCREVUS concentration measured 30 days after the mothers' first postpartum infusion.<sup>6</sup>

ADID=average daily infant dose; RID=relative infant dose.

## B-CELL LEVELS IN INFANTS BREASTFED BY MOTHERS ON OCREVUS<sup>6</sup>

CO-PRIMARY ENDPOINT: NO INFANTS WITH AVAILABLE DATA\* HAD B-CELL LEVELS BELOW LLN AT 30 DAYS AFTER THE FIRST POSTPARTUM OCREVUS INFUSION (n=10/13)



Median (range) time in study for infant participants: 44.57 (8.6-62.7) weeks.<sup>7</sup>  
CCOD: March 29, 2024.

\*10/13 infants had B-cell data available for the primary analysis. One mother discontinued due to difficulties in breastfeeding. For two infants, the mobile nurse was unable to draw blood.<sup>6</sup>

Results based on measurement of B-cell levels in infants 30 days after their mothers' first postpartum infusion of OCREVUS.

### LIMITATIONS:

- Definitive conclusions cannot be drawn based on these data given the duration of the follow-up
- The clinical meaningfulness of the data is unknown due to the variability of dosing, evaluations, or variance in infant age
- The partial use of infant formula along with breastmilk may confound the results

<sup>1</sup>Dynamic changes occur in the ULN and LLN of B-cell levels throughout the first year. A reduction in B-cell levels is observed from cord blood to the first week of life, followed by a rapid increase over the next 2 months. At ~6 months of age, maximum levels are attained, after which levels decrease progressively and stabilize at ~1 year of age.<sup>6</sup>

<sup>2</sup>Infants were between 2 and 24 weeks old at the time of their mothers' first postpartum OCREVUS infusion (corresponding to the WHO and UNICEF recommendations of 6 months of exclusive breastfeeding).<sup>9</sup>

CCOD=clinical cut-off date; CD19=cluster of differentiation 19; LLN=lower limit of normal; ULN=upper limit of normal; UNICEF=United Nations International Children's Fund; WHO=World Health Organization.

## SAFETY OUTCOMES IN INFANTS (N=13)<sup>6</sup>

Infections were typical of childhood or were co-occurring in the mother<sup>6</sup>

	Infants (N=13)
<b>Number of infants with ≥1, n (%)<sup>*</sup></b>	
AE	11 (84.6)
SAE	0 (0.0)
AE of Grade ≥3	1 (7.7)
<b>Infections, n (%)</b>	10 (76.9)
<b>General disorders and administration site conditions<sup>†</sup></b>	
Pyrexia	3 (23.1)
<b>Skin and subcutaneous tissue disorders<sup>†</sup></b>	
Eczema	2 (15.4)

One infant had 1 Grade ≥3 AE, bronchiolitis, which resolved within 12 days

Ten (10/13 [76.9%]) infants had a total of 26 infections, all of which resolved<sup>‡</sup>

- COVID-19, n=4 (30.8%)
- Ear infection, n=3 (23.1%)
- Bronchiolitis, n=2 (15.4%)
- Nasopharyngitis, n=2 (15.4%)
- Other infections, n=1 (7.7%): conjunctivitis, gastroenteritis, hand-foot-and-mouth disease, influenza, oral herpes, otitis media, parainfluenza virus infection, RSV infection, rhinovirus infection, suspected COVID-19, URTI, varicella

Median (range) time in study for infant participants: 44.57 (8.6-62.7) weeks.<sup>7</sup>  
CCOD: March 29, 2024.

### LIMITATIONS:

- This is the primary analysis. The complete safety data and vaccination data are not yet available
- Definitive conclusions cannot be drawn based on these data given the duration of the follow-up
- Safe use of OCREVUS during pregnancy, labor, delivery, or breastfeeding has not been established

### USPI Select Important Safety Information

#### 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

<sup>6</sup>Based on TEAEs, defined as AEs with onset on or after first dose of study drug administered to the mother, or prior to first dose and end date on or after first dose and with a most extreme NCI CTCAE (version 5.0) grade greater than the initial grade. Investigator text for AEs was encoded using MedDRA version 26.1. Percentages are based on N in the column headings.<sup>6</sup>

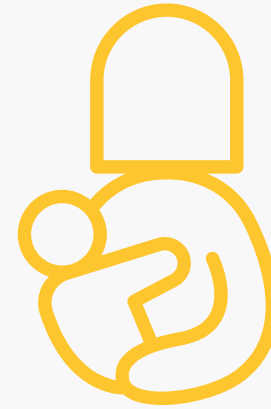
<sup>†</sup>Two or more events reported.<sup>6</sup>

<sup>‡</sup>For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.<sup>6</sup>

AE=adverse event; CCOD=clinical cut-off date; CD19=cluster of differentiation; COVID-19=coronavirus disease 2019; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; NCI=National Cancer Institute; RSV=respiratory syncytial virus; SAE=serious adverse event; TEAE=treatment-emergent adverse event; URTI=upper respiratory tract infection.

## SAFETY OUTCOMES IN MOTHERS (N=13)<sup>6</sup>

	Mothers (N=13)
<b>Number of mothers with ≥1, n (%)<sup>*</sup></b>	
AE	10 (76.9)
Serious AE	0 (0.0)
<b>Number of mothers with ≥1, n (%)</b>	
AE leading to infusion modification/interruption	1 (7.7)
Related AE <sup>†</sup>	3 (23.1)
Infusion-related reaction	2 (15.4)
Infection	9 (69.2)
<b>General disorders and administration-site conditions<sup>‡</sup></b>	
Pain	2 (15.4)
<b>Nervous system disorders<sup>‡</sup></b>	
Paresthesia	2 (15.4)



Nine (9/13 [69.2%]) mothers had a total of 19 infections, all of which were resolved<sup>6</sup>

- COVID-19, n=6 (46.2%)
- Fungal infection, n=2 (15.4%)<sup>§</sup>
- Mastitis, n=2 (15.4%)<sup>||</sup>
- Nasopharyngitis, n=2 (15.4%)
- Other infections, n=1 (7.7%): infected cyst, URTI, UTI, vaginal infection

Median (range) time in study for women participants: 44.57 (8.6-73.3) weeks.<sup>7</sup>  
CCOD: March 29, 2024.

### LIMITATIONS:

- This is the primary analysis. The complete safety data and vaccination data are not yet available
- Definitive conclusions cannot be drawn based on these data given the duration of the follow-up
- Safe use of OCREVUS during pregnancy, labor, delivery, or breastfeeding has not been established

<sup>\*</sup>Based on TEAEs, defined as AEs with onset on or after first dose of study drug administered to the mother, or prior to first dose and end date on or after first dose and with a most extreme NCI CTCAE (version 5.0) grade greater than the initial grade. Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.<sup>6</sup>

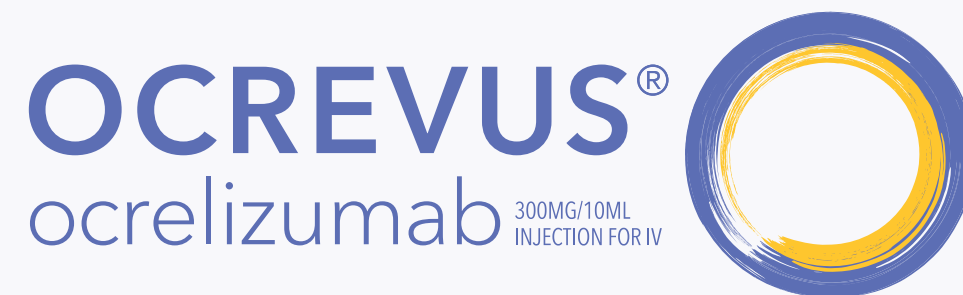
<sup>†</sup>Related AEs in three mothers were IRR, oral pruritus (occurring 1 day after baseline and lasting for 1 day), throat irritation (occurring 1 day after baseline and lasting for 1 day), and COVID-19.<sup>6</sup>

<sup>‡</sup>Two or more events reported.<sup>6</sup>

<sup>§</sup>Contact dermatitis and yeast infections.<sup>6</sup>

<sup>||</sup>According to the World Health Organization, Mastitis: Causes and Management (2000), reported incidence in lactating women are 0-33%, but is normally under 10%.<sup>10</sup>

AE=adverse event; CCOD=clinical cut-off date; COVID-19=coronavirus disease 2019; CTCAE=Common Terminology Criteria for Adverse Events; IRR=infusion-related reaction; MedDRA=Medical Dictionary for Regulatory Activities; NCI=National Cancer Institute; SAE=serious adverse event; TEAE=treatment-emergent adverse event; URTI=upper respiratory tract infection; UTI=urinary tract infection.



**References:** **1.** Hauser SL, Kappos L, Montalban X, et al. Safety of ocrelizumab in multiple sclerosis: updated analysis in patients with relapsing and progressive multiple sclerosis. Presented at: 9th JointECTRIMS-ECTRIMS Meeting; October 11-13, 2023; Milan, Italy. Poster P304. **2.** OCREVUS [prescribing information]. South San Francisco, CA: Genentech, Inc. 2025. **3.** Hauser SL, Bar-Or A, Comi G, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med.* 2017;376(3):221-234. doi:10.1056/NEJMoa1601277 **4.** Montalban X, Hauser SL, Kappos L, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med.* 2017;376(3):209-220. doi:10.1056/NEJMoa1606468 **5.** Bove R, Hellwig K, Pasquarelli N, et al. Ocrelizumab during pregnancy and lactation: rationale and design of the MINORE and SOPRANINO studies in women with MS and their infants. *Mult Scler Relat Disord.* 2022;64:103963. doi:10.1016/j.msard.2022.103963 **6.** Bove R, Oreja-Guevara C, Hellwig K, et al. B-cell levels and breastmilk transfer in infants of lactating women with multiple sclerosis treated with ocrelizumab: primary results of the prospective, multicentre, open-label, phase IV study SOPRANINO. Poster presented at: 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 18-20, 2024; Copenhagen, Denmark. Poster O039. **7.** Data on file. Genentech, Inc. November 2024. **8.** Borriello F, Pasquarelli N, Law L, et al. Normal B-cell ranges in infants: a systematic review and meta-analysis. *J Allergy Clin Immunol.* 2022;150(5):1216-1224. doi:10.1016/j.jaci.2022.06.006 **9.** World Health Organization. Infant and young child feeding. Published December 20, 2023. Accessed January 23, 2025. <https://www.who.int/news-room/fact-sheets/detail/infant-and-young-child-feeding> **10.** World Health Organization. Mastitis: Causes and Management. Published 2000. Accessed January 23, 2025. [https://iris.who.int/bitstream/handle/10665/66230/WHO\\_FCH\\_CAH\\_00.13\\_eng.pdf?sequence=1](https://iris.who.int/bitstream/handle/10665/66230/WHO_FCH_CAH_00.13_eng.pdf?sequence=1)

Please see additional safety information on [pages 4-5](#) and click here for full OCREVUS [Prescribing Information](#) and [Medication Guide](#).