OCREVUS®
ocrelizumab 300MG/10ML INJECTION FOR IV

Study of Placental Transfer of OCREVUS and B-cell Levels in Infants

Key Considerations From the USPI

USPI INFORMATION REGARDING PREGNANCY

USE IN SPECIFIC POPULATIONS RISK SUMMARY

Contraception

- 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.

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.

WELL-ESTABLISHED SAFETY PROFILE WITH 10+ YEARS OF CLINICAL TRIAL DATA

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

AEs PER 100 PATIENT-YEARS (PY) IN OCREVUS TRIAL POPULATION[1]

	OPERA (pooled) treatment period*			ORATORIO treatment period*			OCREVUS all-exposure population†
	OCREVUS n=825	Rebif® n=826	All RMS‡ n=4558	OCREVUS n=486	Placebo n=239	All PPMS§ n=1597	Mean number of doses: 9.6 N=6155
	PY=1448	PY=1399	PY=21,080	PY=1606	PY=729	PY=7190	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‖	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¶#	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

Safety of OCREVUS in pregnant women was not evaluated due to exclusion of pregnancy at the time of study enrollment.

AEs were classified according to Medical Dictionary for Regulatory Activities (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.

*Data as of April–July 2015.[1]

†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).[1]

‡Includes patients with RMS 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).[1]

§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).[1]

‖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.

¶Malignancies are identified using AEs falling into the standard MedDRA query "Malignant tumors (narrow)."[1]

#For malignancies, incidence rates are reported and exposure in PY was calculated from first treatment to onset of first malignancy.[1]

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.[2]

AE=adverse event; EDSS=Expanded Disability Status Scale; OLE=open-label extension; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis.

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

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

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 PY OF EXPOSURE[1]

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

- 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 PY (95% CI: 0.01, 0.06) as of November 2022[1]

PIVOTAL STUDY DESIGN

OPERA I and II (RMS)[2,3]

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 Expanded Disability Status Scale score between 0 and 5.5. The primary outcome of both studies was the annualized relapse rate.

ORATORIO (PPMS)[2,4]

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.

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IMPORTANT SAFETY INFORMATION

Indications

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Contraindications

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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.

Please see additional safety information on **page 5** and click here for full OCREVUS **Prescribing Information** and **Medication Guide**.

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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 ≥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.

Please see additional safety information on page 4 and click here for full OCREVUS Prescribing Information and Medication Guide.

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

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.

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

GENENTECH HAS AN ONGOING PROGRAM EVALUATING OCREVUS EXPOSURE IN THE PERIPARTUM PERIOD[5]

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

MINORE PROSPECTIVE PK/PD STUDY OF OCREVUS IN THE PERIPARTUM PERIOD[5,6]

ASSESSING THE PLACENTAL TRANSFER OF OCREVUS

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

DESIGNED TO EVALUATE:

- Placental transfer of OCREVUS
- B-cell levels in newborns

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

aCD20=anti-CD20; DMT=disease-modifying treatment; MS=multiple sclerosis; PD=pharmacodynamics; PK=pharmacokinetics; RMS=relapsing multiple sclerosis.

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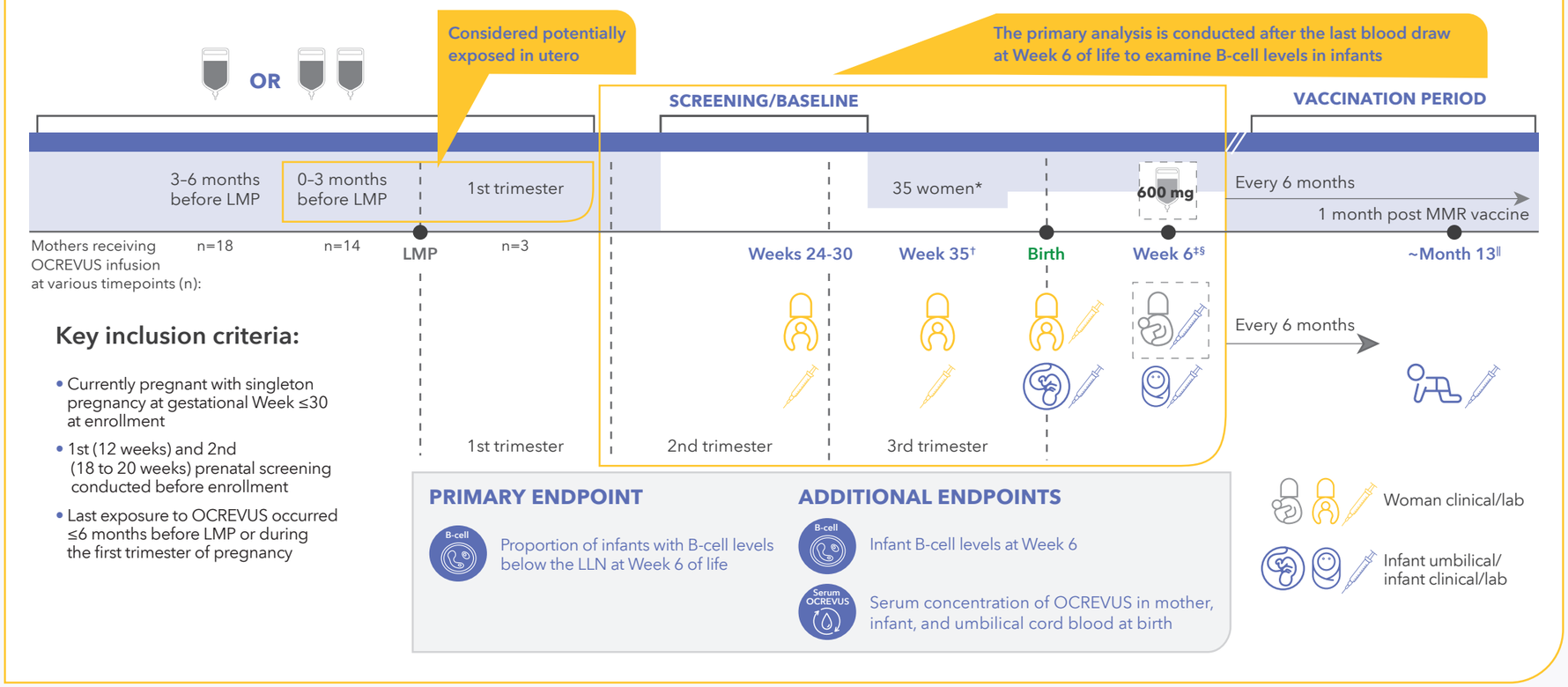
OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

EXAMINING IMPACT OF PLACENTAL TRANSFER OF OCREVUS ON B-CELL LEVELS IN INFANTS[5-7]

This is the primary analysis. The complete safety data and vaccination data are not yet available. The purpose of this study is to measure placental transfer of OCREVUS from mothers (N=35) to infants and B-cell levels in newborns.



Key inclusion criteria:

- Currently pregnant with singleton pregnancy at gestational Week ≤30 at enrollment
- 1st (12 weeks) and 2nd (18 to 20 weeks) prenatal screening conducted before enrollment
- Last exposure to OCREVUS occurred ≤6 months before LMP or during the first trimester of pregnancy

Median (range) time in study for women participants: 58.43 (15.0-79.0) weeks.[8]

Median (range) time in study for infant participants: 52.00 (4.0-66.0) weeks.[8]

CCOD: April 8, 2024.[8]

LIMITATIONS:

- Definitive conclusions cannot be drawn based on these data, given the limited sample size
- There are limited data on placental transfer in infants exposed to OCREVUS during pregnancy in this study
  - 3 infants were exposed to OCREVUS in the first trimester (up to gestational Week 13) of pregnancy, and none were exposed in the 2nd or 3rd trimester
  - 18/35 infants were not considered to have had in utero exposure to OCREVUS based on the timing of the LMP
- This study population may not be fully representative of populations of pregnant women with MS, due to the exclusion of:
  - Women with a history of disorders associated with adverse pregnancy outcomes or a current history of any other gynecological or obstetric disease considered by the investigator to be associated with a high risk of adverse pregnancy outcomes (including preterm birth and history of miscarriage after the first trimester) in the current pregnancy
  - Women in whom genetic disorders that cause major congenital malformations or in whom fetal anomalies had been detected before gestational Week 20

*Per the protocol, approximately 33 women were required to be enrolled.[7]
†±14 days.[7]
‡±7 days.[7]
§Treatment with commercial OCREVUS could be resumed at any time after birth for women who decided not to breastfeed. For women who decided to resume treatment while breastfeeding, the treatment with OCREVUS should have been restarted after collection of the Week 6 infant blood sample, if possible, but the decision was left to the discretion of the woman and the investigator. If the woman decided to switch to another DMT postpartum or to stop DMT after birth, no laboratory/clinical assessments were performed for the woman. The infant's blood sample at Week 6 of life (±7 days) was collected only if the woman was not breastfeeding.[7]
‖One month (+30 days) after the first/second dose of the MMR vaccine, or Month 13 of age (+30 days) if the MMR vaccine is not planned to be administered.[7]
¶LLN was defined as the 2.5th percentile of B-cell levels in a meta-analysis of studies of healthy infants.[7]
CCOD=clinical cutoff date; DMT=disease-modifying treatment; LLN=lower limit of normal; LMP=last menstrual period; MMR=measles, mumps, and rubella.

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

BASELINE CHARACTERISTICS: PREGNANT WOMEN WITH RMS WERE ENROLLED (N=35)[7]

Age, years (range)	34 (26-41)
RRMS, n (%)	35 (100)
Duration since MS diagnosis, years (range)	5.4 (1.0-17.0)
EDSS score (range)	1.5 (0.0-4.5)
Gestational age, weeks (range)	26 (22-30)
History of previous pregnancy,* n (%) Full-term live birth	19 (54.3) 15 (78.9)

Note: displayed values are median (range) unless otherwise stated.

17 mothers were considered to have had in utero exposure to OCREVUS

- 0 to 3 months before LMP (n=14)
- First trimester (up to gestational Week 13) of pregnancy (n=3)

The remaining participants (n=18) were not considered to have had in utero exposure

LIMITATIONS:

- The clinical meaningfulness of the data is unknown due to the variability in timing of exposure to OCREVUS
- This study population may not be fully representative of populations of pregnant women with MS due to the exclusion of:
  - Women with a history of disorders associated with adverse pregnancy outcomes or a current history of any other gynecological or obstetric disease considered by the investigator to be associated with a high risk of adverse pregnancy outcomes (including preterm birth and history of miscarriage after the first trimester) in the current pregnancy
  - Women in whom genetic disorders that cause major congenital malformations or in whom fetal anomalies had been detected before gestational Week 20

*Preterm live birth (n=1/19), spontaneous abortion (n=1/19), therapeutic abortion (n=1/19), elective abortion (n=1/19), ectopic pregnancy (n=2/19).[7]
†Overall, 7/35 women had no other DMT before OCREVUS.[7]
‡A total of 18/35 women received OCREVUS infusions 3–6 months prior to their LMP and 14/35 women received OCREVUS infusions 0–3 months prior to their LMP.[7]
§First-trimester OCREVUS administration was at 13+4 gestational weeks (n=1), 4 days after the LMP (n=1), and 1 month and 25 days after the LMP (n=1). The woman who received OCREVUS 1 month and 25 days after their LMP was lost to follow-up at Week 6.[7]
‖31 women resumed OCREVUS infusions. The first dose was administered as a single 600-mg infusion in 28/31 mothers and as two 300-mg infusions in 3/31 mothers.
CCOD: April 8, 2024. Median (range) time in study, women: 58.43 (15.0-79.0) weeks; median (range) time in study, infants: 52.00 (4.0-66.0) weeks.[7]
CCOD=clinical cutoff date; DMT=disease-modifying treatment; EDSS=Expanded Disability Status Scale; LMP=last menstrual period; MS=multiple sclerosis; RMS=relapsing multiple sclerosis.

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INFANT CHARACTERISTICS AT BIRTH (N=35)

ALL 35 PREGNANCIES RESULTED IN FULL-TERM LIVE BIRTHS[7]

Median head circumference

- 35.0 cm (33.0–37.5)

90% within 3rd–97th age percentiles

Median weight

- 3.4 kg (2.8–4.5)

94.3% within 3rd–97th age percentiles

Median length

- 51.4 cm (48.0–56.0)

66.7% within 3rd–97th age percentiles*

At birth	Infants (N=35)
Delivery, n (%)	
Vaginal	22 (62.9)
Vaginal (forceps/vacuum; instrumental)	4 (11.4)
Cesarean (scheduled)	6 (17.1)
Cesarean (emergency)	3 (8.6)
Gestational age (weeks)	39 (37–42)
Sex, n (%)	
Male	13 (37.1)
Female	22 (62.9)
Minor congenital anomalies,† n (%)	2 (5.7)
Major congenital anomalies,‡ n (%)	1 (2.9)

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 in timing of exposure to OCREVUS

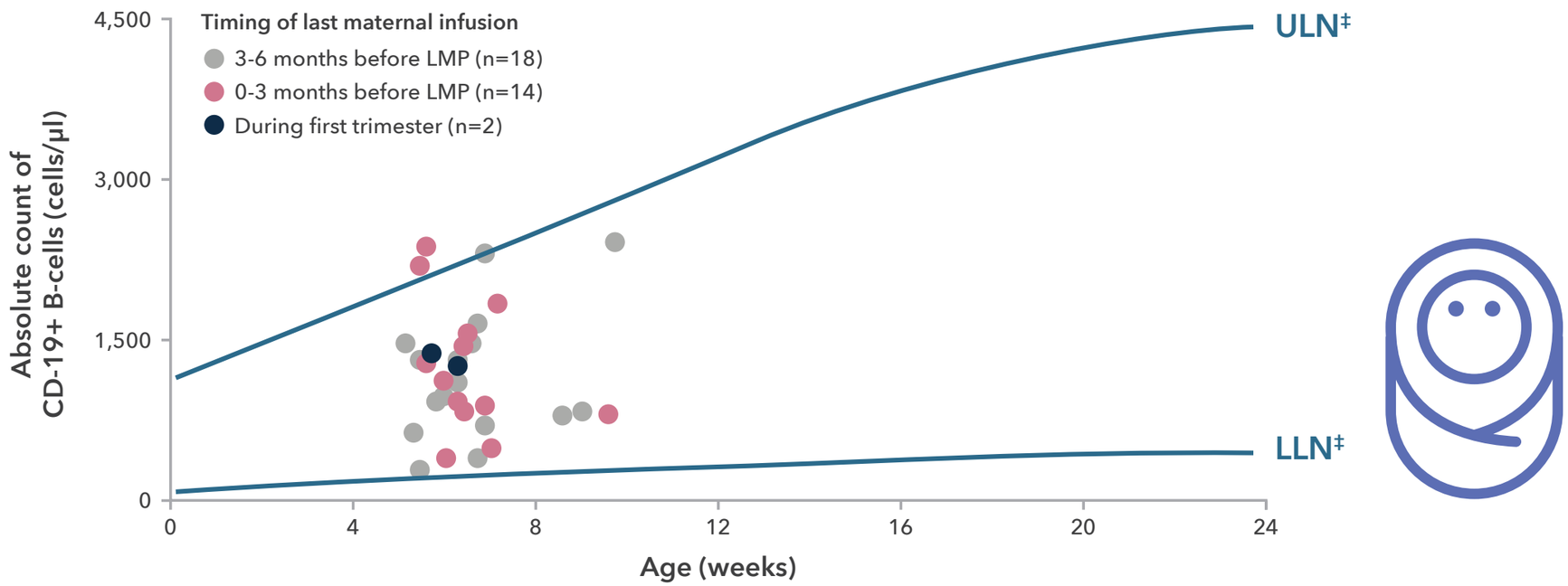
*All babies were above 3rd percentile.[7]
†Cryptorchidism minor CA, persistent foramen ovale minor CA.[7]
‡Hypospadias (unconfirmed) major CA, classified as per EUROCAT Guide 1.5.[7]
CA=congenital anomaly; EUROCAT=European Surveillance of Congenital Anomalies.

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

B-CELL LEVELS IN INFANTS WITH MOTHERS ON OCREVUS (N=34)[7]

PRIMARY ENDPOINT: B-CELL LEVELS IN ALL INFANTS (34/34,* 100%) WERE ABOVE THE AGE-SPECIFIC LLN AT WEEK 6†

INFANT B-CELL LEVELS AT WEEK 6 (N=34)[6]



All infant B-cell levels were above the age-specific LLN

Median (range) time in study for infant participants: 52.00 (4.0-66.0) weeks.[8]
CCOD: April 8, 2024.[8]

†There were 34/35 infants available for serum evaluations at Week 6. The woman who received OCREVUS 1 month and 25 days after LMP was lost to follow-up at Week 6.[7]

LIMITATIONS:

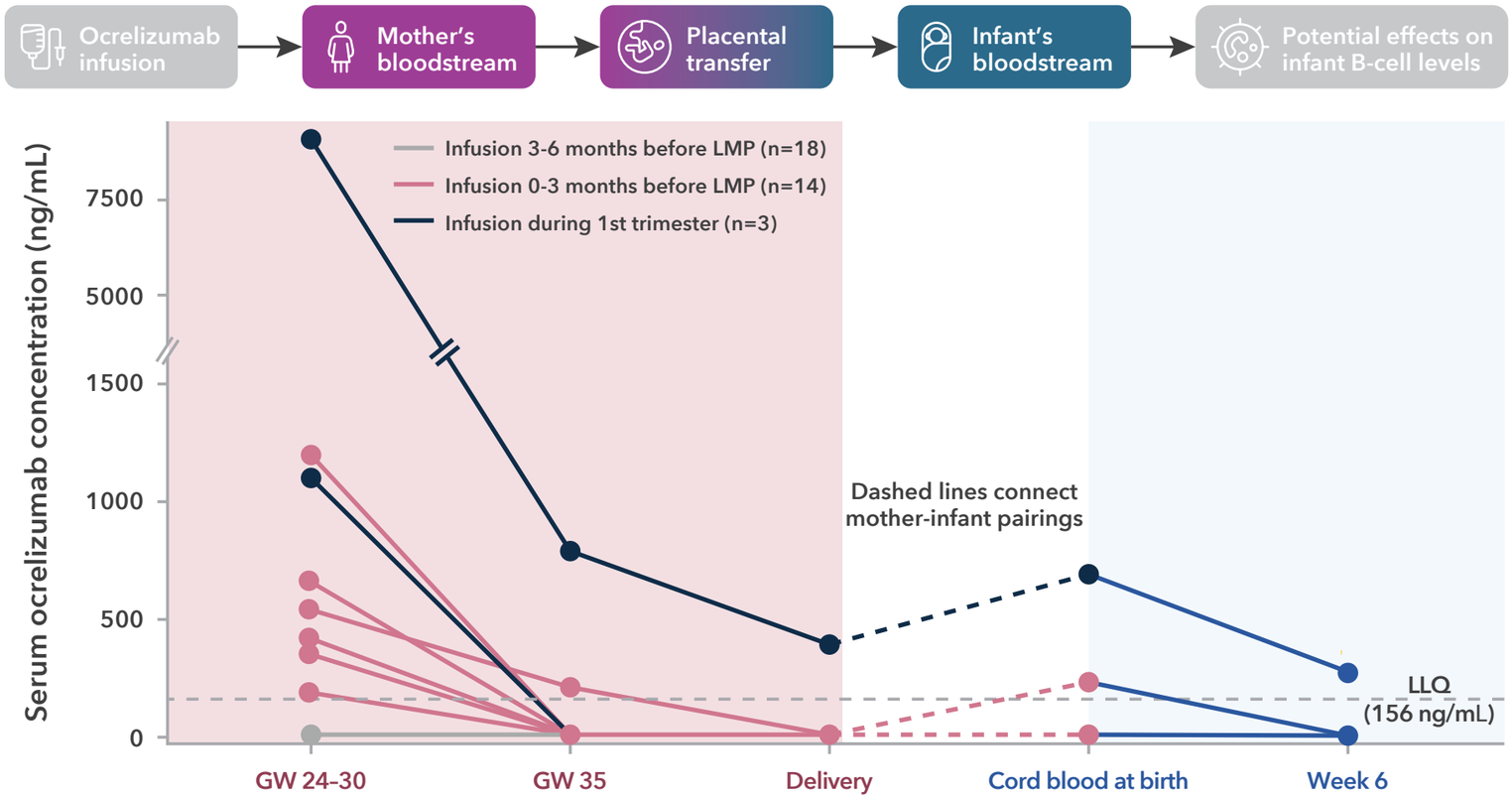
- Definitive conclusions cannot be drawn based on these data
- The clinical meaningfulness of the data is unknown due to the variability in timing of exposure to OCREVUS

*n/N.[9]
‡LLN and ULN were defined as the 2.5th percentile and 97.5th percentile, respectively, of B-cell levels in a meta-analysis of studies in healthy infants.[9]
CCOD=clinical cutoff date; CD19=cluster of differentiation 19; LLN=lower limit of normal; LMP=last menstrual period; ULN=upper limit of normal.

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

OBSERVED OCREVUS LEVELS IN SERUM

MATERNAL, CORD BLOOD, AND INFANT SERUM MEASURED DURING THE PERIPARTUM PERIOD[6]



	GW 24–30	GW 35	Delivery	Cord blood at birth	Week 6
Undetectable serum ocrelizumab, n/N (%)	24/35 (68.6)	32/34 (94.1)	34/35 (97.1)	33/35 (94.3)	32/33 (97.0)
Ocrelizumab levels, median (range), ng/mL	0 (0-9090)	0 (0-787)	0 (0-382)	0 (0-694)	0 (0-263)

Median (range) time in study for women participants: 58.43 (15.0-79.0) weeks.[8]
Median (range) time in study for infant participants: 52.00 (4.0-66.0) weeks.[8]
CCOD: April 8, 2024.[8]

LIMITATIONS:

- Definitive conclusions cannot be drawn based on these data
- Measures of OCREVUS in cord blood and infant serum at Week 6 are used as proxies to assess in utero exposure

CCOD=clinical cutoff date; GW=gestation week; LLQ=lower limit of quantification; LMP=last menstrual period.

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

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

OBSERVED OCREVUS LEVELS IN SERUM

ADDITIONAL ENDPOINTS:

OCREVUS LEVELS IN WOMEN WERE WITHIN THE RANGE SEEN IN OTHER OCREVUS STUDIES AND DECREASED WITH ADVANCING GESTATIONAL AGE (N=35)[7]

The percentage of women who had ocrevus below detectable levels*

- Weeks 24-30: 24/35[†] women (68.6%)
- Week 35: 32/34[†‡] women (94.1%)
- Delivery: 34/35[†] women (97.1%)

[†] n/N.[7]

[‡] 34 out of 35 samples were available at gestational week 35, as 1 sample was discarded after being deemed not suitable for analysis due to improper storage.[7]

OCREVUS WAS BELOW DETECTABLE LEVELS* IN >90% OF INFANTS (N=35)[7]

- Birth: in umbilical cord serum samples (94.3%, 33/35[†])
- Week 6 of life: in infant serum (97.0%, 32/33[†§])

[§] At Week 6, serum samples were available for analysis in 33 out of 35 infants. One sample was not included due to a technical issue that prevented analysis. Data was missing for 1 infant due to the mother being lost to follow-up.[7]

*Below detectable is defined as less than LLQ (156 ng/mL).[7]

LIMITATIONS:

- Definitive conclusions cannot be drawn based on these data
- Measures of OCREVUS in cord blood and infant serum at Week 6 are used as proxies to assess in utero exposure

LLQ=lower limit of quantification.

SAFETY OUTCOMES IN MOTHERS[7]

	Women (N=35)
Number of women with ≥1, n (%)	
AE	32 (91.4)
Serious AE	6 (17.1)
Number of women with ≥1, n (%):	
AE leading to treatment withdrawal*	1 (2.9)
AE leading to infusion modification/interruption	2 (5.7)
Related AE	9 (25.7)
Infections and infestations, n (%)	19 (54.3)
Injury, poisoning, and procedural complications, n† (%)	10 (28.6)
IRR	3 (8.6)
Vulvovaginal injury	3 (8.6)
Perineal injury	2 (5.7)
Respiratory, thoracic, and mediastinal disorders, n† (%)	
Cough	4 (11.4)
Oropharyngeal pain	3 (8.6)

Median (range) time in study for women participants: 58.43 (15.0-79.0) weeks.[8]
CCOD: April 8, 2024.[8]

Overall, 6 women experienced 6 SAEs, all of which resolved

- **Grade 3 AEs in five women:** acute cholecystitis, premature separation of placenta (occurred in 2 women), post-procedural infection,‡ and uterine inflammation
- **Grade 4 AE in one woman:** postpartum hemorrhage
- **No SAEs occurred in pregnant women before labor**
- The majority occurred **within 10 days after delivery**
- There was an **equal distribution of SAEs** between **in utero– and non–in utero–exposed** women

19/35§ (54.3%) women had a total of 42 infections

- **COVID-19,** n=6 (17.1%)
- **Nasopharyngitis,** n=4 (11.4%)
- **Other infections,** n=2 (5.7%): conjunctivitis, sinusitis, URTI, UTI, vulvovaginal mycotic infection; n=1 (2.9%) cystitis, gastroenteritis, gastrointestinal viral infection, herpangina, hordeolum, influenza, nasal herpes, periorbital cellulitis, pharyngitis streptococcal, pneumonia, post-procedural infection, respiratory tract infection, and rhinitis
- **No serious COVID-19 infections occurred**

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

Excerpt for Warning and Precautions for 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.

*Based on the Adverse Event eCRF page, where the response to the statement, "Action taken with ocrelizumab due to SAE/AE" is "Drug Withdrawn." A non-serious grade 2 AE of blood immunoglobulin G decrease (event occurred during the pregnancy and resolved during the study) was initially reported in one woman. The woman did not resume OCREVUS postpartum and switched to another MS DMT (ofatumumab). Late-reported, switching to another MS DMT (ofatumumab) was the reason for withdrawal and not a non-serious event of blood immunoglobulin G decrease.[7]
†Two or more events reported.[7]
‡Due to cesarean.[7]
§n/N. Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.[7]
aCD20=anti-CD20; AE=adverse event; CCOD=clinical cutoff date; COVID-19=coronavirus disease 2019; DMT=disease-modifying treatment; IRR=infusion-related reaction; MedDRA=Medical Dictionary for Regulatory Activities; MS=multiple sclerosis; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis; SAE=serious adverse event; URTI=upper respiratory tract infection; UTI=urinary tract infection.

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

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SAFETY OUTCOMES IN INFANTS[7]

	Infants (N=35)
Number of infants with ≥1, n (%)	
AE	26 (74.3)
Serious AE	4 (11.4)
Infections and infestations, n (%)	16 (45.7)
Respiratory, thoracic, and mediastinal disorders, n* (%)	10 (28.6)
Nasal congestion	4 (11.4)
Cough	2 (5.7)
Oropharyngeal pain	2 (5.7)
Rhinorrhea	2 (5.7)
Gastrointestinal disorders, n* (%)	9 (25.7)
Diarrhea	4 (11.4)
Constipation	2 (5.7)
Gastroesophageal reflux disease	2 (5.7)

Median (range) time in study for infants participants: 52.00 (4.0-66.0) weeks.[8]
CCOD: April 8, 2024.[8]

Overall, 4 infants experienced 5 SAEs, all of which resolved[7]

- **Grade 3 AE in three[†] infants:** neonatal infection and respiratory failure, heart rate decrease,[‡] and RSV infection
- **Grade 4 AE in one infant:** cardiopulmonary failure[§]
- There was an equal distribution between **in utero- (n=2) and non-in utero- (n=2) exposed** infants

16/35[‖] (45.7%) infants had a total of 39 infections[7]

- **Nasopharyngitis,** n=6 (17.1%)
- **Ear infection,** n=5 (14.3%)
- **Bronchitis,** n=5 (14.3%)
- **COVID-19,** n=4 (11.4%)
- **Conjunctivitis,** n=4 (11.4%)
- **RSV infection,** n=2 (5.7%)
- **Other infections,** n=1 (2.9%): bronchiolitis, viral bronchitis, candida infection, croup infectious, gastroenteritis, gastrointestinal infection, neonatal infection, otitis media, pharyngitis, rhinitis, subglottic laryngitis, and tracheitis

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

*Two or more events reported.[7]
[†]A fourth infant with a grade 3 AE had nonserious hyperbilirubinemia.[7]
[‡]Post-CCOD follow-up information: heart rate decrease was downgraded to nonserious AE and associated with mother's contractions due to oxytocin infusion.[7]
[§]Reported term: cardio-respiratory insufficiency postpartal.[7]
[‖]n/N. Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.[7]
AE=adverse event; CCOD=clinical cutoff date; CD19=cluster of differentiation 19; COVID-19=coronavirus disease 2019; RSV=respiratory syncytial virus; SAE=serious adverse event.

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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 Joint ECTRIMS-ACTRIMS 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. Placental and breastmilk transfer of ocrelizumab from women with multiple sclerosis to infants and the potential impact on B-cell levels: primary analysis of the prospective, multicentre, open-label, phase IV studies MINORE and SOPRANINO. Poster presented at: American Academy of Neurology 77th Annual Meeting; April 5-9, 2025; Chicago, IL. **7.** Hellwig K, Bove R, Oreja-Guevara C, et al. B-cell levels and placental transfer in infants potentially exposed to ocrelizumab during pregnancy: primary analysis of the prospective multicentre, open-label phase IV MINORE study. Poster presented at: 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 18-20, 2024; Copenhagen, Denmark. Poster P087. **8.** Data on file. Genentech, Inc. November 2024. **9.** 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

Please see additional safety information on **pages 4-5** and click here for full OCREVUS **Prescribing Information** and **Medication Guide**.

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