Ocrelizumab and Infections

OCREVUS® (ocrelizumab) US Prescribing Information

Section 5.2: 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 [*see Adverse Reactions (6.1)*].

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.

Clinical Trials (Controlled Treatment Period and Open-Label Extension)

Table 1. Incidence of infections in OCR clinical trials per 100 PY[6]

A: OPERA (RMS) cumulative exposure (controlled treatment period/open-label extension)

AE rate per 100 PY (95% CI) unless otherwise specified	CTP[a] (July 2015)		CTP + OLE[b] (November 2022)	
	IFN β-1a	OCR	OCR	OCR (Ex–COVID-19)
Total no. of patients	826	825	1448	1448
Total PY	1399	1448	10,798	10,798
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**71.2** (69.6–72.0)	**65.9** (64.4–67.4)
Serious infections[c]	**1.8** (1.2–2.6)	**0.8** (0.4–1.5)	**2.8** (2.5–3.1)	**1.7** (1.5–2.0)

B: ORATORIO (PPMS) cumulative exposure (controlled treatment period/open-label extension)

AE rate per 100 PY (95% CI) unless otherwise specified	CTP[a] (July 2015)		CTP + OLE[b] (November 2022)	
	Placebo	OCR	OCR	OCR (Ex–COVID-19)
Total no. of patients	239	486	644	644
Total PY	729	1606	4669	4669
Infections and infestations	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)	**74.0** (71.6–76.5)	**70.0** (67.8–72.6)
Serious infections[c]	**3.0** (1.9–4.6)	**2.7** (2.0–3.7)	**5.5** (4.8–6.2)	**4.4** (3.8–5.0)

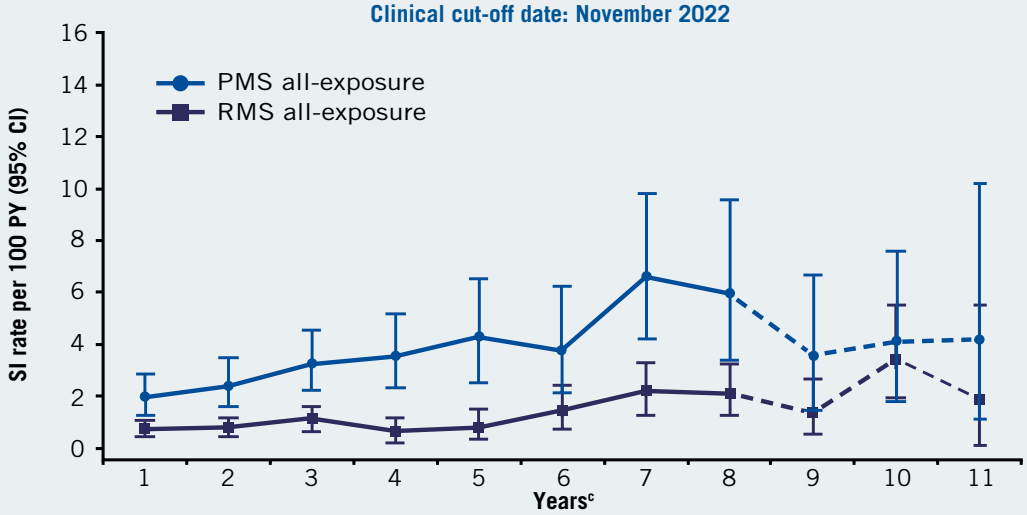
C: All RMS, all PMS, and OCR all-exposure population

AE rate per 100 PY (95% CI) unless otherwise specified	All RMS[d]		All PMS[e]		All OCR trials	
	November 2022					
	OCR	OCR (Ex–COVID-19)	OCR	OCR (Ex–COVID-19)	OCR all-exposure population[f]	OCR all-exposure population[f] (Ex–COVID-19)
Total no. of patients	4558	4558	1597	1597	6155	6155
Total PY	21,080	21,080	7190	7190	28,269	28,269
Infections and infestations	**72.1** (70.9–73.2)	**66.2** (65.1–67.3)	**68.9** (66.9–70.8)	**61.6** (59.8–63.4)	**71.2** (70.3–72.2)	**65.1** (64.1–66.0)
Serious infections[c]	**2.3** (2.1–2.6)	**1.5** (1.3–1.7)	**5.1** (4.6–5.6)	**3.7** (3.3–4.2)	**3.0** (2.8–3.3)	**2.1** (1.9–2.2)

AEs were classified according to 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. [a]Data as of April–July 2015. [b]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the phase 3 studies, including patients originally randomized to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022). [c]Serious infections are defined using AEs falling into the MedDRA SOC 'Infections and Infestations', and using 'Is the event nonserious or serious?' from the AE case report form. [d]Includes patients with RMS who received any dose of OCR during the CTP and associated OLE periods of the phase 2 and phase 3 studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES, and OLERO (data as of November 2022). [e]Includes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of ORATORIO, OBOE, CONSONANCE, and OLERO (data as of November 2022). [f]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the phase 2 and phase 3 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 OCR treatment (data as of November 2022).

- In PPMS, the rate of SIs remained higher than RMS[6] over time; this could be due to the underlying disease condition (eg, increasing disability, age, comorbidities)[7]

Figure 1. Yearly rate of SIs (excluding COVID-19) in RMS[a] and PMS[b] all-exposure populations[6]



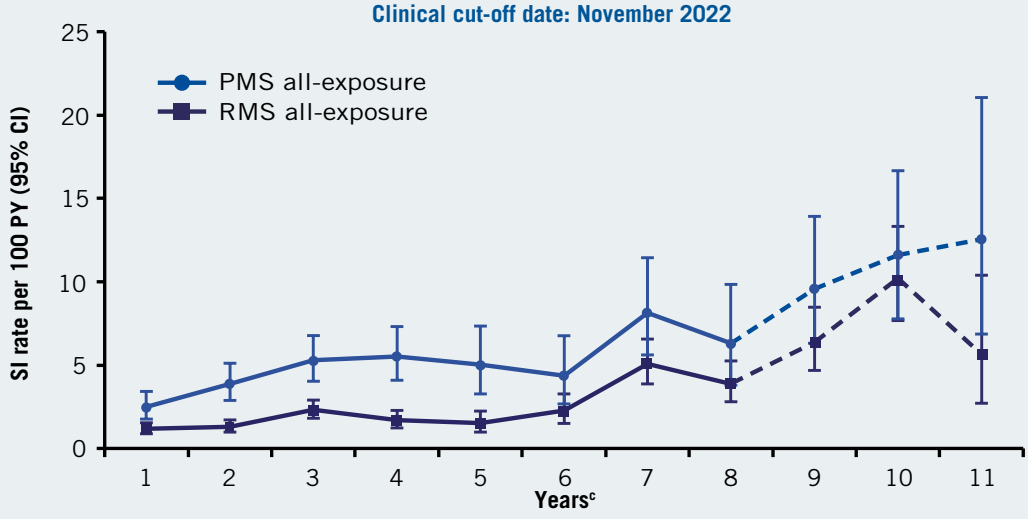
Exposure (PY)	4496 1524	4132 1289	3169 1157	2590 886	1648 519	1239 457	1161 405	1081 302	738 282	529 250	177 112
Event rate (per 100 PY)	1.1 2.4	1.2 2.8	1.5 3.6	1.1 4.0	1.3 4.6	1.7 4.2	2.6 6.9	2.5 6.3	1.8 3.9	3.8 4.4	2.3 4.5
Number of SIs	50 36	51 36	48 42	28 35	21 24	23 19	30 28	27 19	13 11	20 11	4 5
N	4558 1597	4360 1387	3435 1199	2979 1109	1881 583	1351 478	1198 433	1131 322	910 295	611 268	332 200

COVID-19–related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs.

[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the phase 2 and phase 3 studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES, and OLERO (data as of November 2022). [b]Includes patients who received any dose of OCR during the CTP and associated OLE periods of OBOE, CONSONANCE, and OLERO (data as of November 2022). [c]The exposure in PY during Years 8–11 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

- The majority of SIs were of Grade 3 intensity and were not treatment limiting, with >90% resolved[6]
- In the RMS and PMS all-exposure populations, UTI and pneumonia were the most commonly reported SIs; this is consistent with incidence rates and patterns observed in real-world studies[1,6,8,9]
- SI rates remained stable with non-significant year-on-year variation, and within the range reported in real-world registries[1,6,8]

Figure 2. Yearly rate of SIs (including COVID-19) in RMS[a] and PMS[b] all-exposure populations[6]



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Number of SIs	53 38	54 50	73 61	44 49	25 26	28 20	59 33	42 19	47 27	54 29	10 14
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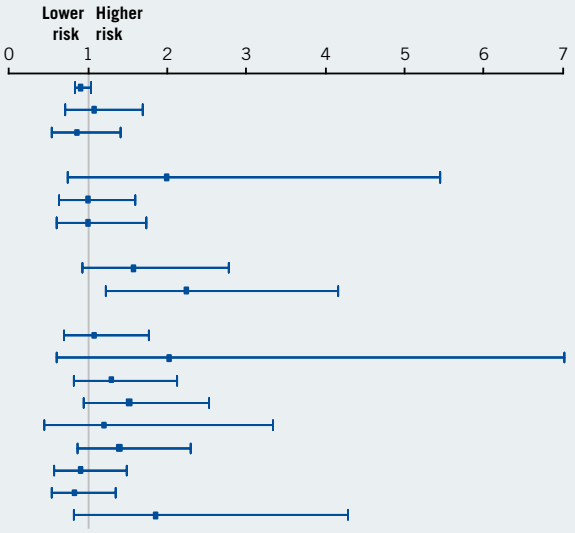
[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the phase 2 and phase 3 studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES, and OLERO (data as of November 2022). [b]Includes patients who received any dose of OCR during the CTP and associated OLE periods of ORATORIO, OBOE, CONSONANCE, and OLERO (data as of November 2022). [c]The exposure in PY during Years 8–11 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

Figure 3. Multivariate model for risk of SIs in OPERA (RMS)[10]

Clinical cut-off date: January 2020

Covariate	Serious infections RR	Lower 95% CI	Upper 95% CI
Time on OCR (per year)	0.92	0.82	1.03
Male (vs female)	1.08	0.70	1.68
≥45 years old at OCR start (vs <45)	0.86	0.53	1.39
BMI (vs 18.5–25.0 kg/m²)			
<18.5 (underweight)	2.01	0.74	5.44
>25.0 (overweight/obese)	0.99	0.62	1.59
USA (vs ROW)	1.01	0.59	1.73
Number of comorbidities (vs 0)			
1	1.59	0.91	2.77
≥2	**2.24**	**1.21**	**4.16**
EDSS (vs <3.0)			
3.0–6.0	1.09	0.68	1.76
>6.0	2.03	0.59	7.01
>10 years disease duration (vs ≤10)	1.31	0.81	2.10
Relapse in year prior to OCR start (vs no relapse)	1.53	0.93	2.51
Relapse during treatment (vs no relapse)	1.21	0.44	3.33
Prior DMT treatment (vs none)	1.40	0.86	2.30
IFN ß-1a arm (vs OCR arm)	0.91	0.56	1.48
IgM<LLN 0.4 g/L (vs ≥LLN)	0.84	0.53	1.33
IgG<LLN 5.65 g/L (vs ≥LLN)	1.86	0.81	4.27



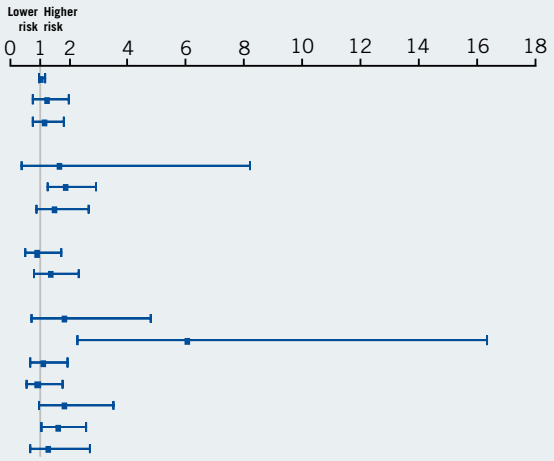
- Treatment with OCR for longer periods of time was not associated with a higher risk of SIs[10]
- The presence of ≥2 comorbidities was associated with an increased risk of SIs in people with RMS[10]

For more information on IgG levels and SIs with OCR, please visit the *Ocrelizumab and serum IgG levels webpage*

Figure 4. Multivariate model for risk of SIs in ORATORIO (PPMS)[10]

Clinical cut-off date: January 2020

Covariate	Serious infections RR	Lower 95% CI	Upper 95% CI
Time on OCR (per year)	1.03	0.92	1.14
Male (vs female)	1.22	0.76	1.97
≥50 years old at OCR start (vs <50)	1.16	0.75	1.80
BMI (vs 18.5–25.0 kg/m²)			
<18.5 (underweight)	1.65	0.33	8.21
>25.0 (overweight/obese)	**1.90**	**1.24**	**2.91**
USA (vs ROW)	1.50	0.86	2.63
Number of comorbidities (vs 0)			
1	0.90	0.48	1.72
≥2	1.37	0.81	2.33
EDSS (vs <3.0)			
3.0–6.0	1.83	0.70	4.76
>6.0	**6.08**	**2.62**	**16.33**
>6 years disease duration (vs ≤6)	1.11	0.63	1.94
Prior DMT treatment (vs none)	0.93	0.50	1.75
Placebo arm (vs OCR arm)	1.82	0.94	3.52
IgM<LLN 0.4 g/L (vs ≥LLN)	**1.64**	**1.05**	**2.55**
IgG<LLN 5.65 g/L (vs ≥LLN)	1.30	0.62	2.69



- Treatment with OCR for longer periods of time was not associated with a higher risk of SIs[10]
- Being overweight or obese, having an EDSS >6.0, and having abnormal IgM levels were found to be associated with an increased risk of SIs in people with PPMS[10]
- For patients who switched to OCR from placebo, a trend towards an increased risk of SIs was noted[10]

Post-Marketing Experience[a]

As of March 2023:

Over 300,000 patients with MS have started OCR in post-marketing and clinical trial settings globally[6]

Corresponding to an exposure of **>750,000 PY**[6]

A **total of 8313 serious events** of infections and infestations were reported in patients receiving OCR in the post-marketing setting[11b]

- No new findings related to the type or pattern of SIs were identified
- In these post-marketing case reports, the most commonly reported SIs by preferred terms, excluding COVID-19, were UTI and pneumonia, which is in line with clinical trial data

[a]There are well-recognized limitations that should be considered when interpreting spontaneous post-marketing safety reports, including events that may not be causally related to drug exposure; in the real-world setting, events are frequently confounded by factors such as multiple drug use and the presence of pre-existing comorbidities; reporting bias may exist for more significant outcomes, which may result in an overrepresentation of the more serious outcomes; and reporting rates can be stimulated by external factors, such as press reports. The causes of infections are recorded as reported to the company; while the company follows up on all reports to identify the cause, an exact diagnosis is not always possible. Some of the investigations remain ongoing and, therefore, the information may be subject to change. [b]From a non-interventional post-marketing study and reports from other solicited sources.

The Prescribing Information is the primary source of information on the known and potential risks associated with ocrelizumab.

Abbreviations:
AE=adverse event; BMI=body mass index; CD=cluster of differentiation; COVID-19=coronavirus disease 2019; CTP=controlled treatment period; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Ex=excluding; IFN β-1a=interferon beta-1a; Ig=immunoglobulin; LLN=lower limit of normal; MedDRA=Medical Dictionary for Regulatory Activities; no=number; OCR=ocrelizumab; OLE=open-label extension; PMS=progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; pwMS=people with multiple sclerosis; PY=patient-year; RMS=relapsing multiple sclerosis; ROW=rest of world; RR=relative risk; SI=serious infection; SOC=System Organ Class; USA=United States of America; UTI=urinary tract infection.

References:
1. Wijnands JMA, et al. *Mult Scler.* 2017;23:1506–1516. 2. Nelson RE, et al. *Int J MS Car.*e 2015;17:221–230. 3. Wijnands JMA, et al. *J Neurol Neurosurg Psychiatry.* 2018;89:1050–1056. 4. Hauser SL, et al. *N Engl J Med.* 2017:376:221–234. 5. Montalban X, et al. *N Engl J Med.* 2017;376:209–220. 6. Hauser SL, et al. Presented at: ECTRIMS-ACTRIMS 2023. October 11-13, 2023. Milan, Italy. Poster P304. 7. Hauser SL, et al. Presented at ECTRIMS 2022. October 25-28, 2022. Amsterdam, The Netherlands. Poster P326. 8. Knapp R, et al. *Mult Scler Relat Disord.* 2022;68:104245. 9. Persson R, et al. Mult Scler Relat Disord. 2020;41:101982. 10. Derfuss T, et al. Presented at EAN 2022. June 25-28, 2022. Vienna, Austria. Poster EPO-403. 11. Genentech. Data on file.

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https://www.genentech-medinfo.com/our-products/neuroscience/ocrevus.html

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