Ocrelizumab and infections

Overview

- PwMS are at greater risk of developing, and being hospitalised for, infections than the general population[1–3]

- In OCR RMS and PPMS pivotal clinical trials, infections were a frequently reported AE[4–6]
- However, no increased risk of serious infections with OCR vs IFN β-1a or placebo was observed[4–6]
- Treatment with OCR in both RMS and PMS populations for longer periods of time was not associated with a higher risk of SIs[6]

- Over a 10-year follow-up period in clinical trials,* OCR continues to exhibit a stable and favourable safety profile[6]

Clinical trials (controlled treatment period and open-label extension)

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

Table 1A: OPERA (RMS) cumulative exposure (controlled treatment period/open-label extension)

AE rate per 100 PY (95% CI) unless otherwise specified	CTP* (Jul 2015)		CTP + OLE† (Nov 2022)
	IFN β-1a	OCR	OCR
Total no. of patients	826	825	1,448
Total PY	1,399	1,448	10,798
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**65.9** (64.4–67.4)
Serious infections‡	**1.8** (1.2–2.6)	**0.8** (0.4–1.5)	**1.7** (1.5–2.0)

Table 1B: ORATORIO (PPMS) cumulative exposure (controlled treatment period/open-label extension)

AE rate per 100 PY (95% CI) unless otherwise specified	CTP* (Jul 2015)		CTP + OLE† (Nov 2022)
	Placebo	OCR	OCR
Total no. of patients	239	486	644
Total PY	729	1,606	4,669
Infections and infestations	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)	**70.0** (67.8–72.6)
Serious infections‡	**3.0** (1.9–4.6)	**2.7** (2.0–3.7)	**4.4** (3.8–5.0)

Table 1C: All RMS, all PMS and OCR all-exposure population

AE rate per 100 PY (95% CI) unless otherwise specified	All RMS§	All PMS‖	All OCR trials
	Nov 2022		
	OCR	OCR	OCR all-exposure population¶
Total no. of patients	4,558	1,597	6,155
Total PY	21,080	7,190	28,269
Infections and infestations	**66.2** (65.1–67.3)	**61.6** (59.8–63.4)	**65.1** (64.1–66.0)
Serious infections‡	**1.5** (1.3–1.7)	**3.7** (3.3–4.2)	**2.1** (1.9–2.2)

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

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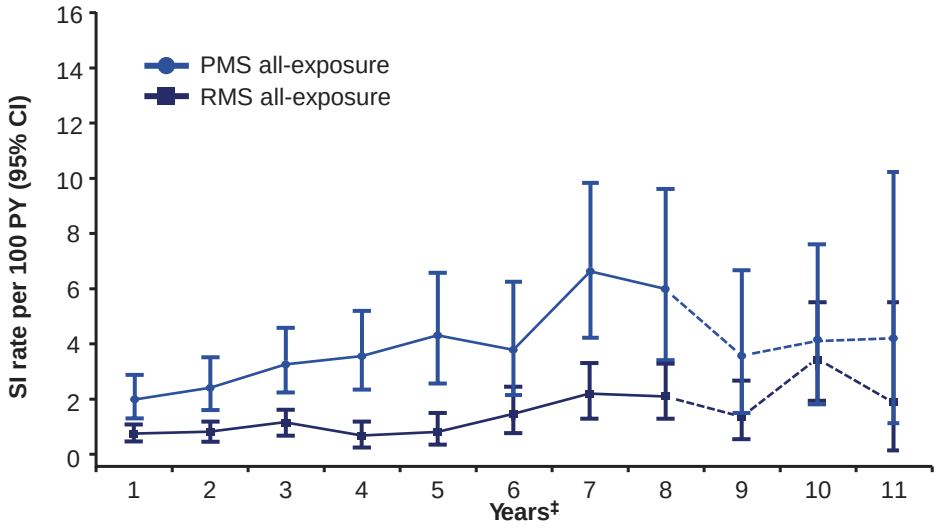
Figure 1: Yearly rate of SIs (excluding COVID-19) in RMS* and PMS† all-exposure populations[6]

Clinical cut-off date: November 2022

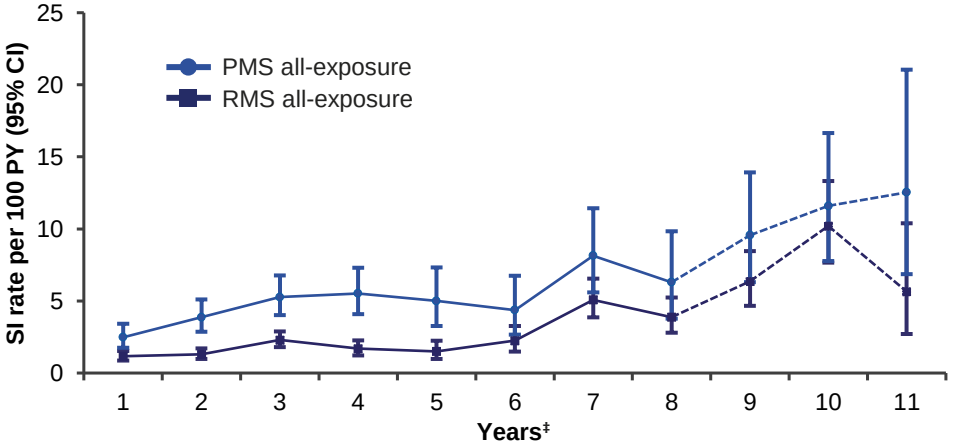


	1	2	3	4	5	6	7	8	9	10	11
Exposure (PY)	4,496 1,524	4,132 1,289	3,169 1,157	2,590 886	1,648 519	1,239 457	1,161 405	1,081 302	738 282	529 250	177 112
Event rate (per 100 PY)	1.1 2.4	1.2 2.8	1.5 3.6	1.1 4.0	1.3 4.6	1.7 4.2	2.6 6.9	2.5 6.3	1.8 3.9	3.8 4.4	2.3 4.5
Number of SIs	50 36	51 36	48 42	28 35	21 24	23 19	30 28	27 19	13 11	20 11	4 5
N	4,558 1,597	4,360 1,387	3,435 1,199	2,979 1,109	1,881 583	1,351 478	1,198 433	1,131 322	910 295	611 268	332 200

- 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* and PMS† all-exposure populations[6]

Clinical cut-off date: November 2022



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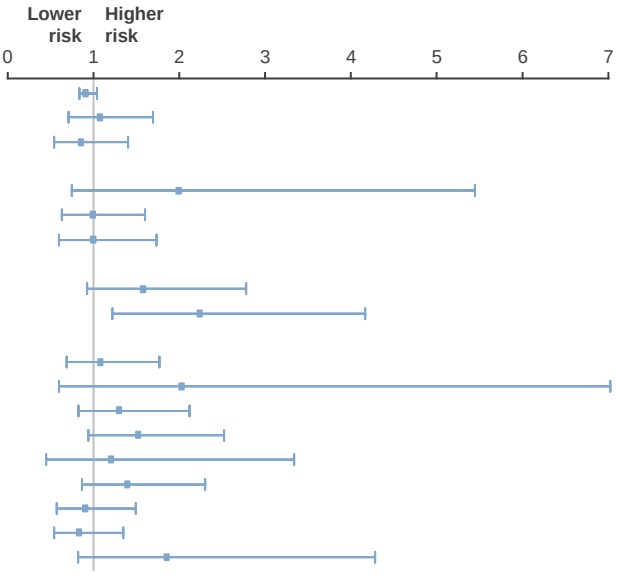
Number of SIs	53 38	54 50	73 61	44 49	25 26	28 20	59 33	42 19	47 27	54 29	10 14
N	4,558 1,597	4,360 1,387	3,435 1,199	2,979 1,109	1,881 583	1,351 478	1,198 433	1,131 322	910 295	611 268	332 200

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/m^2)			
<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



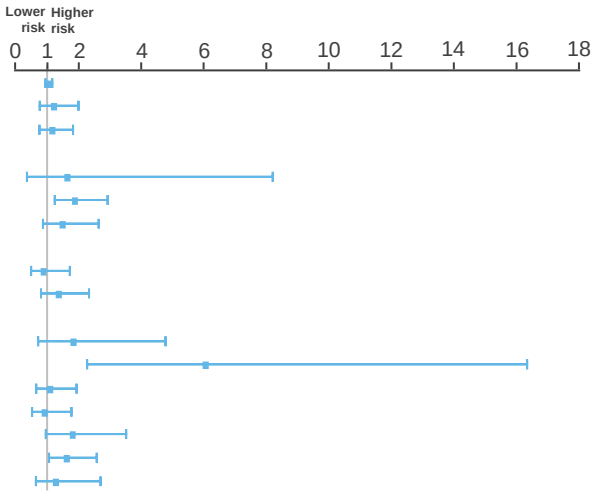
- Treatment with OCR for longer periods of time was **not associated with a higher risk of SIs**[10]
- The presence of ≥2 comorbidities was **associated with an increased risk of SIs in people with RMS**[10]

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/m^2)			
<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** was noted[10]

Post-marketing experience*

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 8,313 serious events** of infections and infestations were reported in patients receiving OCR in the post-marketing setting[†,11]

- **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**

Footnotes

Overview
*Includes patients who received any dose of OCR during the CTP 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 randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022).

Tables 1A, 1B, 1C
COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs. 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.
*Data as of April–July 2015;
†Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase III studies, including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022);
‡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;
§Includes patients with RMS who received any dose of OCR during the CTP 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);
‖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);
¶Includes patients who received any dose of OCR during the CTP 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 randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022).

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Footnotes (cont.)

Figure 1
COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs.
*Includes patients who received any dose of OCR during the CTP 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);
†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);
‡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 2
*Includes patients who received any dose of OCR during the CTP 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);
†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);
‡The exposure in PY during Years 8–11 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

Post-marketing
*There are well-recognised 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.

†From non-interventional post-marketing study and reports from other solicited sources.

Abbreviations
AE, adverse event; BMI, body mass index; CI, confidence interval; 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; IgG, immunoglobulin G; IgM, immunoglobulin M; LLN, lower limit of normal; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive MS; PPMS, primary progressive MS; PY, patient-years; pwMS, people with MS; RMS, relapsing MS; ROW, rest of world; SI, serious infection; SOC, System Organ Class; USA, United States of America; UTI, urinary tract infection.

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