Ocrelizumab and infections

Overview

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

- In clinical trials, infections were a frequently reported AE[4,5]
- However, no increased risk of serious infections with OCR vs IFN β-1a or placebo was observed[4,5]
- The COVID-19 pandemic resulted in an increase in the number of cases of infections related to SARS-CoV-2 during the reporting interval[6]

- The incidence and type of infections seen in the post-marketing setting (data cut-off: March 2022) are consistent with the clinical trial data (data cut-off: November 2021)[7]

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

Incidence rates of SI in ocrelizumab clinical trials per 100 PY[6]

Table 1a: Controlled Treatment Period

Adverse event Rate per 100 PY (95% CI)	CTP*			
	OPERA		ORATARIO	
	IFN β-1a	OCR	Placebo	OCR
Total no. of patients	826	825	239	486
Total PY	1,399	1,448	729	1,606
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)
Serious infections[§]	**1.79** (1.16–2.64)	**0.83** (0.43–1.45)	**3.02** (1.89–4.57)	**2.74** (1.99–3.68)

Table 1b: Cumulative Exposure (Controlled Treatment Period/Open-Label Extension)

Adverse event Rate per 100 PY (95% CI)	CTP/OLE[†]			
	OPERA	OPERA (Ex-COVID-19)	ORATORIO	ORATORIO (Ex-COVID-19)
	OCR	OCR	OCR	OCR
Total no. of patients	1,448	1,448	644	644
Total PY	9,890.8	9,890.8	4,336.4	4,336.4
Infections and infestations	**69.7** (68.1–71.4)	**67.1** (65.5-68.7)	**72.7** (70.1–75.4)	**70.5** (68.1-73.1)
Serious infections[§]	**2.45** (2.15–2.78)	**1.62** (1.38–1.89)	**4.89** (4.25–5.59)	**4.34** (3.74–5.00)

Table 1c: OCR All-Exposure Population

Adverse event Rate per 100 PY (95% CI)	OCR all-exposure population[‡]	OCR all-exposure population (Ex-COVID-19)
Total no. of patients	5,848	5,848
Total PY	25,153	25,153
Infections and infestations	**69.9** (68.9–70.9)	**67.4** (66.4–68.4)
Serious infections[§]	**2.74** (2.54–2.96)	**2.04** (1.87–2.22)

- In the OCR all-exposure population, the rate of SIs was consistent with rates of infection-related hospitalisations reported in a real-world MS cohort[4–6]
- Over a 9-year follow-up period, no new (with the exception of COVID-19 type of infections) or unexpected safety signal were seen in patients treated with ocrelizumab in ongoing clinical trials, ocrelizumab continues to exhibit a stable and favourable safety profile[6]
- The most frequently reported SIs overall were consistent with the frequently reported SIs reported for each year[4–6]
- In PPMS, the rate of SIs remained higher than RMS; over time, the underlying disease condition (e.g. increasing disability, age, comorbidities) appears to drive this possible increase[4–6]
  - The majority of SIs were typical in character, resolved, and were not treatment limiting

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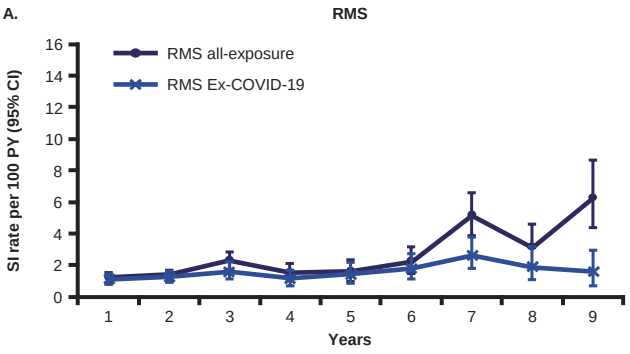
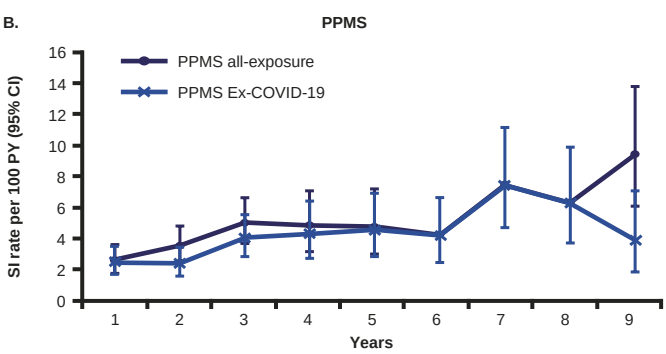
Figure 1: Yearly rate of SIs in OPERA I/II and ORATORIO populations over 9 years*,[6]

RMS (OPERA I/II)



Exposure (PY)	4,320	4,085	2,968	2,214	1,414	1,230	1,138	779	576
	4,320	4,085	2,968	2,214	1,414	1,230	1,138	779	576
Event rate (per 100 PY)	1.16	1.32	2.26	1.54	1.56	2.20	5.10	3.08	6.25
	1.13	1.25	1.58	1.13	1.41	1.79	2.64	1.93	1.56
Number of SIs	50	54	67	34	22	27	58	24	36
	49	51	47	25	20	22	30	15	9
N	4,376	4,257	3,428	2,498	1,593	1,291	1,198	965	642
	4,376	4,257	3,428	2,498	1,593	1,291	1,198	965	642

PPMS (ORATORIO)



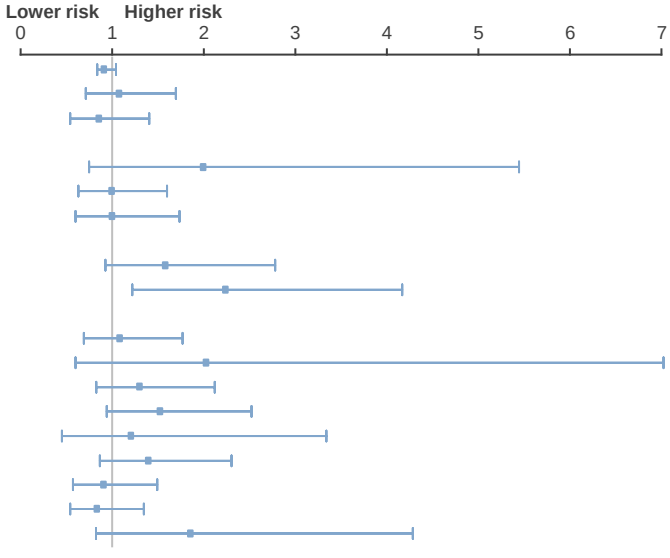
Exposure (PY)	1,345	1,235	971	571	497	443	322	300	278
	1,345	1,235	971	571	497	443	322	300	278
Event rate (per 100 PY)	2.68	3.65	5.05	4.90	4.83	4.29	7.45	6.33	9.35
	2.60	2.51	4.12	4.38	4.63	4.29	7.45	**6.33**	3.95
Number of SIs	36	45	49	28	24	19	24	19	26
	35	31	40	25	23	19	24	19	11
N	1,472	1,272	1,187	654	532	472	343	310	293
	1,472	1,272	1,187	654	532	472	343	310	293

All-exposure population
Total serious infections: n=690
SI rate per 100 PY (95% CI): 2.74 (2.54–2.96)

Excluding COVID-19 cases
Total serious infections: n=513
SI rate per 100 PY (95% CI): 2.04 (1.87–2.22)

Figure 2: Multivariate model for risk of SIs in OPERA (RMS)*,[7]

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
- The presence of ≥2 comorbidities was independently associated with an increased risk of SIs in people with RMS

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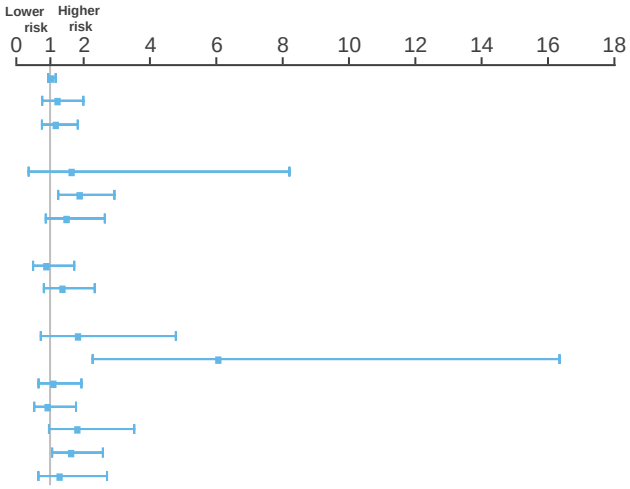
Figure 3: Multivariate model for risk of SIs in ORATORIO (PPMS)*,7

Serious infections

Covariate	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
- Being overweight or obese, having an EDSS >6.0, and having abnormal IgM levels were found to be independently associated with an increased risk of SIs in people with PPMS
- For patients who switched to OCR from placebo, a trend towards an increased risk was noted

Post-marketing experience†,8

As of March 2022…

~250,428 patients with RMS and PPMS have started OCR outside of RCTs

Corresponding to an exposure of **~510,060 PY**

A **total of 6,393 serious events** of infections and infestations were reported in patients receiving OCR

- **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 were **UTI and pneumonia**, which **is in line with clinical trial data**

Footnotes

Tables 1a, 1b, 1c
In the Ex-COVID-19 analysis, 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 2020);
‡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 and CONSONANCE, including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2021);
§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.

Figure 1
*The exposure in PY during Year 9 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

Figure 2
*Clinical data cut-off: 3 January 2020

Figure 3
*Clinical data cut-off: 3 January 2020

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.

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; PPMS, primary progressive MS; PY, patient-years; pwMS, people with MS; RCT, randomised controlled trial; RMS, relapsing MS; ROW, rest of world; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; SI, serious infection; SOC, System Organ Class; UTI, urinary tract infection.

References

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8. Roche data on file.

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