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Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients with Relapsing and Progressive Multiple Sclerosis

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STUDY AIM

To examine safety outcomes of patients continuously treated with OCR in clinical trials over a 10-year period (up to November 2022)

CONCLUSIONS

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

- AE rates in all RMS and PMS populations remained consistent with the rates observed during the CTP
- Rates of SIs remained low and stable over time in both RMS and PMS populations irrespective of IgG levels
- AEs leading to treatment withdrawal remained infrequent and were not driven by serious infections

AE, adverse event; CTP, controlled-treatment period; IgG, immunoglobulin G; OCR, ocrelizumab; PMS, progressive multiple sclerosis; RMS, relapsing multiple sclerosis, SI, serious infections.

RESULTS

- **As of November 2022, 6,155 patients with MS received OCR across 13 clinical trials (all-exposure population), amounting to 28,269 PY of exposure**
- **Approximately 60% of patients (3,677) received at least 8 doses (~4 years of treatment)**
- **As of March 2023, over 300,000 patients with MS (amounting to >750,000 PY of exposure) had started OCR globally**

Over 10 Years of Continuous OCR Treatment, the Overall Safety Profile Remained Consistent

Adverse event Rate per 100 PY (95% CI)	OPERA (RMS)			All RMS[c]	ORATORIO (PPMS)			All PMS[d]	All OCR trials
	CTP[a] (Jul 2015)		CTP + OLE[b] (Nov 2022)	Nov 2022	CTP[a] (Jul 2015)		CTP + OLE[b] (Nov 2022)	Nov 2022	OCR all-exposure population[e]
	IFN β-1a	OCR	OCR	OCR	Placebo	OCR	OCR	OCR	
Total no. of patients	826	825	1,448	4,558	239	486	644	1,597	6,155
Total PY	1,399	1,448	10,798	21,080	729	1,606	4,669	7,190	28,269
Any AEs	**296** (287–305)	**290** (281–299)	**194** (191–196)	**227** (225–229)	**259** (247–271)	**252** (244–260)	**223** (219–228)	**215** (212–219)	**224** (222–226)
AEs leading to withdrawal	**3.9** (3.0–5.1)	**2.4** (1.6–3.3)	**1.3** (1.1–1.5)	**1.0** (0.9–1.2)	**1.1** (0.5–2.2)	**1.2** (0.8–1.9)	**1.1** (0.8–1.4)	**1.0** (0.8–1.3)	**1.0** (0.9–1.2)
Serious AEs	**6.3** (5.1–7.8)	**5.4** (4.3–6.7)	**6.2** (5.8–6.7)	**5.7** (5.4–6.0)	**12.1** (9.7–14.9)	**10.2** (8.7–11.8)	**12.7** (11.7–13.8)	**10.9** (10.1–11.7)	**7.0** (6.7–7.3)
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**65.9** (64.4–67.4)	**66.2** (65.1–67.3)	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)	**70.0** (67.8–72.6)	**61.6** (59.8–63.4)	**65.1** (64.1–66.0)
Serious infections[f]	**1.8** (1.2–2.6)	**0.8** (0.4–1.5)	**1.7** (1.5–2.0)	**1.5** (1.3–1.7)	**3.0** (1.9–4.6)	**2.7** (2.0–3.7)	**4.4** (3.8–5.0)	**3.7** (3.3–4.2)	**2.1** (1.9–2.2)
IRRs	**7.9** (6.5–9.5)	**34.9** (31.9–38.1)	**11.2** (10.5–11.8)	**23.2** (22.6–23.9)	**20.3** (17.2–23.8)	**31.0** (28.3–33.9)	**16.6** (15.5–17.8)	**16.8** (15.9–17.8)	**21.6** (21.1–22.2)
Malignancies[g,h]	**0.1** (0.0–0.5)	**0.3** (0.1–0.7)	**0.4** (0.3–0.6)	**0.4** (0.3–0.4)	**0.3** (0.0–1.0)	**0.9** (0.5–1.5)	**1.0** (0.7–1.3)	**0.9** (0.7–1.2)	**0.5** (0.4–0.6)
Deaths	**0.1** (0.0–0.5)	**0.1** (0.0–0.4)	**0.1** (0.0–0.2)	**0.1** (0.1–0.2)	**0.4** (0.1–1.2)	**0.3** (0.1–0.6)	**0.5** (0.3–0.7)	**0.4** (0.3–0.6)	**0.2** (0.1–0.2)

COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis). 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 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); [c]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); [d]Includes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of OBOE, CONSONANCE and OLERO (data as of November 2022); [e]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); [f]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; [g]Malignancies are identified using AEs falling into the standard MedDRA query 'Malignant tumours (narrow)'; [h]For malignancies, incidence rates are reported and exposure in PY was calculated from first treatment to onset of first malignancy.
AE, adverse event; CI, confidence interval; CTP, controlled treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; MS, Multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SOC, System Organ Class.

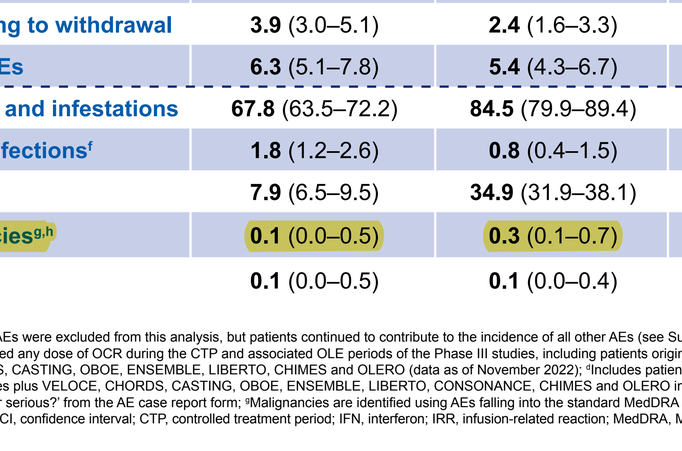
- **Cumulative AE and SAE incidence rates remained consistent with the rates observed during the CTP**
- **The cumulative standardised incidence rates of (a) all malignancies and (b) female breast cancer remained within the range reported in real-world registries[1,2] (see Supplementary Material)**
- **Withdrawal due to AEs was infrequent and did not increase over time**

AE, adverse event; CTP, controlled treatment period; SAE, serious adverse event.

SI Rates Remained Stable with Non-Significant Year-on-Year Variation and Within the Range Reported in Real-World Registries[3,4]

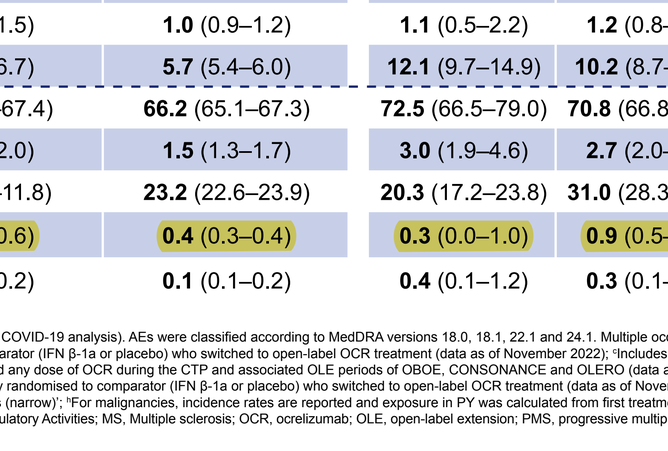
In Both RMS and PPMS Populations, Longer Exposure to OCR Did Not Lead to an Increased Risk of SIs Regardless of IgG Status (Normal Levels or Levels Below the LLN)

RMS[a] and PMS[b] all-exposure population



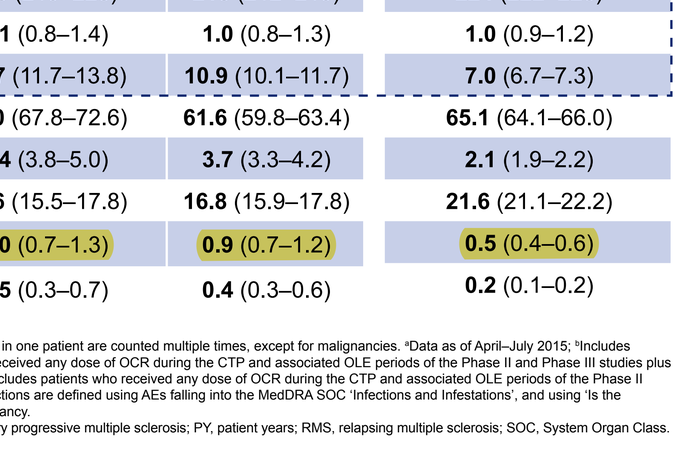
Exposure (PY)	4,496 1,524	4,132 1,289	3,169 1,157	2,590 886	1,648 519	1,239 457	1,161 405	1,081 302	738 282	529 250	177 112
Event rate (per 100 PY)	1.1 2.4	1.2 2.8	1.5 3.6	1.1 4.0	1.3 4.6	1.7 4.2	2.6 6.9	2.5 6.3	1.8 3.9	3.8 4.4	2.3 4.5
Number of SIs	50 36	51 36	48 42	28 35	21 24	23 19	30 28	27 19	13 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

RMS (OPERA I, II and OLERO)



Exposure (PY) IgG<LLN	224	223	222	219	215	212	204	188	135	103	26
Exposure (PY) IgG≥LLN	1,420	1,358	1,275	1,214	1,160	1,119	1,064	987	649	444	95
IgG<LLN number of SIs	0	0	4	1	3	1	3	4	2	6	0
IgG≥LLN number of SIs	17	13	18	16	16	18	23	17	10	13	1

PPMS (ORATORIO and OLERO)



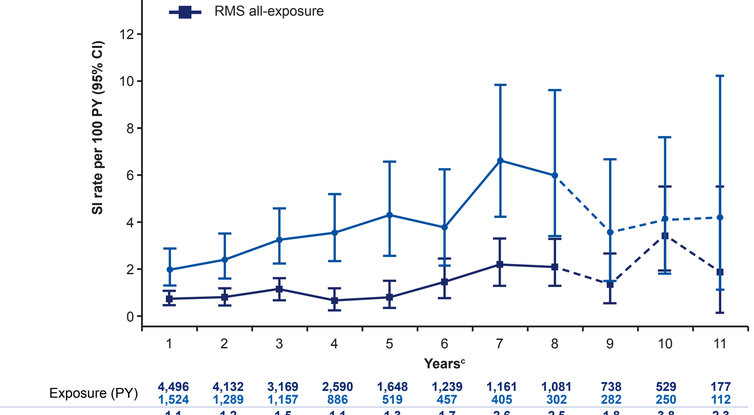
Exposure (PY) IgG<LLN	104	102	99	98	95	93	86	74	73	68	31
Exposure (PY) IgG≥LLN	634	609	574	538	496	456	405	302	282	250	112
IgG<LLN number of SIs	0	2	2	2	0	0	3	2	3	2	1
IgG≥LLN number of SIs	19	18	25	21	23	19	25	17	8	9	4

- **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[4-6]**
- **The type, severity, latency and duration of SIs observed during episodes of IgG<LLN were consistent with the overall SIs observed in patients treated with OCR**

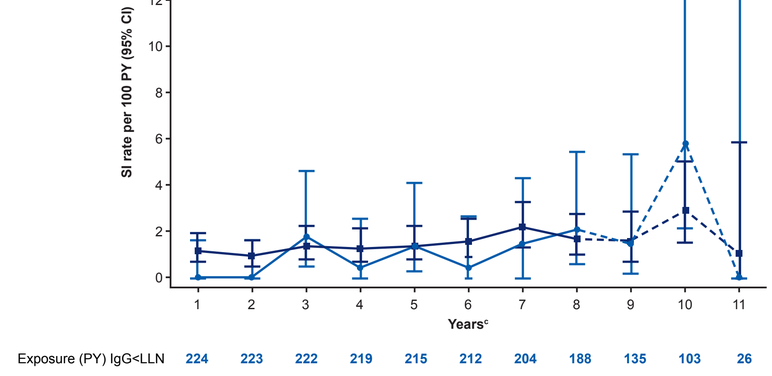
COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis). [a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES and OLERO (data as of November 2022); [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. CI, confidence interval; CTP, controlled-treatment period; IgG, immunoglobulin G; LLN, lower limit of normal; OCR, ocrelizumab; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SI, serious infection; UTI, urinary tract infection.

The Majority of SIs Were of Grade 3 Intensity, >90% Had Resolved (Regardless of IgG Status) and Were Not Treatment Limiting

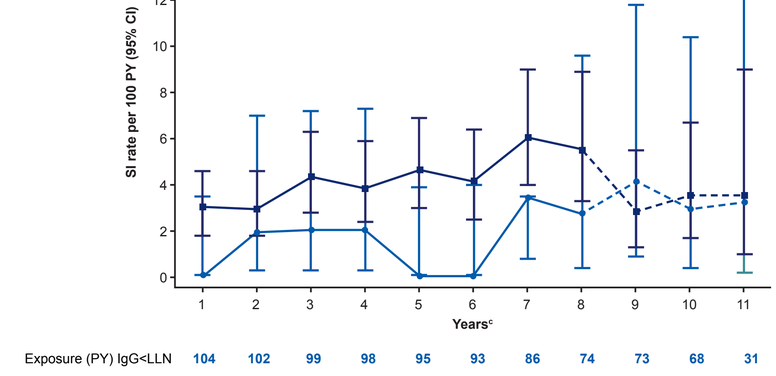
Outcomes of SIs



SI intensity Grade (CTCAE)[c]: OCR all-exposure[a]



SI intensity Grade (CTCAE)[c]: IgG<LLN (OPERA I, II, ORATORIO and OLERO)[b]



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ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; IgG, immunoglobulin G; LLN: Lower limit of normal [LLN=5.65 (g/L)]; OCR, ocrelizumab; SI, serious infection.

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