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

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The aim of this study was to demonstrate the continuity in safety of ocrelizumab (OCR) by reporting longer-term safety evaluations from OCR clinical trials and open-label extension periods over a 9-year follow-up (up to November 2021)

RESULTS

Nov 2021

As of November 2021, 5,848 patients in the OCR all-exposure population (patients with multiple sclerosis [MS] across multiple clinical trials) had received OCR (amounting to 25,153 patient years of exposure); approximately 50% of patients (2,836) received at least 8 doses

Mar 2022

As of March 2022, over 250,000 patients with MS had started OCR globally in the post-marketing setting

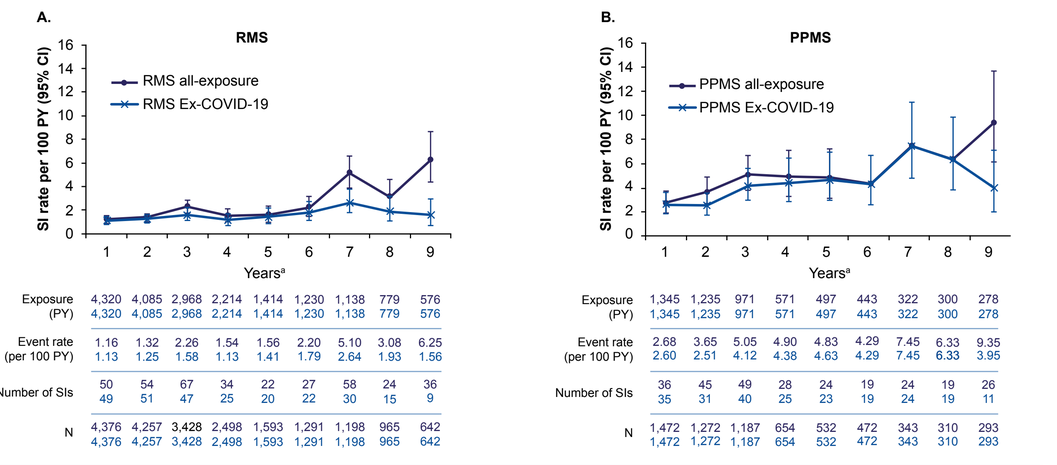
AEs With and Without COVID-19 Cases. Over 9 Years, the Safety Profile of OCR Remained Consistent

Adverse event Rate per 100 PY (95% CI)	CTP[a]				CTP/OLE[b]				OCR all-exposure population[c]	Excl. COVID-19 cases
	OPERA		ORATORIO		OPERA	OPERA (Ex-COVID-19)	ORATORIO	ORATORIO (Ex-COVID-19)		
	IFN β-1a	OCR	Placebo	OCR	OCR	OCR	OCR	OCR		
Total no. of patients	826	825	239	486	1,448	1,448	644	644	5,848	5,848
Total PY	1,399	1,448	729	1,606	9,890.8	9,890.8	4,336.4	4,336.4	25,153.0	25,153.0
Any AEs	**296** (287–305)	**290** (281–299)	**259** (247–271)	**252** (244–260)	**199.64** (196.90–202.40)	**196.91** (194.15–199.70)	**225.30** (220.86-229.81)	**224.00** (219.51–228.44)	**233** (231–235)	**230** (228–232)
AEs leading to discontinuation	**3.93** (2.96–5.12)	**2.35** (1.63–3.28)	**1.10** (0.47–2.16)	**1.25** (0.76–1.92)	**1.23** (1.02–1.47)	**1.18** (0.98–1.42)	**1.01** (0.74–1.36)	**1.01** (0.74–1.36)	**0.97** (0.85–1.10)	**0.93** (0.81–1.06)
Serious AEs	**6.3** (5.1–7.8)	**5.4** (4.3–6.7)	**12.1** (9.7–14.9)	**10.2** (8.7–11.8)	**6.90** (6.40–7.50)	**6.11** (5.63–6.61)	**13.08** (12.02-14.20)	**12.52** (11.49–13.62)	**7.61** (7.27–7.96)	**6.90** (6.60–7.20)
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)	**69.7** (68.1–71.4)	**67.1** (65.5–68.7)	**72.7** (70.1–75.4)	**70.5** (68.1–73.1)	**69.9** (68.9–70.9)	**67.4** (66.4–68.4)
Serious infections[d]	**1.79** (1.16–2.64)	**0.83** (0.43–1.45)	**3.02** (1.89–4.57)	**2.74** (1.99–3.68)	**2.45** (2.15–2.78)	**1.62** (1.38–1.89)	**4.89** (4.25–5.59)	**4.34** (3.74–5.00)	**2.74** (2.54–2.96)	**2.04** (1.87–2.22)
IRRs	**7.9** (6.5–9.5)	**34.9** (31.9–38.1)	**20.3** (17.2–23.8)	**31.0** (28.3–33.9)	**11.91** (11.24–12.61)	**11.91** (11.24–12.61)	**17.6** (16.4–18.9)	**17.6** (16.4-18.9)	**23.0** (22.4–23.6)	**23.0** (22.4–23.6)
Malignancies[e,f]	**0.14** (0.02–0.52)	**0.28** (0.08–0.71)	**0.27** (0.03–0.99)	**0.93** (0.52–1.54)	**0.43** (0.31–0.59)	**0.43** (0.31–0.59)	**1.01** (0.74–1.36)	**1.01** (0.74–1.36)	**0.47** (0.39–0.57)	**0.47** (0.39–0.57)
Deaths	**0.14** (0.02–0.52)	**0.07** (0.00–0.38)	**0.41** (0.08–1.20)	**0.25** (0.07–0.64)	**0.23** (0.15–0.35)	**0.07** (0.03–0.15)	**0.51** (0.32–0.77)	**0.44** (0.26–0.68)	**0.30** (0.24–0.38)	**0.16** (0.12–0.22)

AE rates in the OCR all-exposure population remain generally consistent with the CTP in RMS/PPMS populations
Excluding COVID-19, the rate of SIs remained low and within the range reported in real-world registries[1]
The COVID-19 pandemic resulted in an increase in the number of cases of infections related to SARS-CoV-2 during the reporting interval

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.
[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 2021); [c]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); [d]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; [e]Malignancies are identified using AEs falling into the standard MedDRA query 'Malignant tumours (narrow)'; [f]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; Ex, excluding; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension;
PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SI, serious infection; SOC, System Organ Class.

Excluding COVID-19 Infections, No New or Particular Patterns of SIs Were Identified by Year in Either the (A) RMS or (B) PPMS OCR-Treated Populations



	A. RMS									
Exposure	4,320	4,085	2,968	2,214	1,414	1,230	1,138	779	576
(PY)	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

	B. PPMS									
Exposure	1,345	1,235	971	571	497	443	322	300	278
(PY)	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

Overall, the most frequently reported SIs were consistent with those typically reported for each year
In PPMS, the rate of SIs remained higher than RMS; over time, this could be due to the underlying disease condition (e.g. increasing disability, age, comorbidities)
The majority of SIs were typical in character, resolved and were not treatment limiting

In the Ex-COVID-19 analysis, patients continued to contribute to the incidence of all other AEs.[a]The exposure in PY during Year 9 is limited for meaningful interpretation.
CI, confidence interval; Ex, excluding; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SI, serious infection.

The Majority of Infection AEs Were of Grade 3 Intensity, Had Resolved and Were Not Treatment Limiting Despite the COVID-19 Pandemic

OCR all-exposure population

AEs and outcomes
Total exposure 25,153 PY
Total AEs n=58,534

Total infections
n=17,579

Total serious infections: n=690
Serious infection rate per 100 PY (95% CI): 2.74 (2.54–2.96)

Outcomes:
84.8% (585/690) **resolved**
6.2% (43 events) **resolved with sequelae**
0.9% (6 events) resolving
1.9% (13 events) unresolved
6.2% (43 events) fatal[a]

Intensity grade (CTCAE)[b]
1: <0.1%
2: 1.2%
3: 5.8%
4: 1.0%
5: 0.7%

Action taken with OCR:
Withdrawn 4.5% (31/690 SIs)

Excluding COVID-19 cases

AEs and outcomes
Total exposure 25,153 PY
Total AEs n=57,883

Total infections
n=16,946

Total serious infections: n=513
Serious infection rate per 100 PY (95% CI): 2.04 (1.87–2.22)

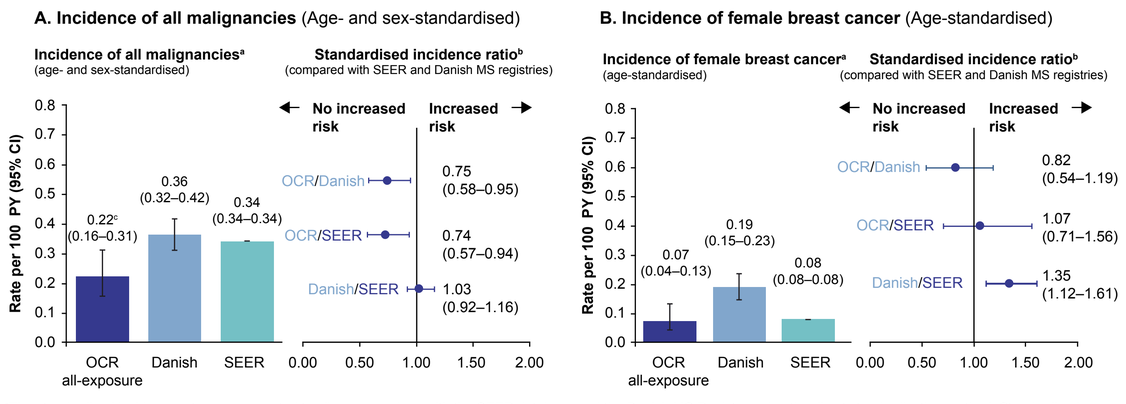
Outcomes:
91.4% (469/513) **resolved**
4.7% (24 events) **resolved with sequelae**
0.4% (2 events) resolving
1.9% (10 events) unresolved
1.6% (8 events) fatal[a]

Intensity grade (CTCAE)[b]
1: <0.1%
2: 1.0%
3: 4.4%
4: 0.7%
5: 0.1%

Action taken with OCR:
Withdrawn 4.1% (21/513 SIs)

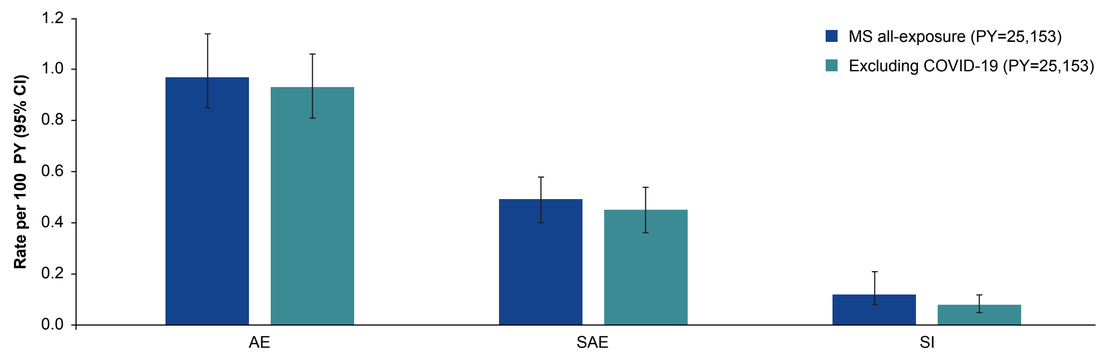
In the Ex-COVID-19 analysis, patients continued to contribute to the incidence of all other AEs. [a]Excluding COVID-19 cases, fatal SIs included pneumonia (n=2), sepsis (n=2), encephalitis (n=1), urosepsis (n=1), enterococcal infection (n=1) and pneumonia aspiration (n=1);
[b]Grade 1 (mild): Asymptomatic or mild symptoms/clinical or diagnostic observation only/intervention not indicated; Grade 2 (moderate): Minimal, local or noninvasive intervention indicated/limiting age-appropriate instrumental ADL; Grade 3 (severe): Severe or medically insignificant but not immediately life-threatening/hospitalisation or prolongation of hospitalisation indicated/disabling/limiting self-care ADL; Grade 4 (life-threatening): Life-threatening consequences/urgent intervention required; Grade 5 (death): Death related to AE (not applicable for all AEs).
ADL, activities of daily living; AE, adverse event; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; Ex, excluding; OCR, ocrelizumab; PY, patient years; SI, serious infection.

Over 9 Years, the Cumulative Standardised Incidence Rates of (A) All Malignancies and (B) Female Breast Cancer Remained Within the Range Reported in Registries[2,3]



[a]The standardised incidence rates were reported to allow comparison with the SEER database and the Danish MS Registry, using the direct standardisation method. Standardised incidence rates were derived by applying age–sex specific rates to the 2,000 USA standard population, with restriction to the age range of the MS clinical trials (15–59 years); [b]The SIR, calculated as observed/expected number of events, was determined for all malignancies (excluding NMSC) and female breast cancer, using the SEER database and the Danish MS Registry as reference populations; [c]It excludes NMSC for comparison with SEER rates, as NMSC is not reported in SEER.
CI, confidence interval; MS, multiple sclerosis; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; PY, patient years; SEER, Surveillance, Epidemiology and End Results; SIR, standardised incidence ratio.

Withdrawals Due to AEs Over 9 Years in the OCR All-Exposure Population



The rate of AEs leading to patient withdrawal remained infrequent with additional exposure, despite the COVID-19 pandemic. SIs or serious COVID-19 infections are not driving the withdrawals due to AEs

In the Ex-COVID-19 analysis, patients continued to contribute to the incidence of all other AEs.
AE, adverse event; CI, confidence interval; AE, adverse event; CI, confidence interval; Ex, excluding; MS, multiple sclerosis; PY, patient years; SAE, serious adverse event; SI, serious infection.

CONCLUSIONS

- Over 9 years of treatment, AE rates in the ocrelizumab all-exposure population remain generally consistent with the controlled treatment period in RMS/PPMS populations
- Despite 2 years of the COVID-19 pandemic, the rate of AEs leading to treatment withdrawal remained infrequent and stable
- Serious infection and malignancy rates remain within the range reported for patients with MS in real-world registries
- Over a 9-year follow-up period, no new (with the exception of COVID-19 type of infections) or unexpected safety signal was seen in patients treated with ocrelizumab in ongoing clinical trials, ocrelizumab continues to exhibit a stable and favourable safety profile
- Long-term follow-up and post-marketing requirement studies will continue to monitor patient safety over time in patients with MS receiving ocrelizumab, including identified and potential risks

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