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

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KEY FINDINGS

ADVERSE EVENT RATES IN THE OCRELIZUMAB ALL-EXPOSURE POPULATION AND POST-MARKETING SETTINGS (EXCLUDING COVID-19 INFECTIONS) REMAIN GENERALLY CONSISTENT WITH THE CONTROLLED TREATMENT PERIOD IN RMS/PPMS POPULATIONS[a]

Serious infection and malignancy rates remain within the range reported for patients with MS in real-world registries

[a]IRRs, upper respiratory tract infections and UTIs remained the most common AEs; infections remained the most reported SAE. AE, adverse event; IRR, infusion-related reaction; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SAE, serious adverse event; UTI, urinary tract infection.

AIM

To report longer-term safety evaluations from ocrelizumab clinical trials and associated open-label extension periods up to November 2020 and selected post-marketing data, excluding COVID-19 cases (see late-breaking Poster P933 for COVID-19 update)

RESULTS

NOV 2020 — As of November 2020, 5,688 patients with MS had received OCR across multiple clinical trials (amounting to 21,675 patient-years of exposure)

>8 Years — Over 8 years, the safety profile of OCR remained consistent

DEC 2020 — As of December 2020, over 200,000 patients with MS had started OCR globally in the post-marketing setting

Adverse event Rate per 100 PY (95% CI)	CTP[a]				CTP/OLE[b]		OCR all-exposure population[c]
	OPERA		ORATORIO		OPERA	ORATORIO	
	IFN β-1a	OCR	Placebo	OCR	OCR	OCR	
Total no. of patients	826	825	239	486	1,448	644	5,688
Total PY	1,399	1,448	729	1,606	8,806	3,937	21,675
Any AEs	**296** (287–305)	**290** (281–299)	**259** (247–271)	**252** (244–260)	**201** (198–204)	**228** (224–233)	**238** (236–240)
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)	**1.17** (0.95–1.42)	**1.07** (0.77–1.44)	**0.96** (0.83–1.10)
SAEs	**6.3** (5.1–7.8)	**5.4** (4.3–6.7)	**12.1** (9.7–14.9)	**10.2** (8.7–11.8)	**6.0** (5.5–6.5)	**12.7** (11.6–13.9)	**7.1** (6.7–7.4)
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)	**70.0** (68.3–71.8)	**72.7** (70.1–75.4)	**71.8** (70.7–73.0)
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)	**1.45** (1.21–1.73)	**4.34** (3.72–5.05)	**2.00**[f] (1.82–2.20)
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)	**12.9** (12.2–13.7)	**18.8** (17.5–20.2)	**24.5** (23.8–25.1)
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)	**0.40** (0.28–0.55)	**1.09** (0.79–1.47)	**0.42** (0.34–0.52)
Deaths	**0.14** (0.02–0.52)	**0.07** (0–0.38)	**0.41** (0.08–1.20)	**0.25** (0.07–0.64)	**0.06** (0.02–0.13)	**0.38** (0.21–0.63)	**0.15** (0.10–0.21)

AEs were classified according to MedDRA versions 18.0, 18.1 and 22.1. 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 2020); [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 2020); [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; CTP, controlled-treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; SAE, serious adverse event; SOC, system organ class; UTI, urinary tract infection.

The rate of serious infections in the OCR all-exposure population remained low

AEs and outcomes
Total exposure 21,675 PY

Total AEs n=51,488

Total infections n=15,570

Total serious infections: n=434
Serious infection rate per 100 PY (95% CI): 2.00 (1.82–2.20)

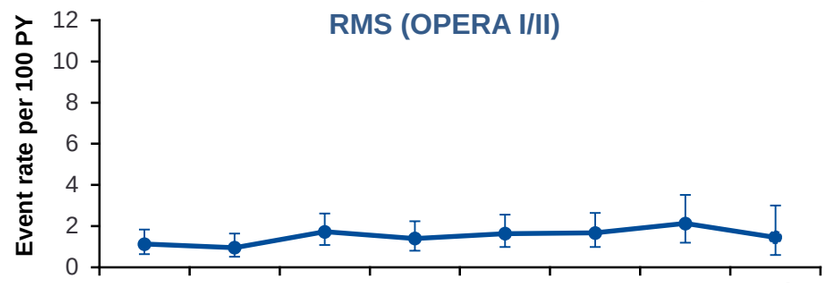
Outcomes:
92.4% (401/434) **resolved**
4.4% (19 events) **resolved with sequelae**
0.7% (3 events) resolving
1.6% (7 events) unresolved
0.9% (4 events) fatal[a]

Intensity grade (CTCAE)[b]
1: <0.1%
2: 1.1%
3: 3.8%
4: 0.7%
5: <0.1%

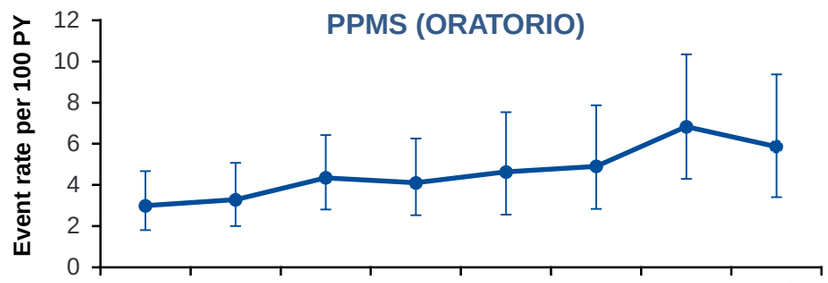
Action taken with OCR:
Withdrawn 3.9% (17/434 SIs)[c]

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[d]
No new or particular patterns of SIs were identified by year in either the RMS or PPMS OCR-treated patients

Yearly Rate of Serious Infections Over 8 years[e]



Years	1	2	3	4	5	6	7	8[e]
Exposure (PY)	1,422	1,359	1,277	1,216	1,162	1,077	705	481
Event rate (per 100 PY)	1.125	0.956	1.723	1.398	1.636	1.671	2.129	1.457
Number of SIs n	16	13	22	17	19	18	15	7
	1448	1396	1317	1242	1190	1141	871	568



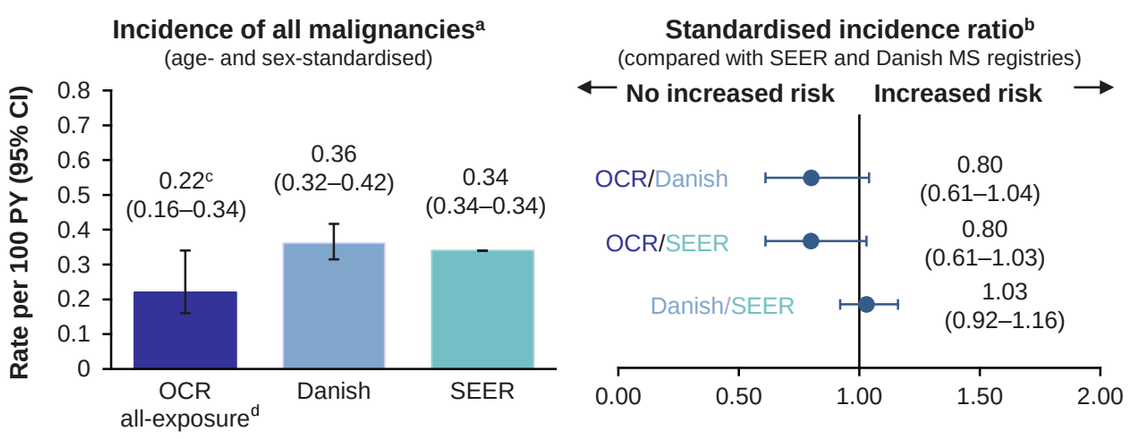
Years	1	2	3	4	5	6	7	8[e]
Exposure (PY)	635	610	575	536	475	347	322	290
Event rate (per 100 PY)	2.993	3.280	4.348	4.102	4.632	4.902	6.827	5.855
Number of SIs n	19	20	25	22	22	17	22	17
	644	626	594	557	513	371	333	308

The most frequently reported SIs overall were consistent with the frequently reported SIs reported for each year.
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. The majority of SIs were typical in character, resolved, and were not treatment limiting.

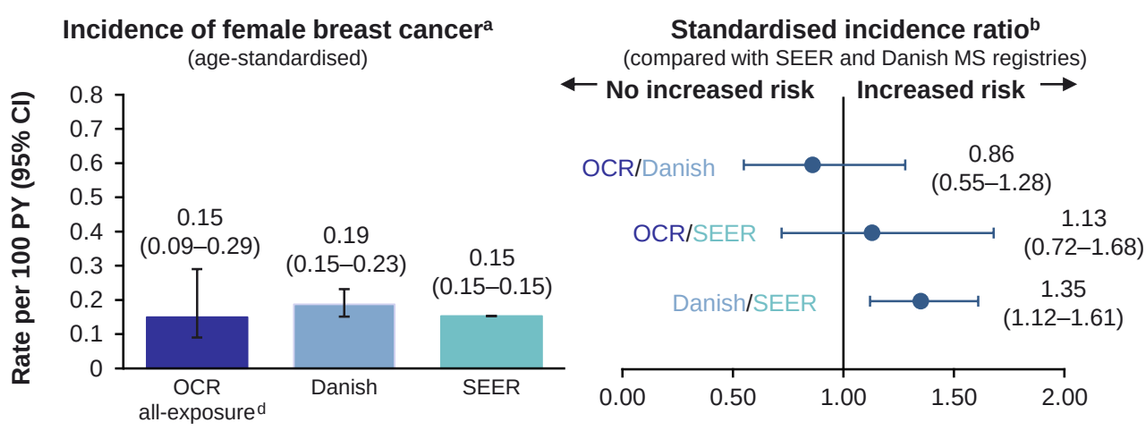
[a]Fatal SIs included urosepsis (n=1), encephalitis (n=1) and pneumonia (n=2); [b]Grade 1 (mild): asymptomatic or mild symptoms/clinical or diagnostic observation only/intervention not indicated; Grade 2 (moderate): minimal, local or noninvasive intervention indicated/ limiting age appropriate instrumental 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); [c]SIs leading to withdrawal included encephalitis (n=2), sepsis (n=2), UTI (n=2), acute hepatitis C (n=1), anal abscess (n=1), bronchitis (n=1), *Clostridium Difficile* colitis (n=1), Herpes Zoster (n=1), infection (n=1), large intestine infection (n=1), mastoiditis (n=1), pneumonia (n=1), viral infection (n=1), septic shock (n=1); [d]Rates of infection-related hospitalizations (1.88 per 100 PY; 95% CI 1.77–2.01) in the British Columbia registry[1] are shown for epidemiological reference; [e]The exposure in PY during Year 8 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.
ADL, Activities of Daily Living; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive MS; PY, patient-years; RMS, relapsing MS; RRMS, relapsing-remitting MS; SI, serious infection; UTI, urinary tract infection.

>8 Years — Over 8 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. Incidence of All Malignancies (Age- and Sex-Standardised)



B. Incidence of Female Breast Cancer (Age-Standardised)



[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 2000 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; [d]OCR all-exposure population.
CTP, controlled-treatment period; IFN, interferon; MS, multiple sclerosis; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; PY, patient years; SEER, Surveillance, Epidemiology and End Results; SIR, standardised incidence ratio.

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