Safety of Ocrelizumab in Multiple Sclerosis: Up to 11 Years of Updated Analysis in Patients with Relapsing and Progressive Multiple Sclerosis

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*During completion of the work related to this presentation, V Punia was an employee of Genentech, Inc. and is now employed by AbbVie, Inc.

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OBJECTIVE

To investigate the long-term safety profile of ocrelizumab across 13 clinical trials up to November 2023

KEY TAKEAWAYS

Over an >11-year follow-up period in clinical trials, ocrelizumab continues to exhibit a stable and favourable safety profile in both RMS and PMS populations

Withdrawal due to AEs was infrequent and did not increase over time

SIs remained infrequent, with rates and types similar to those observed in real-world cohorts[1–3]

- Approximately 90% of SIs resolved and the majority of patients remained on treatment with ocrelizumab
- IgG levels remained above the LLN for >80% of patients with RMS and PPMS. During episodes of IgG<LLN, the type, severity and outcome of SIs were consistent with the overall SIs observed in patients treated with ocrelizumab during the controlled period and OLE phase

INTRODUCTION

- As of March 2024, over 350,000 patients with MS had started OCR globally (amounting to >1 million PY of exposure)
- OCR safety has been characterised in patients with RMS and PPMS in Phase II (NCT00676715) and Phase III clinical trials (NCT01247324, NCT01412333, NCT01194570) and their OLE periods
- The long-term safety and benefit–risk profile of OCR continues to be evaluated via regular safety reporting of clinical trial and post-marketing data

RESULTS

Treatment Exposure Summary

	All RMS (n=4,558)[a]	All PMS (n=1,597)[b]	OPERA (RMS) (n=1,448)	ORATORIO (PPMS) (n=644)
Age at the start of treatment, median (min–max), years	35.0 (18–65)	49.0 (19–66)	38.0 (18–58)	47.0 (20–59)
Total patient years	22,482	7,914	11,461	4,911
Overall duration, years				
Median (IQR)	3.9 (2.2–6.9)	4.1 (2.5–6.9)	9.0 (6.2–10.6)	7.9 (4.8–11.0)
Min–max	0.0–13.9	0.0–12.5	0.0–12.2	0.1–12.5
Number of doses				
Median (IQR)	8 (4–14)	8 (5–14)	20 (12–23)	17 (9–24)
Min–max	1–27	1–28	1–27	1–28

- As of November 2023, 6,155 patients with MS across 13 clinical trials were treated with OCR (amounting to 30,396 PY of exposure)
- ~60% of patients received ≥8 doses, representing ≥4 years of continuous OCR treatment and ~31% of patients received ≥14 doses, representing ≥7 years of continuous OCR treatment

Data cut-off: November 2023. Doses were administered every 6 months.
Limitations inherent in all long-term, observational, open-label extension studies of DMTs remain pertinent (e.g. possible attrition bias due to temporal decrease in patient numbers).
[a]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 2023); [b]Includes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of ORATORIO, OBOE, CONSONANCE and OLERO. Includes patients with PPMS (n=1,076) and SPMS (n=521); see Supplementary Material for further clinical trial information.

Over >11 Years of Continuous OCR Treatment, the Overall Safety Profile Remained Consistent with That Observed in the Controlled Treatment Period of the Pivotal Phase III Trials

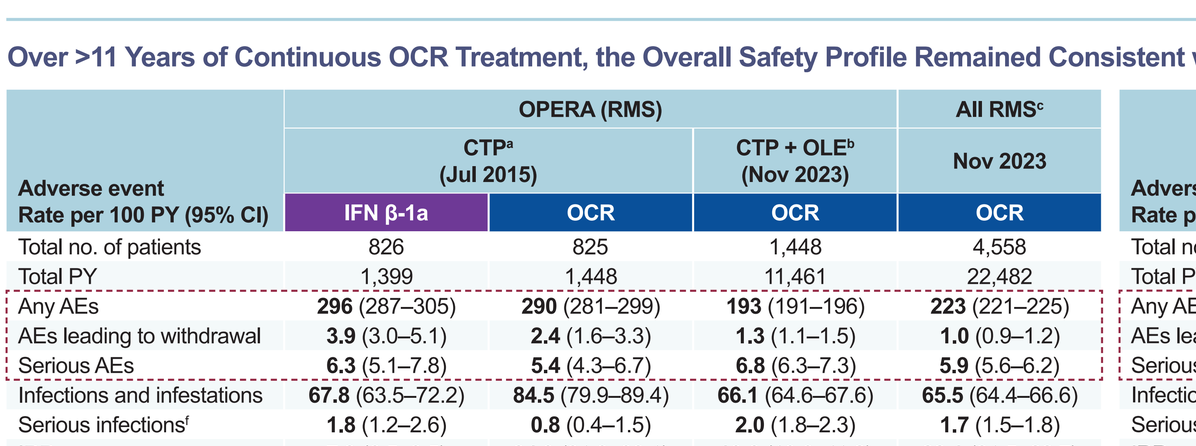
Adverse event Rate per 100 PY (95% CI)	OPERA (RMS) CTP[a] (Jul 2015) IFN β-1a	OPERA (RMS) CTP[a] (Jul 2015) OCR	OPERA (RMS) CTP + OLE[b] (Nov 2023) OCR	All RMS[c] Nov 2023 OCR
Total no. of patients	826	825	1,448	4,558
Total PY	1,399	1,448	11,461	22,482
Any AEs	**296** (287–305)	**290** (281–299)	**193** (191–196)	**223** (221–225)
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)
Serious AEs	**6.3** (5.1–7.8)	**5.4** (4.3–6.7)	**6.8** (6.3–7.3)	**5.9** (5.6–6.2)
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**66.1** (64.6–67.6)	**65.5** (64.4–66.6)
Serious infections[f]	**1.8** (1.2–2.6)	**0.8** (0.4–1.5)	**2.0** (1.8–2.3)	**1.7** (1.5–1.8)
IRRs	**7.9** (6.5–9.5)	**34.9** (31.9–38.1)	**10.6** (10.0–11.2)	**22.1** (21.5–22.7)
Malignancies[g,h]	**0.1** (0.0–0.5)	**0.3** (0.1–0.7)	**0.5** (0.4–0.6)	**0.4** (0.3–0.5)
Deaths	**0.1** (0.0–0.5)	**0.1** (0.0–0.4)	**0.1** (0.1–0.2)	**0.1** (0.1–0.2)

Adverse event Rate per 100 PY (95% CI)	ORATORIO (PPMS) CTP[a] (Jul 2015) Placebo	ORATORIO (PPMS) CTP[a] (Jul 2015) OCR	ORATORIO (PPMS) CTP + OLE[b] (Nov 2023) OCR	All PMS[d] Nov 2023 OCR	All OCR trials MS all-exposure population[e]
Total no. of patients	239	486	644	1,597	6,155
Total PY	729	1,606	4,911	7,914	30,396
Any AEs	**259** (247–271)	**252** (244–260)	**221** (217–225)	**213** (210–216)	**220** (219–222)
AEs leading to withdrawal	**1.1** (0.5–2.2)	**1.2** (0.8–1.9)	**1.1** (0.8–1.4)	**1.0** (0.8–1.2)	**1.0** (0.9–1.1)
Serious AEs	**12.1** (9.7–14.9)	**10.2** (8.7–11.8)	**12.9** (11.9–13.9)	**10.8** (10.1–11.5)	**7.2** (6.9–7.5)
Infections and infestations	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)	**69.7** (67.4–72.0)	**60.8** (59.0–62.5)	**64.3** (63.4–65.2)
Serious infections[f]	**3.0** (1.9–4.6)	**2.7** (2.0–3.7)	**4.5** (4.0–5.2)	**3.7** (3.3–4.1)	**2.2** (2.0–2.4)
IRRs	**20.3** (17.2–23.8)	**31.0** (28.3–33.9)	**16.0** (14.9–17.2)	**15.7** (14.8–16.6)	**20.4** (19.9–20.9)
Malignancies[g,h]	**0.3** (0.0–1.0)	**0.9** (0.5–1.5)	**1.0** (0.8–1.3)	**0.9** (0.7–1.1)	**0.5** (0.4–0.6)
Deaths	**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** (0.2–0.3)

COVID-19–related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs.
[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 PBO) who switched to open-label OCR treatment (data as of November 2023); [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 2023); [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 2023); [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 PBO) who switched to open-label OCR treatment (data as of November 2023); [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; [i]see Supplementary Material for reasons for treatment discontinuation.

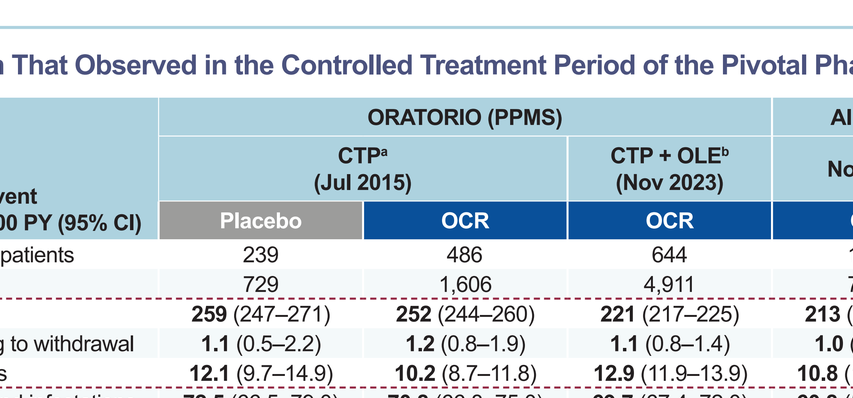
- Cumulative AE and serious AE incidence rates remained consistent with the rates observed during the CTP
- Withdrawal due to AEs was infrequent and did not increase over time[i]

SIs Remain Infrequent with Rates Consistent with Ranges in Real-World Studies[1,2]



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).
[a]Cumulative rates of SIs over a median period of 3.9 years (2016–2019) in a German claims database.[1] For comparability, the rates were calculated in a subpopulation of patients with RMS and PMS up to the age of 64 years.

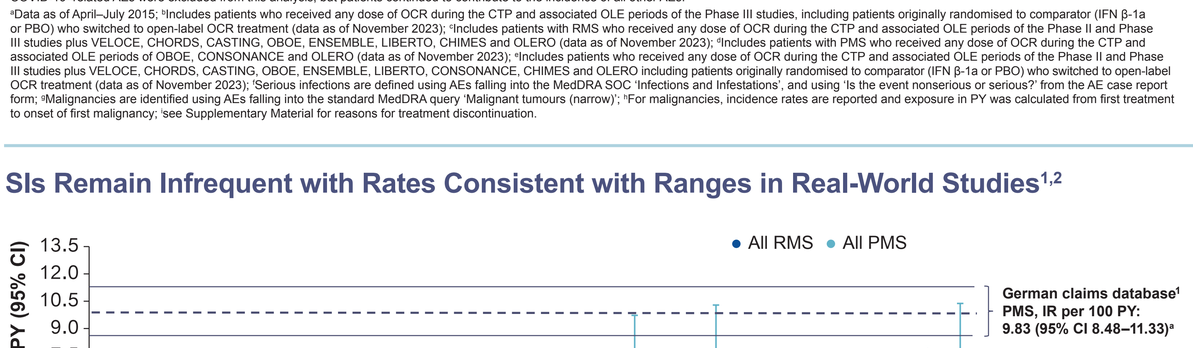
Outcome, Duration and Action Taken with OCR



n indicates the number of events.
COVID-19–related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs. Percentages may not total 100% due to rounding.
[a]Fatal cases are not included.

- In the RMS and PMS populations, most SIs had resolved without sequelae and within ≤2 weeks and most patients remained on treatment with OCR

LRTIs (Mostly Pneumonia) and UTIs Were the Most Commonly Reported Types of SIs



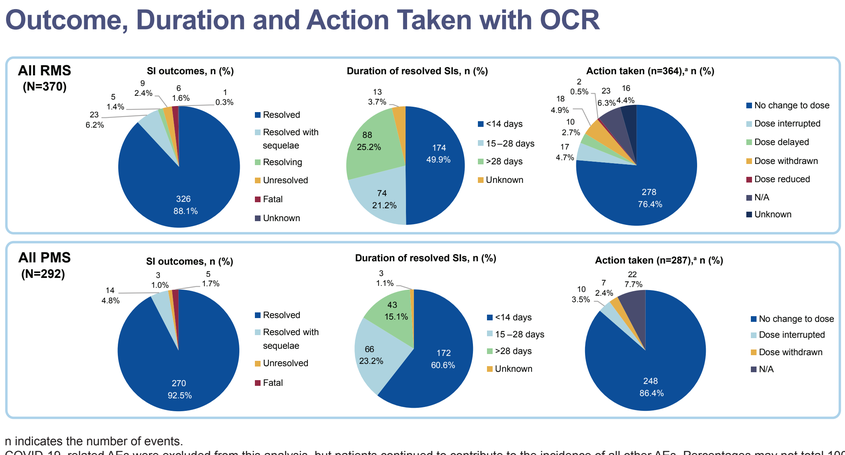
- Respiratory, genitourinary and GI infections are also the most common types of SIs reported in real-world MS cohorts[1,3]

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]Pneumonia was the most frequently reported Preferred Term; [b]These are medical concepts not MedDRA Preferred Terms. Similar AEs were grouped using MedDRA Term Selection and Standardized MedDRA Queries and were used as screening tools to allow for identification of potential types of infections.

SIs Associated with Low IgG Levels by MS Type: OPERA (RMS) and ORATORIO (PPMS)

- Following long-term treatment, IgG levels remained above the LLN for >80% of patients with RMS and PPMS
- During a period with IgG<LLN, 2.0% of patients with RMS and 1.9% of patients with PPMS had an SI
- UTIs, LRTIs, sepsis, abdominal and GI infections, and skin infections were the most common SIs associated with episodes of IgG<LLN, a pattern similar to overall SIs

IgG<LLN and SIs: Outcome and Action Taken with OCR



n indicates the number of events.
COVID-19–related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs. Percentages may not total 100% due to rounding.
SI and IgG analyses are presented for the Phase III OPERA (RMS) and ORATORIO (PPMS) populations only.

- During periods of IgG<LLN, there were no fatal events and most SIs resolved and treatment with OCR was continued in almost all cases

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1. Knapp R, *et al. Mult Scler Relat Disord* 2022;68:104245.
2. Wijnands JMA, *et al. J Neurol Neurosurg Psychiatry* 2018;89:1050–1056.
3. Wijnands JMA, *et al. Mult Scler* 2017;23:1506–1516.

ABBREVIATIONS

AE, adverse event; **CNS**, central nervous system; **COVID-19**, coronavirus disease 2019; **CTP**, controlled treatment period; **DMT,** disease-modifying therapy; **GI**, gastrointestinal; **IFN**, interferon; **IgG**, immunoglobulin G; **IQR**, interquartile range; **IR,** incidence rate; **IRR**, infusion-related reaction; **LLN**, lower limit of normal; **LRTI**, lower respiratory tract infection; **Max**, maximum; **MedDRA**, Medical Dictionary for Regulatory Activities; **Min**, minimum; **MS**, multiple sclerosis; **N/A**, not applicable; **OCR**, ocrelizumab; **OLE**, open-label extension; **PBO**, placebo; **PMS**, progressive multiple sclerosis; **PPMS**, primary progressive multiple sclerosis; **PY**, patient years; **RMS**, relapsing multiple sclerosis; **SI**, serious infection; **SOC**, System Organ Class; **SPMS**, secondary progressive multiple sclerosis; **URTI**, upper respiratory tract infection; **UTI**, urinary tract infection.

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DISCLOSURES

SL Hauser serves on the scientific advisory boards of Accure, Alector and Annexon. He has previously consulted for BD, Moderna, NGM Bio and Pheno Therapeutics, and previously served on the Board of Directors of Neurona. Dr Hauser has also received travel reimbursement and writing support from F. Hoffmann-La Roche Ltd and Novartis AG for anti-CD20 therapy–related meetings and presentations.

L Kappos has received no personal compensation. His institutions (University Hospital Basel/Foundation Clinical Neuroimmunology and Neuroscience Basel) have received and used exclusively for research the following support: Payments for steering committee and advisory board participation, consultancy services and participation in educational activities from Actelion, Bayer, Bristol Myers Squibb, df-mp Molnia & Pohlmann, Celgene, Eli Lilly, EMD Serono, Genentech, Inc., GlaxoSmithKline, Janssen, Japan Tobacco, Merck, MH Consulting, Minoryx, Novartis, F. Hoffmann-La Roche Ltd, Senda Biosciences Inc., Sanofi, Santhera, Shionogi B.V., TG Therapeutics and Wellmera; license fees for Neurostatus-UHB products; and grants from Novartis, Innosuisse and Roche.

X Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with AbbVie, Actelion, Alexion, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, F. Hoffmann-La Roche Ltd, Immunic, Janssen, MedDay, Merck, Mylan, NervGen, Novartis, Sandoz, Sanofi-Genzyme, Teva, TG Therapeutics, Exemed, MSIF and NMSS.

C Chognot, N Pasquarelli and **B El Azzouzi** are employees of and shareholders in F. Hoffmann-La Roche Ltd.

V Punia was an employee of and shareholder in Genentech, Inc. and is now an employee of AbbVie, Inc.

E Incera has received consultancy fees from F. Hoffmann-La Roche Ltd for statistical assistance; and is an employee of IQVIA Inc.

JS Wolinsky has received personal compensation for consulting, serving on scientific advisory boards, other activities with Cleveland Clinic Foundation, EMD Serono, Inmagene, Novartis, F. Hoffmann-La Roche Ltd/Genentech, Sandoz and Zenas Pharma; royalties are received for out-licensed monoclonal antibodies through UTHealth.

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Supplementary Material

Table of Contents

METHODS

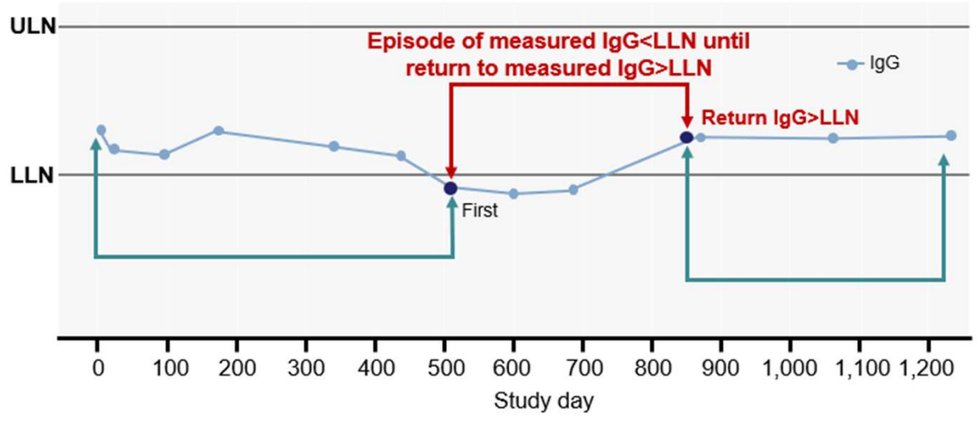
Safety Analyses Were Based on Integrated Data for All Patients Who Received OCR in the Phase III RMS/PPMS and MS All-Exposure MS Clinical Trials

Safety analyses were based on integrated data for all patients who received OCR in the following MS clinical trials:[a]

- **Phase III RMS** (comprising the DBP and OLE periods of pooled OPERA I/II studies)[b]
- **Phase III PPMS** (comprising the ORATORIO DBP and OLE period)[b]
- **MS all-exposure** (Phase II and Phase III MS clinical trials DBP and associated OLE periods, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO,[c] CONSONANCE, OLERO and CHIMES)

- The number of post-marketing OCR-treated patients was based on the estimated number of vials sold and US claims data
- AEs were classified according to the MedDRA, and the rates of AEs were expressed per 100 PY
- The single-drop method was used to examine the risk of SIs during the period of IgG below the LLN compared with the risk of SIs during the period of IgG ≥LLN[1]

Exposure of single-drop IgG<LLN and occurrence of SIs[1]

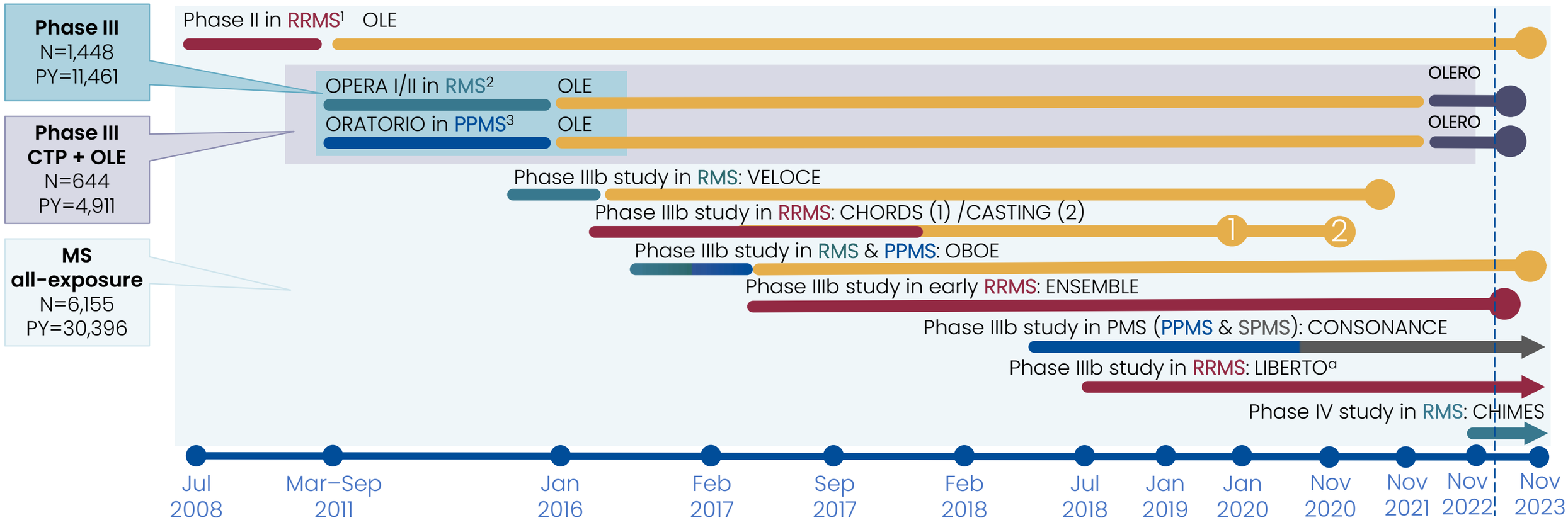


[a]Study name (NCT number) of studies included as of November 2023: Phase II (NCT00676715), OPERA I (NCT01247324), OPERA II (NCT01412333), ORATORIO (NCT01194570), VELOCE (NCT02545868), CHORDS (NCT02637856), CASTING (NCT02861014), OBOE (NCT02688985), ENSEMBLE (NCT03085810), LIBERTO (NCT03599245), CONSONANCE (NCT03523858), OLERO (NCT05269004), CHIMES (NCT04377555); [b]Upon completion of the CTP, patients were eligible to receive OCR in OLEs. In ORATORIO, following completion of the DBP, patients could enter the OLE, via an ECP; [c]LIBERTO is the long-term extension study to CASTING and ENSEMBLE.
AE, adverse event; COVID-19, coronavirus disease 2019; CTP, controlled-treatment period; DBP, double-blind period; ECP, extended-controlled period; IgG, immunoglobulin G; MedDRA, Medical Dictionary for Regulatory Activities; LLN, lower limit of normal; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PY, patient years, SI, serious infection.

1. Cerqueira JJ, *et al. AAN* 2023;Oral presentation number 002–S46.

RESULTS

As of November 2023, 6,155 Patients with Different MS Phenotypes Had Received OCR Across 13 Clinical Trials (Amounting to 30,396 PY of Exposure)



As of March 2024, over 350,000 patients with MS had started OCR globally (amounting to >1 million PY of exposure)[4]

A dot indicates a study's completion date.
[a]LIBERTO is the long-term extension study to CASTING and ENSEMBLE.
CTP, controlled-treatment period; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PMS; progressive MS; PPMS, primary progressive MS; PY, patient years; RMS, relapsing MS; RRMS, relapsing-remitting MS.
1. Kappos L, *et al. Lancet* 2011;378:1779–1787; 2. Hauser SL, *et al. N Engl J Med* 2017;376:221–234; 3. Montalban X, *et al. N Engl J Med* 2017;376:209–220; 4. Roche data on file: post-marketing experience and clinical trials (data cut-off March 2024).

RESULTS
Treatment Exposure by Number of Doses

	RMS all-exposure population (n=4,558)[a]	PMS all-exposure population (n=1,597)[b]	MS all-exposure (N=6,155)[c]
Number of doses, n (%)	Number of patients	Number of patients	Number of patients
≥1	4,558 (100)	1,597 (100)	6,155 (100)
≥2	4,426 (97.1)	1,552 (97.2)	5,978 (97.1)
≥3	4,323 (94.8)	1,519 (95.1)	5,842 (94.9)
≥4	4,161 (91.3)	1,458 (91.3)	5,619 (91.3)
≥5	3,382 (74.2)	1,316 (82.4)	4,698 (76.3)
≥6	3,021 (66.3)	1,188 (74.4)	4,209 (68.4)
≥7	2,871 (63.0)	1,077 (67.4)	3,948 (64.1)
≥8	2,754 (60.4)	975 (61.1)	3,729 (60.6)
≥9	1,996 (43.8)	508 (31.8)	2,504 (40.7)
≥10	1,924 (42.2)	492 (30.8)	2,416 (39.3)
≥11	1,679 (36.8)	461 (28.9)	2,140 (34.8)
≥12	1,450 (31.8)	447 (28.0)	1,897 (30.8)
Number of doses, median (IQR)	8.0 (4.0–14.0)	8.0 (5.0–14.0)	8.0 (5.0–14.0)

[a]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 2023); [b]Includes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of ORATORIO, OBOE, CONSONANCE and OLERO; [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, CHIMES, CONSONANCE and OLERO, including patients originally randomised to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment.
CTP, controlled-treatment period; IFN, interferon; IQR, interquartile range; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PMS, progressive MS; RMS, relapsing MS.

RESULTS

Accounting for the COVID-19 Pandemic, Over >11 Years of Continuous OCR Treatment, the Overall Safety Profile Remained Consistent with the CTP

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 2023)		Nov 2023		CTP[a] (Jul 2015)		CTP + OLE[b] (Nov 2023)		Nov 2023		MS all-exposure population[e]	MS all-exposure population[e] (Ex-COVID-19)
	IFN β-1a	OCR	OCR	OCR (Ex-COVID-19)	OCR	OCR (Ex-COVID-19)	Placebo	OCR	OCR	OCR (Ex-COVID-19)	OCR	OCR (Ex-COVID-19)		
Total no. of patients	826	825	1,448	1,448	4,558	4,558	239	486	644	644	1,597	1,597	6,155	6,155
Total PY	1,399	1,448	11,461	11,461	22,482	22,482	729	1,606	4,911	4,911	7,914	7,914	30,396	30,396
Any AEs	**296** (287–305)	**290** (281–299)	**199** (197–202)	**193** (191–196)	**229** (227–231)	**223** (221–225)	**259** (247–271)	**252** (244–260)	**226** (221–230)	**221** (217–225)	**221** (218–224)	**213** (210–216)	**227** (225–229)	**220** (219–222)
AEs leading to withdrawal	**3.9** (3.0–5.1)	**2.4** (1.6–3.3)	**1.3** (1.1–1.5)	**1.3** (1.1–1.5)	**1.1** (0.9–1.2)	**1.0** (0.9–1.2)	**1.1** (0.5–2.2)	**1.2** (0.8–1.9)	**1.1** (0.8–1.4)	**1.1** (0.8–1.4)	**1.0** (0.8–1.3)	**1.0** (0.8–1.2)	**1..0** (0.9–1.2)	**1.0** (0.9–1.1)
Serious AEs	**6.3** (5.1–7.8)	**5.4** (4.3–6.7)	**7.8** (7.3–8.3)	**6.8** (6.3–7.3)	**6.7** (6.4–7.1)	**5.9** (5.6–6.2)	**12.1** (9.7–14.9)	**10.2** (8.7–11.8)	**14.1** (13.1–15.2)	**12.9** (11.9–13.9)	**12.2** (11.4–13.0)	**10.8** (10.1–11.5)	**8.2** (7.8–8.5)	**7.2** (6.9–7.5)
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**71.9** (70.4–73.5)	**66.1** (64.6–67.6)	**71.7** (70.6–72.8)	**65.5** (64.4–66.6)	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)	**74.2** (71.9–76.7)	**69.7** (67.4–72.0)	**68.9** (67.0–70.7)	**60.8** (59.0–62.5)	**71.0** (70.0–71.9)	**64.3** (63.4–65.2)
Serious infections[f]	**1.8** (1.2–2.6)	**0.8** (0.4–1.5)	**3.1** (2.8–3.4)	**2.0** (1.8–2.3)	**2.5** (2.3–2.7)	**1.7** (1.5–1.8)	**3.0** (1.9–4.6)	**2.7** (2.0–3.7)	**5.8** (5.1–6.5)	**4.5** (4.0–5.2)	**5.1** (4.6–5.6)	**3.7** (3.3–4.1)	**3.2** (3.0–3.4)	**2.2** (2.0–2.4)
Deaths	**0.1** (0.0–0.5)	**0.1** (0.0–0.4)	**0.3** (0.2–0.4)	**0.1** (0.1–0.2)	**0.3** (0.2–0.4)	**0.1** (0.1–0.2)	**0.4** (0.1–1.2)	**0.3** (0.1–0.6)	**0.6** (0.4–0.9)	**0.5** (0.3–0.7)	**0.6** (0.4–0.8)	**0.4** (0.3–0.6)	**0.4** (0.3–0.4)	**0.2** (0.2–0.3)

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 2023); [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 2023); [d]Includes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of OBOE, ORATORIO, CONSONANCE and OLERO (data as of November 2023). [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 2023); [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.
AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; CTP, controlled-treatment period; Ex, excluding; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive MS; PPMS, primary progressive MS; PY, patient years; RMS, relapsing MS; SOC, system organ class.

RESULTS
Withdrawal Due to Adverse Events Was Infrequent

	OCR all-exposure (N=6,155)[a]
Discontinued treatment, n (%)	1,427 (23.2)
Adverse event	240 (3.9)
Commercial OCR	4 (<0.1)
Death	74 (1.2)
Lack of efficacy	101 (1.6)
Lost to follow-up	78 (1.3)
Noncompliance	17 (0.3)
Noncompliance with study drug	5 (<0.1)
Other	259 (4.2)
Patient discontinuing treatment with other DMT(s) outside the study	1 (<0.1)
Physician decision	107 (1.7)
Pregnancy	44 (0.7)
Protocol deviation	6 (<0.1)
Protocol violation	7 (0.1)
Study terminated by sponsor	10 (0.2)
Unknown	3 (<0.1)
Withdrawal by patient	471 (7.7)

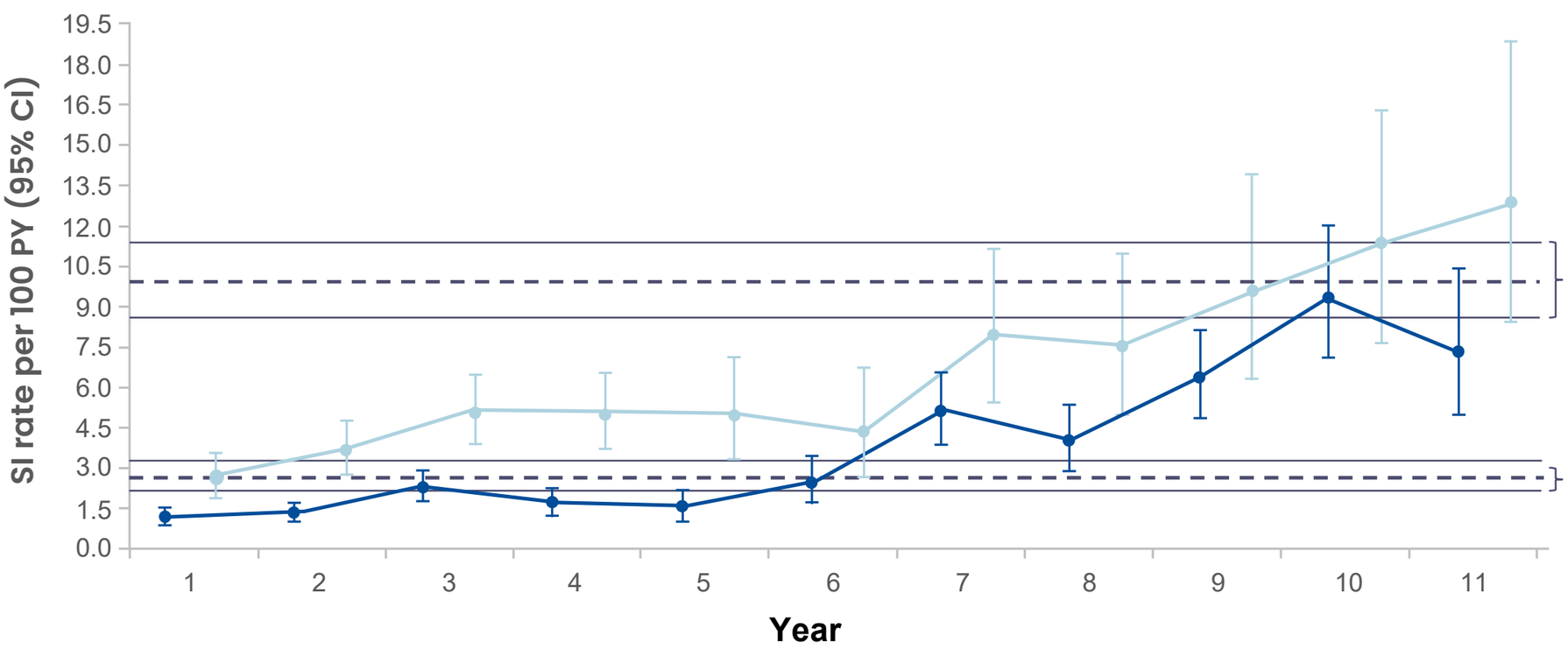
[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES, CONSONANCE and OLERO, including patients originally randomised to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment.
CTP, controlled-treatment period; DMT, disease-modifying therapy; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

Infections

RESULTS

Figure to be DC

When Accounting for COVID-19, the SI Rates Fluctuated Over Time and Remained Within the Ranges Reported in Real-World Studies[1,2]



Exposure (PY)	4,500	4,236	3,207	2,749	1,904	1,409	1,160	1,104	964	643	422
No. of AEs	53	56	73	46	29	35	59	44	61	60	31
Exposure (PY)	1,576	1,456	1,209	1,028	588	460	416	358	283	255	202
No. of AEs	41	53	61	51	29	20	33	27	27	29	26

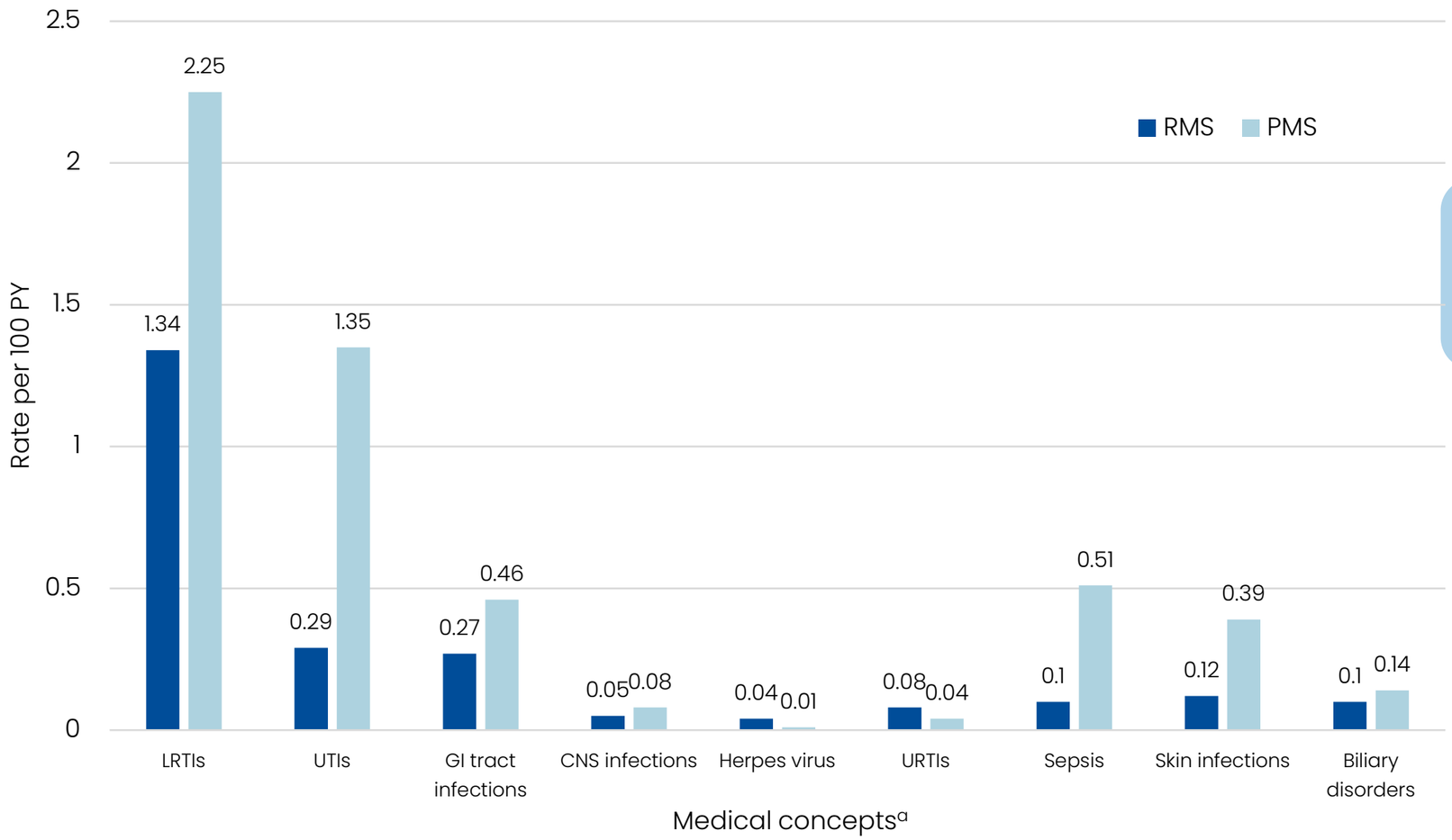
German claims database covers a period of 3.9 years before the COVID-19 pandemic

[a]Cumulative rates of SIs over a median period of 3.9 years (2016–2019) in a German claims database.[2] For comparability, the rates were calculated in a subpopulation of patients with RMS and PMS up to the age of 64 years.
CI, confidence interval; IR, incidence rate; MS, multiple sclerosis; OCR, ocrelizumab; PMS; progressive MS; PY, patient years; RMS, relapsing MS; SI, serious infection; UTI, urinary tract infection.

1. Wijnands JMA, *et al. J Neurol Neurosurg Psychiatry* 2018;89:1050–1056; 2. Knapp R, *et al. Mult Scler Relat Disord* 2022;68:104245.

RESULTS

LRTIs (Mostly COVID-19 Pneumonia and Pneumonia) and UTIs Remained the Most Commonly Reported Types of SIs



COVID-19 pneumonia and COVID-19 were frequently observed SIs in line with the pandemic

[a]These are medical concepts not MedDRA Preferred Terms. Similar AEs were grouped using MedDRA Term Selection and Standardized MedDRA Queries and were used as screening tools to allow for identification of potential type of infections.

GI, gastrointestinal; CNS, central nervous system; LRTI, lower respiratory tract infection; MS, multiple sclerosis; OCR, ocrelizumab; PMS, progressive MS; RMS, relapsing MS; SI; serious infection; URTI, upper respiratory tract infection; UTI, urinary tract infection.

RESULTS
The Rate of Potential Serious Opportunistic Infections Was Low

Over an >11-year follow-up period, in the MS all-exposure population, the rate per 100 PY of potential serious opportunistic infections was low, at a rate of 0.03 per 100 PY (95% CI 0.01–0.06)

No cases of fever of unknown origin, cryptococcosis, aspergillosis, listeriosis, toxoplasmosis, cytomegalovirus infection or progressive multifocal leukoencephalopathy had been reported up to November 2023

CCOD: November 2023.
Potential opportunistic infections were retrieved according to the medical concept of opportunistic infection based on the World Health Organization Standardised MedDRA Queries.
CCOD, clinical cut-off date; CI, confidence interval; MS multiple sclerosis; OCR, ocrelizumab; PY, patient years.

RESULTS
The Risk of PML with OCR Treatment Remains Low

The reported PML incidence rate remains approximately **one case per 100,000 patients**, with the overall **benefit-risk profile of OCR remaining unchanged**[1,2]

16 confirmed PML cases[3] (all in post-marketing setting)

in >350,000 OCR-treated patients globally[4]

- 12 carry-over cases attributed to prior exposure to DMTs causally associated with PML
- Four non–carry-over cases
  - One non–carry-over case was **confounded by advanced age and lymphopenia**
  - Three non–carry-over cases reported where a **potential causal association with OCR** may exist

All of the 16 confirmed cases occurred outside of clinical trials in the post-marketing setting

If PML is suspected, OCR must be withheld[5,6]

For further information, including the clinical case histories of the 4 non–carry-over cases, see https://www.ocrelizumabinfo.global/en/homepage/safety-topics/progressive-multifocal.html.
DMT, disease-modifying therapy; OCR, ocrelizumab; PML, progressive multifocal leukoencephalopathy.
1. Hauser SL, *et al. ECTRIMS* 2023;Poster P304; 2. Roche data on file: Ocrevus CDS version 12.07; 3. Roche data on file: OCR and PML; 4. Roche data on file: post-marketing experience and clinical trials (data cut-off March 2024);
5. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2024; 6. OCREVUS [ocrelizumab] Summary of Product Characteristics. Roche Pharma AG, 2022.

Malignancies

METHODS
Malignancies

Age- and sex-standardised incidence rates of all malignancies (excluding NMSC) and age-standardised incidence rates of female breast cancer, were compared with rates from real-world epidemiological sources, both MS specific (Danish MS Registry)[1] and for the general population (NCI SEER database)[2]

The standardised incidence ratios, calculated as the observed/expected number of events, were determined for all malignancies (excluding NMSC) and female breast cancer, using SEER and Danish MS Registry data as reference populations

MS, multiple sclerosis; NCI, National Cancer Institute; NMSC, nonmelanoma skin cancer; SEER, Surveillance, Epidemiology and End Results.

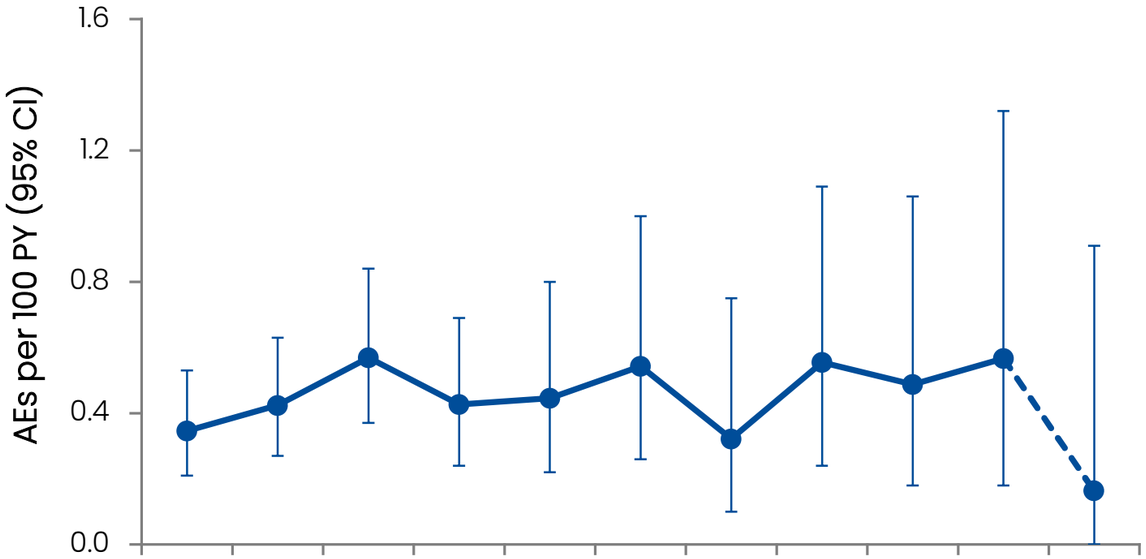
1. Nørgaard M, *et al. Mult Scler Relat Disord* 2019;28:81–85; 2. National Institutes of Health (NIH). Available from: https://seer.cancer.gov.

RESULTS

Over 11 Years of Treatment, Longer Exposure to OCR Did Not Lead to an Increase in the Yearly Incidence Rate

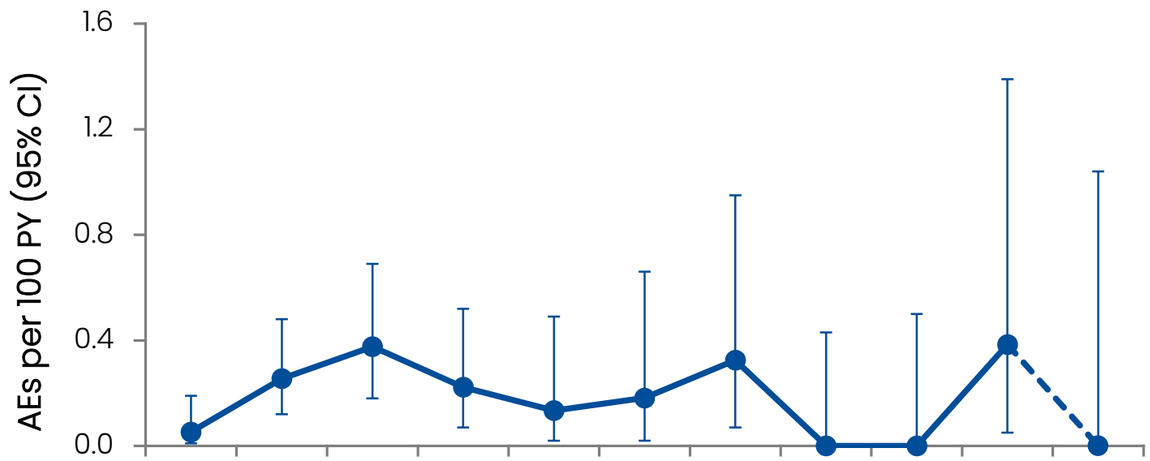
Yearly crude incidence rates of all malignancies including NMSC, and female breast cancer in the MS all-exposure population remained stable over time

All malignancies[a]



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11
Patients (n)	6,155	5,963	4,807	4,069	2,993	2,045	1,610	1,499	1,343	1,041	761
PY	6,065	5,666	4,391	3,743	2,467	1,842	1,551	1,441	1,229	881	613
No. of events	21	24	25	16	11	10	5	8	6	5	1

Female breast cancer[a]



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11
Patients (n)	3,857	3,729	2,940	2,447	1,806	1,229	957	894	806	625	441
PY	3,795	3,525	2,661	2,240	1,488	1,101	924	861	735	521	356
No. of events	2	9	10	5	2	2	3	0	0	2	0

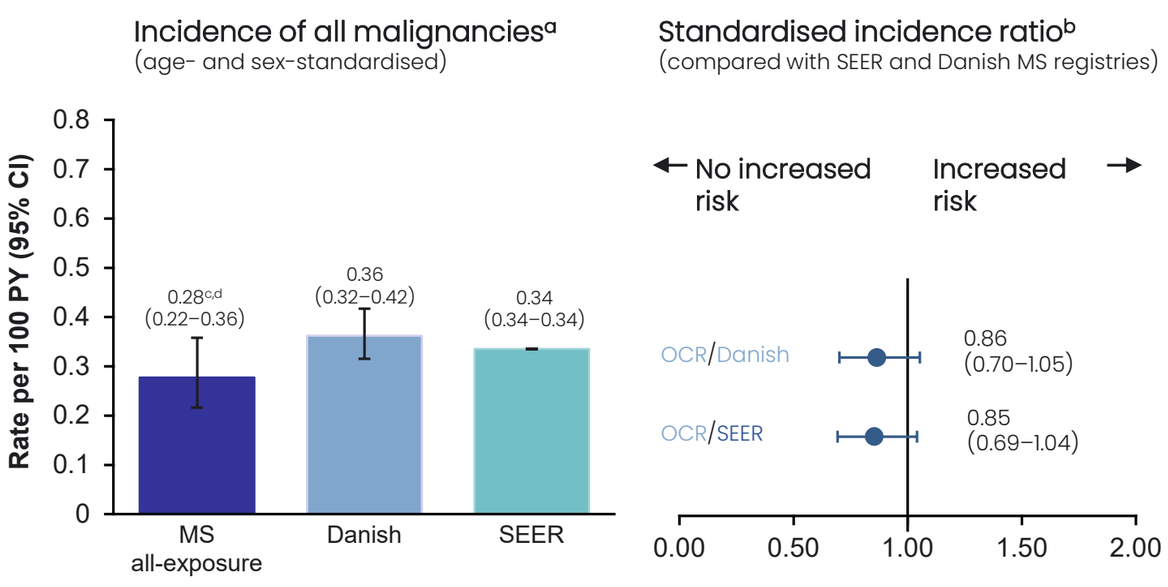
[a]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES, CONSONANCE and OLERO, including patients originally randomised to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment.

AE, adverse event; CI, confidence interval; CTP, controlled-treatment period; IFN, interferon; MS, multiple sclerosis; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PY, patient years; SEER, Surveillance, Epidemiology and End Results.

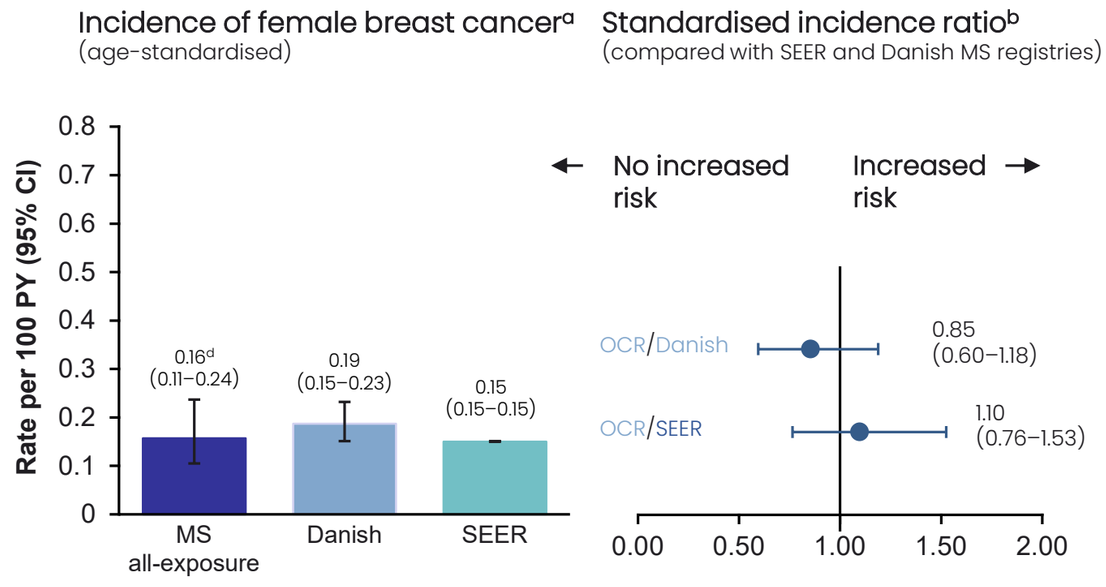
RESULTS

Incidence Rates of All Malignancies and Female Breast Cancer Were Within the Ranges Reported in Real-World MS Cohorts and the General Population[1,2]

Incidence of all malignancies (Age- and sex-standardised)



Incidence of female breast cancer (Age-standardised)



[a]Standardised incidence rates per 100 PY (95% CI) were were reported to allow comparison with the SEER database and the Danish MS Registry, using the direct standardisation method that applies age–sex specific rates to the USA 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]For all malignancies, cases of NMSC were excluded from the MS all-exposure population to allow a comparison with the SEER database; [d]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, CONSONANCE and OLERO, including patients originally randomised to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment.

CI, confidence interval; CTP, controlled-treatment period; IFN, interferon; MS, multiple sclerosis; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PY, patient years; SEER, Surveillance, Epidemiology and End Results; SIR, standardized incidence ratio.

1. Nørgaard M, *et al. Mult Scler Relat Disord* 2019;28:81–85; 2. National Institutes of Health (NIH). Available from: https://seer.cancer.gov.

RESULTS
Malignancy Overview: MS All-Exposure

MeDRA system organ class (MeDRA preferred term)	MS all-exposure[a] (N=6,155) (PY=30,155) Patients (patients per 100 PY) [95% CI]
Overall total number of patients	136 (0.451) [0.378–0.533]
Neoplasms benign, malignant and Unspecified (incl cysts and polyps)	136 (0.451) [0.378–0.533]
Basal cell carcinoma	32 (0.106) [0.073–0.150]
Breast cancer Breast cancer Invasive ductal breast carcinoma Invasive breast carcinoma	 13 (0.043) [0.023–0.074] 13 (0.043) [0.023–0.074] 2 (0.007) [0.001–0.024]
Melanoma Malignant melanoma Malignant melanoma *in situ*	 8 (0.027) [0.011–0.052] 2 (0.007) [0.001–0.024]
Prostate cancer	6 (0.020) [0.007–0.043]
Lung cancer Lung adenocarcinoma Lung neoplasm malignant	 4 (0.013) [0.004–0.034] 4 (0.013) [0.004–0.034]
Bladder cancer	3 (0.010) [0.002–0.029]
Papillary thyroid cancer	3 (0.010) [0.002–0.029]
Adenocarcinoma of the cervix	2 (0.007) [0.001–0.024]
Bowen's disease	2 (0.007) [0.001–0.024]
Colon cancer	2 (0.007) [0.001–0.024]
Neuroendocrine tumour	2 (0.007) [0.001–0.024]
Pancreatic carcinoma metastatic	2 (0.007) [0.001–0.024]
Renal cancer	2 (0.007) [0.001–0.024]
Renal cell carcinoma	2 (0.007) [0.001–0.024]
Squamous cell carcinoma	2 (0.007) [0.001–0.024]
Adenocarcinoma metastatic	1 (0.003) [0.000–0.018]

In patients with multiple malignancies, only the first malignancy was counted. For patients with malignancies, PYs are calculated from first treatment to onset of first malignancy.
[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, CONSONANCE and OLERO, including patients originally randomised to comparator (IFN β-1a or PBO) who switched to open-label OCR treatment.
CI, confidence interval; CTP, controlled-treatment period; IFN, interferon; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PY, patient years; SEER, Surveillance, Epidemiology and End Results.