

# 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 <sup>a</sup>	ORATORIO (PPMS)			All PMS <sup>a</sup>	All OCR trials
	CTP <sup>a</sup> (Jul 2015)		CTP + OLE <sup>b</sup> (Nov 2022)	Nov 2022	CTP <sup>a</sup> (Jul 2015)		CTP + OLE <sup>b</sup> (Nov 2022)	Nov 2022	OCR all-exposure population <sup>a</sup>
	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 <sup>1</sup>	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 <sup>a,h</sup>	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)

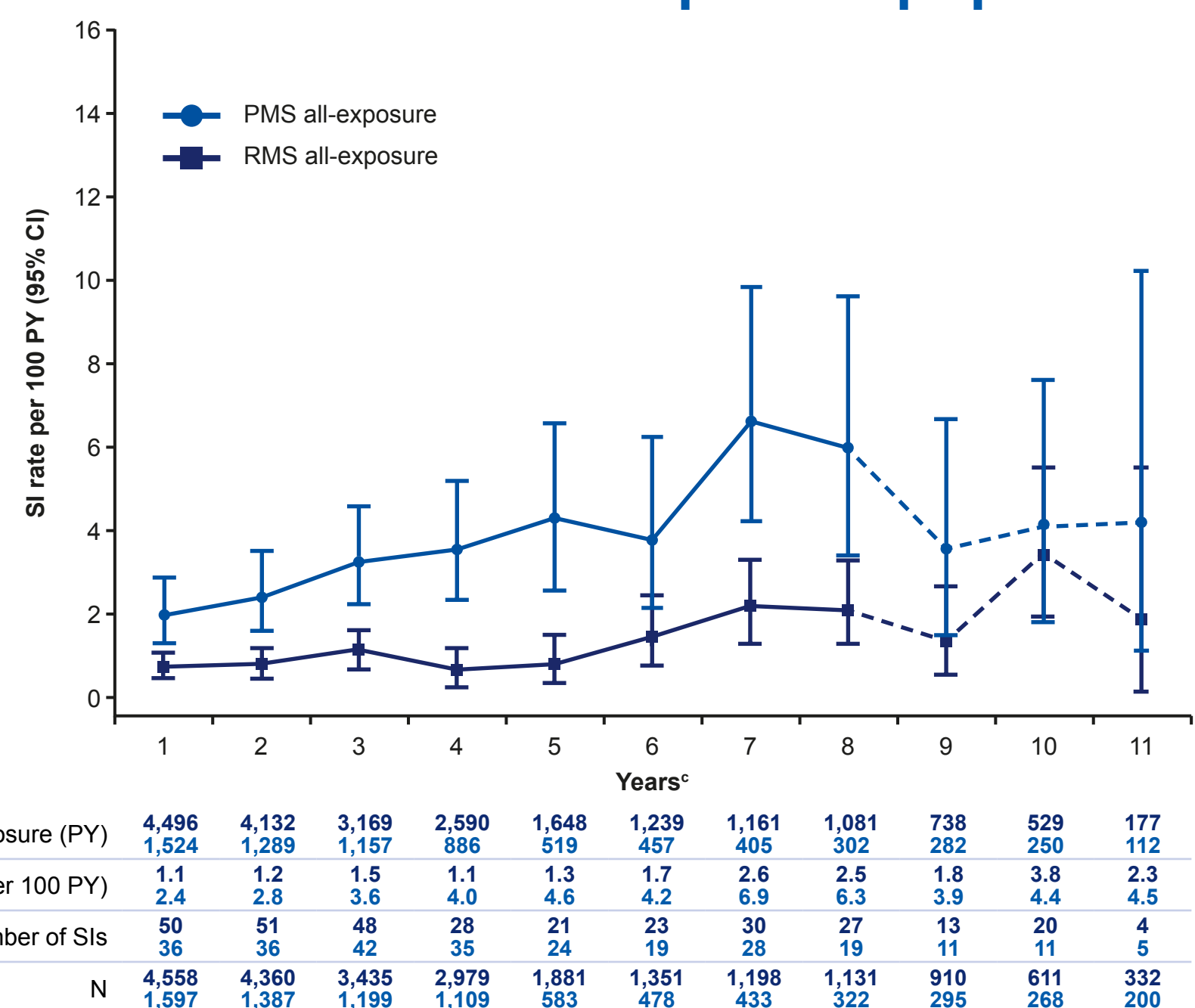
COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis). AEs were classified according to MedDRA versions 18.0, 18.1, 22.1 and 24.1. Multiple occurrences of the same AE in one patient are counted multiple times, except for malignancies. <sup>a</sup>Data as of April–July 2015; <sup>b</sup>Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II studies, including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022); <sup>c</sup>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); <sup>d</sup>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); <sup>e</sup>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); <sup>f</sup>Serious infections are defined using AEs falling into the MedDRA SOC 'Infections and Infestations', and using 'is the event non-serious or serious?' from the AE case report form; <sup>g</sup>Malignancies are identified using AEs falling into the standard MedDRA query 'Malignant tumours (primary)'; <sup>h</sup>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<sup>1,2</sup> (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.

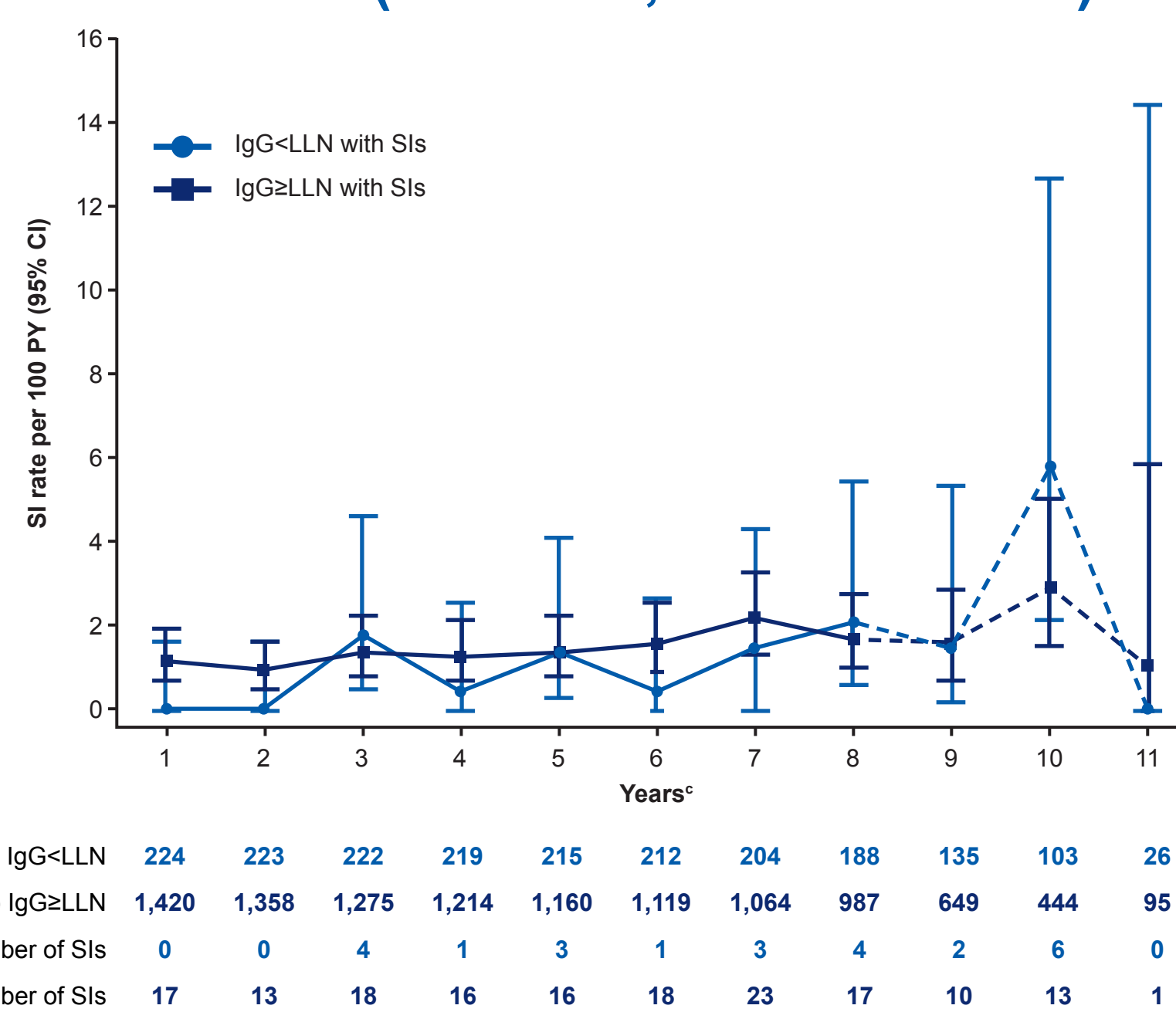
### SI Rates Remained Stable with Non-Significant Year-on-Year Variation and Within the Range Reported in Real-World Registries<sup>3,4</sup>

#### RMS<sup>a</sup> and PMS<sup>b</sup> all-exposure population

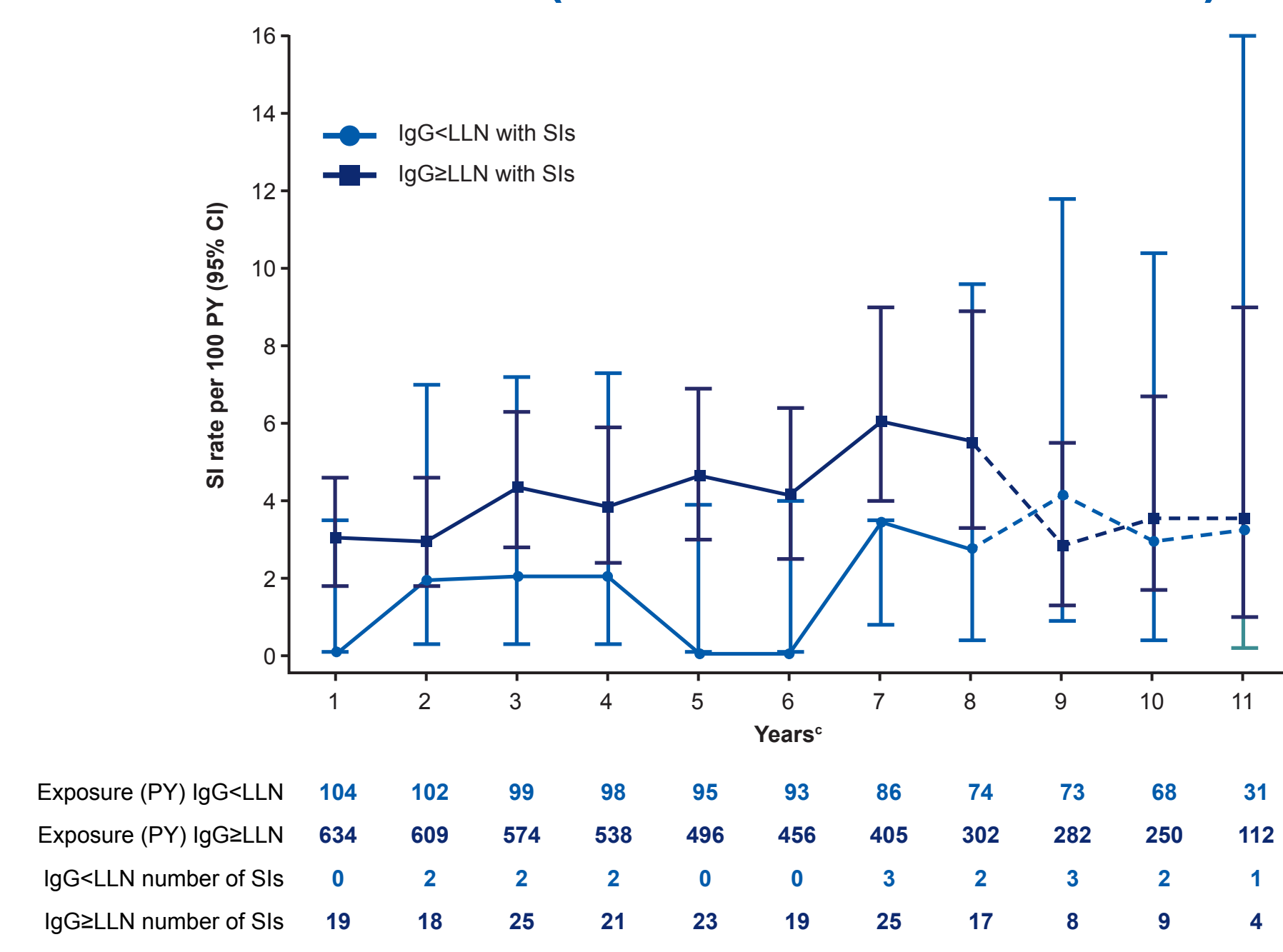


### In Both RMS and PPMS Populations, Longer Exposure to OCR Did Not Lead to an Increased Risk of SIs Regardless of IgG Status (Normal Levels or Levels Below the LLN)

#### RMS (OPERA I, II and OLERO)



#### PPMS (ORATORIO and OLERO)

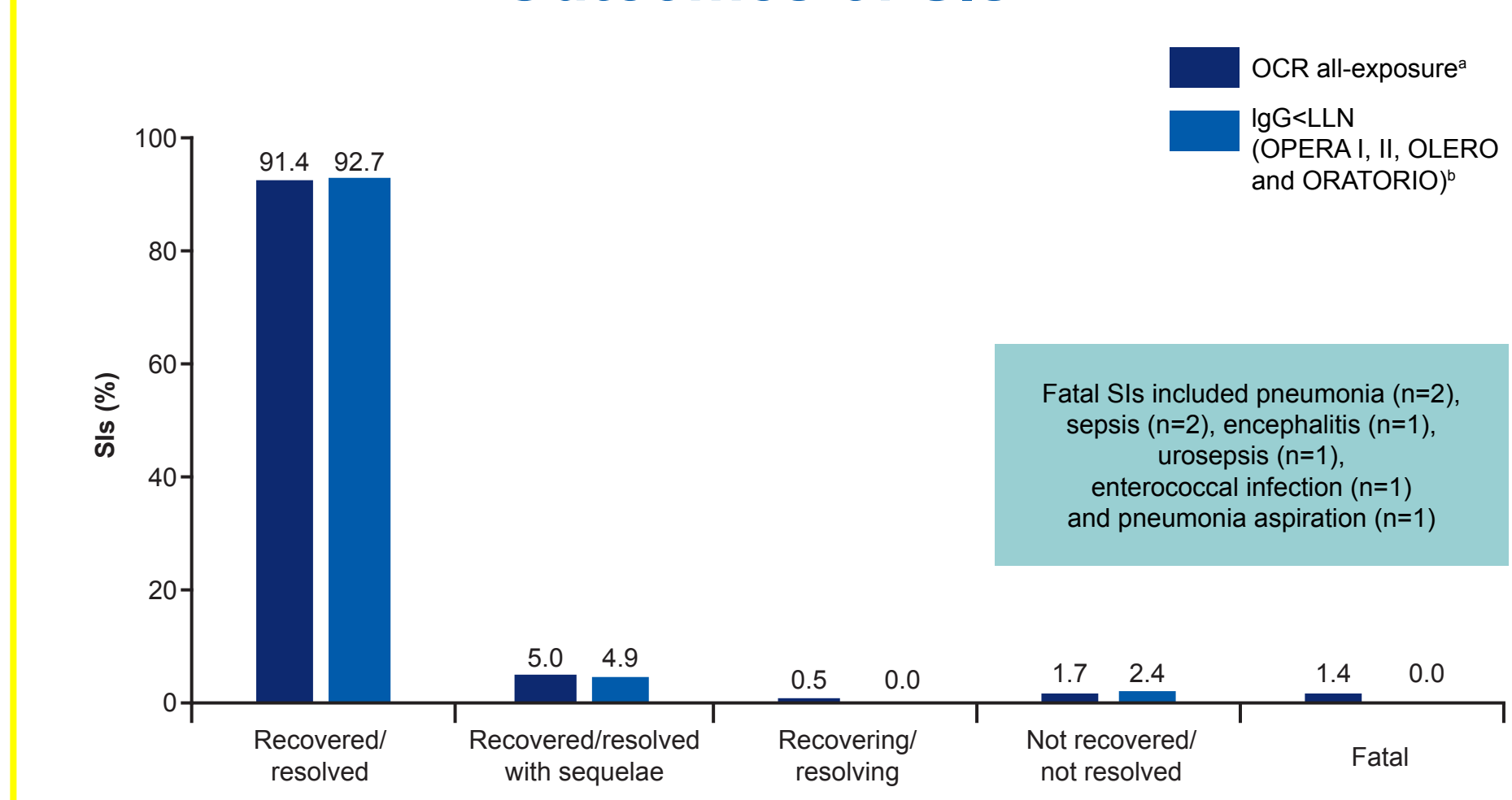


- In the RMS and PMS all-exposure populations, UTI and pneumonia were the most commonly reported SIs; this is consistent with incidence rates and patterns observed in real-world studies<sup>4-6</sup>
- The type, severity, latency and duration of SIs observed during episodes of IgG < LLN were consistent with the overall SIs observed in patients treated with OCR

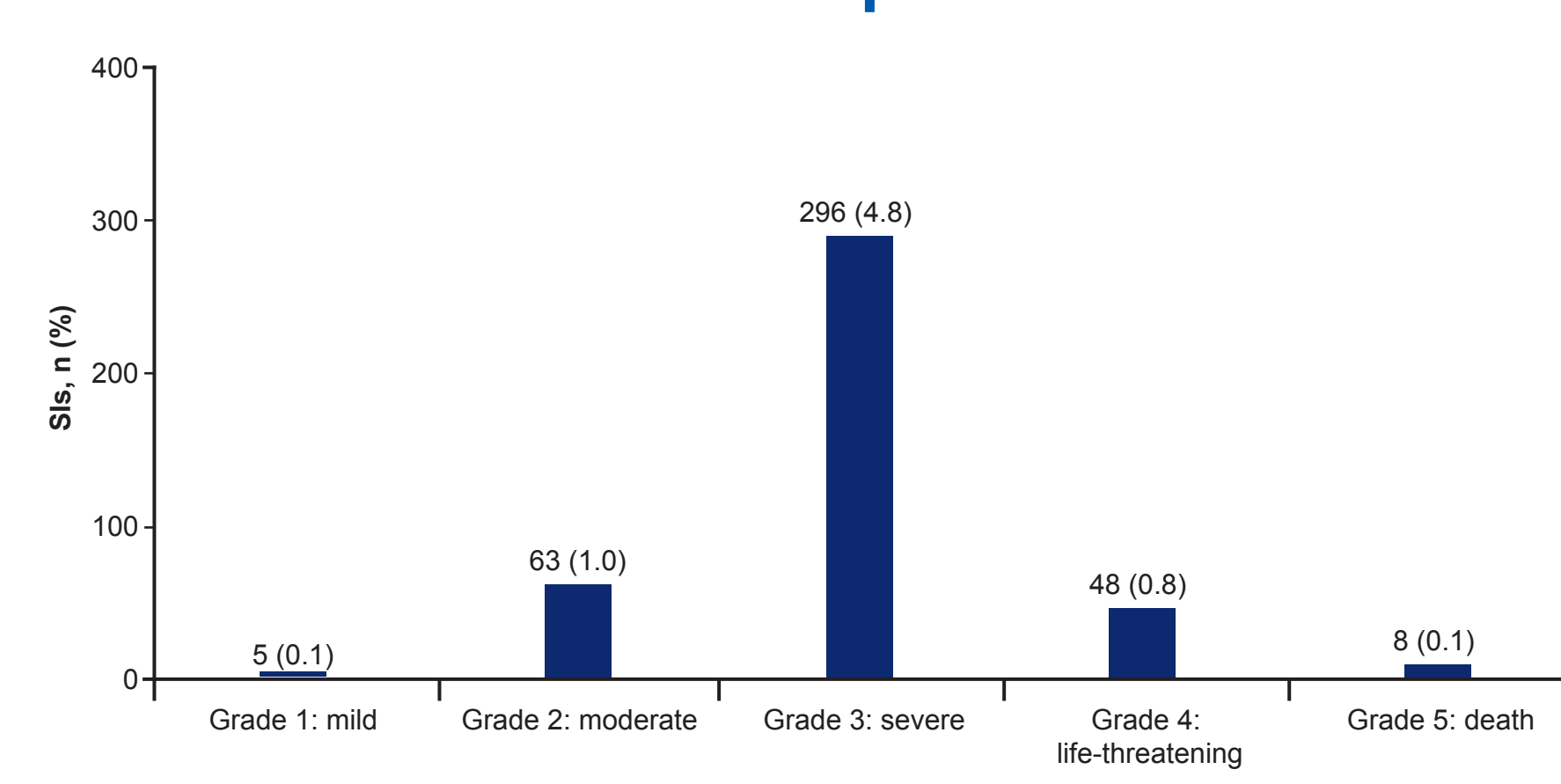
COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis). <sup>a</sup>Includes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES and OLERO (total N=6,155 patients). <sup>b</sup>Single-drop method (total N=2,092). <sup>c</sup>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); percentages are calculated using the number of patients that experienced any number of SIs (counting multiple occurrences once), by the number of patients. 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.

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

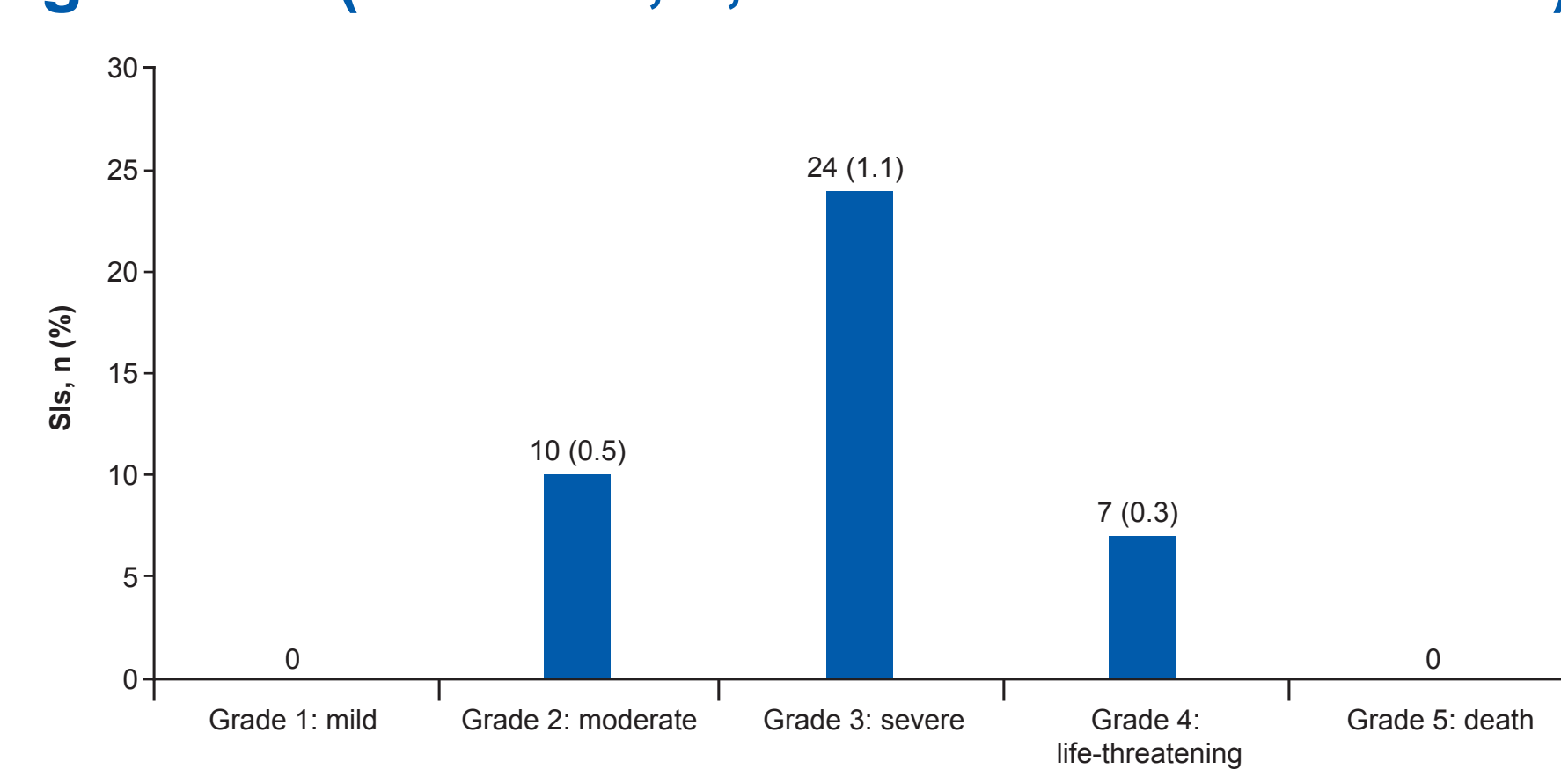
#### Outcomes of SIs



#### SI intensity Grade (CTCAE):<sup>c</sup> OCR all-exposure<sup>a</sup>



#### SI intensity Grade (CTCAE):<sup>c</sup> IgG < LLN (OPERA I, II, ORATORIO and OLERO)<sup>b</sup>



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). <sup>a</sup>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 (total N=6,155 patients). <sup>b</sup>Single-drop method (total N=2,092). <sup>c</sup>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); percentages are calculated using the number of patients that experienced any number of SIs (counting multiple occurrences once), by the number of patients. 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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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 is a shareholder and employee of F. Hoffmann-La Roche Ltd. N Pasquarelli is a shareholder and employee of F. Hoffmann-La Roche Ltd. K Kadner is an employee of F. Hoffmann-La Roche Ltd. B El Azzouzi is an employee of F. Hoffmann-La Roche Ltd. A Pradhan is an employee of Genentech, Inc. E Incera has received consulting fees from F. Hoffmann-La Roche Ltd for statistical assistance, and is an employee of IQVIA Solutions, Inc. JS Wolinsky has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities with Cleveland Clinic Foundation, EMD Serono, Innagen, Novartis, F. Hoffmann-La Roche Ltd/Genentech, Sandoz and Zenas BioPharma; royalties are received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation.

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