Serum Immunoglobulin Levels and Risk of Serious Infections in the Pivotal Phase III Trials of Ocrelizumab in Multiple Sclerosis and Their Open-Label Extensions

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OPERA I/OPERA II (NCT01247324; NCT01412333); ORATORIO (NCT01194570)

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Disclosures

Tobias Derfuss has served on scientific advisory boards, steering committees and data safety monitoring boards for Actelion, Biogen, Celgene, Genzyme, GeNeuro, Merck, Mitsubishi Pharma, Novartis, Roche, Octapharma and MedDay; has received travel and/or speaker honoraria from Biogen, Genzyme, Merck, Novartis, Roche and Merck Serono; and has received research support from Biogen, Novartis, the Swiss MS Society and the Swiss National Foundation.

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Richard Hughes is an employee and shareholder of F. Hoffmann-La Roche Ltd.

Qing Wang is an employee of F. Hoffmann-La Roche Ltd.

Annette Sauter is an employee and shareholder of F. Hoffmann-La Roche Ltd.

Harold Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd.

Licinio Craveiro is an employee of F. Hoffmann-La Roche Ltd.

Stephen L Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Alector, Annexon, Bionure, Molecular Stethoscope, and Symbiotix; and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

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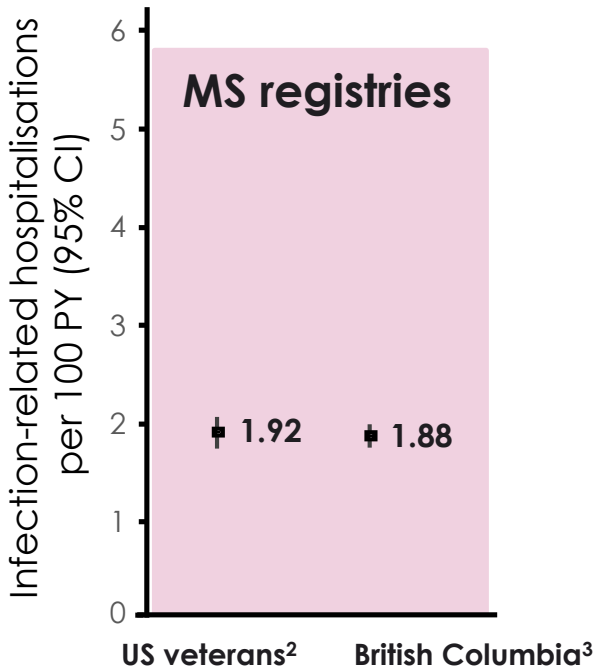
Background: Infections in MS and rates of serious infections with ocrelizumab

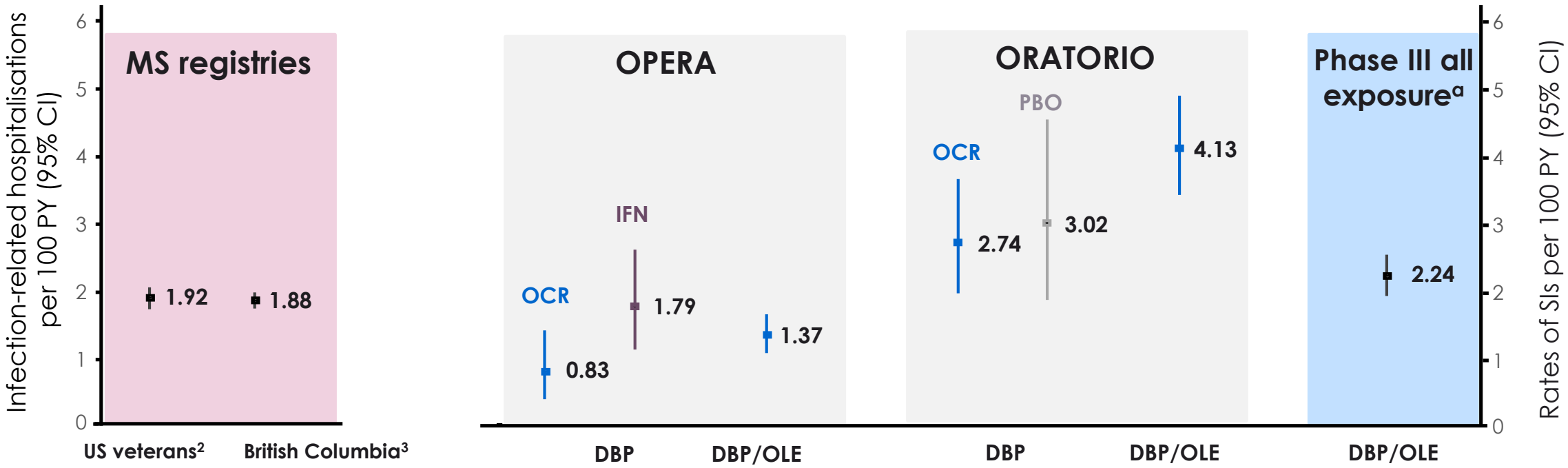
- Patients with MS have a higher risk of infections and of hospital admission rates for infection compared with the general population[1]



[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase III OPERA and ORATORIO studies.
CI, confidence interval; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label ocrelizumab; PY, patient years.
1. Wijnands JM, *et al*. *Mult Scler* 2017;23:1506–1516. 2. Nelson RE, *et al*. *Int J MS Care*. 2015;17:221–230. 3. Wijnands JMA, *et al. J Neurol Neurosurg Psychiatry* 2018;89:1050–1056.

Background: Infections in MS and rates of serious infections with ocrelizumab

- Patients with MS have a higher risk of infections and of hospital admission rates for infection compared with the general population[1]
- In ocrelizumab MS clinical trials, infections were one of the most frequently reported adverse events
  - In Phase III trials, rates of SIs were low, and no increased risk vs IFN β-1a and placebo was observed; rates of SIs remain low at 6-year follow-up



[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase III OPERA and ORATORIO studies.
CI, confidence interval; DBP, double-blind period; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PY, patient years; SI, serious infection.
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Objective

- The risk of serious infections in patients with MS is influenced by diverse factors such as age, body mass index, comorbidities, disability level, concomitant treatments, neutrophil and lymphocyte count[1–3]
- Immunoglobulins also play a major role in adaptive immunity and the risk of certain types of infection is increased when immunoglobulin levels are low[4]
- Reduced blood concentration of IgG, IgM, and/or IgA is known to occur in patients treated with B-cell–depleting therapy (secondary antibody deficiency), including ocrelizumab[5–10]

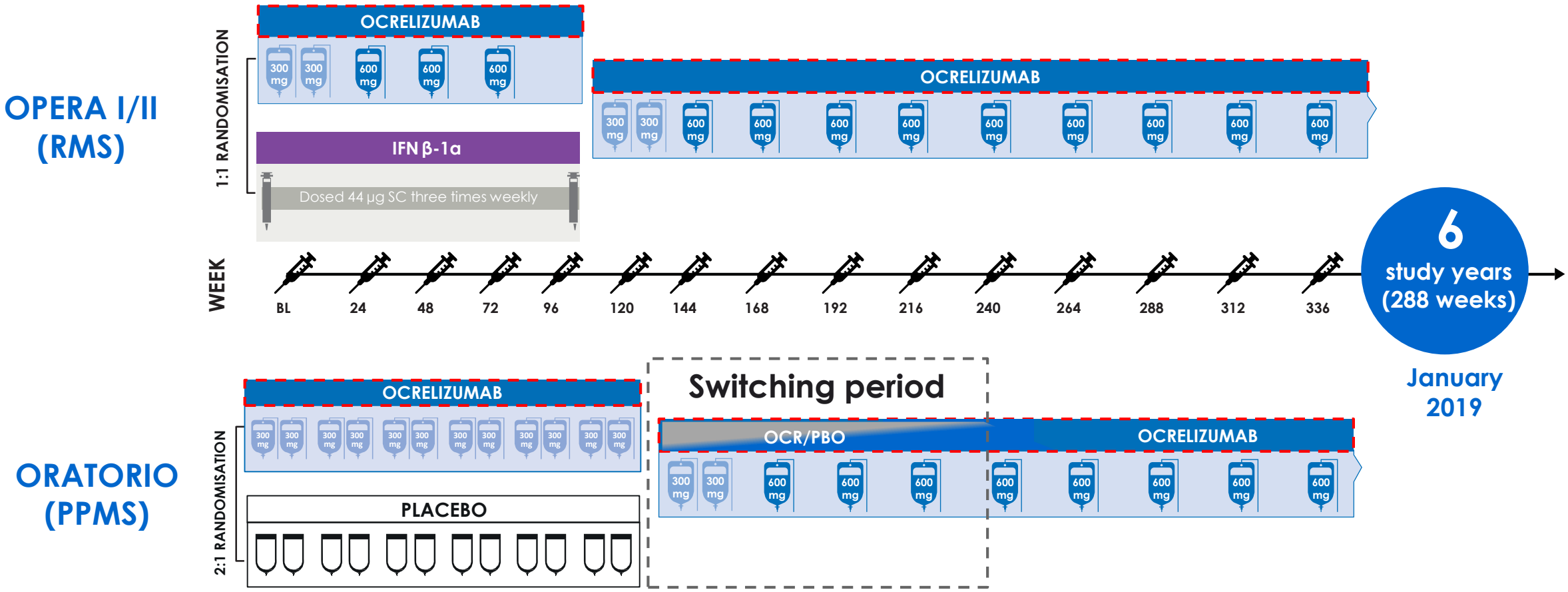
Objective: To assess serum immunoglobulin levels over 6 years (288 weeks) in OPERA and ORATORIO and evaluate a potential association between a decrease in IgG, IgM or IgA levels and serious infections

Ig, immunoglobulin; MS, multiple sclerosis.

1. Nelson RE, *et al. Int J MS Care* 2015;17:221–230. 2. Wijnands JM, *et al. Mult Scler* 2017;23:1506–1516. 3. Md Yusof MY, *et al. Arthritis Rheumatol* 2019; doi: 10.1002/art.40937.
4. Furst DE. *Semin Arthritis Rheum* 2009;39:18–29. 5. Kim SH, *et al. JAMA Neurol* 2013;70:1110–1117. 6. van Vollenhoven RF, *et al. Ann Rheum Dis* 2013;72:1496–1502.
7. Keystone E, *et al. Arthritis Rheum* 2007;56:3896–3908. 8. De la Torre I, *et al. Rheumatology* 2012;51:833–840. 9. Tallantyre EC, *et al. J Neurol* 2018;265:1115–1122.
10. Ocrevus 300 mg concentrate for solution for infusion (Summary of Product Characteristics; 26 June 2019).

Methods: OPERA I/II and ORATORIO study designs

- Serum Ig levels were measured at least every 24 weeks during the DBP and OLE periods

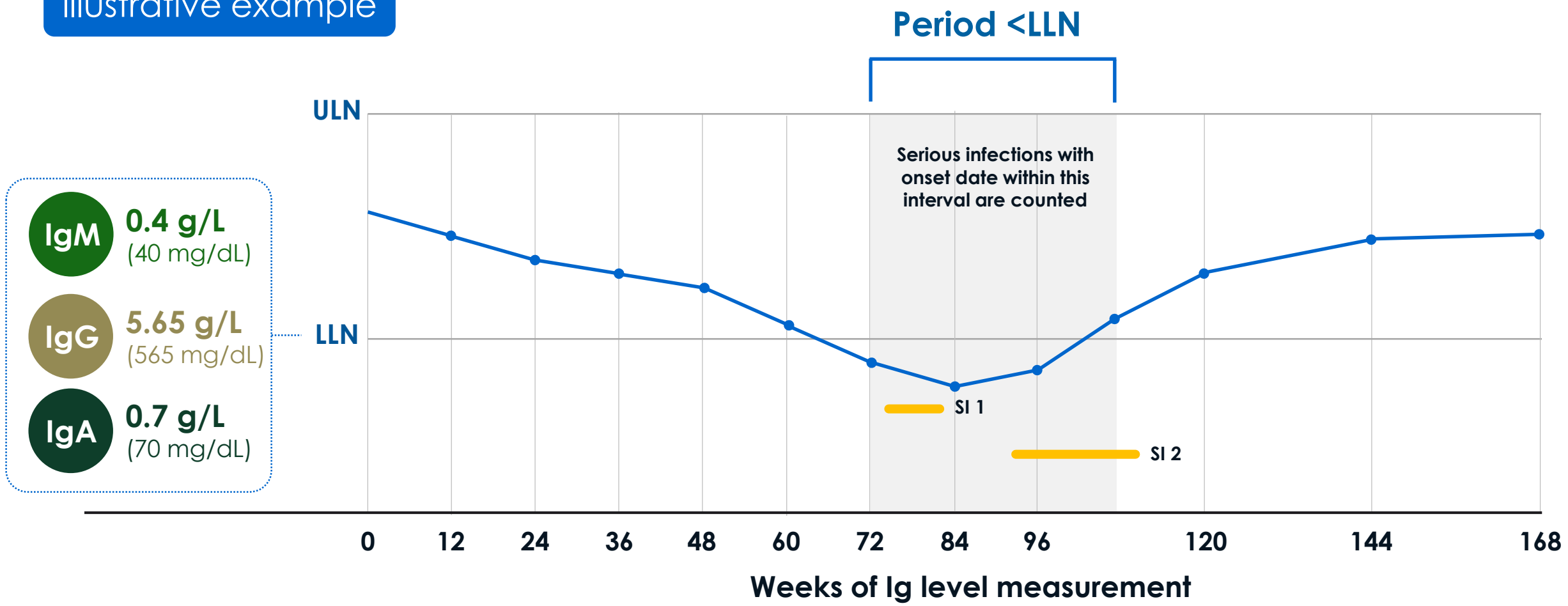


Serum Ig measurement

BL, baseline; DBP, double-blind period; IFN, interferon; Ig, immunoglobulin; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous.

Methods: Counting serious infections during periods of Ig above vs below LLN

Illustrative example



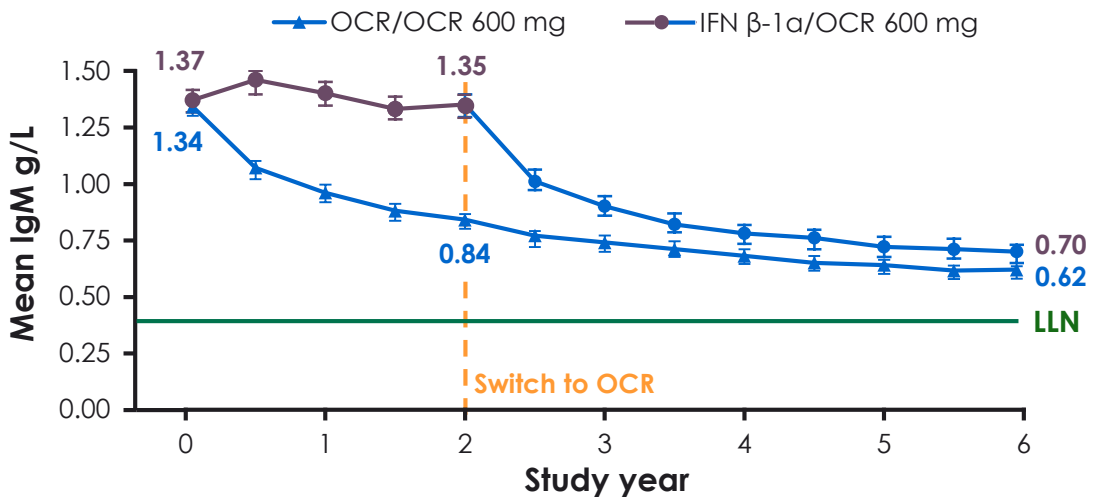
Ig, immunoglobulin; LLN, lower limit of normal; SI, serious infection; ULN, upper limit of normal.

Results

IgM

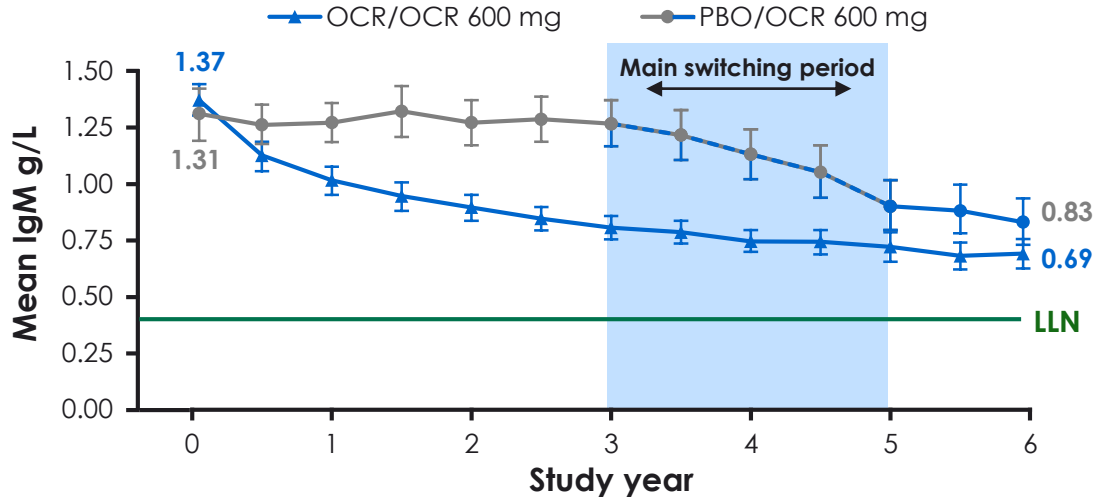
Change in serum IgM (g/L) from baseline through DBP and OLE period

Pooled OPERA



Treatment/Week	BL	24	48	72	96	120	144	168	192	216	240	264	288
IFN/OCR	824	792	726	686	656	582	583	570	565	544	540	522	522
OCR/OCR	823	796	758	747	723	657	645	640	620	611	612	587	594

ORATORIO



Treatment/Week	BL	24	48	72	96	120	144	168	192	216	240	264	288
OCR/OCR	484	471	453	441	421	406	383	371	351	294	256	252	223
PBO/OCR	239	231	218	206	196	182	162	153	146	130	118	118	116

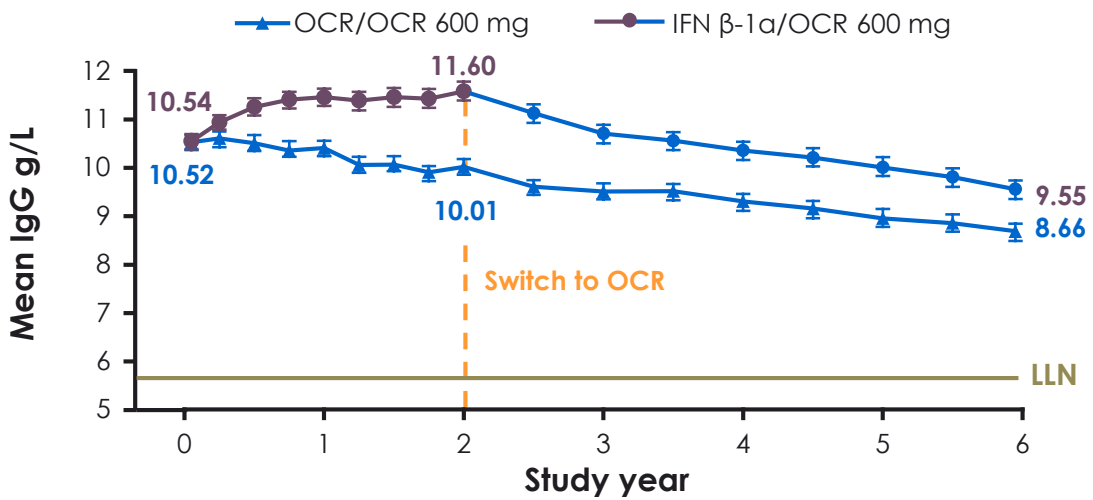
- Over 6 years of OCR treatment, a mean absolute reduction in serum IgM levels of –0.78 g/L (mean relative reduction of 55.4%) in OPERA and –0.77 g/L (mean relative reduction of 53.7%) in ORATORIO was observed
- OCR treatment is associated with a faster drop in serum IgM in the first year followed by a slower decline

BL, baseline; DBP, double-blind period; IFN, interferon; Ig, immunoglobulin; LLN, lower limit of normal; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

IgG

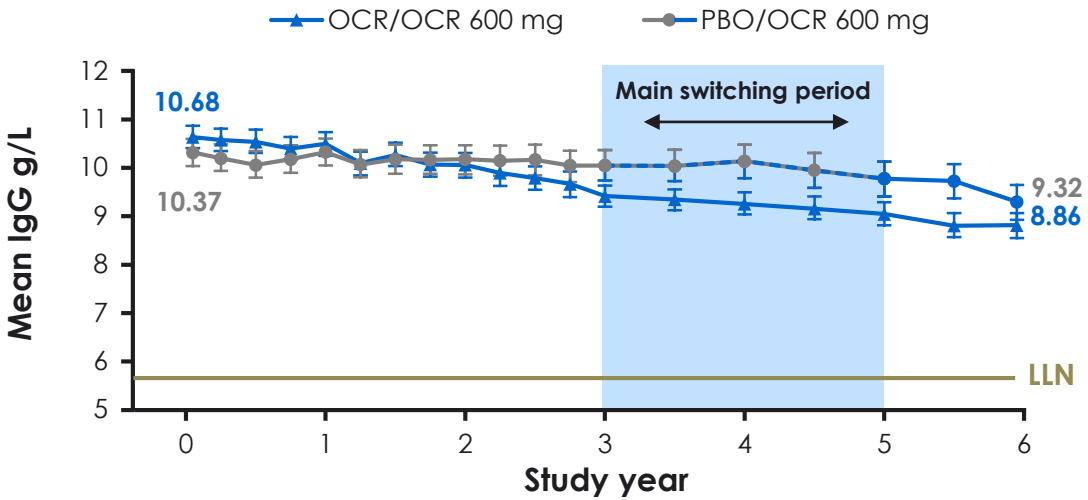
Change in serum IgG (g/L) from baseline through DBP and OLE period

Pooled OPERA



Treatment/Week	BL	24	48	72	96	120	144	168	192	216	240	264	288
IFN/OCR	824	772	711	677	653	582	583	570	565	544	540	522	522
OCR/OCR	823	781	757	741	719	658	647	640	620	611	612	587	595

ORATORIO

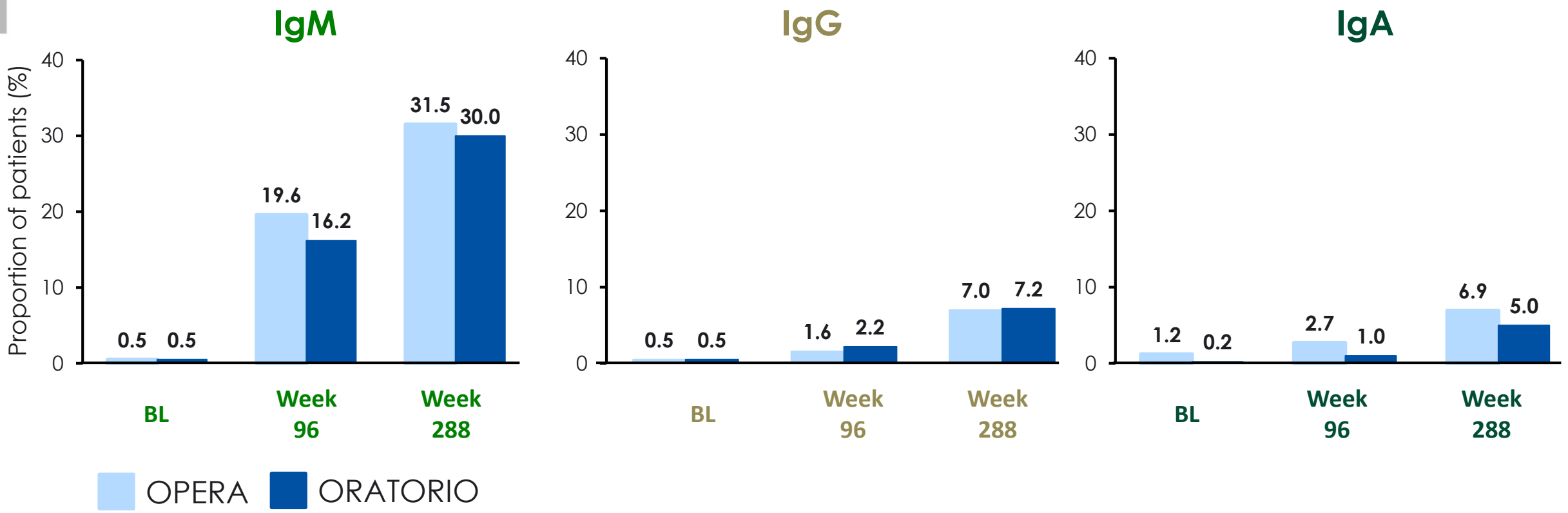


Treatment/Week	BL	24	48	72	96	120	144	168	192	216	240	264	288
OCR/OCR	484	465	455	440	426	413	403	395	375	351	321	311	280
PBO/OCR	239	228	217	205	193	179	165	159	155	153	145	143	136

- Within the first 6 years (288 weeks), treatment with OCR reduces serum IgG concentration at an average rate of **–0.32 g/L per year (–3.0% per year)**
- The trajectory for change in IgA levels over time was similar to IgG

BL, baseline; DBP, double-blind period; IFN, interferon; Ig, immunoglobulin; LLN, lower limit of normal; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

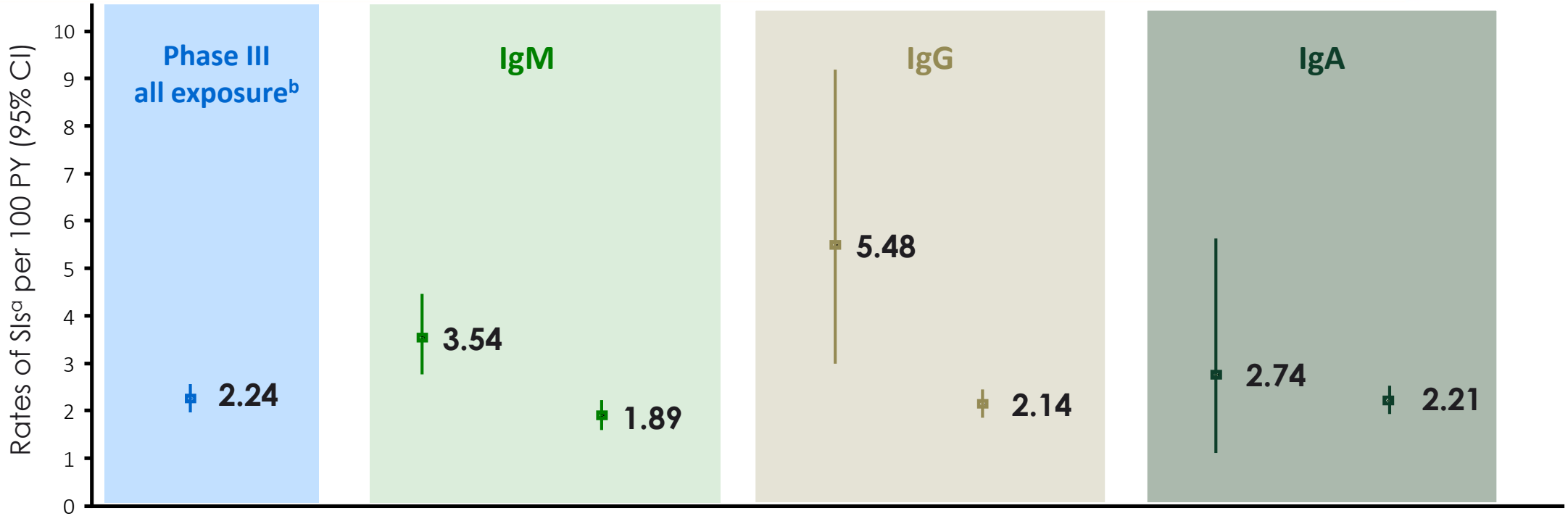
Proportion of patients with Ig levels <LLN



For the majority of patients with either RMS or PPMS, serum immunoglobulin levels remain above LLN at approximately 6 years (288 weeks) of exposure

January 2019 data cut. OPERA and ORATORIO all-exposure population.
BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

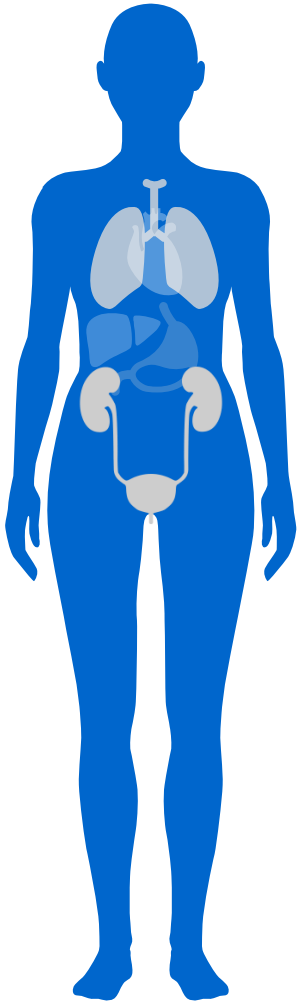
Rates of SIs per 100 PY during IgG, IgM, and IgA values <LLN vs ≥LLN



	Phase III all exposure[b]	IgM		IgG		IgA	
		<LLN	≥LLN	<LLN	≥LLN	<LLN	≥LLN
Patients (n)	2,092	729	1,383	152	1,940	127	1965
Episodes (n)	-	929	2,368	288	2,269	166	2,131
PY	9,891	2,003	7,989	255	9,737	256	9,726
No. of SIs	**222**	**71**	**151**	**14**	**208**	**7**	**215**

January 2019 data cut. [a]Serious infections are defined using adverse events falling into the MedDRA System Organ Class 'Infections and Infestations' and using 'Is the event non-serious or serious' from the adverse events CRF page; [b]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase III OPERA and ORATORIO studies. Multiple occurrences of the same adverse event in one individual are counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution. Exposure of <LLN is counted from the day lab <LLN until the day lab ≥LLN; exposure gap is excluded from PY. CI, confidence interval; CRF, case report form; Ig, immunoglobulin; LLN, lower limit of normal; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; SI, serious infection.

Characteristics and outcomes of SIs associated with low Ig levels



IgM IgG IgA

- Urinary tract infections, cellulitis and pneumonia were the most common serious infections associated with Ig levels <LLN
  - This is similar to overall SIs in patients with MS treated with ocrelizumab
  - This is also consistent with types of serious infections observed in MS registries[1–3]

- Most SIs associated with Ig levels <LLN:
  - Were of **Grade 3** (69.1%). No fatal outcomes or opportunistic infections were observed
  - **Resolved without sequelae** (92.6%), within the expected clinical course (78.5% lasted <28 days) by using standard-of-care treatment
  - Resulted in **no action taken** (dose not changed) with ocrelizumab (87.7%)

January 2019 data cut. Pooled OPERA and ORATORIO all-exposure population.
Ig, immunoglobulin; LLN, lower limit of normal; MS, multiple sclerosis; SI, serious infection.
1. Wijnands JM, *et al*. *Mult Scler* 2017;23:1506–1516. 2. Nelson RE, *et al*. *Int J MS Care* 2015;17:221–230. 3. Wijnands JMA, *et al. J Neurol Neurosurg Psychiatry* 2018;89:1050–1056.

Conclusions

At approximately 6 study years (288 weeks) of ocrelizumab exposure:

1. Rates of serious infections remain low and consistent with rates of infection-related hospitalisations in real-world MS cohorts

2. A reduction in serum Ig levels is observed, at an approximate mean rate of 3–4% per year for IgG, but for the majority of patients Ig levels remain above LLN

3. There is an apparent association between decreased levels of IgG (and less so for IgM or IgA) and serious infections, but overall incidence is low

4. The majority of serious infections following episodes of drop in Ig levels <LLN were urinary tract infections, cellulitis and pneumonia; most resolved with standard of care, and in most cases patients remained on treatment with ocrelizumab

Ig, immunoglobulin; LLN, lower limit of normal; MS, multiple sclerosis.

Acknowledgements

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