

Long-Term Effect of Ofatumumab on Serum Immunoglobulin Levels in Patients With Relapsing Multiple Sclerosis

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SUMMARY

- This study evaluated the effect of ofatumumab on serum immunoglobulin (Ig) levels in 1969 patients with relapsing forms of multiple sclerosis (RMS) during the core (ASCLEPIOS I/II, APLIOS and APOLITOS) and ALITHIOS open-label extension (OLE) studies
- The serum IgG and IgM levels remained above the lower limit of normal (LLN) in the majority of patients (98% and 69.4%, respectively) at all assessments from the first dose of ofatumumab for up to 5 years
- Interruption of ofatumumab treatment due to low IgG/IgM levels (below LLN) did not affect the overall IgG/IgM patterns

INTRODUCTION

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for treating RMS in adults¹
- In the Phase 3 ASCLEPIOS I/II trials, ofatumumab treatment for up to 30 months had a favourable safety profile and was generally well tolerated in RMS patients²
- The cumulative safety data of ofatumumab treatment for up to 5 years have shown that³:
 - Most patients had serum Ig levels that remained above the LLN
 - The mean serum IgG levels remained similar to baseline values
 - The mean serum IgM levels decreased over time but stayed above the LLN

OBJECTIVE

- To evaluate the effect of ofatumumab on serum IgG/IgM levels for up to 5 years during the core and OLE studies

METHODS

Patient Population

- The effect of ofatumumab on IgG and IgM levels for up to 5 years (data cut-off: 25 September 2022; time on ofatumumab: 6670.1 patient-years) was analysed in the overall safety population (N=1969) comprising patients who received ofatumumab in the ASCLEPIOS I/II, APOLITOS or APLIOS core studies, and/or the ALITHIOS OLE

Key Assessments

- The proportion of patients with IgG/IgM levels <LLN (LLN in g/L: IgG, 5.65; IgM, 0.4)
 - Serum IgG/IgM levels** were measured at Week (W) 4, W12 and every 3 months thereafter in ASCLEPIOS; every 3 months in the first year of ALITHIOS and then every 6 months afterwards; and at W4, W12 and every 3 months thereafter in APLIOS and APOLITOS during the safety follow-up
 - Serious infections** that occurred within 1 month prior and until 1 month after single or consecutive values of IgG (or IgM) <LLN were analysed

- Sensitivity analysis** was conducted to determine whether ofatumumab interruption due to low IgG/IgM would impact overall Ig trends
 - IgG and IgM values after the first interruption due to either notably low IgM (10% <LLN) or IgG (20% <LLN) levels were imputed using the last observation carried forward (LOCF)
- The proportion of patients with treatment interruptions*/discontinuations due to IgG/IgM decline was analysed

**In ASCLEPIOS I/II, the investigators were required to interrupt study treatment if IgM levels fell 10% below LLN or IgG levels fell 20% below LLN. Due to a protocol change at the beginning of ALITHIOS, i.e., 03 June 2021, the requirement to interrupt treatment based on a specific threshold due to low IgG/IgM was removed and was left to the discretion of the investigator*

RESULTS

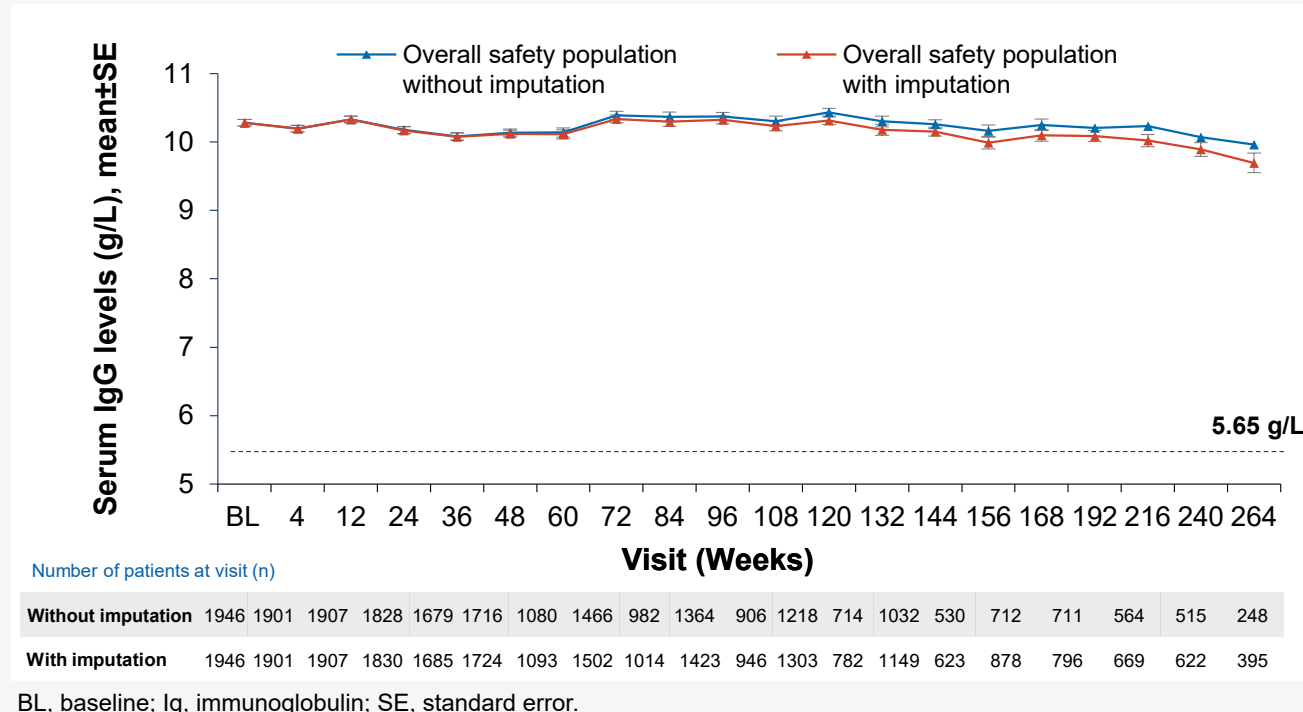
Proportion of Patients With IgG/IgM Levels <LLN

- Serum IgG levels remained above the LLN in 98% of patients, while serum IgM levels remained above the LLN in 69.4% of patients at all assessments from the first dose of ofatumumab for up to 5 years
- Serious infections were reported in 3/40 (7.5%) patients with IgG levels <LLN (vs 99/1926 (5.1%), ≥LLN) and 10/601 (1.7%) patients with IgM levels <LLN (vs 72/1365 (5.3%), ≥LLN)
 - Serious infections in patients with IgG<LLN were pneumonia (n=1), COVID-19 pneumonia (n=1) and chronic pyelonephritis (n=1) and most frequent serious infections in patients with IgM<LLN were COVID-19 (n=4) and urinary tract infection (n=2)
- No clinically meaningful association was observed between decreased IgG/IgM levels and the risk of serious infections

Mean Serum IgG/IgM Levels With and Without Imputation

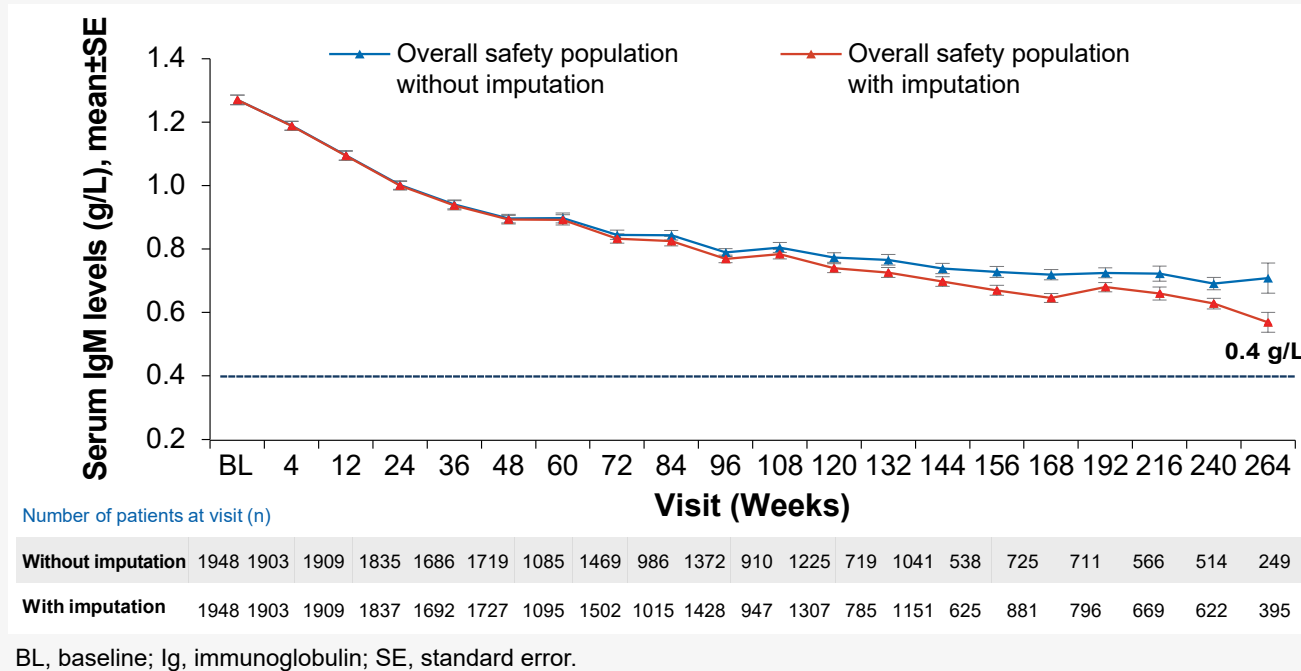
- Sensitivity analysis showed that no major difference was observed in the overall mean IgG and IgM trend after imputing IgG/IgM levels over time for patients who interrupted ofatumumab due to either notably low IgM or IgG levels (**Figure 1A, 1B**)

Figure 1A. Serum IgG Levels



BL, baseline; Ig, immunoglobulin; SE, standard error.

Figure 1B. Serum IgM Levels



BL, baseline; Ig, immunoglobulin; SE, standard error.

Treatment Interruptions/Discontinuations in the Overall Safety Population

- Most patients did not interrupt and did not discontinue ofatumumab treatment (99.8% for both) due to low IgG levels
- Overall, 96.4% of patients did not discontinue treatment and 89.7% did not interrupt treatment due to low IgM levels (**Table 1**)

Table 1. IgG/IgM-related Treatment Interruptions and Discontinuations in the Core, Extension and Overall Safety Population

	Core N=1292 n (%)	Extension N=1703 n (%)	Overall safety population N=1969 n (%)
IgG	Either interruption or discontinuation	3 (0.2%)	3 (0.3%)
	Interruption*	1 (0.1%)	3 (0.2%)
	Discontinuation*	3 (0.2%)	4 (0.2%)
IgM	Either interruption or discontinuation	70 (5.4%)	254 (12.9%)
	Interruption*	46 (3.6%)	202 (10.3%)
	Discontinuation*	27 (2.1%)	71 (3.6%)

*Patients with interruption and discontinuation have been included in both the categories; Ig, immunoglobulin.

CONCLUSIONS

- With up to 5 years of ofatumumab treatment, most patients (IgG 98%, IgM 69.4%) remained above the LLN at all assessments
- Sensitivity analysis showed that interruption/discontinuation of ofatumumab due to low IgG/IgM levels did not affect the overall IgG/IgM patterns

References: 1. KESIMPTA® (ofatumumab) Prescribing Information. <https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf> (accessed 4 Aug 2023); 2. Hauser SL, et al. *N Engl J Med.* 2020;383:546–57; 3. Cohen JA et al; *Poster presented at AAN 2023.* P8.004.

Abbreviations: BL, baseline; CD, cluster of differentiation; Ig, immunoglobulin; LLN, lower limit of normal; LOCF, last observation carried forward; OLE, open-label extension; OMB, ofatumumab; RMS, relapsing multiple sclerosis; W, week.

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