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Over 7 Years, the Risk of Serious Infections Remained Low With Long-Term Ofatumumab Treatment in People With Relapsing Multiple Sclerosis

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KEY FINDINGS & CONCLUSIONS

- The annualised infection rate dropped from Year 1 to Year 2 and then remained stable to Year 7
- The most frequently reported infections were URTIs, followed by COVID-19 and UTIs
- Over 7 years of ofatumumab treatment, serious infections remained infrequent and the rate remained stable
- The most frequently reported serious infections were COVID-19, UTI, lower RTI and appendicitis
- In the majority of serious infections, participants recovered and did not discontinue treatment
- IgG remained above LLN at all timepoints in 96.7% of participants and only 8 (0.4%) participants had serious infections within or beyond 30 days of an observation of IgG<LLN
- These results suggest that the long-term infection risk of ofatumumab in plwRMS remains low and manageable

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This study was sponsored by Novartis Pharma AG, Basel, Switzerland.

Poster P812 presented at the 41st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Barcelona, Spain, 24–26 September 2025.

INTRODUCTION

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosage regimen, is the only anti-CD20 approved for the treatment of relapsing multiple sclerosis (RMS) via self-administration[1,2]
- In the phase 3 ASCLEPIOS I/II trials, treatment with ofatumumab for up to 30 months demonstrated a favourable safety profile and was generally well tolerated in people living with RMS (plwRMS)[3]
- Ofatumumab treatment for up to 6 years in previously reported studies continued to show a favourable safety and tolerability profile, with no new safety concerns identified in plwRMS[4,5]
- Assessing the long-term (7-year) risk of infections and serious infections (SIs) with ofatumumab provides relevant information to help clinicians in their decision-making process for the treatment of RMS

OBJECTIVE

- To evaluate the yearly risk of developing infections and SIs over a period of 7 years of ofatumumab treatment (data cutoff: 25-Sep-2024) in plwRMS

METHODS

Participant population

- Participants who received at least one dose of ofatumumab in ASCLEPIOS I/II, APLIOS, APOLITOS (core studies) or the ALITHIOS open-label extension study were included in the analysis

Assessments

- Infections were selected based on the System Organ Class (SOC) 'Infections and infestations'
- Infections and SIs were classified into the following risk categories: upper respiratory tract infections (URTIs, excluding COVID-19); lower and unspecified RTIs; COVID-19; appendicitis; urinary tract infections (UTIs); herpes viral infections; and others
- Time at risk was defined as starting from the first dose of ofatumumab up to 100 days following the last dose of ofatumumab
- Time-adjacent infections (i.e. concurrent or ≤3 days apart) that were in the same risk category were counted as a single infection
- SIs occurring in participants with immunoglobulin G (Ig) levels below the lower limit of normal (LLN: 5.65 g/L) were evaluated

Statistical analysis

- The annualised rate of infections and SIs for each year was estimated using a negative binomial regression model, with number of infections in each participant in the year as the response variable, year as factor, and time at risk in the year as the offset variable
- COVID-19 incidence was evaluated based on calendar years rather than years on ofatumumab, as cases of COVID-19 were reported predominantly during 2020–2024; a Poisson model was used to analyse the outcome

RESULTS

Summary of infections and serious infections

- A total of 1969 participants were included in the analysis (cumulative exposure of 9258.2 patient-years; [PYs])
- Excluding COVID-19, 1268 (64.40%) participants experienced a total of 4622 infections
- Including COVID-19, 1423 (72.27%) participants experienced a total of 5609 infections
- The most frequently reported infections were URTI (excluding COVID-19) and COVID-19, experienced by 46.22% and 38.39% of participants, respectively (**Table 1**)

Table 1. Summary of overall infections over 7 years

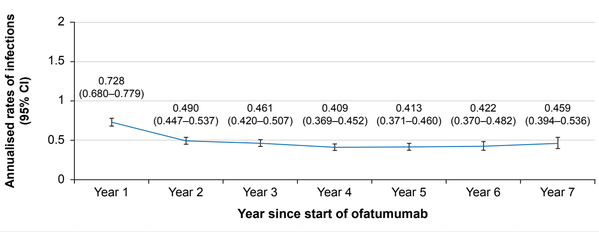
Infection	Incidence of infections: Participants with number of infections	Incidence of infections: Overall N=1969, n (%)	Total number of infections
URTI (excluding COVID-19)	1	395 (20.06)	**2119**
	≥2	515 (26.16)	
COVID-19	1	572 (29.05)	**987**
	≥2	184 (9.34)	
UTI	1	215 (10.92)	**834**
	≥2	171 (8.68)	
Herpes viral infections	1	109 (5.54)	**254**
	≥2	46 (2.34)	
RTI (excluding COVID-19)	1	94 (4.77)	**208**
	≥2	42 (2.13)	
LRTI (excluding COVID-19)	1	144 (7.31)	**199**
	≥2	23 (1.17)	
Appendicitis	1	14 (0.71)	**16**
	≥2	1 (0.05)	
Opportunistic infections	1	9 (0.46)	**11**
	≥2	1 (0.05)	
All other infections	1	277 (14.07)	**981**
	≥2	231 (11.73)	
Total	1	391 (19.86)	**5609**
	≥2	1032 (52.41)	

- Excluding serious COVID-19, 78 (3.96%) participants experienced a total of 90 SIs. A total of 51 participants experienced 51 (2.59%) serious COVID-19 infections. Including serious COVID-19, 123 (6.25%) participants experienced a total of 141 SIs
  - The most frequently reported SIs were COVID-19 (2.59%), UTI (1.01%), lower RTI (excluding COVID-19; 0.96%) and appendicitis (0.76%)
- Ten participants had 11 opportunistic infections, one of which was a case of serious *P. jirovecii* pneumonia which resolved. Of the ten non-serious opportunistic infections, 2 did not resolve up to the cutoff date (fungal oesophagitis and *P. jirovecii* pneumonia in two different participants), while the remaining resolved (ophthalmic herpes zoster [n=3], ophthalmic herpes simplex [n=1], mycetoma mycotic [n=1], herpes zoster cutaneous disseminated [n=1] and opportunistic infections [n=2])
- Excluding COVID-19, 3 participants discontinued ofatumumab due to SIs (URTI [n=1], tubo-ovarian abscess [n=1], pneumonia/septic shock [n=1]). Five additional participants discontinued due to COVID-19/COVID-19 pneumonia

Annualised rates of infections over 7 years (excluding COVID-19)

- The annualised rate of overall infections (excluding COVID-19) was 72.8 per 100 PYs at Year 1, decreasing at Year 2 and then remaining stable thereafter through Year 7 (**Figure 1**)

Figure 1. Annualised rates of infections (excluding COVID-19)

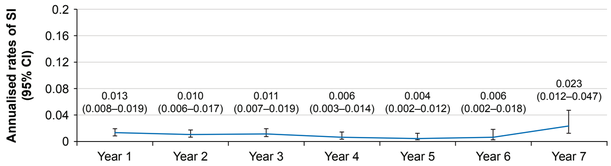


Participants at risk (N)	1969	1812	1619	1500	1408	1217	561
Exposure (PYs)	1904.1	1722.8	1550.8	1455.5	1351.9	783.8	489.4

Annualised serious infection rates over 7 years (excluding COVID-19)

- The annualised rate of SIs (excluding COVID-19) was low and stable over 7 years of treatment (**Figure 2**)

Figure 2. Annualised serious infection rates (excluding COVID-19)



Participants at risk (N)	1969	1812	1619	1500	1408	1217	561
Exposure (PYs)	1904.1	1722.8	1550.8	1455.5	1351.9	783.8	489.4
Number of SI events	25	17	17	9	6	5	11
Participant with ≥1 event, n (%)	24 (1.22)	16 (0.89)	16 (0.99)	7 (0.46)	4 (0.28)	4 (0.33)	9 (1.61)

Summary of serious COVID-19 infections

- Annualised serious COVID-19 infection rates peaked in 2021 followed by a steady reduction up to 2024 (**Table 2**)

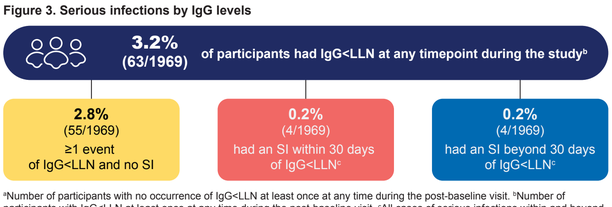
Table 2. Summary of serious COVID-19 infections

Year	2020	2021	2022	2023	2024
Annualised rates (95% CI)	0.004 (0.002–0.009)	0.020 (0.014–0.028)	0.008 (0.005–0.015)	0.001 (0.000–0.005)	0.001 (0.000–0.008)
Participants at risk (N)	1669	1562	1474	1396	1315
Exposure (PYs)	1611.2	1521.8	1435.9	1353.2	938.1
Number of SI events (n)	7	30	12	1	1

Serious infections and IgG levels

- In 96.7% (1903/1969) of participants, IgG levels remained above the LLN at all timepoints for up to 7 years of ofatumumab treatment[a]
- A few participants (3.2%) experienced IgG<LLN, and only 8 (0.4%) of these participants had SIs that occurred within or beyond 30 days of an observation of IgG<LLN (**Figure 3**)

Figure 3. Serious infections by IgG levels



[a]Number of participants with no occurrence of IgG<LLN at least once at any time during the post-baseline visit. [b]Number of participants with IgG<LLN at least once at any time during the post-baseline visit. [c]All cases of serious infections within and beyond 30 days of IgG<LLN resolved and recovered.

Please also refer to the related posters being presented at the congress:

P804: Continuous Ofatumumab Treatment for Up to 7 Years Shows a Favourable Safety and Efficacy Profile in People With Relapsing Multiple Sclerosis

P805: Continuous Ofatumumab Treatment Up to 7 Years Shows a Consistent Safety and Efficacy Profile in Recently Diagnosed Treatment-Naive People Living With Relapsing Multiple Sclerosis

P932: Immunoglobulin G Levels in Ofatumumab-Treated Participants With Episodes of Low Immunoglobulin M: An Analysis of 7-Year Data From the ALITHIOS Extension Study

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2. Kesimpta (ofatumumab). Prescribing information. Novartis; 2024. Accessed 14 July 2025. https://www.novartis.com/us-en/sites/novartis_us/files/kesimpta.pdf.
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Acknowledgements

We thank the participants, their families, and investigators and staff at participating study sites. Medical writing support was provided by **Sonali Satam**, PhD (Novartis Healthcare Pvt. Ltd., Hyderabad, India) and **David McMinn**, PhD (Novartis Ireland Ltd., Dublin, Ireland); design support was provided by **Rupa De** (Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

Abbreviations

CI, confidence interval; **COVID-19**, coronavirus disease of 2019; **IgG**, immunoglobulin G; **LLN**, lower limit of normal; **LRTI**, lower respiratory tract infection; **plwRMS**, people living with RMS; **PY**, patient-year; **RMS**, relapsing multiple sclerosis; **RTI**, respiratory tract infection; **SI**, serious infection; **URTI**, upper respiratory tract infection; **UTI**, urinary tract infection.

Disclosures

Tjalf Ziemssen: Speakers' bureaus-Roche, Merck, TEVA, NovoNordisk, Neuraxpharm, BMS, Novartis, Sanofi, Sandoz and Viatris and has received research support from Novartis, Roche, Sanofi and Neuraxpharm. **Jeffrey Cohen:** personal compensation for consulting- Astoria, Bristol-Myers Squibb, Convelo, and Viatris, and Chairing a DSMB for Celltrion. **Sven Meuth:** honoraria for lecturing, travel expenses and attending meetings from Academy 2, Argenx, Alexion, Almirall, Amicus Therapeutics Germany, AstraZeneca, Bayer HealthCare, Biogen, BioNtech, BMS, Celgene, Datamed, Demecan, Desitin, Diamed, Diaplan, DIU Dresden, DPmed, Gen Medicine and Healthcare products, Genzyme, Hexal AG, IGES, Impulze GmbH, Janssen Cilag, KW Medipoint, MedDay Pharmaceuticals, Medmile, Merck Serono, MICE, Mylan, Neuraxpharm, Neuropoint, Novartis, Novo Nordisk, ONO Pharma, Oxford PharmaGenesis, QuintilesIMS, Roche, Sanofi, Springer Medizin Verlag, STADA, Chugai Pharma, Teva, UCB, Viatris, Wings for Life international and Xcenda. Research funds-German Ministry for Education and Research (BMBF), German Federal Institute for Risk Assessment (BfR), German Research Foundation (DFG), Else Kröner Fresenius Foundation, Gemeinsamer Bundesausschuss (G-BA), German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology, Ministry of Culture and Science of the State of North Rhine-Westphalia and The Daimler and Benz Foundation, Multiple Sclerosis Society North Rhine-Westphalia Regional Association (dmsg), Peek & Cloppenburg Düsseldorf Foundation, Hempel Foundation for Science, Art and Welfare, German Alzheimer Society e.V. Dementia self-help, and Alexion, Almirall, Amicus Therapeutics Germany, Argenx, Bayer Vital GmbH, BGP Products Operations (Viatris Company), Biogen, BMS, Demecan, Diamed, DGM e.V., Fresenius Medical Care, Genzyme, Gesellschaft von Freunden und Förderern der Heinrich-Heine-Universität Düsseldorf e.V., HERZ Burgdorf, Hexal, Janssen, Merck Serono, Novartis, NovoNordisk Pharma, ONO Pharma, Roche and Teva. **Ludwig Kappos** received no personal compensation; his institutions (University Hospital Basel/Stiftung Neuroimmunology and Neuroscience Basel) received payments for steering committee, advisory and data safety monitoring board participation, consultancy services and educational activities from Bayer, Biogen, Bristol Myers Squibb, Celltrion Inc, Clene Nanomedicine Inc., EMD Serono Research and development, Galapagos NV, Genentech, Immunic AG, Janssen, Kiniksa Pharmaceuticals, Merck Healthcare AG, MSD Merck Sharp & Dohme AG, Minoryx Therapeutics S.L., Neurostatus UHB AG, Novartis, Roche, Sanofi, Shionogi BV, Wellmera AG, and Zai Lab and received research support from Novartis, Roche and Innosuisse. **Gabriel Pardo** has received personal compensation for serving as a Consultant for Roche Genentech, Sanofi Genzyme, EMD Serono, Novartis, TG Therapeutics, Alexion Pharmaceuticals and Amgen and for serving on a speakers' bureau for Biogen, Bristol Myers Squibb, EMD Serono, Novartis, Roche Genentech, Janssen, Sanofi Genzyme, TG Therapeutics, Horizon Therapeutics and Alexion Pharmaceuticals. **Scott Zamvil** is Editor-in-Chief of Neurology, Neuroimmunology and Neuroinflammation. He serves on the Advisory Committee for the American Congress on Treatment and Research in Multiple Sclerosis (ACTRIMS). He has served on the Editorial Board of the Journal of Clinical Investigation, The Journal of Immunology, The Journal of Neurological Sciences and Frontiers in Immunology, and has been a charter member of grant review committees for the National Institutes of Health (NIH) Clinical Neuroimmunology and Brain Tumors (CNBT) and the National Multiple Sclerosis Society (NMSS). He has served, or serves, as a consultant and received honoraria from Alexion, Amgen, Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals, Inc., and has served on Data Safety Monitoring Boards for Lilly, BioMS, Teva and Opexa Therapeutics. Currently, Dr. Zamvil receives research grant support from the NIH, NMSS, Sumaira Foundation and Spangler Foundation. **Ichiro Nakashima** serves on the scientific advisory boards for Chugai Pharmaceutical, Biogen Japan, UCB, and Novartis and receives honoraria for speaking engagements with Chugai Pharmaceutical, Alexion Pharmaceuticals, Biogen Japan, Mitsubishi Tanabe Pharma and Novartis. **Jin Nakahara** has received speaker honoraria from Alexion, AstraZeneca, Biogen, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Novartis, Sanofi, Sumitomo, Takeda and Roche; payments for steering committee and/or scientific advisory board from Alexion, AstraZeneca, Biogen, Chugai, Mitsubishi-Tanabe, Novartis, Sanofi and Roche; and research support from Biogen, Chugai, JB, Keio University, Kyowa- Kirin, MEXT, MHLW, Otsuka and Sumitomo. **Anil Abeyewickreme**, **Jun Li**, **Min Wu**, **Maria Solonets** and **Valentine Jehl** are employees of Novartis.

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