

Long-Term Ofatumumab Treatment Over 6 Years Did Not Increase the Risk of Serious Infections

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CONCLUSIONS

- The annualised rates of serious infections remained low and did not increase over time through 6 years of ofatumumab treatment in pwRMS
- The rates of serious COVID-19 cases remained low with ofatumumab treatment
- Overall, IgG levels remained above the LLN in 97.1% of patients at all timepoints during the 6 years of ofatumumab treatment
 - Only isolated cases of serious infections were observed when IgG levels were below the LLN
- These findings reinforce the established, favourable, long-term safety profile of ofatumumab in pwRMS

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INTRODUCTION

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for the treatment of relapsing multiple sclerosis (RMS) in adults and is the only anti-CD20 therapy intended for self-administration^{1,2}
- 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 people with RMS (pwRMS)³
- Ofatumumab treatment up to 6 years showed a favourable safety and tolerability profile, with no new safety signals identified in pwRMS^{4,5}
- Assessment of the risk of serious infections with long-term use of B-cell–depleting therapies such as ofatumumab can help clinicians in their decision-making process

OBJECTIVE

- To evaluate the risk of developing serious infections with ofatumumab treatment over 6 years (cut-off date: 25-Sep-2023) in pwRMS

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

- Serious infections (as assessed by the investigator) were assessed in participants receiving ofatumumab
- 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 serious infections (i.e., concurrent or ≤3 days apart) that were part of the same risk category (i.e., upper, lower and unspecified respiratory tract infections [excluding COVID-19]; COVID-19; appendicitis; urinary tract infections; herpes viral infections and others) were counted as a single infection

- Serious infections occurring within and outside a 30-day window of immunoglobulin (Ig)G levels below the lower limit of normal (LLN: 5.65 g/L) were evaluated; instances where no serious infections were found despite IgG<LLN at any point in time during the study were also investigated
 - The IgG assessment schedule was previously presented elsewhere⁶

Statistical analyses

- The annualised rate of serious infections 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 offset variable
- COVID-19 incidence was evaluated based on calendar years rather than years on ofatumumab, as cases of COVID-19 occurred only during 2020–2023; Poisson model was used to analyse the outcome

RESULTS

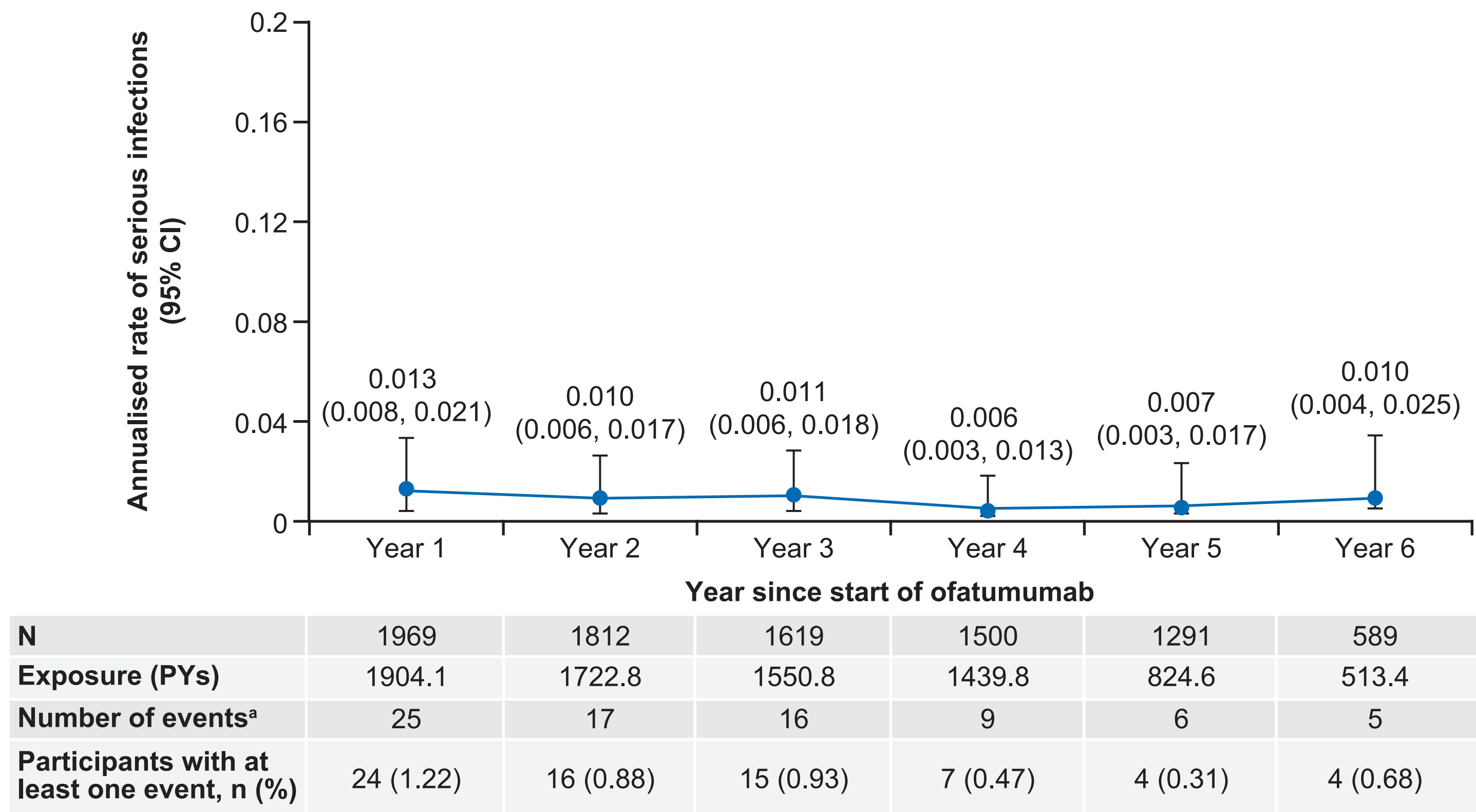
Summary of serious infections

- Overall, 1969 pwRMS were included in the analyses (cumulative exposure, 8042.7 patient-years [PYs]), of which 115 (5.84%) had a total of 130 serious infections over 6 years; most of these serious infections were Grade 1–3 in severity
- Of 115 pwRMS with serious infections:
 - 103 participants had 1 serious infection and 12 had multiple serious infections (9 had two serious infections and 3 had three serious infections)
 - 90.4% (104/115) completely recovered, 3.48% (4/115) recovered with sequelae or were recovering, 0.87% (1/115) had not recovered (at the data cut-off), and 5.22% (6/115) had fatal outcomes
- The most commonly reported serious infections were COVID-19/COVID-19 pneumonia (2.49%; 49/1969), urinary tract infections (0.91%; 18/1969), lower respiratory tract infections (0.81%; 16/1969) and appendicitis (0.76%; 15/1969)
- Eight patients discontinued ofatumumab due to serious infections:
 - COVID-19 or COVID-19 pneumonia (n=5, fatal), upper respiratory tract infection (n=1, recovered), tubo-ovarian abscess (n=1, recovered) and pneumonia and septic shock (n=1, fatal; the participant had a history of kyphosis)
- Up to 6 years of ofatumumab treatment, one case of serious opportunistic infection of *Pneumocystis jirovecii* was reported; external adjudication did not confirm the final diagnosis and further noted that the clinical course was not suggestive of *P. jirovecii* pneumonia:
 - The participant had no change in the dosage or interruption of ofatumumab therapy and fully recovered

Annualised rates of serious infections over time

- The annualised rate of serious infections (excluding COVID-19) was low and stable throughout 6 years of ofatumumab treatment (**Figure 1**)

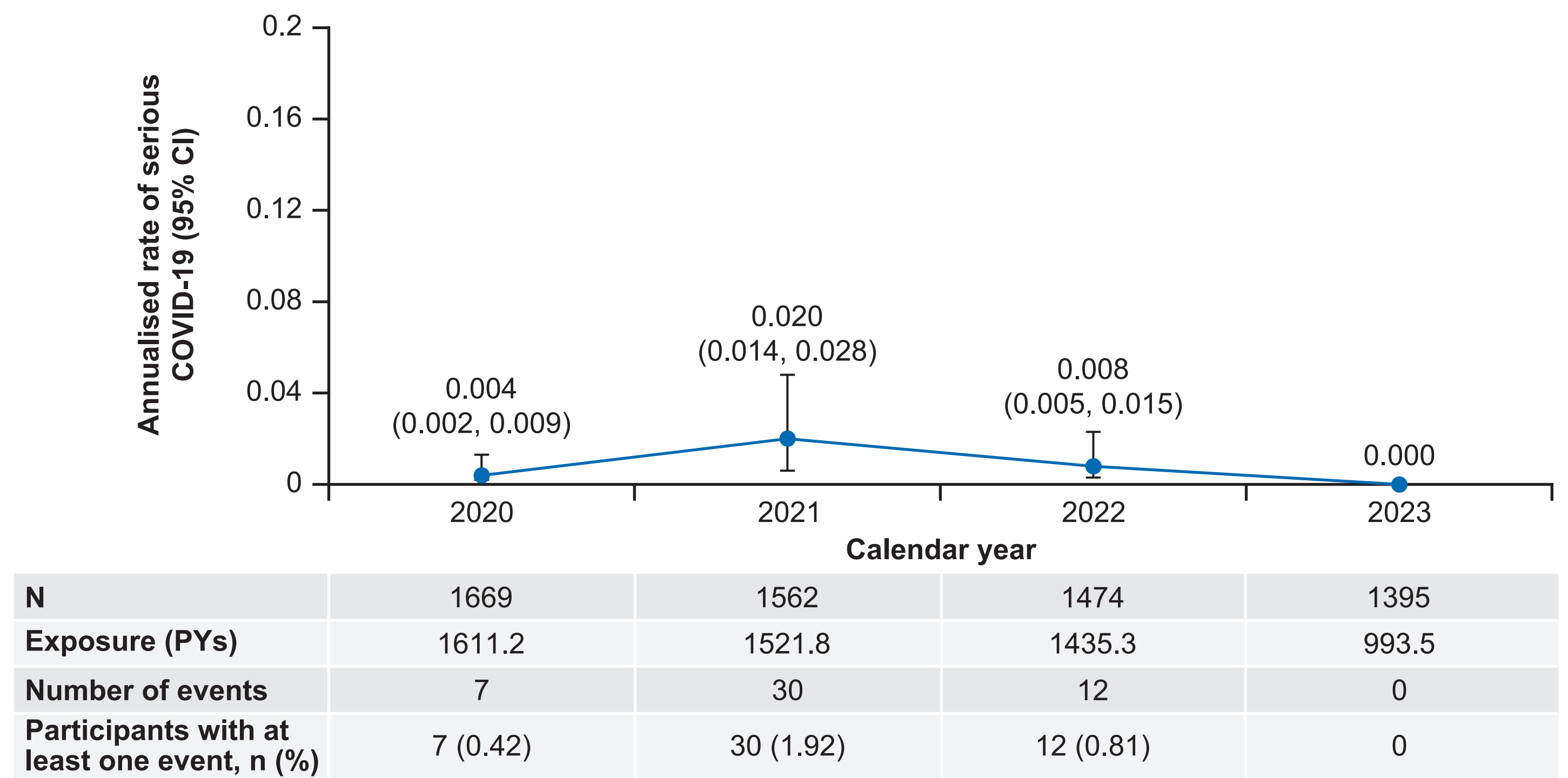
Figure 1. Annualised rates of serious infection (excluding COVID-19; safety analysis set)



^aPossibility of multiple events per participant in a given year. CI, confidence interval; N, number of participants; PY, patient-year.

- From 2020 to 2023, the annualised rate of serious COVID-19 cases remained low, with the highest rate observed in 2021; this number gradually decreased and reached 0 by 2023 (as of data cut-off; **Figure 2**)

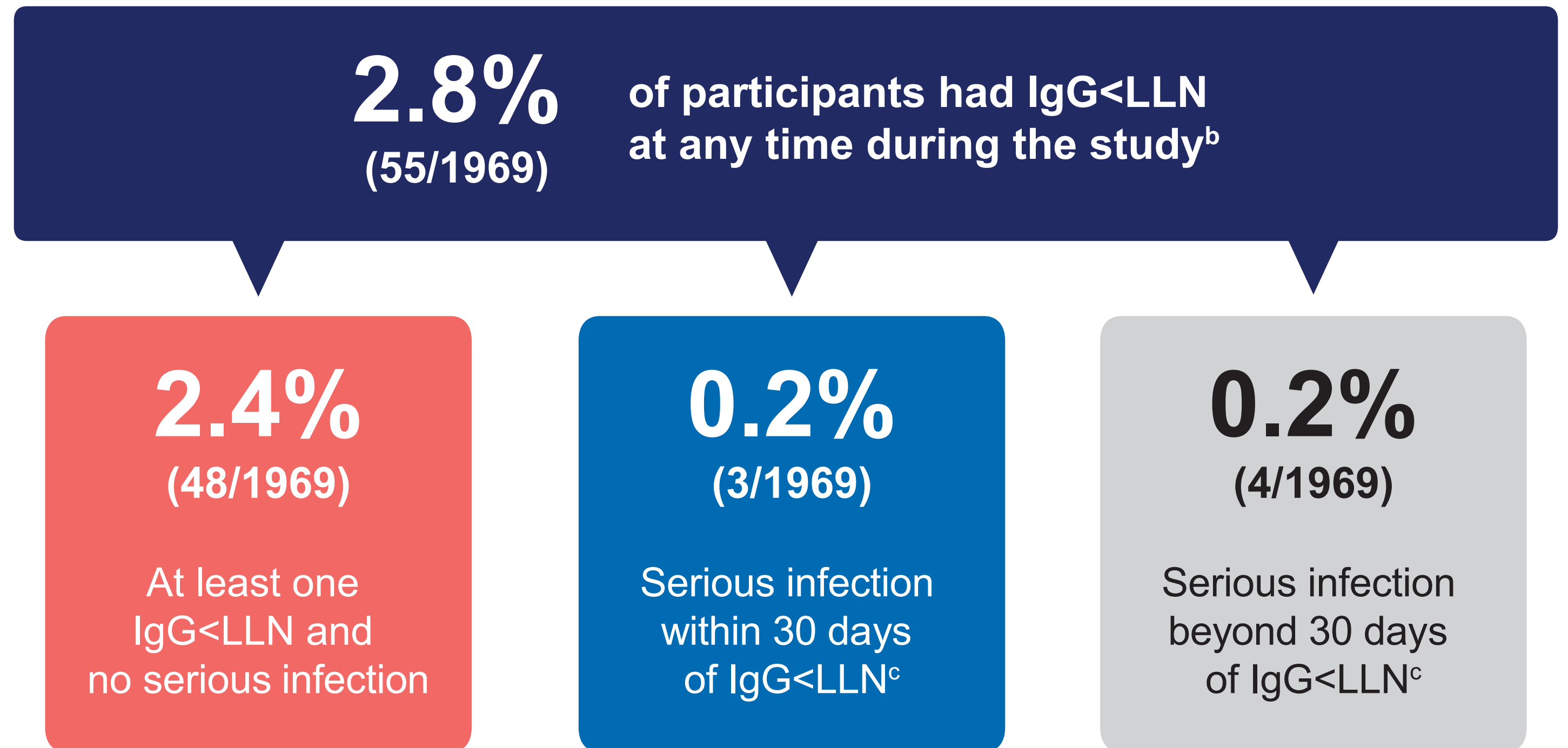
Figure 2. Annualised rate of serious COVID-19 cases (safety analysis set)



CI, confidence interval; N, number of participants; PY, patient-year.

Serious infections and IgG levels

- In 97.1% (1911/1969) of participants, IgG levels remained above the LLN at all timepoints up to 6 years of ofatumumab treatment⁸



^aNumber of participants with no occurrence of IgG<LLN at least once at any time during the post baseline visit. ^bNumber of participants with IgG<LLN at least once at any time during the post baseline visit. ^cAll cases of serious infections within and beyond 30 days of IgG<LLN were resolved and recovered. Ig, immunoglobulin; LLN, lower limit of normal.

References

1. Kesimpta (ofatumumab). Summary of product characteristics. Novartis; 2024. Accessed 03 March 2025. https://www.ema.europa.eu/en/documents/product-information/kesimpta-epar-product-information_en.pdf.
2. Kesimpta (ofatumumab). Prescribing information. Novartis; 2024. Accessed 03 March, 2025. https://www.novartis.com/us-en/sites/novartis_us/files/kesimpta.pdf.
3. Hauser SL, et al. *N Engl J Med*. 2020;383:546–557.
4. Wiendl H, et al. P9.010. Presented at: American Academy of Neurology (AAN) Annual Meeting, Denver, CO, USA; 13–18 April 2024.
5. Wiendl H, et al. EPO-398. Presented at: European Academy of Neurology (EAN), Helsinki, Finland; 29 June–2 July 2024.
6. Wiendl H, et al. P709. Presented at 9th JointECTRIMS-ACRIMS Meeting, Milan, Italy; 11–13 October 2023.

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Disclosures

Heinz Wiendl has acted as a member of the Scientific Advisory Boards of Alexion, Argenx, Biocryst, Bristol Myers Squibb, Cellerys, Galapagos, Janssen, Merck, Novartis, Sandoz-Hexal and Uniqure. He has received speaker honoraria and travel support from Alexion, Biogen, Bristol Myers Squibb, EPG Health, Genzyme, Merck, Neurodiem, Novartis, Ology, Roche, Teva and WebMD Global and acts as a paid consultant for AbbVie, Actelion, Argenx, Biogen, Bristol Myers Squibb and EMD Serono. He is a paid consultant for Actelion, Argenx, BD, Bristol Myers Squibb, Dianthus, EMD Serono, EPG Health, Fondazione Cariplo, Gossamer Bio, Idorsia, Immunic, Immunovant, INmune Bio, Syneos Health, Janssen, LTS, Merck, NexGen, Novartis, Roche, Samsung, Sangamo, Sanofi, Swiss Multiple Sclerosis Society, Toleranzia, UCB, Viatrix, VirBio and Worldwide Clinical Trials. His research is funded by Alexion, Amicus Therapeutics, Argenx, Biogen, CSL Behring, F. Hoffmann-La Roche, Genzyme, Merck, Novartis, Roche and UCB. **Sven G. Meuth** has received honoraria for consulting from Alexion, Almirall, Amicus Therapeutics Germany, Bayer Healthcare, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva. He has received a research grant from German Ministry for Education and Research (BMBF), Bundesinstitut für Risikobewertung (BfR), Deutsche Forschungsgemeinschaft (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 and Alexion, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, HERZ Burgdorf, Merck Serono, Novartis, ONO Pharma, Roche and Teva. **Gabriel Pardo** has received personal compensation for serving as a consultant for Amgen, Biogen, Roche/Genentech Inc., Sanofi-Genzyme, EMD Serono, Horizon Therapeutics, TG Therapeutics and Novartis. He has also received personal compensation for serving on a speakers' bureau for Biogen, Bristol Myers Squibb, Horizon Therapeutics, Roche/Genentech, Sanofi-Genzyme, Novartis, EMD Serono and TG Therapeutics. **Scott S. Zamvil** has received consulting honoraria from Alexion, Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech and Teva Pharmaceuticals and has served on Data Safety Monitoring Boards for Eli Lilly, BioMS, Teva and Therapeutics. **Xavier Montalban** has received speaking honoraria and travel expenses for participation in scientific meetings and has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, medDay, Merck, Mylan, NervGen, Novartis, Roche, Sanofi Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS. **Jeffrey A. Cohen** has received personal compensation for consulting for Astoria, Bristol Myers Squibb, Convelo Therapeutics, EMD Serono, Find Therapeutics, INmune and Sandoz and serves as an Editor in *Multiple Sclerosis Journal*. **Ibolya Boer**, **Alit Bhatt**, **Min Wu**, **Xixi Hu**, **Valentine Jehl** and **Roseanne Sullivan** are employees of Novartis.