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Five-Year Safety of Ofatumumab in People Living With Relapsing Multiple Sclerosis

Jeffrey A. Cohen,[1] Stephen L. Hauser,[2] Anne H. Cross,[3] Kevin Winthrop,[4] Heinz Wiendl,[5] Jacqueline Nicholas,[6] Sven G. Meuth,[7] Paul S. Giacomini,[8] Francesco Sacca,[9] Ronald Zielman,[10] Ayan Das Gupta,[11] Xixi Hu,[12] Roseanne Sullivan,[12] Virginia DeLasHeras,[13] Ludwig Kappos[14]

[1]Department of Neurology, Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA; [2]UCSF Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA; [3]Washington University School of Medicine, St. Louis, MO, USA; [4]Public Health and Preventive Medicine, Division of Infectious Diseases, Oregon Health & Science University, Portland, OR, USA; [5]University of Muenster, Muenster, Germany; [6]OhioHealth Multiple Sclerosis Clinic, Columbus, OH, USA; [7]Department of Neurology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany; [8]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, QC, Canada; [9]NSRO Department, University "Federico II" of Naples, Naples, Italy; [10]Novartis Pharma B.V., Amsterdam, the Netherlands; [11]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [12]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [13]Novartis Pharma AG, Basel, Switzerland; [14]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) and MS Center, Departments of Head, Spine and Neuromedicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland

SUMMARY

1 **This analysis assessed safety and tolerability of ofatumumab (OMB) up to 5 years in patients with RMS who received continuous OMB in the core studies (ASCLEPIOS I/II, APLIOS and APOLITOS) and ALITHIOS, and those newly switched to OMB from teriflunomide in ALITHIOS**

2 **Exposure-adjusted incidence rate of serious infections remained stable, with no increased risk over 5 years; most reported cases of COVID-19 were nonserious and the majority of patients recovered. Mean IgG levels remained stable, whereas mean IgM levels decreased but remained above the LLN; no association between reduction in Ig levels and risk of serious infections was found**

3 **OMB treatment for up to 5 years was well tolerated with no new or increased safety risks identified, supporting the favorable benefit-risk profile for OMB in RMS patients**

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INTRODUCTION

- Ofatumumab (OMB), a fully human anti-CD20 monoclonal antibody with a 20-mg subcutaneous monthly dosing regimen, is approved for treating relapsing multiple sclerosis (RMS) in adults[1]
- In the phase 3 ASCLEPIOS I/II trials, OMB treatment up to 30 months had a favorable safety profile and was generally well tolerated in patients with RMS[2]
- OMB treatment up to 4 years was well tolerated, with no new safety risks identified,[3,4] and efficacy was sustained over time[5]
- Longer-term safety and efficacy assessments are important to further understand OMB's benefit-risk profile in patients with RMS

OBJECTIVE

- To assess the longer-term safety and tolerability of OMB treatment (20 mg every 4 weeks) for up to 5 years (data cutoff: September 25, 2022) in patients with RMS

STUDY DESIGN

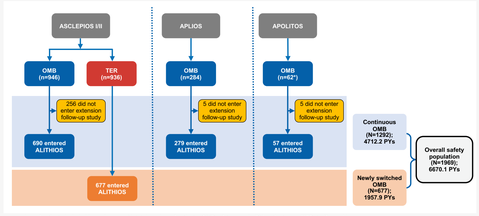
- ALITHIOS (NCT03650114) is a phase 3, open-label, single-arm extension of the core OMB clinical trials (ASCLEPIOS I [NCT02792218] and II [NCT02792231], APLIOS [NCT03560739], and APOLITOS [NCT03249714]) in patients with RMS
- Patients receiving continuous OMB in the core trials and ALITHIOS, and those newly switched to OMB from teriflunomide in ALITHIOS, were included in this analysis
- The following safety outcomes were examined:
  - Overall adverse events (AEs)
  - Risk of serious infections (excluding coronavirus disease 2019 [COVID-19])
  - Risk of COVID-19 infection
  - Serum immunoglobulin G (IgG) and immunoglobulin M (IgM) levels
  - Incidence of malignancies

RESULTS

PATIENT POPULATION

- A total of 1969 patients were included in this pooled safety analysis (**Figure 1**)
- 86.5% of patients completed the core studies and entered ALITHIOS; of these, 83.1% were still receiving OMB treatment at the time of data cutoff

Figure 1. Overall Safety Population



n, number of patients included in each group; N, total number of patients; OMB, ofatumumab; PY, patient-year; TER, teriflunomide
*Patients were either randomized to or switched to OMB during the core study

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Patient baseline demographics were typical of a broad RMS population (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Continuous OMB (N=1292)	Newly switched OMB (N=677)		Overall OMB (N=1969)
		Baseline from core study	Baseline from extension study	
Age, years, mean ± SD	38.0±9.06	38.2±9.22	40.1±9.21	38.7±9.16
BMI, mean ± SD, kg/m²	25.61±6.16	25.69±5.83	25.61±5.85	25.61±6.05
Female, n (%)	889 (68.8)	456 (67.4)	456 (67.4)	1345 (68.3)
Time since MS symptom onset, years, mean ± SD	8.48±7.33	8.06±7.21	9.94±7.23	8.98±7.33
Time since diagnosis, years, mean ± SD	5.87±6.31	5.45±6.00	7.33±6.01	6.37±6.25
EDSS score at baseline, mean ± SD	2.90±1.33	2.77±1.32	2.82±1.46	2.88±1.38
IgG levels at baseline, g/L, mean ± SD	10.31±2.24	10.35±2.09	10.23±2.14	10.28±2.21
IgM levels at baseline, g/L, mean ± SD	1.34±0.65	1.36±0.74	1.14±0.67	1.27±0.66
Median duration of time at risk, years	3.8	3.2	3.2	3.3
Total time at risk, PYs	4712.2	1957.9	1957.9	6670.1

BMI, body mass index; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; IgM, immunoglobulin M; MS, multiple sclerosis; n, number of patients included in each group; N, total number of patients; OMB, ofatumumab; PY, patient-year; RMS, relapsing multiple sclerosis; SD, standard deviation
For OMB newly switched patients, their baseline values from the extension study contribute to the overall OMB baseline values. Baseline values are typical of a broad RMS population

OVERALL AEs

- Exposure-adjusted incidence rate (EAIR) per 100 patient-years (PYs) of AEs and serious AEs over 5 years of OMB treatment remained consistent during the ASCLEPIOS I/II trials and ALITHIOS extension study (**Table 2**) and no new safety signals were identified
- The most common AEs were infections, including COVID-19 (30.3%), nasopharyngitis (19%), upper respiratory tract infection (12.8%), and urinary tract infection (12.7%)
  - Most (90.3%) infections resolved without discontinuing OMB treatment

RISK OF SERIOUS INFECTION

- The overall EAIR per 100 PYs of serious infections (excluding COVID-19) was consistent with the ASCLEPIOS I/II trials (EAIR: 1.55) and no increased risk was observed over 5 years of OMB treatment (**Table 2**)
- Most common serious infections (excluding COVID-19) included appendicitis (n=13) and pneumonia (n=9)
- 1 case of serious opportunistic infection (*Pneumocystis jirovecii pneumoniae*) was reported; the final diagnosis was not confirmed by an external expert and the clinical course was not suggestive of *Pneumocystis jirovecii* pneumonia
- Almost all (95%) patients recovered; however, there was 1 fatal case due to pneumonia and septic shock
- The majority of serious infections were Grade 3 or below in severity (Grade 1: 3.28%; Grade 2: 32.8%; Grade 3: 57.4%; Grade 4: 6.55%)
  - 3 (4.91%) patients discontinued OMB

Table 2. AEs in the Overall Safety Population

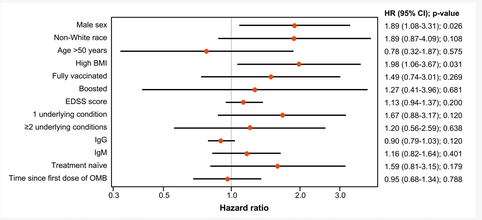
Adverse event	Core, ASCLEPIOS I/II				Core + extension, overall OMB (N=1969)	
	OMB, n (%)	OMB, EAIR (95% CI)	TER, n (%)	TER, EAIR (95% CI)	n (%)	EAIR (95% CI)
Patients with ≥1 AE	791 (83.61)	188.55 (175.86-202.16)	788 (84.2)	188.92 (176.18-202.58)	1771 (89.9)	124.65 (118.97-130.59)
Patients with ≥1 SAE	83 (8.77)	5.56 (4.48-6.89)	73 (7.8)	4.94 (3.93-6.21)	289 (14.7)	4.68 (4.17-5.26)
AEs leading to OMB discontinuation	54 (5.70)	-	49 (5.2)	-	139* (7.1)	-
Infections and infestations	488 (51.58)	51.14 (46.80-55.88)	493 (52.7)	52.59 (48.14-57.44)	1334 (67.75)	40.99 (38.85-43.25)
Serious infections	24 (2.54)	1.55 (1.04-2.31)	17 (1.8)	1.12 (0.69-1.80)	106 (5.38)	1.63 (1.35-1.97)
Serious infections (excluding COVID-19)	24 (2.54)	1.55 (1.04-2.31)	17 (1.8)	1.12 (0.69-1.80)	61 (3.09)	0.93 (0.73-1.20)
Serious COVID-19 infections	0	0	0	0	50 (2.53)	0.75 (0.57-1.00)
Injection-related systemic reactions	195 (20.61)	15.49 (13.46-17.83)	143 (15.3)	10.90 (9.25-12.84)	508 (25.79)	10.06 (9.22-10.98)
Injection site reactions	103 (10.88)	7.21 (5.94-8.74)	52 (5.55)	3.54 (2.70-4.65)	243 (12.34)	4.08 (3.60-4.63)
Malignancies	5 (0.53)	0.32 (0.13-0.77)	4 (0.4)‡	0.26 (0.10-0.69)	21 (1.06)	0.32 (0.21-0.48)
Deaths	0	-	1§	-	9† (0.46)	-

AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; IgM, immunoglobulin M; OMB, ofatumumab; PT, Preferred Term; PY, patient-year; SAE, serious adverse event; TER, teriflunomide
EAIRs per 100 PYs are defined as the number of patients with a particular event during 100 years of exposure to a treatment, estimated by Poisson regression, where patients were censored at time of first event
*AE related to reduced IgM levels was the most common reason for treatment discontinuation (n=71 [3.6%]); †PTs for these 9 cases include the following: sudden death (n=1), committed suicide (n=1), COVID-19 and COVID-19 pneumonia (n=2), COVID-19 (n=2), intestinal metastasis (n=1), pneumonia and septic shock (n=1), pneumothorax (n=1); ‡1 case of basal cell carcinoma was not listed as a SAE; §Death was due to aortic dissection

RISK OF COVID-19 INFECTION

- At data cutoff, 648 of the 1703 patients entering ALITHIOS reported COVID-19 (confirmed [n=603]; suspected [n=45])
- 93.9% were mild or moderate in severity and 92.3% were characterized as nonserious
- In fully vaccinated patients (n=704), most cases of confirmed COVID-19 (n=167 [23.7%]) were mild to moderate and most patients recovered
- 5 patients had a fatal outcome (COVID-19 [n=2], COVID-19 pneumonia [n=1], COVID-19 and COVID-19 pneumonia [n=1], COVID-19 pneumonia and pneumothorax [n=1])
  - 3 of these patients were unvaccinated; 2 were fully vaccinated
- Almost all patients (98.6%) treated with OMB either recovered, recovered with sequalae, or were recovering from COVID-19
- Serious COVID-19 infections were reported in 50 (2.9%) patients during the ALITHIOS extension study
- Of these, the majority (82%) recovered; however, there were 5 fatal cases due to the infection course
- The majority of serious COVID-19 cases were Grade 3 or below in severity (Grade 1: 4%; Grade 2: 32%; Grade 3: 52%; Grade 4: 12%)
  - 5 (10%) patients discontinued OMB
- The only identified risk factors for serious COVID-19 infections were male sex (hazard ratio [HR]: 1.89) and high body mass index (HR: 1.98; **Figure 2**)

Figure 2. Risk Factors of Serious COVID-19

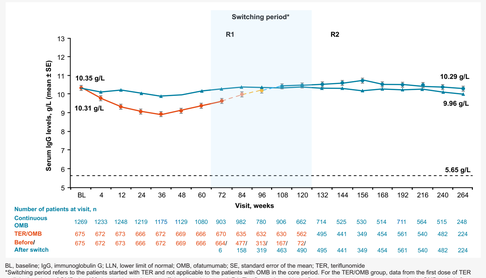


BMI, body mass index; CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IgG, immunoglobulin G; IgM, immunoglobulin M; OMB, ofatumumab
The analysis was based on ALITHIOS patients who were "on OMB" (including 100 days after the last dose) as of the beginning of 2020. It confirmed the association of some factors with serious COVID-19 but did not rule out the potential causation with other factors as reported in literature. Obtained from a Cox model with adjustment for sex, race, age (>50 vs ≤50 years), BMI (≥30 vs <30 kg/m²), EDSS score, number of underlying conditions, previous DMTs, and time since first dose of OMB (years), and with vaccination status, IgG, and IgM as time-varying covariates. For covariates other than vaccination status, IgG, and IgM, the last available value by January 1, 2020 was used

SERUM IgG AND IgM LEVELS

- Mean IgG levels remained stable with up to 5 years of treatment (**Figure 3**); mean IgM levels decreased but remained above the lower limit of normal (LLN; **Figure 4**)
- 98% and 69.4% of patients had IgG and IgM levels above LLN, respectively
- Treatment interruption/discontinuation was reported in 3 (0.2%)/4 (0.2%) patients due to low IgG levels and in 202 (10.3%)/71 (3.6%) patients due to low IgM levels

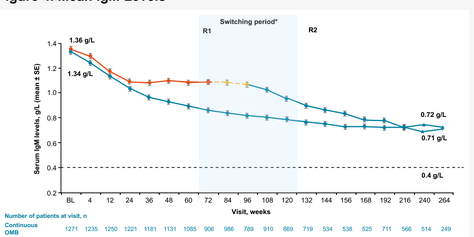
Figure 3. Mean IgG Levels



BL, baseline; IgG, immunoglobulin G; LLN, lower limit of normal; OMB, ofatumumab; SE, standard error of the mean; TER, teriflunomide
*Switching period refers to the patients started with TER and not applicable to the patients with OMB in the core period. For the TER/OMB group, data from the first dose of TER until the last dose of OMB plus 100 days or the analyses cutoff date have been used. R1: The first patient with the first treatment-emergent assessment in the TER period before switching to OMB (120 weeks). R2: The last patient with the last treatment-emergent assessment in the TER period before switching to OMB (120 weeks). For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used (IgG: 5.65 g/L)

- Sensitivity analyses confirmed that interruption/discontinuation of OMB due to low IgG/IgM levels did not affect overall IgG/IgM patterns
- No association between decreased IgG/IgM levels and risk of serious infections was observed (data not shown)

Figure 4. Mean IgM Levels

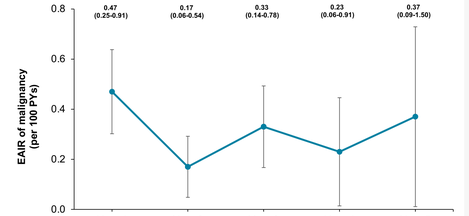


BL, baseline; IgM, immunoglobulin M; LLN, lower limit of normal; OMB, ofatumumab; SE, standard error of the mean; TER, teriflunomide
*Switching period refers to the patients started with TER and not applicable to the patients with OMB in the core period. For the TER/OMB group, data from the first dose of TER until the last dose of OMB plus 100 days or the analyses cutoff date have been used. R1: The first patient with the first treatment-emergent assessment in the TER period before switching to OMB (120 weeks). R2: The last patient with the last treatment-emergent assessment in the TER period before switching to OMB (120 weeks). For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used (IgM: 0.4 g/L)

INCIDENCE OF MALIGNANCIES

- EAIRs for malignancies did not increase over time in the overall OMB population (**Figure 5**)
- Accumulated malignancies (core + extension) were reported in 21 (1.07%) patients with EAIR of 0.32 (95% confidence interval: 0.21-0.48)
- Median onset time since the first dose of OMB was 565 (191-1747) days

Figure 5. Malignancies by Year



	Year 1	Year 2	Year 3	Year 4	Year 5
Patients, N	1969	1812	1618	1381	615
PY	1901	1719	1531	877	535
No. of events	9	3	5	2	2

EAIR, exposure-adjusted incidence rate; N, total number of patients; PY, patient-year

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