Effectiveness and Safety of Ofatumumab in Relapsing Multiple Sclerosis Patients who had Breakthrough Disease Activity on Oral Fumarates or Fingolimod: An Interim Analysis of ARTIOS

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INTRODUCTION

- Ofatumumab, a fully-human anti-CD20 monoclonal antibody with a 20-mg s.c. monthly dosing regimen, is approved for the treatment of relapsing forms of MS in adults, based on results from the ASCLEPIOS Phase 3 studies
- The number of RMS patients transitioning from oral therapies due to breakthrough disease was limited in the ASCLEPIOS I/II Phase 3 trials
- ARTIOS, a Phase 3b open-label, single-arm, prospective, non-comparative study aims to bridge this gap and address relevant clinical practice questions on the effectiveness, safety, and PROs in patients transitioning to ofatumumab from fumarates or fingolimod

OBJECTIVE

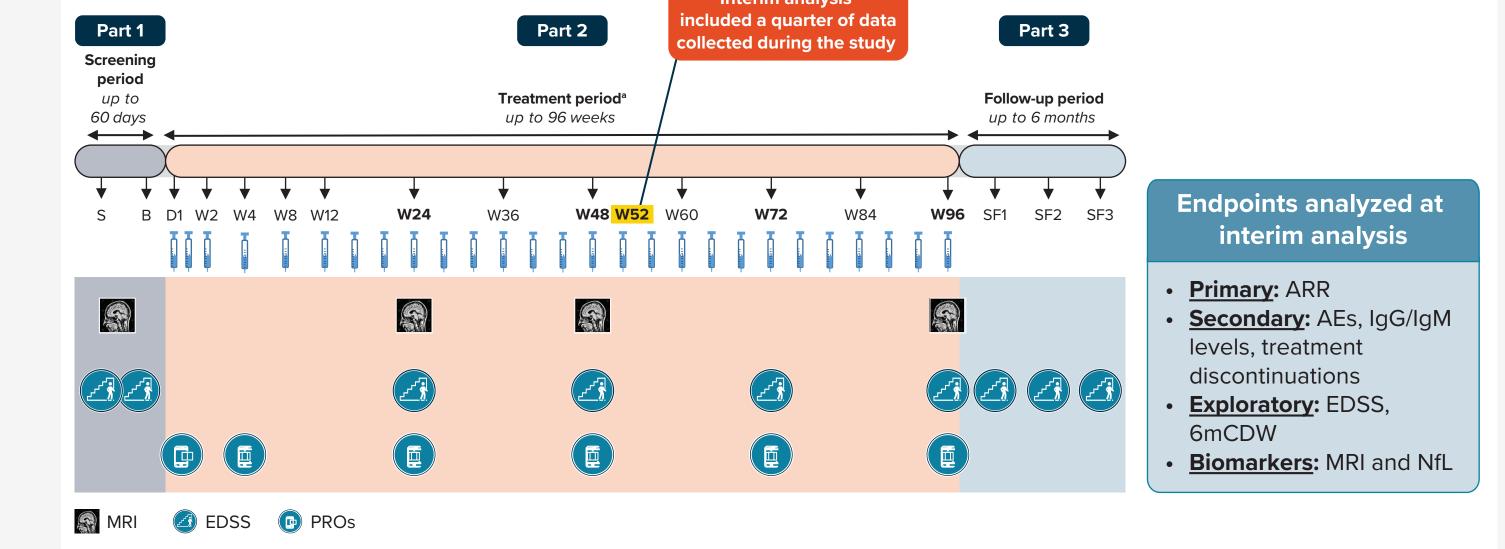
- To assess the effectiveness and safety of ofatumumab 20 mg s.c. in RMS patients with breakthrough disease on oral fumarates or fingolimod
- Primary objective: To demonstrate the effectiveness of ofatumumab 20 mg s.c. as measured
- Secondary objectives: To evaluate the safety of ofatumumab 20 mg s.c. by assessing AEs, proportion of patients with laboratory evaluations or vital signs results meeting abnormal criteria, and the proportion of subjects discontinuing treatment

METHODS

STUDY DESIGN AND ENDPOINTS

- ARTIOS is an ongoing Phase 3b open-label, single-arm, non-comparative study
- Study protocol was in line with the local ofatumumab labels and the local medical practice; thus, several assessments were left to the investigators' discretion (e.g. prior DMT wash-out duration, symptoms assessment, observation time at site, etc.)
- Interim analysis was conducted for administrative purposes after ~50% of planned enrolled subjects completed the Week 48 visit + 4 weeks of follow-up for relapses and AEs

Figure 1. Patient Population

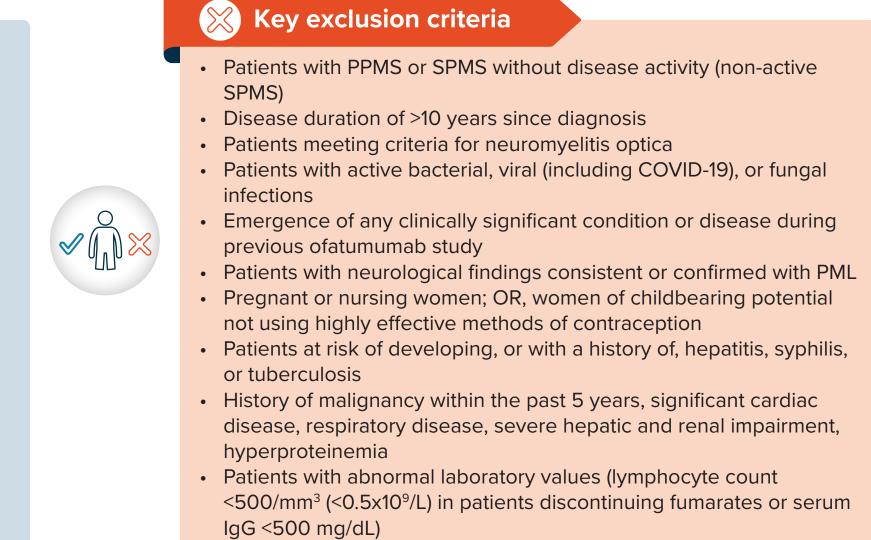


^aOMB 20 mg s.c. injection once every 4 weeks (following initial loading dose regimen of three 20 mg s.c. doses in the first 14 days)

Figure 2. Key Inclusion and Exclusion Criteria

✓ Key inclusion criteria Adults aged 18–60 years (inclusive) at screening

Diagnosis of MS (revised McDonald 2017 criteria) Relapsing forms of MS, including RMS and SPMS EDSS score of 0–4 at screening MS treatment history with a maximum of 3 DMTs Most recent DMT either fumarate-based therapies or fingolimod, administered for at least 6 months, prior to transition to study drug Breakthrough disease activity while the patient was adequately using fumarate-based therapy or fingolimod prior to transitioning, as evidenced by ≥1 clinically reported relapses or ≥1 signs of MRI activity (eg, Gd+, new, or enlarging T2 lesions) Neurologically stable in the prior 1 month of first study drug administration



RESULTS

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- At baseline, mean patient age was approximately 37.4 years; majority were women (>60%) (Table 1)
- The mean EDSS at baseline was approximately 2.4
- Mean exposure was 52 weeks. Only 6 patients discontinued (4 due to subject decision, 1 due to AE, 1 due to physician decision)

Table 1. Baseline Demographics and Clinical Characteristics

all Population N=278 37.4±9.81 472 (61.9) 2.42±1.13 201 (72.3) 1.13±12.03 19 (42.8) 05 (37.8)	Fingolimod N=89 38.1±9.13 57 (64.0) 2.52±1.13 57 (64.0) ^a 13.31±13.24 ^a 20 (22.5) ^a 46 (51.7) ^a	Fumarate-Based Therapy N=189 37.1±10.12 115 (60.8) 2.37±1.13 (76.2) ^a 10.11±11.31 ^a 99 (52.4) ^a 59 (31.2) ^a
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19 (42.8)	20 (22.5)ª	99 (52.4)ª
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05 (37.8)	46 (51.7)ª	59 (31.2) ^a
		7 7 7
54 (19.4)	23 (25.8)ª	31 (16.4) ^a
.67±2.94	6.30±2.68°	5.37±3.01°
0.9±0.68	0.9±0.71	0.9±0.66
9.89±2.0	8.86±1.90°	10.37±1.93°
1.1±0.6	0.90±0.46°	1.19±0.65 ^a
.36±0.55	1.10±0.45°	1.48±0.55°
3.6±42.57	52±39.8ª	39.6±43.35°
18 (42.4)	26 (29.2)ª	92 (48.7)ª
60 (57.6)	63 (70.8) ^a	97 (51.3) ^a
3	0.9±0.68 0.89±2.0 1.1±0.6 36±0.55 3.6±42.57 18 (42.4) 50 (57.6)	0.9±0.68

ANNUALIZED RELAPSE RATE

 Adjusted ARR was low at 0.12 (95% CI: 0.08, 0.18) and met the nominal threshold for significance (p=0.023 [null hypothesis ARR≥0.18])

Table 2. Annualized Relapse Rate

N, total number of subjects included in the analysis.

	ARR ^a		
Treatment	N	Adusted ARR (95% CI)	
Ofatumumab 20 mg	274	0.12 (0.08, 0.18) p=0.023	

MRI LESION ACTIVITY

- Ofatumumab treatment significantly reduced Gd+T1 lesions at Week 24 and was almost completely suppressed at Week 48 versus baseline (Figure 3)
- Number of neT2 lesions was nearly completely suppressed between Week 24 and Week 48

^aConfirmed relapses are those accompanied by a clinically relevant change in the EDSS.

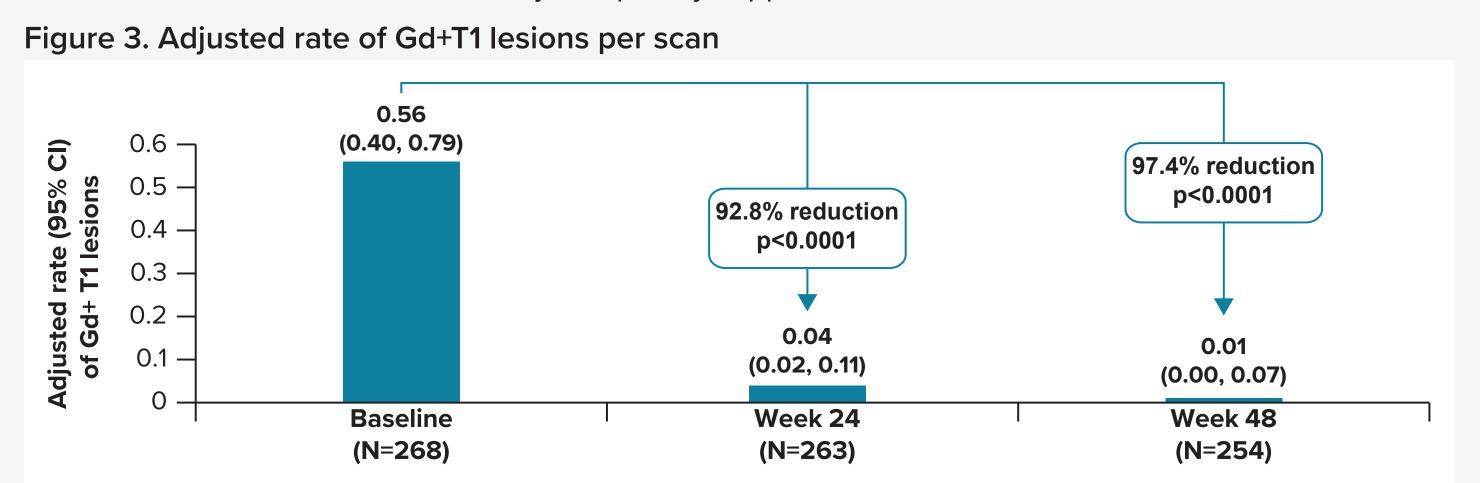
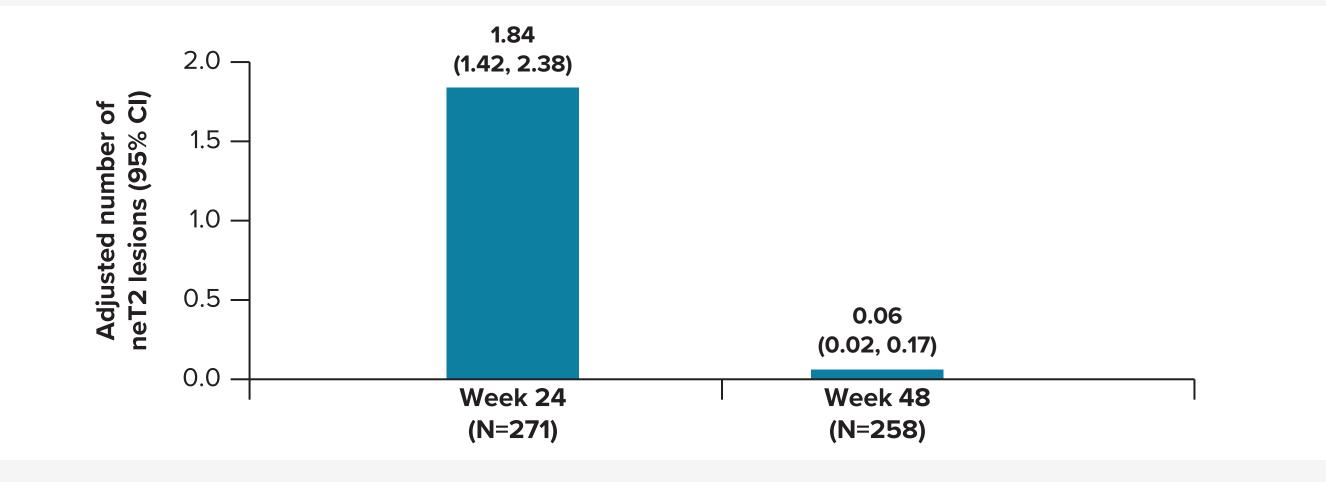


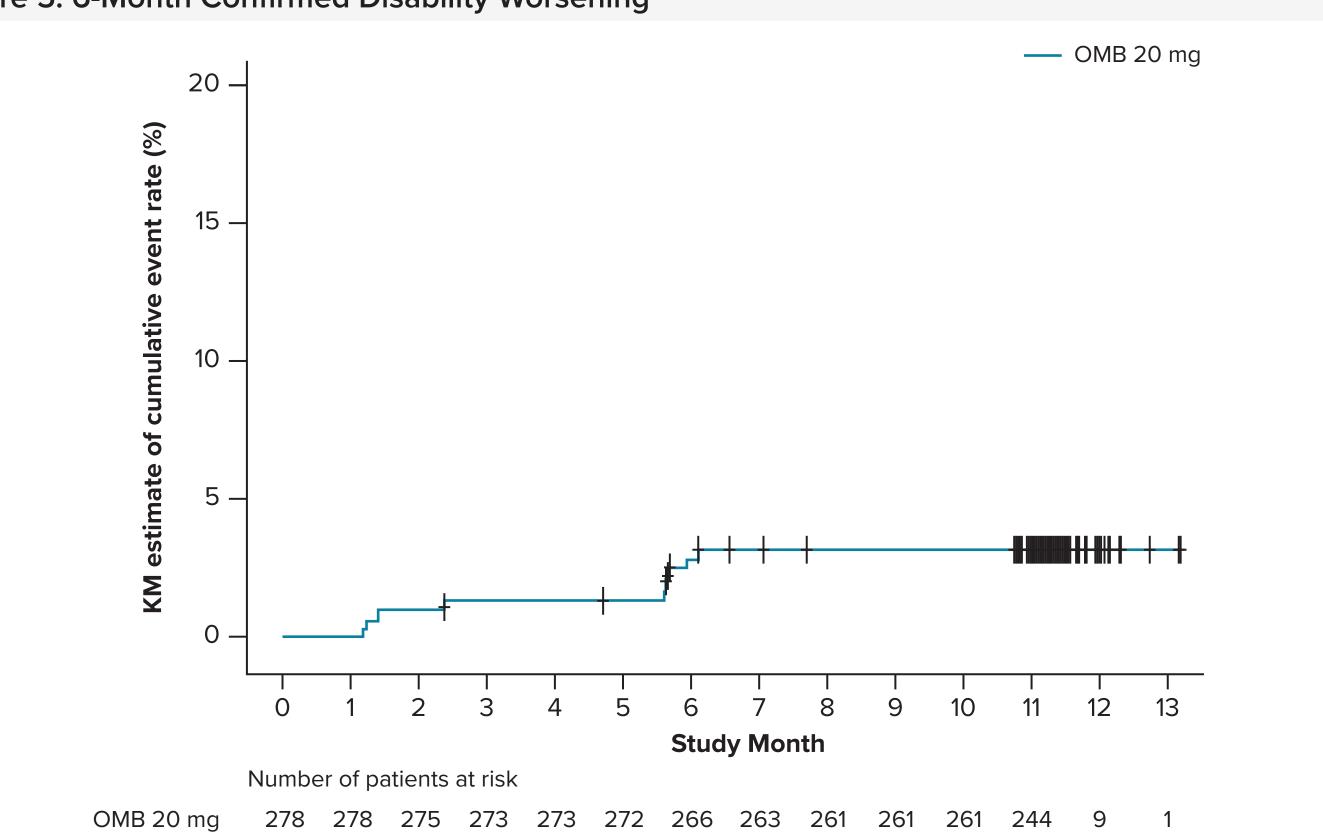
Figure 4. Annualized neT2 Lesions



TIME TO 6-MONTH CONFIRMED DISABILITY WORSENING

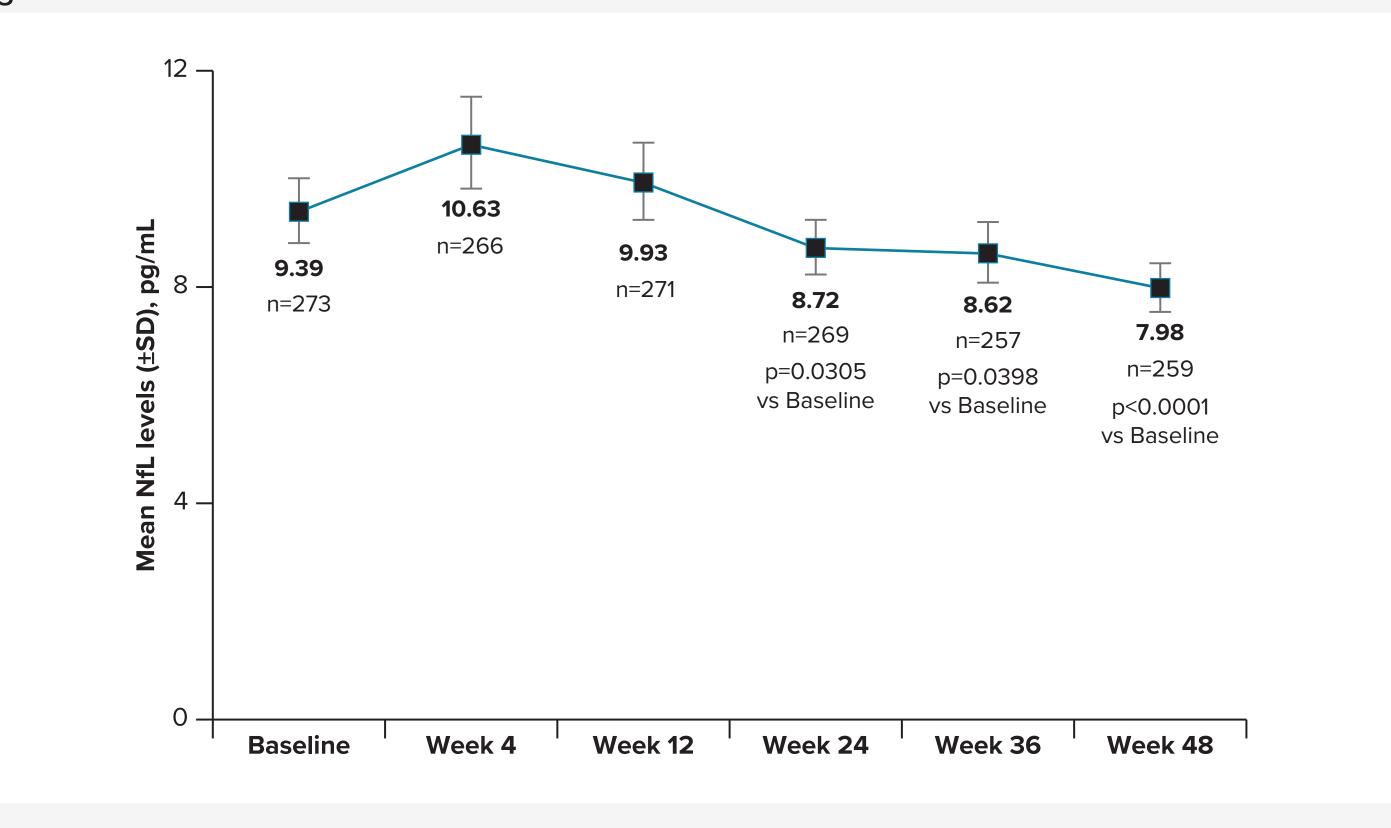
 Only 9 patients (<4%) experienced 6-month confirmed disability worsening over a period of 1 year (Figure 5)

Figure 5. 6-Month Confirmed Disability Worsening



CHANGE IN SERUM NFL LEVELS

 Serum NfL gradually decreased to below baseline levels at Week 24 and continued decreasing over time, in patients with RMS switching to ofatumumab from fingolimod/fumarates (Figure 6) Figure 6. Serum NfL Levels



SAFETY PROFILE

 Overall incidence of AEs and SAEs were similar to those reported in other ofatumumab clinical trials, with a similar trend observed when assessed by prior DMT use

Table 3. Safety Profile of Ofatumumab in Patients With RMS Switching From Fingolimod or Fumarate-based DMTs

		By Last Prior DMT	
All grades — n (%)	Overall Population N=278	Fingolimod N=89	Fumarate-based DMTs N=189
Subjects with at least 1 AE	245 (88.1)ª	74 (83.1)	171 (90.5)
Subjects with at least 1 SAE	9 (3.2)	3 (3 4)	6 (3.2)
Subjects with AE(s) causing study drug discontinuations	1 (O.4) ^b	1 (1.1)	0
Subjects with AE(s) causing study drug interruptions	8 (2.9)°	1 (1.1)	7 (3.7)

^a17(6.1%) patients had grade 3 or 4 AEs; ^bone patient discontinued treatment because of COVID-19; ^cdrug interruptions caused by: COVID-19 (2.2%), abdominal pain (0.4%), urinary tract infection (0.4%).

- Majority of AEs (93.9%) were mild to moderate (Grade 1, 2) in severity
- The incidence of SAEs was low (3.2%). All SAEs resolved without sequelae. No deaths were reported during the study

Table 4. Incidence of SAEs

Dueferued town		By Last Prior DMT	
Preferred term All grades — n (%)	Overall Population N=278	Fingolimod N=89	Fumarate-based DMTs N=189
Any SAE	9 (3.2)	3 (3.4)	6 (3.2)
Tachycardia	1 (0.4)	1 (1.1)	-
Atrial septal defect	1 (0.4)	-	1 (0.5)
Vertigo	1 (0.4)		1 (0.5)
Cholelithiasis	1 (0.4)	-	1 (0.5)
Urinary tract infection	1 (0.4)	-	1 (0.5)
Ulna fracture	1 (0.4)	1 (1.1)	-
Uterine leiomyoma	1 (0.4)		1 (0.5)
MS relapse	1 (0.4)	1 (1.1)	-
Sciatica	1 (0.4)	-	1 (0.5)

Table 5. Incidence of AEs ≥10%

Variable		By Last Prior DMT	
All grades — n (%)	Overall Population N=278	Fingolimod N=89	Fumarate-based DMTs N=189
Infections and infestations	150 (54.0)	36 (40.4)	114 (60.3)
COVID-19	69 (24.8)	18 (20.2)	51 (27.0)
Nasopharyngitis	36 (12.9)	10 (11.2)	26 (13.8)
Urinary tract infection	23 (8.3)	8 (9.0)	15 (7.9)
Upper respiratory tract infection	17 (6.1)	2 (2.2)	15 (7.9)
Systemic injection-related reactions	145 (52.2)	46 (51.7)	99 (52.4)
Headache	45 (16.2)	12 (13.5)	33 (17.5)
Injection site reaction	29 (10.4)	9 (10.1)	20 (10.6)

- Majority of infections were mild or moderate (only two Grade 3 severity and no Grade 4). Serious infection occurred in 1 patient (urinary tract infection)
- Although the study started in the first year of the pandemic, 98.6% of COVID-19 cases were mild or moderate, only 1 case (1.4%) of Grade 3 severity occurred All COVID-19 infections were characterized as non-serious and patients recovered without sequalae
- Almost all (99.3%) of the injection-related reactions (IRRs) were mild to moderate in severity and, as expected, events were primarily reported with first injection (45.3%) with substantial decrease with subsequent injections
- There were no grade 4 or serious events reported
- No IRR led to treatment interruption or discontinuation
- Most common symptoms were fever, chills, headache. Symptoms could be reported both by the patient ar investigators and their assessment were left at the discretion of investigators
- Study protocol followed the ofatumumab label, not requiring the use of premedication, as IRRs can be managed with symptomatic treatment
- Mean serum IgG levels remained stable and above LLN (5.65 g/L, Figure 7a) for up to 48 weeks. Mean serum IgM levels decreased from baseline to Week 48 but remained above LLN (0.4 g/L, (mean IgM at Week 48: 0.783 g/L; Figure 7b). In 97.8% and 81.7% of patients, IgG/IgM levels, respectively, remained above LLN over the analysis period

Figure 7a. Mean Serum IgG Levels

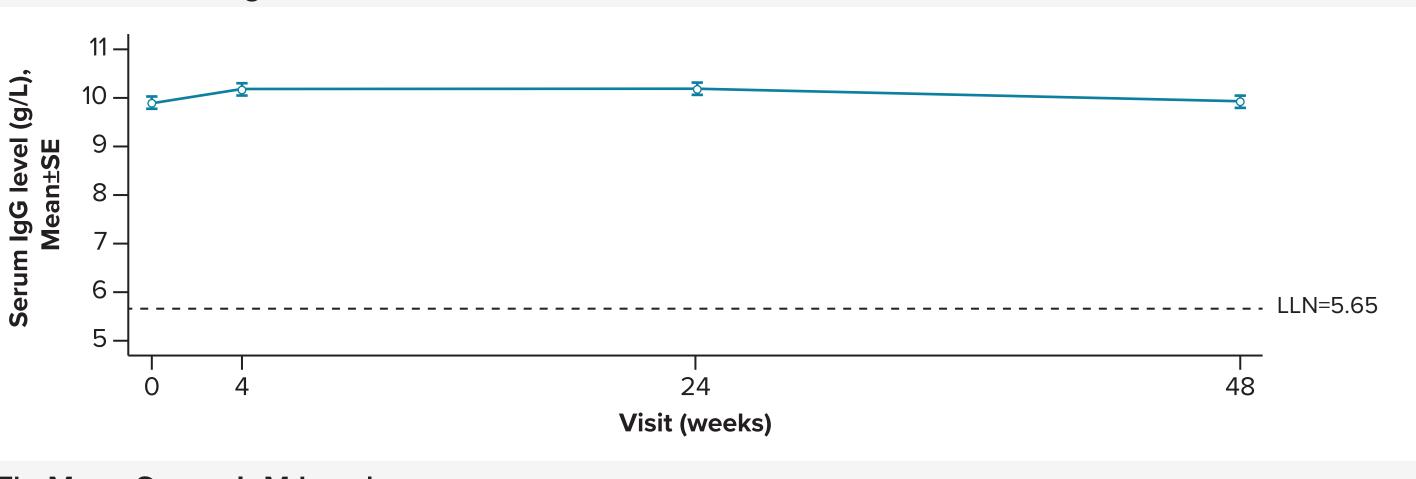
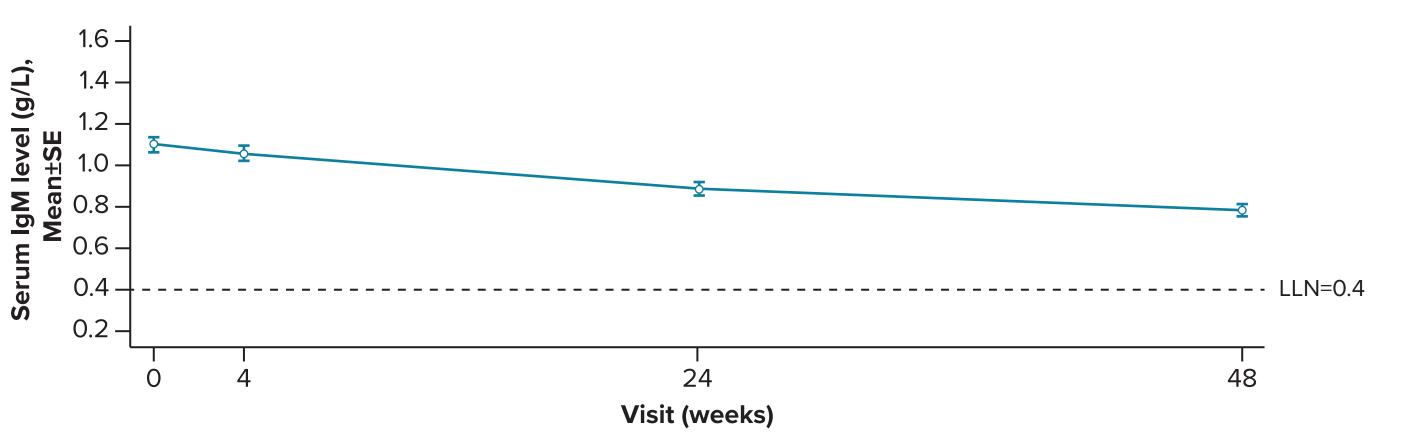


Figure 7b. Mean Serum IgM Levels



- Few patients had at least one Ig level below LLN (2.2% in IgG and 18.3% in IgM) and none led to treatment discontinuation. Only 1 treatment interruption occured in a patient with low IgG and none with low IgM
- An IgG or IgM level <LLN was not associated with an increase in infection-related AEs. No grade 3/4 infection-related AEs or SAEs were reported

CONCLUSIONS

- Patients who switched to ofatumumab after breakthrough disease on fingolimod or fumarate-based therapies had a substantial reduction in disease activity including reduced ARR and MRI lesion activity Few patients (<4%) experiencing disability worsening and disease progression
- No new safety signals with ofatumumab were observed in this switch population
- Overall results from the interim analysis of ARTIOS data suggest that patients with breakthrough disease with fingolimod or fumarate-based therapies could benefit from switching to ofatumumab

Abbreviations

6mCDW, 6-month confirmed disability worsening; AE, adverse event; ARR, annualized relapse rate; B, baseline; CI, confidence interval; D, day; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; Ig, immunoglobulin; IRR, injection-related reaction; MRI, magnetic resonance imaging; MS, multiple sclerosis; neT2, new or emerging T2; NfL, neurofilament light chain; OMB, ofatumumab; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive MS; PRO, patient-reported outcome; LLN, lower limit of normal; RMS, relapsing MS; S, screening; SAE, serious AE; s.c., subcutaneous; SF, safety follow-up; SPMS, secondary progressive MS; W, week

Disclosures

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