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

LB 10

Riley Bove,[1] Matthew Craner,[2] Dawn Langdon,[3] Daniel Sienkiewicz,[4] Javier Ricart,[5] Soudeh Ansari,[6] Sophie Arnould,[7] Ibolya Boer,[7] Tobias Derfuss,[8]

[1]University of California San Francisco, San Francisco, CA, USA; [2]John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK; [3]Royal Holloway, University of London, London, UK; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [5]Novartis Farmacéutica, Barcelona, Spain; [6]Novartis Institutes for Biomedical Research, MA, USA; [7]Novartis Pharma AG, Basel, Switzerland; [8]Neurology Clinic and Policlinic and Research Center for Clinical Neuroimmunology and Neuroscience, Departments of Medicine and Biomedicine, University Hospital and University of Basel, Basel, Switzerland

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

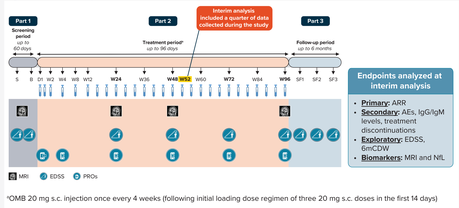
- To assess the effectiveness and safety of ofatumumab 20 mg s.c. in RMS patients with breakthrough disease on oral fumarates or fingolimod
  - Primary objective: To demonstrate the effectiveness of ofatumumab 20 mg s.c. as measured by ARR
  - Secondary objectives: To evaluate the safety of ofatumumab 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



*OMB 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

Key exclusion criteria

- Patients with PPMS or SPMS without disease activity (non-active SPMS)
- Disease duration of >10 years since diagnosis
- Patients meeting criteria for neuromyelitis optica
- Patients with active bacterial, viral (including COVID-19), or fungal infections
- Emergence of any clinically significant condition or disease during previous ofatumumab study
- Patients with neurological findings consistent or confirmed with PML
- Pregnant or nursing women; OR, women of childbearing potential not using highly effective methods of contraception
- Patients at risk of developing, or with a history of, hepatitis, syphilis, or tuberculosis
- History of malignancy within the past 5 years, significant cardiac disease, respiratory disease, severe hepatic and renal impairment, hyperproteinemia
- Patients with abnormal laboratory values (lymphocyte count <500/mm³ (<0.5x10⁹/L) in patients discontinuing fumarates or serum IgG <500 mg/dL)

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

Variable	Overall Population N=278	By Last Prior DMT: Fingolimod N=89	By Last Prior DMT: Fumarate-Based Therapy N=189
Age, years	37.4±9.81	38.1±9.13	37.1±10.12
Female, n(%)	172 (61.9)	57 (64.0)	115 (60.8)
EDSS	2.42±1.13	2.52±1.13	2.37±1.13
Proportion of subjects free of Gd+T1 lesions, n(%)[a]	**201 (72.3)**	**57 (64.0)[a]**	**(76.2)[a]**
Total volume of T2 lesions, cc[a]	**11.13±12.03**	**13.31±13.24[a]**	**10.11±11.31[a]**
Number of prior DMTs, n(%)[a]			
1	**119 (42.8)**	**20 (22.5)[a]**	**99 (52.4)[a]**
2	**105 (37.8)**	**46 (51.7)[a]**	**59 (31.2)[a]**
3	**54 (19.4)**	**23 (25.8)[a]**	**31 (16.4)[a]**
Duration of MS since diagnosis, years[a]	**5.67±2.94**	**6.30±2.68[a]**	**5.37±3.01[a]**
Number of relapses in the last 12 months prior to screening	0.9±0.68	0.9±0.71	0.9±0.66
IgG, g/L[a]	**9.89±2.0**	**8.86±1.90[a]**	**10.37±1.93[a]**
IgM, g/L[a]	**1.1±0.6**	**0.90±0.46[a]**	**1.19±0.65[a]**
Lymphocytes (10⁹/mL)[a]	**1.36±0.55**	**1.10±0.45[a]**	**1.48±0.55[a]**
Duration of washout, days[a]	**43.6±42.57**	**52±39.8[a]**	**39.6±43.35[a]**
<30 days, n(%)	**118 (42.4)**	**26 (29.2)[a]**	**92 (48.7)[a]**
≥30 days, n(%)	**160 (57.6)**	**63 (70.8)[a]**	**97 (51.3)[a]**

[a]p<0.05 between the fingolimod and fumarate-based groups (data highlighted in bold). Unless specified otherwise, values are represented as mean±SD

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

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

Note: The interim analysis only analyzed a quarter of the data that is planned to be collected in the study.
[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
N, total number of subjects included in the analysis.

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

Figure 3. Adjusted rate of Gd+T1 lesions per scan

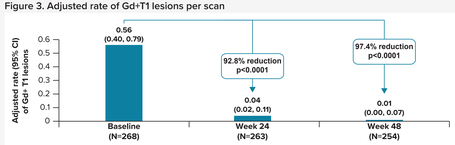
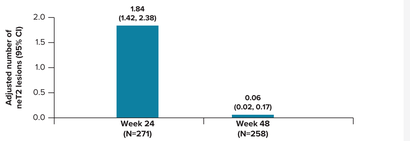


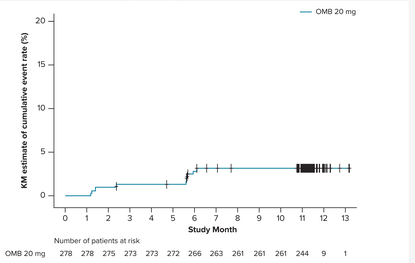
Figure 4. Annualized neT2 Lesions



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**)

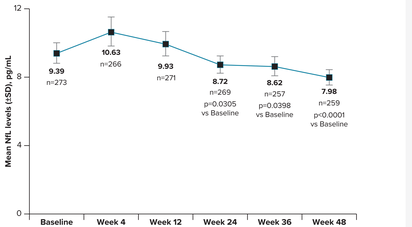
Figure 5. 6-Month Confirmed Disability Worsening



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

All grades — n (%)	Overall Population N=278	By Last Prior DMT: Fingolimod N=89	By Last Prior DMT: 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 (0.4)[b]	1 (1.1)	0
Subjects with AE(s) causing study drug interruptions	8 (2.9)[c]	1 (1.1)	7 (3.7)

[a]17(6.1%) patients had grade 3 or 4 AEs; [b]one patient discontinued treatment because of COVID-19; [c]drug 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

Preferred term All grades — n (%)	Overall Population N=278	By Last Prior DMT: Fingolimod N=89	By Last Prior DMT: 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 All grades — n (%)	Overall Population N=278	By Last Prior DMT: Fingolimod N=89	By Last Prior DMT: 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 and 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

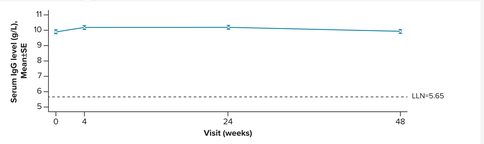
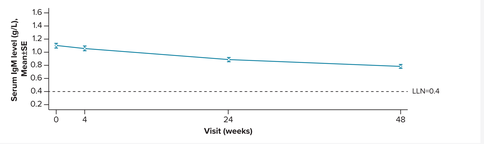


Figure 7b. Mean Serum IgM Levels



- 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

Riley Bove has received research support and/or served on Advisory Boards and/or steering committees of Alexion, Biogen, EMD Serono, Genzyme Sanofi, Novartis, and Roche Genentech. **Matthew Craner** has nothing to disclose. **Dawn Langdon** has participated in speaker bureau for Almirall, Bayer, Biogen, Merck, Novartis, Roche, Sanofi, and Teva; has received consultancy fees from Bayer, Biogen, Merck, Novartis, and Teva; and has received research grants from Bayer, Biogen, Merck, and Novartis. **Daniel Sienkiewicz, Javier Ricart, Soudeh Ansari, Sophie Arnould,** and **Ibolya Boer** are employees of Novartis. **Tobias Derfuss** has received personal compensation from Alexion, Biogen, Celgene, GeNeuro, Novartis, Roche, Medday, Merck, Sanofi, Polyneuron and research grant from Alexion, Roche, Biogen. An immediate family member of Tobias Derfuss has received personal compensation for serving as an employee of Novartis.

Acknowledgments

The authors acknowledge the following Novartis employees: **Venkateswarlu Bonala** and **Sreelatha Komatireddy** for medical writing assistance and coordinating author reviews, and **V.S.Hari Prasad** for creative design assistance. The final responsibility for the content lies with the authors.

Funding

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

Poster presented at the annual meeting of the Consortium of Multiple Sclerosis Centers, May 31–June 3, 2023.

To download a copy of this poster, visit the web at: https://bit.ly/cmsc2023

Scan this QR code to download a copy of Poster