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Long-term Effect of Ofatumumab Treatment on Serum Neurofilament Light Chain Levels and NEDA-3 Status in Patients With RMS: Results From ASCLEPIOS I/II and ALITHIOS

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SUMMARY

1 **The effect of ofatumumab on serum neurofilament levels and the odds of maintaining NEDA-3 status were assessed for up to 4 years in patients with RMS receiving continuous ofatumumab and those switched from teriflunomide from the core ASCLEPIOS I/II and ALITHIOS open-label extension trials**

2 **Early initiation of ofatumumab resulted in earlier reduction in serum neurofilament levels (a marker of neuroaxonal injury) compared with teriflunomide. Additionally, the odds of achieving NEDA-3 status increased annually, indicating gradual decrease of disease activity with continued use of ofatumumab**

3 **These results support the value of earlier initiation of HET, such as ofatumumab, compared with a lower-efficacy therapy**

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INTRODUCTION

- Ofatumumab, a fully human anti-CD20 monoclonal antibody (20 mg subcutaneous), is approved for treating relapsing multiple sclerosis (RMS) in adults[1]
- In the phase 3 ASCLEPIOS I/II trials, ofatumumab demonstrated superior efficacy in reducing the annualized relapse rate, suppressing magnetic resonance imaging lesion activity, and delaying disability worsening, while maintaining a favorable safety profile versus teriflunomide in patients with RMS[2]
- The ASCLEPIOS I/II trials were the first pivotal trials in MS where serum neurofilament light NfL (sNfL) was also included as a predefined key secondary endpoint[2]
- Ofatumumab already significantly reduced sNfL compared with teriflunomide in the first assessment at Month 3 and in all subsequent assessments over 2 years[2]
- In the same ASCLEPIOS I/II trials, ofatumumab increased the chances of patients achieving 3-parameter no evidence of disease activity (NEDA-3) both in the first (5 of 10 patients) and second years (9 of 10 patients) of treatment vs teriflunomide[3]

OBJECTIVE

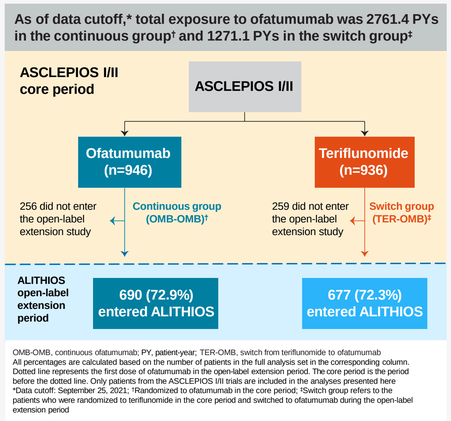
- To assess the longer-term efficacy of ofatumumab on sNfL levels and odds of maintaining NEDA-3 status in patients with RMS receiving continuous ofatumumab and those switched from teriflunomide in the core ASCLEPIOS I/II and ALITHIOS open-label extension trials based on data for up to 4 years

METHODS

PATIENT POPULATION

- Of 1882 patients randomized in the ASCLEPIOS I/II trials, 1367 (72.6%) patients enrolled into the ALITHIOS open-label extension trial and received ofatumumab for up to 4 years cumulatively (**Figure 1**)
- Of these, 1214/1367 (88.8%) patients were still receiving ofatumumab treatment at the time of data cutoff (September 25, 2021)

Figure 1. Patient Disposition



OMB-OMB, continuous ofatumumab; PY, patient-year; TER-OMB, switch from teriflunomide to ofatumumab
All percentages are calculated based on the number of patients in the full analysis set in the corresponding column. Dotted line represents the first dose of ofatumumab in the open-label extension period. The core period is the period before the dotted line. Only patients from the ASCLEPIOS I/II trials are included in the analyses presented here
*Data cutoff: September 25, 2021; †Randomized to ofatumumab in the core period; ‡Switch group refers to the patients who were randomized to teriflunomide in the core period and switched to ofatumumab during the open-label extension period

OUTCOMES

Geometric mean sNfL levels over time

- sNfL levels were assessed using the following:
  - Quanterix Simoa® NF-light™ Advantage Kit validated at Navigate BioPharma Services (Carlsbad, CA, USA) for the ASCLEPIOS I/II core period
  - Siemens Healthcare Laboratory (SHL) NfL laboratory-developed test (LDT) on Atellica® Immunoassay Analyzer, which is a part of the Atellica Solution, validated at SHL (Berkeley, CA, USA) for the ALITHIOS open-label extension period
  - A good correlation of the 2 assays is observed with Pearson's correlation of 0.995 and average quantitation difference of 8%. However, as the 2 assays are not equivalent, to facilitate pooling of core and extension data, which enables the assessment of long-term treatment effect on sNfL in the overall period, transformation from Quanterix Simoa assay to SHL NfL LDT was established by SHL (termed as "assay transformed values"), which can be calculated as 2.06 + 0.83 × original values[a]

[a]This relationship transforms the original values (as measured by the Quanterix Simoa assay used in the core ASCLEPIOS I/II trials) to what the values would have been had the samples been analyzed by the Siemens Atellica assay (used in the extension study)

PROPORTION OF PATIENTS ACHIEVING NEDA-3

- NEDA-3[a] was assessed based on the modified full analysis set using logistic regression model with treatment regimen and region as factors, and age, baseline Expanded Disability Status Scale (EDSS) score, and number of gadolinium-enhancing (Gd+) T1 lesions at baseline as continuous covariates

[a]NEDA-3 is defined as no 6-month confirmed disability worsening, no confirmed MS relapse, no new or enlarging T2 lesions compared with baseline, and no T1 Gd+ lesions

ASSESSMENTS

- Within-group comparisons of outcomes between ASCLEPIOS I and II (Month [M] 0-24) and ALITHIOS (ie, post switch to open-label ofatumumab; M0-24) were assessed
- Between-group comparisons cumulatively up to 4 years, and by the core and extension periods, were assessed

RESULTS

BASELINE CHARACTERISTICS

- At baseline, mean age of patients was approximately 38 years in the ofatumumab continuous and switch groups (**Table 1**)
- The mean EDSS score at baseline was approximately 2.9 for both the continuous and switch groups

Table 1. Patient Demographics and Disease Characteristics

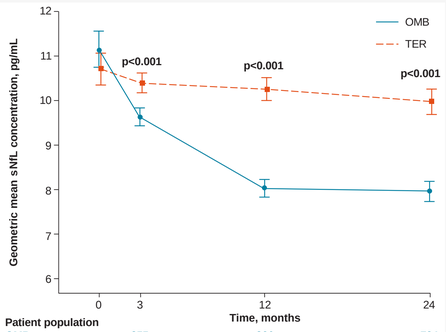
Parameters	OMB-OMB (N=946)		TER-OMB (N=936)	
Demographics and clinical characteristics*	Baseline from core study (N=946)	Baseline from extension study (N=690)	Baseline from core study (N=936)	Baseline from extension study (N=677)
Age, years	38.4 (9.04)	38.1 (8.69)	38.0 (9.22)	40.1 (9.21)
Female, n (%)	637 (67.3)	483 (70)	636 (67.9)	456 (67.4)
BMI, kg/m²	25.86 (6.22)	25.73 (6.0)	25.93 (6.02)	25.61 (5.85)
Treatment-naïve patients,† n (%)	386 (40.8)	Not applicable‡	363 (38.8)	Not applicable‡
EDSS score at baseline	2.93 (1.35)	2.81 (1.48)	2.90 (1.36)	2.81 (1.46)§
Number of relapses in the last 12 months before screening	1.2 (0.69)	0.1 (0.35)	1.3 (0.71)	0.2 (0.49)§
Number of Gd+ T1 lesions	1.7 (4.51)	0.0 (0.21)	1.3 (3.43)	0.8 (2.37)§
Total volume of T2 lesions, cm³	13.72 (13.80)	Not available¶	12.55 (13.81)	Not available¶
sNfL, pg/mL, median	9.93	8.26	9.63	10.42

BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; OMB-OMB, continuous ofatumumab; SD, standard deviation; TER-OMB, switch from teriflunomide to ofatumumab
*Values are represented as mean (SD) unless otherwise specified; †Treatment-naive patients are those who have not received a prior multiple sclerosis disease-modifying therapy; ‡Not applicable because all patients have been pretreated with ofatumumab (OMB-OMB group)/teriflunomide (TER-OMB group); §The baseline from the extension study in the TER-OMB group reflects the teriflunomide treatment effect during the double-blind treatment phase in the ASCLEPIOS I/II trials; ¶Data are not collected for the extension study

sNfL LEVELS OVER TIME BY THE CORE AND EXTENSION PERIODS

- In ASCLEPIOS I/II, sNfL levels (pg/mL) were reduced with ofatumumab vs teriflunomide (M3: 9.62 vs 10.38; M12: 8.03 vs 10.25; M24: 7.96 vs 9.97; p<0.001, all time points)[4] (**Figure 2**)
- In ALITHIOS, sNfL levels were maintained with continuous ofatumumab treatment (M24: 8.50)
- Switching from teriflunomide to ofatumumab resulted in a decline in sNfL levels; the difference vs continuous ofatumumab remained significant up to M6 after switch (9.07 vs 8.31; p<0.001); afterward, similar sNfL levels were observed in both groups (M24: 8.23 vs 8.50) (**Figure 3**)

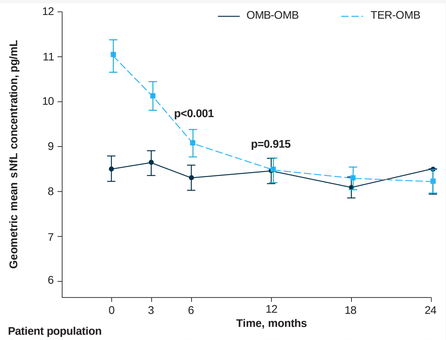
Figure 2. sNfL Levels Over Time (ASCLEPIOS I/II Core Period)



Patient population				
OMB	855	820		734
TER	826	804		709

CI, confidence interval; OMB, ofatumumab; sNfL, serum neurofilament light chain; TER, teriflunomide
Adjusted geometric means with 95% CIs at each time point are from a repeated measures model. Geometric mean sNfL concentrations at baseline are derived as exponentiated arithmetic mean of natural logarithmic of raw values of sNfL concentrations

Figure 3. sNfL Levels Over Time (ALITHIOS Extension Period)



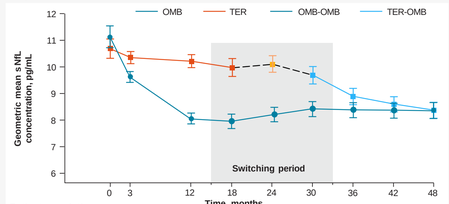
Patient population					
OMB-OMB	631	596	552	528	535
TER-OMB	626	593	572	528	523

CI, confidence interval; OMB-OMB, continuous ofatumumab; sNfL, serum neurofilament light chain; TER-OMB, switch from teriflunomide to ofatumumab
Adjusted geometric means with 95% CIs at each time point are from a repeated measures model

sNfL LEVELS OVER TIME IN THE OVERALL PERIOD

- A sustained reduction of sNfL levels (pg/mL) was observed at all time points with continuous ofatumumab treatment
- Switching from teriflunomide to ofatumumab resulted in a decline in sNfL levels in the open-label extension period, while afterward, similar sNfL levels were observed in both groups (M48: 8.38 vs 8.60) (**Figure 4**)

Figure 4. sNfL Levels During the Overall Period



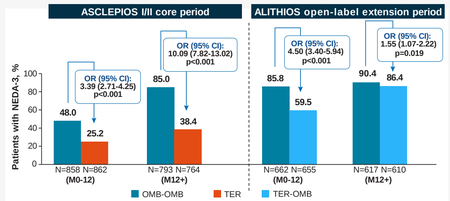
Patient population									
OMB	855	817	332	711	622	563	533	447	
TER	826	802	330	709	628	559	544	434	

CI, confidence interval; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; sNfL, serum neurofilament light chain; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
Adjusted geometric means with 95% CIs at each time point are from a repeated measures model. Geometric mean sNfL concentrations at baseline are derived as exponentiated arithmetic mean of natural logarithmic of raw values of sNfL concentrations

EFFECT OF OFATUMUMAB ON NEDA-3 IN THE CORE AND EXTENSION PERIODS

- In ASCLEPIOS I/II, the odds of achieving NEDA-3 status were ~3-fold higher for ofatumumab vs teriflunomide during Year 1 (48% vs 25.2%; odds ratio [95% confidence interval]: 3.39 [2.71-4.25]; p<0.001) and 10-fold higher during Year 2 (85% vs 38.4%; 10.09 [7.82-13.02]; p<0.001) (**Figure 5**)
- In ALITHIOS, 8 of 10 patients in the continuous ofatumumab group and 6 of 10 patients in the switch group achieved NEDA-3 status in Year 1 (85.8% vs 59.5%; 4.50 [3.40-5.94]; p<0.001). During Year 2, a higher percentage of patients with NEDA-3 status were observed in the continuous ofatumumab and switch groups (90.4% vs 86.4%; 1.55 [1.07-2.22]; p=0.019) (**Figure 5**)

Figure 5. NEDA-3 Status by Study Period

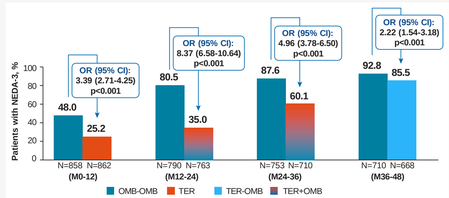


CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; M, Month; NEDA-3, 3-parameter no evidence of disease activity; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; OR, odds ratio; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
All p-values are nominal p-values; statistical model used logistic regression adjusting for treatment and region as factors and age, baseline EDSS score, and number of Gd+ lesions at baseline as covariates; N=total number of patients in the treatment group, excluding those who discontinued treatment early for reasons other than lack of efficacy or death and who had NEDA-3 before early discontinuation

EFFECT OF OFATUMUMAB ON NEDA-3 IN THE OVERALL PERIOD

- In the continuous ofatumumab group, the odds of achieving NEDA-3 increased gradually from Year 2 and reached maximum at Year 4
- In the treatment epoch of M6-48 (Year 4), over 9 of 10 patients in the continuous ofatumumab group achieved NEDA-3 (**Figure 6**)

Figure 6. NEDA-3 Status by Year in the Overall Period



CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; M, Month; NEDA-3, 3-parameter no evidence of disease activity; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; OR, odds ratio; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
Statistical model used logistic regression adjusting for treatment and region as factors and age, baseline EDSS score, and number of Gd+ lesions at baseline as covariates; N=total number of patients in the treatment group, excluding those who discontinued treatment early for reasons other than lack of efficacy or death and who had NEDA-3 before early discontinuation

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