Serum Neurofilament Light Chain Levels and NEDA-3 Status With Ofatumumab Treatment in RMS Patients: Longer-term Analysis from ASCLEPIOS I/II and ALITHIOS

P1198

Jens Kuhle[1], Ludwig Kappos[2], Tjalf Ziemssen[3], Douglas L. Arnold[4,5], Enrique Alvarez[6], Anne H. Cross[7], Ibolya Boer[8], Ayan Das Gupta[9], Xixi Hu[10], Petra Kukkaro[8], Bernd Kieseier[8], Ronald Zielman[11], Stephen L. Hauser[12]

[1]Neurology, MS Center and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Head, Spine and Neuromedicine, Biomedicine and Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland; [2]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; [3]Center of Clinical Neuroscience, Department of Neurology, University Clinic Carl-Gustav Carus, Dresden, Germany; [4]Brain Imaging Centre, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada; [5]NeuroRx Research, Montreal, Quebec, Canada; [6]Department of Neurology, Rocky Mountain MS Center at the University of Colorado, Aurora, CO, United States; [7]Washington University School of Medicine, Saint Louis, MO, United States; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Healthcare Pvt. Ltd, Hyderabad, India; [10]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; [11]Novartis Pharma B.V., Amsterdam, The Netherlands; [12]UCSF Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, United States

Introduction

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

Objective

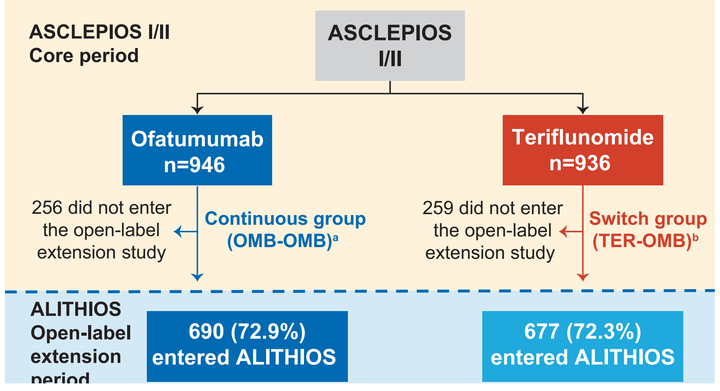
- To assess the longer-term efficacy of ofatumumab on sNfL levels and odds of maintaining NEDA-3 status in RMS patients receiving continuous ofatumumab and those switched from teriflunomide in the core ASCLEPIOS I/II and ALITHIOS open label extension trials based on data for up to 4 years

Methods

Patient Population

- Of 1882 patients randomised 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 cut-off (25-Sep-2021)

Figure 1. Patient disposition



All percentages are calculated based on the number of patients in full analysis set in the corresponding column. Dotted line represents the first dose of ofatumumab in extension period. Core period is period before the dotted line. Only patients from the ASCLEPIOS I/II studies are included in the analyses presented here. *Data cut-off: 25-Sep-2021; [a]randomised to ofatumumab in the core; [b]Switch group refers to the patients who were randomised to teriflunomide in the core and switched to ofatumumab during the extension period. AE, adverse event; PY, patient-years.

Outcomes

Geometric mean serum NfL levels over time

- sNfL levels were assessed using
  - 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 (IM) Analyzer, which is a part of the Atellica® Solution, validated at SHL (Berkeley, CA, USA) for the ALITHIOS extension period
  - A good correlation of the two assays is observed with Pearson's correlation of 0.995 and average quantitation difference of 8%. However, as the two 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 x original values*

**This relationship transforms the original values (as measured by the Quanterix Simoa assay used in the core ASCLEPIOS studies) 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 was assessed based on modified Full analysis set (FAS) using logistic regression model with treatment regimen and region as factors, and age, baseline EDSS, and number of Gd-enhancing T1 lesions at baseline as continuous covariates

NEDA-3 is defined as no 6-month confirmed disability worsening, no confirmed MS relapse, no new or enlarging T2 lesions compared to baseline and no T1 Gd-enhancing lesions.

Assessments

- Within group comparisons of outcomes between ASCLEPIOS I and II (M0-24) and ALITHIOS (i.e., post-switch to open-label OMB; M0-24) were assessed
- Between group comparisons cumulatively up to 4 years, and by 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 at baseline was approximately 2.9 for both the continuous and switch group

Table 1. Patient demographics and disease characteristics

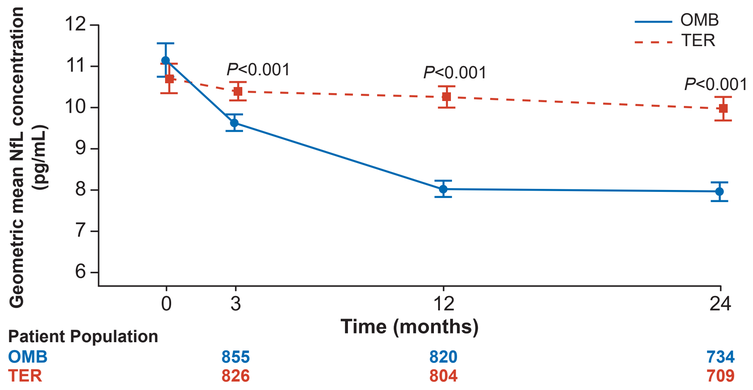
Parameters	Ofatumumab continuous (N=946)		Switch from teriflunomide to ofatumumab (N=936)	
Demographics and clinical characteristics[a]	**Baseline from core study (N=946)**	**Baseline from extension study (N=690)**	**Baseline from core study (N=936)**	**Baseline from extension study (N=677)**
Age, years	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/m^2	25.86±6.22	25.73±6.0	25.93±6.02	25.61±5.85
Treatment-naïve patients[b], n (%)	386 (40.8)	Not applicable[c]	363 (38.8)	Not applicable[c]
EDSS score at baseline	2.93±1.35	2.81±1.48	2.90±1.36	2.81±1.46[d]
Number of relapses in the last 12 months prior to screening	1.2±0.69	0.1±0.35	1.3±0.71	0.2±0.49[d]
Number of Gd+ T1 lesions	1.7±4.51	0.0±0.21	1.3±3.43	0.8±2.37[d]
Total volume of T2 lesions, cm^3	13.72±13.80	Not available[e]	12.55±13.81	Not available[e]
sNfL (pg/mL), median	9.93	8.26	9.63	10.42

[a]Values are represented as mean±SD unless specified otherwise; [b]Treatment naïve patients are those who have not received a prior multiple sclerosis disease modifying therapy; [c]not applicable since all patients have been pre-treated with ofatumumab (continuous group) / teriflunomide (switch group); [d]The baseline from the extension study in the ofatumumab switch from teriflunomide group reflects the teriflunomide treatment effect during the double-blind treatment phase in the ASCLEPIOS studies; [e]data is not collected for the extension study; BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing

sNfL levels over time by core and extension period

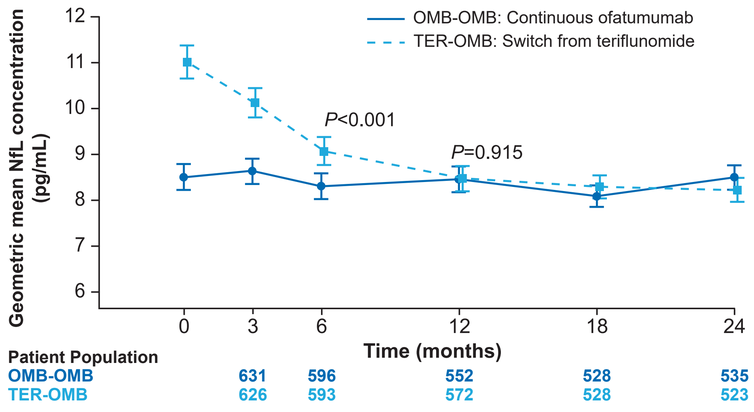
- In ASCLEPIOS I/II, sNfL levels (pg/mL) were reduced with ofatumumab vs teriflunomide (M3: 9.62 vs 10.38; M12: 8.03 vs 10.25; M24: 7.96 vs 9.97; *P*<0.001, all timepoints)[4] (**Figure 2**)
- In ALITHIOS, sNfL levels were maintained with continuous ofatumumab treatment [M24: 8.50]
- Switching from teriflunomide 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), afterwards 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



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

Figure 3. sNfL levels over time – ALITHIOS – Extension period

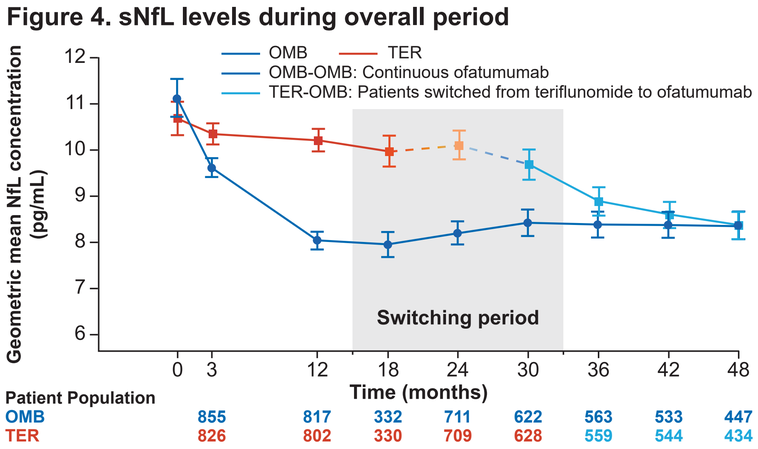


Adjusted geometric means with 95% CIs at each time point are from Repeated measures model. Geometric mean NfL concentrations at baseline are derived as exponentiated arithmetic mean of natural logarithmic of raw values of NfL concentrations
NfL, neurofilament light chain; OMB-OMB, continuous ofatumumab,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

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 afterwards similar sNfL levels were observed in both groups (M48: 8.38 vs 8.60) (**Figure 4**)

Figure 4. sNfL levels during overall period

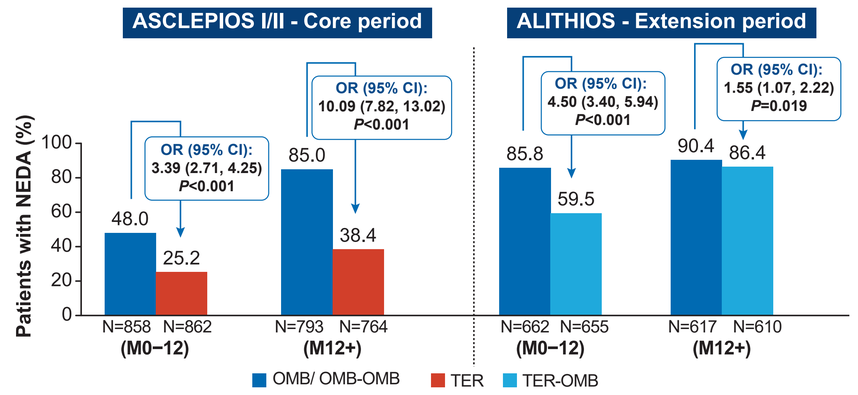


Adjusted geometric means with 95% CIs at each time point are from Repeated measures model. Geometric mean NfL concentrations at baseline are derived as exponentiated arithmetic mean of natural logarithmic of raw values of NfL concentrations
NfL, neurofilament light chain; OMB, ofatumumab; TER, teriflunomide.

Effect of ofatumumab on NEDA-3 in the core and extension period

- 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%; OR [95% CI], 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 out of 10 patients in continuous ofatumumab and 6 out of 10 patients in 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

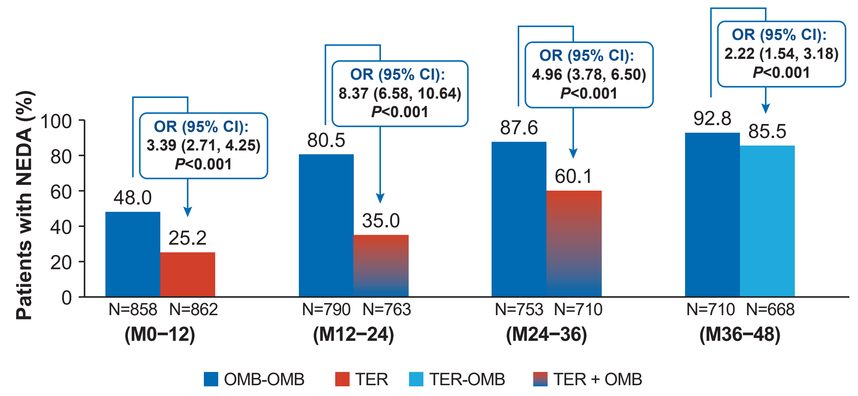


All P values are nominal P values; Statistical model used logistic regression adjusting for treatment and region as factors and age, baseline EDSS, number of Gd-lesions at baseline as covariates; N=The total number of patients in the treatment group excluding those who discontinued treatment early for reasons other than lack of efficacy or death and had NEDA before early discontinuation; CI, confidence interval; NEDA, no evidence of disease activity; OMB, ofatumumab; OR, odds ratio; M, month; TER, teriflunomide.

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 months 36-48 (Year 4), over 9/10 patients in the continuous ofatumumab group achieved NEDA-3 (**Figure 6**)

Figure 6. NEDA-3 status by year in the overall period



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

Conclusions

- Early initiation of ofatumumab resulted in earlier reduction in sNfL (a marker of neuroaxonal injury) compared with teriflunomide
- The odds of achieving NEDA-3 status increased annually indicating gradual decrease of disease activity with continued use of ofatumumab
- Early reduction of sNfL levels and the higher odds of achieving NEDA-3 in the continuous ofatumumab group compared to the switch group support the value of earlier initiation of high-efficacy therapy, such as ofatumumab, compared to a lower efficacy therapy

References

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed February 17, 2022)
2. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57
3. Kappos L, et al. Poster presented at *EAN* 2022. EPR161
4. Kappos L, et al. Oral presentation at *AAN* 2020.

Acknowledgements

The authors acknowledge the following Novartis employees, **Jing Xi** for analysing and interpretation of data; **Amitha Thakur** and **Saimithra Thammera** for medical writing assistance and coordinating author reviews, and **Rupa De** for creative design assistance. The final responsibility for the content lies with the authors

Disclosures

This study was funded by Novartis Pharma AG, Switzerland.

Jens Kuhle received speaker fees, research support, travel support, and/or served on advisory boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Octave Bioscience, Roche, Sanofi. **Ludwig Kappos** institution (University Hospital Basel) has received research support: steering committee, advisory board, consultancy fees: Abbvie, Actelion, AurigaVision AG, Biogen, Celgene, Desitin, Eli Lilly, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, Janssen, Japan Tobacco, Merck, Minoryx, Novartis, Roche, Sanofi, Santhera, Senda, Shionogi, Teva, and Wellmera; speaker fees (Celgene, Janssen, Merck, Novartis, and Roche); support for educational activities (Biogen, Desitin, Novartis, Sanofi, and Teva); license fees for Neurostatus products; and grants (European Union, Innosuisse, Novartis, Roche Research Foundation, Swiss MS Society, and Swiss National Research Foundation). **Tjalf Ziemssen** has received research support, consulting fee, and honoraria for lectures from Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva. **Douglas Arnold** has received personal fees from Acorda, Albert Charitable Trust, Biogen, Celgene, Frequency Therapeutics, GeNeuro, MedDay, Merck Serono, Novartis, Roche, Sanofi-Aventis, and Wave Life Sciences; grants from Biogen, Immunotec, and Novartis; and has equity interest in NeuroRx, outside the submitted work. **Enrique Alvarez** received compensation for consulting from Actelion/Janssen, Alexion, Bayer, Biogen, Celgene/BMS, EMD Serono/Merck, Genentech/Roche, Genzyme, Novartis, Sanofi, and TG Therapeutics and for research from Biogen, Genentech/Roche, Novartis, TG Therapeutics, Patient-Centered Outcomes Research Initiative, National Multiple Sclerosis Society, National Institutes of Health, and Rocky Mountain MS Center. **Anne H. Cross** has received consulting fees, support, and honoraria from Biogen, Celgene, Bristol Myers Squibb, EMD Serono, Merck, Genentech, Roche, Greenwich Biosciences (Jazz Pharmaceuticals), Horizon Therapeutics, Janssen (subsidiary of Johnson & Johnson), Novartis, TG Therapeutics, Academic CME, Projects In Knowledge, CME Outfitters, WebMD, Conrad N. Hilton Foundation, Potomac Center for Medical Education, The Consortium of Multiple Sclerosis Centers, and ACTRIMS; has received a grant from the Department of Defense, USA; has been the secretary (elected) of The Consortium of Multiple Sclerosis Centers, member of the scientific advisory board of Race to Erase MS, program committee (chair) of ACTRIMS, member of the COVID-19 advisory committee of the National Multiple Sclerosis Society and National Multiple Sclerosis Society representative on the Progressive MS Alliance; has participated on the data safety monitoring board or advisory board for National Multiple Sclerosis Society, Novartis and EMD Serono, and holds a patent for "Yablonskiy DA, Sukstansky AL, Wen J, Cross AH. Methods for simultaneous multi-angular relaxometry of tissue using magnetic resonance imaging. Patent 15060-630 (015875). **Ibolya Boer**, **Ayan Das Gupta**, **Xixi Hu**, **Petra Kukkaro**, **Bernd Kieseier**, **Ronald Zielman** are employees of Novartis.
Stephen L. Hauser has received personal compensation from Annexon, Alector, Accure, and Neurona; he has also received travel reimbursement from F. Hoffmann-La Roche Ltd and Novartis for CD20-related meetings and presentations.

Poster presented at the 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 26–28 October, 2022, Amsterdam, the Netherlands

Visit the web at: https://bit.ly/ectrims2022

Presenter email address: Jens.Kuhle@usb.ch

Scan this QR code to download a copy Poster