Thomas P. Leist | thomas.leist@jefferson.edu

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Prognostic Value of On-Treatment Serum Neurofilament Light Chain for New or Enlarging T2 Lesions in People With Relapsing Multiple Sclerosis: Pooled Analysis of the ASCLEPIOS I/II Trials

Thomas P. Leist[1], Stephen L. Hauser[2], Tobias Derfuss[3], Heinz Wiendl[4], Douglas L. Arnold[5], Xavier Montalban[6], Alit Bhatt[7], Wenjia Wei[8], Ibolya Boer[8], Enrique Alvarez[9], Tjalf Ziemssen[10]

[1]Thomas Jefferson University, Philadelphia, PA, USA; [2]UCSF Weill Institute for Neurosciences, University of California, San Francisco, CA, USA; [3]Neurologic Clinic and Policlinic, MS Centre and Research Centre for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University Hospital Basel and University of Basel, Basel, Switzerland; [4]Institute of Translational Neurology, University of Münster, Münster, Germany; [5]Brain Imaging Centre, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada; [6]Department of Neurology-Neuroimmunology, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain; [7]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [8]Novartis Pharma AG, Basel, Switzerland; [9]Rocky Mountain MS Centre, University of Colorado School of Medicine, Aurora, CO, USA; [10]Centre of Clinical Neuroscience, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany

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KEY FINDINGS & CONCLUSIONS

- On-treatment sNfL levels at 3 and 12 months are prognostic for future lesion formation and support the use of a single sNfL threshold to prognosticate MS disease activity in pwRMS on DMT

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INTRODUCTION

- A challenge encountered in clinical practice with relapsing multiple sclerosis (RMS) is the difficulty in prognosticating the risk of future disease activity because of the variable disease course across patients[1]
- Inflammatory disease activity mostly occurs in the younger RMS population and declines with age[2]
  - A biomarker that can prognosticate disease activity may help optimise individualised patient care and limit irreversible neurological damage, even in the absence of overt clinical symptoms or radiological signs[3]
- In the phase 3 ASCLEPIOS I/II trials (ofatumumab vs teriflunomide in people with RMS [pwRMS]), a pre-planned analysis of baseline serum neurofilament light chain (sNfL) levels based on being above or below the baseline median showed that sNfL levels were prognostic for on-study lesion formation and brain volume loss in the overall population and in recently diagnosed treatment-naive participants[4]
- The prognostic value of sNfL was also observed when participants were categorised by baseline sNfL concentration quartiles[5]
  - Irrespective of treatment, participants in the lowest quartile (Q1) had the lowest risk for on-study new or enlarging T2 (neT2) lesions, with the risk for neT2 lesions increasing sequentially up to the highest sNfL quartile (Q4)

OBJECTIVE

- To evaluate the prognostic value of 3- and 12-month on-treatment sNfL levels for future disease activity in pwRMS

METHODS

Study design

- ASCLEPIOS I/II were two phase 3, double-blind, active-controlled trials in which participants with RMS were randomised to receive either ofatumumab or teriflunomide for up to 30 months
- Participants aged 18–55 years with a diagnosis of RMS, Expanded Disability Status Scale (EDSS) score 0–5.5, ≥1 relapse in the year before screening or ≥2 relapses in the last 2 years before screening, or ≥1 gadolinium-enhancing (Gd+) lesion on magnetic resonance imaging (MRI) in the year before randomisation were included
- The primary endpoint was annualised relapse rate. The relationship between sNfL at baseline and the formation of neT2 lesions was an exploratory secondary endpoint in these trials
- Due to the event-driven design, participants were switched to open-label ofatumumab following a variable duration in the core study:
  - The first switches to open-label treatment occurred during Year 1, and all participants were switched by the end of Year 3
  - The median time in the core study was 1.6 years (1.5 years in ASCLEPIOS I and 1.6 years in ASCLEPIOS II), and >30% of the participants had time in trial longer than 2 years
- The baseline sNfL cutoff was predefined in the clinical study protocol (i.e. before measuring sNfL or any clinical or radiological outcomes) as the median sNfL value for the overall population across ASCLEPIOS I/II (9.3 pg/mL)
- Participants were stratified into high (≥9.3 pg/mL) and low (<9.3 pg/mL) sNfL groups based on this median baseline sNfL concentration

Assessments

- Quantification of sNfL levels was performed centrally (Navigate BioPharma Services, Carlsbad, CA, USA), as a single batch at the end of the trials, using a validated Quanterix Simoa® NF-light advantage kit
- MRI scans were performed at baseline, Months 12 and 24, and end of treatment/end of study
- The prognostic value of high versus low sNfL at Months 3 and 12 was analysed for the annualised rate of neT2 lesions

Statistical analysis

- The number of neT2 lesions on the last available scan relative to the Month 12 scan was analysed in a negative binomial regression model adjusting for sNfL category at the respective month, with time (in years) between the two scans as an offset

RESULTS

Participant characteristics

- Of the 1882 participants randomised in the ASCLEPIOS I/II trials, 1746 had baseline sNfL data. Of these 1746 participants, 1393 had neT2 and Month 3 sNfL data, and 1384 had neT2 and Month 12 sNfL data
- Baseline demographic and disease characteristics by sNfL category (low vs high) at Months 3 and 12 were similar between sNfL groups, except the mean number of Gd+ lesions and T2 lesion volume, which were considerably higher in participants with high sNfL versus low sNfL (**Table 1**)

Table 1. Baseline demographic and disease characteristics for participants stratified by sNfL category at Months 3 and 12

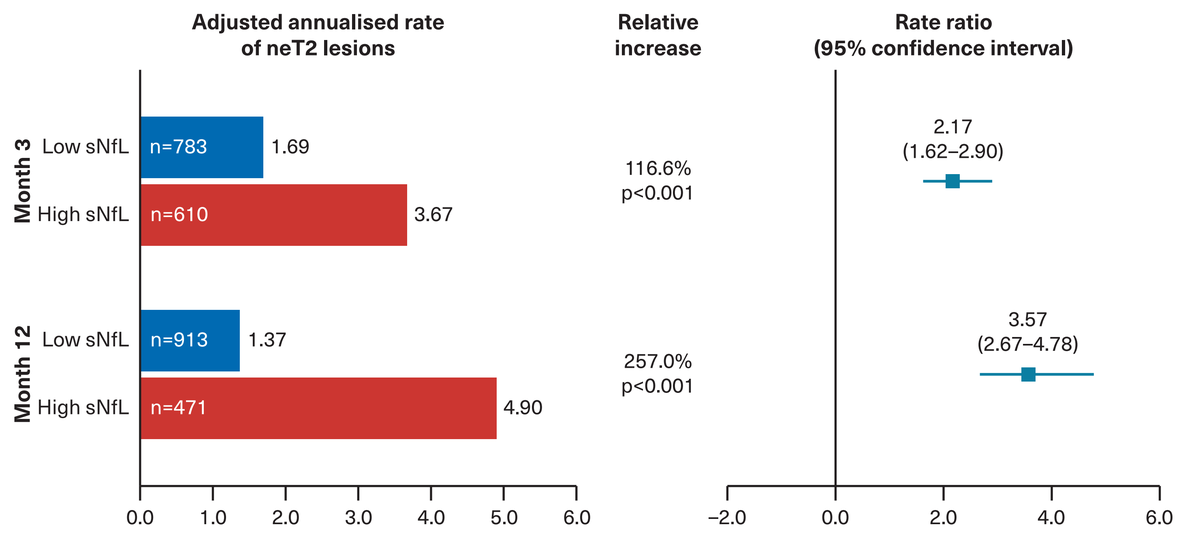
Characteristic	Month 3		Month 12	
	Low sNfL (<9.3 pg/mL) N=951[a]	High sNfL (≥9.3 pg/mL) N=758[a]	Low sNfL (<9.3 pg/mL) N=1059[a]	High sNfL (≥9.3 pg/mL) N=559[a]
Age, years	38.3±8.6	38.2±9.8	37.1±8.7	40.3±9.4
Female, n (%)	647 (68.0)	515 (67.9)	734 (69.3)	373 (66.7)
BMI, kg/m^2	26.8±6.5	24.7±5.3	26.2±6.1	24.9±5.4
MS duration since first symptom, years	8.0±7.2	8.2±7.1	7.4±6.7	9.4±7.6
Previously treated with DMT, n (%)	545 (57.3)	471 (62.1)	596 (56.3)	359 (64.2)
Number of relapses in the year before the study	1.2±0.7	1.3±0.7	1.2±0.7	1.3±0.7
Time since onset of most recent relapse, months	7.8±13.5	6.9±9.1	7.5±13.2	7.3±9.2
EDSS score	2.8±1.3	3.0±1.4	2.7±1.3	3.2±1.4
Normalised brain volume, cm^3	1446.5±75.2	1437.2±81.5	1449.6±74.3	1427.2±80.7
Number of Gd+ T1 lesions	0.5±1.4	2.7±5.5	1.3±3.8	1.9±4.6
Participants free of Gd+ T1 lesions, n (%)	703 (73.9)	342 (45.1)	678 (64.0)	311 (55.6)
T2 lesion volume, cm^3	10.1±11.4	16.7±15.1	11.1±11.9	16.7±15.4
Median sNfL, pg/mL	7.15	13.96	7.98	12.17

[a]Only participants with non-missing sNfL values at Month 3/Month 12 are included. Data are expressed as mean±standard deviation unless specified otherwise.
BMI, body mass index; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; sNfL, serum neurofilament light chain.

Prognostic value of on-treatment sNfL for neT2 lesions

- The mean annualised rate of neT2 lesions was significantly higher in participants with high sNfL versus low sNfL at Months 3 and 12
  - neT2 lesions were 2.2-fold in participants with high sNfL at Month 3 compared with those with low sNfL (116.6% increase, p<0.001; **Figure 1**)
  - Likewise, neT2 lesions were 3.6-fold in participants with high sNfL at Month 12 compared with those with low sNfL (257.0% increase, p<0.001; **Figure 1**)

Figure 1. Mean annualised rate of neT2 lesions in participants based on sNfL level at Months 3 and 12[a]



[a]Analyses were based on the population that had both sNfL and neT2 data available.
neT2, new or enlarging T2 lesion; sNfL, serum neurofilament light chain.

LIMITATIONS

- Based on the pre-planned nature of the analysis, participants were stratified by baseline median sNfL value into 'high' or 'low' with the intention to divide a typical phase 3 trial RMS population into groups of equal size with higher versus lower than median sNfL
- The results reported here are based on the protocol-defined single sNfL threshold; future work should evaluate how this single sNfL threshold could be optimised, with a specific target and population in mind
- The use of a single NfL threshold may be applicable mainly to relatively young RMS populations (18–55 years) such as the population included in these trials, for which prognostication of disease activity is most relevant
- The data presented in this study are based on a population that was selected according to the ASCLEPIOS inclusion/exclusion criteria, and although this population represents a typical population suitable for phase 3 trials/regulatory purposes, it may not reflect the broader population of individuals with RMS seen in everyday clinical practice
  - The population enrolled in the ASCLEPIOS I/II trials may not reflect older RMS 'community-based' populations, who may have comorbidities that may impact NfL levels (e.g. diabetes, neurodegenerative disorders)

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Abbreviations

BMI, body mass index; **DMT,** disease-modifying therapy; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **MRI,** magnetic resonance imaging; **MS,** multiple sclerosis; **neT2,** new or enlarging T2; **pwRMS,** people with relapsing multiple sclerosis; **RMS,** relapsing multiple sclerosis; **sNfL,** serum neurofilament light chain.

Disclosures

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