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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

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Disclosures

Thomas P. Leist serves as site investigator for Biogen, BMS, EMD Serono, Genentech/Roche, Janssen, Novartis, and Sanofi. He has advised Biogen, Genentech/Roche, Horizon, Janssen, and Novartis

Stephen L. Hauser currently serves on the scientific advisory board of Accure, Alector, and Annexon. He has previously consulted for BD, Moderna, NGM Bio, and Pheno Therapeutics and previously served on the Board of Directors of Neurona. Dr. Hauser has also received travel reimbursement and writing support from F. Hoffmann-La Roche and Novartis AG for anti-CD20 therapy–related meetings and presentations. Grants: NIH/NINDS (R35NS111644), NMSS (SI-2001-35701), and Valhalla Foundation

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Heinz Wiendl has acted as a member of the Scientific Advisory Boards of Alexion, Argenx, Biocryst, BMS, Cellerys, Galapagos, Janssen, Merck, Novartis, Sandoz-Hexal, and Uniqure. He has also received speaker honoraria and travel support from Alexion, Biogen, BMS, EPG Health, Genzyme, Merck, Neurodiem, Novartis, Ology, Roche, Teva, and WebMD Global and acts as a paid consultant for AbbVie, Actelion, Argenx, Biogen, BMS, and EMD Serono. He is a paid consultant for Actelion, Argenx, BD, BMS, Dianthus, EMD Serono, EPG Health, Fondazione Cariplo, Gossamer Bio, Idorsia, Immunic, Immunovant, Inmune Bio, Syneos Health, Janssen, LTS, Merck, NexGen, Novartis, Roche, Samsung, Sangamo, Sanofi, Swiss Multiple Sclerosis Society, Toleranzia, UCB, Viatris, VirBio, and Worldwide Clinical Trials. His research is funded by Alexion, Amicus Therapeutics, Argenx, Biogen, CSL Behring, F. Hoffmann-La Roche, Genzyme, Merck, Novartis, Roche, and UCB

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Xavier Montalban has received speaking honoraria and travel expenses for participation in scientific meetings and has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with AbbVie, Actelion, Alexion, Biogen, BMS/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, Merck, Mylan, NervGen, Novartis, Sandoz, Sanofi-Genzyme, Teva, TG Therapeutics, EXCEMED, MSIF, and NMSS

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Alit Bhatt, **Wenjia Wei**, and **Ibolya Boer** are employees of Novartis

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Introduction

- A challenge encountered in clinical practice with 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 optimize individualized 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 pwRMS), a pre-planned analysis of baseline 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 RDTN participants[4]
- The prognostic value of sNfL was also observed when participants were categorized by baseline sNfL concentration quartiles[5]
  - Irrespective of treatment, participants in the lowest quartile (Q1) had the lowest risk for on-study 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

neT2, new or enlarging T2; **pwRMS**, people with RMS; **Q**, quartile; **RDTN**, recently diagnosed treatment-naïve; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

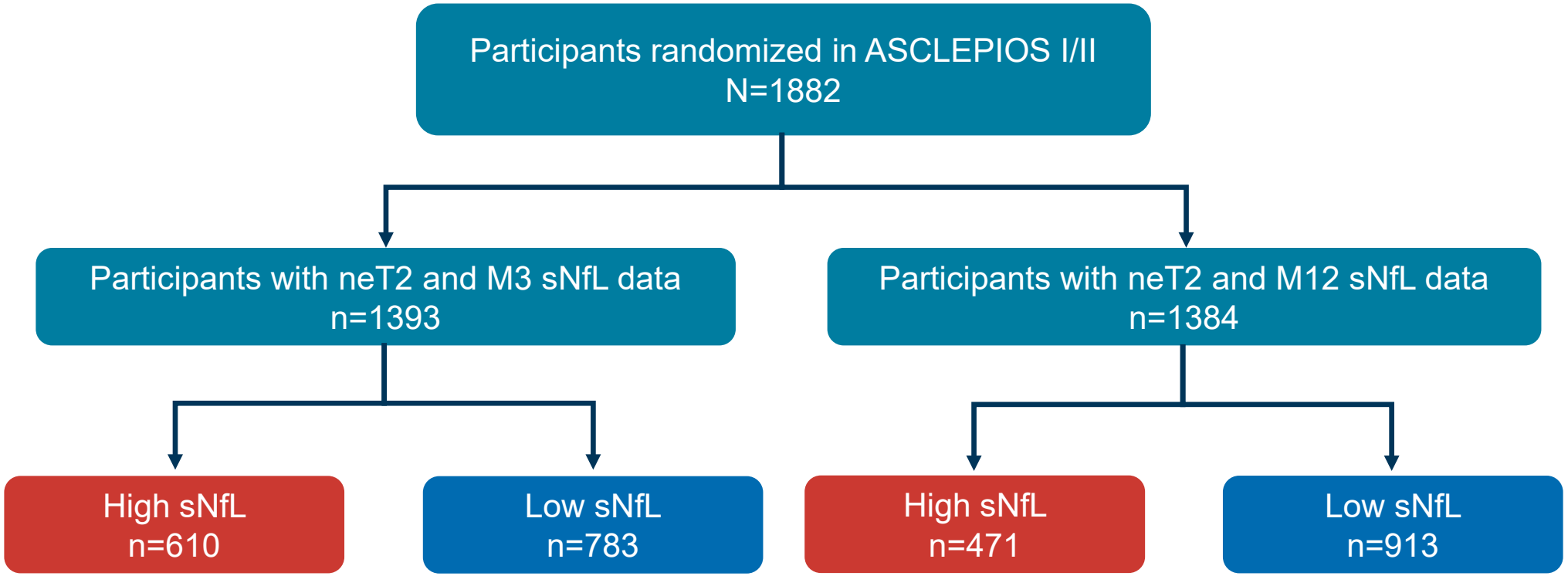
1. Oh J, et al. *Curr Opin Neurol*. 2018;31:752–759; **2.** Dahlke F, et al. *Mult Scler*. 2021;27:2062–2076; **3.** Thebault S, et al. *Mult Scler*. 2022;28:1491–1497; **4.** Ziemssen T, et al. *Front Immunol*. 2022;13:852563; **5.** Hauser SL, et al. *N Engl J Med*. 2020;383:546–557.

Study design, assessments, and statistical analysis

- ASCLEPIOS I/II were two phase 3, double-blind, active-controlled trials in which participants with RMS were randomized to receive either ofatumumab or teriflunomide for up to 30 months
- Participants aged 18–55 years with a diagnosis of RMS, EDSS score 0–5.5, ≥1 relapse in the year before screening or ≥2 relapses in the last 2 years before screening, or ≥1 Gd+ lesion on MRI in the year before randomization were included
- 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
- 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 (Billerica, MA, USA)
- 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 analyzed for the annualized rate of neT2 lesions irrespective of treatment
- The number of neT2 lesions on the last available scan relative to the Month 12 scan was analyzed 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

EDSS, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **neT2**, new or enlarging T2; **NF**, neurofilament; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

Participants with neT2 lesions and Month 3/12 sNfL data



M, month; **neT2**, new or enlarging T2; **sNfL**, serum neurofilament light chain.

Demographic and disease characteristics

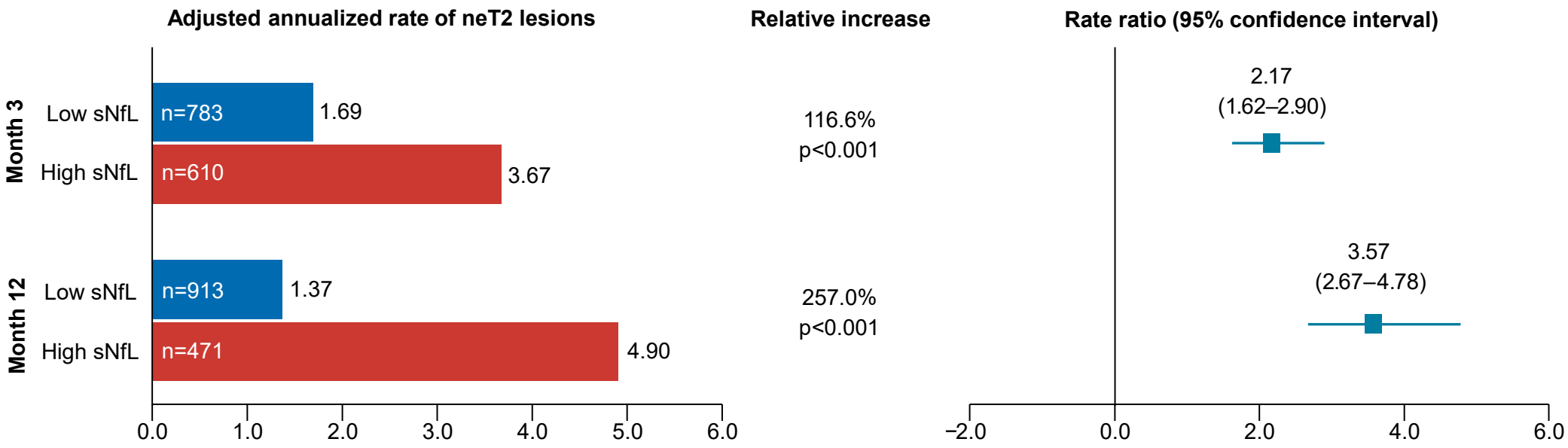
Baseline demographic and disease characteristics for participants stratified by sNfL category at Months 3 and 12

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
Normalized 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.

On-treatment sNfL at Months 3 and 12 is prognostic for neT2 lesions

Mean annualized rate of neT2 lesions in participants based on on-treatment sNfL level at Month 3 and Month 12[a]



- The mean annualized 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) and **3.6-fold** in participants with **high sNfL at Month 12** compared with those with low sNfL (257.0% increase)

[a]Analyses were based on the population that had both sNfL and neT2 data available.
neT2, new or enlarging T2; **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 optimized, with a specific target and population in mind
- The use of a single sNfL threshold may be applicable mainly to relatively young RMS populations (18–55 years) such as the population included in these trials, for whom prognostication of disease activity is most relevant
- This analysis evaluated the prognostic value of sNfL **irrespective of treatment**; treatment effect on sNfL was not assessed
- The data presented are based on a population selected according to the ASCLEPIOS inclusion/exclusion criteria, and although they represent a typical population suitable for phase 3 trials/regulatory purposes, they may not reflect the broader RMS population 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)

NfL, neurofilament light chain; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

Conclusion

- **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

DMT, disease-modifying therapy; **MS**, multiple sclerosis; **pwRMS**, people with relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

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- The study was sponsored by Novartis Pharma AG, Basel, Switzerland

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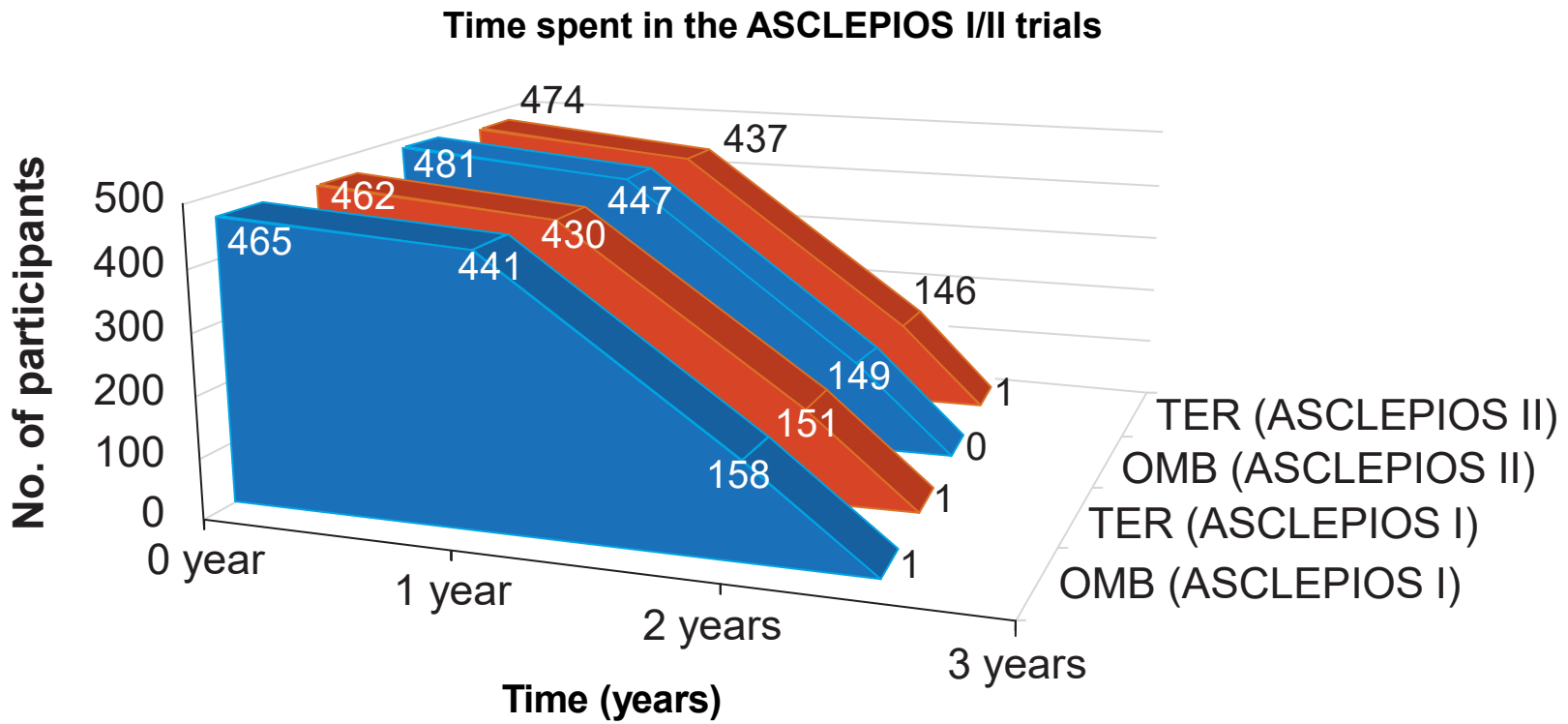
Supplementary Slides

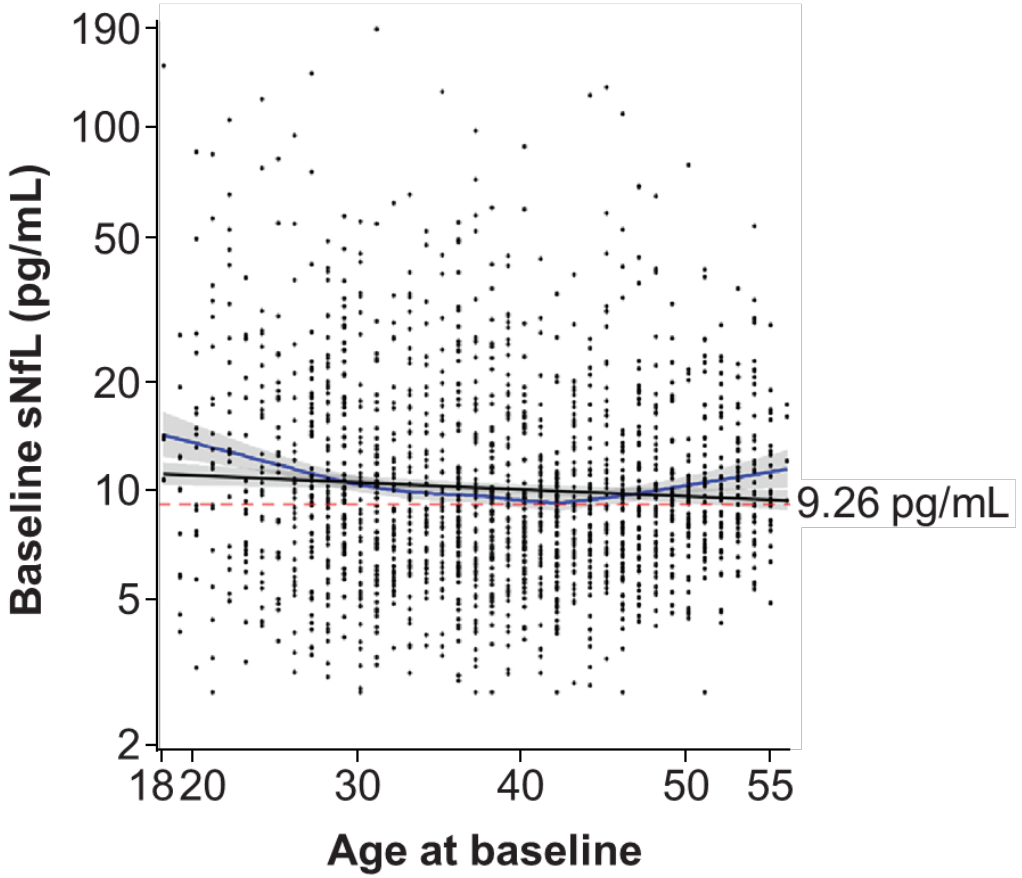
Time spent by participants in the ASCLEPIOS I/II trials



- 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 a time in trial longer than 2 years

OMB, ofatumumab; **TER**, teriflunomide.
Hauser SL, et al. *N Engl J Med*. 2020;383:546–557.

Use of a single sNfL threshold by age

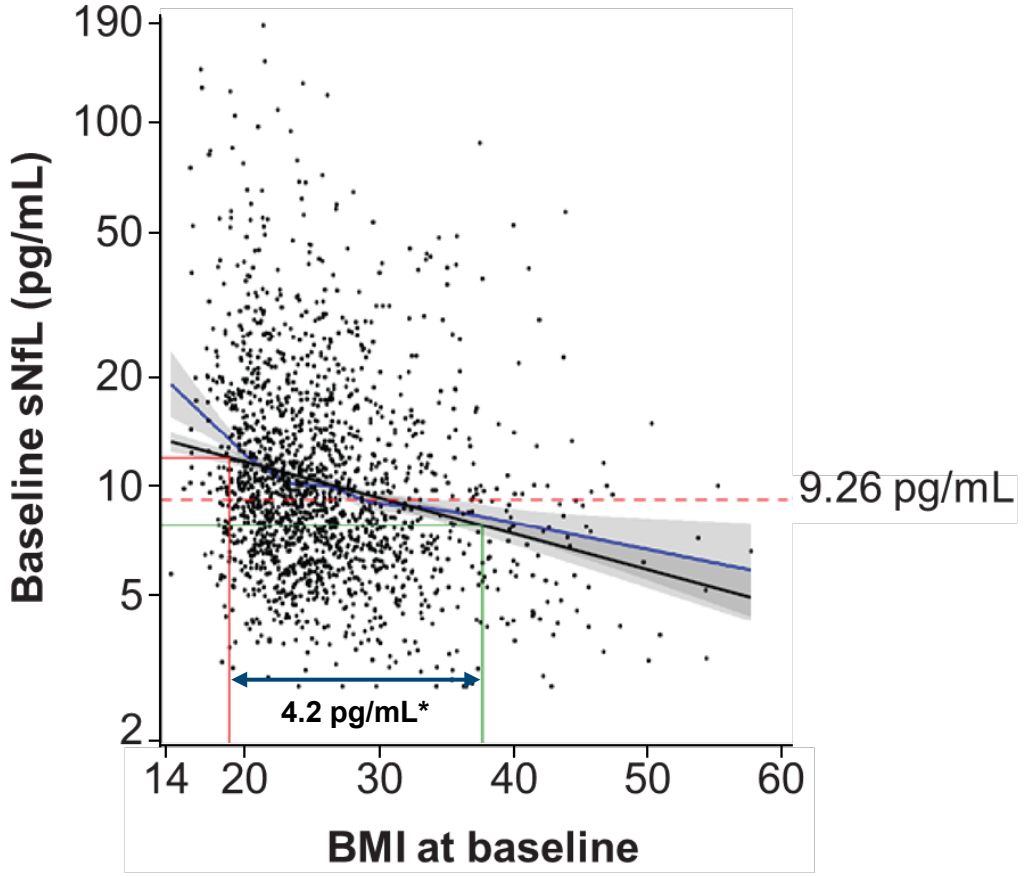


- In ASCLEPIOS I/II (pwRMS aged 18–55 years), the variability in sNfL levels associated with age is much lower than the observed overall variability in sNfL (likely due to MS disease activity)
- Compared with inflammatory-associated sNfL elevations, the age dependency of sNfL may not be a relevant confounder in clinical practice in younger patients with RMS without comorbidities[1]

Black line is from linear regression of log (baseline sNfL) on age; blue line is when applying a non-linear relationship; dashed red line indicates median baseline sNfL.
MS, multiple sclerosis; **pwRMS**, people with RMS; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

1. Bittner S, et al. *Brain*. 2021;144:2954–2963.

Use of a single sNfL threshold by BMI



- Based on data from ASCLEPIOS I/II (pwRMS aged 18–55 years), there is an association between BMI and sNfL levels, mainly driven by extreme values of BMI
  - Underweight individuals (BMI<18.5) were associated with higher mean sNfL levels, while extremely obese individuals (BMI>40) were associated with lower mean sNfL levels
  - However, the magnitude of individual variability in sNfL driven by MS disease activity by far exceeded the magnitude of change explained by BMI*
- Thus, for most patients with RMS in these studies, sNfL ≥9.3 pg/mL was prognostic of future MS disease activity irrespective of BMI

*Difference in mean sNfL within the inner 90% of the BMI range.
Black line is from linear regression of log (baseline sNfL) on BMI; blue line is when applying a non-linear relationship; dashed red line indicates median baseline sNfL. The vertical and horizontal red lines indicate the 5th percentile of BMI (18.78) and the corresponding mean sNfL (12.10 pg/mL). The vertical and horizontal green lines indicate the 95th percentile of BMI (37.74) and the corresponding mean sNfL (7.86 pg/mL).
BMI, body mass index; **MS**, multiple sclerosis; **pwRMS**, people with RMS; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.