Poster: P6.011
P9: Multiple Sclerosis – Clinical Assessments Including Digital Tools and Outcome Measures 2
Tuesday, April 16; 8.00 am–9.00 am

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Prognostic Value of Serum Neurofilament Light Chain for Disease Activity in Patients With Relapsing Multiple Sclerosis: Results From Subgroup Analysis Based on Body Mass Index and Age From the Phase 3 ASCLEPIOS I/II Trials

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Disclosures

Anne H. Cross received personal compensation from Biogen, Bristol Myers Squibb, EMD Serono, Genentech/Roche, Horizon, Novartis, Octave, and TG Therapeutics

Tjalf Ziemssen has received personal compensation for participating in advisory boards, trial steering committees, and data and safety monitoring committees, as well as for scientific talks and project support from Almirall, Bayer, BAT, Biogen, Celgene, Sanofi Genzyme, Merck, Novartis, Roche, Vitaccess, and Teva

Douglas L. Arnold reports personal fees from Biogen, Biohaven, Bristol Myers Squibb, Eli Lilly, EMD Serono, Find Therapeutics, Frequency Therapeutics, Gossamer Bio, GSK, Kiniksa, Merck, Novartis, Sanofi, and Shionoggi, outside of the submitted work; and ownership interest in NeuroRx

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Scott S. Zamvil has received consulting honoraria from Alexion, Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals, Inc and has served on Data Safety Monitoring Boards for Eli Lilly, BioMS, Teva, and Therapeutics

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Heinz Wiendl declares that he has acted as a member of the Scientific Advisory Boards of Alexion, Argenx, Biocryst, Bristol Myers Squibb, Cellerys, Galapagos, Janssen, Merck, Novartis, Sandoz-Hexal, and Uniqure. He also declares that he has received speaker honoraria and travel support from Alexion, Biogen, Bristol Myers Squibb, EPG Health, Genzyme, Merck, Neurodiem, Novartis, Ology, Roche, Teva, and WebMD Global and acts as a paid consultant for AbbVie, Actelion, Argenx, Biogen, Bristol Myers Squibb, and EMD Serono. He is acting as a paid consultant for Actelion, Argenx, BD, Bristol Myers Squibb, 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

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

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The final responsibility for the content lies with the authors

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Introduction and objective

- 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 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 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 categorized by baseline sNfL concentration quartiles
  - 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)[5]
- Some factors such as age and/or body mass index (BMI) may influence sNfL levels; however, in younger pwRMS without comorbidities, the impact of these factors on sNfL levels is expected to be limited compared to the effect of MS neuroinflammation itself [6-10]

Objective: To evaluate the prognostic value of low versus high sNfL (based on a pre-planned analysis of baseline sNfL being above or below the baseline median) for future disease activity according to BMI and age in pwRMS

BMI, body mass index; **pwRMS**, people with relapsing mulitple sclerosis; **Q**, quartile; **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. **6.** Consortium of Multiple Sclerosis Centers. *Int J MS Care*.2021;23:1–36. **7.** Bittner S, et al. *Brain.* 2021;144:2954–2963. **8.** Bar-Or A, et al. *EBioMedicine.* 2023;93:104462. doi: 10.1016/j.ebiom.2023.104662. **9.** Kapoor R, et al. *Neurol.* 2020;95:436–444. **10.** Barro C, et al. *Ann Clin Transl Neurol.* 2020;7:2508–2523.

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Study design

- 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, 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 randomization were included
- The baseline sNfL cut-off 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 the median baseline sNfL concentration

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

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

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Assessments and statistical analysis

- 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 baseline sNfL for the annualized rate of neT2 lesions was assessed in baseline BMI (<24.5 vs ≥24.5 kg/m^2) and age (<38.0 vs ≥38.0 years) subgroups
- Negative binomial regression model adjusting for sNfL group and sNfL group by BMI/age subgroup interaction was used to estimate the lesion rate ratio for high versus low sNfL levels in each BMI/age subgroup

BMI, body mass index; **MRI**, magnetic resonance imaging; **neT2**, new or enlarging T2; **sNfL**, serum neurofilament light chain.

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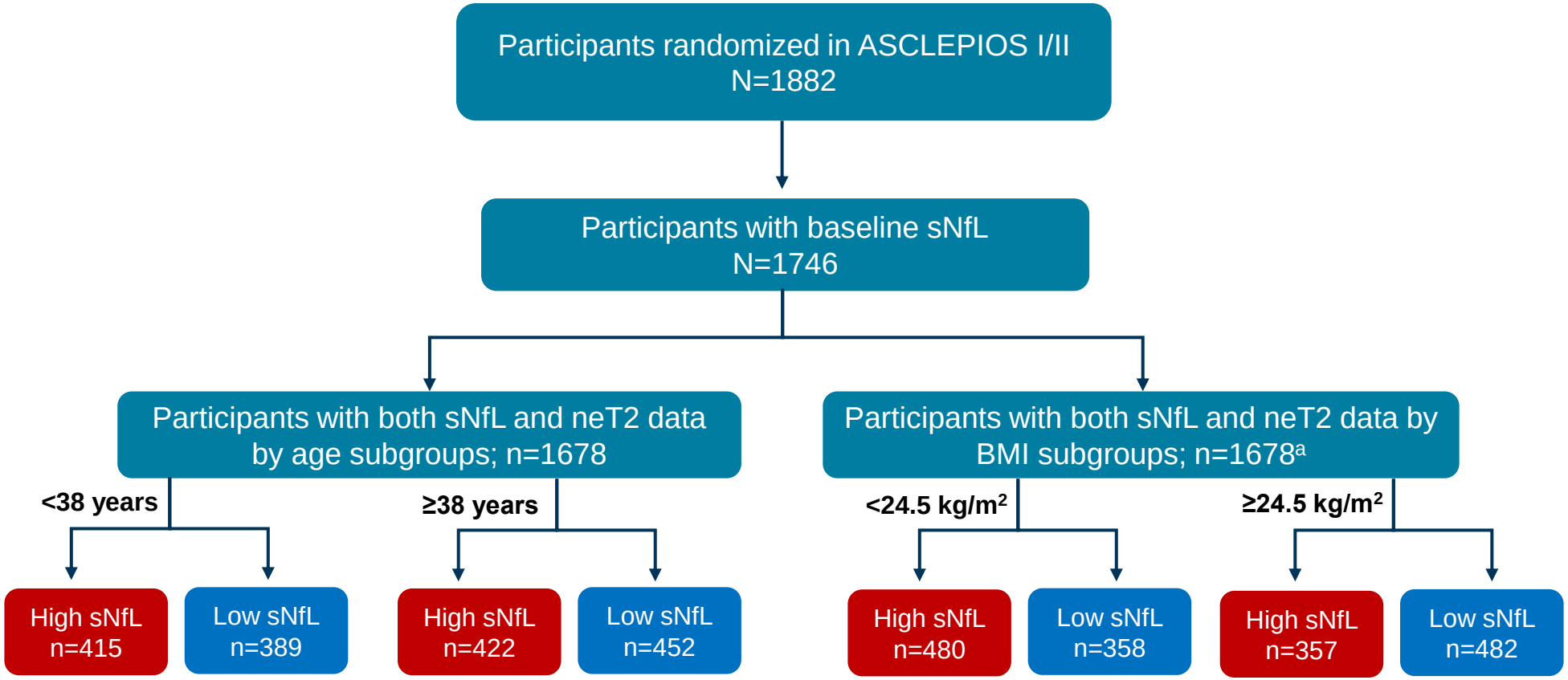
Participants with sNfL and neT2 data available



[a]BMI data was not available for one patient.
BMI, body mass index; **neT2**, new or enlarging T2; **sNfL**, serum neurofilament light chain.

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Demographic and disease characteristics by sNfL category at baseline

Characteristic	Low sNfL category (<9.3 pg/mL); N=876[a]	High sNfL category (≥9.3 pg/mL); N=870[a]
Age, years	38.6±8.5	37.8±9.7
BMI, kg/m^2	27.0±6.4	24.7±5.5
Female, n (%)	588 (67.1)	602 (69.2)
MS duration since first symptom, years	8.3±7.2	7.9±6.9
Previously treated with DMT, n (%)	537 (61.3)	507 (58.3)
Number of relapses in the year before the study	1.2±0.7	1.3±0.7
Time since onset of most recent relapse, months	7.8±13.5	7.0±9.3
EDSS score	2.8±1.3	2.9±1.4
Normalized brain volume, cm^3	1447.6±74.8	1437.2±81.0
Number of Gd+ T1 lesions	0.4±1.2	2.6±5.4
Patients free of Gd+ T1 lesions, n (%)	679 (77.5)	383 (44.0)
T2 lesion volume, cm^3	9.4±10.6	16.7±15.0
Median sNfL, pg/mL	6.76	14.23

- Baseline demographic and disease characteristics were similar between sNfL groups, except the **mean number of Gd+ lesions** and **T2 lesion volume,** which were considerably higher in participants with high versus low baseline sNfL

[a]Only participants with non-missing baseline sNfL values are included. Data are expressed as mean±SD unless specified otherwise.
BMI, body mass index; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **Gd**+, gadolinium-enhancing; **MS**, multiple sclerosis; **neT2**, new or enlarging T2; **SD**, standard deviation; **sNfL**, serum neurofilament light chain.

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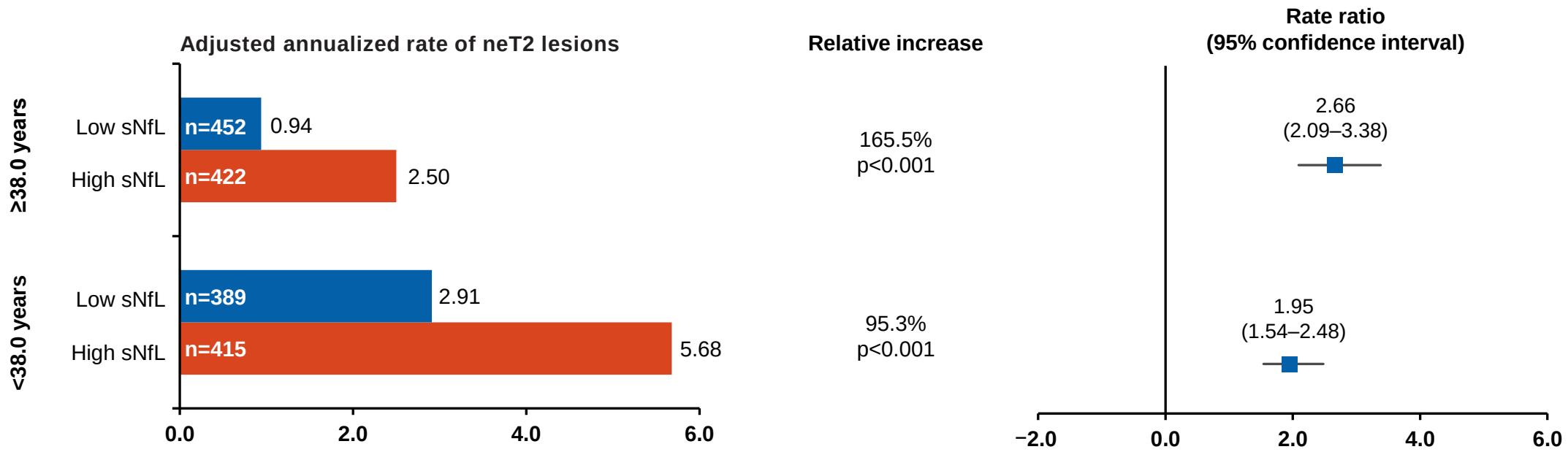
Prognostic value of sNfL for neT2 lesions by age subgroups

Mean annualized rate of neT2 lesions by age[a]



- Across age subgroups, the mean annualized rate of neT2 lesions was **significantly higher** in participants with high (≥9.3 pg/mL) versus low sNfL (<9.3 pg/mL) levels

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

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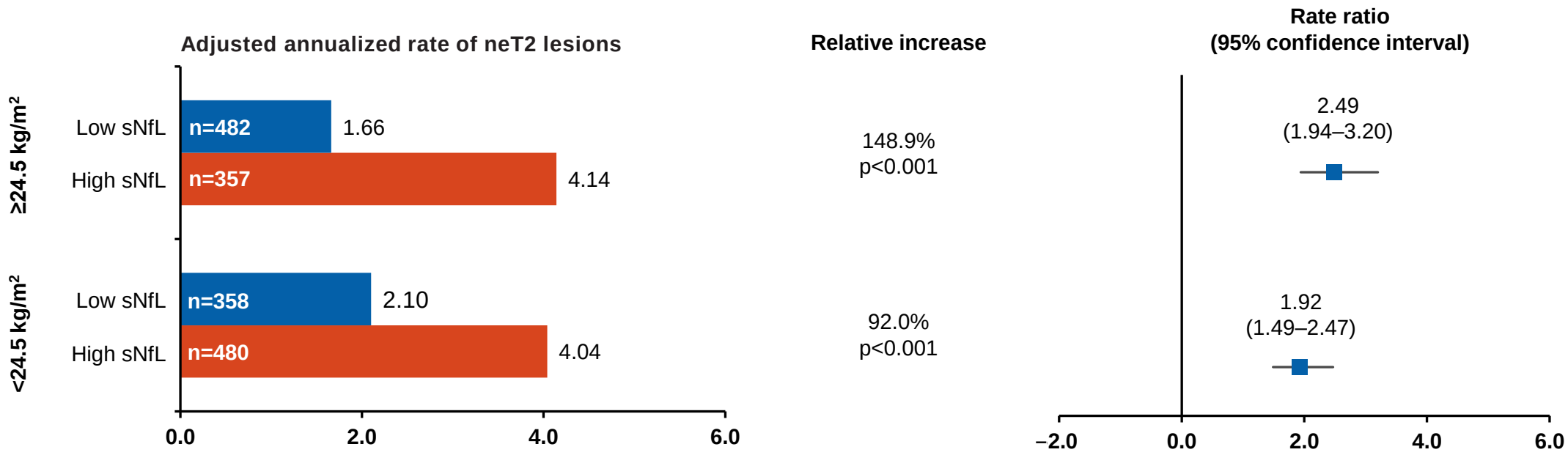
Prognostic value of sNfL for neT2 lesions by BMI subgroups

Mean annualized rate of neT2 lesions by BMI[a]



- Across BMI subgroups, the mean annualized rate of neT2 lesions was **significantly higher** in participants with high (≥9.3 pg/mL) versus low sNfL (<9.3 pg/mL) levels

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

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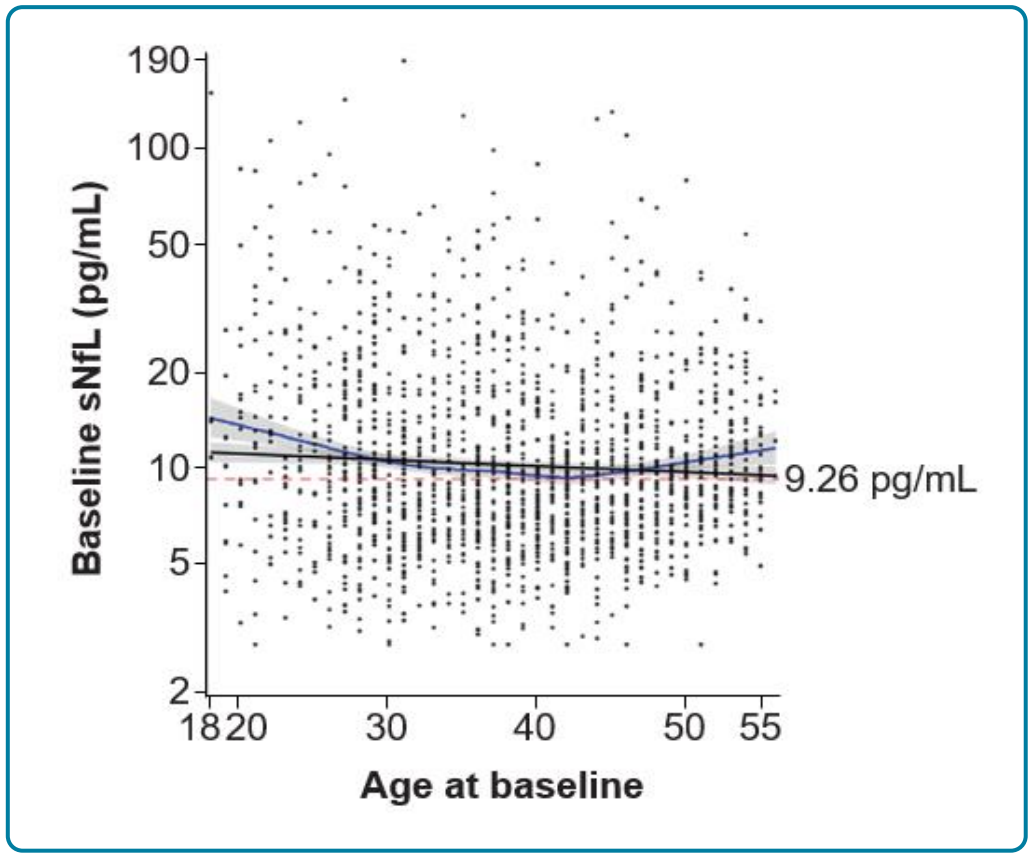
Additional analyses of data using a single sNfL threshold by age



- Based on data from participants aged 18–55 years in ASCLEPIOS I and II, the variability in sNfL levels associated with age is much lower than the observed overall variability in sNfL (likely due to MS disease activity) in patients with RMS
- Compared to inflammatory-associated sNfL elevations, the age dependency of sNfL may not be a relevant confounder in clinical practice in younger RMS patients 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; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

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

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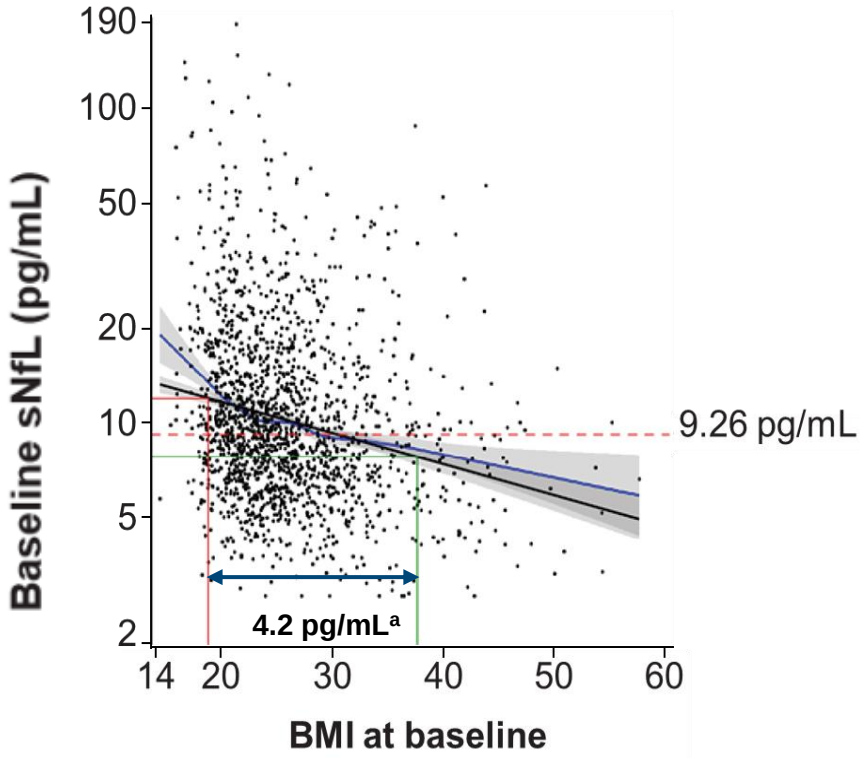

- Based on data from participants aged 18–55 years in ASCLEPIOS I and II, there is an association between BMI and sNfL levels, mainly driven by extreme values of BMI
  - Underweight individuals (BMI<18.5) were associated with higher mean sNfL levels, while extremely obese individuals (BMI>40) were associated with lower mean sNfL levels
  - However, the magnitude of individual variability in sNfL driven by MS disease activity far exceeded the magnitude of change explained by BMI (mean sNfL ranges from 7.9 to 12.1 pg/mL, i.e., 4.2 pg/mL difference within the inner 90% of the BMI range)
- Thus, for most RMS patients in these studies, sNfL ≥9.3 pg/mL was prognostic of future MS disease activity irrespective of BMI

[a]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; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

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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 phase 3 trial RMS population into groups of equal size with higher versus lower than median sNfL
- The use of a **single sNfL threshold** may be **mostly applicable to relatively young RMS populations** (18–55 years) such as the population included in these trials; for understanding sNfL changes outside of this age range, the use of sNfL as a continuous variable may be preferable
- While results support the **applicability of sNfL for most patients across the BMI range**, in those with extreme BMI (<18.5 and >40.0), prognostication using a single sNfL value should take into account the effect of BMI on sNfL
- The results reported here are based on the **protocol-defined single sNfL threshold**; future work should evaluate how sNfL as a prognostic factor could be optimized with a specific target and population in mind
- The data presented in this study are based on a population that was selected according to the ASCLEPIOS inclusion/exclusion criteria to represent a population suitable for phase 3 trials/regulatory purposes, and it may not reflect the broader population of individuals with RMS seen in everyday clinical practice
- Recent findings suggest that sNfL has comparable prognostic value to gadolinium-enhancing lesions on MRI scans for future lesion formation.[1] The relative prognostic value of sNfL and baseline MRI characteristics should be further confirmed

BMI, body mass index; **MRI**, magnetic resonance imaging; **RMS**, relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

1. Bar-Or A, et al. *Neurol Ther*. 2023;12:303–317.

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Conclusions

- The use of a single sNfL threshold, as defined in the ASCLEPIOS I/II study protocols, was prognostic of future lesion formation in the overall study population, including subgroups defined by BMI and age
- Overall, these data support further work on the optimization of sNfL for prognostication of future MS disease activity that would be applicable for pwRMS

BMI, body mass index; **MS**, multiple sclerosis; **pwRMS**, people with relapsing multiple sclerosis; **sNfL**, serum neurofilament light chain.

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