P036

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Baseline Serum Neurofilament Light Chain Levels Predict Future Disease Activity Irrespective of Race/Ethnicity: Results From the Phase 3 ASCLEPIOS I/II Trials

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KEY FINDINGS & CONCLUSIONS

- In racial/ethnic subpopulations (described as Asian, Black, and Other) in the ASCLEPIOS I/II trials, baseline sNfL levels were prognostic for neT2 lesions
- These results were consistent with those found in the Caucasian subgroup and overall cohort of patients in ASCLEPIOS I/II

Please refer to these related posters for more details on the prognostic value of sNfL

- 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 (**P032**)
- 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 (**P037**)

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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]
- There are disparities in MS prognosis and disease severity between different racial/ethnic groups, with certain ethnic groups often experiencing increased disease burden as compared to Caucasian groups[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 found 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 use of sNfL for future disease activity among diverse racial/ethnic subgroups from the trials has not yet been explored
  - Such data can help support the generalizability of sNfL as a prognostic biomarker to pwRMS with different racial/ethnic backgrounds

OBJECTIVE

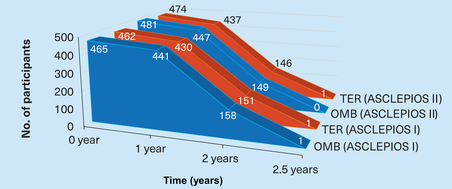
- To evaluate the prognostic value of baseline sNfL for future magnetic resonance imaging (MRI) disease activity in diverse racial/ethnic subpopulations (Asian, Black, and Other) of pwRMS in ASCLEPIOS I/II

METHODS

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 MRI in the year before randomization were included
- Due to the event-driven design, participants were switched to open-label ofatumumab following a variable duration in the core study (**Figure 1**)
  - 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
- 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 as having high (≥9.3 pg/mL) versus low (<9.3 pg/mL) based on the median baseline sNfL concentration

Figure 1. Time spent in the ASCLEPIOS I/II trials



Time in trial is defined as the time each participant spent in the trial (Day 1 to end of study). OMB, ofatumumab; TER, teriflunomide.

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 baseline sNfL for the annualized rate of neT2 lesions was assessed, irrespective of treatment, in the overall population and racial/ethnic subgroups (including Caucasian, Asian, Black, and Other [i.e., racial subgroups described as "other" or "unknown" upon data collection]) from ASCLEPIOS I/II

Statistical analysis

- The neT2 lesion number on the last available scan (relative to baseline scan) was analyzed using a negative binomial model with time (in years) between the two scans as offset, adjusting for baseline sNfL groups
- The prognostic value was assessed via the lesion rate ratio (RR) attained using this single cutoff threshold for high versus low sNfL

RESULTS

Participant characteristics

- Of the 1,882 participants randomized in ASCLEPIOS I/II trials, 1,746 had baseline sNfL data, including 1,678 participants with neT2 and sNfL data available
- Baseline 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 (**Table 1**)

Table 1. Demographic and disease characteristics of participants by baseline sNfL category

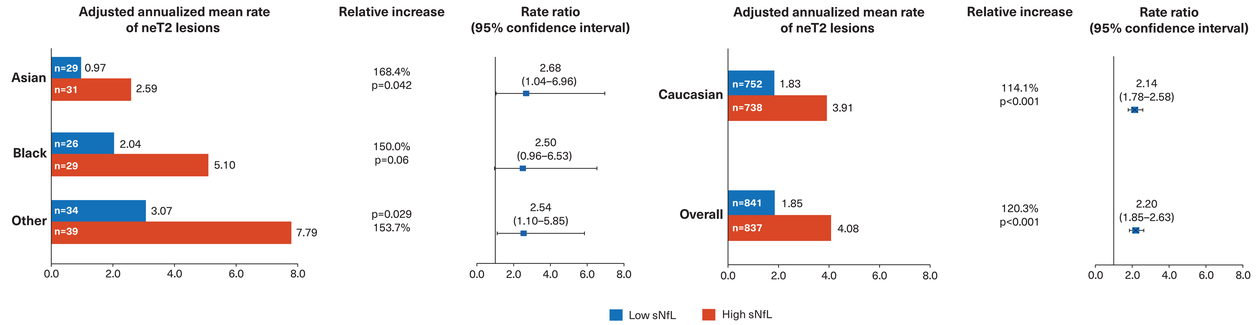
Characteristic	Low sNfL category (<9.3 pg/mL) N=876[a]	High sNfL category (≥9.3 pg/mL) N=870[a]
Age, years	38.6 ± 8.5	37.8 ± 9.7
Female, n (%)	588 (67.1)	602 (69.2)
Race, n (%)		
Caucasian	780 (89.0)	763 (87.7)
Asian	33 (3.8)	32 (3.7)
Black	27 (3.1)	34 (3.9)
Other[b]	36 (4.1)	41 (4.7)
MS duration since 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
Participants 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

[a]Only participants with non-missing baseline sNfL values are included. [b]Racial subgroups described as "other" or "unknown" upon data collection. Data are expressed as mean±standard deviation unless specified otherwise. DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; sNfL, serum neurofilament light chain.

Prognostic value of sNfL for neT2 lesions

- The annualized mean rate of neT2 lesions was consistently higher in participants with high versus low sNfL levels across all racial/ethnic subgroups; these results were also significantly higher in participants with high versus low sNfL levels for the overall ASCLEPIOS I/II population (**Figure 2**)

Figure 2. Mean annualized rate of neT2 lesions per year by racial/ethnic subgroups and in the overall population[a]



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

Limitations

- This analysis evaluated the prognostic value of sNfL irrespective of treatment; treatment effect on sNfL was not assessed
- The data presented for the racial/ethnic subgroups from ALITHIOS I/II are based on small sample sizes
- 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 RMS population for a phase 3 trial into groups of equal size with higher versus lower than median sNfL
- 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 NfL threshold may be applicable mainly to relatively young RMS populations (18–55 years), such as the population included in these trials; since prognostication of MS disease activity is primarily a concern in patients who are younger and/or are early in their disease course, this is not considered a strong limitation
- The data presented in this study are based on a population that was 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 population of individuals with RMS seen in everyday clinical practice

References

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Abbreviations

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

Disclosures

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