Prognostic Value of on-treatment sNfL for neT2 lesions in people with Relapsing Multiple Sclerosis: Pooled Analysis of the ASCLEPIOS I/II Trials


INTRODUCTION
- A challenge encountered in clinical practice with relapsing multiple sclerosis (RMS) is the difficulty in predicting the risk of future disease activity because of the variable clinical course in individual patients.
- Inflammation activity mostly occurs in the younger RMS population and declines with age.
- A marker 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.
- In the phase 3 ASCLEPIOS I/II trials (ofatumumab vs teriflunomide in people with RMS), 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 brain lesion formation and brain volume loss in the overall population and in recently diagnosed treatment-naïve participants.
- The prognostic value of sNfL was also observed when participants were categorised by baseline characteristics:
  - 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 RMS.

METHODS
STUDY DESIGN
- As there were two 3, double-blind, active-controlled trials in which participants with RMS were randomised to receive either ofatumumab or placebo for 3 years, the endpoints analysis for novel and enlarging T2 (neT2) lesions provided a 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 had switched to open-label treatment by the end of the study.
- 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 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/I (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 value.

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 at 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.

RESULTS
PARTICIPANT CHARACTERISTICS
- Of the 1882 participants randomised in the ASCLEPIOS I/I trials, 1744 had baseline sNfL data. Of these, 1744 participants, 1392 had neT2 and Month 3 sNfL data, 384 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 vs low sNfL levels (Table 1).

Table 1. Baseline demographic and disease characteristics for participants stratified by sNfL category.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Month 3</th>
<th>Month 12</th>
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<tbody>
<tr>
<td>Low sNfL (&lt;9.3 pg/mL)</td>
<td>High sNfL (≥9.3 pg/mL)</td>
<td>Low sNfL (&lt;9.3 pg/mL)</td>
</tr>
<tr>
<td>Age, years</td>
<td>38.3±8.6</td>
<td>38.2±8.9</td>
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<tr>
<td>Female, n (%)</td>
<td>647 (50.8)</td>
<td>515 (67.9)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>26.8±5.8</td>
<td>24.1±5.3</td>
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<tr>
<td>MS duration since first symptom, years</td>
<td>8.0±7.2</td>
<td>8.2±7.1</td>
</tr>
<tr>
<td>Previously treated with DMF, n (%)</td>
<td>545 (73.7)</td>
<td>471 (60.2)</td>
</tr>
<tr>
<td>Number of relapses in the year before the study</td>
<td>1.2±0.7</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>Time since onset of most recent relapse, months</td>
<td>7.8±12.5</td>
<td>8.0±9.1</td>
</tr>
<tr>
<td>EDSS score</td>
<td>2.8±1.3</td>
<td>3.0±1.4</td>
</tr>
<tr>
<td>Normalised brain volume, cm³</td>
<td>144.6±57.2</td>
<td>143.7±21.8</td>
</tr>
<tr>
<td>Patients with Gd-lesions, n (%)</td>
<td>703 (73.7)</td>
<td>424 (60.2)</td>
</tr>
<tr>
<td>T2 lesion volume, cm³</td>
<td>10.1±11.4</td>
<td>16.7±15.1</td>
</tr>
<tr>
<td>Median sNfL, pg/mL</td>
<td>7.1±9.6</td>
<td>7.9±8.8</td>
</tr>
</tbody>
</table>

LIMITATIONS
- Based on the pre-planned nature of the analysis, participants were stratified by median baseline sNfL value into high and low sNfL groups with the intention to divide a typical phase 3 trials RMS population into groups of equal size with higher versus lower median sNfL value.
- 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 NIL threshold may be applicable mainly to relatively young RMS populations (18–55 years) as such the population included in these trials, which were comprised of patients for whom the prognostication of disease activity is less relevant.
- The data presented in this study are based on a population which 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.

DISCUSSION
- The mean annualised rate of neT2 lesions was significantly higher in participants with high sNfL vs low sNfL at Month 3 and Month 12 (>9.3 pg/mL) versus <9.3 pg/mL) (Figure 1).
- The mean annualised rate of neT2 lesions was 2.2-fold in participants with high sNfL at Month 3 compared with those with low sNfL (11.6% increase, p<0.001; Figure 1).
- The mean annualised rate of neT2 lesions was 3.6-fold in participants with high sNfL at Month 12 compared with those with low sNfL (25.0% increase, p<0.001; Figure 1).

Figure 1. Mean annualised rate of neT2 lesions in participants based on sNfL level at Month 3 and 12*.

*Analyses were based on the population that had both high and low sNfL data available.

LOW sNfL group
- High sNfL group

4.30
3.67
2.17
1.69

Figure 2. Prognostic value of on-treatment sNfL for neT2 lesions.
- The annualised rate of neT2 lesions was 1.7-fold in participants with high sNfL at Month 12 compared with those with low sNfL (11.6% increase, p<0.001).

REFERENCES

ACKNOWLEDGEMENTS
- The authors thank the patients and investigators involved in the ASCLEPIOS I/I trials. The data presented in this study are based on a population which was selected according to the ASCLEPIOS inclusion/exclusion criteria, and although this population represents a typical population suitable for phase 3 trials.

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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 relative sNfL threshold to prognosticate MS disease activity in prior RMS DMT trials.