Baseline serum neurofilament light levels have prognostic value for on-study MRI activity: Results from ASCLEPIOS trials

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Program Number: P0033

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Poster Presentation at the 8th Joint ACTRIMS-ECTRIMS Meeting, MSVirtual2020, September 11-13, 2020
Disclosures

**Jens Kuhle** has nothing to disclose. His institution (University Hospital Basel) received and used exclusively for research support: consulting fees from Biogen, Novartis, Protagen AG, Roche, and Teva; speaker fees from the Swiss MS Society, Biogen, Novartis, Roche, and Genzyme; travel expenses from Merck Serono, Novartis, and Roche; grants from the ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation (320030_160221), Bayer AG, Biogen, Genzyme, Merck, Novartis, and Roche.

**Ludwig Kappos** has nothing to disclose. His institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the Department: steering committee, advisory board, consultancy fees and support of educational activities from: Actelion, Allergan, Almirall, Baxalta, Bayer, Biogen, Celgene/Receptos, CSL-Behring, Desitin, Excemed, Eisai, Genzyme, Japan Tobacco, Merck, Minoryx, Novartis, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi Aventis, Santhera, Teva, and license fees for Neurostatus-UHB products; the Research of the MS Center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, Inno-Suisse, the European Union, and Roche Research Foundations.

**Anne H. Cross** has consulted for Biogen, Celgene, EMD Serono, Genentech/Roche, and Novartis.

**Stephen L. Hauser** received personal compensation from Annexon, Alector, Bionure and Neurona; he has also received travel reimbursement from F. Hoffmann-La Roche Ltd and Novartis for CD20-related meetings and presentations.

**Roman Willi, Bingbing Li, Petra Kukkaro, Harald Kropshofer, Dieter A. Häring, Krishnan Ramanathan, and Martin Merschhemke** are employees of Novartis.

The study was funded by Novartis Pharma AG, Basel, Switzerland.

Medical writing support was provided by **Uma Kundu** and **Anuja Shah** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.
Background and objective

- Serum neurofilament light (sNfL) reflects neuro-axonal damage and is a surrogate marker of disease activity and treatment response in RMS\(^1\)-\(^4\).
- sNfL may complement MRI assessments for disease prognosis and patient monitoring in routine clinical practice.
- In the Phase 3 ASCLEPIOS I/II trials, ofatumumab significantly lowered sNfL levels versus teriflunomide\(^5^*\).
  - The effect was seen in the first assessment at Month 3 and sustained over Month 24.

**Objective**

To investigate the prognostic value of baseline sNfL for on-study disease activity and worsening in patients with RMS, particularly in newly diagnosed, treatment-naïve patients.
Methods: Study assessments and analysis

Patients
- Pooled ASCLEPIOS I and II trials (N=1882); patients who received ofatumumab or teriflunomide for up to 30 study months
- Patients were stratified into two categories based on median baseline sNfL level (9.3 pg/mL)
  - Low sNfL category (sNfL level \leq\ population median sNfL level)
  - High sNfL category (sNfL level > population median sNfL level)
- Analyses were performed in all patients and in the subgroup of newly diagnosed (within 3 years of screening), treatment-naïve (no prior MS DMT) patients

NfL
- NfL levels in serum was quantitated using Quanterix Simoa NF-light Assay Advantage Kit*

<table>
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<th>Outcomes</th>
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<td>MRI measures</td>
<td>• Annualized rate of new or enlarging T2 lesions</td>
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<td>Clinical measures</td>
<td>• Annualized relapse rate</td>
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<td></td>
<td>• 3-month confirmed disability progression</td>
<td>• Cox regression model</td>
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*The analytical sensitivity was confirmed to be 2.817 pg/mL, and the reportable range was 2.817 – 1546 pg/mL. Linearity of the assay was assessed across a range of below LLoQ to 1538 pg/mL in serum. Linear regression result was $R^2 = 0.9964$. Intra-assay precision was demonstrated by testing 8 samples across assay reportable range independently for 6 times in a single run with highest observed CV of 10%. Inter-assay precision was demonstrated by testing 8 samples independently for 3 times per run for 6 runs (2 runs per day), with the highest observed CV of 11%.

CV, coefficient of variance; DMT, disease modifying therapy; LLoQ, lower limit of quantification; MRI, magnetic resonance imaging; MS, multiple sclerosis; sNfL, serum neurofilament light chain

## Patient demographics and disease characteristics

*By baseline sNfL category*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low sNfL category</th>
<th>High sNfL category</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N=876</td>
<td>N=870</td>
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<tr>
<td>Age (years)</td>
<td>38.6±8.5</td>
<td>37.8±9.7</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>588 (67)</td>
<td>602 (69)</td>
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<tr>
<td>MS duration since first symptom (years)</td>
<td>8.3±7.3</td>
<td>7.9±6.9</td>
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<tr>
<td>No. of relapses in the year before the study</td>
<td>1.2±0.7</td>
<td>1.3±0.7</td>
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<tr>
<td>Time since onset of most recent relapse (months)</td>
<td>7.8±13.5</td>
<td>7.0±9.4</td>
</tr>
<tr>
<td>EDSS score</td>
<td>2.8±1.3</td>
<td>3.0±1.4</td>
</tr>
<tr>
<td>Normalized brain volume (cc)</td>
<td>1447.6±74.8</td>
<td>1437.2±81.0</td>
</tr>
<tr>
<td>No. of Gd+T1 lesions</td>
<td>0.4±1.2</td>
<td>2.6±5.4</td>
</tr>
<tr>
<td>Patients free of Gd+T1 lesions, n (%)</td>
<td>679 (78)</td>
<td>383 (44)</td>
</tr>
<tr>
<td>T2 lesion volume (cc)</td>
<td>9.4±10.6</td>
<td>16.7±15.0</td>
</tr>
<tr>
<td>sNfL (pg/mL)</td>
<td>6.6±1.6</td>
<td>20.0±17.5</td>
</tr>
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</table>

- At baseline, MRI disease activity was higher in patients with high sNfL levels than those with low sNfL levels.

*Data are expressed as mean±standard deviation*

EDSS, Expanded Disability Status Scale; Gd+ gadolinium-enhancing; MS, multiple sclerosis; sNfL, serum neurofilament light chain
On-study new or enlarging T2 lesions per year
By baseline sNfL category

- Patients with high sNfL levels at baseline had more new of enlarging T2 lesions than patients with low sNfL levels, irrespective of treatment, and in all patients as well as in newly-diagnosed, treatment-naïve patients.
- The prognostic value of baseline sNfL persisted for year-2 (all patients: Ofatumumab: 0.09 vs 0.06, 65%, p=0.124; teriflunomide: 4.53 vs 3.12, 46%, p=0.003)

Comparisons are between high vs low sNfL categories. 1Adjusted annualized mean rate of neT2 lesions. 2Indicates statistical significance (2-sided) at the 0.05 level. 3The number of neT2 lesions (compared to baseline or Month 12) is analyzed in a negative binomial model with adjustments for treatment, baseline sNfL category, region and study as factors, and age, baseline volume of T2 lesions as continuous covariates, and treatment by baseline sNfL category interaction. The natural log of the time from the baseline scan (in years) is used as the offset.

CI, confidence interval; neT2, new or enlarging T2 lesions; sNfL, serum neurofilament light
On-study brain volume loss per year

By baseline sNfL category

- Patients with high sNfL levels at baseline had increased annual rate of BVL versus patients with low sNfL levels
- These results were consistent in the subgroup of newly-diagnosed, treatment-naïve patients

Comparisons are between high vs low sNfL categories. 1Adjusted mean annual rate of percent change from baseline. 2Indicates statistical significance (2-sided) at the 0.05 level. 3Obtained from a random coefficients model with study, treatment as fixed effects (factors), and time as continuous covariates and treatment by time interaction for the overall analysis, with additional co-factors of subgroup, treatment by subgroup, treatment by time by subgroup interactions for the subgroup analysis. Random terms for slopes and intercept are included.

CI, confidence interval; BVL, brain volume loss; LS, least square; sNfL, serum neurofilament light
Relapse and disability progression

By baseline sNfL category

- In these studies, a single sNfL assessment at baseline had no prognostic value for on-study relapses and disability worsening.
- The lack of evidence of a prognostic value of sNfL is possibly due to a low number of events observed in ASCLEPIOS trials.

Comparisons are between high vs low sNfL categories. n: Total number of events included in the analysis; Y: number of patients-years in study; N: Total number of patients included in the analysis. 1Negative binomial regression model with log-link to the number of relapses adjusted for treatment, baseline sNfL category, region and study as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd+T1 lesions and the patient's age at baseline as covariates and treatment by baseline sNfL category interaction. The natural log of the time-in-study was used as offset to annualize the relapse rate. 2Cox regression adjusted study as stratum, treatment, region and sNfL baseline high-low subgroup as factors and baseline EDSS as a continuous covariate along with treatment-by-sNfL baseline high-low subgroup interaction. ARR, annualized relapse rate; CDW, confirmed disability worsening; sNfL, serum neurofilament light.
Ofatumumab treatment effect was similar irrespective of baseline sNfL levels

**Clinical measures**

- **Relapses**
  - High sNfL: 0.08, 0.12
  - Low sNfL: 0.21, 0.23

- **Disability progression**
  - High sNfL: 11.80, 15.80
  - Low sNfL: 9.00, 13.40

- **Rate/risk reduction**
  - ARR: 60%, p<0.001
  - 3mCDW: 48%, p<0.001

**MRI measures**

- **neT2 lesions**
  - High sNfL: 0.95, 0.39
  - Low sNfL: 5.28, 3.02

- **Brain volume loss**
  - High sNfL: -0.43, -0.23
  - Low sNfL: -0.32, -0.29

Arr: 82%, p<0.001

ARR, annualized relapse rate; BVL, brain volume loss; 3mCDW, 3-month confirmed disability progression; MRI, magnetic resonance imaging; neT2, new or enlarging T2 lesions; n.s., non-significant; sNfL, serum neurofilament light chain.
Conclusions

• Baseline sNfL levels were prognostic for on-study lesion formation and brain volume loss over 1-2 years, in the pooled Phase 3 ASCLEPIOS I/II trials.

• Prognostic value of a single sNfL assessment at baseline for clinical outcomes was not shown in this study.

• The superiority of ofatumumab over teriflunomide and the magnitude of treatment effect was consistent irrespective of baseline sNfL levels.

• sNfL levels can prospectively inform of the risk of ongoing and future disease activity and subclinical worsening in patients with RMS.

• sNfL may complement clinical and imaging assessments in the evaluation of the individual benefit/risk of patients with RMS.

DMT, disease modifying therapy; RMS, relapsing multiple sclerosis; sNfL, serum neurofilament light chain.
Thank you