Investigating the Correlation Between Serum Neurofilament Light Chain (sNfL) Concentration and Magnetic Resonance Imaging (MRI)-Outcomes in Patients with a First Clinical Demyelinating Event in the REFLEX Trial

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CONCLUSIONS

At baseline, higher sNfL levels moderately correlated with lesion load and T1 Gd-enhancing lesion count in patients presenting with FCDE

At 24 months, sNfL strongly correlated with lesion count during the study in the placebo group. However, the same variables were only weakly correlated in the sc IFN β-1a tiw group, in which lesion counts were significantly reduced compared to placebo

CUA, combined unique active; **FCDE**, first clinical demyelinating event; **Gd**, gadolinium; **IFN**, interferon; **MRI**, magnetic resonance imaging; **sc**, subcutaneous; **sNfL**, serum neurofilament light chain; **tiw**, three times weekly

INTRODUCTION

- sNfL has been characterized as a biomarker of disease activity, prognosis and treatment response in patients with MS.[1]
  - sNfL levels in MS patients can be used to predict clinical and radiological outcomes.
- sc IFN β-1a has proven efficacy in the treatment of patients with a FCDE.[2]
  - In the REFLEX trial, the onset of CDMS or McDonald MS 2005 was significantly delayed.
- During REFLEX, patients treated with sc IFN β-1a had reduced sNfL levels as early as 6 months post-baseline.[3]

CDMS, clinically definite multiple sclerosis; **CSF**, cerebrospinal fluid; **FCDE**, first clinical demyelinating event; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous, **sNfL**, serum neurofilament light chain

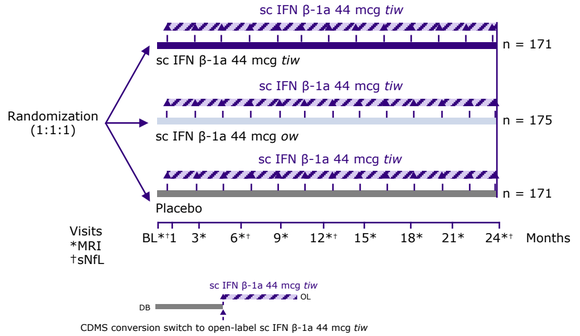
OBJECTIVES

Post-hoc assessment of correlation between sNfL concentration and MRI/clinical-outcomes in patients with a first clinical demyelinating event in REFLEX

METHODS

The REFLEX Trial Study Design[2]

- This analysis has been conducted on the double blind period (up to CDMS conversion).



CDMS conversion switch to open-label sc IFN β-1a 44 mcg *tiw*

sNfL Analysis

- sNfL levels were analyzed[4] at baseline (M0), M6, M12, and M24.
- Patients with sNfL data at baseline and ≥1 post-baseline time-point were included.
  - Baseline sNfL was correlated with baseline characteristics (age, time since first demyelinating event and EDSS) and baseline MRI (lesion count and normalized brain volume).
  - sNfL level at M24 was correlated with MRI at Month 24 (new lesions); MRI during the 24 month DB (mean number of CUA/new lesions[†]) and clinical outcomes (change in EDSS, % change in brain volume, and number of relapses).

Statistical Analysis

- Correlations between sNfL and MRI/clinical-outcomes were assessed by Spearman's rank correlation coefficient (r; p<0.001 for all numerical correlations described).
- Strength of correlation based on r value[5]:
  - Very strong: 0.80 – 1.00
  - **Strong: 0.60 – 0.79**
  - **Moderate: 0.40 – 0.59**
  - Weak: 0.20 – 0.39
  - Very weak: 0.00 – 0.19
- Correlation analyses were performed on observed data; number of observations per outcome is reported.

Note: Patients who converted to CDMS during the study were switched to open-label sc IFN β-1a 44 µg tiw
*MRI every 3 months. †sNfL measured, †per subject per scan. **BL**, baseline; **CDMS**, clinically definite multiple sclerosis; **DB**, double blind; **HR**, hazard ratio; **IFN**, interferon; **M**, month; **MRI**, magnetic resonance imaging; **ow**, once weekly; **OL**, open label; **sc**, subcutaneous; **sNfL**, serum neurofilament light chain; **tiw**, three times weekly

RESULTS

Table 1. Correlation between baseline sNfL and baseline MRI/characteristics

Spearman's rank correlation coefficient	Overall N = 494
Volume of T2 lesions	**0.545**
Volume of T1 Gd-enhancing lesions	**0.490**
Number of T1 Gd-enhancing lesions	**0.464**
Volume of T1 hypointense lesions	0.358
Number of T2 lesions	0.345
Number of T1 hypointense lesions	0.298
EDSS	0.076
Normalized brain volume, cm^3	0.010
Time since first demyelinating event, days	-0.001
Age, years	-0.073

Correlation

- **Moderate correlations** were observed between baseline sNfL and volume of **T2** lesions and volume/number of **T1 Gd-enhancing** lesions at baseline.

Table 2. sNfL and MRI lesion counts at end of study

Variable	Placebo	sc IFN β-1a 44 mcg tiw	*P* value*
Mean sNFL at month 24, pg/mL	21.94	17.38	0.051
Lesion count per subject per scan during the 24 month DB period			
Mean number of CUA lesions	13.21	3.53	<0.002
Mean number of new T1 Gd-enhancing lesions	0.90	0.10	0.007
Mean number of new T1 hypointense lesions	0.63	0.29	0.004
Mean number of new T2 lesion count lesions	0.91	0.35	0.003

*Based on t-test of mean differences between treatment groups

- During the 24 month DB period, the mean number of **MRI lesions** was significantly **lower** in the sc IFN β-1a 44 mcg tiw group compared with the placebo group.

Table 3. Correlation between sNfL and MRI/clinical outcomes at end of study

- In the placebo group, **strong correlations** were observed between sNfL at month 24 and mean number of CUA, new T2 and new T1 Gd-enhancing lesions during 24 month DB period.
- No correlations were observed between sNfL at month 24 and clinical outcomes in the placebo or sc IFN β-1a groups.

Spearman's rank correlation coefficient	Placebo	sc IFN β-1a 44 mcg ow	sc IFN β-1a 44 mcg tiw
Lesion count per subject per scan during the 24 month DB period*	N = 91	N = 113	N = 115
Mean number of CUA lesions	**0.70**	**0.49**	0.13
Mean number of new T2 lesions	**0.72**	**0.46**	0.11
Mean number of new T1 Gd-enhancing lesions	**0.60**	**0.40**	0.31
Mean number of new T1 hypointense lesions	**0.49**	**0.48**	0.18
Lesion count at month 24	N = 133	N = 139	N = 138
Number of new T2 lesions	**0.56**	0.37	0.27
Volume of total T2 lesions, mm^3	**0.45**	0.29	0.22
Volume of total T1 hypointense lesions, mm^3	**0.43**	0.27	0.19
EDSS (change from BL) at month 24	N=138 0.01	N=140 -0.15	N=145 -0.01
Brain volume (% change from BL) at month 24	N=127 -0.14	N=136 -0.08	N=135 -0.22
Qualifying relapses during 24 month DB period	N=141 0.01	N=141 -0.03	N=148 0.08

N is the number of patients with NfL and MRI/clinical data available for analysis. *MRI metrics collected at several timepoints during 24 month period were used for the correlation

BL, baseline; **CUA**, combined unique active; **DB**, double blind; **EDSS**, Expanded Disability Status Scale; **Gd**, gadolinium; **IFN**, interferon; **MRI**, magnetic resonance imaging; **ow**, once weekly; **NfL**, neurofilament light chain; **sc**, subcutaneous; **sNfL**, serum neurofilament light chain; **tiw**, three times weekly

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