Abstract No. 40

Effect of Interferon β-1a Treatment on Serum Neurofilament Light Chain Levels in Patients with a First Clinical Demyelinating Event in the REFLEX Trial

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INTRODUCTION

- Serum neurofilament light chain (NfL) is a promising biomarker of neuronal injury in patients with multiple sclerosis (MS), including those with a first clinical demyelinating event (FCDE).[1,2]
  - Levels of serum NfL correlate with both clinical (e.g. relapses and Expanded Disability Status Scale scores) and MRI (e.g. T2 and T1 gadolinium-enhancing lesion loads) outcomes in patients with MS.[2,3]
- It is of interest to investigate the value of using serum NfL levels as a potential biomarker of treatment efficacy in MS patients.
- Subcutaneous (sc) interferon (IFN) β-1a is an established therapy for patients with a FCDE, which significantly delayed the onset of clinically definite MS (CDMS) or McDonald MS 2005 in the REFLEX trial.[4]

OBJECTIVES

- To assess the effect of sc IFNβ-1a 44 µg once (qw) or three times (tiw) weekly versus placebo on serum NfL levels in patients with a FCDE in REFLEX.
- To explore the predictive value of NfL for conversion to CDMS or McDonald MS.

METHODS

Patients

- In REFLEX, patients were randomised to sc IFNβ-1a 44 µg tiw (n = 171) or qw (n = 175), or placebo (n = 171) for 24 months.[4]
- Those who converted to CDMS were subsequently switched to open label sc IFNβ-1a tiw.
  - To assess treatment effect on NfL, only data that were collected prior to conversion to CDMS were included in this analysis.

NfL Analysis

- Serum NfL levels were analysed *post hoc* using samples collected at baseline (Month [M] 0), M6, M12 and M24.
- Patients with NfL data at M0 and at least one other time point (M6, M12 or M24) were included in the analysis.

Statistical Analysis

- Since NfL values were skewed, in order to retrieve normal assumptions, NfL data were log-transformed for statistical analysis.
- At M0, mean (standard deviation [SD]) and median (minimum, maximum) NfL concentrations are reported.
- Least square mean (LSM; 95% confidence intervals [CI]) NfL concentrations, calculated using back log-transformation, are reported for M6 and M12.
  - Treatment effect on NfL levels was compared using ANCOVA on log-transformed NfL data, with M0 log-NfL concentration as a covariate.
- Kaplan–Meier curves showing time to CDMS or McDonald MS 2005 are presented.
  - Patients in each treatment group were classified according to baseline NfL levels. At M0, a median NfL concentration of 26.1 pg/mL was used to define the low and high NfL subgroups:
    - Low NfL subgroup: NfL value ≤ median M0 NfL value.
    - High NfL subgroup: NfL value > median M0 NfL value.
  - Two-sided unstratified log-rank *P* values were calculated to compare treatment groups within each subgroup.
  - Hazard ratios (HR; 95% CI) versus placebo, estimated using an adjusted Cox's proportional hazards model with baseline log-NfL as a covariate, are reported.
  - The percentage of patients who converted to CDMS or McDonald MS 2005 by M24 (from Kaplan–Meier estimates) are also reported for each subgroup.
- All analyses were performed *post hoc* without any adjustment for multiple testing and *P* values should be considered exploratory only.

RESULTS

Serum NfL Concentration

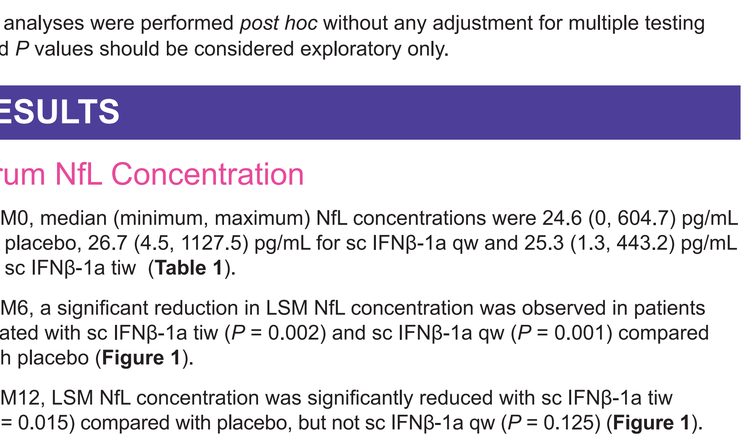
- At M0, median (minimum, maximum) NfL concentrations were 24.6 (0, 604.7) pg/mL for placebo, 26.7 (4.5, 1127.5) pg/mL for sc IFNβ-1a qw and 25.3 (1.3, 443.2) pg/mL for sc IFNβ-1a tiw (**Table 1**).
- At M6, a significant reduction in LSM NfL concentration was observed in patients treated with sc IFNβ-1a tiw (*P* = 0.002) and sc IFNβ-1a qw (*P* = 0.001) compared with placebo (**Figure 1**).
- At M12, LSM NfL concentration was significantly reduced with sc IFNβ-1a tiw (*P* = 0.015) compared with placebo, but not sc IFNβ-1a qw (*P* = 0.125) (**Figure 1**).

Table 1. Baseline Serum NfL Concentration by Treatment Group

	Placebo	sc IFNβ-1a 44 µg qw	sc IFNβ-1a 44 µg tiw
Number of patients, n	165	168	161
NfL concentration, pg/mL Mean (±SD) Median (min, max)	 9.3 (90.8) 24.6 (0, 604.7)	 54.6 (106.2) 26.7 (4.5, 1127.5)	 45.7 (62.4) 25.3 (1.3, 443.2)

IFN, interferon; **qw**, once weekly; **sc**, subcutaneous; **SD**, standard deviation; **tiw**, three times weekly.

Figure 1. Serum NfL Concentrations (LSM [95% CI]) at Month 6 and 12 by Treatment Group



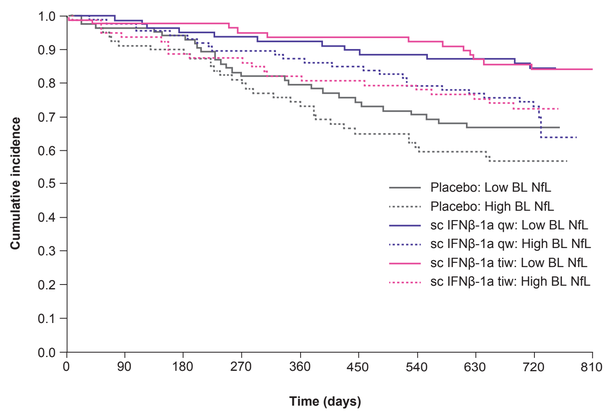
Statistical significance versus placebo: **P* = 0.001, †*P* = 0.002, ‡*P* = 0.015, **NS** = non-significant.
CI, confidence intervals; **IFN**, interferon; **LSM**, least square mean; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly.

Time to Conversion to CDMS

- In both NfL subgroups, time to conversion to CDMS (**Figure 2**) was delayed versus placebo with:
  - sc IFNβ-1a tiw (HR [95% CI] low NfL subgroup: 0.40 [0.20–0.79], *P* = 0.006; high NfL subgroup: 0.58 [0.33–1.00], *P* = 0.047).
  - sc IFNβ-1a qw (low NfL subgroup: 0.42 [0.21–0.82], *P* = 0.009; high NfL subgroup: 0.56 [0.33–0.95], *P* = 0.028).
- For all treatment groups in the low and high NfL subgroups, median time to conversion CDMS was not reached and therefore is not reported.

Figure 2. Time to Conversion to CDMS by Baseline NfL Subgroup and Treatment Group

	Placebo: Low BL NfL	Placebo: High BL NfL	sc IFNβ-1a qw: Low BL NfL	sc IFNβ-1a qw: High BL NfL	sc IFNβ-1a tiw: Low BL NfL	sc IFNβ-1a tiw: High BL NfL
	(n = 85)	(n = 80)	(n = 80)	(n = 88)	(n = 82)	(n = 79)
No. of events	27	33	12	25	12	21
MEDIAN	(-)	(-)	(-)	(-)	(-)	(-)
(95% CI)	(-)	(537.0–)	(-)	(731.0–)	(-)	(-)



At risk										
Placebo: Low BL NfL	85	82	79	67	63	58	55	52	43	0
Placebo: High BL NfL	80	73	71	62	54	48	45	43	28	0
sc IFNβ-1a qw: Low BL NfL	80	79	75	73	70	68	66	65	48	0
sc IFNβ-1a qw: High BL NfL	88	86	81	77	75	73	68	65	48	0
sc IFNβ-1a tiw: Low BL NfL	82	80	78	75	72	71	68	64	55	1
sc IFNβ-1a tiw: High BL NfL	79	74	70	67	62	61	56	54	48	0

Baseline NfL subgroups were defined using the median baseline NfL value (26.1 pg/mL) as a cut off; low NfL subgroup: NfL value ≤ median M0 NfL value; high NfL subgroup: NfL value > median M0 NfL value.
BL, baseline; **CDMS**, clinically definite multiple sclerosis; **CI**, confidence intervals; **NfL**, neurofilament light chain.

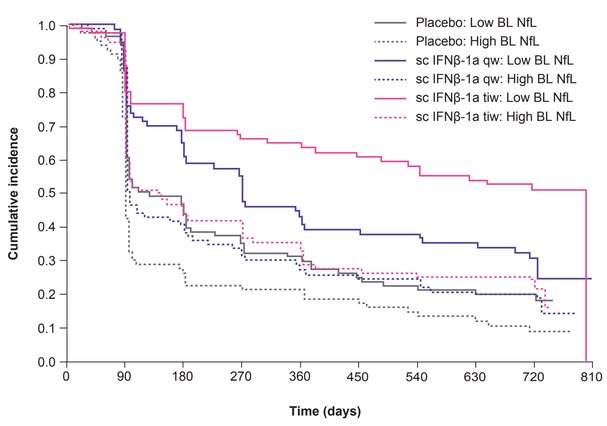
- Proportionally fewer patients in the low NfL subgroups converted to CDMS by M24 (from Kaplan–Meier) than in the high NfL subgroups, irrespective of treatment group (**Table 2**).
- For those who received treatment with sc IFNβ-1a tiw or qw in both the high and low NfL subgroups, proportionally fewer converted to CDMS by M24 than in the corresponding placebo groups.

Time to McDonald MS 2005

- In the low and high NfL subgroups, time to conversion to McDonald MS (**Figure 3**) was delayed versus placebo with:
  - sc IFNβ-1a tiw (HR [95% CI] low NfL subgroup: 0.41 [0.27–0.61], *P* < 0.001; high NfL subgroup: 0.64 [0.45–0.90], *P* = 0.008).
  - sc IFNβ-1a qw (low NfL subgroup: 0.68 [0.48–0.97], *P* = 0.031; high NfL subgroup: 0.71 [0.51–0.99], *P* = 0.040).
- Median time to McDonald MS was longer in patients in the low NfL subgroup (128.0 days, 272.0 days and 801.0 days for placebo, sc IFNβ-1a qw and tiw, respectively) than in the high NfL subgroup (93.0 days, 97.0 days, and 142.0 days for placebo, sc IFNβ-1a qw and tiw, respectively) for each treatment group.

Figure 3. Time to Conversion to McDonald MS 2005 by Baseline NfL Subgroup and Treatment Group

	Placebo: Low BL NfL	Placebo: High BL NfL	sc IFNβ-1a qw: Low BL NfL	sc IFNβ-1a qw: High BL NfL	sc IFNβ-1a tiw: Low BL NfL	sc IFNβ-1a tiw: High BL NfL
	(n = 85)	(n = 80)	(n = 80)	(n = 88)	(n = 82)	(n = 79)
No. of events	68	72	55	72	39	62
MEDIAN	128.0	93.0	272.0	97.0	801.0	142.0
(95% CI)	(96.0–184.0)	(92.0–97.0)	(182.0–368.0)	(93.0–181.0)	(449.0–801.0)	(94.0–272.0)



At risk										
Placebo: Low BL NfL	85	75	39	28	25	20	18	16	12	0
Placebo: High BL NfL	80	57	22	17	16	14	11	9	2	0
sc IFNβ-1a qw: Low BL NfL	80	72	52	41	33	29	27	25	15	1
sc IFNβ-1a qw: High BL NfL	88	74	35	29	24	21	20	17	16	0
sc IFNβ-1a tiw: Low BL NfL	82	73	60	51	48	45	42	38	33	0
sc IFNβ-1a tiw: High BL NfL	79	68	36	32	27	21	19	19	17	0

Baseline NfL subgroups were defined using the median baseline NfL value (26.1 pg/mL) as a cut off; low NfL subgroup: NfL value ≤ median M0 NfL value; high NfL subgroup: NfL value > median M0 NfL value.
BL, baseline; **CI**, confidence intervals; **NfL**, neurofilament light chain.

- In each treatment group, proportionally fewer patients in the low NfL subgroup converted to McDonald MS by M24 than in the high NfL subgroup (**Table 2**).
- Proportionally fewer patients who received treatment with sc IFNβ-1a tiw or qw in both the high and low NfL subgroups converted to McDonald MS by M24 than in the corresponding placebo groups.

Table 2. Percentage* of Patients that Converted to CDMS or McDonald MS 2005 by M24 According to Treatment Group and NfL Subgroup

NfL subgroup	Placebo	sc IFNβ-1a 44 µg qw	sc IFNβ-1a 44 µg tiw
Conversion to CDMS			
ITT population			
Number of patients	171	175	171
% converted to CDMS at M24	38	22	21
(95% CI)	(30–45)	(15–28)	(14–27)
Low NfL subgroup			
Number of patients	85	80	82
% converted to CDMS at M24	33	16	16
(95% CI)	(23–44)	(8–24)	(8–24)
High NfL subgroup			
Number of patients	80	88	79
% converted to CDMS at M24	43	27	28
(95% CI)	(32–55)	(18–36)	(18–38)
Conversion to McDonald MS			
ITT population			
Number of patients	171	175	171
% converted to McDonald MS 2005 at M24 (95% CI)	86 (80–91)	76 (69–82)	62 (55–70)
Low NfL subgroup			
Number of patients	85	80	82
% converted to McDonald MS 2005 at M24 (95% CI)	80 (72–89)	69 (59–80)	49 (38–60)
High NfL subgroup			
Number of patients	80	88	79
% converted to McDonald MS 2005 at M24 (95% CI)	91 (85–98)	81 (72–89)	75 (66–85)

*Estimated from Kaplan–Meier curves. Baseline NfL subgroups were defined using the median baseline NfL value (26.1 pg/mL) as a cut off; low NfL subgroup: NfL value ≤ median M0 NfL value; high NfL subgroup: NfL value > median M0 NfL value.
CDMS, clinically definite multiple sclerosis; **IFN**, interferon; **MS**, multiple sclerosis; **NfL**, neurofilament light chain; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly.

CONCLUSIONS

- **Treatment with sc IFNβ-1a tiw or qw reduced NfL levels in patients with FCDE as early as 6 months post-baseline.**
- **Conversion to CDMS or McDonald MS was delayed in patients treated with sc IFNβ-1a tiw or qw with both high and low baseline NfL values.**
- **Higher NfL levels at baseline were associated with earlier conversion to McDonald MS.**

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