Baseline Serum Neurofilament Light Chain Levels Predict Conversion to McDonald 2005 Multiple Sclerosis (MS) Within 2 Years of a First Clinical Demyelinating Event in Patients with MS

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CONCLUSIONS

Higher baseline sNfL levels were associated with an increased risk of conversion to McDonald 2005 MS in patients with a FCDE

Age, multifocal disease and number of T1 or T2 lesions at baseline were also confirmed as significant determinants for risk of conversion to McDonald 2005 MS.

Conversion to CDMS or McDonald MS was delayed in patients treated with sc IFN β-1a tiw or qw with both high and low baseline sNfL values.

CDMS, clinically definite multiple sclerosis; **FCDE**, first clinical demyelinating event; **IFN,** interferon; **MS**, multiple sclerosis; **qw**, once weekly; **sc**, subcutaneous; **sNfL**, serum neurofilament light chain; **tiw**, three times weekly

INTRODUCTION

- Serum neurofilament light chain (sNfL) is a biomarker of neuronal damage, reflecting disease activity and drug response in patients with MS.[1]
  - Levels of sNfL can be used to predict future disability in established MS.[2]
- sc IFN β-1a has proven efficacy in the treatment of patients with a FCDE.[3]
  - 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.[4]

FCDE, first clinical demyelinating event; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **sNfL**, serum neurofilament light chain

OBJECTIVES

***Post hoc* analysis to assess whether baseline sNfL levels can predict conversion to McDonald 2005 MS in patients with a FCDE receiving sc IFN β-1a in REFLEX.**

FCDE, first clinical demyelinating event; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **sNfL**, serum neurofilament light chain

METHODS

The REFLEX Trial Study Design[3]

- This analysis has been conducted on the double blind period (up to CDMS conversion; Figure 1)

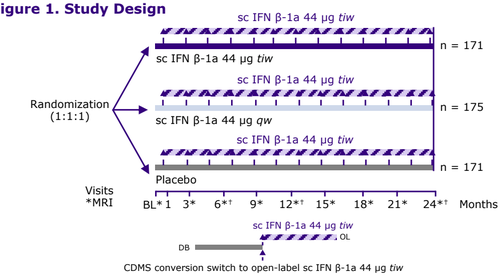
sNfL Analysis

- sNfL levels were analyzed[5] at baseline (M0), M6, M12, and M24.
- M0 sNfL subgroups were defined by median M0 sNfL concentration (26.1 pg/ml)
  - Low M0 sNfL: M0 sNfL ≤ median
  - High M0 sNfL: M0 sNfL > median

Statistical Analysis

- HRs (95% CI) to determine the factors influencing risk of conversion to McDonald MS were calculated using a univariate Cox's proportional hazard model.
- A stepwise multivariate Cox's proportional hazard model was performed using factors selected from univariate model.
- For both models, variable selection was based on a two-sided Wald test.

Figure 1. Study Design



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. **BL,** baseline; **CDMS**, clinically definite multiple sclerosis; **CI,** confidence interval; **DB**, double blind; **HR**, hazard ratio; **IFN**, interferon; **M**, month; **MRI**, magnetic resonance imaging; **qw**, once weekly; **OL**, open label; **sc**, subcutaneous; **sNfL**, serum neurofilament light chain; **tiw**, three times weekly

RESULTS

Table 1. Univariate and Multivariate Analyses of Time to McDonald 2005 MS

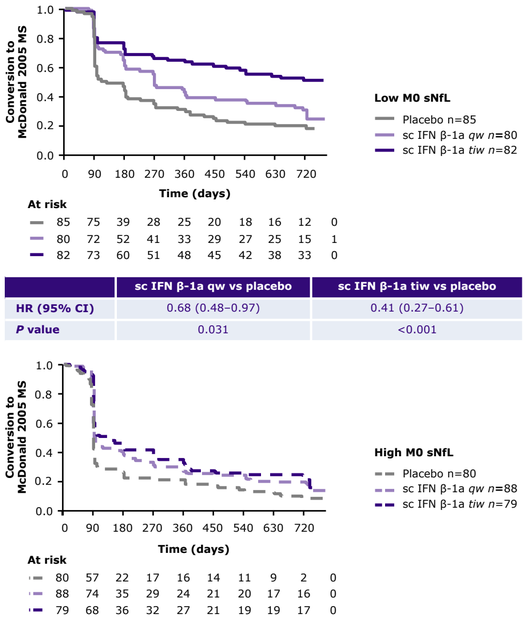
Factor	Factor Level	Parameter Estimate[a]	SE	HR (95% CI)[a]	P value[b]
Univariate					
Treatment	sc IFN β-1a tiw / placebo sc IFN β-1a qw / placebo	−0.63 −0.34	0.13 0.12	0.53 (0.41;0.69) 0.71 (0.56;0.91)	<0.001 0.006
Age	<30 years / ≥30 years	0.26	0.10	1.29 (1.05;1.59)	0.014
Classification of FCDE	Monofocal / multifocal	−0.39	0.10	0.68 (0.55;0.83)	<0.001
Steroid use at FCDE	Yes / No	−0.06	0.11	0.94 (0.75;1.18)	0.617
Presence of T1 Gd+ lesions at baseline	Yes / No	0.60	0.11	1.81 (1.48;2.23)	<0.001
Number of T2 lesions at baseline		0.02	0.00	1.02 (1.02;1.03)	<0.001
Number of T1 Gd+ lesions at baseline		0.13	0.01	1.14 (1.11;1.17)	<0.001
Number of T1 hypointense lesions at baseline		0.04	0.01	1.04 (1.02;1.05)	<0.001
Brain volume at baseline		0.00	0.00	1.00 (1.00;1.00)	0.496
Baseline sNfL subgroup	Low M0 sNfL / High M0 sNfL	−0.54	0.11	0.58 (0.47;0.72)	<0.001
Multivariate					
Treatment	sc IFN β-1a tiw / placebo sc IFN β-1a qw / placebo	−0.80 −0.53	0.14 0.13	0.45 (0.34;0.59) 0.59 (0.46;0.76)	<0.001 <0.001
Age	<30 years / ≥30 years	0.39	0.11	1.47 (1.19;1.82)	<0.001
Classification of FCDE	Monofocal / multifocal	−0.38	0.11	0.69 (0.55;0.85)	<0.001
Number of T2 lesions at baseline		0.02	0.00	1.02 (1.01;1.03)	<0.001
Number of T1 Gd+ lesions at baseline		0.07	0.02	1.07 (1.02;1.11)	0.001
Baseline sNfL subgroup	Low M0 sNfL / High M0 sNfL	−0.26	0.12	0.77 (0.61;0.97)	0.024

[a]Univariate or stepwise multivariate Cox's proportional hazards models were used for the respective analyses.
[b]Two-sided Wald test.

- Baseline sNfL subgroup significantly affected the risk of conversion to McDonald MS in the univariate model (Table 1).
- The effect of baseline sNfL subgroup on risk of conversion to McDonald MS was confirmed using a multivariate model (Table 1).

CI, confidence interval; **FCDE**, first clinical demyelinating event; **Gd+**, gadolinium-enhancing; **HR**, hazard ratio; **IFN**, interferon; **M**, Month; **MS**, multiple sclerosis; **qw**, once weekly; **sc**, subcutaneous; **SE**, standard error; **sNfL**, serum neurofilament light chain; **tiw**, three times weekly

Figure 2. Time to McDonald 2005 MS by Baseline sNfL Subgroup and Treatment Group



	sc IFN β-1a qw vs placebo	sc IFN β-1a tiw vs placebo
HR (95% CI)	0.68 (0.48–0.97)	0.41 (0.27–0.61)
***P* value**	0.031	<0.001

	sc IFN β-1a qw vs placebo	sc IFN β-1a tiw vs placebo
HR (95% CI)	0.71 (0.51–0.99)	0.64 (0.45–0.90)
***P* value**	0.040	0.008

Baseline sNfL subgroups were defined using the median baseline sNfL value (26.1 pg/mL) as a cut off; low sNfL subgroup: sNfL value ≤ median M0 sNfL value; high sNfL subgroup: sNfL value > median M0 sNfL value.

1. Kuhle J, et al. *Neurol.* 2019;92:e1007–e1015; 2. Barro C, et al. *Brain.* 2018;141:2382–2391; 3. Comi G, et al. *Lancet Neurol.* 2012;11:33–41; 4. Kuhle J, et al. *Mult Scler.* 2019;25(S2):785. 5. Disanto G, et al. *Ann Neurol.* 2017;81:857–870

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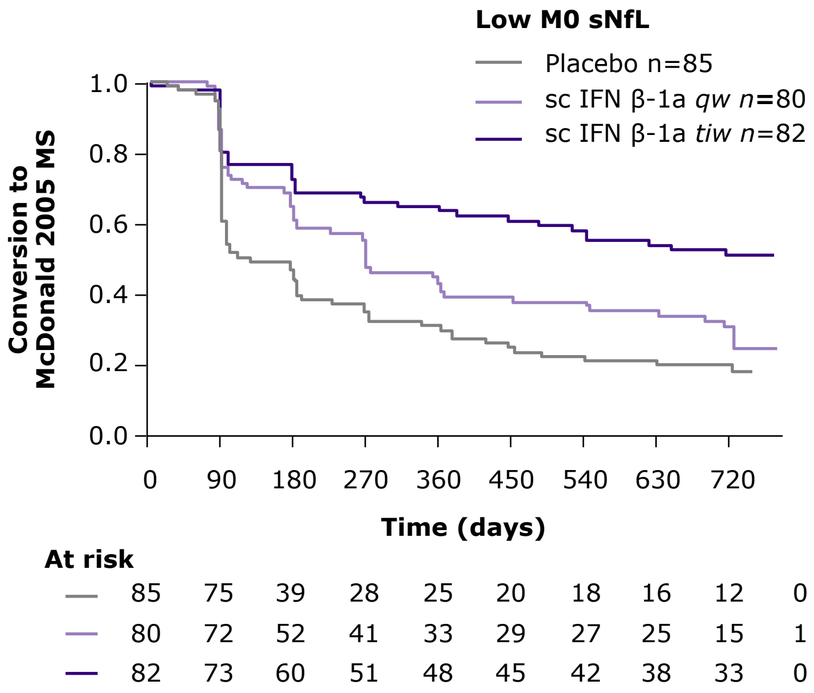

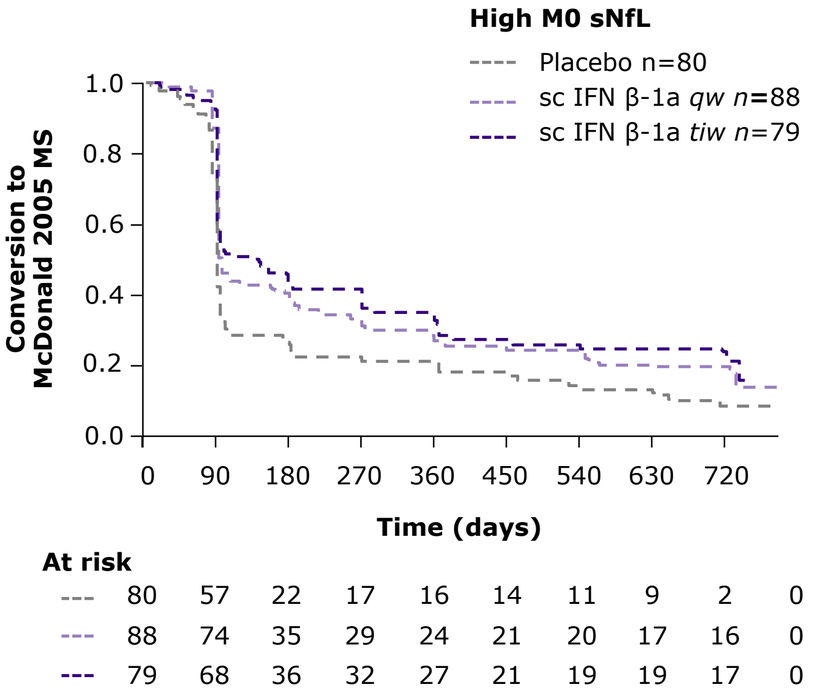

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RESULTS

Supplementary Table 1. Baseline demographics and MRI characteristics stratified by conversion to McDonald 2005 MS status

Characteristic	Placebo (n =140)	sc IFN β-1a qw (n = 127)	sc IFN β-1a tiw (n =101)
Non-converters to McDonald 2005 MS			
Age	33.5 ±7.9	32.3 ±8.8	31.7 ±8.5
Female, n (%)	14 (56.0)	28 (68.3)	44 (73.3)
Baseline sNfL value, median (Q1; Q3)	15.99 (12.26; 40.50)	18.82 (10.97; 38.45)	17.90 (11.48; 29.41)
Number of Gd+ lesions at M0	0.3 ±0.7	0.3 ±0.7	0.5 ±1.3
Number of T1 Hypointense Lesions	1.4 ±1.8	2.6 ±4.4	4.7 ±6.0
Number of T2 Lesions	7.8 ±6.3	10.6 ±11.1	15.3 ±12.2
Normalized Brain Volume (cm^3)	1536.69 ±52.59	1542.47 ±75.82	1535.37 ±66.13
Converters to McDonald 2005 MS			
Age	30.2 ±7.6	30.5 ±7.9	30.2 ±8.6
Female, n (%)	94 (67.1)	76 (59.8)	62 (61.4)
Baseline sNfL value, median (Q1; Q3)	27.92 (15.84; 65.59)	29.20 (18.09; 56.89)	32.54 (17.18; 62.81)
Number of Gd+ lesions at M0	1.4 ±3.0	1.9 ±4.0	1.8 ±2.9
Number of T1 Hypointense Lesions	6.2 ±8.1	7.1 ±8.1	6.5 ±7.3
Number of T2 Lesions	23.2 ±20.6	28.3 ±22.0	26.4 ±21.1
Normalized Brain Volume (cm^3)	1547.55 ±65.53	1534.01 ±64.04	1536.72 ±78.96

Values are mean ±SD unless otherwise specified. **IFN**, interferon; **M**, Month; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **Q**, quartile; **qw**, once weekly; **sc**, subcutaneous; **SD**, standard deviation; **tiw**, three times weekly