Abstract No. 39

Efficacy of Subcutaneous Interferon β-1a in Patients with a First Clinical Demyelinating Event: the REbif FLEXible Dosing in Early Multiple Sclerosis (REFLEX) Study – Outcomes in Patients Stratified by the 2017 McDonald Criteria

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INTRODUCTION

- Traditionally, the diagnosis of multiple sclerosis (MS) was made based on recurrent attacks on different areas of the central nervous system (CNS) linked to CNS demyelination.[1]
  - At least two separate attacks (dissemination in time; DIT) and clinical evidence of two distinct lesions (dissemination in space; DIS) were required for the diagnosis of "clinically definite" MS (CDMS).
- Advances in magnetic resonance imaging (MRI) techniques and cerebrospinal fluid analysis has led to the development of more sensitive diagnoses.[2]
- The McDonald relapsing-remitting MS (RRMS) criteria, introduced in 2001 and revised in 2005 and 2010, suggest that MS diagnosis requires ≥ 1 T2 lesions in ≥ 2 of the four locations characteristic for MS as evidence of DIS.[3]
  - The simultaneous presence of asymptomatic gadolinium enhancing (Gd+) and non-enhancing lesions at any time, or a new T2 and/or Gd+ lesion(s) on a follow-up MRI, is required to satisfy DIT.
- In 2017 the McDonald RRMS criteria were revised further to include the presence of cerebrospinal fluid specific oligoclonal bands (which can substitute for demonstration of DIT), symptomatic MRI lesions (demonstration of DIT and DIS), and cortical lesions (demonstration of DIS).[4]
  - These changes potentially allow earlier MS diagnosis.
- The REFLEX trial demonstrated that subcutaneous interferon β-1a (sc IFNβ-1a) reduced conversion to multiple sclerosis (McDonald 2005 criteria) and to CDMS versus placebo in patients with a first clinical event suggestive of MS.[5]
- A retrospective analysis of the study showed that the overall results were unchanged by the application of the McDonald 2010 MS criteria.[6]

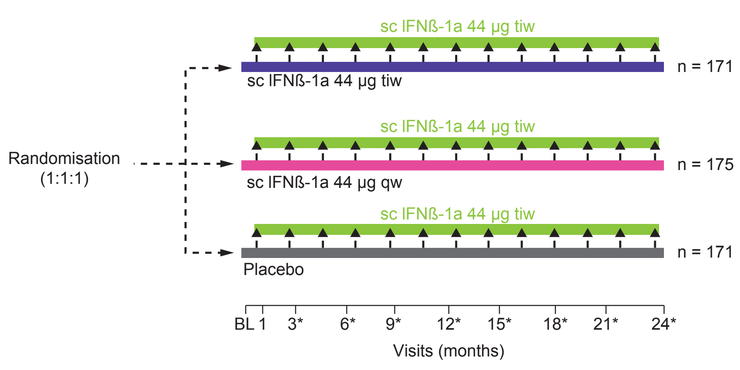
OBJECTIVE

- To assess the effects of two dosing frequencies of sc IFNβ-1a on time to McDonald 2005 criteria defined MS-related event (time to relapse, Expanded Disability Status Scale [EDSS] progression or MS-related MRI lesion or lesions) and CDMS (time to relapse or EDSS progression), and annualised relapse rate (ARR) during REFLEX, stratified by retrospective diagnosis at baseline in patients that either meet or do not meet the updated McDonald 2017 MS criteria.

METHODS

- During REFLEX, patients were randomised 1:1:1 to either sc IFNβ-1a 44 µg three times weekly (tiw) or once weekly (qw), or placebo, for 2 years (**Figure 1**).
- This retrospective analysis stratified patients randomised to the intent-to-treat (ITT) population in REFLEX into McDonald 2017-positive (defined as those that retrospectively met the 2010 McDonald MS criteria at baseline or those with positive oligoclonal bands) and -negative subgroups.
  - A proxy definition of the 2017 McDonald criteria was used in place of the literature definition[4] as MRI data on cortical lesions were not available for all patients and the analysis of positive oligoclonal bands was not mandatory during REFLEX.
- Kaplan–Meier curves were used to estimate time to McDonald 2005 criteria defined MS-related event and time to CDMS by treatment group and for each McDonald 2017 subgroup.
  - The hazard ratios were calculated using Cox's proportional hazards.
- Relapse rates were analysed using a Poisson regression model with factors for treatment and randomisation stratification factors as a covariate.
- All analyses were performed *post hoc* without any adjustment for multiple testing and *P* values should be considered exploratory only.

Figure 1. REFLEX Trial Design



CDMS, clinically definite multiple sclerosis; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **qw**, once weekly; **sc IFNβ-1a**, subcutaneous interferon β-1a; **tiw**, three times weekly.

RESULTS

Baseline Characteristics

- A total of 235/517 patients were classified as McDonald 2017-positive at baseline (**Table 1**).
- Of the 235 patients classified as McDonald 2017-positive, 40 were McDonald 2010-negative but had positive oligoclonal bands (**Table 2**).

Time to McDonald 2005 Criteria Defined MS-Related Event

- Treatment with tiw or qw sc IFNβ-1a significantly delayed time to McDonald 2005 criteria defined MS-related event versus placebo in the McDonald 2017-positive subgroup (hazard ratio [HR] tiw versus placebo = 0.47; *P* < 0.001, qw versus placebo = 0.58; *P* = 0.002; **Figure 2a**).
  - Treatment with tiw sc IFNβ-1a significantly delayed time to McDonald 2005 criteria defined MS-related event versus placebo in the McDonald 2017-negative subgroup (HR = 0.54; *P* < 0.001; **Figure 2b**).

Table 1. Patient Baseline Demographics

Characteristic	Placebo		sc IFNβ-1a 44 µg qw		sc IFNβ-1a 44 µg tiw		Overall	
	McDonald 2017 positive (N = 77)	McDonald 2017 negative (N = 94)	McDonald 2017 positive (N = 85)	McDonald 2017 negative (N = 90)	McDonald 2017 positive (N = 73)	McDonald 2017 negative (N = 98)	McDonald 2017 positive (N = 235)	McDonald 2017 negative (N = 282)
Age, mean (SD), years	30.1 (7.4)	31.5 (7.8)	29.4 (7.8)	32.0 (8.3)	28.6 (8.0)	32.2 (8.6)	29.4 (7.7)	31.9 (8.4)
Women, n (%)	54 (70.1)	58 (61.7)	47 (55.3)	59 (65.6)	50 (68.5)	64 (65.3)	151 (64.3)	181 (64.2)
Time since first demyelinating event, mean (SD), days	57.8 (4.5)	57.4 (4.0)	57.8 (3.5)	57.6 (3.4)	57.3 (3.6)	57.8 (3.8)	57.7 (3.9)	57.6 (3.7)
Classification of first clinical demyelinating event as monofocal,* n (%)	35 (45.5)	62 (66.0)	50 (58.8)	54 (60.0)	40 (54.8)	59 (60.2)	125 (53.2)	175 (62.1)
Steroid use at first clinical demyelinating event, n (%)	53 (68.8)	68 (72.3)	57 (67.1)	66 (73.3)	53 (72.6)	68 (69.4)	163 (69.4)	202 (71.6)
EDSS score, mean (SD)	1.61 (0.80)	1.54 (0.73)	145 (0.75)	1.66 (0.71)	1.67 (0.84)	1.48 (0.79)	1.57 (0.80)	1.56 (0.75)

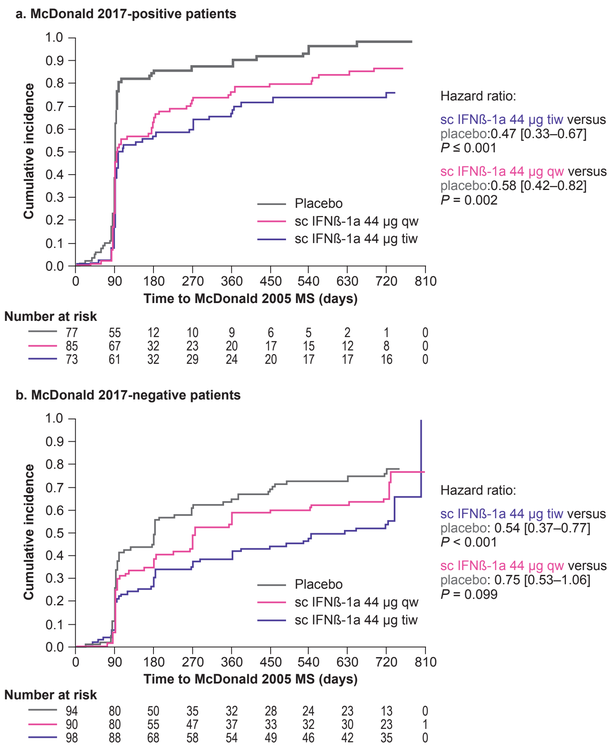
*According to the investigator.
EDSS, Expanded Disability Status Scale; **qw**, once weekly; **sc IFNβ-1a**, subcutaneous interferon beta-1a; **SD**, standard deviation; **tiw**, three times weekly.

Table 2. Patients in the REFLEX Intent-to-Treat Population Classified as McDonald 2017-Positive at Baseline

	Placebo (N = 171) N (%)	sc IFNβ-1a 44 µg qw (N = 175) N (%)	sc IFNβ-1a 44 µg tiw (N = 171) N (%)	Overall (N = 517) N (%)
McDonald 2017-positive at baseline (McDonald 2010-negative at baseline with CSF positive at baseline)	10 (5.8)	19 (10.9)	11 (6.4)	40 (7.7)
McDonald 2017-positive at baseline (McDonald 2010-positive at baseline)	67 (39.2)	66 (37.7)	62 (36.3)	195 (37.7)
McDonald 2017-negative	94 (55.0)	90 (51.4)	98 (57.3)	282 (54.5)

McDonald 2017 subjects are defined as subjects previously classified as McDonald 2010 plus having CSF positive oligoclonal bands (optional and done locally).
CSF, cerebrospinal fluid; **qw**, once weekly; **sc IFNβ-1a**, subcutaneous interferon beta-1a; **tiw**, three times weekly.

Figure 2. Time to McDonald 2005 Criteria Defined MS-Related Event by McDonald 2017 Status at Baseline: Kaplan–Meier Cumulative Incidence Plot (ITT Population)



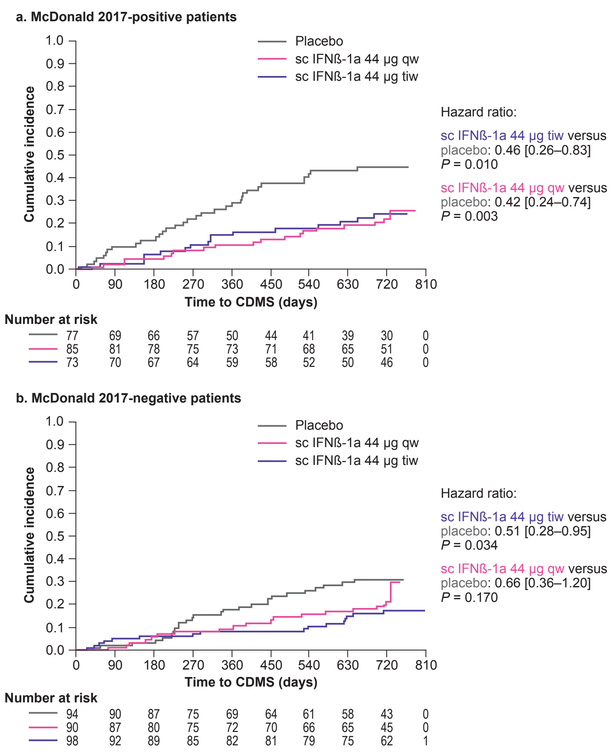
CDMS, clinically definite multiple sclerosis; **ITT**, intention to treat; **qw**, once weekly; **sc IFNβ-1a**, subcutaneous interferon beta-1a; **tiw**, three times weekly.

- In placebo-treated patients, the risk of McDonald 2005 MS at 2 years was 76% in patients who were McDonald 2017 MS-negative at baseline and 98% in patients who were McDonald 2017 MS-positive at baseline.

Time to CDMS

- Treatment with tiw or qw sc IFNβ-1a significantly delayed time to CDMS versus placebo in the McDonald 2017-positive subgroup (HR tiw versus placebo = 0.46; *P* = 0.010; qw versus placebo = 0.42; *P* = 0.003; **Figure 3a**).
- Treatment with tiw sc IFNβ-1a significantly delayed time to CDMS versus placebo in McDonald 2017-negative at baseline (HR = 0.51; *P* = 0.034; **Figure 3b**).

Figure 3. Time to CDMS by McDonald 2017 Status at Baseline: Kaplan–Meier Cumulative Incidence Plot (ITT Population)



CDMS, clinically definite multiple sclerosis; **ITT**, intention to treat; **qw**, once weekly; **sc IFNβ-1a**, subcutaneous interferon beta-1a; **tiw**, three times weekly.

- In placebo-treated patients, the risk of CDMS at 2 years was 31% in patients who were McDonald 2017 MS-negative at baseline and 45% in patients who were McDonald 2017 MS-positive at baseline.

ARR

- In McDonald 2017-positive patients treatment with tiw or qw significantly reduced mean ARR versus placebo in McDonald 2017-positive patients (reductions of 59.3% and 69.1%, respectively; *P* < 0.001 for both).
- However, in McDonald 2017-negative patients the reductions in mean ARR versus placebo were not significant for either dosing regimen (tiw versus placebo = 40.4%; *P* = 0.083, qw versus placebo = 26.2%; *P* = 0.294).

CONCLUSIONS

- **Both regimens of sc IFNβ-1a significantly reduced the risk versus placebo of McDonald 2005 MS and CDMS, irrespective of McDonald 2017 status at baseline.**
- **Compared with placebo, tiw and qw dosing showed significant reduction of time to either McDonald 2005 and CDMS in patients who were positive for McDonald 2017 MS at baseline.**
- **Compared with qw dosing, tiw dosing showed significant reduction of time to either McDonald 2005 and CDMS in patients who were negative for McDonald 2017 MS at baseline.**
- **Retrospective diagnosis of McDonald MS by the 2017 criteria, suggest that the main conclusions of the REFLEX study, sc IFNβ-1a reducing the risk of McDonald 2005 MS and CDMS in patients with a first clinical demyelinating event, is not affected.**
- **As the detection of oligoclonal bands was optional during REFLEX, only a small number of patients were added from the McDonald 2010 analysis.**

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