# LONG-TERM SUBCUTANEOUS INTERFERON BETA-1A TREATMENT IN RELAPSING–REMITTING MULTIPLE SCLEROSIS: CUMULATIVE DOSE EFFECTS

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## Introduction

- The Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study showed that interferon (IFN) beta-1a, 22 or 44 mcg subcutaneously (sc) three times weekly (tiw), was associated with significant benefits in terms of relapses, disability progression, and magnetic resonance imaging (MRI) lesion burden and activity measures compared with placebo in patients with relapsing–remitting multiple sclerosis (RRMS).[1]
- Data over 4 years showed that clinical and MRI benefits continued for both doses, with evidence of a dose response.[2]
- Long-term follow up (LTFU; up to 8 years) demonstrated the continued benefit of sc IFN beta-1a and a greater therapeutic effect in patients originally randomized to the higher dose compared with those in whom treatment was delayed.[3]
- The objective of this post-hoc exploratory analysis of the PRISMS LTFU cohort was to examine long-term (up to 8 years) clinical and MRI outcomes based on cumulative dose of, and time exposure to, sc IFN beta-1a in RRMS.

## Methods

### Study design

- The PRISMS study comprised the phases outlined below.
  - In the initial 2-year, double-blind phase, patients with RRMS were randomized to receive IFN beta-1a, 22 or 44 mcg sc tiw, or placebo.
  - Patients originally randomized to placebo were then re-randomized to IFN beta-1a, 22 or 44 mcg sc tiw, for 2 additional years (years 3–4).
  - On study completion, all patients were given the choice of continuing to receive blinded or open-label treatment during years 5–6.
  - Beyond year 6, patients could continue on any or no disease-modifying drug.
- Patients were eligible to participate in the LTFU study if they had been randomized in the original PRISMS study.
- Patients had a single LTFU assessment close to the seventh or eighth anniversary of their baseline visit.
  - The assessment included neurologic evaluation, as well as a retrospective review of data collected since the 4-year assessment.

### Post-hoc exploratory analysis

- Patient data from the three original study arms were pooled and ranked into quartiles from lowest to highest estimated cumulative dose of sc IFN beta-1a received (from baseline to LTFU).
  - Clinical and MRI outcomes were assessed in the minimum (lowest quartile, MIN) and maximum (highest quartile, MAX) dose groups.
  - Only descriptive statistics were applied.
- Similar post-hoc analyses were performed based on estimated cumulative time exposure to sc IFN beta-1a.

## Results

- Of 560 patients originally randomized in the PRISMS study, 178 (31.8%) were lost to follow up; 382 (68.2%) participated in the LTFU visit.
  - Of these 382 patients, 123 patients were originally randomized to IFN beta-1a 22 mcg, 136 to IFN beta-1a 44 mcg, and 123 to placebo.

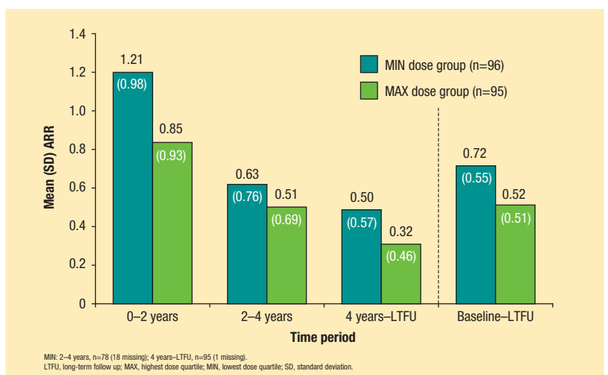
### Cumulative dose

- Mean (standard deviation [SD]) cumulative dose exposure was:
  - 10.8 (5.98) mg/patient in the MIN cumulative dose group (n=96)
  - 46.6 (4.56) mg/patient in the MAX cumulative dose group (n=95).
- The MIN cumulative dose group mainly comprised patients originally randomized to placebo or the lower dose of sc IFN beta-1a, whereas the MAX cumulative dose group comprised predominantly patients originally randomized to the higher dose of sc IFN beta-1a (**Table 1**).
- Patients in the MAX dose group had a lower mean annual relapse rate (ARR) than those in the MIN dose group, from baseline to LTFU, and over each study period analyzed (**Figure 1**).

*Table 1. Frequency of original PRISMS study randomization groups by cumulative dose group*

| | Original PRISMS study randomization group, n (%) | | | |
|---|---|---|---|---|
| | Placebo | IFN beta-1a 22 mcg sc tiw | IFN beta-1a 44 mcg sc tiw | Total |
| MIN cumulative dose group | 54 (56) | 28 (29) | 14 (15) | 96 (100) |
| MAX cumulative dose group | 4 (4) | 0 (0) | 91 (96) | 95 (100) |

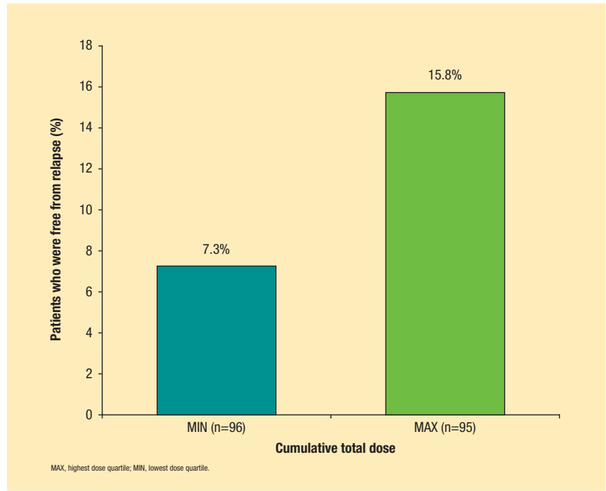
IFN, interferon; MAX, highest dose quartile; MIN, lowest dose quartile; sc, subcutaneous; tiw, three times weekly.




MIN: 2–4 years, n=78 (18 missing); 4 years–LTFU, n=95 (1 missing).
LTFU, long-term follow up; MAX, highest dose quartile; MIN, lowest dose quartile; SD, standard deviation.

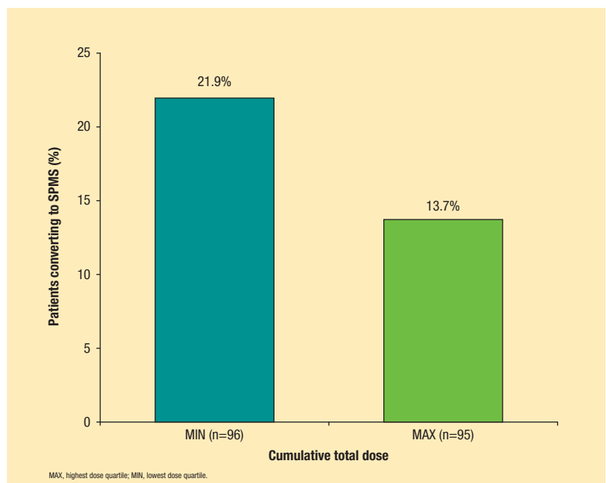
*Figure 1. Effect of subcutaneous interferon beta-1a cumulative dose on annualized relapse rate (ARR).*

- In addition, the proportion of patients who were free from relapses was greater (**Figure 2**), and the proportion of patients who converted to secondary progressive MS (SPMS) was lower (**Figure 3**) in the MAX dose group compared with the MIN dose group from baseline to LTFU.




MAX, highest dose quartile; MIN, lowest dose quartile.

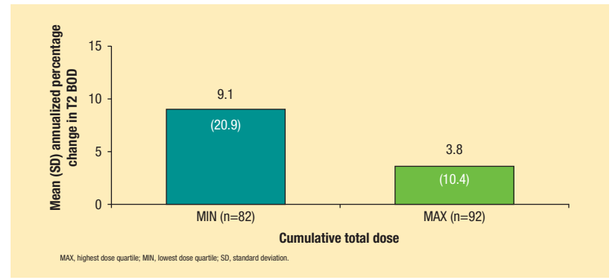
*Figure 2. Effect of subcutaneous interferon beta-1a cumulative dose on the proportion of patients who were free from relapse (baseline to long-term follow up).*




MAX, highest dose quartile; MIN, lowest dose quartile.

*Figure 3. Effect of subcutaneous interferon beta-1a cumulative dose on the proportion of patients converting to secondary progressive multiple sclerosis (SPMS) (baseline to long-term follow up).*

- Patients in the MAX dose group also had a lower increase in annualized T2 burden of disease (BOD) from baseline to LTFU than those in the MIN dose group (**Figure 4**).




MAX, highest dose quartile; MIN, lowest dose quartile; SD, standard deviation.

*Figure 4. Effect of subcutaneous interferon beta-1a cumulative dose on annualized percentage change in T2 burden of disease (BOD) (baseline to long-term follow up).*

### Cumulative time

- In the MIN (n=96) and MAX (n=95) cumulative time groups, mean (SD) cumulative time on sc IFN beta-1a was 157 (88) and 390 (6) weeks, respectively.
- From baseline to LTFU, compared with the MIN time group, the MAX time group had:
  - a lower mean (SD) ARR (0.51 [0.49] versus 0.76 [0.55])
  - a greater proportion of patients remaining free from relapse (16.8% versus 7.3%)
  - a lower proportion of patients converting to SPMS (15.8% versus 29.2%)
  - a lower increase in annualized T2 BOD (mean [SD] percentage change: 5.9% [15.9] versus 11.6% [24.4]).

## Conclusions

- Results from exploratory analyses of data from the PRISMS LTFU study demonstrated that patients with RRMS exposed to the highest cumulative dose of sc IFN beta-1a experienced greater benefits on clinical and MRI outcomes than those with lower cumulative dose exposure, for up to 8 years.
- Greater benefits were also seen in patients with the highest cumulative time exposure to sc IFN beta-1a.
- These findings support the importance of treating early with high-dose, high-frequency sc IFN beta-1a and maintaining therapy over the long term.

## References

1. PRISMS Study Group. Lancet 1998;352:1498–504.
2. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. Neurology 2001; 56:1628–36.
3. Kappos L et al. Neurology 2006;67:944–53.

## Acknowledgments

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