

Impact of Early Interferon Beta-1b Treatment on Disease Evolution Over 5 Years in Patients with a First Event Suggestive of Multiple Sclerosis

ABSTRACT

Background: The BENEFIT study (Betaferon®/Betaferon® in Newly Emerging MS For Initial Treatment) was designed to evaluate the impact of early treatment initiation with interferon beta-1b (IFNB-1b; Betaferon®/Betaferon®) in patients with a first event suggestive of multiple sclerosis (MS).

Objective: To present the 5-year results.

Methods: In the placebo-controlled phase, patients were randomized to IFNB-1b 250 µg or placebo, subcutaneously every other day, for 2 years or until clinically definite MS (CDMS), if earlier. Patients could then enroll in a follow-up phase and were offered, but not required to take, IFNB-1b. Patients and physicians remained blinded to the initial treatment allocation. Patients initially randomized to IFNB-1b are defined as 'early-treatment' group and those initially randomized to placebo as 'delayed treatment'. Primary outcome measures included time to CDMS and time to confirmed disability progression, measured by the Expanded Disability Status Scale (EDSS). Analyses were prospectively planned at 3 and 5 years using a predefined hierarchical statistical analysis plan.

Results: Of the 468 patients originally randomized (IFNB-1b: 292, placebo: 176), 358 (76%) were followed for 5 years. In line with the 3-year analysis, early treatment with IFNB-1b versus delayed treatment reduced the risk of developing CDMS by 37% over 5 years ($p=0.003$), and led to an overall 20% reduction in relapse rate ($p=0.014$) as well as a significant reduction in new lesion formation. Early treatment reduced the risk of confirmed EDSS progression by 40% ($p=0.0218$) at 3 years; the respective risk reduction was 24% after 5 years, not reaching statistical significance. Quality of life remained high and stable over time in both groups. At 5 years ($p=0.0045$), patients in the early-treatment group performed better in the Paced Auditory Serial Addition Test (PASAT).

Conclusions: The 5-year results of the BENEFIT study provide further evidence supporting early initiation of treatment with IFNB-1b in patients with a first event suggestive of MS.

Introduction

- There is now ample evidence that treatment initiated early after a first demyelinating event can delay conversion to clinically definite multiple sclerosis (CDMS).¹⁻³
 - The BENEFIT study (Betaferon®/Betaferon® in Newly Emerging MS For Initial Treatment) was the first to demonstrate that interferon beta-1b (IFNB-1b; Betaferon®/Betaferon®) treatment also delays the onset of MS as defined by the McDonald criteria,^{3,4} newer criteria that allow earlier diagnosis of MS in patients following a clinically isolated syndrome (CIS).
- The pre-planned follow-up phase of the BENEFIT study was designed to assess the differences in the effects of treatment initiation at the time of a CIS versus initiation after conversion to CDMS, or 2 years after the CIS.

- Results from the planned analysis at 3 years showed that early treatment with IFNB-1b delayed disability progression, with a reduction in time to CDMS by 41% ($p=0.0011$) and a reduction in time to confirmed baseline Expanded Disability Status Scale (EDSS)⁵ progression by 40% ($p=0.0218$).⁶

Methods

Study Design

- BENEFIT comprised a 2-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase III study, and a pre-planned 3-year follow-up phase.

Placebo-Controlled Phase

- Eligible patients had presented with a first neurological event suggestive of MS that lasted for at least 24 hours, and had an EDSS score between 0.0 and 5.0.
- Patients were randomly assigned IFNB-1b 250 µg subcutaneously (sc), every other day (eod), or placebo for up to 24 months, or until CDMS was diagnosed using Poser criteria.⁷ Treatment was initiated within 60 days after confirmation of the first clinical event.³

Follow-Up Phase

- Patients completing the placebo-controlled phase were eligible to enter the follow up. All patients were offered IFNB-1b sc eod up to a maximum of 5 years.
- Primary efficacy measures are:
 - Time to CDMS
 - Time to confirmed EDSS progression
 - Health-related quality of life (HRQoL) as measured by the Functional Assessment of Multiple Sclerosis-Trial Outcome Index (FAMS-TOI) at the end of Month 60.⁸
- Secondary efficacy variables include:
 - Time to MS as specified by the McDonald criteria⁴
 - Annualized relapse rate
 - Several magnetic resonance imaging (MRI) outcomes
 - Neurological status as measured by the Multiple Sclerosis Functional Composite (MSFC)⁹
 - QoL as measured by the EuroQoL 5-Dimensional questionnaire (EQ-5D).¹⁰
- EDSS and MSFC data were collected at 6-monthly intervals, from the date of entry into the randomized phase. MRI and QoL data were collected 12-monthly.
- In patients whose baseline EDSS score was ≤ 5.5 , EDSS progression was defined as an increase in EDSS score of ≥ 1.0 point compared with the lowest score obtained during screening and baseline. In patients whose baseline EDSS score was > 5.5 , EDSS progression was defined as an increase of ≥ 0.5 point compared with the lowest score obtained during screening and baseline. This progression had to be confirmed 6 months later.
- Sampling for neutralizing antibodies (NAbs) was performed every 6 months.

Statistical Analyses

- To restrict the overall type-I-error probability to 0.05, evaluation of the primary outcomes was based on a sequential, conditional approach in the following order: time to CDMS, time to EDSS progression, HRQoL as rated by the FAMS-TOI.
- To adjust for multiple testing, a nominal two-sided significance level of 0.0253 was assigned to the 3-year and to this 5-year analyses (Sidak's adjustment).
- Time to CDMS and time to EDSS progression were analyzed by the log-rank test and by proportional hazards regression, with adjustment for steroid use during the first clinical event, onset of disease (mono-/multifocal), age, gender, and number of T2 and gadolinium-enhancing (Gd+) lesions at screening. The FAMS-TOI was analyzed using non-parametric analysis of covariance.

Results

- 418 patients (89% of all patients in BENEFIT) entered the follow-up study (261 originally on IFNB-1b [early-treatment group]; 157 originally taking placebo [delayed-treatment group]).⁶
- 235 (80%) patients from the early-treatment group and 123 (70%) of the delayed-treatment group completed the full 5 years of the study.
- Patients were essentially similar in terms of their demographic, clinical, and MRI characteristics for the two treatment groups on entry to the randomized phase, and on entry to the follow-up phase (Table 1). Key baseline characteristics were also essentially similar in the patients from both groups who did not enter the follow-up phase, making it unlikely that dropouts biased the study.
- The median duration of exposure to IFNB-1b was approximately 5 years for the early-treatment group, and 2 years and 9 months for the delayed-treatment group. For the latter group, the mean time on placebo was 1 year and 4 months.

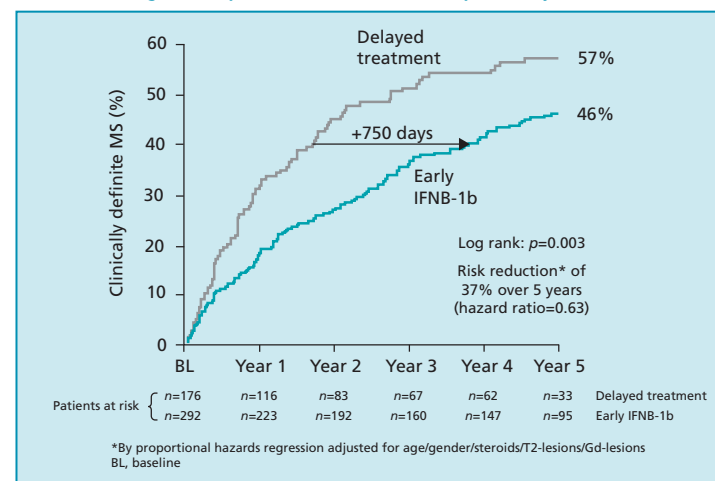
	BENEFIT placebo-controlled		BENEFIT follow-up	
	IFNB-1b	Placebo	Early IFNB-1b	Delayed treatment
n	292	176	261	157
Gender (% female)	71	71	71	69
Median age, years (Q1, Q3)	30 (24.0, 37.5)	30 (35.0, 36.0)	30 (24.0, 37.0)	30 (25.0, 36.0)
Monofocal disease onset (%)	52	53	51	54
Patients using steroid treatment for the first event (%)	72	70	69	69
Median number of T2 lesions at screening (Q1, Q3)	18 (7.0, 38.5)	17 (7.5, 36.5)	18 (7.0, 39.0)	17 (8.0, 37.0)
Median number of Gd+ lesions at screening (Q1, Q3)	0 (0.0, 1.0)	0 (0.0, 1.0)	0 (0.0, 1.0)	0 (0.0, 1.0)
Median EDSS score at screening (Q1, Q3)	1.5 (1.5, 2.5)	2 (1.0, 2.5)	2 (1.5, 2.5)	2 (1.0, 2.5)

Gd, gadolinium; INFB, interferon beta.

Time to CDMS

- Adjusted proportional hazards regression showed that the risk of CDMS in the early-treatment group was reduced by 37% over 5 years compared with the delayed-treatment group ($p=0.003$; Figure 1).

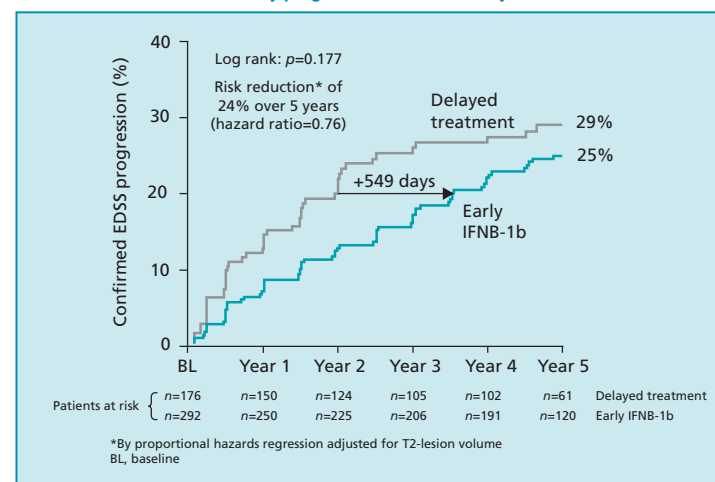
Figure 1. Kaplan-Meier estimates for the probability of CDMS



Time to Confirmed EDSS Progression

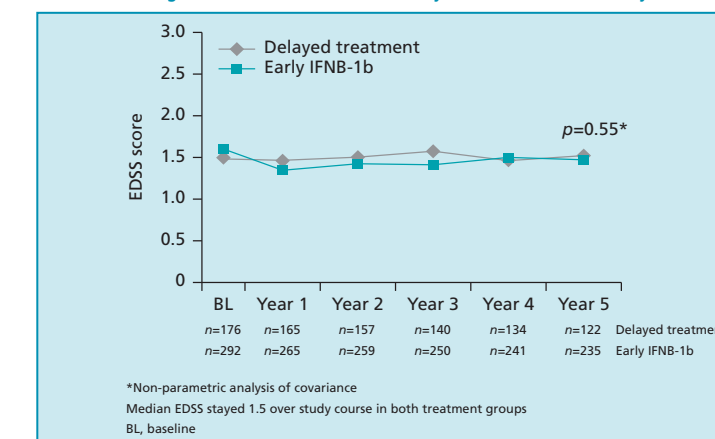
- The risk for confirmed EDSS progression in the early-treatment group was reduced by 24%, according to adjusted proportional hazards regression (Figure 2). This risk reduction was not significant at 5 years.
- Disability, as measured by EDSS, remained stable over time (Figure 3).

Figure 2. Kaplan-Meier estimates for the probability of confirmed disability progression as measured by EDSS



- At the 60 months' visit, 11% of the examined patients in the early-treatment group had an EDSS ≥ 3.0 compared with 15% in the delayed-treatment group.

Figure 3. EDSS mean scores over 5 years of the BENEFIT study



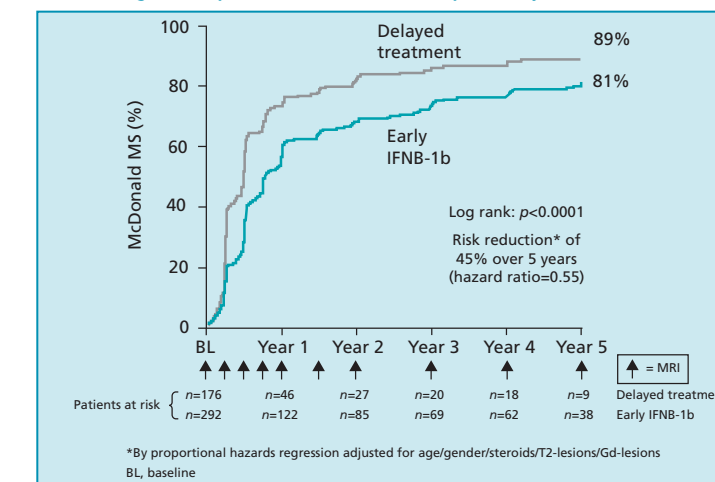
HRQoL

- QoL as measured by the FAMS-TOI and the EQ-5D remained high without differences between treatment groups.

Secondary Efficacy Measurements

- Adjusted proportional hazards regression showed that the time to McDonald MS in the early-treatment group was reduced by 45% over 5 years compared with the delayed-treatment group ($p<0.0001$; Figure 4).

Figure 4. Kaplan-Meier estimates for the probability of McDonald MS



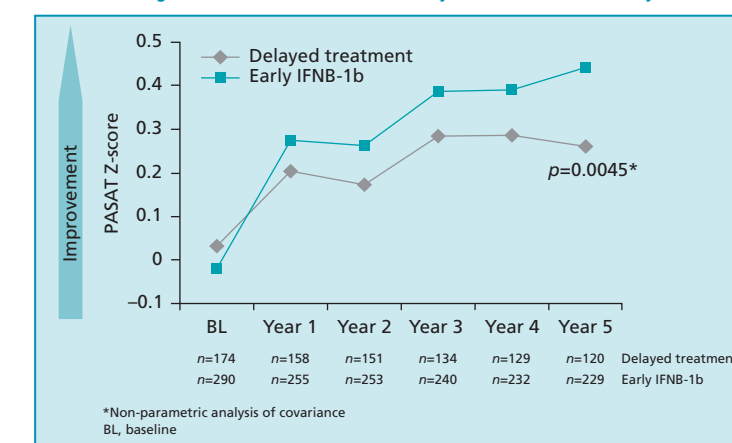
- The median cumulative number of newly active lesions (new or enlarging T2 lesions, Gd+ lesions), as shown by MRI, was significantly lower in the early-treatment group than in the delayed-treatment group 5 years after screening ($p=0.0062$).
- No significant difference of early versus delayed treatment was seen for any other MRI parameters at 5 years (change of T2-lesion volume, T1 hypointense lesions and brain volume).
- Over the 5-year period, the annualized relapse rate was lower in the early-treatment group ($p=0.014$), as compared with the delayed-treatment group (Table 2).
- A significant difference was seen in the Paced Auditory Serial Addition Test (PASAT) score after 5 years in favor of early treatment ($p=0.0045$, Figure 5). No significant differences were seen in the other MSFC subscales or the MSFC overall (Table 2).

Table 2. Relapse rate and MSFC scores from the BENEFIT study at 5 years

Outcome parameter	Delayed treatment	Early IFNB-1b	p-value		
Annualized relapse rate	0.270	0.214	0.0141* (0.1061)		
MSFC Z-scores and MSFC subtest Z-scores at Month 60 (mean)	Mean (SD)	Median (Q1/Q2)	Mean (SD)	Median (Q1/Q2)	
Overall MSFC	0.121 (0.717)	0.225 (-0.207/0.619)	0.084 (0.710)	0.226 (-0.163/0.502)	0.6078†
Timed 25-foot walk	-0.126 (0.960)	0.043 (-0.489/0.397)	-0.224 (1.159)	0.026 (-0.456/0.413)	0.9412‡
Nine-hole peg test	0.228 (1.086)	0.261 (-0.408/0.809)	0.045 (1.056)	0.067 (-0.573/0.724)	0.4415‡
PASAT	0.261 (0.970)	0.674 (1.115/0.798)	0.443 (0.708)	0.674 (0.301/0.922)	0.0045‡

*Generalized linear Poisson regression model.
†Andersen-Gill extension of the Cox proportional hazards regression model.
‡Non-parametric analysis of covariance.
MSFC, Multiple Sclerosis Functional Composite; PASAT, Paced Auditory Serial Addition Test.

Figure 5. PASAT mean Z-score over 5 years of the BENEFIT study



NAbs

- 32.1% of patients in the early-treatment group had at least one positive antibody finding during the 5 years. Of these, 60% converted back to stable negative titers by the end of the 5 years.
- Results of prespecified NAb evaluations: development of NAbs, regardless of titer, did not negatively impact clinical efficacy as measured by time to CDMS and annualized relapse rate.

Adverse Events

- The frequency of adverse events was within the well-established safety and tolerability profile for IFNB-1b 250 µg sc eod.
- The number of patients experiencing at least one serious adverse event was similar in each group, and the vast majority of these had no relation to the study medication.
- No patient died during participation in the study.

Discussion

- Early treatment with IFNB-1b (250 µg eod, sc) after the first event suggestive of MS versus delayed treatment, reduced the risk of CDMS by 37% over 5 years ($p=0.003$) and postponed CDMS by more than 2 years (750 days; 40th percentile).
- Annualized relapse rate over 5 years was lower in the early-treatment group, despite the fact that the delayed-treatment group received at least 3 years of IFNB-1b after CDMS or after 24 months.
- Early treatment with IFNB-1b after the first event suggestive of MS prolonged the onset of confirmed disability progression by 1.5 years (549 days; 20th percentile). Over 5 years the risk of confirmed disability progression was numerically reduced by 24% in the early versus delayed group (not statistically significant). Of note, initiation of IFNB-1b in the delayed-treatment group at the latest 2 years after the first event was followed by a remarkable drop of the progression rate in the third year and onwards.
- On average, disability was low and stable over 5 years in both patient groups, and quality of life remained high.
- The initiation of early treatment with IFNB-1b led to greater improvement in the cognitive measure (PASAT) at 5 years ($p=0.0045$), an effect that was seen early on and became more pronounced throughout the trial.
- The findings of this study, and the established safety profile of IFNB-1b (250 µg eod, sc), makes it the preferable choice for starting immunomodulatory treatment at the time of the first event suggestive of MS.

REFERENCES

- Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med* 2000;343:898-904.
- Corni G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet* 2001;357:1576-1582.
- Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006;67:1242-1249.
- McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for MS. Guidelines from the international panel on the diagnosis of MS. *Ann Neurol* 2001;50:121-127.
- Kurtzke JF. Rating neurological impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983;33:1444-1452.
- Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet* 2007;370:389-397.
- Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227-231.
- Cella DF, Dineen K, Arason B, et al. Validation of the functional assessment of multiple sclerosis quality of life instrument. *Neurology* 1996;47:129-139.
- Cuttler GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* 1995;118:871-882.
- EuroQoL group. EuroQoL - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.