London, 01 June 2006
Product name: **BETAFERON**
Procedure no: **EMEA/H/C/00081/II/0038**

SCIENTIFIC DISCUSSION

1. Introduction

Multiple sclerosis (MS) is a common, non-traumatic cause of neurologic dysfunction in young adults, and is the commonest disabling neurological disease of young people in the northern temperate zones. The highest prevalence is in Northern Europe (> 200/100,000 in Scotland). The estimated number of newly diagnosed cases in Europe is more than 10,000 per year. The median age of onset is 33 years.

Betaferon was approved in the European Union in November 1995 in the relapsing-remitting multiple sclerosis (RRMS) and in January 1999 in the secondary-progressive multiple sclerosis (SPMS).

The RRMS indication was granted based on two randomized, placebo-controlled trials in patients with RRMS which showed that IFN beta-1b administered subcutaneously (s.c.) at a dose of 250 µg every other day (e.o.d.) reduces the frequency and severity of relapses, and reduces the development of brain lesions as measured by magnetic resonance imaging (MRI) (IFNB Multiple Sclerosis Study Group 1993, *Paty 1993*).

The SPMS indication was granted based on a randomized, placebo-controlled trial conducted in patients with SPMS, in which IFN beta-1b given s.c. at a dose of 250 µg e.o.d. was shown to delay disease progression as measured by the Expanded Disability Status Scale (EDSS; Kurtzke 1983). It also showed benefits for relapse and MRI-related endpoints (European Study Group on Interferon beta-1b in Secondary Progressive MS 1998).

Betaferon is currently authorized with the following indications:

- Treatment of patients with relapsing remitting multiple sclerosis and two or more relapses within the last two years.
- Treatment of patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

Within the last years, increasing evidence has been obtained from the literature that more frequent clinical events indicative of a stronger inflammatory disease activity in the early course of the disease result in a more rapid accumulation of neurological deficits (*Comi 2000; Chofflon 2000*). It therefore has been proposed that the disease should be treated early with disease modifying treatments, thus preventing or delaying the initiation or progression of irreversible neurodegenerative processes.

Treatment with IFNB has also been evaluated in patients with a first clinical demyelinating event before the diagnosis of clinically definite MS (CDMS) was made. In such patients, two studies have recently demonstrated beneficial effects of two IFNB -1a preparations using a once-weekly administration schedule (*Jacobs et al. 2000 and Comi et al. 2001*).

Therefore, since the original authorization of Betaferon, initiation of IFNB treatment as early as possible to achieve maximum therapeutic effects have been encouraged by clinical experts.

Based on the results of a 2-year randomized, controlled study investigating the safety, tolerability and efficacy of Betaferon treatment in patients with a first clinical demyelinating event suggestive of MS (BENEFIT study), the MAH applied to add the following indication to the already authorised ones:

"Betaferon is indicated for the treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent MRI lesions, if alternative diagnoses have been excluded."

The MAH also proposes to update SPC section 5.1 (Pharmacodynamic properties) to include the new clinical data generated by the BENEFIT study, as well as sections 4.2, 4.4 and 4.8. Finally, the Package Leaflet is revised according to these changes.

2. Quality aspects

Not applicable

3. Non-clinical aspects

Not applicable

4. Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has also provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Not applicable

Pharmacodynamics

Not applicable

Clinical efficacy

The clinical efficacy programme was based on the BENEFIT study, a multi-center, double-blind, placebo-controlled, parallel-group, two-arm, randomized study in patients with a first (single) clinical demyelinating event suggestive of MS. The study enrolled patients after the onset of a single clinical event suggestive of MS (often referred to as "Clinically Isolated Syndrome", "CIS").

To further explore the long-term effects of early Betaferon treatment in patients with CIS, patients who reached end of the BENEFIT study due to CDMS or after 24 month of double blind treatment were offered enrolment in a pre-planned open-label follow-up extension of the trial. The follow-up study will examine all patients for a total observation period of 60 months after start of treatment in the BENEFIT study. Relapses, neurological disability and patient reported health outcomes will be evaluated, among other outcome variables.

METHODS

Objectives

The objective of the study was to determine the safety, tolerability and efficacy of 250 µg (8 million international units) Betaferon s.c. e.o.d. over a period of up to 24 months in patients with a first clinical demyelinating event suggestive of MS.

Study Participants

The study enrolled patients within 60 days after the onset of a single clinical event suggestive of MS, based on the appearance of a new neurological abnormality which had to be present for at least 24 hours. T2-weighted brain MRI scan had to show at least two clinically silent lesions with a size of at least 3 mm, at least one of which had to be ovoid or periventricular or infratentorial. Patients were of age 18 to 45 years, with an EDSS of $\leq$ 5.0 and could have a monofocal or multifocal onset of the disease. Any disease other than MS that could better explain patients´ signs and symptoms had to be

excluded. Patients with complete transverse myelitis or bilateral optic neuritis as well as patients who had received prior immunosuppressant therapy were also excluded. The MAH also clarified that patients with neurological symptoms (including visual disturbance) lasting less than 24 hours prior to the index period (i.e. first episode with neurological symptoms lasting more than 24 hours) were not eligible for the study. Steroid treatment of the first event, based on a treatment schedule defined in the study protocol, was performed at the discretion of the investigator.

Treatments

- Study treatment

Each patient was assigned to one of the two parallel treatment groups :
- Group 1: 250 microgram (8 million IU) IFNB-1b
- Group 2: Placebo

Both treatments were given as s.c. injections e.o.d. Treatment duration was up to 2 years or until progression to the primary efficacy variable of CDMS was reached. A dose titration was performed as described in Table I below. The dose of 8 mIU Betaferon s.c. e.o.d was selected for treatment of CIS patients based on findings of the previous pivotal study in patients with RRMS, in which this dose had superior efficacy to a dose of 1.6 mIU s.c., e.od. as compared to placebo treatment. Considering that the disease characteristics of patients with CIS closely resemble those of patients with RRMS and that the dose 8 mIU was shown to be safe in more than on decade of market experience, no further dose finding was performed in this patient population.

Table I.

Injection No.	Study Day	Dose	Volume
1 to 3	1, 3, 5	0.0625 mg	0.25 mL
4 to 6	7, 9, 11	0.125 mg	0.5 mL
7 to 9	13, 15, 17	0.1875 mg	0.75 mL
10 etc.	19, etc.	0.25 mg	1.0 mL

In countries where an autoinjector for the administration of IFNB-1b was available, patients were encouraged to its use. During the study, after the titration period, the proportion of patients using an autoinjector ranged from 75.8% to 81.6% in the IFNB-1b group (month 2 onwards).

- Prohibited concomitant therapy

Any immunomodulatory or immunosuppressive treatment and other therapeutic agents for MS or other investigational pharmacological therapy for MS were prohibited throughout the study and would have been required termination of treatment.

- Permitted concomitant therapy

1. Treatment of flu-like symptoms

For the first 3 months of treatment with study drug, all patients were to be instructed to take non-steroidal anti-inflammatory drugs (NSAIDs) prior to each injection in order to minimize flu-like symptoms due to study drug (recommended dose: 500 to 1000 mg acetaminophen/paracetamol or 200 to 400 mg ibuprofen). In addition, patients could have received additional acetaminophen/paracetamol (up to a maximum of 3 grams within any 24-hour period) or ibuprofen (up to a maximum of 1200 mg within any 24-hour period), as necessary for relief of expected interferon-related flu-like symptoms. At the discretion of the treating physician, these agents could be given throughout this study.

2. Steroid treatment

Steroid treatment of the single clinical demyelinating event was at the discretion of the investigator. The screening MRI scan was not to be performed while a patient was on intravenous (i.v.) corticoid therapy. The MRI was to be performed before initiation of steroid treatment.

Randomisation and sample size

Patients were assigned to IFNB-1b 250 µg (8 MIU), or placebo (both s.c. injections e.o.d.). A randomization procedure was designed to keep the overall treatment allocation ratio close to 5:3 (IFNB-1b : placebo). A minimization procedure with an element of randomization was used to minimize imbalances of treatment groups for factors that might affect the manifestation of definite MS: (i) steroid use during the first clinical event, (ii) investigator's classification of the first event, (iii) categorized number of T2 lesions on the screening MRI, and (iv) cerebrospinal fluid result.

Patient enrolment was planned to continue until a total of at least 400 patients had reached at least the Month-1 visit of the treatment period without EOS medication. In the end, 603 patients were screened, and 487 patients were randomized. Of these 468 patients were included in the analysis and treated.

Endpoints

Primary efficacy variables:

- Time to CDMS according to Poser (Poser 1983).
- Time to MS according to the diagnostic criteria by McDonald (McDonald et al. 2001).

Secondary efficacy variables:

- Cumulative number of newly active lesions observed between the screening MRI scan and the last scan at/before the EOS visit.
- Absolute change in T2 lesion volume (T2 lesion load), observed between the screening MRI scan and the last scan at/before the EOS visit.

Exploratory MRI efficacy variables:

- Absolute change in volume of non-enhancing hypointense T1 lesions ("black holes") observed between the screening MRI scan and the last scan at/ before the EOS visit.
- Percentage change in brain volume (PBVC according to the SIENA method 21) observed between the screening MRI scan and the last scan at/ before the EOS visit.
- Cumulative number of new non-enhancing hypointense lesions seen on T1-weighted scans ("black holes") observed between the screening MRI scan and the last scan at/ before the EOS visit.

Exploratory clinical efficacy variables were derived from the following test procedures: EDSS score and Kurtzkes FS scores; MSFC score and scores of subtests.

Patient-reported outcome variables were: Functional assessment of MS Trial Outcome Index (FAMS-TOI) and EuroQoL-5 dimensions (EQ-5D).

Statistical methods

Analyses of efficacy variables were based on 468 patients (292 IFNB-1b patients and 176 placebo patients) who had at least one administration of study drug. This "Full Analysis Set" (FAS) was predefined as the primary analysis set of the study. Analyses of the primary efficacy variables were also performed with the "All Randomized Analysis Set" (ARS), i.e. all 487 patients who were randomized, which was introduced during the course of the study.

Primary efficacy variables were analyzed by the log-rank test (primary statistical analysis) and by proportional hazards regressions (secondary statistical analysis). According to the statistical analysis plan, proportional hazards regressions were performed with covariates used in the minimization procedure.

For both primary efficacy variables the null hypothesis of no difference between IFNB-1b treatment and placebo was considered. The efficacy of IFNB-1b was tested by a sequential, conditional approach which restricts the overall probability of a type-I-error to 0,05:

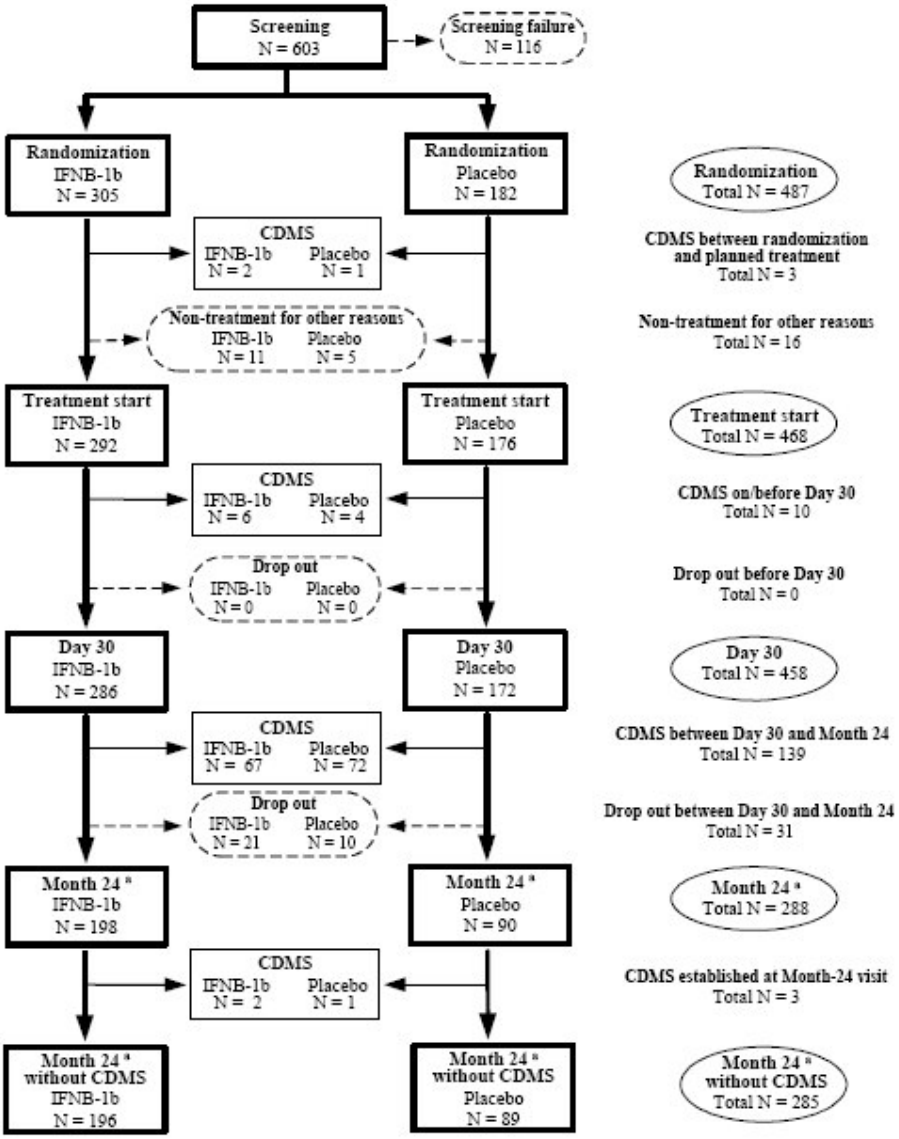
1. The null hypothesis of no difference in survival functions between IFNB-1b treatment and placebo was tested for "Time to clinically definite MS" with a two-sided significance level of □ = 0,05.
2. Only in a case the above mentioned null hypothesis was rejected, the null hypothesis of no difference in survival functions between IFNB-1b treatment and placebo was tested for "Time to MS according to McDonald criteria" with a two-sided significance level of □ = 0,05.

Post-hoc analyses of the primary efficacy variables were performed with respect to key clinical and MRI baseline factors characterizing dissemination and activity of the disease at the time of the first event, including: (i) Age (< 30 versus ≥ 30 years), (ii) onset of disease (monofocal versus multifocal), (iii) number of T2 lesions (< 9 versus ≥ 9), (iv) number of Gd+ lesions (0 versus ≥ 1), (v) steroid treatment of the first event (yes versus no), and (vi) sex. For each of these covariates, the impact on the progression to CDMS (log-rank test as well as proportional hazards regression using the covariate as the only stratum), the interaction with IFNB-1b (proportional hazards regression: IFNB-1b by covariate interaction), and the efficacy of IFNB-1b in the respective subgroups (log-rank test and proportional hazards regression in two subgroups resulting from dichotomization of the BENEFIT FAS with regards to these covariates) were evaluated.

MRI efficacy variables were analyzed by nonparametric analysis of covariance for "annualized" and "non-annualized" (i.e. not modified) secondary and supportive secondary variables. Corresponding MRI parameters measured in the screening MRI scan were used as covariates.

RESULTS

Participant flow



All patients were to be titrated up to a dose of 8 mIU within a period of three weeks unless any significant local or systemic side effects occur. All patients reached the full dose according to this schedule, i.e. within 3 weeks.

Recruitment

The study was performed between February 2002 and April 2005. 98 centres in 20 countries were involved into the conduct of the study and numbers of recruited patients vary from 1 (0.2%) for the smallest centers, up to 19 (4.1%) for the biggest center.

Baseline data

Analysis of the baseline characteristics showed that treatment groups were very similar with respect to demographic and key clinical as well as MRI parameters, as shown in Table II below. Baseline characteristics in the treatment groups of the ARS were close to FAS.

Table II.

Baseline characteristics (FAS)	**IFN beta-1b N=292**	**Placebo N=176**
Female – % (n)	70.9% (207)	70.5% (124)
Age – median (quartiles)	30 (24-37.5)	30 (25-36)
Caucasian – % (n)	97.9% (286)	98.9% (174)
Monofocal onset – % (n)	52.4% (153)	52.8% (93)
Steroid treatment – % (n)	71.6% (209)	69.9% (123)
CSF sample taken – % (n) of these: CSF positive – % (n)	67.8% (198) 86.4% (171)	65.9% (116) 82.8% (96)
≥9 T2 lesions – % (n)	70.9% (207)	69.9% (123)
At least 1 Gd+ lesion % (n)	43.5% (127)	39.7% (70)

The analysis sets are summarised in Table III below.

Table III.

		IFNB-1b		Placebo		Overall	
All randomized set ARS	Complete	305	100.0%	182	100.0%	487	100.0%
	CSF subset *	204	66.7%	119	65.4%	323	66.3%
Full analysis set FAS	Complete	292	95.7%	176	96.7%	468	96.1%
	CSF subset *	198	64.9%	116	63.7%	314	64.5%
Safety analysis SFS		292	95.7%	176	96.7%	468	96.1%
Per-protocol set PPS	Screening	284	93.1%	170	93.4%	454	93.2%
	Baseline	284	93.1%	170	93.4%	454	93.2%
	Day 1	284	93.1%	170	93.4%	454	93.2%
	Month 1	284	93.1%	170	93.4%	454	93.2%
	*≥ 1 data point after Month 1 ***	*283*	*92.8%*	*170*	*93.4%*	*453*	*93.0%*
	Month 2	272	89.2%	165	90.7%	437	89.7%
	Month 3	258	84.6%	156	85.7%	414	85.0%
	Month 6	245	80.3%	140	76.9%	385	79.1%
	Month 9	233	76.4%	124	68.1%	357	73.3%
	Month 12	218	71.5%	110	60.4%	328	67.4%
	Month 18	196	64.3%	94	51.6%	290	59.5%
	EOS / Month 24	253	83.0%	159	87.4%	412	84.6%

* Patients for whom screening CSF data were available

<u>All randomized set (ARS) (by-patient allocation):</u>
All 487 patients randomized for this study were included in the ARS.

Full analysis set (FAS) (by-patient allocation):
Among the 487 ARS patients, the 19 randomized patients (4%) who never received any study medication were not included into the FAS, leading to a total of 468 (96%) included in the FAS. Two of these patients were not treated as randomized. There were no relevant differences between the treatment groups with regard to the allocation of randomized patients to the FAS.

Per-protocol set (PPS) (by-visit allocation):
During the course of the study, there was a tendency of fewer exclusions from the PPS in the IFNB-1b group as compared to the placebo group. At Month 18, 64% of the IFNB-1b patients versus 52% of the placebo patients were included into the PPS.

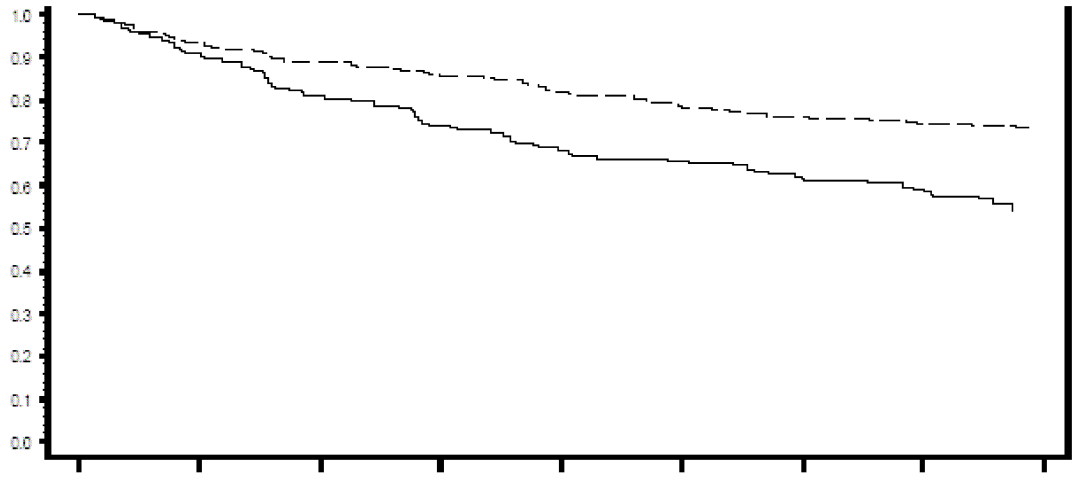
Safety analysis set (SFS) (by-patient allocation):
All 468 patients with at least one dose of study medication were included into the SFS. Two of these patients were not treated. There were no relevant differences between the treatment groups with regard to the allocation of randomized patient to the SFS.
Outcomes and estimation

- **Primary efficacy variables – Primary analysis**

Time to CDMS according to Poser

The total number of patients with CDMS at any time-point during the study was 152/468 (32.5%), 75 in the INFB-1b group (25.7%) and 77 patients in the placebo arm (43.8%). All other patients were censored with regard to CDMS.
By the end of the 2-year treatment period (on Day 720), the probability of not being diagnosed for CDMS (as estimated by Kaplan-Meier statistics) was 72.5% in the IFNB-1b group and 54.7% in the placebo group (see figure 1).

Figure 1: "Time to CDMS " – Kaplan-Meier product-limit estimates (FAS)



Ordinate depicts the survival distribution function estimate. Patient numbers at abscissa denote the number of patients at risk.

In all three analysis sets, the log-rank-tests for comparison of the treatment groups led to p-values below the chosen significance level of $\alpha = 0.05$:

- FAS: $p = 0.000075$
- ARS: $p = 0.000096$
- PPS: $p = 0.000014$

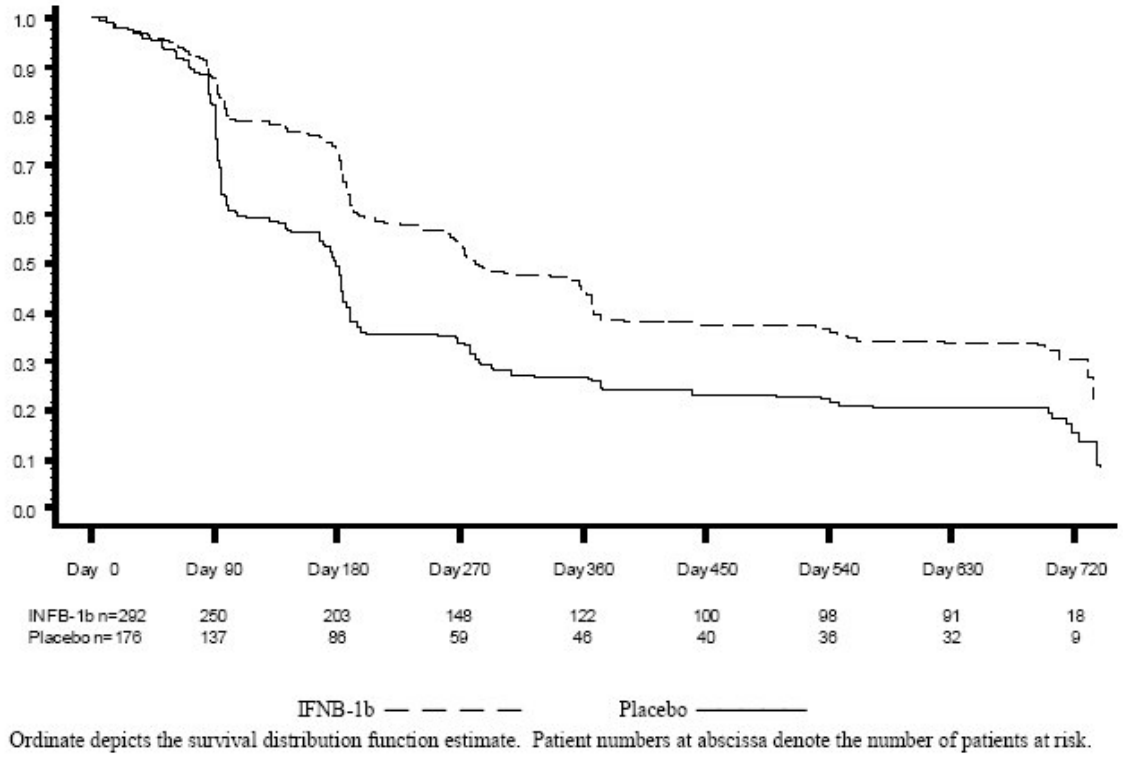
Time to MS according to the diagnostic criteria by McDonald

For the establishment of dissemination in space, no relevant differences between the treatment groups were seen; for nearly half of the patients (47% in both groups), dissemination in space was established by the multifocal onset of the single event.

The proportion of patients for whom dissemination in time was established via the criterion "$\geq$ 1 new Gd+ lesion at Month-3" was notably higher in the placebo group (29.5%) than in the IFNB-1b group (12.0%). Conversely, the proportion of patients for whom dissemination in time was never established was higher in the IFNB-1b group (31.5%) than in the placebo group (15.3%).

By the end of the 2-year treatment period, the probability of not being diagnosed for MS according to the McDonald criteria (as estimated by Kaplan-Meier statistics) was 30.6% in the IFNB-1b group and 15.5% in the placebo group. The Kaplan-Meier product-limit estimates for FAS are shown in Figure 2. MRI scans were performed at Months 3, 6, 9, 12, 18 and 24 which explains the step-like shape of the curve.

Figure 2: "Time to MS according to the McDonald criteria " – Kaplan-Meier product-limit estimates (FAS)



Ordinate depicts the survival distribution function estimate. Patient numbers at abscissa denote the number of patients at risk.

In all three analysis sets, the log-rank-tests for comparison of the treatment groups led to p-values below the chosen significance level of $\alpha = 0.05$:

- FAS: $p = 0.000006$
- ARS: $p = 0.000007$
- PPS: $p = 0.000001$

Primary efficacy variables – Secondary analysis

A semi-parametric proportional hazards regression showed that, for both primary efficacy variables, the respective confidence intervals for the hazard ratios of the covariates "treatment" and "steroid use during single event" do not include the value 1, thus suggesting an effect. For "time to MS according to the McDonald criteria", this held also true for "≥ 9 T2 lesions at screening". For the other covariates, the corresponding confidence intervals for the hazard ratios do not suggest demonstrable effects on either primary efficacy variable (see Table IV).

Table IV. Primary efficacy variables: Proportional hazards regression

	Time to CDMS				Time to MS according to the McDonald criteria			
	Parameter		Hazard ratio		Parameter		Hazard ratio	
Covariate	Estimate	SE	Estimate	95% CI	Estimate	SE	Estimate	95% CI
Treatment: IFNB-1b *versus* placebo	-0.63285	0.16249	**0.531**	**0.386 – 0.730**	-0.56564	0.11129	**0.568**	**0.457 – 0.706**
Steroid use during single event: yes *versus* no	0.49274	0.19707	**1.637**	**1.112 – 2.408**	0.41328	0.12694	**1.512**	**1.179 – 1.939**
Type of disease onset: multifocal *versus* monofocal	0.05501	0.16349	1.057	0.767 – 1.456	0.11460	0.10988	1.121	0.904 – 1.391
5-8 **T2 lesions at screening** *versus* 2-4 lesions	0.09345	0.34680	1.098	0.556 – 2.167	0.18142	0.23493	1.199	0.757 – 1.900
≥ 9 **T2 lesions at screening** *versus* 2-4 lesions	0.49668	0.27595	1.643	0.957 – 2.822	0.90741	0.18684	**2.478**	**1.718 – 3.574**

CI = confidence interval; SE = standard error

Secondary MRI efficacy variables

Cumulative number of newly active lesions

For the non-annualized values, the gradual increase of the mean and median cumulative number of newly active lesions was more expressed in the placebo group than in the IFNB-1b group. A significant group difference in favour of IFNB-1b was also found for the annualized rates. The cumulative number of newly active lesions (FAS) is summarised in Table V below.

Table V.

		IFNB-1b			Placebo			p-values *
		N N_{min}	Mean ± SD	Median $Q_1 – Q_3$	N N_{min}	Mean ± SD	Median $Q_1 – Q_3$	
Non-annualized values	**Month 3**	266 -	**1.0** ± 2.5	**0.0** 0 – 1.0	155 -	**2.4** ± 4.9	**1.0** 0 – 3.0	*not calculated*
	Month 6	246 -	**1.8** ± 4.0	**0.0** 0 – 2.0	140 -	**4.3** ± 7.1	**1.5** 0 – 5.0	*not calculated*
	Month 9	238 -	**2.3** ± 5.1	**1.0** 0 – 3.0	130 -	**5.5** ± 8.4	**2.0** 0 – 7.0	*not calculated*
	Month 12	228 -	**3.0** ± 5.4	**1.0** 0 – 3.0	117 -	**6.9** ± 10.1	**3.0** 0 – 8.0	**< 0.0001**
	Month 18	202 -	**3.8** ± 6.6	**2.0** 0 – 5.0	105 -	**7.6** ± 10.6	**4.0** 1.0 – 8.0	*not calculated*
	Month 24	187 -	**5.0** ± 9.2	**2.0** 0 – 6.0	88 -	**9.5** ± 12.1	**5.0** 0 – 14.0	*not calculated*
	End of Study**	269 -	**4.8** ± 9.0	**2.0** 0 – 5.0	161 -	**8.7** ± 11.2	**4.0** 1.0 – 11.0	**< 0.0001**
Annualized rate			**3.73** ± 8.16	**1.34** 0.0 – 3.62		**8.47** ± 13.93	**3.16** 0.96 – 10.43	**< 0.0001**

N refers to the number of patients with MRI scans actually performed
* Non-parametric analysis of covariance, 2-sided
** Last scan at or before EOS

Absolute change in T2 lesion volume (T2 lesion load),

The change in T2 lesion load during the course of the study exhibited a substantial interindividual variability. From screening to all subsequent visits, the T2 lesion load decreased in the majority of patients in both treatment groups. Changes in T2 lesion volume relative to screening expressed as mm3 – FAS are summarised in Table VI below.

Table VI.

		IFNB-1b			Placebo			p-values *
		N N_{miss}	Mean ± SD	Median $Q_1 - Q_3$	N N_{miss}	Mean ± SD	Median $Q_1 - Q_3$	
Non-annualized values	**Month 3**	262 4	**-731.9** ± 2734.6	**-122.5** -689.0 – 20.0	152 3	**-457.0** ± 2002.9	**-96.5** -558.5 – 133.0	*not calculated*
	Month 6	243 3	**-900.7** ± 3209.1	**-206.0** -766.0 – 19.0	136 4	**-317.2** ± 2527.1	**-114.5** -663.0 – 162.5	*not calculated*
	Month 9	237 1	**-934.1** ± 3333.0	**-212.0** -916.0 – 35.0	128 2	**-520.2** ± 2371.2	**-143.5** -723.0 – 166.0	*not calculated*
	Month 12	227 1	**-921.2** ± 3565.0	**-186.0** -953.0 – 75.0	115 2	**-268.7** ± 2326.7	**-83.0** -572.0 – 127	**0.0441**
	Month 18	202 -	**-844.2** ± 3523.0	**-170.0** -901.0 – 183.0	103 2	**-89.6** ± 1446.8	**-52.0** -543.0 – 232.0	*not calculated*
	Month 24	182 5	**-885.5** ± 3473.3	**-162.0** -807.0 – 112.0	84 4	**-244.4** ± 1355.9	**-92.0** -616.5 – 192.5	*not calculated*
	End of study	263 6	**-888.5** ± 3312.6	**-206.0** -827.0 – 95.0	154 7	**-431.6** ± 2226.5	**-93.0** -624.0 – 295.0	**0.0498**
Annualized rate			**-818.5** ± 3169.9	**-119.7** -607.3 – 57.4		**-554.1** ± 2644.1	**-57.5** -572.0 – 168.2	**0.1906**

* Non-parametric analysis of covariance, 2-sided

Exploratory MRI efficacy variables

The results for the exploratory MRI efficacy variables (FAS) are summarized in the Table VII below.

Table VII.

			IFNB-1b			Placebo			p-values *
			N N_{miss}	Mean ± SD	Median $Q_1 - Q_3$	N N_{miss}	Mean ± SD	Median $Q_1 - Q_3$	
T1 hypointense lesions ("black holes"**)	Absolute change in lesion volume (mm^3) [a]	Month 12 non-annualized	227 1	**24.6** ± 618.3	**0.0** -63.0 – 60.0	115 2	**19.1** ± 436.3	**0.0** -68.0 – 80.0	**0.9460**
		End of study non-annualized	232 37	**8.0** ± 604.1	**0.0** -106.0 – 75.5	131 30	**-47.6** ± 639.9	**0.0** -69.0 – 63.0	**0.8724**
		annualized		**-0.567** ± 487.7	**0.0** -57.6 – 41.2		**-94.0** ± 755.3	**0.0** -63.5 – 46.1	**0.6143**
	Cumulative number of new lesions [b]	Month 12 non-annualized	228 -	**0.1** ± 0.3	**0.0** 0.0 – 0.0	117 -	**0.1** ± 0.9	**0.0** 0.0 – 0.0	**0.0159**
		End of study non-annualized	269 -	**0.2** ± 0.6	**0.0** 0.0 – 0.0	161 -	**0.3** ± 1.1	**0.0** 0.0 – 0.0	**0.0397**
		annualized		**0.17** ± 0.84	**0.0** 0.0 – 0.0		**0.30** ± 1.15	**0.0** 0.0 – 0.0	**0.0335**
Brain volume	% change [c]	Month 12 non-annualized	184 44	**-0.42%** ± 0.97	**-0.29%** -0.81 – 0.09	95 22	**-0.27%** ± 0.90	**-0.34%** -0.80 – 0.27	**0.4992**
		End of study non-annualized	197 72	**-0.80%** ± 1.18	**-0.63%** -1.31 – -0.10	126 35	**-0.43%** ± 1.10	**-0.39%** -1.12 – 0.24	**0.0054**
		annualized		**-0.51%** ± 1.17	**-0.36%** -0.83 – -0.06		**-0.12%** ± 1.16	**-0.28%** -0.72 – 0.31	**0.0203**

* Non-parametric analysis of covariance, 2-sided

** For technical reasons, a T1 hypointense lesion was only identified if there was a corresponding new or enlarging T2 lesion; "black holes" that also showed enhancement were not identified. Thus, lesions identified as black hole in this study, "black hole*", represent only a fraction of all black holes.

Exploratory clinical efficacy variables

EDSS score and Kurtzkes FS scores

The EDSS results show no statistical significance between the treatment groups as shown (Table VIII below).

Table VIII.

	IFNB-1b			Placebo		
	N	Mean ± SD	Median $Q_1 - Q_3$	N	Mean ± SD	Median $Q_1 - Q_3$
Baseline	292	**1.59** ± 0.86	**1.50** 1.0 – 2.0	176	**1.49** ± 0.88	**1.50** 1.0 – 2.0
Month 6	253	**1.30** ± 0.93	**1.50** 1.0 – 2.0	152	**1.30** ± 0.90	**1.50** 1.0 – 2.0
Month 12	229	**1.24** ± 0.89	**1.50** 1.0 – 2.0	120	**1.32** ± 0.85	**1.50** 1.0 – 1.5
Month 18	210	**1.24** ± 0.87	**1.00** 1.0 – 2.0	111	**1.18** ± 0.81	**1.00** 1.0 – 1.5
Month 24	196	**1.26** ± 0.96	**1.00** 1.0 – 2.0	91	**1.18** ± 0.83	**1.00** 1.0 – 2.0
End of study	277	**1.49** ± 1.05	**1.50** 1.0 – 2.0	167	**1.53** ± 1.08	**1.50** 1.0 – 2.0

MSFC score and scores of subtests.

The results for the MSFC Z-scores show no statistical significance between the treatment groups (see Table IX).

Table IX . Multiple Sclerosis Functional Composite (MSFC) - Changes from baseline to end of study - FAS

	IFNB-1b			Placebo		
	N N_{miss}	Mean ± SD	Median $Q_1 - Q_3$	N N_{miss}	Mean ± SD	Median $Q_1 - Q_3$
Overall Z-score	271 4	**0.126** ± 0.518	**0.119** -0.129 – 0.410	165 1	**-0.003** ± 0.660	**0.060** -0.188 – 0.251
Timed 25-foot walk Z-score	275 -	**-0.138** ± 1.220	**-0.064** -0.322 – 0.161	166 -	**-0.076** ± 1.476	**-0.064** -0.290 – 0.129
9-hole peg test Z-score	274 1	**0.191** ± 0.846	**0.219** -0.185 – 0.744	166 -	**0.037** ± 0.806	**0.137** -0.249 – 0.488
PASAT Z-score	272 3	**0.271** ± 0.758	**0.124** 0.00 – 0.497	165 1	**0.031** ± 0.728	**0.00** -0.248 – 0.373

PASAT: Paced auditory serial addition test.

Patient-reported outcome (PRO) variables

The PRO results were comparable between both treatment groups.

The Functional assessment of MS Trial Outcome Index (FAMS-TOI) had been pre-specified as the most important PRO variable. Starting from nearly identical median baseline values in both treatment groups (IFNB-1b: 129.8; placebo: 130.0), only little changes over time and only minor differences between the treatment groups were seen; at EOS, median values of 128.0 were recorded in both treatment. The same picture was found for the FAMS total score: Very similar baseline values as recorded in both treatment groups (IFNB-1b: 146; placebo: 147) were followed by EOS values of 147 (IFNB-1b) and 146 (placebo).

The EQ-5D results indicate that the long-term treatment with IFNB-1b does not have a measurable impact on the patients' HRQL. For the five dimensions of the health state classification ("mobility", "self-care", "pain/discomfort", "usual activities", "anxiety/depression") no significant changes over time were found. Starting from similar median baseline values in both treatment groups (IFNB-1b: 85.0; placebo: 89.0), no significant differences between the treatment groups were seen for the EQ-5D Visual analogue scale; at EOS, median values of 88.0 (IFNB-1b) and 89.0 (placebo) were recorded.

Ancillary analyses

Results of log-rank test and proportional hazards regression in lag time subgroups

Further to CHMP request, the MAH performed post hoc analyses of primary endpoints for different "lag time" categories (i.e. measured from onset of the first episode to treatment start). Tables X and XI provide results of log-rank tests and unadjusted proportional hazards regressions for time to CDMS / time to McDonald MS in the two subgroups "15 – 45 days" and "≥ 46 days" for lag time. Results show that treatment effects were more pronounced in patients with shorter period between the onset of the first event and start of treatment.

Table X: Results of log-rank test and proportional hazards regression in lag time subgroups for time to CDMS.

Lag time category	Log-rank p-value	Hazard ratio	95% confidence interval for hazard ratio
15 – 45 days (N=109)	0.025	0.48	0.25 – 0.93
≥ 46 days (N=359)	0.001	0.55	0.38 – 0.79

see tables 32 to 35 in Appendix D

Table XI: Results of log-rank test and proportional hazards regression in lag time subgroups for time to McDonald MS.

Lag time category	Log-rank p-value	Hazard ratio	95% confidence interval for hazard ratio
15 – 45 days (N=109)	0.001	0.48	0.31 – 0.76
≥ 46 days (N=359)	<0.001	0.66	0.51 – 0.84

see tables 44 to 47 in Appendix D

Modified proportional hazards regression model and unadjusted hazard ratios

The results of the post-hoc analyses using the proportional hazards model with the modified, more complete, set of covariates that may affect the progression to MS and, the unadjusted proportional hazards regressions are summarized in Table XII. The results obtained for the FAS analysis were very similar to the ARS results.

Table XII.

Variable	Covariate	Parameter Estimate	SE	p-value	Hazard ratio Estimate	95% CI
					Model with extended set of covariates	
Time to CDMS	**Treatment**: IFNB-1b *versus* placebo	-0.68494	0.16623	0.000038	**0.504**	**0.36 – 0.70**
	Steroid use during single event: yes *versus* no	0.45528	0.19784	0.021376	**1.577**	**1.07 – 2.32**
	Type of disease onset: multifocal *versus* monofocal	0.05527	0.16725	0.741034	1.057	0.76 – 1.47
	Age at screening	-0.04467	0.01195	0.000186	**0.956**	**0.93 – 0.98**
	Sex: female *versus* male	0.03184	0.18009	0.859684	1.032	0.73 – 1.47
	Number of T2 lesions at screening	0.00356	0.00285	0.210988	1.004	0.998 – 1.009
	Number of Gd+ lesions at screening	0.06381	0.02032	0.001690	**1.066**	**1.02 – 1.11**
					Model with treatment as single covariate ("unadjusted hazard ratio")	
	Treatment: IFNB-1b *versus* placebo	-0.63233	0.16236	0.000098	**0.531**	**0.39 – 0.73**
					Model with extended set of covariates	
Time to MS according to the McDonald criteria	**Treatment**: IFNB-1b *versus* placebo	-0.62094	0.11395	0.000000	**0.537**	**0.430 – 0.672**
	Steroid use during single event: yes *versus* no	0.35850	0.12793	0.005075	**1.431**	**1.114 – 1.839**
	Type of disease onset: multifocal *versus* monofocal	0.06039	0.11413	0.596709	1.062	0.849 – 1.329
	Age at screening	-0.02913	0.00770	0.000155	**0.971**	**0.957 – 0.986**
	Sex: female *versus* male	-0.01617	0.12104	0.893699	0.984	0.776 – 1.247
	Number of T2 lesions at screening	0.01027	0.00188	<0.000000	**1.010**	**1.007 – 1.014**
	Number of Gd+ lesions at screening	0.04079	0.01482	0.005910	**1.042**	**1.012 – 1.072**
					Model with treatment as single covariate ("unadjusted hazard ratio")	
	Treatment: IFNB-1b *versus* placebo	-0.49422	0.11057	0.000008	**0.610**	**0.49 – 0.76**

CI = confidence interval; SE = standard error

1. Time to CDMS

The modified proportional hazards regression indicates that "time to CDMS" is influenced in a statistically significant manner by IFNB-1b (decreased the risk for progression to CDMS, hazard ratio: 0.50), by the steroid treatment of the single event (hazard ratio: 1.58), by the age at screening (hazard ratio: 0.96), and by the Gd-enhancing lesions on the screening MRI (hazard ratio: 1.07). The number of T2 lesions showed a trend for an increase in risk (hazard ratio: 1.004) which did not reach statistical significance. Neither the sex nor the type of disease onset (mono- or multifocal) influenced the progression to CDMS.

2. Time to MS according to the McDonald criteria

The modified proportional hazards regression for "time to McDonald MS" resulted in very similar findings, with statistically significant impact of treatment, steroid treatment of the single event and age at screening. In addition, the number of T2 lesions was also statistically significantly associated with an increased risk (hazard ratio: 1.01 per T2 lesion). As for "time to CDMS", by use of the extended set of covariates, an even stronger reduction in the risk for progression to MS according to the McDonald criteria was seen for IFNB-1b treatment (hazard ratio: 0.54) than in the hazards regressions using the initial set of covariates (hazard ratio: 0.57) or treatment as single covariate ("unadjusted hazard ratio": 0.61).

Time course of "CDMS" versus "MS according to the McDonald criteria"

In both treatment groups, the cumulative proportion of patients with MS according to the McDonald criteria is substantially larger than the cumulative proportion of patients with CDMS (see Table XIII). By the end of the 2-year observation period, the cumulative probability for the disease development in placebo patients was 84.5% (MS according to the McDonald criteria) and 45.3% (CDMS).

Table XIII. Time course of "CDMS" *versus* "MS according to the McDonald criteria" (FAS)

	IFNB-1b						Placebo					
	CDMS			McDonald			CDMS			McDonald		
	Actual number of patients		Kaplan-Meier estimate	Actual number of patients		Kaplan-Meier estimate	Actual number of patients		Kaplan-Meier estimate	Actual number of patients		Kaplan-Meier estimate
Days of treatment	at risk	with event*		at risk	with event*		at risk	with event*		at risk	with event*	
0	292	0	0.0%	292	0	0.0%	176	0	0.0%	176	0	0.0%
90	267	19	6.6%	250	36	12.2%	158	16	9.2%	137	37	21.2%
180	249	32	11.2%	203	80	28.0%	139	33	19.0%	86	88	50.6%
270	237	41	14.4%	148	132	46.5%	126	45	26.0%	59	115	66.1%
360	223	52	18.4%	122	157	55.6%	115	55	31.9%	46	127	73.1%
450	210	62	22.1%	100	176	62.6%	111	59	34.3%	40	133	76.6%
540	205	67	24.0%	98	178	63.4%	101	67	39.1%	36	135	77.8%
630	200	72	25.8%	91	185	76.0%	96	70	40.9%	32	138	79.7%
720	47	75	27.5%	18	191	69.4%	24	77	45.3%	9	142	84.5%

* Cumulative numbers

Differential risks for CDMS and treatment effects in mono- versus multifocal patients

In order to better understand the level of treatment response in subgroups of patients with different degree of disease activity, the impact of baseline MRI findings was further evaluated separately in mono- and multifocal patients.

In monofocal CIS patients, the risk for CDMS in placebo patients and the treatment response increased with a higher number of T2-lesions and the presence of at least one Gd-enhancing lesion. The risk for CDMS in the placebo group increased from 31% in patients with less than 9 T2-lesions to 55% in patients with at least 9 T2-lesions. Similarly the risk for CDMS increased from 36% in placebo patients without Gd-enhancing lesions to 63% in patients with Gd-enhancing lesions.

In multifocal CIS patients, the risk for CDMS in placebo patients and the treatment effect was not increased by higher disease dissemination or activity on the baseline MRI. The risk for CDMS in multifocal placebo patients with less than 9 T2-lesions was comparable to the risk of patients with at least 9 T2-lesions. Similarly, the risk for CDMS did not differ in multifocal placebo patients without vs. with Gd-enhancing lesions.

There were also differences between multifocal and monofocal CIS patients with regard to the treatment response. The treatment effect of multifocal patients with less MRI disease activity/dissemination at baseline was substantial, and numerically even more pronounced than in multifocal patients with such MRI findings (in multifocal patients with less than 9 T2- lesions vs. at least 9 T2-lesions the hazard ratios were 0.24 [0.09-0.66] vs. 0.84 [0.50-1.41]; in multifocal patients without vs. with Gd-enhancing lesions the hazard ratios were 0.42 [0.22- 0.80] vs. 0.95 [0.48-1.87]).

ANALYSIS PERFORMED ACROSS TRIALS (POOLED ANALYSES AND META-ANALYSIS)

In the pivotal RRMS study that supported the granting of the original RRMS indication, the hazard ratio estimate for "Time to first relapse after start of treatment" for IFN beta-1b versus placebo was 0.69, corresponding to a reduction in the risk for a relapse by 31% (*Bogumil et al. 2005*).

In the BENEFIT study, the reduction in risk for "Time to first relapse" overall was 46% (hazard ratio 0.54), and in the subgroups of patients with higher dissemination / activity of the disease at the first event, 34% (hazard ratio 0.66) in multifocal patients, 41% (hazard ratio 0.59) in patients with 9 or more T2 lesions, and 38% in patients with enhancement on the screening MRI (hazard ratio 0.62).

DISCUSSION ON CLINICAL EFFICACY

The clinical efficacy programme was based on a multi-center, double-blind, placebo-controlled, randomized study in patients with a first clinical demyelinating event suggestive of MS.

The benefit of Betaferon in patients with a first demyelinating event suggestive of MS is supported by the primary endpoint as the results demonstrated a significant elongation of the time to CDMS according to the classifications of Poser and of McDonald at the end of two years. Conversely, a significant decrease of the cumulative number of new active MS lesions on MRI in the IFNB-1b group in comparison with the placebo group was demonstrated.

The convincing results obtained regarding the time to CDMS and MRI lesions were not accompanied by improvements in the clinically efficacy variables (EDSS, MSFC score) and the patient-reported outcome variables, which raises questions concerning the clinical relevance of early treatment with Betaferon. In that respect, it is noted that the beneficial effects of Betaferon on relapse re-occurrence in the BENEFIT study were comparable to the effects of Betaferon observed in the pivotal study in RRMS patients that were the basis for approval of Betaferon in this patient population. Besides, there is a substantial body of evidence that relapse and also MRI activity are associated with irreversible CNS damage in the early disease period (*Trapp, 1998; Kuhlmann, 2002*), and that relapse and MRI activity during the early rather than during the late disease periods predict long-term disease outcome (*Brex, 2002; Ebers, 2005; Lublin, 2003*). Therefore, even a small effect could be considered clinically relevant. The lack of significance of the results obtained on clinically efficacy variables and patient-reported outcomes may be explained by the fact that these parameters are too insensitive to measure disease progression during this earliest clinical period of the disease. The MAH performed additional statistical tests on MSFC outcome parameters (non-parametric analysis of covariance with baseline MSFC result as covariate) which notably showed a statistically significant beneficial effect for Betaferon patients with respect to the change of the overall MSFC score from baseline to the end of study (the median change of the MSFC z-score from baseline to end of study was 0.119 in Betaferon and 0.060 in placebo patients; p=0.0386). These results should be viewed with caution as these analyses have not been adjusted for multiplicity.

The results obtained after 2 years provide a limited follow-up of patients and it is unclear how patients who develop MS who have been pre-treated with Betaferon will fair in the long-term. Therefore, the MAH committed to provide an accurate follow-up of data from the open-label follow-up extension of the trial, when available. In addition, the indication should be restricted to those patients with a first event of sufficient severity to warrant the use of Betaferon and with a high risk for MS. Although there is no well established definition of a high risk patient, subgroups of patients that were seen of being at higher risk to develop CDMS in the BENEFIT study were specified in section 5.1.

Clinical safety

PATIENT EXPOSURE

There were 468 patients in the SFS (96.1% of all patients randomized). Of these 468 patients, a total of 292 patients (95.7% of all patients randomized to this treatment group) were of the IFNB-1b group and 176 patients (96.7%) of the placebo group. For a total of 458 patients, data on the duration from start of treatment to end of study drug was available (missing for 10 patients of the SFS).

ADVERSE EVENTS

A total of 3056 adverse events (AEs) in 443 out of 468 patients (94.7%) were reported, with more AEs and a higher proportion of patients with AEs reported in the IFNB-1b group: 2180 AEs occurred in 281 out of 292 IFNB-1b patients (96.2%) compared to 876 AEs in 162 out of 176 (92.0%) placebo patients. Differences between the treatment groups were observed for the number of AEs per patient. Patients of the IFNB-1b group had more AEs per patient than patients of the placebo group. No AE was recorded in 11 patients (3.8%) of the IFNB-1b group and 14 (8.0%) of the placebo patients.

Most AEs were either mild or moderate in intensity, with no clear differences between treatment groups: 82.9% of all IFNB-1b patients had mild or moderate AEs compared with 86.4% of all placebo patients. The most frequent AEs were injection site reaction, flu-like symptoms, headache and asthenia, all of which were more frequent in the IFN beta-1b group than the placebo group. The most frequently reported AEs with more than 10% of patients for any treatment are summarised in Table XIV.

Table XIV.

	IFNB-1b (N=292)			Placebo (N=176)		
HARTS terms, except*	No. of AEs	Patients No.	%	No. of AEs	Patients No.	%
Injection site reaction (various kinds)*	n.a.	152	52.1%	n.a.	19	10.8%
of these: Injection site reaction	171	141	48.3%	18	15	8.5%
Flu-like syndrome complex*	n.a.	135	46.2%	n.a.	34	19.3%
of these: Flu syndrome	195	129	44.2%	54	32	18.2%
Headache	117	78	26.7%	35	30	17.0%
Asthenia	74	63	21.6%	34	30	17.0%
Multiple sclerosis	55	54	18.5%	67	61	34.7%
Leukopenia	131	53	18.2%	19	10	5.7%
Upper respiratory tract infection	74	52	17.8%	52	34	19.3%
Paresthesia	61	48	16.4%	50	30	17.0%
SGPT increased	74	45	15.4%	11	8	4.5%
Fever	48	38	13.0%	9	8	4.5%
SGOT increased	42	32	11.0%	5	5	2.8%
Rash	38	32	11.0%	5	5	2.8%
Depression	32	30	10.3%	22	20	11.4%

* "Injection site reaction (various kinds)" comprises all AEs occurring at the injection site, *i.e.*, the HARTS terms "injection site hemorrhage", "injection site hypersensitivity", "injection site inflammation", "injection site mass", "injection site necrosis", "injection site pain" and "injection site reaction".

"Flu-like syndrome complex" denotes the HARTS terms "flu syndrome" and/or a combination of at least two AEs from "fever", "chills", "myalgia", "malaise" or "sweating".

More patients of the IFNB-1b group had AEs that were assessed as study drug-related. A total of 254 patients (87.0%) of the IFNB-1b group and 76 patients (43.2%) of the placebo group had at least one AE that was classified as being treatment-related. The frequency of typical IFNB-1b-related AEs decreased substantially from the first year to the second year of the study. Of note, the proportion of IFN beta-1b-treated patients experiencing flu syndrome was reduced from 42% to 13% of the patients. AEs related to flu syndrome such as fever and chills were observed less frequently during the second year. Also injection site reactions occurred less frequently during the second year (30%) than during the first year (46%).

SERIOUS ADVERSE EVENT/DEATHS/OTHER SIGNIFICANT EVENTS

A total of 42 AEs (out of 3056 AEs, 1.4%) were reported for 32 of 468 patients (6.8%) as serious adverse events (SAE), i.e., 28 SAEs (of 2180 AEs, 1.3%) in 20 of 292 patients (6.8%) of the IFNB-1b group and 14 SAEs (of 876 AEs, 1.6%) in 12 of 176 patients (6.8%) of the placebo group.

The majority of patients (23 of 32 patients with SAEs) had recovered from their SAEs by the end of the study, 4 were still recovering (all of the IFNB-1b group), 3 had not recovered (2 patients of the IFNB-1b group, 1 of the placebo group), and 2 had recovered with residual effects (one patient of each treatment group). No deaths were reported during this study.

LABORATORY FINDINGS

For lymphocytes, SGPT, absolute neutrophile count (ANC), white blood cells (WBC) and SGOT, the proportion of affected patients was statistically significantly higher in the IFNB-1b group as compared to placebo. The most pronounced group differences were found for lymphocytes (< 1500 /mm3; IFNB-1b: 79.1%) and increased SGPT values (> 5 × baseline value; IFNB-1b: 17.8%).

The five laboratory variables are summarized in Table XV for group comparisons with respect to the number/percentage of patients beyond the respective threshold value used in the summary of product characteristics.

Table XV.

		IFNB-1b (n=292)		Placebo (n=176)		p-value	Difference [%]*		
Variable	SPC threshold value	Number/percentage of patients beyond the threshold value				X^2 two-sided	Absolute value	95% CI limits Lower	Upper
Lymphocytes	< 1500 /mm^3	231	79.1%	80	45.5%	< 0.0001	33.7	24.9	42.4
SGPT	> 5 × baseline value	52	17.8%	8	4.5%	< 0.0001	13.3	7.9	18.6
ANC	< 1500 /mm^3	31	10.6%	4	2.3%	0.0009	8.3	4.2	12.5
WBC	< 3000 /mm^3	31	10.6%	3	1.7%	0.0003	8.9	4.9	12.9
SGOT	> 5 × baseline value	18	6.2%	1	0.6%	0.0030	5.6	2.6	8.6

* Difference = Percentage in IFNB-1b group minus percentage in placebo group
SPC: Summary of product characteristics

NEUTRALIZING ANTIBODIES (NABS)

The available data for NAbs (By-visit results of the 6-monthly measurements) are shown in Table XVI. Neutralizing activity was measured at least once in 30% (75) of the IFNB-1b patients; of these, 23% (17) converted to negative status during the later study course.

Table XVI.

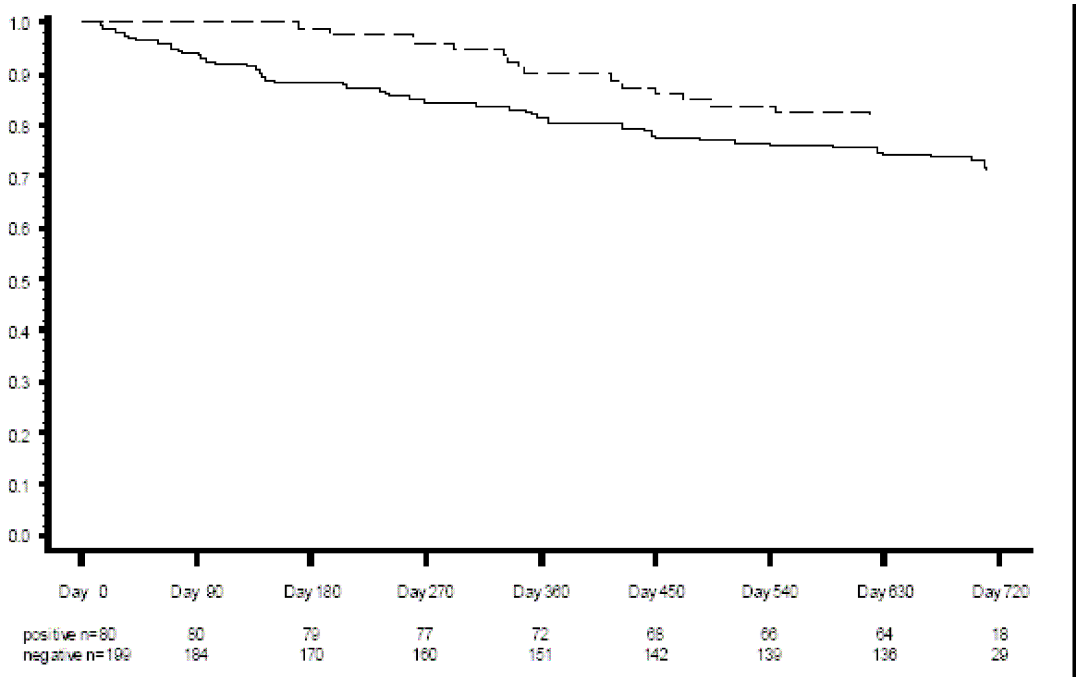
	Baseline		Month 6		Month 12		Month 18		Month 24		End of Study	
No. of subjects	292	100%	254	100%	230	100%	209	100%	196	100%	282	100%
Missing	5	1.7%	0	-	3	1.3%	0	-	3	1.5%	13	4.6%
Negative	287	98.3%	212	83.5%	169	73.5%	160	76.6%	144	73.5%	208	73.8%
Positive*	0	-	42	16.5%	58	25.2%	49	23.4%	49	25.0%	61	21.6%

* Positive: ≥ 20 NU/mL

The assay specificity was adequate as evidenced by the fact that only 1 placebo patient had a positive NAb titer at any time; moreover, no positive baseline titer was recorded.

A post hoc analysis indicated that there was no significant effect between positive titres for NAbs and "Time to CDMS". For the evaluation of potential correlations between NAb titers and efficacy, a log-rank test stratified for "all available NAb titers negative" versus "≥ 1 positive NAb titer was performed for the primary variable time to CDMS" in FAS patients randomized to IFNB-1b.
The log-rank test did not detect a statistically significant difference between the two strata (p = 0.11). Likewise, the proportional hazards regression with covariate NAb status did not provide statistically significant results for this covariate (hazard ratio: 0.626, p = 0.11). Moreover, the results of the additional proportional hazards regression with covariate NAb status and the covariates used for the pre-specified analyses of the primary variables ("type of disease onset"; "steroid use at first event"; "number of T2 lesions at screening") are consistent with these findings. Figure 3 below illustrates the time to CDMS in patients with at least 1 positive NAb titer compared to patients who remained NAb-negative throughout the study.

Figure 3. Time to CDMS" by NAb status – Kaplan-Meier product-limit estimates (FAS)



Ordinate depicts the survival distribution function estimate. Patient numbers at abscissa denote the number of patients at risk.

At the request of the CHMP, the MAH performed additional statistical analyses with regard to the relationship of positive NAb status ("at least once positive") and time to CDMS to further evaluate the effect of the NAb on the efficacy in patients with persisting levels of antibodies. This additional analysis excluded Betaferon patients with end of study (EOS) before 6 months, 9 months and 12

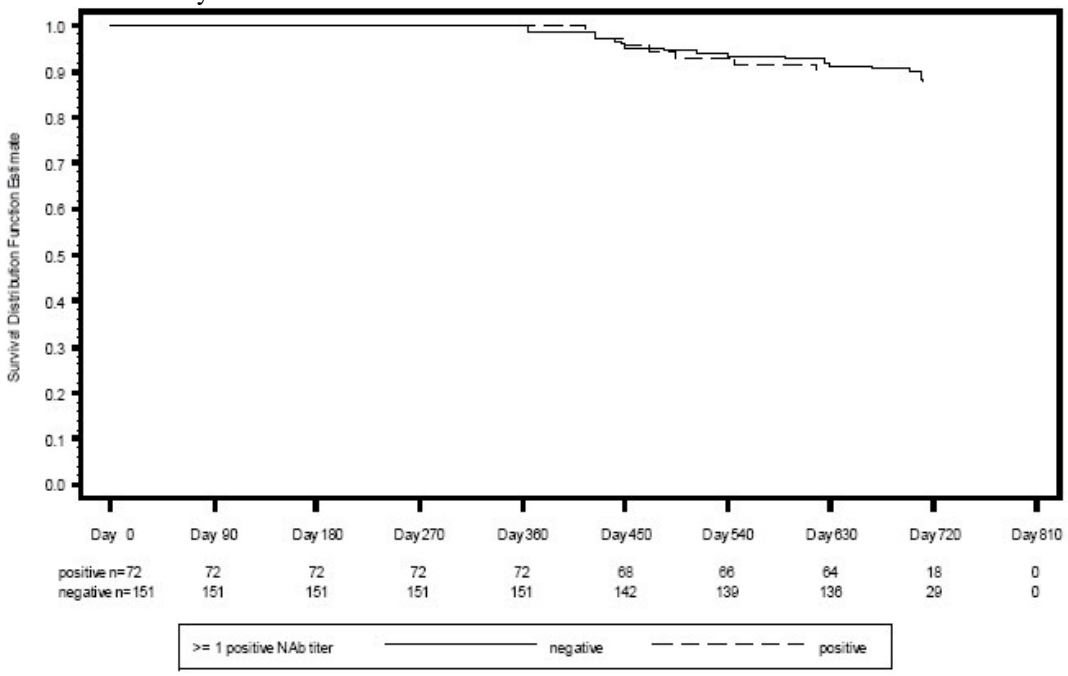
months, respectively. Such an approach was motivated by the common understanding that NAbs against Betaferon are typically not present (or measurable) during the first 6 to 12 months after initiation of Betaferon therapy (*Polman, 2003; Soerensen, 2005*). Key results are displayed in Table XVII and Figure 4.

Table XVII: Association of NAb positive status and time to CDMS

Variable	Log-rank p-value	Hazard ratio[#]	95% confidence interval for hazard ratio
All Betaferon patients (N=279)	0.11	0.63	0.35 – 1.11
EOS after 180 days (N=249)	0.97	1.01	0.54 – 1.92
EOS after 270 days (N=237)	0.71	1.14	0.56 – 2.30
EOS after 360 days (N=223)	0.84	0.91	0.38 – 2.22

NAb positive versus NAb negative status

Figure 4: Time to CDMS by NAb status (at least once positive) for IFN beta-1b patients with EOS after at least 360 days.



DISCONTINUATION DUE TO ADVERSE EVENTS

Significant AE(s) leading to premature discontinuation of study drug and study (SAEs and non-serious AEs) are summarised in Table XVIII below.

Table XVIII.

HARTS code	Country / PID	Reason for withdrawal from study medication (* and study)	Treatment relationship
IFN beta-1b			
Injection site reaction	CA / 110106	Lost to follow-up	Probable
Abnormal liver function test	CA / 110501	AE	Possible
Rash	DE / 311408	AE	Definite
Tachycardia	DE / 311703	AE*	Possible
Abnormal liver function test	DE / 311707	AE*	Probable
Abnormal liver function test	DE / 312102	AE	Probable
Headache	DE / 312104	AE	Possible
Asthenia	FI / 440306	AE*	Definite
Chills	FI / 440510	AE	Definite
Depression	FI / 440605	AE	Probable
Flu syndrome, injection site reaction	FI / 440608	AE	Probable, definite
Injection site reaction	FI / 440611	AE	Definite
Emotional lability	FR / 510502	Other (AE, then withdrawn)	Probable
Urtikaria	FR / 511402	AE*	Definite
Flu syndrome	GB / 610702	AE	Definite
Abnormal liver function test	IL / 830401	AE	Definite
Thyroid disorder	IT / 910402	AE	Probable
Depression, psychotic depression	DE / 311502	SAE* (2 SAEs)	Probable
Injection site necrosis	DE / 311504	SAE*	Definite
Injection site necrosis	DE / 312604	SAE	Definite
Liver function tests, cholelithiasis	FI / 440105	SAE	Unlikely
Breast carcinoma	FI / 440602	SAE	Unlikely
(Transient) psychosis	FI / 440612	SAE	Possible
Allergic reaction (to Magnevist)	FR / 510501	SAE*	Unlikely
Injection site reaction	CZ / 720603	SAE*	Definite
Placebo			
None			

Abbreviations: Canada (CA), Germany (DE), Finland (FI), France (FR), United Kingdom (GB), Israel (IL), Italy (IT)
* AEs/SAEs also resulting in premature discontinuation of study (premature EOS).

COMPARISON OF AES AND LABORATORY ABNORMALITIES AMONG THE PIVOTAL IFNB-1B STUDIES

The safety and tolerability profile of IFNB-1b (250 µg e.o.d.) in patients with a first demyelinating event as observed during the BENEFIT study was compared with results obtained in previous studies in patients with RRMS or SPMS. In general, in comparison to the previous pivotal studies, AEs and laboratory abnormalities were reported in the BENEFIT study in IFN beta-1b patients with a single clinical event either with a similar incidence, or less often. It is noted that injection site reactions (ISRs) occurred in a smaller number of both IFNB-1b and placebo treated patients in the BENEFIT study. An injection site necrosis was observed in 1% of the IFNB-1b treated patients as compared to 5% to 6% in the other three pivotal studies. Similarly, flu-like symptoms was reported for a smaller portion of the IFNB-1b treated patients with a single clinical event (46.2%) as compared to the previous pivotal studies (43% to 61%). With regard to ISRs, the MAH also referred to a three-month, multicenter, randomized, controlled study which is accepted for publication. Objective of the study was to compare ISRs with two different autoinjectors during two one-month open-label cross-over periods versus ISRs during the one-month initiation period using a standard s.c. hand injection technique in patients presenting with RRMS and starting treatment with IFN beta-1b. The mean proportion of ISRs was significantly higher in the hand injection group (35.9%) than in the respective autoinjectors groups (24.0%; $p < 0.0001$ and 24.1%; $p < 0.0001$).

DISCUSSION ON CLINICAL SAFETY

The safety and tolerability profile for Betaferon found in the available study was as expected and without new aspects. In comparison to the previous studies, AEs and laboratory abnormalities were reported with a similar incidence or less often. This comparison across studies should be interpreted with caution as it is made between different population samples**.** However, it is likely that the titration scheme at the start of therapy, as well as the use of concomitant medication (i.e. non-steroid anti-inflammatory drugs) have contributed to the good tolerability at treatment initiation. In addition, the use of an autoinjector in most of the IFNB-1b treated patients at each visit, after completion of the titration phase, might have contributed to the relatively low occurrence of AEs affecting the injection site.

Although there was no indication that the presence of NAbs reduced the efficacy of Betaferon with regard to prolongation of time to CDMS, potential effects of NAbs beyond two years could not be assessed. Previous pivotal studies using Betaferon in RRMS and SPMS patients showed no attenuating effect of NAb development on progression in disability. Evaluation of the European Betaferon SPMS study showed that effects of NAb on relapse rate were substantially varied, depending on the statistical approach and definition of positivity, although analyses comparing low- and high-NAb positive periods with NAb negative periods suggested a titer-related effect. However, it is worthy of note that substantial proportion of NAb positive patients became NAb negative during the course of the study, similar to a follow-up report from RRMS patients from the pivotal study, with 88% of Nab positive becoming NAb negative over a period of 9 years (*Polman et al, 2003*). The impact of persisting NAbs will be further analysed in the BENEFIT follow-up study, in which the effects of NAbs on relapse rate and disability progression will be evaluated over a time period of up to 60 months.

5. Pharmacovigilance

The CHMP did not require the MAH to submit a risk management plan because other patients similar to the proposed target population have already been exposed to this class of drugs.

6. Overall conclusions, risk/benefit assessment

The data provided support the benefit of Betaferon in patients with a first demyelinating event suggestive of MS as the results from the pivotal study demonstrated a significant elongation of the time to CDMS according to the classifications of Poser and of McDonald. Conversely, a significant decrease of the cumulative number of new active MS lesions on MRI in the IFNB-1b group in comparison with the placebo group was demonstrated.

The study also confirmed the safety profile of Betaferon observed in previous studies. The safety and tolerability profile for Betaferon was as expected and without new aspects.

In light of this favourable benefit/risk profile and the clarifications provided by the MAH, Betaferon may be recommended for the treatment of patients with a first demyelinating event suggestive of MS. Therefore, the following indication is added to those already authorised:

"patients with a single demyelinating event with an active inflammatory process if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1)."

Consequential amendments were also made to sections 4.2, 4.4, 4.8 and 5.1 of the SPC, and the package leaflet was updated accordingly.