J Neurol
DOI 10.1007/s00415-007-0733-2

ORIGINAL COMMUNICATION

# Subgroups of the BENEFIT study: Risk of developing MS and treatment effect of interferon beta-1b

**Chris H. Polman**
**Ludwig Kappos**
**Mark S. Freedman**
**Gilles Edan**
**Hans-Peter Hartung**
**David H. Miller**
**Xavier Montalbán**
**Frederik Barkhof**
**Krzysztof Selmaj**
**Bernard M. J. Uitdehaag**
**Susanne Dahms**
**Lars Bauer**
**Christoph Pohl***
**Rupert Sandbrink***
**for the BENEFIT investigators****

Received: 16 April 2007
Received in revised form: 23 July 2007
Accepted: 3 September 2007
Published online: 15 November 2007

C. H. Polman · F. Barkhof ·
B. M. J. Uitdehaag
Vrije Universiteit Medical Centre
Amsterdam, The Netherlands

L. Kappos
University Hospital
Basel, Switzerland

M. S. Freedman
The Ottawa Hospital
Ottawa, Canada

G. Edan
Centre Hospitalier Universitaire
Rennes, France

H.-P. Hartung
Heinrich-Heine-Universität
Düsseldorf, Germany

D. H. Miller
Institute of Neurology
University College
London, UK

X. Montalbán
Hospital Vall d'Hebron
Barcelona, Spain

K. Selmaj
Medical Academy
Lodz, Poland

S. Dahms · L. Bauer · C. Pohl · R. Sandbrink
Bayer Schering Pharma AG
Berlin, Germany

Prof. C. Polman, MD, PhD (✉)
Dept. of Neurology
Academic Hospital Vrije Universiteit
PO Box 7057
1007 MB Amsterdam
The Netherlands
Tel: + 31 204440742
Fax: + 31 204440715
E-Mail: ch.polman@vumc.nl

Data analysis was performed by S. Dahms.

**Disclosures**

C. Polman has received: consulting fees from Biogen Idec, Bayer Schering Pharma AG, Teva, Serono, Novartis, Antisense, and GlaxoSmithKline; lecture fees from Biogen Idec, Bayer Schering Pharma AG, and Teva and grant support from Biogen Idec, Bayer Schering Pharma AG, Wyeth, and GlaxoSmithKline.

L. Kappos has received honoraria and research support from the Swiss MS Society, Aventis, Bayer, Berlex, Biogen Idec, Elan, Genzyme, GlaxoSmithKline, Novartis, Bayer Schering Pharma AG, Serono, Teva, Wyeth, and others. These payments were exclusively used for support of MS research at his department.

M. Freedman has received honoraria from Serono, Bayer Schering Pharma AG, Berlex, Teva, Pfizer, and a research grant from Serono.

G. Edan has received honorariua/consulting fees from Novartis, LFB, Aventis, Serono, Bayer Schering Pharma AG; lecture grants from Biogen Idec, Serono, and grant support from Serono, Bayer Schering Pharma AG and Teva.

H.-P. Hartung has received fees for speaking at scientific symposia and honoraria for consulting ad-hoc from Bayer, Biogen Idec, Bayer Schering Pharma AG, Teva, and Serono.

D. Miller has received: honoraria/consulting fees from Biogen Idec, Wyeth, Novartis, UCB Pharma, and Bristol Myers Squibb; lecture fees from Biogen Idec and Serono and grant support from Biogen Idec, GlaxoSmithKline, and Bayer Schering Pharma AG.

X. Montalbán has received: honoraria/consulting fees, grant support and lecture fees from Biogen Idec, Wyeth, Novartis, Serono, Bayer Schering Pharma AG, Bayer Schering España SA and Teva.

F. Barkhof has served as a consultant to various pharmaceutical companies, including Aventis, Wyeth, Astra, Teva, Biogen, Bayer Schering Pharma AG, and Serono. As the director of the Image Analysis Centre, he has been remunerated for time spent conducting the blind MRI analyses.

L. Bauer, S. Dahms†, C. Pohl, and R. Sandbrink are salaried employees of Bayer Schering Pharma AG.

* Both authors contributed equally to the work.
** See the Appendix for a list of the BENEFIT Study Investigators.

JON 2733

**Abstract** *Background* The BENEFIT study examined interferon beta (IFNB)-1b treatment in patients with clinically isolated syndrome (CIS) and ≥2 clinically silent brain MRI lesions. *Methods* Subgroups of 468 patients (IFNB-1b: $n = 292$; placebo: $n = 176$) were created for demographics, clinical, laboratory, and MRI findings at onset. The 'natural' risk of clinically definite MS (CDMS) over 2 years was estimated by Kaplan Meier statistics in placebo-treated patients; the IFNB-1b treatment effect was analysed by Cox proportional hazards regression. *Results* The risk of CDMS was increased in placebo-treated patients (overall 45 %) if they were younger (< 30 years: 60 %), were cerebrospinal fluid (CSF)-positive (49 %), or had received steroid treatment (48 %). MRI parameters implied a higher risk in placebo-treated patients with ≥9 T2-lesions (48 %) or ≥1 gadolinium (Gd)-enhancing lesions (52 %). The CDMS risk was highest (75 %) in placebo-treated patients with monofocal disease onset displaying MRI disease activity (≥1 Gd-lesion) and dissemination (≥9 T2-lesions). Treatment effects were significant across almost all subgroups including patients with less disease dissemination/activity at onset (monofocal: 55 %; < 9 T2-lesions: 60 %; no Gd-lesions: 57 %) and patients without steroid treatment for the CIS (62 %). Monofocal patients had greater treatment effects if they had ≥9 T2-lesions (61 %), Gd-lesions (58 %), or both (65 %). *Conclusions* This study confirms the impact of age of onset, CSF and MRI findings on risk of conversion from CIS to CDMS. IFNB-1b treatment effect was robust across the study population including patients without MRI disease activity and less clinical or MRI disease dissemination at onset and patients not receiving steroids for the CIS.

**Key words** multiple sclerosis · CIS · MRI

## Introduction

Interferon beta-1b (IFNB-1b) administered subcutaneously (sc) every other day (eod) has been demonstrated to be a beneficial treatment for patients with relapsing-remitting multiple sclerosis (RRMS) [9, 16] and secondary progressive MS [7, 14]. Recently, the BEtaferon/BEtaseron in Newly Emerging MS For Initial Treatment (BENEFIT) study showed that IFNB-1b sc eod is also effective at slowing the development of recurrent active disease from a first clinical event (clinically isolated syndrome; CIS) to the second event, suggesting that this therapy should be considered as a therapeutic option immediately after presentation of the disease [11].

As a well-controlled, multi-centre study with the highest number of CIS patients studied to assess the effect of early IFNB therapy to date, the BENEFIT study was well suited to address questions on risk modification and treatment response in various subgroups of the CIS population, which included patients with or without steroid treatment for the first event.

We performed further analyses on the BENEFIT data to determine (i) the impact of the key demographic, clinical and MRI parameters on the 'natural' risk of MS in placebo-treated patients and (ii) the IFNB-1b treatment effect in subgroups of the study population. We focused on 'time to clinically definite MS' (CDMS) which we considered to have the highest clinical relevance for the evaluation of the disease evolution and treatment response in a CIS population over a 2-year observation period.

## Patients and methods

### Study design, patients, and procedures

The design and main outcomes of the BENEFIT trial have been reported elsewhere [11]. Briefly, the BENEFIT study was a double-blind, placebo-controlled, randomised, parallel-group, multi-centre, phase III study that evaluated the safety, tolerability and efficacy of IFNB-1b 250 µg (8 MIU) sc eod in CIS patients. Eligible patients were aged between 18 and 45 years; had presented with a first clinical event suggestive of MS that lasted for at least 24 hours; had at least 2 clinically silent lesions on a T2-weighted brain MRI scan with a minimum size of 3 mm of which at least 1 was ovoid, periventricular or infratentorial; and had a baseline Expanded Disability Status Scale (EDSS) score between 0 and 5. Patients with signs and symptoms that could be explained by a disease other than MS, and patients with a previous demyelinating event, complete transverse myelitis or bilateral optic neuritis or previous immunosuppressive therapy were excluded.

Patient eligibility was confirmed prior to randomisation by the central reading centre at the VU Medical Center (Amsterdam, The Netherlands) – documented clinical signs and symptoms were used to classify the first demyelinating event, as either monofocal (signs and symptoms could be explained by 1 CNS lesion) or multifocal (signs and symptoms could only be explained by more than 1 CNS lesion). Considerable emphasis was given to a systematic classification of the clinical presentation. In all patients, the local neurologist was asked to document all neurological symptoms reported by the patient at the time of the first event, as well as all clinical signs obtained at the neurological examination. At the central reading centre, all patients were subsequently classified as mono- or multifocal according to a standardised scheme that took all information on patients' signs and symptoms into account, as previously described [21]. Briefly, based on the reported neurological symptoms, the location of the minimum number of lesions that could explain all symptoms was determined. Subsequently, using all information from the standardised neurological examination (i.e. the signs), a decision was made regarding whether or not these abnormalities could be explained by the lesions already identified based on symptoms. If not, the presence of an additional lesion (due to signs) was indicated. This classification was performed by two neurologists who were unaware of the MRI results and treatment allocation.

Patients were randomly assigned in a 5:3 ratio to IFNB-1b 250 µg

or placebo sc eod for up to 24 months or until CDMS was diagnosed using modified Poser criteria [17]. The study treatment was initiated within 60 days after establishment of the first clinical event. Visits were scheduled for collection of EDSS, MRI, and other efficacy data, as well as for safety data, at months 3, 6, 9, 12, 18 and 24. All MRI scans were performed with 0.1 mmol/kg gadolinium (Gd)-diethylenetriamine penta-acetic acid (DTPA). MRI scan assessment was performed centrally at the VU Medical Centre, Amsterdam, The Netherlands by readers who were blinded to clinical data and treatment allocation.

### Statistics

Subgroups were created for demographic characteristics, clinical, laboratory (cerebrospinal fluid; CSF), and MRI findings at disease onset. Patients were differentiated with respect to steroid treatment for the first event, monofocal versus multifocal disease presentation. Patients who had a CSF analysis were differentiated with respect to the absence or presence of positive findings (defined by the occurrence of oligoclonal bands and/or increased intrathecal immunoglobulin G production). Subgroup analyses were also performed in patients with symptoms exclusively indicating optic neuritis or brainstem/cerebellar syndrome or spinal cord syndrome, with or without additional signs (i.e. patients with presenting syndromes similar to those enrolled in the Controlled High-risk subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) on the effect of once-weekly intramuscular IFNB-1a treatment at a dose of 30 μg) [3, 10]. Based on findings of the screening MRI scan, subgroups were created of patients with $<3$ or $\geq 3$ Barkhof criteria, $<9$ or $\geq 9$ hyper-intense lesions on the T2-weighted scan (T2-lesions) and with respect to the absence or presence of Gd-enhancing lesions on the T1-weighted scan (Gd-lesions). Since another study on once-weekly subcutaneous IFNB-1a treatment at a dose of 22 μg (the ETOMS trial) reported that MRI characteristics at baseline are only indicative for risk of CDMS in patients with symptoms indicating monofocal involvement of the CIS (referred to as unifocal in the respective manuscript), the impact of MRI findings was also examined in the subpopulation of monofocal BENEFIT patients [2].

To descriptively show the impact of each of the aforementioned demographic, clinical and MRI characteristics on the 'natural' risk of CDMS independent of the IFNB-1b treatment effect, the 2-year cumulative probability for CDMS was calculated in the placebo-treated group using the Kaplan-Meier product-limit method. Data for patients in whom CDMS did not develop were censored on the date that the patient was last clinically evaluated in the study.

The treatment effect within each subgroup was assessed by unadjusted Cox proportional hazards regressions, giving unadjusted hazard ratios (HRs) with 95 % CIs for the development of CDMS over the 2-year study period. To provide an estimate of the clinical relevance of these findings, HRs are additionally expressed as risk reductions (risk reduction = [1 – HR] × 100 %). All subgroup analyses were performed on a *post hoc* basis and *p*-values were not adjusted for multiple testing.

## Results

A total of 468 patients commenced treatment in the BENEFIT study and contributed to the subgroup analyses (see Fig. 1 for patient disposition); 292 patients received IFNB-1b and 176 received placebo. Of these, 437 patients (93.4 %) completed the study as planned (either reached month 24 or had CDMS before month 24). Further disposition data are presented in Kappos et al. [11]. Baseline characteristics (presented in this manuscript for the variables used for the subgroup analyses) did not differ significantly between treatment groups for any demographic, clinical or MRI variable (Table 1). Approximately half of the patients had either a monofocal or multifocal disease presentation.

### Overall risk of CDMS and treatment effect

As reported previously [11], the risk of CDMS over 2 years was 45 % in the placebo group and 28 % in the IFNB-1b group, based on Kaplan-Meier estimates, resulting in a treatment effect of 47 % according to unadjusted Cox proportional hazards regression (unadjusted HR: 0.53; 95 % CI: 0.39–0.73; $p < 0.0001$) and 50 % using the covariates age, sex, steroid treatment for the first event, mono- or multifocal presentation at disease onset, number of Gd-lesions and T2-lesions on the screening MRI (HR: 0.50; 95 % CI: 0.36–0.70).

**Fig. 1** Patient disposition

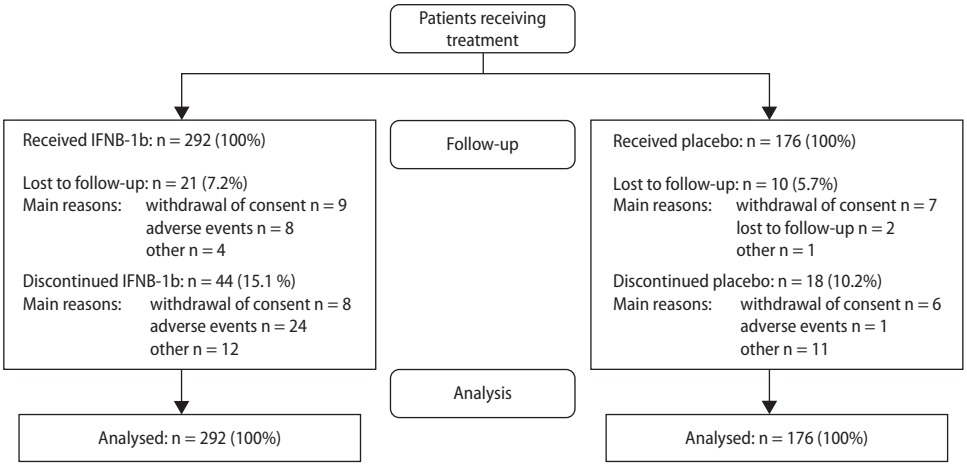


**Table 1** Baseline characteristics for the BENEFIT treatment groups

| | IFNB-1b ($n = 292$) | Placebo ($n = 176$) |
|---|---|---|
| Women (%) | 71 | 70 |
| Age at onset below 30 years (%) | 46 | 50 |
| Steroid treatment for the first event (%) | 72 | 70 |
| CSF sample taken at the first event (%) | 68 | 66 |
| Of these: CSF typical for MS (%)* | 86 | 83 |
| Presenting syndromes (%)** | | |
| Optic neuritis | 23 | 28 |
| Brainstem/cerebellar syndrome | 16 | 16 |
| Spinal cord syndrome | 20 | 17 |
| Mono- or multifocal clinical onset | | |
| Monofocal onset (%) | 52 | 53 |
| Multifocal onset (%) | 48 | 47 |
| Patients with ≥ 3 Barkhof criteria | 65 | 64 |
| Patients with ≥ 9 T2-lesions (%) | 71 | 70 |
| Patients with ≥ 1 Gd-lesion (%) | 44 | 40 |
| In monofocal patients (n = 246): | | |
| Patients with ≥ 9 T2-lesions (%) | 71 | 63 |
| Patients with ≥ 1 Gd-lesion (%) | 44 | 40 |
| Patients with ≥ 9 T2 and ≥ 1 Gd-lesion(s) (%) | 35 | 31 |

* Either positive oligoclonal bands or raised immunoglobulin G index.
** Patients with syndromes exclusively indicating damage to either the optic nerves, brainstem/cerebellum or spinal cord
*CSF* cerebrospinal fluid; *IFNB-1b* interferon beta-1b; *Gd* gadolinium; *MS* multiple sclerosis

## Subgroup analyses

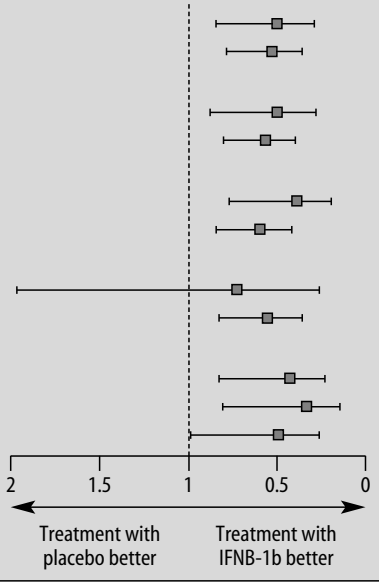
### Demographics, steroid treatment, CSF findings, presenting symptoms

As shown in Table 2, for the placebo-treated CIS patients, the risk of CDMS was higher in younger patients (patients with age at onset of < 30 vs. ≥ 30 years: 60 % vs. 33 %, respectively; 30 years was the median age of the BENEFIT population), in patients who were treated with steroids (vs. without steroid treatment: 48 % vs. 38 %, respectively), and in patients who had positive CSF findings (vs. negative CSF findings: 49 % vs. 36 %, respectively). The risk of CDMS in female and male placebo-treated patients was comparable (45 % vs. 47 %). The risk of CDMS ranged from 42 % in placebo-treated patients with optic neuritis to 51 % in patients with a spinal cord syndrome (43 % in patients with brainstem/cerebellar syndrome).

With respect to demographics, steroid treatment, CSF findings and presenting symptoms, the IFNB-1b treatment effect was significant for all subgroups analysed, with the exception of the small group of CSF-negative patients ($n = 47$ patients). The treatment effect size was comparable (approximately 50 %) in subgroups of different age and gender (Table 2). The treatment effect tended to be more pronounced in patients who did

**Table 2** Risk for CDMS and treatment effects in subgroups: Demographics, steroids, CSF findings, and presenting syndromes

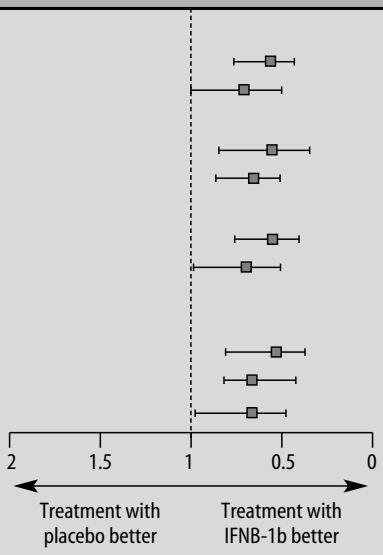
| | n | Risk for CDMS in placebo[a] | Risk reduction by IFNB-1b[b] | Hazard ratio ±95% CI for treatment effect | p-value |
|---|---|---|---|---|---|
| Age | | | | | |
| <30 years | 242 | 60 % | 51 % | | 0.009 |
| ≥30 years | 226 | 33 % | 48 % | | 0.001 |
| Sex | | | | | |
| Male | 137 | 47 % | 52 % | | 0.017 |
| Female | 331 | 45 % | 45 % | | 0.002 |
| Steroids | | | | | |
| No steroids | 136 | 38 % | 62 % | | 0.006 |
| Steroids | 332 | 48 % | 41 % | | 0.004 |
| CSF[c] | | | | | |
| CSF negative | 47 | 36 % | 28 % | | 0.522 |
| CSF positive | 267 | 49 % | 45 % | | 0.004 |
| Presenting syndrome[d] | | | | | |
| Optic neuritis | 116 | 42 % | 58 % | | 0.016 |
| Brainstem/cerebellum syndrome | 74 | 43 % | 68 % | | 0.013 |
| Spinal syndrome | 89 | 51 % | 51 % | | 0.048 |




[a] According to Kaplan-Meier estimates; [b] According to unadjusted proportional hazards regression; risk reduction expressed as (1 – hazard ratio) x 100; [c] CSF was tested in 314 patients; [d] More than one symptom at presentation could occur

**Table 3** Risk for CDMS and treatment effects in subgroups: Clinical and MRI measures indicating dissemination/activity of disease (all patients)

| | n | Risk for CDMS in placebo[a] | Risk reduction by IFNB-1b[b] | Hazard ratio ±95% CI for treatment effect | p-value |
|---|---|---|---|---|---|
| Clinical presentation | | | | | |
| Monofocal | 246 | 47% | 55% | | 0.001 |
| Multifocal | 222 | 44% | 37% | | 0.044 |
| Number of T2 lesions | | | | | |
| 2–8 T2 lesions | 138 | 39% | 60% | | 0.008 |
| ≥9 T2 lesions | 330 | 48% | 43% | | 0.002 |
| Presence of Gd lesions[c] | | | | | |
| No Gd+ lesions | 266 | 41% | 57% | | <0.001 |
| ≥1 Gd+ lesions | 198 | 52% | 38% | | 0.032 |
| Barkhof criteria fulfilled (after mono/multi) | | | | | |
| ≤2 Barkhof criteria | 167 | 42% | 58% | | 0.0036 |
| ≥3 Barkhof criteria | 301 | 47% | 41% | | 0.0058 |
| ≥9 T2 and ≥1 Gd+ lesions | 164 | 55% | 40% | | 0.0323 |




[a] According to Kaplan-Meier estimates; [b] According to unadjusted proportional hazards regression; risk reduction expressed as (1 – hazard ratio) x 100; [c] Gadolinium administration was not performed in four patients

not receive steroid treatment for the first event (vs. with steroid treatment: 62% vs. 41%, respectively). In patients in whom symptoms were restricted to 1 of the 3 areas brainstem/cerebellar, optic nerve and spinal cord, the treatment effect was 51%, 58% and 68%, respectively.

## Clinical disease dissemination as well as MRI disease dissemination and/or activity

As shown in Table 3, the risk of CDMS in placebo-treated patients with a monofocal vs. multifocal disease presentation was 47% vs. 44%. The risk of CDMS was 47% vs. 42% in patients with ≥3 Barkhof criteria vs. <3 Barkhof criteria, 48% vs. 39% in patients with ≥9 T2-lesions vs. <9 T2-lesions, and 52% vs. 41% in patients with at least one Gd-lesion vs. no Gd-lesions on the screening MRI.

A significant IFNB-1b treatment effect was found irrespective of the presence of disease activity and dissemination at presentation (Table 3). The treatment effect tended to be more pronounced in patients without findings indicating disease dissemination clinically or on MRI (treatment effect in monofocal vs. multifocal patients: 55% vs. 37%, respectively; patients with <3 Barkhof criteria vs. ≥3 Barkhof criteria: 58% vs. 41%, respectively; patients with <9 T2-lesions vs. ≥9 T2-lesions: 60% vs. 43%, respectively), but these trends did not reach statistical significance. Similarly, the treatment effect appeared more pronounced in patients without activity on MRI (treatment effect in patients without Gd-lesions vs. ≥1 Gd-lesions: 57% vs. 38%, respectively).

## MRI measures of dissemination and disease activity in the monofocal subpopulation

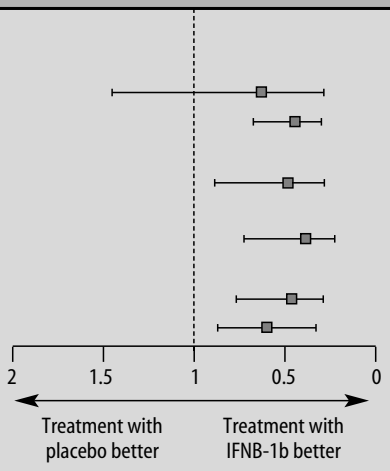
As shown in Table 4, the risk of CDMS in monofocal placebo-treated patients with ≥9 T2-lesions was 55% and 31% in patients with <9 T2-lesions. The risk of CDMS in patients with Gd-lesions at screening was 63%, and 36% in patients without Gd-lesions. The risk of CDMS was highest in monofocal patients with ≥9 T2-lesions and ≥1 Gd-lesion (75%).

A significant treatment effect of IFNB-1b was seen in monofocal patients with ≥9 T2-lesions (61%), and in those with or without Gd-lesions (58% versus 56%, respectively). In monofocal patients with <9 T2-lesions, the treatment effect was less pronounced (41%) and did not reach statistical significance. The treatment effect was most pronounced (65%) in monofocal patients with ≥9 T2-lesions and ≥1 Gd-enhancing lesion.

Of note, neither the risk of CDMS nor the treatment effect was increased in multifocal patients with ≥9 T2-lesions and/or at least 1 Gd-lesion at screening (data not shown).

**Table 4** Risk for CDMS and treatment effects in subgroups: MRI measures indicating subclinical disease dissemination/activity in monofocal patients

| | n | Risk for CDMS in placebo[a] | Risk reduction by IFNB-1b[b] | Hazard ratio ±95% CI for treatment effect | p-value |
|---|---|---|---|---|---|
| Analysis in monofocal patients | 246 | | | | |
| Number of T2 lesions | | | | | |
| 2–8 T2 lesions | 78 | 31% | 41% | | 0.264 |
| ≥9 T2 lesions | 168 | 55% | 61% | | <0.001 |
| Presence of Gd lesions[c] | | | | | |
| No Gd+ lesins | 141 | 36% | 56% | | 0.019 |
| ≥1 Gd+ lesions | 104 | 63% | 58% | | 0.005 |
| ≥9 T2 lesions and ≥1 Gd+ lesions | 82 | 75% | 65% | | 0.004 |
| Barkhof criteria fulfilled | | | | | |
| ≤2 Barkhof criteria | 167 | 42% | 58% | | 0.0036 |
| ≥3 Barkhof criteria | 301 | 47% | 41% | | 0.0058 |




[a] According to Kaplan-Meier estimates; [b] According to unadjusted proportional hazards regression; risk reduction expressed as (1 – hazard ratio) x 100; [c] Gadolinium administration was not performed in one monofocal patient

## Discussion

Certain variables, such as demographic factors, CSF findings, treatment of the first event with steroids, as well as clinical and MRI findings, have all been suggested to impact on the risk of conversion to CDMS in addition to the magnitude of the IFNB-1b treatment effect. We evaluated the effects of these variables on the BENEFIT study population and compared these with results observed in other treatment trials or natural history studies in CIS patients [1–5, 10, 12, 19, 20].

We found conversion to CDMS to occur more frequently in younger patients, which is in line with the CHAMPS study [5]. Accordingly, relapse frequency has previously been recognised to be higher in younger patients [8, 13]. Also, the observation that patients who had positive CSF findings convert more frequently has been reported previously [18, 19]. The finding that patients in whom the presenting episode was treated with intravenous steroids had a higher conversion rate appears to be somewhat surprising in the light of previous observations, mainly from the Optic Neuritis Treatment Trial, which indicated that steroids might have some protective effects [4]. However, in our study, steroid treatment of the first event was not randomly allocated but provided at the discretion of the investigator. Subsequent analysis confirmed that there was an association between the severity of the first event and steroid use in BENEFIT patients (data not shown), hence the rate of conversion paralleled (to some degree) the severity of onset, which is more intuitive.

The rate of CDMS in our patients with optic neuritis was similar to that of patients with a brainstem/cerebellar syndrome and only slightly lower than that of patients with a spinal cord syndrome. This finding is in line with a recent study by Tintore et al. that showed that the CDMS rate was relatively independent of the presenting symptom if additional MRI lesions were present; the presence of at least 2 additional MRI lesions was a necessary inclusion criterion in our study [12]. Tintore et al. also reported that the lower rate of CDMS in patients with optic neuritis observed in some epidemiologic studies may be explained by a somewhat higher percentage of optic neuritis patients who had no lesions on their MRI [6, 12].

The effect of IFNB-1b treatment on prolonging the time to CDMS was robust in the entire cohort as well as all pre-defined subgroups. However, in 2 of the additional subgroups examined here, treatment effect did not reach statistical significance: patients with negative CSF findings and monofocal patients with fewer than 9 T2-lesions. This may be in part due to the low numbers of patients in these groups ($N = 47$ and $N = 78$, respectively). The magnitude of the treatment effect was largely independent of gender and age. It was interesting to note that there was a profound treatment effect in patients who did not receive steroid treatment, which indicated that this cohort with a potentially milder clinical presentation also responded favourably to IFNB-1b treatment. As previously reported, we found that the efficacy of IFNB-1b was robust in both mono- and multifocal CIS patients regardless of whether patients had subclinical disease dissemination (< 9 vs. ≥ 9 T2-lesions)

or MRI activity (no vs. ≥ 1 Gd-lesions) on the screening MRI [11].

Significant and strong treatment effects were also observed in subgroups of patients with symptoms exclusively indicating optic neuritis, brainstem/cerebellar or spinal cord syndromes. In these groups, treatment effects were numerically stronger in patients with brainstem/cerebellar syndromes, followed by optic neuritis and spinal cord syndromes. These results are slightly different from the respective subgroup analyses of data from CHAMPS study, where stronger IFNB-1a effects were observed in patients with spinal cord syndromes, followed by brainstem/cerebellar syndromes and optic neuritis [3].

The BENEFIT study went to considerable effort to centrally characterise the clinical findings as mono- or multifocal in order to standardise the clinical assessment.

Based on this thorough clinical characterisation, the risk of CDMS was not found to be increased in multifocal CIS patients. The contribution of MRI parameters to defining prognosis is essentially restricted to patients without clinical signs of disease dissemination at the time of the CIS. Similar findings were reported for the mono- and multifocal subpopulations of the ETOMS study, as defined on the basis of the local investigator's assessment of patients' symptoms [2].

When analysing the impact of MRI on the IFNB-1b treatment effect in BENEFIT patients with clinically monofocal disease presentation, we observed that the treatment effect appeared to be stronger in monofocal patients with at least 9 T2-lesions or Gd enhancement on the initial MRI. This is in line with the numerically stronger IFNB-1a treatment effect in CIS patients with at least 9 T2-lesions and/or Gd enhancement as reported for the CHAMPS study [3, 15]. Therefore, such MRI findings at the time of the CIS appear to indicate a pronounced treatment effect if patients do not have clinical signs of disease dissemination (as with the monofocal BENEFIT patients) or if they present with optic neuritis, brainstem/cerebellar or spinal cord syndromes (as with those enrolled in CHAMPS). Strikingly, in our study, MRI findings were not a determinant of treatment efficacy in the total study population, in either monofocal or multifocal patients.

Our analyses have some limitations that must be taken into consideration. Most importantly, since all of the subgroup analyses were done on a *post hoc* basis and *p*-values were not adjusted for multiple testing, the presented results are exploratory and do not allow final conclusions for therapeutic decisions. In addition, our analyses were performed on data from a 2-year observation period only, wherein only 45 % of placebo patients reached CDMS; longer-term data with more conversions would help to clarify if the early subgroup trends we observed are significant. Most patients are being followed as part of an ongoing study and part of the planned analysis will be to examine these early trends over time.

In summary, our subgroup analyses show that patients included in the BENEFIT study had a risk factor pattern for conversion to CDMS that is essentially in line with that observed in other studies. There was a robust treatment effect across the study population regardless of: anatomical presentation syndrome, MRI disease burden or activity, clinical features of dissemination or initial treatment with steroids. In monofocal CIS patients MRI measures of subclinical disease dissemination or activity at the time of the CIS seem to be especially valuable indicators of a higher risk of CDMS and also a more pronounced treatment effect.

**Acknowledgment** This study was sponsored by Bayer Schering Pharma AG, Germany.

## Appendix

BENEFIT Study Group

**Principal Investigators:** *Austria:* S. Strasser-Fuchs, Graz; T. Berger, Innsbruck; K. Vass, Wien. *Belgium:* C. Sindic, Brussels; B. Dubois, Leuven; D. Dive, Liège; J. Debruyne, Gent. *Canada:* L. Metz, Calgary; G. Rice, London (ON); P. Duquette, Y. Lapierre, Montreal; M. Freedman, Ottawa; A. Traboulsee, Vancouver; P. O'Connor, Toronto. *The Czech Republic:* P. Štourač, Brno; R. Taláb, Hradec Kralove; O. Zapletalová, Ostrava; I. Kovářová, E. Medová, Praha; J. Fiedler, Plzen. *Denmark:* J. Frederiksen, Glostrup. *France:* B. Brochet, Bordeaux; T. Moreau, Dijon; P. Vermersch, Lille; J. Pelletier, Marseille; G. Edan, Rennes; M. Clanet, Toulouse; P. Clavelou, Clermont Ferrand; C. Lebrun-Frenay, Nice; O. Gout, Paris. *Finland:* M. Kallela, Helsinki; T. Pirttilä, Kuopio; J. Ruutiainen, Turku; K. Koivisto, Seinäjoki; M. Reunanen, Oulu; I. Elovaara, Tampere. *Germany:* A. Villringer, H. Altenkirch, Berlin; K. Wessel, Braunschweig; H.-P. Hartung, W. Steinke, Düsseldorf; H. Kölmel, Erfurt; P. Oschmann, Giessen; R. Diem, Göttingen; A. Dressel, Greifswald; F. Hoffmann, Halle/Saale; K. Baum, Hennigsdorf; S. Jung, Homburg/Saar; H. Felicitas Petereit, Köln; M. Sailer, Magdeburg; J. Köhler, Mainz; N. Sommer, Marburg; R. Hohlfeld, München; K.-H. Henn, Offenbach; A. Steinbrecher, Regensburg; H. Tumani, Ulm; R. Gold, P. Rieckmann, Würzburg; R. Kiefer, Münster. *Hungary:* S. Komoly, G. Gács, G. Jakab, Budapest; L. Csiba, Debrecen; L. Vécsei, Szeged. *Israel:* A. Miller, Haifa; D. Karussis, Jerusalem; J. Chapman, Tel-Hashomer. *Italy:* A. Ghezzi, Gallarate; G. Comi, Milano; P. Gallo, Padova; V. Cosi, Pavia; L. Durelli, Torino. *The Netherlands:* B. Anten, Sittard; L. Visser, Tilburg. *Norway:* K.-M. Myhr, Bergen. *Poland:* A. Szczudlik, Kraków; K. Selmaj, Łódź; Z. Stelmasiak, Lublin; R. Podemski, Wrocław; Z. Maciejek, Bydgoszcz. *Portugal:* L. Cunha, Coimbra. *Slovenia:* S. Sega-Jazbec, Ljubljana. *Spain:* X. Montalbán, T. Arbizu, A. Saiz, Barcelona; J. Bárcena, Barakaldo; R. Arroyo, Madrid; O. Fernández, Málaga; G. Izquierdo, Sevilla; B. Casanova, Valencia. *Sweden:* J. Lycke, Mölndal. *Switzerland:* L. Kappos, Basel; H. Mattle, Bern; K. Beer, St. Gallen; *United Kingdom:* R. Coleman, Aberdeen; J. Chataway, London; J. O'Riordan, Dundee; S. Howell, Sheffield.

**Steering Committee:** G. Edan, M. Freedman, H.-P. Hartung, L. Kappos, D. H. Miller, X. Montalbán, C. H. Polman, L. Bauer, M. Ghazi, R. Sandbrink.

**Eligibility Review Committee:** C. H. Polman, F. Barkhof, B. Uitdehaag.

**CDMS Confirmation Committee:** L. Kappos, A. de Vera, S. Wu.

**Central MRI Analysis:** F. Barkhof.

**Independent Advisory Board:** H. F. McFarland, J. Kesselring, A. J. Petkau, K. V. Toyka.

## References


1. Barkhof F, Filippi M, Miller DH, et al. (1997) Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 120 (Pt 11):2059–2069
2. Barkhof F, Rocca M, Francis G, et al. (2003) Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a. Ann Neurol 53: 718–724
3. Beck RW, Chandler DL, Cole SR, et al. (2002) Interferon beta-1a for early multiple sclerosis: CHAMPS trial subgroup analyses. Ann Neurol 51:481–90
4. Beck RW, Cleary PA, Anderson MM Jr, et al. (1992) A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med 326:581–588
5. CHAMPS Study Group (2002) Predictors of short-term disease activity following a first clinical demyelinating event: analysis of the CHAMPS placebo group. Mult Scler 8:405–409
6. Confavreux C, Vukusic S, Adeleine P (2003) Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 126:770–782
7. European Study Group on interferon beta-1b in secondary progressive MS (1998) Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet 352: 1491–1497
8. Held U, Heigenhauser L, Shang C, Kappos L, Polman C (2005) Predictors of relapse rate in MS clinical trials. Neurology 65:1769–1773
9. IFNB Multiple Sclerosis Study Group (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomised, double-blind, placebo-controlled trial. Neurology 43:655–661
10. Jacobs LD, Beck RW, Simon JH, et al. (2000) Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 343:898–904
11. Kappos L, Polman CH, Freedman MS, et al. (2005) Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 67:1242–1249
12. Korteweg T, Tintore M, Uitdehaag B, et al. (2006) MRI criteria for dissemination in space in patients with clinically isolated syndromes: a multicentre follow-up study. Lancet Neurol 5: 221–227
13. Li DK, Held U, Petkau J, et al. (2006) MRI T2 lesion burden in multiple sclerosis: a plateauing relationship with clinical disability. Neurology 66:1384–1389
14. Miller DH, Molyneux PD, Barker GJ, et al. (1999) Effect of interferon-beta1b on magnetic resonance imaging outcomes in secondary progressive multiple sclerosis: results of a European multicenter, randomized, double-blind, placebo-controlled trial. Ann Neurol 46:850–859
15. O'Connor P (2003) The effects of intramuscular interferon beta-Ia in patients at high risk for development of multiple sclerosis: a post hoc analysis of data from CHAMPS. Clin Ther 25: 2865–2874
16. Paty DW, Li DK (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 43:662–667
17. Poser CM, Paty DW, Scheinberg L, et al. (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13:227–231
18. Soderstrom M, Ya-Ping J, Hillert J, Link H (1998) Optic neuritis: prognosis for multiple sclerosis from MRI, CSF, and HLA findings. Neurology 50:708–714
19. Tintore M, Rovira A, Brieva L, et al. (2001) Isolated demyelinating syndromes: comparison of CSF oligoclonal bands and different MR imaging criteria to predict conversion to CDMS. Mult Scler 7:359–363
20. Tintore M, Rovira A, Rio J, et al. (2005) Is optic neuritis more benign than other first attacks in multiple sclerosis? Ann Neurol 57:210–215
21. Uitdehaag BM, Kappos L, Bauer L, et al. (2005) Discrepancies in the interpretation of clinical symptoms and signs in the diagnosis of multiple sclerosis. A proposal for standardization. Mult Scler 11:227–231