Clinical trial results:
BENEFIT 11 a long-term, follow-up study (16401) of the BENEFIT (304747), BENEFIT Follow-up (305207) Studies and BENEFIT Extension (311129) Study to further evaluate the progress of patients with first demyelinating event suggestive of multiple sclerosis

Summary

EudraCT number	2012-005262-35
Trial protocol	BE SE PT HU CZ NO AT FI DK GB ES IT SI PL
Global end of trial date	18 June 2014

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	BAY86-5046/16401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01795872
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser Wilhelm Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were to describe the disease course (in particular conversion to clinically-definite multiple sclerosis [CDMS]), relapse activity, change in disability, cognitive function, resource use, and employment status, in relation to Interferon beta-1b treatment.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Slovenia: 4
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Italy: 8

Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Israel: 3
Worldwide total number of subjects	278
EEA total number of subjects	258

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	278
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 19 countries from 20 September 2013 (first subject first visit) to 11 April 2014 (last subject last visit). Subjects who did not participate in a physical/face-to-face visit, had the option of being assessed via telephone on selected key outcomes, in an attempt to keep the subject's ascertainment as high as possible.

Pre-assignment

Screening details:

All subjects who were randomized and treated at least once in the BENEFIT Study NCT00185211 (inclusive of subjects, who prematurely discontinued study participation in that study) and enrolled into the BENEFIT 11 Study 2012-005262-35. Of 468 subjects from original BENEFIT study, a total of 278 subjects were enrolled into the BENEFIT 11 study.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)

Arm description:

Initial Betaferon/Betaseron treatment (Interferon beta-1b, IFNB-1b), 250 microgram administered subcutaneously every other day in original BENEFIT (304747 / 92012 / NCT00185211) study; continued in BENEFIT Follow-up (305207 / 91031/ NCT00185211) phase. Subjects at the time of this current study assessment were on any treatment or had no treatment, upon their choice.

Arm type	Experimental
Investigational medicinal product name	Interferon Beta-1b (IFNB-1b)
Investigational medicinal product code	BAY86-5046
Other name	Betaserons, Betaferon
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Initial Betaferon/Betaseron treatment (Interferon beta-1b, IFNB-1b), 250 microgram administered subcutaneously every other day in original BENEFIT (304747 / 92012 / NCT00185211) study; continued in BENEFIT Follow-up (305207 / 91031) phase. Subjects at the time of this current study assessment were on any treatment or had no treatment, upon their choice.

Arm title	Initial Placebo

Arm description:

Initial placebo treatment administered in original BENEFIT (304747 / 92012 / NCT00185211) study; Betaferon/Betaseron, 250 microgram administered subcutaneous every other day offered in BENEFIT Follow-up (305207 / 91031) phase. Subjects at the time of this current study assessment were on any treatment or had no treatment, upon their choice.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo
Started	167	111
Completed	167	109
Not completed	0	2
Death	-	1
Unspecified reason	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)
Reporting group description:	
Initial Betaferon/Betaseron treatment (Interferon beta-1b, IFNB-1b), 250 microgram administered subcutaneously every other day in original BENEFIT (304747 / 92012 / NCT00185211) study; continued in BENEFIT Follow-up (305207 / 91031/ NCT00185211) phase. Subjects at the time of this current study assessment were on any treatment or had no treatment, upon their choice.	
Reporting group title	Initial Placebo
Reporting group description:	
Initial placebo treatment administered in original BENEFIT (304747 / 92012 / NCT00185211) study; Betaferon/Betaseron, 250 microgram administered subcutaneous every other day offered in BENEFIT Follow-up (305207 / 91031) phase. Subjects at the time of this current study assessment were on any treatment or had no treatment, upon their choice.	

Reporting group values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo	Total
Number of subjects	167	111	278
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	31.2	30.8	
standard deviation	± 7.5	± 7.2	-
Gender categorical Units: Subjects			
Female	122	73	195
Male	45	38	83

End points

End points reporting groups

Reporting group title	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)

Reporting group description:

Initial Betaferon/Betaseron treatment (Interferon beta-1b, IFNB-1b), 250 microgram administered subcutaneously every other day in original BENEFIT (304747 / 92012 / NCT00185211) study; continued in BENEFIT Follow-up (305207 / 91031/ NCT00185211) phase. Subjects at the time of this current study assessment were on any treatment or had no treatment, upon their choice.

Reporting group title	Initial Placebo

Reporting group description:

Initial placebo treatment administered in original BENEFIT (304747 / 92012 / NCT00185211) study; Betaferon/Betaseron, 250 microgram administered subcutaneous every other day offered in BENEFIT Follow-up (305207 / 91031) phase. Subjects at the time of this current study assessment were on any treatment or had no treatment, upon their choice.

Subject analysis set title	BENEFIT 11 set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

BENEFIT 11 set is a subset of the FAS and included all subjects who were enrolled in the BENEFIT 11 study (16401) and treated with IFNB-1b (N=167) and Placebo (N=111).

Primary: Time to First Relapse by Kaplan-Meier Estimates

End point title	Time to First Relapse by Kaplan-Meier Estimates

End point description:

Relapses are key features of the clinical presentation of multiple sclerosis. Relapses were assessed retrospectively based on clinical records and subject history. Time to first relapse is the difference from date of first relapse to the date of the BENEFIT baseline visit +1 or time to first relapse is the difference from date of last clinical visit to the date of the BENEFIT baseline visit + 1 (right censored).

End point type	Primary

End point timeframe:

Up to Year 11 (Day 3960)

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[1]	111[2]		
Units: cumulative probability of relapse				
number (not applicable)	71.9	77.5		

Notes:

[1] - BENEFIT 11 set

[2] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1034
Method	Logrank

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

An increase in hazard is indicated by hazard ratios greater than (>) 1. Covariates included actual treatment in BENEFIT (304747; that is IFNB-1b 250 microgram versus placebo), steroid use during first event (yes versus no), onset of disease (multifocal versus monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2 - 4, 5 - 8, >=9).

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0991
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.792
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.045

Primary: Time to Clinically Definite Multiple Sclerosis (CDMS) Represented by Kaplan-Meier Estimates

End point title	Time to Clinically Definite Multiple Sclerosis (CDMS) Represented by Kaplan-Meier Estimates

End point description:

CDMS could be reached due to a qualifying relapse or sustained progression of 1.5 points on the expanded disability status scale (EDSS) as compared to the lowest EDSS obtained during screening or Day 1 and a total EDSS of >=2.5. The validity of CDMS diagnoses was confirmed by a central committee. The EDSS scale quantifies disability in multiple sclerosis (MS) in 8 functional systems, values vary between 0="normal neurological examination" and 10="death due to MS" measured in half-points on an ordinal scale. Time to CDMS = the difference from date of CDMS to the date of Day 1 + 1 or time to CDMS = the difference from date of last clinical visit to the Day 1+1 (right censored).

End point type	Primary

End point timeframe:

Up to Year 11 (Day 3960)

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[3]	111[4]		
Units: cumulative probability of CDMS				
number (not applicable)	68.1	74.8		

Notes:

[3] - BENEFIT 11 set

[4] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1307
Method	Logrank

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

An increase in hazard is indicated by hazard ratios greater than (>) 1. Covariates included actual treatment in BENEFIT (304747; that is, IFNB-1b 250 microgram versus placebo), steroid use during first event (yes versus no), onset of disease (multifocal versus monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2 - 4, 5 - 8, >=9).

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1204
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.799
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.601
upper limit	1.061

Primary: Number of Subjects With Diagnosis of Multiple Sclerosis Within Eleven years after Clinically-Isolated Syndrome (CIS) According to McDonald 2001 and 2010 Criteria

End point title	Number of Subjects With Diagnosis of Multiple Sclerosis Within Eleven years after Clinically-Isolated Syndrome (CIS) According

	to McDonald 2001 and 2010 Criteria[5]

End point description:

MS according to the criteria by McDonald was reached if, in addition to the single clinical demyelinating event, both dissemination in space (DIS) and dissemination in time (DIT) were established by magnetic resonance imaging (MRI) criteria or a new relapse. Number of subjects with diagnosis of MS within 11 years after CIS according to McDonald 2001 and 2010 criteria were reported. In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Primary

End point timeframe:

Year 11

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159[6]	107[7]		
Units: Subjects				
McDonald 2010: DIS (n=159,107)	154	105		
McDonald 2010: DIT (n=159,107)	154	106		
McDonald 2010: McDonald MS (n=159,107)	150	104		
McDonald 2001: DIS (n=155,106)	152	104		
McDonald 2001: DIT (n=155,106)	150	103		
McDonald 2001: McDonald MS (n=155,106)	148	102		

Notes:

[6] - BENEFIT 11 set with evaluable subjects

[7] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Primary: Disease Course as Assessed at the Time of BENEFIT 11

End point title	Disease Course as Assessed at the Time of BENEFIT 11[8]

End point description:

Current diagnosis of MS type were categorized with regard to McDonald 2001 and McDonald 2010 criteria were recorded. CIS and silent disease (no relapse, no sustained EDSS progression and no new MRI lesion), McDonald MS not fulfilling the criteria for CDMS, RRMS (CDMS with relapses without evidence for a secondary disease course), SPMS (CDMS with relapses and evidence for a progressive disease course), Revised diagnosis (other reason than MS found for CIS) and Not assessable. Not assessable means McDonald 2001 and McDonald 2010 criteria could not be judged due to missing MRI scan at BENEFIT 11. Number of subjects with current diagnosis of MS at the time of BENEFIT 11 was assessed.

End point type	Primary

End point timeframe:

Year 11

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[9]	111[10]		
Units: subjects				
McDonald2001: CIS and silent disease	19	15		
McDonald2001: Not fulfilling the criteria for CDMS	10	3		
McDonald2001: RRMS	127	87		
McDonald2001: SPMS	7	5		
McDonald2001: Revised diagnosis	1	0		
McDonald2001: Not assessable	3	1		
McDonald2010: CIS and silent disease	19	15		
McDonald2010: Not fulfilling the criteria for CDMS	10	4		
McDonald2010: RRMS	127	87		
McDonald2010: SPMS	7	5		
McDonald2010: Revised diagnosis	1	0		
McDonald2010: Not assessable	2	0		
McDonald2010: CIS not qualifying for McDonald MS	1	0		

Notes:

[9] - BENEFIT 11 set

[10] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Converting to Secondary Progressive Multiple Sclerosis (SPMS)

End point title	Percentage of Subjects Converting to Secondary Progressive Multiple Sclerosis (SPMS)[11]

End point description:

SPMS was defined for this study as progressive deterioration observed and sustained for at least 6 months with or without superimposed attacks.
Percentage of subjects converting to SPMS were stratified by actual treatment group and baseline EDSS. Baseline EDSS defined as lowest of the EDSS scores obtained during BENEFIT screening or baseline (less than or equal to [<=] median or greater than [>] median). In the below table, "N" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Primary

End point timeframe:

Year 11

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[12]	111[13]		
Units: percentage of subjects				
number (not applicable)				
Baseline EDSS <= median (N=100,64)	9	7.8		
Baseline EDSS > median (N=67,47)	4.5	10.6		

Notes:

[12] - BENEFIT 11 set

[13] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Primary: Time to Secondary Progressive Multiple Sclerosis (SPMS) Represented by Kaplan-Meier Estimates

End point title	Time to Secondary Progressive Multiple Sclerosis (SPMS) Represented by Kaplan-Meier Estimates

End point description:

SPMS was defined for this study as progressive deterioration observed and sustained for at least 6 months with or without superimposed attacks. Time to SPMS was represented by Kaplan-Meier estimates.

End point type	Primary

End point timeframe:

Up to Year 11 (Day 3960)

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[14]	111[15]		
Units: cumulative probability of SPMS				
number (not applicable)	4.8	9		

Notes:

[14] - BENEFIT 11 set

[15] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.525
Method	Logrank

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

An increase in hazard is indicated by hazard ratios greater than (>) 1. Covariates included actual treatment in BENEFIT (304747; that is, IFNB-1b 250 microgram vs. placebo), steroid use during first event (yes versus no), onset of disease (multifocal versus monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2 - 4, 5 - 8, >=9).

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.504
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.751
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.324
upper limit	1.741

Primary: Expanded Disability Status Scale (EDSS) at Year 11

End point title	Expanded Disability Status Scale (EDSS) at Year 11[16]

End point description:

The EDSS scale is a method of quantifying disability in multiple sclerosis in eight functional systems and values vary between 0="normal neurological examination" and 10="death due to MS" measured in half-points on a scale. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = normal neurologic exam; to (5) = ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities; to (10) = death due to MS.

End point type	Primary

End point timeframe:

Year 11

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[17]	111[18]		
Units: subjects				
EDSS score: 0	31	11		
EDSS score: 1	20	18		
EDSS score: 1.5	25	18		
EDSS score: 2	23	20		
EDSS score: 2.5	19	9		
EDSS score: 3	18	11		
EDSS score: 3.5	13	8		
EDSS score: 4	6	8		
EDSS score: 4.5	3	2		
EDSS score: 5	4	0		
EDSS score: 5.5	0	0		
EDSS score: 6	2	5		
EDSS score: 6.5	1	1		
EDSS score: 7	1	0		
EDSS score: 7.5	0	0		
EDSS score: 8	1	0		

Notes:

[17] - BENEFIT 11 set

[18] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Confirmed and Sustained 1-point Expanded Disability Status Scale (EDSS) Progression at Year 11

End point title	Number of Subjects With Confirmed and Sustained 1-point Expanded Disability Status Scale (EDSS) Progression at Year 11[19]

End point description:

The EDSS scale is a method of quantifying disability in multiple sclerosis in eight functional systems and values vary between 0="normal neurological examination" and 10="death due to MS" measured in half-points on a scale. EDSS progression was defined as an increase in the EDSS of at least 1.0 point compared to initial EDSS score or an increase in the EDSS of at least 1.5 points compared to initial EDSS score, if this score was = 0 points. Confirmed EDSS progression status in any of the previous BENEFIT studies (304747, 305207, 311129) was defined as an EDSS progression observed at two consecutive scheduled visits at least 140 days apart from each other. A confirmed EDSS progression is defined as a confirmed EDSS progression in any of the previous BENEFIT studies or EDSS progression in BENEFIT 11. A sustained EDSS progression is defined as a confirmed EDSS progression in any of the previous BENEFIT studies sustained up to and including the BENEFIT 11 visit.

End point type	Primary

End point timeframe:

Year 11

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[20]	111[21]		
Units: subjects				
Confirmed 1-point EDSS progression	75	52		
Sustained 1-point EDSS progression	31	27		

Notes:

[20] - BENEFIT 11 set

[21] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Confirmed 2.5-point Expanded Disability Status Scale (EDSS) Progression at Year 11

End point title	Number of Subjects With Confirmed 2.5-point Expanded Disability Status Scale (EDSS) Progression at Year 11[22]

End point description:

The EDSS scale is a method of quantifying disability in multiple sclerosis in eight functional systems and values vary between 0="normal neurological examination" and 10="death due to MS" measured in half-points on a scale. EDSS progression was defined as an increase in the EDSS of at least 2.5 points compared to initial EDSS score, if this score was <= 3.5 points, or an increase in the EDSS of at least 2.0 points compared to initial EDSS score, if this score was > 3.5 points. Confirmed EDSS increase status in any of the previous BENEFIT studies (304747, 305207, 311129) was defined as an EDSS increase confirmed at scheduled visits after at least 140 days. A confirmed EDSS increase is defined as a confirmed EDSS increase in any of the previous BENEFIT studies or EDSS increase in BENEFIT 11.

End point type	Primary

End point timeframe:

Year 11

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[23]	111[24]		
Units: subjects	19	14		

Notes:

[23] - BENEFIT 11 set

[24] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects who Ever Reached a Disability Status Scale (DSS) 3 and 6

End point title	Percentage of Subjects who Ever Reached a Disability Status Scale (DSS) 3 and 6[25]

End point description:

The DSS 3, and DSS 6 are important milestones in the course of disability progression and were documented if reached by the subject.

End point type	Primary

End point timeframe:

Year 11

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[26]	111[27]		
Units: percentage of subjects				
number (not applicable)				
DSS 3 reached	27.5	28.8		
DSS 6 reached	3	4.5		

Notes:

[26] - BENEFIT 11 set

[27] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Primary: Disability Based Efficacy Domain: Time to Disability Status Scale (DSS) 3 by Kaplan-Meier Estimates

End point title	Disability Based Efficacy Domain: Time to Disability Status Scale (DSS) 3 by Kaplan-Meier Estimates

End point description:

The DSS 3 is an important milestones in the course of disability progression and were documented if reached by the subject. The time point of reaching DSS 3 was obtained retrospectively in the BENEFIT 11 study. Time to respective DSS is the difference between the date of respective DSS and the date of the BENEFIT baseline visit +1. Subjects without event at BENEFIT 11 were censored at the BENEFIT 11 visit. This constituted a right-censored observation. Cumulative probability of reaching DSS 3 at Year 11 were estimated by Kaplan-Meier.

End point type	Primary

End point timeframe:

Up to Year 11 (Day 3960)

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[28]	111[29]		
Units: cumulative probability of DSS 3				
number (not applicable)	19.1	27.6		

Notes:

[28] - BENEFIT 11 set

[29] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5609
Method	Logrank

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

An increase in hazard is indicated by hazard ratios greater than (>) 1. Covariates included actual treatment in BENEFIT (304747; that is IFNB1b 250 microgram versus placebo), steroid use during first event (yes versus no), onset of disease (multifocal versus monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2 4, 5 8, >=9).

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4768
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.525
upper limit	1.351

Primary: Disability Based Efficacy Domain: Time to Disability Status Scale (DSS) 6 by Kaplan-Meier Estimates

End point title	Disability Based Efficacy Domain: Time to Disability Status Scale (DSS) 6 by Kaplan-Meier Estimates

End point description:

The DSS 6 is an important milestones in the course of disability progression and were documented if reached by the subject. The time point of reaching DSS 6 was obtained retrospectively in the BENEFIT 11 study. Time to respective DSS is the difference between the date of respective DSS and the date of the BENEFIT baseline visit +1. Subjects without event at BENEFIT 11 were censored at the BENEFIT 11 visit. This constituted a right-censored observation. Cumulative probability of reaching DSS 6 at Year 11 were estimated by Kaplan-Meier.

End point type	Primary

End point timeframe:

Up to Year 11 (Day 3960)

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[30]	111[31]		
Units: cumulative probability of DSS 6				
number (not applicable)	3	3.7		

Notes:

[30] - BENEFIT 11 set

[31] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5011
Method	Logrank

Primary: Multiple Sclerosis Functional Composite (MSFC) at Year 11

End point title	Multiple Sclerosis Functional Composite (MSFC) at Year 11[32]

End point description:

The MSFC score consists of three subtests (Timed 25 Foot Walk, 9 Hole Peg Test, 3" Paced Auditory Serial Addition Test [PASAT]) whose Z-standardized results (based on baseline values on Day 1 in Study 304747) were combined into a composite score including upper and lower extremities function, and cognitive function. Standardized results (Z-scores) of the subtests and the overall MSFC Z-score as an average of the three Z-scores were derived using baseline data pooled over both treatment arms as reference population. Higher Z-scores reflect a better neurological status.

End point type	Primary

End point timeframe:

Year 11

Notes:

[32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[33]	87[34]		
Units: Z-scores				
median (inter-quartile range (Q1-Q3))	-0.137 (-0.765 to 0.307)	0.014 (-0.548 to 0.269)		

Notes:

[33] - BENEFIT 11 set with evaluable subjects

[34] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Primary: Multiple Sclerosis Severity Score (MSSS) at Year 11

End point title	Multiple Sclerosis Severity Score (MSSS) at Year 11[35]

End point description:

The MSSS added the element of disease duration to the EDSS and was designed to provide a measure of disease severity. It was derived from the EDSS during the data evaluation. The MSSS corrects the EDSS for the duration of disease by using an arithmetical method to compare an individual's disability with the distribution of scores in case of having equivalent disease duration.

End point type	Primary

End point timeframe:

Year 11

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[36]	111[37]		
Units: scores on a scale				
median (inter-quartile range (Q1-Q3))	1.978 (0.641 to 3.246)	1.978 (0.641 to 3.246)		

Notes:

[36] - BENEFIT 11 set

[37] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Primary: Cognitive Function: Paced Auditory Serial Addition Test-3 (PASAT-3) at Year 11

End point title	Cognitive Function: Paced Auditory Serial Addition Test-3 (PASAT-3) at Year 11

End point description:

The Paced Auditory Serial Addition Test (PASAT) is a measure of cognitive function that specifically

assesses auditory information processing speed and flexibility, as well as calculation ability.

End point type	Primary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[38]	90[39]		
Units: PASAT-3 total scores				
median (inter-quartile range (Q1-Q3))	56 (50 to 59)	56 (49 to 59)		

Notes:

[38] - BENEFIT 11 set with evaluable subjects

[39] - BENEFIT 11 set with evaluable subjects

Statistical analyses

Statistical analysis title	Statistical analysis 1: PASAT-3 score at baseline

Statistical analysis description:

Parametric longitudinal linear mixed model, including PASAT-3 score at baseline in addition to time and initial treatment. An inferential statistical analysis included subjects with baseline and post-baseline values, hence number of subjects analysed for this analysis were 222. EudraCT database does auto-addition of number of subjects while reporting an explorative analysis of two treatment groups. Due to this format constraint, below table represents number of subjects in this analysis as 223.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Linear
Parameter estimate	longitudinal linear mixed model
Point estimate	0.7415
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6829
upper limit	0.8001

Statistical analysis title	Statistical analysis 2: Treatment (IFNB-1b)

Statistical analysis description:

Parametric longitudinal linear mixed model, including PASAT-3 score at baseline in addition to time and initial treatment. An inferential statistical analysis included subjects with baseline and post-baseline values, hence number of subjects analysed for this analysis were 222. EudraCT database does auto-addition of number of subjects while reporting an explorative analysis of two treatment groups. Due to this format constraint, below table represents number of subjects in this analysis as 223.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0083
Method	Regression, Linear
Parameter estimate	longitudinal linear mixed model
Point estimate	1.3346
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3461
upper limit	2.323

Statistical analysis title	Statistical analysis 3: Time

Statistical analysis description:

Parametric longitudinal linear mixed model, including PASAT-3 score at baseline in addition to time and initial treatment. An inferential statistical analysis included subjects with baseline and post-baseline values, hence number of subjects analysed for this analysis were 222. EudraCT database does auto-addition of number of subjects while reporting an explorative analysis of two treatment groups. Due to this format constraint, below table represents number of subjects in this analysis as 223.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.016
Method	Regression, Linear
Parameter estimate	longitudinal linear mixed model
Point estimate	-0.0138
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0251
upper limit	-0.0026

Statistical analysis title	Statistical analysis 4: Time*Treatment (IFNB-1b)

Statistical analysis description:

Parametric longitudinal linear mixed model, including PASAT-3 score at baseline in addition to time and initial treatment. An inferential statistical analysis included subjects with baseline and post-baseline values, hence number of subjects analysed for this analysis were 222. EudraCT database does auto-addition of number of subjects while reporting an explorative analysis of two treatment groups. Due to this format constraint, below table represents number of subjects in this analysis as 223.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8947
Method	Regression, Linear
Parameter estimate	longitudinal linear mixed model
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0155
upper limit	0.0136

Statistical analysis title	Statistical analysis 5: PASAT-3 at baseline-ANCOVA

Statistical analysis description:

Parametric analysis of covariance including PASAT-3 score at baseline in addition to initial treatment. An inferential statistical analysis included subjects with baseline and post-baseline values, hence number of subjects analysed for this analysis were 222. EudraCT database does auto-addition of number of subjects while reporting an explorative analysis of two treatment groups. Due to this format constraint, below table represents number of subjects in this analysis as 223.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis 6: Treatment - ANCOVA

Statistical analysis description:

Parametric analysis of covariance including PASAT-3 score at baseline in addition to initial treatment. An inferential statistical analysis included subjects with baseline and post-baseline values, hence number of subjects analysed for this analysis were 222. EudraCT database does auto-addition of number of subjects while reporting an explorative analysis of two treatment groups. Due to this format constraint, below table represents number of subjects in this analysis as 223.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.422
Method	ANCOVA

Primary: Cognitive function: Symbol Digit Modalities Test (SDMT)

End point title	Cognitive function: Symbol Digit Modalities Test (SDMT)

End point description:

The Symbol Digit Modalities Test (SDMT) is a cognitive test for sustained attention, concentration, and

information-processing speed, with a high sensitivity. Nine different geometrical symbols have one corresponding number each. One-hundred-ten symbols are presented without these numbers; the subject must find the matching number from the top line and verbalize the number to the examiner. The subject is allowed to proceed for 90 seconds, and the number of correct responses in 90 seconds is counted as the total correct score. Also, the numbers of correct responses at 30 and 60 seconds were recorded in this study. Total score ranged from 0 (worst outcome) to best (outcome).
In the below table, "N" signifies number of subjects analysed who were evaluable for the specified parameter for each arm, respectively.

End point type	Primary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[40]	111[41]		
Units: correct response				
median (inter-quartile range (Q1-Q3))				
Number of correct responses in 30 sec (N=131,85)	19 (16 to 21)	19 (16 to 21)		
Number of correct responses in 60 sec (N=131,85)	34 (28 to 40)	34 (28 to 40)		
Number of correct responses in 90 sec (N=141,92)	53 (42 to 60)	52.5 (44.5 to 59)		

Notes:

[40] - BENEFIT 11 set

[41] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Time*Treatment (2nd interval, IFNB-1b)

Statistical analysis description:

Parametric linear mixed-effect model including age and education status (categorized as primary school, high school diploma, vocational school diploma, collegial studies, university diploma) at BENFIT 11 in addition to time interval and initial treatment group.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7396
Method	Parametric linear mixed-effect model
Parameter estimate	SDMT scores
Point estimate	0.228
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1195
upper limit	1.5754

Statistical analysis title	Time*Treatment (3rd interval, IFNB-1b)

Statistical analysis description:

Parametric linear mixed-effect model including age and education status (categorized as primary school, high school diploma, vocational school diploma, collegial studies, university diploma) at BENFIT 11 in addition to time interval and initial treatment group.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1352
Method	Parametric linear mixed-effect model
Parameter estimate	SDMT scores
Point estimate	-1.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3734
upper limit	0.3215

Primary: Relapse-Based Efficacy domain: Hazard Ratio for Recurrent Relapses

End point title	Relapse-Based Efficacy domain: Hazard Ratio for Recurrent Relapses[42]

End point description:

A relapse was defined as the appearance of a new neurological abnormality or the reappearance of a neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. The time to the onset of recurrent relapses was determined for each subject according to the counting process representation for recurrent events. Time to a relapse was right censored if a relapse risk period ended without relapse. Based on the Andersen Gill model the hazard ratio for recurrent relapses was estimated with actual treatment in BENEFIT (304747; i.e. IFNB-1b 250 microgram vs. placebo), steroid use during first event (yes vs. no), onset of disease (multifocal vs. monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2-4, 5-8, >=9) included in the model.

End point type	Primary

End point timeframe:

Year 11

Notes:

[42] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT database does not allow to report only one treatment group in statistical analyses section. Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	BENEFIT 11 set			
Subject group type	Subject analysis set			
Number of subjects analysed	278[43]			
Units: ratio				
number (not applicable)	0.821			

Notes:
[43] - BENEFIT 11 set

Attachments (see zip file)	Statistical Analysis_HR for Recurrent

Statistical analyses

No statistical analyses for this end point

Primary: Relapse Based Efficacy Domain: Annualized Relapse Rate

End point title	Relapse Based Efficacy Domain: Annualized Relapse Rate

End point description:

The annualized relapse rate is defined as total number of relapses up to Year 11 divided by the total observation time (last clinical visit minus first day of study treatment administration plus 1 of all subjects) in years.

End point type	Primary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[44]	111[45]		
Units: number of relapses per subject and year				
arithmetic mean (confidence interval 95%)	0.2123 (0.192 to 0.2341)	0.2536 (0.2264 to 0.2831)		

Notes:
[44] - BENEFIT 11 set
[45] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Relapse rate was analyzed by a generalized linear Poisson regression model with individual relapse counts as dependent variable, covariates: actual treatment in BENEFIT (304747; i.e., IFNB-1b 250 microgram vs. placebo), steroid use during first event (yes vs. no), onset of disease (multifocal vs. monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2-4, 5-8, >=9) and offset variable natural log of time (in years) as difference between last clinical and baseline visits+1.

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0094
Method	generalized linear Poisson regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.8224
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7096
upper limit	0.9531

Primary: Time to use of Ambulatory Device Represented by Kaplan-Meier Estimates

End point title	Time to use of Ambulatory Device Represented by Kaplan-Meier Estimates

End point description:

Date of use of ambulatory device is defined as the retrospectively obtained time point of first use/dependence. Time to use of ambulatory device is the difference between the date of first use/dependence and the date of the BENEFIT baseline visit +1.

End point type	Primary

End point timeframe:

Up to Year 11 (Day 3960)

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[46]	111[47]		
Units: cumulative probability of device usage				
number (not applicable)	4.2	7.3		

Notes:

[46] - BENEFIT 11 set

[47] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2895
Method	Logrank

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

An increase in hazard is indicated by hazard ratios greater than (>) 1. Covariates included actual treatment in BENEFIT (304747; that is IFNB-1b 250 microgram versus placebo), steroid use during first event (yes versus no), onset of disease (multifocal versus monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2 - 4, 5 - 8, >=9).

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2951
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.581
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.211
upper limit	1.605

Primary: Time to Dependence of Ambulatory Device for Walking Represented by Kaplan-Meier Estimates

End point title	Time to Dependence of Ambulatory Device for Walking Represented by Kaplan-Meier Estimates

End point description:

Date of dependence from ambulatory device is defined as the retrospectively obtained time point of first use/dependence. Time to dependence from ambulatory device is the difference between the date of first use/dependence and the date of the BENEFIT baseline visit +1. Cumulative probability of dependence of ambulatory device for walking represented by Kaplan-Meier estimates at Year 11.

End point type	Primary

End point timeframe:

Up to Year 11 (Day 3960)

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[48]	111[49]		
Units: probability of subjects				
number (not applicable)	4.2	7.3		

Notes:

[48] - BENEFIT 11 set

[49] - BENEFIT 11 set

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2904
Method	Logrank

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

An increase in hazard is indicated by hazard ratios greater than (>) 1. Covariates included actual treatment in BENEFIT (304747; that is IFNB-1b 250 microgram versus placebo), steroid use during first event (yes versus no), onset of disease (multifocal versus monofocal) and number of T2 lesions on BENEFIT screening MRI (categorized as 2 - 4, 5 - 8, >=9).

Comparison groups	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046) v Initial Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2957
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.582
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.211
upper limit	1.606

Primary: Number of Subjects With Wheelchair Use After 11 years

End point title	Number of Subjects With Wheelchair Use After 11 years[50]

End point description:

End point type	Primary

End point timeframe:

Year 11

Notes:

[50] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[51]	111[52]		
Units: subjects	2	1		

Notes:

[51] - BENEFIT 11 set

[52] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Education Status at Year 11

End point title	Education Status at Year 11

End point description:

Subjects with educational status was categorized as primary school, high school diploma, vocational diploma, collegial studies, university diploma, and missing educational status.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[53]	111[54]		
Units: subjects				
Missing	1	1		
Primary school	17	11		
High school diploma	41	34		
Vocational diploma	28	18		
Collegial studies	33	17		
University diploma	47	30		

Notes:

[53] - BENEFIT 11 set

[54] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Living Conditions at Year 11

End point title	Living Conditions at Year 11

End point description:

Subjects living condition were categorized as 'living alone', 'long term care facility', living with spouse, partner, family', 'other' and 'missing'.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[55]	111[56]		
Units: subjects				
Missing	1	0		
Living alone	20	12		
Long term care facility	3	0		
Living with spouse, partner, family	141	98		
Other	2	1		

Notes:

[55] - BENEFIT 11 set

[56] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Employment Status at Year 11

End point title	Employment Status at Year 11

End point description:

Subject's employment status was categorized as 'retired', 'homemaker', 'long term disability', 'employment less than 20 hours (hrs) per week (hrs/week)', employment more than 20 hours per week, 'early retired', 'other', and 'missing'.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[57]	111[58]		
Units: subjects				
Missing	1	0		
Retired	0	4		
Homemaker	14	9		
Long term disability	7	5		
Employment, less than 20 hrs/week	14	11		
Employment, more than 20 hrs/week	111	68		
Early retired	13	9		
Other	7	5		

Notes:

[57] - BENEFIT 11 set

[58] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Multiple Sclerosis Impact on Employment at Year 11

End point title	Multiple Sclerosis Impact on Employment at Year 11

End point description:

Subject's MS impact on employment was categorized as, 'unrelated to MS condition', 'ceased work due to MS', 'never worked', 'reduced working hours', or missing.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[59]	111[60]		
Units: subjects				
Missing	1	1		
Unrelated to MS condition	108	71		
Ceased work due to MS	22	15		
Never worked	5	1		
Reduced working hours	31	23		

Notes:

[59] - BENEFIT 11 set

[60] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Resource Use: Hospitalization During Last 12 months

End point title	Resource Use: Hospitalization During Last 12 months

End point description:

Hospitalizations were assessed at year 11 only referring to past 12 months. Number of hospitalizations per subject were categorized as, 'none', '1', '2', '3', and '6'.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[61]	111[62]		
Units: subjects				
Number of hospitalizations per subject: none	154	100		
Number of hospitalizations per subject: 1	12	8		
Number of hospitalizations per subject: 2	0	1		
Number of hospitalizations per subject: 3	1	1		
Number of hospitalizations per subject: 6	0	1		

Notes:

[61] - BENEFIT 11 set

[62] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Resource Use: Visits to Other Specialists During Last 12 months

End point title	Resource Use: Visits to Other Specialists During Last 12 months

End point description:

Visits to Other Specialists were assessed at year 11 only referring to past 12 months. The visits to other specialists were categorized as, 'missing', 'no', 'yes', 'never', and 'unsure'. The other specialists includes, neurologist, nurse clinician, home health aide, visiting nurse, physiotherapist, psychiatrist, psychologist, physician, urologist, social worker and gynecologist.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[63]	111[64]		
Units: subjects				
Neurologist: missing	7	1		
Neurologist: no	19	16		
Neurologist: yes	134	86		
Neurologist: never	5	6		
Neurologist: unsure	2	2		
Nurse clinician: missing	14	2		
Nurse clinician: no	39	30		
Nurse clinician: yes	58	34		
Nurse clinician: never	55	45		
Nurse clinician: unsure	1	0		
Home health aide: missing	17	2		
Home health aide: no	24	16		
Home health aide: yes	4	2		
Home health aide: never	120	89		
Home health aide: unsure	2	2		
Visiting nurse: missing	17	2		
Visiting nurse: no	27	19		
Visiting nurse: yes	4	6		
Visiting nurse: never	119	83		
Visiting nurse: unsure	0	1		
Physiotherapist: missing	16	2		
Physiotherapist: no	31	27		
Physiotherapist: yes	37	27		
Physiotherapist: never	80	52		
Physiotherapist: unsure	3	3		
Psychiatrist: missing	16	3		
Psychiatrist: no	28	21		
Psychiatrist: yes	16	13		
Psychiatrist: never	106	73		
Psychiatrist: unsure	1	1		
Psychologist: missing	16	2		
Psychologist: no	34	22		
Psychologist: yes	12	15		
Psychologist: never	103	71		
Psychologist: unsure	2	1		
Physician: missing	12	2		
Physician: no	24	20		
Physician: yes	88	60		
Physician: never	32	25		
Physician: unsure	11	4		
Urologist: missing	16	2		
Urologist: no	33	26		
Urologist: yes	10	12		
Urologist: never	107	70		
Urologist: unsure	1	1		

Social worker: missing	17	3		
Social worker: no	25	21		
Social worker: yes	3	9		
Social worker: never	120	77		
Social worker: unsure	2	1		
Gynecologist: missing	15	4		
Gynecologist: no	38	20		
Gynecologist: yes	53	39		
Gynecologist: never	53	42		
Gynecologist: unsure	8	6		

Notes:

[63] - BENEFIT 11 set

[64] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Resource Use Assessment Questionnaire: Help from Family/Regular Ambulatory Services

End point title	Resource Use Assessment Questionnaire: Help from Family/Regular Ambulatory Services

End point description:

Resources use data was assessed cross-sectionally at 11 years. Supportive care was assessed as "assistance given" for the help from family members or friends with "care given" for the number f hors per week needed, as well as "ambulatory services-yes/no" with sub-categories home care, home help, day care center, meals on wheels and child care for the help from professional caregiver.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[65]	111[66]		
Units: subjects				
Assistance given: missing	0	1		
Assistance given: no	142	92		
Assistance given: yes	25	18		
Care given: missing	1	1		
Care given: none	142	92		
Care given: 1-8 hours/week	16	11		
Care given: 9-16 hours/week	3	6		
Care given: 17-24 hours/week	2	0		
Care given: 32-40 hours/week	1	1		
Care given: >40 hours/week	2	0		
Ambulatory services: missing	0	1		
Ambulatory services: no	162	107		
Ambulatory services: yes	5	3		

Home care: missing	0	1		
Home care: no	167	109		
Home care: yes	0	1		
Home help: missing	0	1		
Home help: no	162	108		
Home help: yes	5	2		
Day care center: missing	0	1		
Day care center: no	167	110		
Meals on wheels: missing	0	1		
Meals on wheels: no	167	110		
Child care: missing	0	1		
Child care: no	167	110		

Notes:

[65] - BENEFIT 11 set

[66] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Resource Use Assessment Questionnaire: Additional Ambulatory Services During Relapse

End point title	Resource Use Assessment Questionnaire: Additional Ambulatory Services During Relapse

End point description:

Resources use data was assessed cross-sectionally at 11 years. Additional ambulatory services during relapse were categorized as, 'missing', 'no', and 'yes'. The additional ambulatory services during relapses were home care, home help, day care center, meals on wheels, and child care.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[67]	111[68]		
Units: subjects				
Ambulatory services during relapse: missing	0	2		
Ambulatory services during relapse: no	161	106		
Ambulatory services during relapse: yes	6	3		
Home care: missing	0	2		
Home care: no	167	109		
Home help: missing	0	2		
Home help: no	164	107		
Home help: yes	3	2		
Day care center: missing	0	2		
Day care center: no	166	108		
Day care center: yes	1	1		

Meals on wheels: missing	0	2		
Meals on wheels: no	166	109		
Meals on wheels: yes	1	0		
Child care: missing	0	2		
Child care: no	166	109		
Child care: yes	1	0		

Notes:

[67] - BENEFIT 11 set

[68] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Resource Use Assessment Questionnaire: Adaptions past 6 months

End point title	Resource Use Assessment Questionnaire: Adaptions past 6 months

End point description:

Resources use data was assessed cross-sectionally at 11 years. The kind of adaptation was categorized as “other part of living”, “star lift”. “ramps”, “alarm”, “work”, “car”, “walking aids”, “wheel chair”, “spectacles”, “special kitchen utensils”, “special hygiene utensils”, “special writing devices” and “ other” with sub-categories as 'missing', 'no', and 'yes'.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[69]	111[70]		
Units: subjects				
Adaptions: missing	0	1		
Adaptions: no	156	100		
Adaptions: yes	11	10		
Other part of living: missing	0	1		
Other part of living: no	165	106		
Other part of living: yes	2	4		
Stair lift: missing	0	1		
Stair lift: no	167	110		
Stair lift: yes	0	0		
Ramps: missing	0	1		
Ramps: no	166	110		
Ramps: yes	1	0		
Alarm: missing	0	1		
Alarm: no	167	110		
Work: missing	0	1		
Work: no	166	109		
Work: yes	1	1		

Car: missing	0	1		
Car: no	162	107		
Car: yes	5	3		
Walking aids: missing	0	1		
Walking aids: no	163	105		
Walking aids: yes	4	5		
Wheel chair: missing	0	1		
Wheel chair: no	165	109		
Wheel chair: yes	2	1		
Spectacles: missing	0	1		
Spectacles: no	167	110		
Special kitchen utensils: missing	0	1		
Special kitchen utensils: no	165	109		
Special kitchen utensils: yes	2	1		
Special hygiene utensils: missing	0	1		
Special hygiene utensils: no	163	110		
Special hygiene utensils: yes	4	0		
Special writing devices: missing	0	1		
Special writing devices: no	167	110		
Other: missing	0	1		
Other: no	165	109		
Other: yes	2	1		

Notes:

[69] - BENEFIT 11 set

[70] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-Reported Outcomes (PRO)-based Efficacy Domain: Center of Epidemiological Studies Depression Scale (CES-D) Total Score at Year 11

End point title	Patient-Reported Outcomes (PRO)-based Efficacy Domain: Center of Epidemiological Studies Depression Scale (CES-D) Total Score at Year 11

End point description:

The CES-D is a measure of depressive symptomatology. The CES-D was a self-administered questionnaire for adults comprising 20 items which evaluated the frequency and severity of depressive symptoms. Subjects were asked to recall the previous 7 days. The total score (0-60) was the sum of the scores of the 20 items. A score of >= 16 suggested a mild to moderate level of depressive symptoms; a score >21 suggested major depressive symptoms.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165[71]	110[72]		
Units: scores on a scale				
arithmetic mean (standard deviation)	12.44 (± 11.91)	12.12 (± 11.15)		

Notes:

[71] - BENEFIT 11 set with evaluable subjects

[72] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: PRO-based Efficacy Domain: Fatigue Scale for Sensory and Motor Functions (FSMC)

End point title	PRO-based Efficacy Domain: Fatigue Scale for Sensory and Motor Functions (FSMC)

End point description:

The cognitive and physical fatigue was assessed by the FSMC. The scale comprised of 20 questions (10 items for physical and 10 items for cognitive fatigue) and could be completed within 5 minutes. The items are rated on a 5-point Likert scale (1=does not apply at all to 5=applies completely). The FSMC total score ranges from 20 to 100 where a higher score is associated with a higher severity of fatigue.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[73]	110[74]		
Units: scores on a scale				
arithmetic mean (standard deviation)	49.08 (± 22.68)	47.23 (± 23.11)		

Notes:

[73] - BENEFIT 11 set with evaluable subjects

[74] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Multiple Sclerosis (FAMS) Trial Outcome Index (TOI) at Year 11

End point title	Functional Assessment of Multiple Sclerosis (FAMS) Trial Outcome Index (TOI) at Year 11

End point description:

The Functional Assessment of Multiple Sclerosis (FAMS) instrument is a self-reporting, multi-dimensional, health-related QoL index for use in subjects diagnosed with MS. It comprised 58 items on 7 subscales (mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being, and additional concerns). FAMS-TOI is the sum of the subscale scores mobility, symptoms, thinking/fatigue, and additional concerns. The items were rated on a 5-point scale (0 to 4). Score range of FAM-TOI is 0 to 148; the higher the score, the higher the quality of life. The evaluation period was the previous 7 days.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[75]	108[76]		
Units: scores on a scale				
arithmetic mean (standard deviation)	110.82 (± 28.09)	111.91 (± 26.08)		

Notes:

[75] - BENEFIT 11 set with evaluable subjects

[76] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Multiple Sclerosis (FAMS) Total Score at Year 11

End point title	Functional Assessment of Multiple Sclerosis (FAMS) Total Score at Year 11

End point description:

The Functional Assessment of Multiple Sclerosis (FAMS) instrument is a self-reporting, multi-dimensional, health-related QoL index for use in subjects diagnosed with MS. It comprised 58 items on 7 subscales: mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being, and additional concerns. The items were rated on a 5-point scale (0 to 4). Total score is sum of all sub-scale scores except 14 items for "Additional concerns", ranging 0 to 176; the higher the score, the higher the quality of life. The evaluation period was the previous 7 days.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[77]	108[78]		
Units: scores on a scale				
arithmetic mean (standard deviation)	133.99 (± 33.03)	134.93 (± 30.67)		

Notes:

[77] - BENEFIT 11 set with evaluable subjects

[78] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: PRO-based Efficacy Domain: European Quality of Life – 5 Dimensions (EQ-5D) Score at Year 11

End point title	PRO-based Efficacy Domain: European Quality of Life – 5 Dimensions (EQ-5D) Score at Year 11

End point description:

The EQ-5D measured five state-of-health dimensions: mobility, self-care, usual activities (work, leisure, etc.), pain/discomfort, and anxiety/depression. Every item had a score of 1 (no problems), 2 (some/moderate problems), or 3 (extreme problems). An individual's health status was defined in a combination of 5 digits. Subjects with missing answers to all questions were not considered for the respective visit.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[79]	110[80]		
Units: subjects				
EQ-5D, question 1, mobility: missing	1	0		
EQ-5D, question 1, mobility: 1	119	79		
EQ-5D, question 1, mobility: 2	46	31		
EQ-5D, question 2, self care: missing	0	0		
EQ-5D, question 2, self care: 1	150	99		
EQ-5D, question 2, self care: 2	15	11		
EQ-5D, question 2, self care: 3	1	0		
EQ-5D, question 3, usual activities: missing	0	0		
EQ-5D, question 3, usual activities: 1	120	77		
EQ-5D, question 3, usual activities: 2	44	31		
EQ-5D, question 3, usual activities: 3	2	2		
EQ-5D, question 4, pain/ discomfort: missing	0	0		

EQ-5D, question 4, pain/ discomfort: 1	88	62		
EQ-5D, question 4, pain/ discomfort: 2	71	48		
EQ-5D, question 4, pain/ discomfort: 3	7	0		
EQ-5D, question 5, anxiety/ depression: missing	0	0		
EQ-5D, question 5, anxiety/ depression: 1	107	60		
EQ-5D, question 5, anxiety/ depression: 2	52	46		
EQ-5D, question 5, anxiety/ depression	7	4		

Notes:

[79] - BENEFIT 11 set with evaluable subjects

[80] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life – 5 Dimensions (EQ-5D) Health-related quality of life (HRQoL) Score at Year 11

End point title	European Quality of Life – 5 Dimensions (EQ-5D) Health-related quality of life (HRQoL) Score at Year 11

End point description:

Based on large population surveys, an algorithm was developed to combine the recordings of each of these five EQ-5D dimensions in 1 single HRQoL score, ranging from +1 (best imaginable HRQoL score) to -0.59 (worst imaginable HRQoL score). A relatively higher score represents better quality of life.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165[81]	110[82]		
Units: scores on a scale				
arithmetic mean (standard deviation)	0.7842 (± 0.2487)	0.7965 (± 0.2)		

Notes:

[81] - BENEFIT 11 set with evaluable subjects

[82] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Started Second Line Therapy at Year 11

End point title	Number of Subjects who Started Second Line Therapy at Year 11

End point description:

Subjects were treated exclusively at the discretion of their treating physician and according to locally

applicable standards and treatment guidelines. Subjects received second line therapy as a MS treatment such as alemtuzumab, cyclophosphamide, ciclosporin, fingolimod, methotrexate, mycophenolate mitoxantrone, natalizumab, etc.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[83]	111[84]		
Units: subjects	31	24		

Notes:

[83] - BENEFIT 11 set

[84] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Started First Disease-Modifying Treatment (DMT) other than IFNB at Year 11

End point title	Number of Subjects who Started First Disease-Modifying Treatment (DMT) other than IFNB at Year 11

End point description:

Subjects were treated exclusively at the discretion of their treating physician and according to locally applicable standards and treatment guidelines. All DMTs other than interferon beta, interferon beta-1a und interferon beta-1b were recorded as DMT other than IFNB.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[85]	111[86]		
Units: subjects	54	39		

Notes:

[85] - BENEFIT 11 set

[86] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Magnet-Resonance Imaging (MRI): Number of Newly Active Lesions

End point title	Magnet-Resonance Imaging (MRI): Number of Newly Active Lesions

End point description:

Contrast-enhanced MRI (with an extracellular gadolinium-based contrast agent) technique was used for the evaluation of brain lesions in MS. Newly active lesions defined as displaying either new enhancement on T1-weighted scans, or non-enhancing on T1-weighted scan but new on T2-weighted scans.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[87]	77[88]		
Units: subjects				
Gd-enhancing lesions on T1: missing	6	4		
Gd-enhancing lesions on T1: 0	96	69		
Gd-enhancing lesions on T1: 1	7	3		
Gd-enhancing lesions on T1: 2-5	5	1		
New lesions in T2: missing	1	1		
New lesions in T2: 0	37	26		
New lesions in T2: 1	13	9		
New lesions in T2: 2-5	34	19		
New lesions in T2: 6-9	10	10		
New lesions in T2: >=10	19	12		
Hypointense lesions on T1: missing	2	2		
Hypointense lesions on T1: 0	17	16		
Hypointense lesions on T1: 1	16	11		
Hypointense lesions on T1: 2-5	33	29		
Hypointense lesions on T1: 6-9	13	10		
Hypointense lesions on T1: >=10	33	9		
Count of cortical lesions: missing	8	3		
Count of cortical lesions: 0	27	21		
Count of cortical lesions: 1	15	16		
Count of cortical lesions: 2-5	39	23		
Count of cortical lesions: 6-9	14	5		
Count of cortical lesions: >=10	11	9		

Notes:

[87] - BENEFIT 11 set with evaluable subjects

[88] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Magnet-Resonance Imaging (MRI): Number of Lesions on T1- and T2-Weighted Scans

End point title	Magnet-Resonance Imaging (MRI): Number of Lesions on T1- and T2-Weighted Scans

End point description:

Contrast-enhanced MRI (with an extracellular gadolinium-based contrast agent) technique was used for the evaluation of brain lesions in MS. Number of lesions on T1- and T2-Weighted scans were recorded. In the below table, "N" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[89]	111[90]		
Units: lesions				
arithmetic mean (standard deviation)				
Hypointense lesions on T1 (N=112,75)	7.1 (± 8.9)	4.7 (± 6.6)		
New lesions in T2 (N=113,76)	6 (± 11.4)	4.9 (± 8)		

Notes:

[89] - BENEFIT 11 set

[90] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Magnet-Resonance Imaging (MRI): Volume of Lesions on T1- and T2-Weighted Scans

End point title	Magnet-Resonance Imaging (MRI): Volume of Lesions on T1- and T2-Weighted Scans

End point description:

Contrast-enhanced MRI (with an extracellular gadolinium-based contrast agent) technique was used for the evaluation of brain lesions in MS. Volume of lesions on T1- and T2-Weighted scans were recorded. In the below table, "N" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[91]	111[92]		
Units: cubic millimeter				

arithmetic mean (standard deviation)				
Gd-enhancing lesion on T1 (N=108,73)	16.6 (± 78.7)	4.1 (± 25.5)		
Hypointense lesion on T1 (N=112,75)	1044.8 (± 2294.8)	470.9 (± 742.5)		
Hyperintense lesion on T2 (N=113,76)	4232.9 (± 5920.4)	3139.9 (± 4447.5)		

Notes:

[91] - BENEFIT 11 set

[92] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Magnet-Resonance Imaging (MRI): Normalized Brain Volume

End point title	Magnet-Resonance Imaging (MRI): Normalized Brain Volume

End point description:

Contrast-enhanced MRI (with an extracellular gadolinium-based contrast agent) technique was used for the evaluation of brain lesions in MS. Brain volume was analysed and reported.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111[93]	72[94]		
Units: cubic centimeter				
arithmetic mean (standard deviation)	1496.6 (± 135.4)	1502.1 (± 114.2)		

Notes:

[93] - BENEFIT 11 set with evaluable subjects

[94] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Optical Coherence Tomography (OCT) Parameter - Retinal Nerve Fiber Layer (RNFL)

End point title	Optical Coherence Tomography (OCT) Parameter - Retinal Nerve Fiber Layer (RNFL)

End point description:

OCT is a noninvasive ocular imaging recognized in MS as a marker of axonal loss. Retinal nerve fiber layer (RNFL) thinning measured by OCT in subjects with MS occurs even in the absence of acute optic neuritis and is associated with worse scores for low-contrast letter acuity and other visual acuity tests. OCT measures peripapillary RNFL.
In the below table, "N" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[95]	111[96]		
Units: micrometer				
arithmetic mean (standard deviation)				
Right eye: Global RNFL at 12 degree (N=41,27)	93.8 (± 11)	89.6 (± 14.3)		
Right eye: Global RNFL at 14 degree (N=42,27)	81.3 (± 8.7)	77 (± 11.5)		
Right eye: Global RNFL at 16 degree (N=43,27)	71.3 (± 8)	67.8 (± 9.9)		
Right eye: PMB RNFL at 12 degree (N=41,27)	48.3 (± 9.6)	47.4 (± 11.1)		
Right eye: PMB RNFL at 14 degree (N=42,27)	42.5 (± 7.5)	41.9 (± 9)		
Right eye: PMB RNFL at 16 degree (N=43,27)	37.7 (± 7.2)	36.2 (± 6.9)		
Right eye: Temp. RNFL at 12 degree (N=41,27)	64.2 (± 12.4)	64 (± 14.7)		
Right eye: Temp. RNFL at 14 degree (N=42,27)	57.9 (± 10.5)	57.4 (± 12.6)		
Right eye: Temp. RNFL at 16 degree (N=43,27)	53.2 (± 9.7)	52.5 (± 10.6)		
Left eye: Global RNFL at 12 degree (N=42,26)	92 (± 11.2)	90.7 (± 15.9)		
Left eye: Global RNFL at 14 degree (N=40,25)	80 (± 9.6)	77.7 (± 14.3)		
Left eye: Global RNFL at 16 degree (N=42,26)	70.6 (± 8.2)	68.4 (± 11.8)		
Left eye: PMB RNFL at 12 degree (N=42,26)	45.3 (± 9.3)	45.2 (± 10.7)		
Left eye: PMB RNFL at 14 degree (N=41,25)	39.6 (± 7.8)	37.7 (± 8.6)		
Left eye: PMB RNFL at 16 degree (N=42,26)	35.6 (± 6.2)	34 (± 6.5)		
Left eye: Temp. RNFL at 12 degree (N=42,26)	58.9 (± 11.3)	58.9 (± 13.7)		
Left eye: Temp. RNFL at 14 degree (N=41,25)	53.2 (± 9.9)	52.1 (± 11.8)		
Left eye: Temp. RNFL at 16 degree (N=42,26)	48.8 (± 8.6)	48.6 (± 9.8)		

Notes:

[95] - BENEFIT 11 set

[96] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Optical Coherence Tomography (OCT) Parameter - Total Macular Volume (TMV)

End point title	Optical Coherence Tomography (OCT) Parameter - Total Macular Volume (TMV)

End point description:

OCT is a noninvasive ocular imaging recognized in MS as a marker of axonal loss. OCT is a potential method for capturing neuronal in addition to axonal degeneration in MS. In the below table, "N" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[97]	111[98]		
Units: cubic millimeter				
arithmetic mean (standard deviation)				
Right eye: TMV (N=48,28)	7.798 (± 1.836)	8.044 (± 1.538)		
Left eye: TMV (N=45,28)	7.775 (± 1.929)	8.002 (± 1.536)		

Notes:

[97] - BENEFIT 11 set

[98] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Optical Coherence Tomography (OCT) Parameter - Pupillo Macular Bundle (PMB)

End point title	Optical Coherence Tomography (OCT) Parameter - Pupillo Macular Bundle (PMB)

End point description:

OCT is a noninvasive ocular imaging recognized in MS as a marker of axonal loss. OCT is a potential method for capturing neuronal in addition to axonal degeneration in MS. In the below table, "N" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[99]	111[100]		
Units: micrometer				
arithmetic mean (standard deviation)				
Right eye: PMB (N=47,26)	309.4 (± 19)	306.7 (± 15)		
Left eye: PMB (N=45,28)	307.4 (± 17.3)	303.8 (± 18.9)		

Notes:

[99] - BENEFIT 11 set

[100] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Optical Coherence Tomography (OCT) Parameter – Ganglion Cell Inner Plexiform Layer

End point title	Optical Coherence Tomography (OCT) Parameter – Ganglion Cell Inner Plexiform Layer

End point description:

OCT is a noninvasive ocular imaging recognized in MS as a marker of axonal loss. OCT is a potential method for capturing neuronal in addition to axonal degeneration in MS. In the below table, "N" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[101]	111[102]		
Units: micrometer				
arithmetic mean (standard deviation)				
Right eye (N=47,31)	78.9 (± 10.1)	77.6 (± 10.5)		
Left eye (N=44,29)	78.6 (± 9.7)	76.8 (± 13.2)		

Notes:

[101] - BENEFIT 11 set

[102] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Secondary: Ophthalmological examination – Optic Nerve Head

End point title	Ophthalmological examination – Optic Nerve Head

End point description:

Standard clinical ophthalmic examination and test were applied for visual assessment and the differential diagnosis of OCT-related findings.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[103]	32[104]		
Units: subjects				
Right eye: Optic nerve head-normal	48	27		
Right eye: Optic nerve head-abnormal	3	5		
Left eye: Optic nerve head-normal	46	27		
Left eye: Optic nerve head-abnormal	5	5		

Notes:

[103] - BENEFIT 11 set with evaluable subjects

[104] - BENEFIT 11 set with evaluable subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Ophthalmological examination - Slit lamp Biomicroscopy

End point title	Ophthalmological examination - Slit lamp Biomicroscopy

End point description:

Standard clinical ophthalmic examination and test were applied for visual assessment and the differential diagnosis of OCT-related findings. Ocular medical and surgical history, visual acuity (Early Treatment Diabetic Retinopathy Study Chart), low-contrast letter acuity (Sloan charts), and eye examination through slit-lamp biomicroscopy were assessed.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[105]	34[106]		
Units: subjects				
Right: Anterior segment and vitreous body-missing	1	1		
Right: Anterior segment and vitreous body-normal	48	31		

Right: Anterior segment and vitreous body-abnormal	1	2		
Right: Pupil-missing	0	0		
Right: Pupil-normal	46	33		
Right: Pupil-abnormal	4	1		
Left: Anterior segment and vitreous body-missing	1	1		
Left: Anterior segment and vitreous body-normal	47	31		
Left: Anterior segment and vitreous body-abnormal	2	2		
Left: Pupil-missing	1	0		
Left: Pupil-normal	49	33		
Left: Pupil-abnormal	0	1		

Notes:

[105] - Subjects with ophthalmological examination from BENEFIT 11 set.

[106] - Subjects with ophthalmological examination from BENEFIT 11 set.

Statistical analyses

No statistical analyses for this end point

Secondary: Ophthalmological examination - Visual Acuity

End point title	Ophthalmological examination - Visual Acuity

End point description:

Standard clinical ophthalmic examination and test were applied for visual assessment and the differential diagnosis of OCT-related findings. Ocular medical and surgical history, visual acuity (Early Treatment Diabetic Retinopathy Study Chart), low-contrast letter acuity (Sloan charts), and eye examination through slit-lamp biomicroscopy were assessed.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[107]	30[108]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Right eye	86.5 (± 6.9)	87.3 (± 7.1)		
Left eye	86.3 (± 5.7)	83.9 (± 8.7)		

Notes:

[107] - Subjects with ophthalmological examination from BENEFIT 11 set.

[108] - Subjects with ophthalmological examination from BENEFIT 11 set.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Vitamin D Intake

End point title	Number of Subjects with Vitamin D Intake

End point description:

Number of subjects with intake of Vitamin D were categorized as, 'since beginning of the BENEFIT study', and 'within the past 12 months'.

End point type	Secondary

End point timeframe:

Year 11

End point values	Initial Interferon Beta-1b (IFNB-1b, Betaseron, BAY86-5046)	Initial Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[109]	111[110]		
Units: subjects				
Since beginning of the BENEFIT study: missing	2	0		
Since beginning of the BENEFIT study: no	136	102		
Since beginning of the BENEFIT study: yes	29	9		
Within the past 12 months: missing	21	11		
Within the past 12 months: no	100	68		
Within the past 12 months: yes	46	32		

Notes:

[109] - BENEFIT 11 set

[110] - BENEFIT 11 set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After signing the informed consent form up to the end of study (approximately 1 year)

Adverse event reporting additional description:

The death reported in this study was not considered an AE or an SAE as per the definitions provided in the protocol, but rather was categorized under "Medical history."

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Overall

Reporting group description:

This overall reporting group includes both of the reporting groups below: Initial Interferon Beta-1b: Initial Betaferon/Betaseron treatment (Interferon beta-1b, IFNB-1b), 250 microgram administered subcutaneously every other day in original BENEFIT (304747 / 92012 / NCT00185211) study. Initial Placebo: Initial placebo treatment administered in original BENEFIT study; Betaferon/Betaseron, 250 microgram administered subcutaneous every other day offered in BENEFIT Follow-up (305207 / 91031) phase. At the time of study 16401 subjects were on any MS disease modifying or on no therapy.

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 278 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 278 (8.63%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	3 / 278 (1.08%)		
occurrences (all)	3		
MICROANGIOPATHY			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
Pregnancy, puerperium and perinatal			

conditions PREGNANCY subjects affected / exposed occurrences (all)	1 / 278 (0.36%) 1		
General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all) INJECTION SITE INFLAMMATION subjects affected / exposed occurrences (all) PYREXIA subjects affected / exposed occurrences (all)	 1 / 278 (0.36%) 1 3 / 278 (1.08%) 3 1 / 278 (0.36%) 2 1 / 278 (0.36%) 1		
Respiratory, thoracic and mediastinal disorders CHRONIC OBSTRUCTIVE PULMONARY DISEASE subjects affected / exposed occurrences (all) ASTHMA subjects affected / exposed occurrences (all) RHINITIS ALLERGIC subjects affected / exposed occurrences (all) PULMONARY EMBOLISM subjects affected / exposed occurrences (all)	 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1		
Psychiatric disorders DYSTHYMIC DISORDER subjects affected / exposed occurrences (all) ANXIETY	 1 / 278 (0.36%) 1		

subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
DEPRESSION			
subjects affected / exposed	4 / 278 (1.44%)		
occurrences (all)	4		
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
RIB FRACTURE			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
LIGAMENT SPRAIN			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
FALL			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
Nervous system disorders			
EPILEPSY			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
MULTIPLE SCLEROSIS RELAPSE			

subjects affected / exposed occurrences (all) DIABETIC NEUROPATHY subjects affected / exposed occurrences (all) PRESYNCOPE subjects affected / exposed occurrences (all)	6 / 278 (2.16%) 11 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1		
Blood and lymphatic system disorders LEUKOPENIA subjects affected / exposed occurrences (all)	 1 / 278 (0.36%) 1		
Eye disorders VISION BLURRED subjects affected / exposed occurrences (all) GLAUCOMA subjects affected / exposed occurrences (all)	 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1		
Gastrointestinal disorders HYPERCHLORHYDRIA subjects affected / exposed occurrences (all)	 1 / 278 (0.36%) 1		
Skin and subcutaneous tissue disorders ECZEMA subjects affected / exposed occurrences (all) PSORIASIS subjects affected / exposed occurrences (all) LIPOATROPHY subjects affected / exposed occurrences (all) SKIN REACTION subjects affected / exposed occurrences (all)	 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1 1 / 278 (0.36%) 1		
Endocrine disorders			

HYPOTHYROIDISM			
subjects affected / exposed	2 / 278 (0.72%)		
occurrences (all)	2		
HYPERTHYROIDISM			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
MENISCAL DEGENERATION			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
Infections and infestations			
FUNGAL SKIN INFECTION			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
PYELONEPHRITIS			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
SINUSITIS			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
PERIODONTITIS			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
ABNORMAL LOSS OF WEIGHT			
subjects affected / exposed	1 / 278 (0.36%)		
occurrences (all)	1		

DIABETES MELLITUS subjects affected / exposed occurrences (all)	1 / 278 (0.36%) 1		
VITAMIN B12 DEFICIENCY subjects affected / exposed occurrences (all)	1 / 278 (0.36%) 1		
HYPERCHOLESTEROLAEMIA subjects affected / exposed occurrences (all)	1 / 278 (0.36%) 1		
HYPERLIPIDAEMIA subjects affected / exposed occurrences (all)	2 / 278 (0.72%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2013	This amendment was included following change: - modifications were made to provide clearer study procedures and provide greater consistency; generalized contrast agent procedure guidance instead of confining to Gadobutrol administration; removed references to magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) imaging procedures; clarification of Adverse events reporting details
05 December 2013	The enrollment date as extended to increase the number of subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Results of the DNA, RNA and Biomarkers were not reported as they would be reported in a separate report, as planned.

Notes: