Clinical trial results:
BENEFIT 15 long-term follow-up study of the BENEFIT and BENEFIT follow-up studies

Summary

EudraCT number	2017-001176-31
Trial protocol	HU ES SE GB AT CZ FI DK BE FR PT IT
Global end of trial date	22 May 2018

Results information

Result version number	v1 (current)
This version publication date	30 May 2019
First version publication date	30 May 2019

Trial information

Trial identification

Sponsor protocol code	BAY86-5046/19215

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03269175
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	22 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives are to describe the course of disease over time including, relapse, disability, cognitive function) and the healthcare resource utilization (HRU) (resource use, employment status), in relation to treatment with IFNB-1b.

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	27 September 2017
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	Austria: 3
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czech Republic: 42
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 6

Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	261
EEA total number of subjects	244

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)	261
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted in 18 countries between 29 SEP 2017 (FPFV) and 24 MAY 2018 (LPLV).

Pre-assignment

Screening details:

Out of the 468 subjects enrolled in the original BENEFIT trial (304747), 261 subjects had been enrolled into the BENEFIT 15 long-term follow-up study with 161 of them in the early IFNB-1b treatment group (treatment received in BENEFIT: IFNB-1b 250 µg) and 100 subjects in the delayed IFNB-1b treatment group (treatment received in BENEFIT: Placebo)

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	Early IFNB-1b treatment

Arm description:

Initial Betaferon/Betaseron treatment (Interferon beta1b, IFNB1b), 250 microgram administered subcutaneously every other day in original BENEFIT study (304747) study; Different to previous BENEFIT studies, the IFNB-1b group is labelled with “Early IFNB-1b Treatment.”

Arm type	Experimental
Investigational medicinal product name	Interferon Beta1b
Investigational medicinal product code	BAY86-5046
Other name	Betaseron, Betaferon
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Initial Betaferon/Betaseron treatment (Interferon beta1b, IFNB1b), 250 microgram administered subcutaneously every other day in original BENEFIT study (304747).

Arm title	Delayed IFNB-1b treatment

Arm description:

Initial placebo treatment in original BENEFIT study (304747); Different to previous BENEFIT studies, the placebo group is labelled with “Delayed IFNB-1b Treatment". If and when a patient assigned to this arm developed Clinically Definite Multiple Sclerosis (CDMS), or after 2 years, Betaferon was offered to use.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Early IFNB-1b treatment	Delayed IFNB-1b treatment
Started	161	100
Completed	161	100

Baseline characteristics

Reporting groups	
Reporting group title	Early IFNB-1b treatment
Reporting group description:	
Initial Betaferon/Betaseron treatment (Interferon beta1b, IFNB1b), 250 microgram administered subcutaneously every other day in original BENEFIT study (304747) study; Different to previous BENEFIT studies, the IFNB-1b group is labelled with "Early IFNB-1b Treatment."	
Reporting group title	Delayed IFNB-1b treatment
Reporting group description:	
Initial placebo treatment in original BENEFIT study (304747); Different to previous BENEFIT studies, the placebo group is labelled with "Delayed IFNB-1b Treatment". If and when a patient assigned to this arm developed Clinically Definite Multiple Sclerosis (CDMS), or after 2 years, Betaferon was offered to use.	

Reporting group values	Early IFNB-1b treatment	Delayed IFNB-1b treatment	Total
Number of subjects	161	100	261
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	30.9	30.9	
standard deviation	± 7.0	± 7.5	-
Gender categorical			
Units: Subjects			
Female	115	69	184
Male	46	31	77

End points

End points reporting groups

Reporting group title	Early IFNB-1b treatment

Reporting group description:

Initial Betaferon/Betaseron treatment (Interferon beta1b, IFNB1b), 250 microgram administered subcutaneously every other day in original BENEFIT study (304747) study; Different to previous BENEFIT studies, the IFNB-1b group is labelled with "Early IFNB-1b Treatment."

Reporting group title	Delayed IFNB-1b treatment

Reporting group description:

Initial placebo treatment in original BENEFIT study (304747); Different to previous BENEFIT studies, the placebo group is labelled with "Delayed IFNB-1b Treatment". If and when a patient assigned to this arm developed Clinically Definite Multiple Sclerosis (CDMS), or after 2 years, Betaferon was offered to use.

Subject analysis set title	BENEFIT 15 set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set was a subset of the FAS and included all subjects who were enrolled in the BENEFIT 15 study (19215).

Primary: Number of subjects with diagnosis of multiple sclerosis within fifteen 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 fifteen years after Clinically-Isolated Syndrome (CIS) according to McDonald 2001 and 2010 Criteria[1]

End point description:

The McDonald criteria (2001 and 2010, respectively) were applied to identify subjects who developed MS according to the respective criteria. Subjects participating in BENEFIT 15 without valid MRI assessment at BENEFIT 15 who did not develop McDonald MS in the previous studies (BENEFIT, BENEFIT follow-up study, BENEFIT extension study, BENEFIT 11) and who did not develop CDMS were excluded from the analysis.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

Notes:

[1] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	98		
Units: Subjects				
McDonald 2001: McDonald MS (n=157, 98)	149	94		
McDonald 2001: McDonald MS (n=155, 97)	146	92		

Statistical analyses

No statistical analyses for this end point

Primary: Disease course since start of BENEFIT as assessed at the time of BENEFIT 15

End point title	Disease course since start of BENEFIT as assessed at the time of BENEFIT 15[2]

End point description:

The disease course was assessed and categorized (CIS without MRI activity, relapses or disability progression after first Event; CIS with MRI activity but no relapses or disability progression after first Event; Relapsing-remitting MS [RRMS] ; Secondary progressive MS [SPMS]; Primary progressive MS [PPMS].

End point type	Primary

End point timeframe:

Over 15 years since the subject`s first clinical event

Notes:

[2] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
CIS without MRI activity	12	7		
CIS with MRI activity	9	7		
RRMS	130	80		
SPMS	9	6		
PPMS	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Time to first relapse

End point title	Time to first relapse

End point description:

Date of the first relapse is defined as the onset date of the first neurological event that is classified as a relapse and has an onset not earlier than the BENEFIT baseline visit. The observed median "Time to first relapse" was reported.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Days				
median (confidence interval 95%)	1729 (1334 to 2245)	1098 (672 to 1948)		

Statistical analyses

Statistical analysis title	Time to first relapse
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2239
Method	Logrank

Primary: Time to recurrent relapse

End point title	Time to recurrent relapse[3]

End point description:

This efficacy variable is based on the temporal occurrence of relapses. In general, there was more than one of such periods per subject, so that each subject is represented as a series of observations (rows of data). The first period starts with the baseline visit in BENEFIT (day 1). Periods that end without a relapse were indicated by a censoring variable (0 indicates censored, 1 indicates relapse); final censoring date is the date of final clinical visit and BENEFIT 15 visit, respectively.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

Notes:

[3] - 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: No statistical Analysis for this endpoint.

End point values	BENEFIT 15 set			
Subject group type	Subject analysis set			
Number of subjects analysed	259			
Units: ratio				
number (not applicable)	0.917			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized relapse rate

End point title	Annualized relapse rate[4]

End point description:

Relapse rate was analyzed by a generalized linear Poisson regression model, with individual relapse counts as dependent variable, actual treatment group and the set of covariates and offset variable natural log of time (in years) in the period being analyzed.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

Notes:

[4] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: rate				
number (confidence interval 95%)	0.1956 (0.1786 to 0.2138)	0.2163 (0.1937 to 0.2408)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to conversion to Clinically-Definite Multiple Sclerosis (CDMS)

End point title	Time to conversion to Clinically-Definite Multiple Sclerosis (CDMS)

End point description:

Clinically-definite MS is reached for a patient if either of the following is documented: New neurological event (relapse), i.e., the appearance of new neurologicalabnormality or reappearance of a neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event; OR Sustained progression of 1.5 points on the EDSS and a total EDSS of 2.5.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: cumulative probability of CDMS				
number (not applicable)	70.8	73.0		

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment

Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2052
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.823
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.609
upper limit	1.112
Variability estimate	Standard deviation

Statistical analysis title	Statistical analysis 1
Comparison groups	Delayed IFNB-1b treatment v Early IFNB-1b treatment
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2555
Method	Logrank

Primary: Time to conversion to Secondary Progressive Multiple Sclerosis (SPMS)

End point title	Time to conversion to Secondary Progressive Multiple Sclerosis (SPMS)[5]

End point description:

The diagnosis of Secondary progressive multiple sclerosis (SPMS) is defined by sustained disability progression in the absence of relapse, with or without superimposed relapses. Specifically, sustained disability progression is defined for this study as an increase in EDSS: by 1 point if the last EDSS before conversion was <= 5.5; OR by 0.5 points if the last EDSS before conversion was above 5.5,

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: cumulative probability of SPMS				
number (not applicable)	10.2	9.9		

Statistical analyses

No statistical analyses for this end point

Primary: Expanded Disability Status Scale these scores (EDSS score) for disability assessed by the investigator during the neurological examination

End point title	Expanded Disability Status Scale these scores (EDSS score) for disability assessed by the investigator during the neurological examination[6]

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 halfpoints 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:

15 years after the subject´s first clinical event

Notes:

[6] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
EDSS score: 0	15	13		
EDSS score: 1	22	15		
EDSS score: 1.5	24	10		
EDSS score: 2	25	14		
EDSS score: 2.5	14	10		
EDSS score: 3	14	9		
EDSS score: 3.5	10	11		
EDSS score: 4	14	7		
EDSS score: 4.5	5	2		
EDSS score: 5	3	1		
EDSS score: 5.5	3	1		
EDSS score: 6	3	3		
EDSS score: 6.5	4	2		
EDSS score: 7	4	1		
EDSS score: 7.5	0	0		
EDSS score: 8	1	0		
EDSS score: 8.5	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with confirmed and sustained 1-point EDSS progression (Disability progression)

End point title	Number of subjects with confirmed and sustained 1-point EDSS progression (Disability progression)[7]

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 halfpoints 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. A confirmed EDSS progression is defined as a confirmed EDSS progression in any of the previous BENEFIT studies or EDSS progression in BENEFIT 15. 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 15 visit.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

Notes:

[7] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
Confirmed 1-point EDSS progression	91	49		
Sustained 1-point EDSS progression	47	34		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with confirmed 2.5-point EDSS progression (Disability progression)

End point title	Number of subjects with confirmed 2.5-point EDSS progression (Disability progression)[8]

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 halfpoints 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. A confirmed EDSS increase is defined as a confirmed EDSS increase in any of the previous BENEFIT studies or EDSS increase in BENEFIT 15.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects	32	18		

Statistical analyses

No statistical analyses for this end point

Primary: Multiple Sclerosis Functional Composite (MSFC) score (Neurological status)

End point title	Multiple Sclerosis Functional Composite (MSFC) score (Neurological status)[9]

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:

Over 15 years since the subject´s first clinical event

Notes:

[9] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	66		
Units: Z-scores				
median (inter-quartile range (Q1-Q3))	-0.104 (-0.822 to 0.351)	-0.060 (-0.705 to 0.281)		

Statistical analyses

No statistical analyses for this end point

Primary: Paced Auditory Serial Addition Test (PASAT-3) score (Cognitive function)

End point title	Paced Auditory Serial Addition Test (PASAT-3) score (Cognitive function)[10]

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:

Over 15 years since the subject´s first clinical event

Notes:

[10] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	67		
Units: PASAT-3 total scores				
median (inter-quartile range (Q1-Q3))	55.0 (50.0 to 58.0)	54.0 (49.0 to 57.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to use of ambulatory device

End point title	Time to use of ambulatory device

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:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: cumulative probability of device				
number (not applicable)	11.2	9.0		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4918
Method	Logrank

Statistical analysis title	Statistical analysis 2
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8257
Method	PH regression
Parameter estimate	Hazard ratio (HR)
Point estimate	1.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.482
upper limit	2.494

Primary: Time to dependence on ambulatory device

End point title	Time to dependence on ambulatory device

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 15.

End point type	Primary

End point timeframe:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: probability for subjects				
number (not applicable)	8.7	9.0		

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6811
Method	PH Regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.834

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.351
upper limit	1.98

Statistical analysis title	Statistical analysis 1
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9479
Method	Logrank

Primary: Time to use of wheelchair

End point title	Time to use of wheelchair[11]

End point description:

Date of use of wheelchair is defined as the retrospectively obtained time point of first use/dependence. Time to use of wheelchair 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:

Over 15 years since the subject´s first clinical event

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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects	6	2		

Statistical analyses

No statistical analyses for this end point

Primary: Employment status (Standardized questions)

End point title	Employment status (Standardized questions)[12]

End point description:

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

End point type	Primary

End point timeframe:

At one single visit, 15 years after the subject’s first clinical event

Notes:

[12] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
Missing	3	1		
Unemployed	11	3		
Retired	6	3		
Homemaker	7	4		
Long term disability	12	7		
Employment, less than 20 hrs/week	13	17		
Employment, more than 20 hrs/week	91	52		
Early retired	15	9		
Other	3	4		

Statistical analyses

No statistical analyses for this end point

Primary: Multiple sclerosis impact on employment

End point title	Multiple sclerosis impact on employment[13]

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	Primary

End point timeframe:

At one single visit, 15 years after the subject’s first clinical event

Notes:

[13] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
Missing	12	9		
Unrelated to MS condition	96	59		
Ceased work due to MS	23	11		
Never worked	6	0		
Reduced working hours	24	21		

Statistical analyses

No statistical analyses for this end point

Primary: Resource use assessment questions: Help from family/regular ambulatory services

End point title	Resource use assessment questions: Help from family/regular ambulatory services[14]

End point description:

Resources use data was assessed cross-sectionally at 15 years. Supportive care was assessed as "assistance given" for the help from family members or friends with "care given" for the number of hours 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	Primary

End point timeframe:

At one single visit, 15 years after the subject's first clinical event

Notes:

[14] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
Assistance given: missing	3	0		
Assistance given: no	132	86		
Assistance given: yes	26	14		
Care given: missing	7	0		
Care given: none	132	86		
Care given: 1-8 hours/week	8	9		
Care given: 9-16 hours/week	7	3		
Care given: 17-24 hours/week	1	1		
Care given: 25-32 hours/week	1	0		
Care given: 33-40 hours/week	2	1		
Care given: >40 hours/week	3	0		
Ambulatory services: missing	3	0		
Ambulatory services: no	155	99		
Ambulatory services: yes	3	1		
Home care: missing	3	0		
Home care: no	158	99		
Home care: yes	0	1		
Home help: missing	3	0		
Home help: no	155	99		
Home help: yes	3	1		
Day care center: missing	3	0		

Day care center: no	158	100		
Meals on wheels: missing	3	0		
Meals on wheels: no	157	99		
Meals on wheels: yes	1	1		
Child care: missing	3	0		
Child care: no	158	100		

Statistical analyses

No statistical analyses for this end point

Primary: Resource use assessment questions: Additional ambulatory services during relapse

End point title	Resource use assessment questions: Additional ambulatory services during relapse[15]

End point description:

Resources use data was assessed cross-sectionally at 15 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	Primary

End point timeframe:

At one single visit, 15 years after the subject's first clinical event

Notes:

[15] - 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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
Ambulatory services during relapse: missing	4	0		
Ambulatory services during relapse: no	154	98		
Ambulatory services during relapse: yes	3	2		
Home care: missing	4	0		
Home care: no	156	99		
Home care: yes	1	1		
Home help: missing	4	0		
Home help: no	156	99		
Home help: yes	1	1		
Day care center: missing	4	0		
Day care center: no	157	100		
Meals on wheels: missing	4	0		
Meals on wheels: no	156	99		
Meals on wheels: yes	1	1		
Child care: missing	4	0		
Child care: no	156	99		
Child care: yes	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Resource use assessment questions: Adaptions (past 6 months)

End point title	Resource use assessment questions: Adaptions (past 6 months)[16]

End point description:

Resources use data was assessed cross-sectionally at 15 years using diferent categories "adaptations", “other part of living”, “stair 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	Primary

End point timeframe:

At one single visit, 15 years after the subject’s first clinical event

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: No statistical Analysis for this endpoint.

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	100		
Units: Subjects				
Adaptions: missing	3	0		
Adaptions: no	142	87		
Adaptions: yes	16	13		
Other part of living: missing	3	0		
Other part of living: no	150	97		
Other part of living: yes	8	3		
Stair lift: missing	3	0		
Stair lift: no	157	100		
Stair lift: yes	1	0		
Ramps: missing	3	0		
Ramps: no	156	98		
Ramps: yes	2	2		
Alarm: missing	3	0		
Alarm: no	158	99		
Alarm: yes	0	1		
Work: missing	3	0		
Work: no	156	98		
Work: yes	2	2		
Car: missing	3	0		
Car: no	156	97		
Car: yes	2	3		
Walking aids: missing	3	0		

Walking aids: no	149	92		
Walking aids: yes	9	8		
Wheel chair: missing	3	0		
Wheel chair: no	156	98		
Wheel chair: yes	6	2		
Spectacles: missing	3	0		
Spectacles: no	156	100		
Spectacles: yes	2	0		
Special kitchen utensils: missing	3	0		
Special kitchen utensils: no	155	99		
Special kitchen utensils: yes	3	1		
Special hygiene utensils: missing	3	0		
Special hygiene utensils: no	153	97		
Special hygiene utensils: yes	5	3		
Special writing devices: missing	3	0		
Special writing devices: no	158	100		
Other: missing	3	0		
Other: no	157	98		
Other: yes	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Symbol Digit Modalities Test score (SDMT score)

End point title	Symbol Digit Modalities Test score (SDMT score)

End point description:

The Symbol Digit Modalities Test (SDMT) is a cognitive test for sustained attention, concentration, and information processing speed. The numbers of correct responses after 90 seconds were reported, and standardized results (Z-scores) for the number of correct responses after 90 seconds were calculated.

End point type	Secondary

End point timeframe:

At one single visit, 15 years after the subject's first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	69		
Units: correct responses				
arithmetic mean (standard deviation)				
Number of correct responses in 90 sec	51.0 (± 12.6)	50.6 (± 11.6)		
Z-score of correct responses in 90 sec	0.010 (± 1.031)	-0.020 (± 0.946)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relation of SDMT and FSMC (Fatigue Scale for Motor and Cognitive Functions)

End point title	Relation of SDMT and FSMC (Fatigue Scale for Motor and Cognitive Functions)

End point description:

SDMT number of correct responses in 90 seconds and Fatigue Scale for Motor and Cognitive Functions (FSMC) Cognitive scale were summarized for the subjects who had non-missing values for both, SDMT in 90 seconds and FSMC Cognitive scale. Spearman partial rank-order correlation of SDMT number of correct responses with FSMC cognitive scale score while adjusting for age and sex were estimated.

End point type	Secondary

End point timeframe:

At one single visit, 15 years after the subject's first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: correlation coefficient				
number (not applicable)				
Correct responses in 90 sec	-0.333	-0.391		

Statistical analyses

No statistical analyses for this end point

Secondary: Relation of mental processing speed and MRI parameters

End point title	Relation of mental processing speed and MRI parameters

End point description:

Mental processing speed was defined as the sum of the adjusted PASAT-3 Z-scores and SDMT Z-scores (for number of correct responses in 90 seconds). MRI parameters of interest included: volume of hyperintense lesions on T2 (mm^3), volume of hypointense lesions on T1 (mm^3), normalized brain volume (cm^3), mean cortical thickness (mm), normalized thalamic volume (mm^3), mean upper spinal cord area (mm^2). Spearman partial rank-order correlation coefficients were estimated.

End point type	Secondary

End point timeframe:

At one single visit, 15 years after the subject's first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	46		
Units: correlation coefficient				
number (not applicable)				
Volume of hyperintense lesions on T2	-0.162	-0.191		
Volume of hypointense lesions on T1	-0.137	-0.201		
Normalized brain volume	0.171	-0.040		
Mean cortical thickness	0.265	0.184		
Normalized thalamic volume	0.312	0.349		
Mean upper spinal cord area	0.216	0.126		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The EQ-5D measures 5 state-of-health dimensions: mobility, self-care, usual activities (work, leisure, etc.), pain/discomfort, and anxiety/depression. Every item has a score of 1 (no problems), 2 (some/moderate problems), or 3 (extreme problems). Accordingly, the individual’s health status was defined in a combination of 5 digits.

End point type	Secondary

End point timeframe:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	100		
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.7807 (± 0.2492)	0.7860 (± 0.2178)		

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life-5 Dimensions Visual Analog Scale (EQ-5D VAS) score

End point title	European Quality of Life-5 Dimensions Visual Analog Scale (EQ-5D VAS) score

End point description:

A second assessment recorded the perception of the subject's overall health on a 100-mm visual analog scale (VAS), with 0 denoting death and 100 denoting perfect health. The VAS was only used in subjects who attended a clinical visit in BENEFIT 15 (i.e. regular assessment), but not in subjects with a phone assessment.

End point type	Secondary

End point timeframe:

Over 15 years since the subject`s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	69		
Units: Scores on a scale				
arithmetic mean (standard deviation)	76.00 (± 20.68)	78.30 (± 19.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Multiple Sclerosis (FAMS score)

End point title	Functional Assessment of Multiple Sclerosis (FAMS score)

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 comprises 58 items and has 7 subscales: mobility, symptoms, emotional well-being, general contentment, thinking, fatigue, and family/social well-being. The FAMS total score (range 0-176) is the sum of all subscales except the 14 items from the subscale additional concerns. A higher FAMS total score reflects a higher quality of life.

End point type	Secondary

End point timeframe:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	100		
Units: Scores on a scale				
arithmetic mean (standard deviation)	133.30 (± 32.07)	131.56 (± 32.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue Scale for Motor and Cognitive Functions (FSMC score)

End point title	Fatigue Scale for Motor and Cognitive Functions (FSMC score)

End point description:

Fatigue Scale for Motor and Cognitive Functions (FSMC) measures both, cognitive and physical fatigue, equally. The Scale comprises 20 questions (10 items for physical and 10 items for cognitive fatigue). 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:

At one single visit, 15 years after the subject's first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	100		
Units: scores on a scale				
arithmetic mean (standard deviation)	48.43 (± 22.04)	49.01 (± 22.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Center of Epidemiological Studies for Depression (CES-D) score

End point title	Center of Epidemiological Studies for Depression (CES-D) score

End point description:

The Center of Epidemiological Studies for Depression Scale (CES-D) is a measure of depressive symptomatology. The CES-D is a self-administered questionnaire for adults comprising 20 items which evaluate the frequency and severity of depressive symptoms. The total score (0-60) is the sum of the scores of the 20 items. A score of ≥16 suggests a mild to moderate level of depressive symptoms.

End point type	Secondary

End point timeframe:

At one single visit, 15 years after the subject's first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	100		
Units: scores on a scale				
arithmetic mean (standard deviation)	12.61 (± 10.99)	12.96 (± 11.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to second line therapy

End point title	Time to second line therapy

End point description:

Time to second line therapy is the difference between the date of second line therapy and the date of the BENEFIT baseline visit + 1. This constitutes an uncensored observation. Number of subjects with 2nd line therapy at Year 15 (5400 days) was reported.

End point type	Secondary

End point timeframe:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	68		
Units: subjects				
number (not applicable)	42	22		

Statistical analyses

Statistical analysis title	Time to 2nd line therapy
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4203
Method	Logrank

Secondary: Time to first Disease-Modifying Therapies (DMT) other than IFNB-1b

End point title	Time to first Disease-Modifying Therapies (DMT) other than IFNB-1b

End point description:

Time to first DMT other than IFNB is the difference between the date of first DMT other than IFNB and the date of the BENEFIT baseline visit + 1. This constitutes an uncensored observation. Number of subjects with DMT other than IFNB at Year 15 (5400 days) was reported.

End point type	Secondary

End point timeframe:

Over 15 years since the subject´s first clinical event

End point values	Early IFNB-1b treatment	Delayed IFNB-1b treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	48		
Units: subjects				
number (not applicable)	74	48		

Statistical analyses

Statistical analysis title	Time to first DMT other than IFNB
Comparison groups	Early IFNB-1b treatment v Delayed IFNB-1b treatment
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8409
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected after signing the informed consent until 30 days after end of the BENEFIT 15 study

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Overall

Reporting group description:

This overall reporting group includes both of the reporting groups below: 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. 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 19215 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 / 261 (0.00%)		
number of deaths (all causes)	0		
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	2 / 261 (0.77%)		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences (all)	1		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 261 (0.38%) 1		
Rhinitis subjects affected / exposed occurrences (all)	1 / 261 (0.38%) 1		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 261 (0.38%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

An integrated statistical analysis was performed according to the study protocol, including 468 subjects from the previous studies 304747, 305207, 311129, 16401 and the present study 19215.

Notes: