Clinical trial results:
Open Label Study to Evaluate the Effect, Safety and Tolerability of 250µg (8 MIU) Interferon Beta 1b (Betaferon) Given Subcutaneously Every Other Day (for 24 Weeks) in Patients of Chinese Origin With Multiple Sclerosis

Summary

EudraCT number	2014-004613-93
Trial protocol	Outside EU/EEA
Global end of trial date	26 September 2008

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	05 July 2015

Trial information

Trial identification

Sponsor protocol code	BAY86-5046/91386

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00370071
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol number: 308720, Other: MP-00102

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 September 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that interferon beta 1b treatment in multiple sclerosis (MS) subjects of Chinese origin positively impacts on the course of their disease as evidenced by magnetic resonance imaging (MRI).

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 and/or their legally authorized representative. Participating subjects and/or their legally authorized representative 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	08 November 2006
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	China: 39
Worldwide total number of subjects	39
EEA total number of subjects	0

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)	1

Adults (18-64 years)	38
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in China between 08 November 2006 (first subject first visit) and 26 September 2008 (last subject last visit).

Pre-assignment

Screening details:

After a 3-month pre-treatment period with no MS-specific treatment, 39 subjects entered the 6-month treatment period. Of the 84 subjects screened, 40 subjects did not meet the inclusion/exclusion criteria, 3 subjects withdrew their consent, and 2 subjects died during pre-treatment.

Period 1

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

Arms

Arm title	Interferon Beta-1b (Betaseron, BAY86-5046)

Arm description:

Interferon Beta-1b 250 micrograms (8 MIU [million international units]) subcutaneously every other day.

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

Dosage and administration details:

Interferon Beta-1b 250 micrograms (8 MIU) subcutaneously every other day.

Number of subjects in period 1	Interferon Beta-1b (Betaseron, BAY86-5046)
Started	39
Completed	37
Not completed	2
Consent withdrawn by subject	2

Baseline characteristics

Reporting groups	
Reporting group title	Interferon Beta-1b (Betaseron, BAY86-5046)
Reporting group description:	
Interferon Beta-1b 250 micrograms (8 MIU [million international units]) subcutaneously every other day.	

Reporting group values	Interferon Beta-1b (Betaseron, BAY86-5046)	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean full range (min-max)	 31.6 17 to 58	 -	
Gender categorical Units: Subjects			
Female Male	26 13	26 13	
Gadolinium enhancing lesions (T1) at screening Units: Subjects			
no lesions 1-3 lesions >= 4 lesions	5 23 11	5 23 11	
Type of Multiple Sclerosis Units: Subjects			
Relapsing-remitting (RR) Secondary progressive (SP)	36 3	36 3	
Expanded disability status scale at screening (EDSS)			
The EDSS is a scale based on the standardized neurological examination which comprised of optic, brain stem/cranial nerves, pyramidal, cerebellar, sensory, vegetative, and cerebral functions, as well as walking ability.The EDSS scores range from 0.0 (normal) to 10.0 (dead). A score of 2 to 3 indicates minimal to moderate disability.			
Units: Scores on a scale arithmetic mean full range (min-max)	 2.26 0 to 5	 -	
New Gd-enhancing lesions during 3-month pre-treatment Units: Lesions arithmetic mean standard deviation	 2.6 ± 4.1	 -	
New or enlarging T2 lesions during 3-month pre-treatment Units: Lesions arithmetic mean	 2.2	 	

standard deviation	± 3.2	-	
Newly active lesions during 3-month pre-treatment			
Units: Lesions			
arithmetic mean	4.8		
standard deviation	± 7.1	-	
Previous Multiple Sclerosis relapses			
Units: relapses			
arithmetic mean	2.8		
standard deviation	± 1.7	-	
T2 lesions at screening			
Units: Lesions			
arithmetic mean	45.1		
standard deviation	± 32.9	-	
Time since onset of Multiple Sclerosis			
Units: Years			
arithmetic mean	3.5		
standard deviation	± 4.6	-	

End points

End points reporting groups

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

Reporting group description:

Interferon Beta-1b 250 micrograms (8 MIU [million international units]) subcutaneously every other day.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS (N=39) was defined as all subjects with receipt of at least one dose of study medication and at least one post-baseline visit.

Subject analysis set title	MRI set (MRS)
Subject analysis set type	Full analysis

Subject analysis set description:

MRS (N=39) included all FAS subjects with at least one evaluable post-baseline MRI scan.

Primary: Difference Between the Number of Newly Active Lesions in Magnetic Resonance Imaging (MRI) Per Three Months During the 6-month Treatment Period and the Number of Newly Active Lesions During 3-month Pre-treatment

End point title	Difference Between the Number of Newly Active Lesions in Magnetic Resonance Imaging (MRI) Per Three Months During the 6-month Treatment Period and the Number of Newly Active Lesions During 3-month Pre-treatment[1]

End point description:

The primary efficacy variable was calculated by subtracting the number of newly active lesions during the 3-month pre-treatment period from the cumulative number of newly active lesions during the 6-month treatment period divided by 2 (number of newly active lesions per three months, new lesion frequency per 3 months).

End point type	Primary

End point timeframe:

After 6 months of treatment as compared to 3-month pre-treatment

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: EudraCT database does not allow reporting statistics for a reporting group in a single-arm study. Due to this format constraint, we have uploaded charts with the accurate details of statistical analysis for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	38[2]			
Units: Lesions				
median (full range (min-max))	-1.5 (-35 to 6.5)			

Notes:

[2] - MRS with subjects evaluable for this endpoint

Attachments (see zip file)	Statistical Analysis_Primary_Difference_MRI

Statistical analyses

No statistical analyses for this end point

Secondary: Difference Between the Number of New Gadolinium-enhancing Lesions Per 3 Months During the 6-month Treatment Period and the Number of New Gadolinium-enhancing Lesions During 3-month Pre-treatment

End point title	Difference Between the Number of New Gadolinium-enhancing Lesions Per 3 Months During the 6-month Treatment Period and the Number of New Gadolinium-enhancing Lesions During 3-month Pre-treatment

End point description:

This secondary endpoint (component of the primary endpoint) was calculated by subtracting the number of new gadolinium-enhancing lesions during the 3-month pre-treatment period from the cumulative number of new gadolinium-enhancing lesions during the 6-month treatment period divided by 2 (number of new gadolinium-enhancing lesions per three months). Please find the statistical analysis in the attachment below.

End point type	Secondary

End point timeframe:

After 6 months of treatment as compared to 3-month pre-treatment

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	38[3]			
Units: Lesions				
median (full range (min-max))	-0.5 (-22 to 1.5)			

Notes:

[3] - MRS with subjects evaluable for this endpoint

Attachments (see zip file)	Statistical Analysis_Secondary_Difference_Gd-enh

Statistical analyses

No statistical analyses for this end point

Secondary: Difference Between the Number of New or Enlarging T2 Lesions Per 3 Months During the 6-month Treatment Period and the Number of New or Enlarging T2 Lesions During 3-month Pre-treatment

End point title	Difference Between the Number of New or Enlarging T2 Lesions Per 3 Months During the 6-month Treatment Period and the Number of New or Enlarging T2 Lesions During 3-month Pre-treatment

End point description:

This secondary endpoint (component of the primary endpoint) was calculated by subtracting the number of new or enlarging T2 lesions during the 3-month pre-treatment period from the cumulative number of new or enlarging T2 lesions during the 6-month treatment period divided by 2 (number of new T2 lesions per three months) based on non-enhancing lesions on T1 weighted scans. Please find the statistical analysis in the attachment below.

End point type	Secondary

End point timeframe:

After 6 months of treatment as compared to the 3-month pre-treatment

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	38[4]			
Units: Lesions				
median (full range (min-max))	0 (-13 to 6.5)			

Notes:

[4] - MRS with subjects evaluable for this endpoint

Attachments (see zip file)	Statistical Analysis_Secondary_Difference_T2

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Gadolinium-enhancing Lesions at Baseline, Weeks 12 and 24

End point title	Volume of Gadolinium-enhancing Lesions at Baseline, Weeks 12 and 24

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the timepoints. Please find the statistical analysis in the attachment below.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	39[5]			
Units: cubic millimeter (mm^3)				
arithmetic mean (standard deviation)				
Baseline (N=39) Week 12 (N=38) Week 24 (N=37)	585 (± 869) 93 (± 184) 648 (± 2788)			

Notes:

[5] - MRS

Attachments (see zip file)	Statistical Analysis_Secondary_Volume_Gd-enh

Statistical analyses

No statistical analyses for this end point

Secondary: Number of New Gadolinium (T1)-enhancing Lesions at Baseline, Weeks 12 and 24

End point title	Number of New Gadolinium (T1)-enhancing Lesions at Baseline, Weeks 12 and 24

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the timepoints.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	39[6]			
Units: Lesions				
arithmetic mean (standard deviation)				
Baseline (N=39)	2.8 (± 4.15)			
Week 12 (N=38)	0.5 (± 1.01)			
Week 24 (N=37)	0.8 (± 1.83)			

Notes:

[6] - MRS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of T2 Lesions at Baseline, Weeks 12 and 24

End point title	Number of T2 Lesions at Baseline, Weeks 12 and 24

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the timepoints.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	39[7]			
Units: Lesions				
arithmetic mean (standard deviation)				

Baseline (N=39)	48.7 (± 35.77)			
Week 12 (N=38)	48.8 (± 35.21)			
Week 24 (N=37)	44.6 (± 31.54)			

Notes:

[7] - MRS

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Relapses: Relapse Rate

End point title	Assessment of Relapses: Relapse Rate

End point description:

A relapse was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical event. The abnormality must be present for at least 24 hours and occur in the absence of fever (axillary temperature more than (>) 37.5 degree celsius / 99.5 degree fahrenheit) or known infection. A relapse must be confirmed by a documented report from a physician or by objective assessment. The relapse rate was calculated on an annualized basis. Annualized relapse rate is the average number of relapses in a year calculated by negative binomial regression as the sum of confirmed relapses of all subjects in the group divided by the sum of the number of days on study of all subjects in the group and multiplied by 365.25.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	39[8]			
Units: relapses per year				
number (not applicable)	0.38			

Notes:

[8] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Relapses: Number of Relapses

End point title	Assessment of Relapses: Number of Relapses

End point description:

A relapse was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical event. The abnormality must be present for at least 24 hours and occur in the absence of fever (axillary temperature >37.5 degree celsius / 99.5 degree fahrenheit) or known infection. A relapse must be confirmed by a documented report from a physician or by objective assessment. In the categories listed below, "N" signifies the number of subjects evaluable for the timepoints, and same subjects were counted more than once under each category.

End point type	Secondary

End point timeframe:

3 and 6 months

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	10[9]			
Units: relapses				
3 months (N=6)	6			
6 months (N=6)	7			

Notes:

[9] - FAS with all subjects who had reported relapses

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Relapses: Percentage of Relapse-free Subjects After 24 Weeks

End point title	Assessment of Relapses: Percentage of Relapse-free Subjects After 24 Weeks

End point description:

A relapse was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical event. The abnormality must be present for at least 24 hours and occur in the absence of fever (axillary temperature >37.5 degree celsius / 99.5 degree fahrenheit) or known infection. A relapse must be confirmed by a documented report from a physician or by objective assessment.

End point type	Secondary

End point timeframe:

After 24 weeks

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	39[10]			
Units: percentage of subjects				
number (not applicable)	84.6			

Notes:

[10] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Relapses: Relapse Severity

End point title	Assessment of Relapses: Relapse Severity

End point description:

A relapse was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical event. The abnormality must be present for at least 24 hours and occur in the absence of fever (axillary temperature >37.5 degree celsius / 99.5 degree fahrenheit) or known infection. A relapse must be confirmed by a documented report from a physician or by objective assessment. A major relapse was defined based on changes on EDSS with the following additional criteria to be met: objective neurological impairment, correlating with the subject's reported symptoms, defined as either increase in at least one of the functional systems of the EDSS score or increase of the total EDSS score. Relapses which did not meet the criteria of major relapses were considered as non-major.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	10[11]			
Units: relapses				
Major	1			
Non-major	12			

Notes:

[11] - FAS with all subjects who had reported relapses

Statistical analyses

No statistical analyses for this end point

Secondary: Expanded Disability Status Scale (EDSS)

End point title	Expanded Disability Status Scale (EDSS)

End point description:

The EDSS is a scale based on the standardized neurological examination which comprised of optic, brain stem/cranial nerves, pyramidal, cerebellar, sensory, vegetative, and cerebral functions, as well as walking ability. The EDSS scores range from 0.0 (normal) to 10.0 (dead). A score of 2 to 3 indicates minimal to moderate disability.

End point type	Secondary

End point timeframe:

Pre-treatment on Day 1, Week 24

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	37[12]			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Pre-treatment on Day 1 Week 24	2.06 (± 1.6) 1.81 (± 1.72)			

Notes:

[12] - FAS subjects with EDSS assessments at the end of the study (Week 24)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without EDSS Progression

End point title	Percentage of Subjects Without EDSS Progression

End point description:

The EDSS is a scale based on the standardized neurological examination which comprised of optic, brain stem/cranial nerves, pyramidal, cerebellar, sensory, vegetative, and cerebral functions, as well as walking ability.The EDSS scores range from 0.0 (normal) to 10.0 (dead). A score of 2 to 3 indicates minimal to moderate disability. An EDSS progression was defined as increase in EDSS greater than or equal to (>=) 1.0 points (in the treatment period as compared to baseline).

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Interferon Beta-1b (Betaseron, BAY86-5046)			
Subject group type	Reporting group			
Number of subjects analysed	39[13]			
Units: percentage of subjects				
number (not applicable)	87.2			

Notes:

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to the end of the study (Week 24)

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as adverse events which were not recorded before the start of study treatment or, if pre-existent, had increased in intensity after the start of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

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

Reporting group description:

Interferon Beta-1b 250 micrograms (8 MIU) subcutaneously every other day.

Serious adverse events	Interferon Beta-1b (Betaseron, BAY86-5046)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (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	Interferon Beta-1b (Betaseron, BAY86-5046)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 39 (87.18%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Influenza like illness			

subjects affected / exposed	16 / 39 (41.03%)		
occurrences (all)	17		
Injection site erythema			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Injection site pain			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Injection site reaction			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Menstruation delayed			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	2		
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
White blood cell count decreased			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Facial palsy			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	8		
Tremor			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	2		
Eye disorders			
Eye movement disorder			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Mouth ulceration			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1 1 / 39 (2.56%) 4		
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	 7 / 39 (17.95%) 7		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Subcutaneous nodule subjects affected / exposed occurrences (all) Hypoaesthesia facial subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1 1 / 39 (2.56%) 1 1 / 39 (2.56%) 1 1 / 39 (2.56%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Nephrolithiasis subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1 1 / 39 (2.56%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1		
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Limb discomfort			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2007	1.Updated the list of study personnel and central laboratories: Administrative changes related to study personnel and central laboratories were described. 2. Update of the enrollment period: The expected enrollment period was extended from the 1st quarter of 2007 to the 3rd quarter of 2007. 3. Modification of inclusion criterion 2 (Subject's age): The minimum age for study participation was lowered from 18 to 16 years to reflect the Betaferon label change in Europe. 4. Modification of exclusion criterion 15 (prohibited medication before study start): Clarification was provided that certain medication was prohibited within 30 days prior to informed consent (instead of 30 days prior to first application of the study medication). This change made exclusion criterion 15 consistent with other sections of the protocol. 5. Clarification on documentation-requirements for relapse associated serious adverse events (SAEs): Clarification was provided that, even though hospitalization due to steroid treatment of a relapse was not to be recorded as an SAE, all other events meeting the seriousness criteria were to be reported appropriately as SAEs whether connected to a relapse of the disease or not. 6. Pretreatment MRI activity check: It was clarified that pretreatment MRI scans were centrally analyzed to determine the number of active lesions before completion of enrollment in order to verify the correctness of the assumptions made with respect to the baseline-to-treatment-comparison trial design. 7. Implementation of safety interim analysis: This safety interim analysis was implemented to allow early analysis and reporting of safety data in this Chinese study population. 8. Use of subject diaries: The protocol amendment provided guidance on diary dispensing, use and return. 9. Additional secondary MRI varaible: The volume of Gd-enhancing lesions was introduced as additional secondary variable to allow determination of the disease burden.

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.

Decimal places were automatically truncated if last decimal equals zero.

Notes: