Clinical trial results:
An 18-month, open-label, rater-blinded, randomized, multicenter, active-controlled, parallel-group pilot study to assess efficacy and safety of fingolimod in comparison to interferon beta-1b in treating the cognitive symptoms associated to relapsing-remitting multiple sclerosis and to assess possible relationship of these effects to regional brain atrophy

Summary

EudraCT number	2010-023023-19
Trial protocol	IT DE
Global end of trial date	01 September 2015

Results information

Result version number	v1 (current)
This version publication date	16 September 2016
First version publication date	16 September 2016

Trial information

Trial identification

Sponsor protocol code	CFTY720DIT01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01333501
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	01 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2015
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 evaluate, by means of a specific cognitive test battery [Brief Repeatable Battery (BRB) and Delis-Kaplan Executive Function System scale - Sorting Test (DKEFS)], the slowing/reduction of cognitive dysfunction progression in RRMS patients after 18 months of treatment with fingolimod in comparison with interferon beta-1b treatment, and to evaluate which test of the battery was the most sensitive in detecting differences between treatment groups.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 May 2011
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	Germany: 12
Country: Number of subjects enrolled	Italy: 145
Worldwide total number of subjects	157
EEA total number of subjects	157

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)	157

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The number of total patients randomized in the study (157) together with the number of the safety population (patients who took at least one dose of study drug) (151). In the study there were 6 patients who were enrolled but who never took any dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fingolimod

Arm description:

0.5 mg in capsules for oral administration once daily

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg in capsules for oral administration once daily

Arm title	Interferon beta 1b

Arm description:

250 µg injected s.c. every other day

Arm type	Active comparator
Investigational medicinal product name	Interferon beta 1b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

250 µg injected s.c. every other day

Number of subjects in period 1	Fingolimod	Interferon beta 1b
Started	106	51
Full Analysis Set (FAS)	80 [1]	28 [2]
Safety Population	104	47
Completed	97	30
Not completed	9	21

Adverse event, non-fatal	3	1
Unsatisfactory therapeutic effect	1	7
Abnormal laboratory value	2	1
Withdrawn consent	3	12

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Total patients randomized in the study (157). Patients who took at least one dose of study drug are 151. The study there were 6 patients who were enrolled but who never took any dose of study drug

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Total patients randomized in the study (157). Patients who took at least one dose of study drug are 151. The study there were 6 patients who were enrolled but who never took any dose of study drug

Baseline characteristics

Reporting groups	
Reporting group title	Fingolimod
Reporting group description:	
0.5 mg in capsules for oral administration once daily	
Reporting group title	Interferon beta 1b
Reporting group description:	
250 µg injected s.c. every other day	

Reporting group values	Fingolimod	Interferon beta 1b	Total
Number of subjects	106	51	157
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	106	51	157
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	39.53	37.53	
standard deviation	± 9.28	± 9.27	-
Gender, Male/Female Units: Participants			
Female	68	32	100
Male	38	19	57

End points

End points reporting groups	
Reporting group title	Fingolimod
Reporting group description:	
0.5 mg in capsules for oral administration once daily	
Reporting group title	Interferon beta 1b
Reporting group description:	
250 µg injected s.c. every other day	

Primary: Change from screening in Selective Reminding Test – Long-Term Storage (SRT-LTS) raw score	
End point title	Change from screening in Selective Reminding Test – Long-Term Storage (SRT-LTS) raw score
End point description:	
Brief Repeatable Battery (BRB)- widely used as a clinical and research tool, with 68% sensitivity and 85% specificity. It consists of the serial administration of 5 tests. One of the tests is SRT (Selective Reminding Test) for episodic memory (verbal learning and delayed recall). A word recalled on two consecutive trials is considered to have entered long-term storage (LTS) on the first of these trials and scored as LTS on all following trials. The total of the words in LTS of all six trials is then summed.	
End point type	Primary
End point timeframe:	
Screening (-1month), 18 month	

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: raw score				
least squares mean (standard error)	6.32 (± 1.33)	4.46 (± 2.28)		

Statistical analyses

Statistical analysis title	Change from screening in Selective Reminding Test
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.494
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	7.23
Variability estimate	Standard error of the mean
Dispersion value	2.7

Primary: Change from screening in Selective Reminding Test – Consistent Long Term Retrieval (SRT-CLTR) raw score

End point title	Change from screening in Selective Reminding Test – Consistent Long Term Retrieval (SRT-CLTR) raw score

End point description:

Brief Repeatable Battery (BRB)- widely used as a clinical and research tool, with 68% sensitivity and 85% specificity. It consists of the serial administration of 5 tests. One of the tests is SRT (Selective Reminding Test) for episodic memory (verbal learning and delayed recall). A word recalled on two consecutive trials is considered to have entered long-term storage (LTS) on the first of these trials and scored as LTS on all following trials. The total of the words in LTS of all six trials is then summed. If a word in LTS is consistently recalled on all subsequent trials, it is then scored as Consistent Long Term Retrieval (CLTR). The total of the words in CLTR of all six trials is summed.

End point type	Primary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	5.93 (± 1.49)	3.96 (± 2.56)		

Statistical analyses

Statistical analysis title	Change from screening in (SRT-CLTR)
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5183
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.06
upper limit	7.99
Variability estimate	Standard error of the mean
Dispersion value	3.03

Primary: Change from screening in Spatial Recall Test (SPART) raw score	
End point title	Change from screening in Spatial Recall Test (SPART) raw score

End point description:

Spatial Recall Test (SPART) for visuospatial learning and delayed recall.Spatial Recall Test (10/36): The spatial recall test assesses visuospatial learning and delayed recall (10/36-D). A checkerboard with ten checkers arranged in a pattern is shown to the subject for ten seconds. The subject is then asked to reproduce the same pattern with ten checkers on an empty checkerboard. The test includes three consecutive trials. The score is the total number of correct responses for the tree trials

End point type	Primary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	1.46 (± 0.52)	3.06 (± 0.89)		

Statistical analyses

Statistical analysis title	Change from screening in (SPART) raw score
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1334
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.69
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	1.05

Primary: Change from screening in Symbol Digit Modalities Test (SDMT) raw score	
End point title	Change from screening in Symbol Digit Modalities Test (SDMT) raw score
End point description:	
Symbol Digit Modality Test (SDMT) for sustained attention and information processing speed. It presents a series of nine symbols, each of which is paired with a single digit labeled 1-9 in a key at the top of the sheet. The reminder of the page has a pseudo-randomized sequence of symbols, and the patient must respond with the digit associated with each of these as quickly as possible. The score is the number of correct answers in 90 seconds	
End point type	Primary
End point timeframe:	
Screening (-1month), 18 month	

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	2.19 (± 1.12)	3.93 (± 1.93)		

Statistical analyses

Statistical analysis title	Change from screening in (SDMT) raw score
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4501
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.27
upper limit	2.81
Variability estimate	Standard error of the mean
Dispersion value	2.29

Primary: Change from screening in Paced Auditory Serial Addition Test – 3 seconds (PASAT 3) raw score	
End point title	Change from screening in Paced Auditory Serial Addition Test –

	3 seconds (PASAT 3) raw score

End point description:

Paced Auditory Serial Addition Test (PASAT) for working memory (and sustained attention and information processing speed). The patient hears a series of numbers from recordings that are presented at the rate of one every 3 seconds in the first part of the test (PASAT-3). The patient is asked to add each consecutive digit to the one immediately preceding it. Sixty-one digits are presented for each part, and each part has a maximum of 60 correct answers.

End point type	Primary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	7.14 (± 1.24)	6.68 (± 2.13)		

Statistical analyses

Statistical analysis title	Change from screening in (PASAT 3) raw score
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8561
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.57
upper limit	5.49
Variability estimate	Standard error of the mean
Dispersion value	2.53

Primary: Change from screening in Paced Auditory Serial Addition Test – 2 (PASAT 2) raw score

End point title	Change from screening in Paced Auditory Serial Addition Test – 2 (PASAT 2) raw score

End point description:

Paced Auditory Serial Addition Test (PASAT) for working memory (and sustained attention and information processing speed). The patient hears a series of numbers from recordings that are presented at the rate of one every 2 seconds in the second part of the test (PASAT-2). The patient was asked to add each consecutive digit to the one immediately preceding it. Sixty-one digits are presented for each part, and each part has a maximum of 60 correct answers.

End point type	Primary
End point timeframe:	
Screening (-1month), 18 month	

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	4.79 (± 1.25)	4.42 (± 2.14)		

Statistical analyses

Statistical analysis title	Change from screening in (PASAT 2) raw score
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8858
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.67
upper limit	5.4
Variability estimate	Standard error of the mean
Dispersion value	2.53

Primary: Change from screening in Selective Reminding Test – delayed recall (SRT-D) raw score

End point title	Change from screening in Selective Reminding Test – delayed recall (SRT-D) raw score
End point description:	
The tests SRT (Selective Reminding Test) for episodic memory (verbal learning and delayed recall). The Delayed SRT test is the total number of words recalled after a delayed period	
End point type	Primary
End point timeframe:	
Screening (-1month), 18 month	

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	0.57 (± 0.23)	0.39 (± 0.4)		

Statistical analyses

Statistical analysis title	Change from screening in (SRT-D) raw score
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7119
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	1.11
Variability estimate	Standard error of the mean
Dispersion value	0.47

Primary: Change from screening in Spatial Recall Test – delayed recall (SPART-D)

End point title	Change from screening in Spatial Recall Test – delayed recall (SPART-D)

End point description:

Spatial Recall Test (SPART) for visuospatial learning and delayed recall.Spatial Recall Test (10/36): The spatial recall test assesses visuospatial learning and delayed recall (10/36-D). A checkerboard with ten checkers arranged in a pattern was shown to the subject for ten seconds. The subject was then asked to reproduce the same pattern with ten checkers on an empty checkerboard. The test includes three consecutive trials. The score was the total number of correct responses for the tree trials

End point type	Primary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	0.41 (± 0.21)	0.44 (± 0.36)		

Statistical analyses

Statistical analysis title	Change from screening in (SPART-D)
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9496
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	0.81
Variability estimate	Standard error of the mean
Dispersion value	0.42

Primary: Change from screening in Word List Generation (WLG)	
End point title	Change from screening in Word List Generation (WLG)
End point description:	
Word List Generation (COWAT/WLG): The COWAT assesses verbal fluency on semantic stimulus by asking the patient to produce as many words as possible belonging to a semantic category in 90 seconds. The score was the number of correct words	
End point type	Primary
End point timeframe:	
Screening (-1month), 18 month	

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	0.39 (± 0.58)	0.24 (± 0.99)		

Statistical analyses

Statistical analysis title	Change from screening in (WLG)
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8944
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.18
upper limit	2.5
Variability estimate	Standard error of the mean
Dispersion value	1.18

Primary: Change from screening in Delis-Kaplan Executive Function System (DKEFS) condition 1: free sorting, confirmed correct sort- card set 1+2

End point title	Change from screening in Delis-Kaplan Executive Function System (DKEFS) condition 1: free sorting, confirmed correct sort- card set 1+2

End point description:

The Delis-Kaplan Executive Function System – Sorting Test is one of the nine tests presented in the DKEFS manual and explores the patient's executive abilities. It has a standard form (version A, administered at screening and Month-18 visit) and an alternate form (version B, administered at Month-9 visit). The standard form consists of the practice card set, card set 1 and card set 2. The alternate form consists of the same practice card set, card set 3 and card set 4. The DKFES test consisted of two testing procedures: free sorting and sort recognition. In free sorting, six scores were obtained: Confirmed Correct sorts for card sets 1 and 2 (or 3 and 4 for version B), sum of confirmed Correct Sorts, Free Sorting Description score for card set 1 and 2 (or 3 and 4 for version B) and sum of Free Sorting Description scores. In sort recognition, a description score for card set 1 and 2 (or 3 and 4 for version B) was obtained, as well as the sum of description scores of both sets.

End point type	Primary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	0.57 (± 0.31)	0.82 (± 0.48)		

Statistical analyses

Statistical analysis title	Change from screening in (DKEFS) condition 1
Comparison groups	Fingolimod v Interferon beta 1b
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6757
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.59

Primary: Change from screening in DKEFS condition 1: free sorting, free sorting, description score, card set 1+2

End point title	Change from screening in DKEFS condition 1: free sorting, free sorting, description score, card set 1+2

End point description:

The Delis-Kaplan Executive Function System – Sorting Test is one of the nine tests presented in the DKEFS manual and explores the patient's executive abilities. It has a standard form (version A, administered at screening and Month-18 visit) and an alternate form (version B, administered at Month-9 visit). The standard form consists of the practice card set, card set 1 and card set 2. The alternate form consists of the same practice card set, card set 3 and card set 4. The DKFES test consisted of two testing procedures: free sorting and sort recognition. In free sorting, six scores were obtained: Confirmed Correct sorts for card sets 1 and 2 (or 3 and 4 for version B), sum of confirmed Correct Sorts, Free Sorting Description score for card set 1 and 2 (or 3 and 4 for version B) and sum of Free Sorting Description scores. In sort recognition, a description score for card set 1 and 2 (or 3 and 4 for version B) was obtained, as well as the sum of description scores of both sets.

End point type	Primary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	1.52 (± 1.23)	3.69 (± 1.92)		

Statistical analyses

Statistical analysis title	Change from screening in DKEFS condition 1
Comparison groups	Fingolimod v Interferon beta 1b

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3585
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.82
upper limit	2.5
Variability estimate	Standard error of the mean
Dispersion value	2.34

Primary: Change from screening in DKEFS condition 2: sort recognition, sort recognition description score- card set 1+2

End point title	Change from screening in DKEFS condition 2: sort recognition, sort recognition description score- card set 1+2

End point description:

The Delis-Kaplan Executive Function System – Sorting Test is one of the nine tests presented in the DKEFS manual and explores the patient's executive abilities. It has a standard form (version A, administered at screening and Month-18 visit) and an alternate form (version B, administered at Month-9 visit). The standard form consists of the practice card set, card set 1 and card set 2. The alternate form consists of the same practice card set, card set 3 and card set 4. The DKFES test consisted of two testing procedures: free sorting and sort recognition. In free sorting, six scores were obtained: Confirmed Correct sorts for card sets 1 and 2 (or 3 and 4 for version B), sum of confirmed Correct Sorts, Free Sorting Description score for card set 1 and 2 (or 3 and 4 for version B) and sum of Free Sorting Description scores. In sort recognition, a description score for card set 1 and 2 (or 3 and 4 for version B) was obtained, as well as the sum of description scores of both sets.

End point type	Primary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	2.15 (± 1.9)	7.38 (± 2.97)		

Statistical analyses

Statistical analysis title	Change from screening in DKEFS condition 2
Comparison groups	Fingolimod v Interferon beta 1b

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.161
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.62
upper limit	2.14
Variability estimate	Standard error of the mean
Dispersion value	3.69

Secondary: Change from screening in the Volume of total T2 lesions

End point title	Change from screening in the Volume of total T2 lesions

End point description:

Change in volume of total T2-weighted lesions by visit were summarized. Negative values indicate improvement (reduction in lesion volume) and positive values worsening (increase in lesion volume

End point type	Secondary

End point timeframe:

Screening (-1 month), 18 months

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	27		
Units: mm3				
arithmetic mean (standard deviation)	176.25 (± 1355.31)	711.81 (± 1584.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from screening in Montgomery-Asberg Depression Rating Scale (MADRS)

End point title	Change from screening in Montgomery-Asberg Depression Rating Scale (MADRS)

End point description:

MADRS measures the overall severity of depressive symptoms. The MADRS had a 10-item checklist. Items are rated on a scale of 0-6, for a total numeric range of scores from 0 (depressive symptoms absent) to 60 (numerically highest level of depressive symptoms).

End point type	Secondary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Raw score				
least squares mean (standard error)	-0.77 (± 0.79)	0.13 (± 1.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in quality of life, by means of the Multiple Sclerosis Quality of Life (MSQoL-54)

End point title	Changes in quality of life, by means of the Multiple Sclerosis Quality of Life (MSQoL-54)

End point description:

A 54 question measure covers 12 domains; assesses mental and physical health. Each domain score is converted into a 0-100 score based on individual item responses; higher scores=better health status. The physical health composite score is a weighted average of the physical health scales, such as physical function, health perceptions, and energy. The mental health composite score is a weighted average of the mental health scales, such as overall quality of life, cognitive function, and health distress

End point type	Secondary

End point timeframe:

Baseline, 18 months

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Score				
least squares mean (standard error)				
Mental health composite score	4.76 (± 2.01)	-2.31 (± 3.36)		
Physical health composite score	-1.8 (± 1.41)	-4.75 (± 2.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in Fatigue Impact Scale (mFIS, total score and scores of the 3 individual domains).

End point title	Changes from baseline in Fatigue Impact Scale (mFIS, total score and scores of the 3 individual domains).

End point description:

Modified Fatigue Impact Scale (mFIS) questionnaire is described at each time point to evaluate fatigue by means of usual descriptive statistics. Three domains were also defined: Physical Subscale (sum of items 4, 6, 7, 10, 13, 14, 17, 20, 21 and therefore ranging from 0 to 36), Cognitive Subscale (sum of items 1, 2, 3, 5, 11, 12, 15, 16, 18, 19 and therefore ranging from 0 to 40) and Psychosocial Subscale (sum of items 8, 9 and therefore ranging from 0 to 8). Finally, the mFIS total score was computed as the sum of scores for each item.

End point type	Secondary

End point timeframe:

Baseline, 18 months

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Score				
least squares mean (standard error)	0.46 (± 0.86)	4.34 (± 1.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from screening in the Number of new T2 lesions

End point title	Change from screening in the Number of new T2 lesions

End point description:

New T2 lesions at a specific visit were assessed relative to the previous visit scan. The total number of lesions (visit 8 to 18 month) is calculated as the sum of the number of lesions.

End point type	Secondary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Number				
arithmetic mean (standard deviation)	1.25 (± 2.05)	3.33 (± 4.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from screening in the Volume of total T1 hypointense lesions

End point title	Change from screening in the Volume of total T1 hypointense lesions

End point description:

Volume of hypointense post-gadolinium T1 lesion component was measured by MRI scan. Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) by-visit interaction.

End point type	Secondary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: mm3				
arithmetic mean (standard deviation)	391.96 (± 986.85)	213.93 (± 312.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from screening in the Number of T1 Gd+ enhancing lesions

End point title	Change from screening in the Number of T1 Gd+ enhancing lesions

End point description:

Total number of post-baseline Gd-enhanced lesions is calculated as a sum of all Gd-enhanced lesions seen on post-baseline scans per visit. Real (not per slice) lesions are counted in this analysis

End point type	Secondary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Number				
arithmetic mean (standard deviation)	-0.64 (± 1.27)	0.59 (± 3.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from screening in the Percentage of Brain volume change

End point title	Change from screening in the Percentage of Brain volume change

End point description:

Calculations of brain volume change were performed using the structural image evaluation of normalized atrophy (SIENA), software included in the Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library. SIENA is a fully automated method for estimating temporal brain volume change.

End point type	Secondary

End point timeframe:

Screening (-1month), 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: percentage				
arithmetic mean (standard deviation)	-0.6 (± 0.83)	-0.96 (± 0.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: changes in the Environmental Status Scale score (ESS)

End point title	changes in the Environmental Status Scale score (ESS)

End point description:

The Environmental Status Scale (ESS) is used to quickly evaluate a patient for handicap. It was derived from a measure of socio-economic status. It consists of seven parameters: (1) actual work status, (2) financial and economic status, (3) personal residence or home, (4) personal assistance required, (5) transportation, (6) community services, (7) social activity. Each parameter has a single score from minimum 0 to maximum 5. ESS score is the sum of the points for all 7 parameters: minimum score: 0; maximum score: 35. The higher the score the greater the handicap

End point type	Secondary

End point timeframe:

Baseline, 18 month

End point values	Fingolimod	Interferon beta 1b		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	28		
Units: Score				
arithmetic mean (standard deviation)	1.08 (± 3.45)	0.91 (± 1.98)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Interferon beta 1b
Reporting group description:	
Interferon beta 1b	
Reporting group title	Fingolimod 0.5 mg
Reporting group description:	
Fingolimod 0.5 mg	

Serious adverse events	Interferon beta 1b	Fingolimod 0.5 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)	9 / 104 (8.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood glucose abnormal			
subjects affected / exposed	1 / 47 (2.13%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic brain injury			

subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Uterine polypectomy			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 47 (0.00%)	2 / 104 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			

subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Interferon beta 1b	Fingolimod 0.5 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 47 (46.81%)	44 / 104 (42.31%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	9 / 104 (8.65%)	
occurrences (all)	1	11	
Blood triglycerides increased			
subjects affected / exposed	3 / 47 (6.38%)	0 / 104 (0.00%)	
occurrences (all)	3	0	
Transaminases increased			
subjects affected / exposed	4 / 47 (8.51%)	4 / 104 (3.85%)	
occurrences (all)	5	6	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 47 (8.51%)	11 / 104 (10.58%)	
occurrences (all)	4	12	
Multiple sclerosis relapse			
subjects affected / exposed	4 / 47 (8.51%)	2 / 104 (1.92%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	5 / 47 (10.64%)	1 / 104 (0.96%)	
occurrences (all)	5	1	
Pyrexia			

subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4	6 / 104 (5.77%) 6	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3	 7 / 104 (6.73%) 8	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3	 3 / 104 (2.88%) 3	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 8	 4 / 104 (3.85%) 9	
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	 2 / 47 (4.26%) 2	 7 / 104 (6.73%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2012	1.Germany was included as participating country in the study. Two more sites were added in Italy. 2. Implementation of CHMP recommendations concerning intensified cardiovascular monitoring during treatment start and upon re-initiation of treatment with fingolimod. These recommendations were considered necessary after Novartis had informed the European Medicines Agency of the unexplained sudden death of a 59-year-old female patient with multiple sclerosis in the United States of America within 24 hours of taking the first dose of fingolimod. Six other cases of unexplained death had also been reported, three of which were sudden. In addition, other reports included three deaths due to heart attack and one due to disruption of heart rhythm. At the time of its authorization, no cases of sudden or unexplained death had been reported in studies with fingolimod. However, fingolimod is known to cause transient bradycardia and may be associated with atrioventricular block after the first dose, as stated in the current Summary of Product Characteristics. 3. A new study objective was included concerning the evaluation of how the Symbol Symbol Transcode Test (SSTT) correlates with the results of the BRB or D-KEFS. The SSTT was to be administered only in a subgroup of patients/sites, namely new patients/sites included in Germany. 4. Eligibility criteria were updated to exclude patients with an acute relapse of MS and to better clarify the exclusions relevant to patients presenting with chronic diseases of the immune system. In addition, further details were added concerning prohibited previous treatments and related timelines. As the study drug was already marketed in Germany and Italy, exclusion criterion n. 24 was also modified to exclude patients previously treated with fingolimod, regardless of the participation in a previous clinical trial.
07 September 2012	In April 2012, the CHMP completed the review of fingolimod cardiovascular safety data that started following the case of sudden death mentioned in Amendment 1. The overall positive benefit-risk profile of Gilenya was confirmed and final recommendations for the use of the drug were released. The major changes made to the protocol are summarized below: Exclusion criteria related to cardiovascular conditions were updated. 2. Exclusion of patients taking medications that lower heart rate was added. 3. Appendix 1 "Guidance for observation of patients taking their first dose of fingolimod and for management of bradycardia" was updated to reflect final CHMP recommendations
04 March 2013	The protocol was amended in order to add the option for patients completing study CFTY720DIT01 to be included in protocol CFTY720DIT07, an open label study aimed at providing access to fingolimod to patients who benefited from treatment or did not have adequate alternative treatment options, but who did not have access to reimbursement from the Italian National Health Service. Long-term safety and tolerability data was also to be collected in a population of patients different from the then current indications. In addition, the age upper limit of 55 years previously indicated in inclusion criterion n.2 was extended to 60 years. Finally, the Gilenya Pregnancy Exposure Registry was introduced, an observational study to evaluate the effect of fingolimod on pregnancy, to which any patient taking fingolimod that became pregnant during the course of this study was encouraged to participate in.

18 November 2013	Study CFTY720DIT07 mentioned in Amendment 3 initially called for the enrollment of roughly 200 patients. It was however later demonstrated that the number of patients who needed to continue therapy were actually not more than 40, a number not compatible with the study objectives, especially due to the reduced significance of the tolerability and safety data emerging from such a limited number of cases. The need to guarantee therapeutic continuity in situations like these can be more simply and adequately met through a compassionate use program, as per Ministerial Decree May 8, 2003. Novartis decided to provide the drug for compassionate use, on an individual basis, to guarantee therapeutic continuity to patients in treatment with fingolimod who were present for their end of study visit. The protocol was updated also with cumulative data from clinical studies in line with Investigator Brochure v.16.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported