Clinical trial results:
A Multicenter, Randomized, Open-Label Study to Assess the Impact of Natalizumab versus Fingolimod on Central Nervous System Tissue Damage and Recovery in Active Relapsing-Remitting Multiple Sclerosis Subjects

Summary

EudraCT number	2013-004622-29
Trial protocol	IT CZ GB SE ES DE DK
Global end of trial date	17 May 2016

Results information

Result version number	v1 (current)
This version publication date	02 June 2017
First version publication date	02 June 2017

Trial information

Trial identification

Sponsor protocol code	101MS408

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02342704
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street,, Cambridge, Massachusetts, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.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	17 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the effect of natalizumab compared to fingolimod on the evolution of new on-treatment T1-gadolinium-enhancing (Gd+) lesions to persistent black holes (PBH) over 52 weeks. The secondary objectives of this study in this study population are to assess the effect of natalizumab compared to fingolimod on: magnetic resonance imaging (MRI) measures of central nervous system (CNS) tissue destruction as measured by the number of new T1-Gd+ lesions; various other MRI measures of disease activity; No Evidence of Disease Activity (NEDA); Relapse on treatment over 52 weeks; The change in information processing speed as measured by the Symbol Digit Modalities Test (SDMT).

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2014
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	Czech Republic: 40
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	111
EEA total number of subjects	80

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)	111
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

128 subjects were screened for this study, and 111 were enrolled. Three subjects were not randomized and did not receive any dose of study drug.

Pre-assignment period milestones

Number of subjects started	111
Number of subjects completed	108

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Enrolled, not randomized: 3

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	Natalizumab

Arm description:

Open-label natalizumab 300 mg IV every 4 weeks

Arm type	Experimental
Investigational medicinal product name	natalizumab
Investigational medicinal product code	BG00002
Other name	Tysabri
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects randomly assigned to the natalizumab group were to receive open-label natalizumab 300 mg IV infused over a 1-hour period (or per local label) every 4 weeks with the last dose planned for administration at Week 52.

Arm title	Fingolimod

Arm description:

Open-label fingolimod 0.5 mg once daily orally

Arm type	Active comparator
Investigational medicinal product name	fingolimod
Investigational medicinal product code	FTY720
Other name	Gilenya
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects randomly assigned to the fingolimod group were to receive open-label fingolimod 0.5 mg orally once daily with the last dose planned to be administered at Week 52. Subjects were instructed to take their oral medication at the same time each day.

Number of subjects in period 1[1]	Natalizumab	Fingolimod
Started	54	54
Completed	1	3
Not completed	53	51
Consent withdrawn by subject	1	-
Physician decision	-	3
Adverse event, non-fatal	1	3
Sponsor Termination	49	43
Not Specified	-	1
Lost to follow-up	2	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 111 subjects were enrolled. Three subjects were not randomized and did not receive any dose of study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Natalizumab
Reporting group description:	
Open-label natalizumab 300 mg IV every 4 weeks	
Reporting group title	Fingolimod
Reporting group description:	
Open-label fingolimod 0.5 mg once daily orally	

Reporting group values	Natalizumab	Fingolimod	Total
Number of subjects	54	54	108
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	38.19	34.87	
standard deviation	± 8.811	± 8.731	-
Gender, Male/Female Units: Subjects			
Female	37	38	75
Male	17	16	33

End points

End points reporting groups

Reporting group title	Natalizumab
Reporting group description:	
Open-label natalizumab 300 mg IV every 4 weeks	
Reporting group title	Fingolimod
Reporting group description:	
Open-label fingolimod 0.5 mg once daily orally	

Primary: Cumulative Number of ≥ 6-Month Confirmed T1-Hypointense Lesions Arising From New On-Treatment T1-Gadolinium-ENhancing (Gd+) Lesions

End point title	Cumulative Number of ≥ 6-Month Confirmed T1-Hypointense Lesions Arising From New On-Treatment T1-Gadolinium-ENhancing (Gd+) Lesions[1]
End point description:	
End point type	Primary
End point timeframe:	
Up to Week 52	

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: Descriptive statistics are presented, per protocol.

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: lesions				

Notes:

[2] - Due to lack of data, this analysis was not done.

[3] - Due to lack of data, this analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Number of New T1-Gd+ Lesions

End point title	Cumulative Number of New T1-Gd+ Lesions
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 4, Week 12, Week 24	

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	45		
Units: lesions				
arithmetic mean (standard deviation)				
From Baseline to Week 4	0.62 (± 1.512)	1.69 (± 4.122)		
From Baseline to Week 12	0.68 (± 1.695)	2.27 (± 4.499)		
From Baseline to Week 24	0.72 (± 1.69)	2.6 (± 4.745)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 4	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.126
Method	Wilcoxon rank-sum test

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 4	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3525
Method	negative binomial regression

Statistical analysis title	Statisical Analysis 3
Statistical analysis description: Week 12	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0127
Method	Wilcoxon rank-sum test

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Week 12	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0299
Method	negative binomial regression

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Week 24	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123
Method	Wilcoxon rank-sum test

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Week 24	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0076
Method	negative binomial regression

Secondary: Change From Baseline in Total T1-Hypointense and Total T2-Hyperintense Lesion Volumes at Week 24

End point title	Change From Baseline in Total T1-Hypointense and Total T2-Hyperintense Lesion Volumes at Week 24
End point description: As assessed by magnetic resonance imaging (MRI).	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: percentage change				
arithmetic mean (standard deviation)				
T1 Lesion Volume Change	0.5 (± 31.235)	1.81 (± 19.703)		
T2 Lesion Volume Change	0.08 (± 4.399)	3.32 (± 5.036)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: T1 Lesion Volume Change	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5318
Method	Wilcoxon rank-sum test

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: T2 Lesion Volume Change	
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0528
Method	Wilcoxon rank-sum test

Secondary: Change From Baseline in Total T1-Hypointense and Total T2-Hyperintense Lesion Volumes at Week 52

End point title	Change From Baseline in Total T1-Hypointense and Total T2-Hyperintense Lesion Volumes at Week 52
End point description: As assessed by MRI.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	1[5]		
Units: percentage change				
arithmetic mean (standard deviation)				
T1 Lesion Volume Change	()	-15.31 (± 99999)		
T2 Lesion Volume Change	()	5.6 (± 99999)		

Notes:

[4] - No subjects were evaluated at this time point.

[5] - 99999=not applicable; only 1 subject was evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Number of New or Enlarging T2 Lesions

End point title	Cumulative Number of New or Enlarging T2 Lesions

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: lesions				
arithmetic mean (standard deviation)	1.33 (± 2.469)	1.94 (± 2.205)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Natalizumab v Fingolimod
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2632
Method	Wilcoxon rank-sum test

Secondary: Proportion of Subjects With No Evidence of Disease Activity (NEDA)

End point title	Proportion of Subjects With No Evidence of Disease Activity (NEDA)

End point description:

NEDA was defined as all of the following: no relapses; no 12-week confirmed disability progression based on Expanded Disability Status Scale (EDSS; defined as an increase of 1.0 or more on the EDSS from baseline of 1.0 or more, or an increase of 1.5 or more from a baseline score of 0) that was sustained for 12 weeks; no new T1-Gd+ lesions on brain MRI. No new or enlarging T2-hyperintense lesions.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: proportion of subjects				

Notes:

[6] - Due to lack of data, this analysis was not done.

[7] - Due to lack of data, this analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Relapse

End point title	Time to First Relapse

End point description:

A clinical relapse was defined as new or recurrent neurological symptoms, not associated with fever, lasting for at least 24 hours, and followed by a period of 30 days of stability or improvement.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: weeks				

Notes:

[8] - Due to lack of data, this analysis was not done.

[9] - Due to lack of data, this analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Risk of Relapse

End point title	Cumulative Risk of Relapse

End point description:

A clinical relapse was defined as new or recurrent neurological symptoms, not associated with fever,

lasting for at least 24 hours, and followed by a period of 30 days of stability or improvement.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: ratio				

Notes:

[10] - Due to lack of data, this analysis was not done.

[11] - Due to lack of data, this analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Recovery From First Relapse

End point title	Time to Complete Recovery From First Relapse

End point description:

12-week confirmed complete EDSS recovery from first on-treatment relapse is defined as an EDSS score that is equal to or lower than the last pre-relapse EDSS score and sustained for at least 12 weeks.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: days				

Notes:

[12] - Due to lack of data, this analysis was not done.

[13] - Due to lack of data, this analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Symbol Digit Modalities Test (SDMT) at Week 24

End point title	Change From Baseline in Symbol Digit Modalities Test (SDMT) at Week 24

End point description:

The SDMT measures the time to pair abstract symbols with specific numbers. The test requires elements of attention, visuoperceptual processing, working memory, and psychomotor speed. The score is the number of correctly coded items from 0-110 in 90 seconds. The total score provides a measure of the speed and accuracy of symbol-digit substitution.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: units on a scale				
arithmetic mean (standard deviation)	3.79 (± 8.684)	3.24 (± 4.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SDMT at Week 52

End point title	Change From Baseline in SDMT at Week 52

End point description:

The SDMT measures the time to pair abstract symbols with specific numbers. The test requires elements of attention, visuoperceptual processing, working memory, and psychomotor speed. The score is the number of correctly coded items from 0-110 in 90 seconds. The total score provides a measure of the speed and accuracy of symbol-digit substitution.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Natalizumab	Fingolimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	9		
Units: units on a scale				
arithmetic mean (standard deviation)	()	2.11 (± 8.492)		

Notes:

[14] - No subjects were evaluated at this time point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 64 weeks.	
Adverse event reporting additional description:	
Treatment-emergent adverse events are presented.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Natalizumab
Reporting group description:	
Open-label natalizumab 300 mg IV every 4 weeks	
Reporting group title	Fingolimod
Reporting group description:	
Open-label fingolimod 0.5 mg once daily orally	

Serious adverse events	Natalizumab	Fingolimod	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	2 / 54 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 54 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine with aura			
subjects affected / exposed	0 / 54 (0.00%)	1 / 54 (1.85%)	
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	Natalizumab	Fingolimod	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 54 (25.93%)	23 / 54 (42.59%)	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	0 / 54 (0.00%)	5 / 54 (9.26%)	
occurrences (all)	0	5	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 54 (11.11%)	4 / 54 (7.41%)	
occurrences (all)	21	12	
Multiple sclerosis relapse			
subjects affected / exposed	1 / 54 (1.85%)	8 / 54 (14.81%)	
occurrences (all)	4	16	
Hypoaesthesia			
subjects affected / exposed	0 / 54 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Migraine			
subjects affected / exposed	0 / 54 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 54 (5.56%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 54 (5.56%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 54 (1.85%)	3 / 54 (5.56%)	
occurrences (all)	1	4	
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 2	5 / 54 (9.26%) 10	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2	3 / 54 (5.56%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2014	- A tertiary endpoint for atrophy was revised and a tertiary endpoint for magnetization transfer ratio (MTR) was added. - "Freedom from Measured Disease Activity" was replaced with "No Evidence of Disease Activity". - The "abstinence" description under contraceptives was revised with language consistent with the Medicines and Healthcare Products Regulatory Agency. -The definition of End of Study was revised to be consistent with other similar protocols.
13 October 2014	- The number of study visits during which study assessments were collected was decreased for subjects with MS. - Inclusion criteria were revised such that subjects on certain therapies at study screening were required to have at least 9 T2-hyperintense lesions on a brain MRI scan instead of 2 T2-hyperintense lesions, and subjects who were DMT naïve at study screening must have had at least 2 disabling relapses within 1 year prior to study screening instead of 2 unspecified relapses. - Exclusion criteria for subjects with relapsing MS were expanded. Additional criteria were added to exclude a history of congenital QT prolongation and unexplained hypokalemia, and any current therapy with drugs that prolong the corrected QT interval or are potent inducers of CYP450. - Exclusion criteria for subjects with MS were expanded; exclusion criteria for healthy volunteers were expanded. - Absolute lymphocyte count was added to the list of hematology assessments. - Treatment precautions with fingolimod were expanded. - Disallowed concomitant therapy was expanded; cautionary text was added for concomitant administration of certain therapies in patients with relevant risk factors. - Hematology assessments at certain weeks were eliminated. - Blood chemistry assessments at certain weeks were eliminated for natalizumab subjects but retained for fingolimod subjects; an additional blood chemistry assessment was added at Week 4 for fingolimod subjects. - Urinalysis assessments were eliminated for all subjects. - Pulmonary function test at Screening was revised. - Vital sign assessments for fingolimod subjects were eliminated from certain weeks. - Discontinuation of study treatment was expanded to include MS subjects who developed any contraindications to fingolimod and natalizumab, as well as any medical conditions described in the warnings and precautions of the 2 study treatments that made the subject unsuitable for study participation in the opinion of the Investigator.
01 May 2015	- Clarification of the requirements in inclusion criteria #5 and #6 to expand the list of permitted prior DMTs - Reduction of the time required for a subject to be on a DMT at screening - Inclusion of potential subjects who had highly-active disease.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported