Clinical trial results:
A 21-week, Multicenter, Open Label Study to Evaluate the Safety and Tolerability Profile of the Combination of a SSRI or SNRI Antidepressive Therapy With Oral Fingolimod in the Treatment of RRMS Patients With Mild to Moderate Depression

Summary

EudraCT number	2011-001692-39
Trial protocol	DE
Global end of trial date	02 September 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CFTY720DDE06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01436643
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	02 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety and tolerability profile of the combination therapy of an antidepressant type SSRI or SNRI with oral fingolimod with respect to adverse events and laboratory parameters.

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	08 November 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: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	54
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The safety set was used for analysis, which consists of 54 patients, of whom 2 patients did not start treatment with any antidepressant

Period 1

Period 1 title	2-week pre-treatment
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Pre-treatment with Fingolimod

Arm description:

During 2weeks pre-treatment period patients received Fingolimod 0.5 mg per capsule (hard gelatin capsules) orally once daily.

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

Dosage and administration details:

Dosage of 0.5 mg per capsule (hard gelatin capsules) was taken p.o.

Number of subjects in period 1	Pre-treatment with Fingolimod
Started	54
Completed	44
Not completed	10
Adverse event, non-fatal	5
Abnormal Test result	1
Protocol deviation	4

Period 2

Period 2 title	core phase (16 weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fluoxetine and Fingolimod

Arm description:

Fingolimod 0.5 mg per capsule(hard gelatin capsules) was taken p.o. once daily. Fluoxetine, supplied in blistered packs containing 20 tablets; starting dose 20 mg; final dose 40 mg

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

Dosage and administration details:

Dosage of 0.5 mg per capsule (hard gelatin capsules) was taken p.o.

Investigational medicinal product name	Fluoxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Fluoxetine starting dose was 20 mg and given once daily for at least 7

Arm title	Venlafaxine and Fingolimod

Arm description:

Fingolimod 0.5 mg per capsule(hard gelatin capsules) was taken p.o. once daily. Venlafaxine, supplied in blistered packs containing 14 capsules; starting dose 75 mg; final dose 150 mg

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

Dosage and administration details:

Dosage of 0.5 mg per capsule (hard gelatin capsules) was taken p.o.

Investigational medicinal product name	Venlafaxine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Venlafaxine starting dose was 75 mg and given once daily for at least

Arm title	Citalopram and Fingolimod

Arm description:

Fingolimod 0.5 mg per capsule(hard gelatin capsules) was taken p.o. once daily. Citalopram, supplied in blistered packs containing 20 tablets; starting dose 20 mg, final dose 40 mg

Arm type	Experimental
Investigational medicinal product name	Citalpram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details: Citalopram starting dose was 20 mg and given once daily for at least 7	
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage of 0.5 mg per capsule (hard gelatin capsules) was taken p.o.

Number of subjects in period 2	Fluoxetine and Fingolimod	Venlafaxine and Fingolimod	Citalopram and Fingolimod
Started	17	15	20
Completed	16	11	17
Not completed	1	4	3
Adverse event, non-fatal	-	3	1
Abnormal Test result	-	-	1
Protocol deviation	1	1	1

Baseline characteristics

Reporting groups

Reporting group title	Pre-treatment with Fingolimod

Reporting group description:

During 2weeks pre-treatment period patients received Fingolimod 0.5 mg per capsule (hard gelatin capsules) orally once daily.

Reporting group values	Pre-treatment with Fingolimod	Total	
Number of subjects	54	54	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	54	54	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	41.8		
standard deviation	± 9.87	-	
Gender, Male/Female Units: Participants			
Male	10	10	
Female	44	44	

Subject analysis sets

Subject analysis set title	Fingolimod
Subject analysis set type	Intention-to-treat

Subject analysis set description:

2 Week Pre-treatment Period: Fingolimod 0.5 mg per capsule (hard gelatin capsules) was taken p.o. once during 2 week pre-treatment period.

Reporting group values	Fingolimod		
Number of subjects	54		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	54		
From 65-84 years	0		
85 years and over	0		
Age Continuous |			
Units: years			
arithmetic mean	41.8		
standard deviation	± 9.87		
Gender, Male/Female			
Units: Participants			
Male	10		
Female	44		

End points

End points reporting groups

Reporting group title	Pre-treatment with Fingolimod
Reporting group description:	
During 2weeks pre-treatment period patients received Fingolimod 0.5 mg per capsule (hard gelatin capsules) orally once daily.	
Reporting group title	Fluoxetine and Fingolimod
Reporting group description:	
Fingolimod 0.5 mg per capsule(hard gelatin capsules) was taken p.o. once daily. Fluoxetine, supplied in blistered packs containing 20 tablets; starting dose 20 mg; final dose 40 mg	
Reporting group title	Venlafaxine and Fingolimod
Reporting group description:	
Fingolimod 0.5 mg per capsule(hard gelatin capsules) was taken p.o. once daily. Venlafaxine, supplied in blistered packs containing 14 capsules; starting dose 75 mg; final dose 150 mg	
Reporting group title	Citalopram and Fingolimod
Reporting group description:	
Fingolimod 0.5 mg per capsule(hard gelatin capsules) was taken p.o. once daily. Citalopram, supplied in blistered packs containing 20 tablets; starting dose 20 mg, final dose 40 mg	
Subject analysis set title	Fingolimod
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
2 Week Pre-treatment Period: Fingolimod 0.5 mg per capsule (hard gelatin capsules) was taken p.o. once during 2 week pre-treatment period.	

Primary: Number of participants who experienced Adverse Events, Serious Adverse Events and Death

End point title	Number of participants who experienced Adverse Events, Serious Adverse Events and Death[1]
End point description:	
In this analysis patients with all (serious and non-serious) adverse events, and death were reported. See Safety Section.	
End point type	Primary
End point timeframe:	
21 weeks	

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: Only descriptive summary statisctics .

End point values	Pre-treatment with Fingolimod	Fluoxetine and Fingolimod	Venlafaxine and Fingolimod	Citalopram and Fingolimod
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	17	15	20
Units: Participants				
Any Adverse Event	15	11	12	12
Death	0	0	0	0
Serious Adverse Event	1	0	1	1

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	17.0

Reporting groups

Reporting group title	Fingolimod
Reporting group description:	
Fingolimod	
Reporting group title	Venlafaxine
Reporting group description:	
Venlafaxine	
Reporting group title	Citalopram
Reporting group description:	
Citalopram	
Reporting group title	Fluoxetine
Reporting group description:	
Fluoxetine	

Serious adverse events	Fingolimod	Venlafaxine	Citalopram
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 54 (1.85%)	1 / 15 (6.67%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			

subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Fluoxetine		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fingolimod	Venlafaxine	Citalopram
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 54 (27.78%)	12 / 15 (80.00%)	12 / 20 (60.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vascular disorders			

Flushing			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Feeling hot			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Ejaculation disorder			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Metrorrhagia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rhinitis allergic			

subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Yawning			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 54 (1.85%)	2 / 15 (13.33%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Libido disorder			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram abnormal			
subjects affected / exposed	1 / 54 (1.85%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	2
Laboratory test abnormal			
subjects affected / exposed	1 / 54 (1.85%)	1 / 15 (6.67%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Weight decreased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Fall			

subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 54 (1.85%)	1 / 15 (6.67%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Hypoaesthesia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Loss of consciousness			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Multiple sclerosis relapse			
subjects affected / exposed	2 / 54 (3.70%)	2 / 15 (13.33%)	0 / 20 (0.00%)
occurrences (all)	2	3	0
Optic neuritis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Parosmia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Sedation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Somnolence			

subjects affected / exposed	1 / 54 (1.85%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Tremor			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	6 / 54 (11.11%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	6	0	0
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Dry mouth			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 54 (0.00%)	3 / 15 (20.00%)	4 / 20 (20.00%)
occurrences (all)	0	3	4
Toothache			

subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 54 (0.00%)	2 / 15 (13.33%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Skin lesion			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Arthritis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Influenza			

subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 54 (3.70%)	1 / 15 (6.67%)	1 / 20 (5.00%)
occurrences (all)	2	1	1
Rhinitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 15 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 15 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1

Non-serious adverse events	Fluoxetine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 17 (64.71%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Feeling hot			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		

Pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Ejaculation disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Metrorrhagia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Yawning			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Libido disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		

Sleep disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Electrocardiogram abnormal			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Laboratory test abnormal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Headache			

subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Hypoaesthesia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Loss of consciousness			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Multiple sclerosis relapse			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Optic neuritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Parosmia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Sedation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Eye disorders			
Asthenopia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Conjunctival haemorrhage			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Toothache			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Dermatitis allergic			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Arthritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2011	Issued before inclusion of patients after review from ethics committee and additional feedback from investigators to further specify inclusion and exclusion criteria and to implement changes to the schedule of assessments. The changes were as follows: - The inclusion/exclusion criteria were modified to add a diagnosis of depression according to ICD-10 criteria to further characterize the patient population having a definite diagnosis of depression. - Exclusion criterion number 10 was revised to specify the exclusion of patients with arrhythmia receiving antiarrhythmic drugs. - An additional study drug discontinuation criterion in terms of QTc-prolongation was added to the protocol. - In order to assess possible QTc-prolongations after uptitration of antidepressants and during the clinical assessment additional ECG recordings were included at visit 3.1 and visit 4. Visit 3.1 was changed to be a site visit for patients in the ECG-subgroup. - The correct Modified Fatigue Impact Scale was added to the Appendix; the Fatigue Impact Scale (39 items) was incorrectly inserted in the original protocol.
06 August 2011	Issued before inclusion of patients based on recommendations from ethics committee: - Exclusion criterion number 10 is revised to specify the exclusion of patients with an increased QT-interval. - In section 7.5.6 the 3-lead ECG was replaced by a 12-lead ECG.
26 August 2011	Issued before inclusion of patients after additional feedback from investigators to eliminate the sertraline arm. It introduced the following changes: - The study design was amended and the sertraline arm was eliminated. - The patient number of the ECG group was increased to 125 patients.
31 January 2012	Issued to implement recommendations of the CHMP to strengthen cardiovascular monitoring during treatment initiation of fingolimod. The EMA was reviewing the benefits and risks of fingolimod. The review had been started after Novartis had informed EMA 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 in November. The patient was being treated with metoprolol and amlodipine for hypertension. 6 other cases of unexplained death had been reported, 3 of which were sudden. In addition, other reports included 3 deaths due to heart attack and 1 due to disruption of the heart rhythm. At the time of its authorisation, no cases of sudden or unexplained death had been reported in studies with fingolimod. However, fingolimod was known to cause a transient bradycardia and might be associated with atrioventricular block after the first dose.

31 January 2012	In agreement with the EMA, the following recommendations are effective immediately for patients treated with fingolimod as described in "Dear Health Care Professional Letter" as follows: 'For all patients starting treatment, monitoring during the first 6 hours after dosing should include:- a 12-lead ECG prior and 6 hours after the first dose; - continuous 6-hour ECG monitoring; -lood pressure and heart rate measurement every hour. -In those patients with evidence of clinically important cardiac effects, monitoring should be extended until resolution. The following criteria for extended monitoring are recommended: - The presence at the 6-hour time-point after first dose of: o heart rate less than 40 beats per minute; -decrease in heart rate of more than 20 beats per minute compared with baseline; - persistent new-onset 2nd degree atrioventricular block, Mobitz Type I (Wenckebach). - The occurrence at anytime during the 6-hour-monitoring of: - symptomatic bradycardia; - new onset 2nd degree atrioventricular block, Mobitz Type II; - new onset 3rd degree atrioventricular block. When fingolimod treatment is interrupted for more than 14 days for re-commencing the above recommendations for first dose monitoring will also apply.' On January 27, 2012 the "Dear Health Care Professional Letter" was sent to all FTY720 study sites. These recommendations were effective immediately. Sites were required to inform the patients about these new recommendations and patients were required to reconsent their participation.
20 June 2012	The citalopram arm was being closed due to ethics committee request to increase the frequency of ECG recordings in the citalopram arm. This request could not be fulfilled as a higher frequency of ECG controls on a weekly basis would extremely minimize acceptance of investigators and patients and therefore strongly affect recruitment. Treatment with the combination of fingolimod and citalopram therapy was available without any additional ECG in clinical routine. Therefore the sample size was reduced to 250 patients. The inclusion of patients with cardiac risk factors was revised according to the new recommendations of CHMP and EMA. - Patients who had already been on fingolimod for at least 7 days could be enrolled or patients where the first dose observation took place in the study CFTY720DDE17 and completed this study were also eligible for inclusion. The study CFTY720DDE17 was implemented to collect additional safety data on bradyarrythmic events after the first dose of fingolimod. Patients were monitored by ECG (pre-dose 12-lead ECG, 6h continuous ECG and a 12-lead ECG 6h post dose) following the first dose of fingolimod. - The uptitration period was prolonged to max. 28 days and the wash-out period for prior antidepressant therapy was shortened to 14 days prior visit 2. - The most recent recommendations from EMA in terms of cardiac response monitoring following the first dose of fingolimod were included. Sites were required to inform the patient about these new recommendations and patients were required to re-consent their participation.
06 August 2012	Issued to implement corrective changes: - A well-known mode of action of fingolimod is a reduction of peripheral lymphocyte count to values which are approximately 70-75% lower than baseline counts. If patients are pretreated with fingolimod lymphocyte counts can be lower than 800 cells/mm3. Exclusion criterion #12 was modified to reflect the inclusion of pretreated patients. - The number of dispensed packs of antidepressant medication at visit 3 was corrected according to the longer titration period implemented with Amendment 5. - Treatment initiation recommendations in cardiac risk patients were removed as these patients could not be included in the trial.
12 March 2013	Issued to stop recruitment due to slow enrollment. The first patient was recruited on 11 Nov 2011 and the necessary patient number had still not been reached, even though the recruitment phase had been extended by 30 weeks. 54 out of the 250 anticipated patients had entered the study and it was considered unlikely that the planned number of patients could be achieved in a reasonable period of time. Therefore, the recruitment for this study was stopped prematurely. The analysis was performed as planned. Centers were notified to stop recruitment of patients on 30 Apr 2013. Patients, who had already been recruited into the study performed all planned visits according to the protocol.

01 August 2013	Issued to implement an update of the Gilenya (fingolimod) label in the EU approved by the Committee for Medicinal Products for Human Use (CHMP): - The label update provides refined guidance on when existing first dose monitoring procedures should be repeated. In patients, who are re-initiated after a certain treatment interruption, a repetition of first-dose-monitoring strategy is necessary. - In patients, who require pharmacological intervention during the first dose monitoring and who are monitored overnight in a medical facility, monitoring should be repeated after the second dose of fingolimod.

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.

Statistical Analysis was not completed as the Primary Outcome Measure was safety.

Notes: