Clinical trial results:
A 3-year multi-center study to describe the long term changes of optical coherence tomography (OCT) parameters in patients under treatment with Gilenya®

Summary

EudraCT number	2012-000674-31
Trial protocol	DE
Global end of trial date	18 February 2019

Results information

Result version number	v1 (current)
This version publication date	01 March 2020
First version publication date	01 March 2020

Trial information

Trial identification

Sponsor protocol code	CFTY720DDE15TS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01705236
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	18 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the change in average RNFL thickness (RNFLT) in RRMS subjects treated with fingolimod over 36 months as assessed by OCT.

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	20 August 2012
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: 77
Country: Number of subjects enrolled	Switzerland: 10
Worldwide total number of subjects	87
EEA total number of subjects	77

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)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened at 10 study centers in Germany (9 centers) and Switzerland (1 center).

Pre-assignment

Screening details:

Subjects who passed the screening were enrolled in the trial.

Period 1

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

Arms

Arm title	Fingolimod - Longitudinal Assessment

Arm description:

No study drug was provided. Fingolimod was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study.

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:

Fingolimod was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study.

Number of subjects in period 1	Fingolimod - Longitudinal Assessment
Started	87
Completed	60
Not completed	27
Abnormal laboratory value(s)	4
Consent withdrawn by subject	5
Adverse event, non-fatal	5
Unsatisfactory therapeutic effect	3
Administrative problems	2
Lost to follow-up	1
Abnormal test procedure result(s)	4
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Fingolimod - Longitudinal Assessment
Reporting group description:	
No study drug was provided. Fingolimod was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study.	

Reporting group values	Fingolimod - Longitudinal Assessment	Total	
Number of subjects	87	87	
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)	87	87	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	35.9		
standard deviation	± 9.5	-	
Sex: Female, Male Units: Participants			
Female	55	55	
Male	32	32	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	84	84	
Other	3	3	

End points

End points reporting groups

Reporting group title	Fingolimod - Longitudinal Assessment

Reporting group description:

No study drug was provided. Fingolimod was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study.

Primary: Change from baseline to month 36 in average Retinal Nerve Fiber Layer Thickness (RNFLT)

End point title	Change from baseline to month 36 in average Retinal Nerve Fiber Layer Thickness (RNFLT)[1]

End point description:

The primary endpoint was the change, i.e. the absolute difference, in average RNFL thickness from baseline to month 36 (or last values in case of missing data) in the Full Analysis Set (FAS). Average RNFL thickness was the average of valid measurements of the right and left eye and assessed by optical coherence tomography (OCT).

End point type	Primary

End point timeframe:

Baseline, month 36

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: single arm trial.

End point values	Fingolimod - Longitudinal Assessment			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: micrometer				
arithmetic mean (standard deviation)	-1.5 (± 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to month 12 and 24 in average Retinal Nerve Fiber Layer Thickness (RNFLT)

End point title	Change from baseline to month 12 and 24 in average Retinal Nerve Fiber Layer Thickness (RNFLT)

End point description:

Change from baseline in average RNFL thickness to months 12 and 24 (or last values in case of missing data) in the Full Analysis Set (FAS). Average RNFL thickness was the average of valid measurements of the right and left eye and assessed by optical coherence tomography (OCT).

End point type	Secondary

End point timeframe:

Baseline, month 12, month 24

End point values	Fingolimod - Longitudinal Assessment			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: micrometer				
arithmetic mean (standard deviation)				
Change from baseline to month 12	-0.8 (± 2.4)			
Change from baseline to month 24	-1.1 (± 2.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to month 12, 24 and 36 in average quadrant Retinal Nerve Fiber Layer Thickness (RNFLT)

End point title	Change from baseline to month 12, 24 and 36 in average quadrant Retinal Nerve Fiber Layer Thickness (RNFLT)

End point description:

Change from baseline in average quadrant RNFL thickness to months 12, 24 and 36 (or last values in case of missing data) in the Full Analysis Set (FAS). Average quadrant RNFL thickness was the average of valid measurements of the right and left eye and assessed by optical coherence tomography (OCT). Quadrant RNFL thickness were: Nasal-inferior; nasal-superior; temporal-inferior; temporal-superior.

End point type	Secondary

End point timeframe:

Baseline, month 12, month 24, month 36

End point values	Fingolimod - Longitudinal Assessment			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: micrometer				
arithmetic mean (standard deviation)				
Nasal-superior RNFL thickness: month 12	0.5 (± 4.0)			
Nasal-superior RNFL thickness: month 24	-0.4 (± 3.4)			
Nasal-superior RNFL thickness: month 36	-0.7 (± 3.9)			
Nasal-inferior RNFL thickness: month 12	-1.2 (± 4.9)			
Nasal-inferior RNFL thickness: month 24	-1.6 (± 5.1)			
Nasal-inferior RNFL thickness: month 36	-2.1 (± 5.2)			
Temporal-inferior RNFL thickness: month 12	-1.2 (± 2.5)			
Temporal-inferior RNFL thickness: month 24	-1.6 (± 3.1)			

Temporal-inferior RNFL thickness: month 36	-2.3 (± 4.1)			
Temporal-superior RNFL thickness: month 12	-0.5 (± 3.9)			
Temporal-superior RNFL thickness: month 24	-0.4 (± 3.4)			
Temporal-superior RNFL thickness: month 36	-1.1 (± 4.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to month 12, 24 and 36 in Total Macular Volume (TMV)

End point title	Change from baseline to month 12, 24 and 36 in Total Macular Volume (TMV)

End point description:

Change from baseline in TMV to months 12, 24 and 36 (or last values in case of missing data) in the Full Analysis Set (FAS).

End point type	Secondary

End point timeframe:

12, 24 and 36 months

End point values	Fingolimod - Longitudinal Assessment			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Cubic millimeter				
arithmetic mean (standard deviation)				
Change from baseline to month 12	-0.03 (± 0.08)			
Change from baseline to month 24	-0.04 (± 0.08)			
Change from baseline to month 36	-0.06 (± 0.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to month 12, 24 and 36 in Ganglion Cell Inner Plexiform (GCIP)

End point title	Change from baseline to month 12, 24 and 36 in Ganglion Cell Inner Plexiform (GCIP)

End point description:

Change from baseline in GCIP to months 12, 24 and 36 (or last values in case of missing data) in the Full Analysis Set (FAS).
The change in Ganglion cell layer thickness (GCLT) had been defined as secondary endpoint in the protocol, but OCT measured the GCIP instead. This was done because both layers were not clearly

separable by OCT. GCIP was calculated as mean of the inner sectors (nasal, superior, temporal, and inferior) and declared as usual parameter instead. This change was introduced prior to data base lock, but the derivation of GCIP was corrected after data base lock.

End point type	Secondary

End point timeframe:

Baseline, month 12, month 24, month 36

End point values	Fingolimod - Longitudinal Assessment			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: micrometer				
arithmetic mean (standard deviation)				
Change from baseline to month 12	-0.49 (± 2.39)			
Change from baseline to month 24	-0.42 (± 2.74)			
Change from baseline to month 36	-0.46 (± 3.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events

End point title	Number of participants with adverse events

End point description:

Number of participants with adverse events and specifically macular edema.

End point type	Secondary

End point timeframe:

36 months

End point values	Fingolimod - Longitudinal Assessment			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: Participants				
No. of subjects with any AE	80			
No. of subjects with macular edema	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study Treatment until end of study treatment up to maximum duration of 36 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Total

Reporting group description:

Total

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 87 (12.64%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CERVIX CARCINOMA STAGE 0			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NASAL NEOPLASM			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
UTERINE LEIOMYOMA			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
LOWER LIMB FRACTURE			

subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RADIUS FRACTURE				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUTURE RELATED COMPLICATION				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
AORTIC VALVE INCOMPETENCE				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
MULTIPLE SCLEROSIS RELAPSE				
subjects affected / exposed	2 / 87 (2.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
NEURALGIC AMYOTROPHY				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UHTHOFF'S PHENOMENON				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
CERVICAL DYSPLASIA				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ERYSIPELAS			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OPHTHALMIC HERPES ZOSTER			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
WOUND INFECTION			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 87 (78.16%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	12 / 87 (13.79%)		
occurrences (all)	12		
Nervous system disorders			

DIZZINESS subjects affected / exposed occurrences (all) HEADACHE subjects affected / exposed occurrences (all) MULTIPLE SCLEROSIS RELAPSE subjects affected / exposed occurrences (all) PARAESTHESIA subjects affected / exposed occurrences (all)	5 / 87 (5.75%) 5 10 / 87 (11.49%) 10 21 / 87 (24.14%) 31 5 / 87 (5.75%) 5		
Blood and lymphatic system disorders LYMPHOPENIA subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 10		
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 8		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 7		
Skin and subcutaneous tissue disorders ALOPECIA subjects affected / exposed occurrences (all)	5 / 87 (5.75%) 5		
Psychiatric disorders DEPRESSION subjects affected / exposed occurrences (all)	5 / 87 (5.75%) 5		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) BACK PAIN	5 / 87 (5.75%) 5		

subjects affected / exposed	7 / 87 (8.05%)		
occurrences (all)	10		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	8		
CONJUNCTIVITIS			
subjects affected / exposed	5 / 87 (5.75%)		
occurrences (all)	7		
NASOPHARYNGITIS			
subjects affected / exposed	41 / 87 (47.13%)		
occurrences (all)	68		
SINUSITIS			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	9		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	7 / 87 (8.05%)		
occurrences (all)	13		
URINARY TRACT INFECTION			
subjects affected / exposed	7 / 87 (8.05%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
VITAMIN D DEFICIENCY			
subjects affected / exposed	8 / 87 (9.20%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2013	Implementation of an update of the Gilenya® (fingolimod) label providing refined guidance on when existing first dose monitoring procedures should be repeated after treatment interruption or after pharmacological intervention during first dose monitoring.
27 March 2014	Further definition of blood biomarker sampling was added and the period of one month was defined as 28 days. Furthermore, the specifications for contraception and for elevated liver function tests were adjusted and some inconsistencies within the protocol were corrected.
20 May 2015	Blood biomarker sampling was removed from the protocol and a responsible person for OCT quality control was added.
26 July 2016	Clarification that the minimum pre-treatment with fingolimod was 28 days and adaption of the visit schedule to the recommended visit schedule in the fingolimod product information which recommends visits every 3 months of treatment. Therefore, one month during the observational period of this study was re-defined as 28–31 days depending on the actual length of the respective month. The definition of one month as 28 days was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported