Clinical trial results:
A 32-week, monocentric, exploratory, single arm study to assess immune function and MRI disease activity in patients with relapsing remitting multiple sclerosis (RRMS) transferred from previous treatment with Natalizumab to Gilenya® (Fingolimod)

Summary

EudraCT number	2013-004616-21
Trial protocol	DE
Global end of trial date	12 February 2016

Results information

Result version number	v1 (current)
This version publication date	10 March 2017
First version publication date	10 March 2017

Trial information

Trial identification

Sponsor protocol code	CFTY720D2415T | V1.00 | 04-Dec-2013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02325440
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor code: UKM12_0037

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Münster, Germany, 48149
Public contact	Head of Administrative Department, Universitätsklinikum Münster, 0049 251 835 5967, dorothee.kreuznacht@ukmuenster.de
Scientific contact	Coordinating Investigator, Universitätsklinikum Münster, 0049 25183444-52, LuisaHildegard.Klotz@ukmuenster.de

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	03 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2016
Global end of trial reached?	Yes
Global end of trial date	12 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of changes in the reconstitution of immune surveillance over time upon switching from natalizumab to fingolimod assessed by a change in the expression of CD49d.
Evaluation of changes in the migratory capacity of immune cells/PBMCs upon switching from natalizumab to fingolimod in an in-vitro model of the blood-brain-barrier (BBB).
Evaluation of changes in paraclinical disease activity over time upon switching from natalizumab to fingolimod assessed by MRI

Protection of trial subjects:

Safety monitoring (adverse Events, serious adverse Events, adverse drug reactions)
Continous assessment of laboratory values (blood/urine)

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	03 March 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	Germany: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	15

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 patients were enrolled. The duration of the recruitment phase was one year. First patient was enrolled on 22-Apr-2014 (FPFV) and last patient was enrolled on 15-Apr-2015 (LPFV).

Pre-assignment

Screening details:

Suitable patients were selected by the investigator. 15 patients were screened. One of the patients was initially deemed screening failure, but re-screened at a later point of time and subsequently enrolled.

Period 1

Period 1 title	Natalizumab - Washout
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment arm

Arm description:

One final dose of natalizumab 300mg followed by an 8-week washout phase

Arm type	Experimental
Investigational medicinal product name	Natalizumab
Investigational medicinal product code	EU/1/06/346/001
Other name	Tysabri
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

300 mg i.v. (once at baseline);

Number of subjects in period 1	Treatment arm
Started	15
Completed	15

Period 2

Period 2 title	Fingolimod Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment arm
Arm description: 24-week treatment phase with fingolimod 0.5mg o.i.d.	
Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	EU/1/11/677/001-005
Other name	Gilenya
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 0.5 mg p.o. (o.i.d)	

Number of subjects in period 2	Treatment arm
Started	15
Completed	14
Not completed	1
Serious adverse event	1

Period 3	
Period 3 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment arm
Arm description: Optional 8-week follow-up phase	
Arm type	Optional follow-up
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Treatment arm
Started	14
Completed	13
Not completed	1
Rejection of optional follow-up phase	1

Baseline characteristics

Reporting groups	
Reporting group title	Natalizumab - Washout

Reporting group description: -

Reporting group values	Natalizumab - Washout	Total	
Number of subjects	15	15	
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)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	38.9		
standard deviation	± 9.2	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	4	4	
Ethnicity Units: Subjects			
Caucasian	15	15	

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description:	
One final dose of natalizumab 300mg followed by an 8-week washout phase	
Reporting group title	Treatment arm
Reporting group description:	
24-week treatment phase with fingolimod 0.5mg o.i.d.	
Reporting group title	Treatment arm
Reporting group description:	
Optional 8-week follow-up phase	
Subject analysis set title	FAS (Baseline)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set - Population (Baseline)	
Subject analysis set title	FAS - (EOS; Immunology)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set - Population (EOS | Immunology)	
Subject analysis set title	FAS - (EOS | DTI)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set - Population (EOS | DTI)	

Primary: Changes in expression of marker CD49d/CD4+ on peripheral blood mononuclear cells (PBMC) from week 0 to week 32

End point title	Changes in expression of marker CD49d/CD4+ on peripheral blood mononuclear cells (PBMC) from week 0 to week 32
End point description:	
First co-primary endpoint: Difference in the expression of marker CD49d (mean fluorescence intensity [MFI]) between the measurement at EOS (week 32) and the baseline value (week 0)	
End point type	Primary
End point timeframe:	
32 weeks	

End point values	FAS (Baseline)	FAS - (EOS; Immunology)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	14[1]		
Units: Mean Fluorescence Intensity (MFI)				
arithmetic mean (standard deviation)	6.03 (± 1.05)	10.11 (± 3.71)		

Notes:

[1] - Data for one patient in the FAS was missing at week 32 (EOS)

Statistical analyses

Statistical analysis title	Paired t-test
Statistical analysis description: Paired t-test with a significance level of 0.05%	
Comparison groups	FAS (Baseline) v FAS - (EOS; Immunology)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	t-test, 2-sided

Primary: Changes in migratory capacity of immune cells/peripheral blood mononuclear cells (PBMCs) in an in-vitro model of the blood-brain-barrier (BBB) from week 0 to week 32

End point title	Changes in migratory capacity of immune cells/peripheral blood mononuclear cells (PBMCs) in an in-vitro model of the blood-brain-barrier (BBB) from week 0 to week 32
End point description: Second co-primary endpoint: Difference between migratory capacities of unstimulated CD4+ cells at EOS (week 32) compared to baseline (week 0)	
End point type	Primary
End point timeframe: 32 weeks	

End point values	FAS (Baseline)	FAS - (EOS; Immunology)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	14[2]		
Units: Fluorescence intensity				
arithmetic mean (standard deviation)	1.44 (± 0.54)	3.33 (± 2.71)		

Notes:

[2] - Data for one patient in the FAS was missing at week 32 (EOS)

Statistical analyses

Statistical analysis title	Paired t-test
Statistical analysis description: Paired t-test with a significance level of 0.05%	
Comparison groups	FAS (Baseline) v FAS - (EOS; Immunology)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.028
Method	t-test, 2-sided

Secondary: MRI Disease activity - Number of new Gd+ lesions from week 0 to week 32

End point title	MRI Disease activity - Number of new Gd+ lesions from week 0 to week 32

End point description:

Number of new Gd+ lesions counted from baseline until EOS

End point type	Secondary

End point timeframe:

32 weeks

End point values	FAS - (EOS; Immunology)			
Subject group type	Subject analysis set			
Number of subjects analysed	15[3]			
Units: Number of new Gd+ lesions				
median (inter-quartile range (Q1-Q3))	3 (0 to 6)			

Notes:

[3] - Data for one patient at one visit missing | Reason: Study discontinuation

Statistical analyses

No statistical analyses for this end point

Secondary: MRI disease activity - Number of new T2w lesions from week 0 to week 32

End point title	MRI disease activity - Number of new T2w lesions from week 0 to week 32

End point description:

Number of new T2w lesions counted from baseline until EOS.

End point type	Secondary

End point timeframe:

32 weeks

End point values	FAS - (EOS; Immunology)			
Subject group type	Subject analysis set			
Number of subjects analysed	15[4]			
Units: Number of new T2w lesions				
median (inter-quartile range (Q1-Q3))	1 (0 to 5)			

Notes:

[4] - Data for one patient at one visit missing | Reason: Study discontinuation

Statistical analyses

No statistical analyses for this end point

Secondary: MRI disease activity - Change in DTI fractional anisotropy from week 0 to week 32

End point title	MRI disease activity - Change in DTI fractional anisotropy from week 0 to week 32

End point description:

Change in DTI fractional anisotropy from baseline to EOS

End point type	Secondary

End point timeframe:

32 weeks

End point values	FAS (Baseline)	FAS - (EOS | DTI)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10[5]		
Units: DTI fractional anisotropy				
median (inter-quartile range (Q1-Q3))	0.29 (0.28 to 0.3)	0.29 (0.29 to 0.3)		

Notes:

[5] - Data for five patients in the FAS were missing at week 32 (EOS)

Statistical analyses

Statistical analysis title	Paired t-test

Statistical analysis description:

Paired t-test with a significance level of 0.05%

Comparison groups	FAS (Baseline) v FAS - (EOS | DTI)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.975
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events were recorded from baseline (week 0) until end of follow-up phase (week 40)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	Safety Set
Reporting group description:	
Full-Analysis-Set = Safety Set	

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Nuclear magnetic resonance imaging brain abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
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	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood triglycerides increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Lymphocyte count decreased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Nuclear magnetic resonance imaging brain abnormal			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	15		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Concussion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Peroneal nerve injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			

Cervicobrachial syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	13		
Multiple sclerosis relapse			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Muscle spasticity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Enteritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			

Skin fissures			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Dental fistula			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Herpes simplex			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	13 / 15 (86.67%)		
occurrences (all)	24		

Oral herpes			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Periodontitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26099927