



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)
Continuous 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 | |
| Weight | | | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 82.5 | | |
| standard deviation | ± 22.5 | - | |
| Body-Mass-Index (BMI) | | | |
| Body-Mass-Index (BMI) | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 27.6 | | |
| standard deviation | ± 7.5 | - | |
| Height | | | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 172.9 | | |
| standard deviation | ± 7.3 | - | |

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

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

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