Trial Description

Title

A 24-week, multicenter, exploratory, two arm study to assess the effect of Dimethyl fumarate on Immune-Modulatory Action on T cells in patients with relapsing remitting Multiple Sclerosis (DIMAT-MS)

Trial Acronym

DIMAT-MS

URL of the trial

[---]*

Brief Summary in Lay Language

**This is an exploratory study, which allows analysis of multiple immune parameters derived from peripheral blood
mononuclear cells (PBMCs) from patients with relapsing remitting multiple sclerosis before and during immunemodulatory
treatment with dimethyl fumarate in comparison to PBMCs from healthy subjects.**

Brief Summary in Scientific Language

Investigation of the effect of Dimethyl fumarate on T cells in patients with relapsing remitting Multiple Sclerosis

Do you plan to share individual participant data with other researchers?

[---]*

Description IPD sharing plan

[---]*

Organizational Data

- DRKS-ID: **DRKS00008037**
- Date of Registration in DRKS: **2015/05/22**
- Date of Registration in Partner Registry or other Primary Registry: **2015/02/17**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **2015-066-f-A , Ethik-Kommission der Ärztekammer Westfalen-Lippe und der med. Fakultät der Westfälischen Wilhelms-Universität**

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Ethics Approval/Approval of the Ethics Committee: **Approved**

Münster

Secondary IDs

- Universal Trial Number (UTN): **U1111-1164-2476**
- EudraCT-No.
(for studies acc. to Drug Law): **2014-003481-25**
- Primary Registry-ID: **EUCTR2014-003481-25-DE (EUCTR)**

Health condition or Problem studied

- ICD10: **G35.1 - message.icd10.coding.redirected.en**
- MedDRA: **Relapsing-remitting multiple sclerose (10063399)**

Interventions/Observational Groups

- Arm 1: **Patients with relapsing remitting multiple sclerosis will receive dimethyl fumarate from week 0 to week 24. Dimethyl fumarate treatment is initiated by daily administration of 120 mg p.o. in the morning in week 0. At week 1, the dose is increased to 120 mg p.o. twice daily, split into a morning and an evening dose. At week 2, the daily dose is further increased to 240 mg p.o. in the morning and 120 mg p.o. in the evening. Finally at week 3, the dose will be increased to the final daily dose of 240 mg p.o. in the morning and 240 mg p.o. in the evening and maintained to week 24.**
- Arm 2: **Healthy subject without active treatment**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Non-randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***

Study Type: **Interventional**

Study Type Non-Interventional: **[---]***

Allocation: **Non-randomized controlled trial**

Blinding: **[---]***

Who is blinded: **[---]***

- Control: **Other**
- Purpose: **Other**
- Assignment: **Other**
- Phase: **IV**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **No**

Primary Outcome

changes in lymphocyte subpopulations upon dimethyl fumarate (Tecfidera)-treatment in RRMS patients at week 8, 16 and 24 compared to baseline.

changes in lymphocyte subpopulations of dimethyl fumarate (Tecfidera)-treated RRMS patients compared to healthy subjects at week 0, 8, 16 and 24.

Secondary Outcome

changes in T cell effector functions, in terms of cytokine production of CD4+ and CD8+ T cells derived of PBMC of dimethyl fumarate (Tecfidera)-treated patients at weeks 8, 16 and 24 as compared to baseline.

changes in T cell effector functions, in terms of cytokine production of CD4+ and CD8+ T cells derived of PBMC of dimethyl fumarate (Tecfidera)-treated patients compared to PBMCs of healthy subjects at week 0, 8, 16 and 24.

changes of the differentiation capacity of helper T cell subpopulations (Th1 and Th17 cells) upon dimethyl fumarate (Tecfidera) treatment in RRMS patients treatment at week 24 compared to baseline.

changes of the differentiation capacity of helper T cells from dimethyl fumarate (Tecfidera)-treated patients compared to T cells from healthy subjects at baseline and week 24.

changes in the migratory capacity of immune cells/PBMCs upon dimethyl fumarate (Tecfidera) treatment in an in-vitro model of the blood-brain-barrier (BBB) at week 24 compared to baseline.

changes in the migratory capacity of immune cells/PBMCs from dimethyl fumarate (Tecfidera)-treated patients compared to immune cells/PBMCs from healthy subjects in an in-vitro model of the blood-brain-barrier (BBB) at baseline and weeks 24.

changes on the suppressive capacity of regulatory T cells in respect to

suppression of effector T cell responses upon dimethyl fumarate (Tecfidera) treatment at week 24 compared to baseline.

changes on the suppressive capacity of regulatory T cells of dimethyl fumarate (Tecfidera)-treated patients compared to regulatory T cells from healthy subjects in respect to suppression of effector T cell responses at baseline and week 24.

changes in lymphocyte subpopulations upon dimethyl fumarate (Tecfidera) treatment in RRMS patients at week 48 compared to baseline.

changes in lymphocyte subpopulations of dimethyl fumarate (Tecfidera)-treated RRMS patients compared to healthy subjects at baseline and week 48.

changes in the T cell effector functions of CD4+ and CD8+ T cells derived of PBMC of dimethyl fumarate (Tecfidera)-treated patients at week 48 compared to baseline.

changes in the T cell effector functions of CD4+ and CD8+ T cells derived of PBMC of dimethyl fumarate (Tecfidera)-treated patients compared to PBMCs of healthy subjects at baseline and week 48.

changes in the migratory capacity of immune cells/PBMCs upon dimethyl fumarate (Tecfidera) treatment in an in-vitro model of the blood-brain-barrier (BBB) at week 48 compared to baseline.

changes in the migratory capacity of immune cells/PBMCs from dimethyl fumarate (Tecfidera)-treated patients compared to immune cells/PBMCs from healthy subjects in an in-vitro model of the blood-brain-barrier (BBB) at baseline and week 48.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Klinik für Allgemeine Neurologie, Münster**
- University Medical Center **Neurologische Klinik, Heidelberg**
- University Medical Center **Klinik und Poliklinik für Neurologie, Mainz**
- Doctor's Practice **Frankfurt a.M.**
- Doctor's Practice **Bonn**
- Medical Center **MVZ-Neurologie, Osnabrück**

Recruitment

- Planned/Actual: **Actual**

Planned/Actual: **Actual**

- (Anticipated or Actual) Date of First Enrollment: **2015/06/05**
- Target Sample Size: **75**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **60 Years**

Additional Inclusion Criteria

Healthy subjects:
H-1. Written informed consent must be obtained before any assessment is performed.
H-2. Male and female subjects aged 18 - 60 years.
H-3. No history of multiple sclerosis or clinically isolated syndrome.
H-4. No history of other autoimmune diseases, which has been treated systemically with corticosteroids, immunomodulators or immunosuppressive drugs at any time point.

Patients with relapsing remitting multiple sclerosis:
MS-1. Written informed consent must be obtained before any assessment is performed.
MS-2. Male and female subjects aged 18 - 60 years.
MS-3. Patients with RRMS, defined by 2010 revised McDonald criteria.
MS-4. Patients with an Expanded Disability Status Scale (EDSS) score of 0-6.0.
MS-5. Patients with one of the following treatment status: Naïve to disease modifying (DM) treatment (i.e. no DM treatment for at least 1 month), Currently on MS therapy with interferon β-1 or glatiramer acetate and willing to switch to dimethyl fumarate (Tecfidera®).
MS-6. MRI-scan of the brain ≤ 3 months at screening.

Exclusion criteria

RRMS patients:
MS-1. Known hypersensitivity to dimethyl fumarate or any ingredients of Tecfidera® (microcrystalline cellulose; croscarmellose-sodium; talcum; high dispersion, hydrophobic silicon dioxide; magnesiumstearate (Ph. Eur.); triethylcitrate; methacrylic acid-methacrylate copolymer (1:1) (Ph. Eur.); methacrylic acid-ethylacrylate copolymer (1:1)-dispersion 30% (Ph. Eur.), simeticon, sodiumdodecylsulfate, polysorbate 80, gelantine, titanium oxide (E171), brilliant blue (E133), hydrated Iron(III)-oxide hydroxide (E172), shellac, potassium hydroxide.
MS-2. A MS-relapse within 30 days prior to screening.
MS-3. Known history of active tuberculosis or active tuberculosis determined by a

positive QuantiFERON® TB Gold test (i.e. a negative test result has to be provided at screening unless a negative test result exists from the last 3 months prior to screening).
MS-4. Moderate to severe impairment of liver function or persisting elevations > 2 x ULN (confirmed by retest) of serum glutamic pyruvic transaminase/ alanine aminotransferase (SGPT/ALT) or serum glutamic oxaloacetic transaminase/aspartate aminotransferase (SGOT/AST), except patients with confirmed Gilbert´s syndrome (Meulengracht´s disease).
MS-5. Moderate to severe impairment of renal function, as shown by serum creatinine > 133 µmol/L (or > 1.5 mg/dL).
MS-6. Patients with significantly impaired bone marrow function or significant anemia, leukopenia, neutropenia or thrombocytopenia.
MS-7. Women of childbearing potential not utilizing highly effective contraception.

Both populations:
MS/H-1. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
MS/H-2. Subjects unlikely to comply with protocol as determined by investigator, e.g., uncooperative attitude, inability to return for follow-up visits (e.g. major physical disability), and known unlikelihood of completing the study.
MS/H-3. Clinically relevant cardiovascular, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the subject at risk by participating in the study.
MS/H-4. Subjects with ulcerative colitis or Crohn´s disease.
MS/H-5. Subjects with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymph proliferative disease, or any subject who has received lymphoid irradiation.
MS/H-6. Human immunodeficiency virus (HIV) positive, hepatitis B virus positive or hepatitis C virus positive subjects (i.e. a negative test result has to be provided at screening. In the presence of a negative test result from the last 3 months prior to screening, the test has not to be repeated at screening.).
MS/H-7. Acute or chronic infection.
MS/H-8. History of drug or alcohol abuse.
MS/H-9. Use of adrenocorticotrophic hormone (ACTH) or systemic corticosteroids for 4 weeks prior to screening.
MS/H-10. Prior or concomitant use of cytokine therapy or intravenous immunoglobulins in the 3 months prior to screening.
MS/H-11. Prior use of alemtuzumab or cladribine.
MS/H-12. Prior use (within 1 year) of fingolimod (Gilenya®) or natalizumab (Tysabri®).
MS/H-13. Prior use (within 2 years) of mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporine, methotrexate or mycophenolate mofetil.
MS/H-14. Prior treatment with teriflunomide or leflunomide, unless successful wash-out, confirmed by plasma concentration of < 0.02 µg/ml.
MS/H-15. Prior use of any investigational drug in the 6 months preceding screening.
MS/H-16. Pregnant or breast-feeding women.

Addresses

- **Primary Sponsor**

Primary Sponsor

Universitätsklinikum Münster
Albert-Schweitzer-Campus 1, Geb. D5
48149 Münster
Germany

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URL: **www.klinikum.uni-muenster.de**

■ **Contact for Scientific Queries**

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Sources of Monetary or Material Support

■ **Commercial (pharmaceutical industry, medical engineering industry, etc.)**

Biogen Idec GmbH
Carl-Zeiss-Ring 6
85737 Ismaning
Germany

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Commercial (pharmaceutical industry, medical engineering industry, etc.)

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Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*