# Characterization of the immuno-modulatory effects of Tecfidera in multiple sclerosis patients: exploration of drug mechanism and methodological feasibility.

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The main purpose of the study is to assess immune cell dynamics in Tecfidera-treated MS patients and untreated healthy subjects, and to explore whether differences in immune cell dynamics exist between both populations. The data generated in this...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | White blood cell disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON42490

**Source**
ToetsingOnline

**Brief title**
Characterization immuno-modulatory effects of Tecfidera: feasibility study.

### Condition

- White blood cell disorders

**Synonym**
Reduced lymphocyte count. Reduced white bloodcell count.

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Centre for Human Drug Research
**Source(s) of monetary or material Support:** Biogen,CHDR

## Intervention

**Keyword:** Heavy water, Multiple sclerosis, Reduced lymphocyte counts, Tecfidera

## Outcome measures

### Primary outcome

Standard safety:

- nature, frequency, and severity of adverse events;

- concomitant medication.

Immuno-monitoring:

- total leukocyte count and (automated) differential count;

- immunophenotyping for absolute cell counts of the target populations (CD4+ T-cells, naïve and memory CD8+ T-cells, CD19+ B-cells) from whole blood, including Annexin V expression and PI incorporation (FACS);

- mitochondrial membrane potential for target populations (Mitoscreen according to GBS SOP T272E, from PBMCs, when sufficient material is available);

- lymphocyte dynamics per isolated target population* (deuterium incorporation by GCMS, after immunomagnetic purification of target populations from PBMCs):

o production rate;

o disappearance rate.

* also requires assessment of deuterium enrichment in granulocytes and

deuterium enrichment in urine (GCMS)

The specific markers mentioned above are indicative. Other or additional markers may be selected, as long as no deviation is made from the number and volume of blood samples reported in the study protocol.

**Secondary outcome**

Protein or lipid composition and incorporation of deuterium in stratum corneum proteins or lipids, including ceramides and other lipid classes.

# Study description

**Background summary**

Early 2013, Tecfidera (dimethyl fumarate, DMF) was approved by the European Medicine Agency (EMA) as oral treatment for adult patients with relapsing remitting multiple sclerosis (RRMS). In clinical studies in RRMS patients, Tecfidera treatment resulted in a clinically meaningful and statistically significant reduction disease relapse (Fox et al., 2012; Gold et al., 2012) Long-term treatment with Tecfidera may result in reductions in lymphocyte counts (Spencer et al., 2015; Rosenkranz et al., 2015; Khatri et al., 2015; Berkovich et al., 2015). DMF-induced reduction in lymphocyte counts does not appear to be disease-related since reductions in lymphocyte counts are also observed in DMF-treated psoriasis patients (Harries et al., 2005; Wain et al., 2010). Although some mechanistic insight is available on the immune-modulating activity of DMF, detailed insight into the specific time course of the drug effects is lacking. Moreover, neither the exact causes nor the functional consequences of DMF-induced reductions in lymphocyte counts have been documented. Therefore, dedicated clinical studies are proposed to gain this information.

It is not known whether the Tecfidera-induced reductions in blood lymphocyte counts can be explained by a diminished production, by an enhanced cell death, or by homing of the immune cells to lymphoid tissues. To obtain mechanistic insight into the Tecfidera-induced reductions in lymphocyte counts, circulating lymphocytes can be labelled in vivo with deuterium. This procedure will allow quantification of the production rate and disappearance rate of the cell populations of interest. By combining these cell kinetic parameters with

cellular markers for cellular stress (mitochondrial dysfunction) and cell death and, we aim to investigate whether reduced lymphocyte numbers in Tecfidera-treated RRMS patients are explained by a reduced production rate, or a shorter life span due to cell death. In vivo deuterium labeling of human immune cells has been performed before, both in healthy volunteers and in patient populations (Vrisekoop et al., 2008; Westera et al., 2015; Hellerstein et al., 2003). The clinical study described in this protocol aims to assess immune cell dynamics in Tecfidera-treated MS patients and untreated healthy subjects, and will explore whether differences in immune cell dynamics exist between both populations. Based on the data generated in this clinical study, a subsequent clinical study may be designed exploring the effects of Tecfidera on lymphocyte counts and dynamics in a more controlled setting.

Apart from the main study objective (exploration of differences in immune cell dynamics between healthy subjects and Tecfidera-treated MS patients), this study will also explore the protein or ceramide kinetics in tape stripped skin from healthy subjects. This tape stripping is non-invasive and not directly related to Tecfidera effects, and is intended to explore a non-invasive method for assessment of the epidermal protein or lipid synthesis. Future application of this methodology could provide insight into the mechanisms and dynamic processes underlying skin (patho)physiology, and allow objective quantification of the response to therapeutic agents in clinical trials.

**Study objective**

The main purpose of the study is to assess immune cell dynamics in Tecfidera-treated MS patients and untreated healthy subjects, and to explore whether differences in immune cell dynamics exist between both populations. The data generated in this clinical study may support the design and specific methodology of a subsequent clinical study exploring Tecfidera effects on lymphocyte counts and dynamics in a more controlled setting.

Primary objectives:

1. Quantification of CD4+, naive and memory CD8+ T-cell and CD19+ B-cell numbers in Tecfidera-treated MS patients and untreated healthy subjects over time;
2. Quantification of production and disappearance rates of CD4+, naive and memory CD8+ T-cells and CD19+ B-cells in Tecfidera-treated MS patients and untreated healthy subjects;
3. Assessment of markers for cell death and cellular stress, in relation to cell production and disappearance rates.

Secondary objective:
Quantification of protein or ceramide kinetics in tape stripped skin from healthy subjects (unrelated to Tefidera effects; independent objective): exploration of a non-invasive method for assessment of epidermal protein

synthesis, which can also be adapted to measure epidermal lipids. This methodology could serve as a tool providing insight into the mechanisms and dynamic processes underlying skin (patho)physiology, and as an objective scale for quantification of the response to therapeutic agents in clinical trials.

### Study design

This is a prospective, single-center, observational study. Eight MS patients receiving Tecfidera treatment for at least six months will be enrolled. In addition, eight age- and gender-matched healthy subjects will be included. No pharmacological intervention will be performed, but all study participants will receive an investigational product (deuterated water) for the quantification of production and disappearance rate of circulating immune cells.

In addition, tape stripping will also be performed on the healthy volunteers.

### Intervention

All subjects enrolled in this study will be administered deuterated water for 9 weeks. The administration of deuterated water is a methodological intervention, and as such deuterated water is not regarded as investigational product.

### Study burden and risks

Burden: Deuterated water administration, measurements, blood sampling, compliance with strict lifestyle restrictions and time investment.
Risks: potential side effects of deuterated water and potential complaints caused by being fasted and blood sample collection.

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Inclusion criteria, MS patients
- male and female subjects;
- minimal age 18 years at the time of informed consent;
- confirmed relapsing remitting multiple sclerosis (RRMS) patients, with:
- a diagnosis of RRMS according to the revised McDonald criteria;
- a baseline score of 0 to 5.0 on the Expanded Disability Status Scale;
- patients on Tecfidera treatment for at least 6 months;
- ability to participate, and willingness to give written informed consent and to comply with the study restrictions and protocol requirements.;Inclusion criteria, healthy subjects
- healthy male and female subjects;
- minimal age of 18 years at the time of informed consent;
- ability to participate, and willingness to give written informed consent and to comply with the study restrictions and protocol requirements.

## Exclusion criteria

Exclusion criteria, MS patients
- positive test result for human immunodeficiency virus antibody (HIV-Ab), hepatitis C antibody (HCV-Ab), and/or hepatitis B surface antigen (HbsAg) at screening;
- evidence of any active or chronic disease or condition, other than MS (based on medical history, a physical examination, vital signs, 12 lead ECG, haematology, blood chemistry and urinalysis) that could, in the opinion of the investigator, interfere with the conduct of the study or the study objectives, or pose an unacceptable risk to the subject;
- a treatment history that includes steroids within one month prior to screening, or any other therapy that in the judgment of the investigator potentially interferes with the study objectives (in case of an insufficient washout period);
- body weight < 50 kg.

- subject is pregnant or breast feeding;
- current substance abuse, including alcohol and drugs;
- positive alcohol test or test for drugs of abuse at screening, with the exception of a positive test due to medicinal cannabis use;
- previous deuterium administration;
- participation in an investigational drug or device study within 3 months prior to screening;
- loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening;
- unwillingness or inability to comply with the study protocol for any other reason.;Exclusion criteria, healthy subjects
- positive test result for human immunodeficiency virus antibody (HIV-Ab), hepatitis C antibody (HCV-Ab), and/or hepatitis B surface antigen (HbsAg) at screening;
- evidence of any active or chronic disease or condition (based on medical history, a physical examination, vital signs, 12 lead ECG, haematology, blood chemistry and urinalysis) that could, in the opinion of the investigator, interfere with the conduct of the study or the study objectives, or pose an unacceptable risk to the subjects;
- a treatment history that includes steroids within 1 months prior to screening, or any other therapy that in the judgment of the investigator potentially interferes with the study objectives (in case of an insufficient washout period);
- body weight < 50 kg;
- subject is pregnant or breast feeding;
- current substance abuse, including alcohol and drugs;
- positive alcohol test or test for drugs of abuse at screening;
- previous deuterium administration;
- participation in an investigational drug or device study within 3 months prior to screening;
- loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening;
- unwillingness or inability to comply with the study protocol for any other reason.

# Study design

## Design

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| Study phase: | 4 |
| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Other |

### Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 03-08-2016 |
| Enrollment: | 16 |
| Type: | Actual |

## Ethics review

Approved WMO

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| Date: | 28-10-2015 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| CCMO | NL55042.056.15 |