# Randomized, placebo-controlled study to immunomonitor Mycophenolate mofetil (MMF) in healthy volunteers

Published: 15-04-2019
Last updated: 15-05-2024

Objective(s)* To investigate the pharmacokinetic behaviour of a single dose of MMF;o Plasma concentrationso Cellular concentrationso Relationship between plasma and cellular concentrations* To investigate the pharmacodynamic effects of a single dose...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48101

**Source**
ToetsingOnline

**Brief title**
Mycophenolate mofetil (MMF) in healthy volunteers

### Condition

- Other condition

**Synonym**
Immunosuppression

**Health condition**

Prophylaxis of the rejection of an allogeneic organ

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Immunomonitoring, Mycophenolate mofetil

## Outcome measures

### Primary outcome

Tolerability / safety endpoints

(Serious) adverse events ((S)AEs) will be collected throughout the study at every study visit. Laboratory safety and vital signs will be obtained multiple times during the course of the study according to the Visit and Assessment Schedule

Pharmacokinetic endpoints

- Plasma MPA levels

- Cellular MPA levels in T-cells and/or PBMCs

Pharmacodynamic endpoints

Drug effects will be monitored by:

- T cell proliferation

- Cytokine production

In addition, the drug concentration * response relationship will be determined in vitro for each individual participant at baseline.

### Secondary outcome

Exploratory endpoints

- Effect of single dose of MMF on B cell proliferation

# Study description

### Background summary

Kidney transplantation is a successful treatment option for patients with end-stage renal disease. To prevent allograft rejection, renal transplant patients need long-term immunosuppression that is mostly calcineurin inhibitor-based (Tacrolimus and Cyclosporine A). These calcineurin inhibitors are combined with Mycophenolate mofetil (MMF). MMF emerged in the 1990*s as a immunosuppressive agent. The main difference with the *older* drugs Cyclosporine A and Tacrolimus is the mechanism of action. Hydrolysis of MMF releases mycophenolic acid (MPA), the active component. MPA inhibits the synthesis of guanosine monophosphate (GMP) from inosine monophosphate (MP), a rate-limiting step in the biosynthesis of purines crucial to cell cycling in T and B lymphocytes. Consequently, MPA blocks the proliferation and clonal expansion of T and B lymphocytes, preventing antibody production and prevents the generation of cytotoxic T cells, as well as other effector T cells.
Although most other medications used as maintenance immunotherapy after solid organ transplantation are dosed to achieve target concentration ranges in plasma or blood, MMF is usually administered at a fixed dose, and thus not individualized. The main reason for the fixed dose is the low toxicity of MMF compared to other immunosuppressants.
A too low dose leads to a risk of acute rejection and formation of donor-specific antibodies, while too much exposure leads to an increased risk of infection and nephrotoxicity. Because of the large pharmacodynamic intra- and interpatient variability, therapeutic drug monitoring should be routinely performed to maintain optimal drug concentration and minimize the risk of overexposure.
For this reason, quantitative measures for optimizing MMF dose and regimen are required to minimize the risk of toxicity and improve long-term allograft survival. By immune-monitoring transplantation patients, using functional immune tests, the immunosuppressive state can help finding the right dosing strategy. In this study we therefore aim to identify clinically relevant immune tests for quantification of immunosuppression, which can help understanding the inter- and intra-patient variability in the response to MMF treatment.
These immune tests will be focused on quantifying the T cell response, and the correlation of this response to intracellular and plasma drug concentrations. Furthermore, to determine if ex vivo experiments with MMF can predict individual PK/PD relationships, the correlation between drug effect ex vivo and in vivo will be explored.

### Study objective

Objective(s)
* To investigate the pharmacokinetic behaviour of a single dose of MMF;

o Plasma concentrations
o Cellular concentrations
o Relationship between plasma and cellular concentrations
* To investigate the pharmacodynamic effects of a single dose of MMF;
o T cell function (proliferation)
o Cytokine production
* To investigate the relationship between the pharmacokinetic behaviour of MMF (in plasma and intracellular) and the pharmacodynamic effects ex vivo;
* To explore the correlation between drug effects in vitro and ex vivo.
* To explore the pharmacodynamics effects of a single dose of MMF on B cell function (proliferation and activation)
Primary Objective
To investigate the relationship between the pharmacokinetic behaviour of MMF (in plasma and intracellular) and the pharmacodynamic effects ex vivo
Secondary Objectives
To investigate the pharmacokinetic and dynamic effects of a single dose of MMF.

**Study design**

Parallel, randomized, placebo-controlled study in 16 healthy volunteers receiving a single dose of MMF or placebo.

**Intervention**

Mycophenolate mofetil, a single oral dose (2 tablets of 500 mg) or matching placebo.

**Study burden and risks**

No medical benefit can be expected from this study for the participating subjects.
The study drug is a registered medicinal product for the prevention of rejection of the transplanted organ in transplantation patients, and has been used before in healthy volunteer studies. All study drug administrations will be done in the clinic under medical supervision. The subjects receiving the study drug will remain in the clinic for at least 6 hours after the study drug administration for the subjects to be closely monitored for any adverse signs during the treatment.

# Contacts

**Public**
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL
**Scientific**
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria at screening:
1. Willing to give written informed consent and willing and able to comply with the study protocol;
2. Healthy male or female subjects, 18 to 55 years of age (inclusive) at screening. The health status is verified by absence of evidence of any clinical significant active or uncontrolled chronic disease following a detailed medical history and a complete physical examination including vital signs, laboratory measurements and 12-lead ECG;
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum bodyweight of 50 kg;
4. All women of child bearing potential and all males must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment;
5. All women of child bearing potential must be willing to take a pregnancy test at screening, check-in and follow-up. Men cannot donate any sperm during the study and for three months after EOS.
6. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

## Exclusion criteria

1. Any disease associated with immune system impairment, including auto-immune diseases, HIV, any confirmed history of severe allergic reaction and transplantation patients;
2. Evidence of any other active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG) at screening or pre-dose). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance;
3. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis) at screening or pre-dose. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects;
4. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening, or other known infection requiring antibiotic therapy within the last three months prior to the study;
5. Use of any medications (prescription or over-the-counter [OTC]), within 21 days of study drug administration, or less than 5 half-lives (whichever is longer). Exception is paracetamol (up to 4 g/day). Other exceptions will only be made if the rationale is clearly documented by the investigator;
6. Received immunosuppressive or immunomodulatory medication within 30 days prior to enrollment or planned to use during the course of the study;
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator;
8. Participation in an investigational drug or device study within 3 months prior to first dosing;
9. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 14 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillisers, or any other addictive agent;
10. Positive test for drugs of abuse at screening or pre-dose;
11. Alcohol will not be allowed from at least 24 hours before screening and every return visit, and during unit stay;
12. Smoking cigarettes (or equivalent) and/or using nicotine based products within 3 months prior to study drug administration;
13. Is demonstrating excess in xanthine consumption (more than eight cups of coffee or equivalent per day) from 7 days prior to the first dose of the study drug until EOS;
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable);
15. Loss or donation of blood over 500 mL within three months prior to screening or intention to donate blood or blood products during the study and up until 6 weeks after the EOS;
16. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study;

17. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease,

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Single blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 28-05-2019 |
| Enrollment: | 16 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | CellCept |
| Generic name: | Mycophenolate mofetil |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 15-04-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

| | |
|---|---|
| Approved WMO Date: | 30-04-2019 |
| 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

ID: 28654
Source: NTR
Title:

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2019-001091-11-NL |
| CCMO | NL69579.056.19 |
| OMON | NL-OMON28654 |