A randomized, open-label, four-way cross-over, single dose study to compare the pharmacokinetics of monomethyl fumarate and other metabolites after administration of dimethyl fumarate as a delayed- and slow-release formulation of FP187 and Tecfidera® in healthy volunteers.

Published: 26-04-2016
Last updated: 16-04-2024

Primary ObjectiveThe primary objective is to investigate the PK of the MMF * the main metabolite of DMF * following administration of a delayed-and slow-release tablet formulation (FP187-GC) and the marketed enteric-coated delayed release...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON42906

Source
ToetsingOnline

Brief title
PK comparison of DMF as a FP187 formulation and Tecfidera®

Condition

- Neurological disorders NEC

Synonym
Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Forward Pharma GmbH
Source(s) of monetary or material Support: Forward Pharma GmbH (Leipzig;Germany)

Intervention

Keyword: FP187, MS, PK, Tecfidera

Outcome measures

Primary outcome

PK endpoints

The plasma PK parameters for MMF in plasma will be derived by non-compartmental analysis of the plasma concentration-time profiles, as will the PK parameters for the amount of the DMF and MMF metabolites determined in plasma, whole blood, and urine.

The PK parameters to be determined are:

* Plasma PK parameters of Area under the curve (AUC)0-*, AUC0-t, and Cmax of MMF after single dose administration

* Plasma PK parameters of AUCext%, tmax, tlag, t*, *z, Cmax/AUC (AI), and mean residence time of MMF after single dose administration. Exploratory analyses of AUC8-24, AUC10-24, and AUC12-24.

* Exploratory analyses of whole blood PK parameters of AUC0-*, AUC0-t, and Cmax of the DMF and MMF metabolites after single dose administration

* Exploratory analyses of whole blood PK parameters of AUCext%, tmax, tlag, and

Cmax/AUC (AI) of the DMF and MMF metabolites after single dose administration

* Exploratory analyses of urine PK parameters of Ae(0-t), and Fe(0-t) of DMF

and MMF metabolites after single dose administration.

Additional exploratory analyses of DMF and MMF metabolites in plasma may be

performed at a later stage.

Secondary outcome

Safety and tolerability endpoints

(Serious) treatment-emergent AEs ((S)TEAEs).

Concomitant medication

Clinical laboratory tests

Haematology

Chemistry

Urinalysis

Vital signs

Pulse rate (beats per minute (bpm))

Systolic blood pressure (mmHg)

Diastolic blood pressure (mmHg)

ECG

Heart rate (bpm), PR, QRS, QT, QTc calculated using Fredericia's method

(QTcF).

Study description

Background summary

The clinical use of fumaric acid esters (FAE) was initially based on empiric data on efficacy in patients with moderate to severe psoriasis. Clinical investigations showed already in 1990 that dimethyl fumarate (DMF) alone could be used for the treatment instead of a mixture of FAE and from 2006 it was shown that a DMF was also effective in relapsing-remitting multiple sclerosis (MS). While the exact mode of action of DMF as a drug is not fully understood, it is believed that at least some of its therapeutic effects are mediated via modulation of the immune system via redox-sensitive pathways. A portion of the ingested DMF is thought to be metabolized by esterases (enzymes ubiquitous in the gastro-intestinal (GI) tract) to produce monomethyl fumarate (MMF). In contrast to DMF, MMF can be measured in the systemic circulation, but the extent to which it may contribute to clinical efficacy is unclear at present.
The key issues for DMF treatment are the initial side effects (most pronounced within the first eight weeks) which cause patients to stop treatment. The tolerability issues consist of flushing and GI effects e.g., diarrhea, abdominal pain, and nausea. It is believed that the GI side effects can, at least partially, be explained by high local concentration of the drug in the intestines as DMF has an irritation potential to the mucosa. Flushing is possibly related to the immediate release properties of the formulations, leading to high peak levels of the first metabolite MMF that reacts with nicotinic acid receptors. Beside the discomfort at the start, the safety and particularly the long term safety of DMF treatment is positive. However, attention has to be paid to the lymphocyte count as there is in general a decrease in the lymphocyte count during the first year and for about 6% there is a severe decrease.
Forward Pharma has tested various formulations of FP187 in several Phase I and a single Phase II psoriasis study to describe the pharmaceutical and tolerability profile and demonstrate safety and efficacy. The tolerability of the drug seems to depend on the release profile. Especially the correlation of reduced flushing reports and reduced Cmax values of MMF have been demonstrated with other formulations of FP187 vs. Tecfidera® and Fumaderm®. During the development, the manufacturing process was optimized. As a result, Forward Pharma has developed the present delayed and slow-release erosion matrix formulation, containing only DMF as the active ingredient, with the aim of providing an optimal FAE formulation that demonstrates efficacy while addressing some of the side effects of the delayed- and immediate-release formulations. The investigated formulations contain the same excipients as such but in different ratios, leading to different extended release profiles. This study is intended to investigate the pharmacokinetics (PK) of MMF, to compare the relative bioavailability and related side effect profile of a delayed- and slow-release DMF formulation (FP187-GC) to the marketed product Tecfidera®, and to evaluate dose-linearity of FP187-GC with respect to the plasma MMF parameters.

Study objective

Primary Objective

The primary objective is to investigate the PK of the MMF * the main metabolite of DMF * following administration of a delayed-and slow-release tablet formulation (FP187-GC) and the marketed enteric-coated delayed release formulation Tecfidera® after single dose administration under fasted conditions.

Secondary Objectives
The secondary objectives are to:
- determine the relative bioavailability of MMF following administration of a delayed- and slow-release DMF formulation (FP187-GC) at three dose levels compared to Tecfidera® after single dose administration under fasted conditions;
- monitor the safety and tolerability of a delayed- and slow-release DMF formulation (FP187-GC) and Tecfidera® based on clinical investigations, adverse event (AE) reporting and safety laboratory investigations;
- to investigate dose-linearity with the administered doses of FP187-GC.

Exploratory objectives
The exploratory objectives are to investigate the DMF and MMF metabolites in plasma, whole blood, and urine.

Study design

This study will be conducted as a randomized, open-label, four-way cross-over, single-dose study in healthy male and female subjects. During the study, PK data of MMF will be collected during 24 hours after administration, and safety data will be observed until one days after the last dose administration. Between each administration, there will be a wash-out period of about seven days.

Intervention

A. 120 mg DMF (1 tablet of 120 mg DMF) as FP187-GC.
B. 240 mg DMF (2 tablets of 120 mg DMF) as FP187-GC.
C. 480 mg DMF (4 tablets of 120 mg DMF) as FP187-GC.
T. 240 mg DMF (1 capsule of 240 mg DMF) as Tecfidera®.

Study burden and risks

This study requires physical examination, vital signs, collection of blood and urine samples. The burden for the volunteer related to the study procedures is limited. All collections will be performed in a state of the art clinical unit and medically supervised by qualified medical staff.

The most common side effects of Tecfidera® are:
Very common (> 10%): flushing (prickling, itching, redness and sensation of heat in the face), gastro-intestinal disorder (diarrhoea, nausea, (upper) abdominal pain), ketones in urine.

Common (1-10%): gastroenteritis, reduced amount of immune cells (lymphopenia, leukopenia), burning sensation, hot flush, vomiting, dyspepsia, gastritis, gastrointestinal disorder, pruritus, rash, erythema, proteinuria, feeling hot, increased liver enzymes.
Uncommon (0.1-1%): hypersensitivity.
Otherwise reported: severe inflammation of the central nerve system (brain and spinal cord) (progressive multifocal leukoencephalopathy (PML)).
Since FP187 consists of the same pharmaceutical ingredient as Tecfidera®, comparable side effects are expected. In the clinical studies testing FP187 the reported adverse events consisted of flushing and gastrointestinal complaints. For new drugs such as FP187 however, not all side effects are known yet and there thus may be unexpected side effects.

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

Eligible subjects must meet all of the following inclusion criteria at screening:
1. Is informed and given ample time and opportunity to think about participation and has given his/her informed consent in writing.
2. Is a healthy Caucasian male or female aged between 18 and 55 years (inclusive) at screening.
3. Is in good general health in the opinion of the Investigator, as determined by absence of evidence of any active or chronic disease following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), 12-lead electrocardiogram (ECG), and clinical laboratory parameters (hematology, blood chemistry, and urinalysis). Minor deviations of laboratory values from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
4. Is a female with childbearing potential and is either surgically sterile (hysterectomy or tubal ligation) or uses a highly effective (failure rate <1%) medically accepted contraceptive method during the investigational periods as well as 90 days after trial is finished such as:
o Systemic contraceptive (implant, injection),
o Intrauterine device inserted for at least one month prior to trial entrance,
o Sexual abstinence or vasectomized partner;
OR
5. Is a male subjects who agrees to use a condom or abstain from sexual intercourse throughout the trial (including washout intervals between treatment periods) until 90 days after the last dose of trial drug in the last treatment period.
AND
Agrees not to donate sperm during participation in the trial and up to three months after follow-up visit.
OR
Has been surgically sterilized prior to inclusion.
6. Has a body weight of at least 50 kg and a body mass index between 18.5 - 30.0 kg*m2 (inclusive) at screening.
7. Is non-smoker or smokes up to ten cigarettes per day (or equivalent) and willing to abstain smoking during the in house period.
8. Shows a negative alcohol breath test and drug urine test.
9. Has the ability to communicate well with the investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria at screening:
1. Has legal incapacity or inability to understand or comply with the requirements of the study.
2. Has clinically significant abnormalities in physical examination, vital signs, 12-lead ECG, or clinical laboratory parameters (especially for leukocytes and differential count, liver enzymes, and serum creatinine) according to the Investigator*s judgment. In the case of uncertain or

questionable results, tests performed during screening may be repeated once before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. Has leukopenia (leukocyte count <3.5 x 10*9/L) or eosinophilia (count > 0.75 x 10*9/L) or lymphocytopenia (count <1.02 x 10*9/L) at screening and Day -1 of Period 1.
4. Has a creatinine value outside the normal range (female: <90 *mol/L; male: <110 *mol/L) and an estimated creatinine clearance (Modification of Diet in Renal Disease) <90 mL/min at screening and Day -1 of Period 1.
5. Has standard liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (*-GT) exceeding the upper limit of normal for the local laboratory at Screening and Day -1 of Period 1. Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
6. Has a history or symptoms of any clinically significant neurologic, gastrointestinal (including surgical (abdominal) interventions likely influencing medication absorption), renal, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, hematological, or other major disorders.
7. Has a supine blood pressure at screening, after resting for at least 5 min: systolic blood pressure >139 or <90 mmHg, or diastolic blood pressure >89 or <55 mmHg.
8. Has a supine pulse rate at screening, after resting for at least 5 min, outside the range of <45 or >90 beats/min.
9. Has Hepatitis B surface antigen (HBsAg), anti-Hepatitis B core antibody (anti-HBcore), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
10. Has any significant allergic reactions (urticarial, rash, or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
11. Has a history of chronic alcohol (regular intake of more than three units per day) or drug abuse within the last six months prior to first administration or evidence of such abuse as indicated by the laboratory profile conducted during the screening examination. Alcohol consumption will be prohibited during study confinement and at least 24 hours before screening, before dosing, and before each scheduled visit.
12. Is demonstrating excess in xanthine consumption (more than eight cups of coffee or equivalent per day
13. Uses any medications (prescription or over-the-counter (OTC)) within 21 days of study drug administration, or less than five half-lives (whichever is longer). Exception is paracetamol (up to 4000 mg/day). Other exceptions will only be made if the rationale is discussed with the Principal Investigator and clearly documented.
14. Received any treatment agents known to alter the major organs or systems within one month prior to the first administration (e.g., barbiturates, phenothiazines, cimetidine, etc.).
15. Participated in an investigational drug or device study within three months prior to screening.
16. Lost or donated blood over 500 mL within three months (males) or four months (females) prior to screening.
17. Is female and has a positive pregnancy test, is pregnant or lactating, or plans to become pregnant during the course of the study.
18. Is male and plans to father a child during the course of the study
19. Has a concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-05-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	FP187-GC
Generic name:	Dimethyl fumarate
Product type:	Medicine
Brand name:	Tecfidera
Generic name:	Dimethyl fumarate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	26-04-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	11-05-2016
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
EudraCT	EUCTR2016-001670-14-NL
CCMO	NL57276.056.16