A Phase I, single-center, open-label, randomized four-period, randomized five-period or randomized two period crossover study to investigate the pharmacokinetics of five different DMF-containing formulations of FP187 and the comparator products Tecfidera® and Fumaderm® in healthy volunteers after oral administration in fasted or fed state

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Part IPrimary objectiveTo investigate the pharmacokinetics of the main metabolite of dimethyl fumarate (DMF) - monomethyl fumarate (MMF) - following administration of 3 different controlled release tablet formulations (FP187: V1, V2B, and V3B) and...

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

Summary

ID

NL-OMON42556

Source
ToetsingOnline

Brief title
FP187-106

Condition

- Other condition
- Skin and subcutaneous tissue disorders NEC

Synonym
multiple sclerosis, psoriasis

Health condition

Psoriasis, multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Forward Pharma GmbH
Source(s) of monetary or material Support: Forward Pharma GmbH;Deutscher Platz 5a;04103 Leipzig;Germany

Intervention

Keyword: pharmacokinetics

Outcome measures

Primary outcome

Pharmacokinetic

Secondary outcome

none

Study description

Background summary

The clinical use of fumaric acid esters is based on empiric data on efficacy in patients with moderate to severe psoriasis. The first description of efficacy of fumaric acid esters dates back to 1959 when Schweckendiek reported his experience with these compounds for the treatment of psoriasis. While initially different mixtures of fumaric acid esters were produced and distributed in

Southern German pharmacies, the clinical experience resulted in a development of a fixed combination of fumaric acid esters as gastric resistant tablets under the trade name Fumaderm® in Germany, which obtained marketing authorization in Germany in 1994. Clinical investigations showed already in 1990 that dimethyl fumarate (DMF) alone could be used for the treatment instead of a mixture of fumaric acid esters. Preclinical data support that DMF and monomethyl fumarate (MMF) are also effective in chronic experimental autoimmune encephalomyelitis and suppress macrophage infiltration in a mouse model of multiple sclerosis (MS). In 1998, full publication 2006, it was shown the first time that fumaric acid esters, using Fumaderm®, are also effective in the treatment of relapsing-remitting MS. Further investigations could consolidate this result with a DMF alone product. In fact, recently this DMF-only product obtained marketing authorization for the treatment of relapsing recurrent MS in the United States of America (March 2013) and the European Union (January 2014) under the trade name Tecfidera®.
Many preclinical and clinical investigations have shown that DMF is rapidly metabolized by esterases before reaching the systemic circulation. Only the first metabolite, MMF, can be detected in the blood. DMF is taken up directly in the intestine mucosa into various cell types including immune cells where it reacts with glutathione. This results in a depletion of glutathione in the cells which changes the redox status of the cells and modulate the interaction of and between the immune cells. The effects observed are e.g., reduced inflammation, reduced proliferation of keratinocytes, reduced formation of new gadolinium-enhanced lesions, reduced annual relapse rate. More details can be found in the investigator*s brochure.
The key issues for DMF treatment (reported for Fumaderm® in psoriasis treatment and Tecfidera® in MS treatment) are the initial side effects (most pronounced within the first 4-8 weeks) which causes patients to stop treatment due to these tolerability issues such as flushing and gastro-intestinal adverse effects (e.g., diarrhea, abdominal pain, nausea). For both types of tolerability issues it is reported that they do diminish or disappear over the time course of the treatment. Beside this discomfort at the start of treatment the safety of a DMF treatment is excellent and now demonstrated with at least 200.000 patients years exposure to DMF and controlled experience in MS over the last 4-6 years. No important effects on the cardiovascular system, liver or kidney have appeared. Attention has to be paid to the lymphocyte count during longer term treatment as there is in general a decrease in the lymphocyte count during the first year and for about 6% of patients a severe decrease. A continued severe low lymphocyte count over years could cause severe infections as shown in single case reports for Fumaderm® and also Tecfidera®. No increased risk of infection has been observed when patients are treated according to current DMF treatment guidelines and drug label.
It is believed that the gastrointestinal 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, while flushing is possibly related to the immediate release properties of the formulations, leading to high peak levels of the first metabolite MMF. For this metabolite it is demonstrated that

it reacts with the nicotinic receptors leading to the flushing reaction.

Study objective

Part I
Primary objective

To investigate the pharmacokinetics of the main metabolite of dimethyl fumarate (DMF) - monomethyl fumarate (MMF) - following administration of 3 different controlled release tablet formulations (FP187: V1, V2B, and V3B) and the marketed enteric-coated delayed release formulation Tecfidera® after single dose administration under fasted conditions.

Secondary objectives

To determine the relative bioavailability of 3 different, delayed and controlled DMF formulations (FP187: V1, V2B, and V3B) compared to Tecfidera® after single dose administration under fasted conditions.

To monitor the safety and tolerability of 3 different FP187 formulations (V1, V2B, and V3B) and Tecfidera® based on clinical investigations, adverse event (AE) reporting and safety laboratory investigations.

Part II
Primary objective:

•To investigate the pharmacokinetics of the main metabolite of dimethyl fumarate (DMF) - monomethyl fumarate (MMF) - following administration of 3 different batches of controlled release DMF tablets (FP187-V2B, FP187-BC batch W006224 manufactured in 2009, and FP187-BC batch W025241 manufactured in 2015) and the marketed formulations Tecfidera® and Fumaderm® after single dose administration under fasted conditions.

Secondary objectives:

To determine the relative bioavailability of 3 different batches of controlled release DMF tablets (FP187-V2B, FP187-BC batch W006224 manufactured in 2009, and FP187-BC batch W025241 manufactured in 2015) compared to Tecfidera® and Fumaderm® after single dose administration under fasted conditions.

To monitor the safety and tolerability of 3 different batches of controlled release DMF tablets (FP187-V2B, FP187-BC batch W006224 manufactured in 2009, and FP187-BC batch W025241 manufactured in 2015) and Tecfidera® and Fumaderm® based on clinical investigations, adverse event (AE) reporting and safety laboratory investigations

Part III

Primary objective:
To investigate the pharmacokinetics of the main metabolite of dimethyl fumarate (DMF) - monomethyl fumarate (MMF) - following administration of marketed formulations Tecfidera® and Fumaderm® after single dose administration under fed conditions.

Secondary objectives:
- To determine the relative bioavailability of Tecfidera® compared to Fumaderm® after single dose administration under fed conditions.
- To monitor the safety and tolerability of Tecfidera® and Fumaderm® based on clinical investigations, adverse event (AE) reporting and safety laboratory investigations.

Study design

Part I: A single center, open-label, randomized, 4-period crossover design with 4 treatments and 4 treatment sequences.
Part II: A single center, open-label, randomized, 5-period crossover design with 5 treatments and 5 treatment sequences.
Part III: A single center, open-label, randomized, 2-period crossover design with 2 treatments and 2 treatment sequences.

A single oral dose of DMF will be given in each treatment period separated by a wash-out phase of at least 7 days between single dose administrations.

Part I
The following treatments will be administered in a randomized order:
A: 240 mg DMF (2 tablets of 120 mg DMF) as FP187-V1
B: 240 mg DMF (2 tablets of 120 mg DMF) as FP187-V2B
C: 240 mg DMF (2 tablets of 120 mg DMF) as FP187-V3B
D: 240 mg DMF (2 capsules of 120 mg DMF) as Tecfidera®

Part II
The following treatments will be administered in a randomized order:
E: 240 mg DMF (2 tablets of 120 mg DMF) as FP187-V2B
F: 250 mg DMF (2 tablets of 125 mg DMF) as FP187-BC batch W006224 manufactured in 2009
G: 250 mg DMF (2 tablets of 125 mg DMF) as FP187-BC batch W025241 manufactured in 2015
H: 240 mg DMF (2 capsules of 120 mg DMF) as Tecfidera®
I: 240 mg DMF (2 tablets of 120 mg DMF) as Fumaderm®

Part III
The following treatments will be administered in a randomized order:
J: 240 mg DMF (2 tablets of 120 mg DMF) as Fumaderm®
K: 240 mg DMF (1 capsule of 240 mg DMF) as Tecfidera®

Intervention

The study will start with a screening. At the screening a physical examination will take place and a few other standard medical assessments will be performed (ECG, vital signs). Furthermore a blood and urine sample will be taken for laboratory tests and a alcohol breath test and drug screen will be done. During the stay in the clinic the subject will receive the research medication once on Day 1. Safety will be monitored and will be assessed throughout the study. Venous serial blood samples will be collected. The subjects will be asked for possible side effects on regular basis. Finally, a follow-up visit will take place.

Study burden and risks

FP187 is not a registered drug. It has been tested in humans before. For the treatment with DMF containing products tolerability issues as flushing (prickling, itching, redness and sensation of heat in the face or spread out to more parts of the body) and gastrointestinal complaints (e.g., loose stools, watery stools, diarrhea, abdominal pain, nausea) are described specially at the beginning of the treatment.

With any trial product, unusual, unexpected, or previously unreported side effects could occur. Therefore, it is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the trial product.

The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally, fainting or an infection at the blood sampling site can occur.

Your health and possible side-effects from the medication will be closely monitored by the research physicians. If you develop any symptoms during the trial, whether or not you are staying in the clinic at the time, you will be treated by the research physicians. If new information about the safety of the test medication becomes available, you will be informed as soon as possible.

If you notice changes in your physical or mental state, during or after the end of the treatment session, please inform the research physician immediately. This is important for your own safety and for the quality of the research. You will be given an emergency card containing information about the trial and contact details.

Contacts

Public
Forward Pharma GmbH

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Scientific
Forward Pharma GmbH

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is informed and given ample time and opportunity to think about his participation and has given his/her informed consent in writing.;2. Subject is male or female, Caucasian, and in the age range between 18 and 55 years (inclusive).;3. Females of childbearing potential must be either surgically sterile (hysterectomy or tubal ligation) or use a highly effective (failure rate <1%) medically accepted contraceptive method during the investigational periods as well as three months after trial is finished such as:;- Systemic contraceptive (oral, implant, injection),;- Intrauterine device inserted for at least one month prior to trial entrance;- Sexual abstinence or vasectomized partner;4. Male subjects must agree to use a condom with spermicide 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.;OR;Have been surgically sterilized prior to inclusion.;AND;Agree not to donate sperm during participation in the trial and up to 3 months

after follow-up visit.;5. Subject has a body weight of at least 50 kg and a body mass index in the range of 18.5 and 30.0 kg/m2 (inclusive) at screening.;6. Subject is non-smoker or smokes up to 10 cigarettes per day (or equivalent).;7. Subject shows negative alcohol breath test and drug urine test.;8. Subject is in good general health in the opinion of the Investigator, as determined by medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), 12-lead electrocardiogram (ECG), and clinical laboratory parameters (hematology, clinical 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.;9. Standard liver function tests including ALT, AST, γ-GT should not exceed 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.;10. Be willing and able to consume the entire high-calorie, high-fat breakfast meal in the designated timeframe required in the designated study period;11. Subject is willing and able to comply with all conditions and requirements of the study.

Exclusion criteria

1. Subject shows 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.
2. Has leukopenia (leukocyte count <3.5 x 109/L)or eosinophilia (count > 0.75 x 109/L) or lymphocytopenia (count <1.02 x 109/L) at screening and Day -1 of Period 1.
3. Has a creatinine value outside the normal range (female: <90 µmol/L; male: <110 µmol/L) and an estimated creatinine clearance (Cockcroft-Gault) <90 mL/min at screening and Day -1 of Period 1.
4. Subject with, or a history of clinically significant neurologic, gastrointestinal, renal, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, hematological, or other major disorders.
5. Subject who 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.
6. Subject who has a supine pulse rate at screening, after resting for at least 5 min, outside the range of <50 or >90 beats/min.
7. Subject who donated blood or who had a comparable blood loss (approximately 500 mL) during the last 30 days prior to start of this study.
8. Subject with a known history of drug allergies or with a known allergy to any medicine chemically related to the study medication.
9. Subject who has had a clinically significant illness within 4 weeks prior to screening.
10. Subject with a history of chronic alcohol (regular intake ofmore than 35 g ethanol per day) or drug abuse within the last 6 monthsprior to first administration or evidence of such abuse as indicated by the laboratory profile conducted during the screening examination.
11. Subject who is demonstrating excess in xanthine consumption (more than 6 cups of coffee or equivalent per day).
12. Subject who has received prescription drugsor over-the-counter medication within 2 weeks prior to the first administration (withthe exception of up to 1000 mg paracetamol per

day).
13. a. For Part I: Subject who received any investigational medication within 1 month prior to the first administration.
b. For Part II: Subject who received any investigational medication within 1 month prior to the first administration or subject who participated in Part I of the study.
c. For Part III: Subject who received any investigational medication within 1 month prior to the first administration
14. Subject who received any treatment agents known to alter the major organs or systems within 1 month prior to the first administration (e.g., barbiturates, phenothiazines, cimetidine, etc.).
15. Subject shows positive hepatitisB surface antigen (HBsAg), hepatitis C virus antibodies (anti-HCV), or human immunodeficiency virus (HIV) I/II antibodies and antigen tests.
16. Male subjects and female subjects of childbearing potential not using a highly effective method of birth control. Highly effective methods of birth control are defined as those which result in a low failure rate, i.e., less than 1% per year, when used consistently and correctly (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner) [1]. Female subjects will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation, or post-menopausal for at least 2 years.
17. Female subject who has a positive pregnancy test, is pregnant or lactating, or plans to become pregnant during the course of the study.
18. Male subject who plans to father a child during the course of the 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):	08-04-2015
Enrollment:	84

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	FP187 V1
Generic name:	NAp
Product type:	Medicine
Brand name:	FP187 V2B
Generic name:	NAp
Product type:	Medicine
Brand name:	FP187 V3B
Generic name:	NAp
Product type:	Medicine
Brand name:	FP187-BC batch W006224 and W025241
Generic name:	NAp
Product type:	Medicine
Brand name:	Tecfidera
Generic name:	NAp
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-04-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-07-2015
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2016
Application type:	Amendment
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	EUCTR2014-005645-45-NL
CCMO	NL52929.056.15