Phase I , single-center, open-label, two-period study to investigate the pharmacokinetics of the DMF-containing formulation FP187-GC in healthy volunteers after oral administration in fasted and fed state

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Primary objective* To investigate the plasma pharmacokinetics of the first metabolite of dimethyl fumarate (DMF) - monomethyl fumarate (MMF) - following administration of the delayed- and slow-release FP187-GC tablet formulation after single dose...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON43151

Source
ToetsingOnline

Brief title
FP187-116 (GC)

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
Multiple sclerosis, psoriasis

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, Safety, Single dose, Tolerability

Outcome measures

Primary outcome

Pharmacokinetic

Secondary outcome

Bioavailability of a delayed and slow-released DMF formulation;

Safety and tolerability of FP187-GC

Study description

Background summary

Forward Pharma has developed a delayed- and slow-release erosion matrix formulation, containing only DMF as active ingredient, with the aim of providing an optimal fumaric acid ester formulation that demonstrates efficacy while addressing some of the side effects of the delayed immediate-release formulations. The study is intended to show if there are differences in the bioavailability, the peak plasma concentration and the related side effect profile in the fasted state compared to the fed state.
FP187-GC is a white small biconvex oval tablet with a length of approximately 10 mm, a thickness of approximately 5 mm and a height of approximately 5 mm. The only active ingredient is 120 mg DMF. DMF is embedded in an erosion matrix and will be released controlled at the same rate as the matrix is dissolved.
The core tablet is surrounded by a thin enteric coat to prevent the release of DMF in the stomach but allowing a fast onset of release after the tablet has reached the upper intestine where the enteric coat dissolves due to the change in the pH of the environment. Other excipients of the core tablets are: hydroxypropyl cellulose, lactose monohydrate, colloidal anhydrous silica,

magnesium stearate and for the coating Eudragit® L30 D55, glycerol monohydrate, triethyl citrate and polysorbate.

Study objective

Primary objective
* To investigate the plasma pharmacokinetics of the first metabolite of dimethyl fumarate (DMF) - monomethyl fumarate (MMF) - following administration of the delayed- and slow-release FP187-GC tablet formulation after single dose administration under fasted and fed conditions.

Secondary objectives
* To determine the relative bioavailability of MMF from FP187-GC after single dose administration under fasted and fed conditions.
* To monitor the safety and tolerability of FP187-GC based on clinical investigations, adverse event (AE) reporting and safety laboratory investigations.
* To investigate the DMF metabolites in urine and whole blood.

Study design

This study will be conducted as a single center, open-label, Phase I study, with 2 single dose periods in healthy male and female subjects.
The study will consist of an ambulant screening visit, 2 treatment periods of 3 days each (Day -1 to Day 2), and a follow-up visit. The subjects will be hospitalized from Day -1 to the morning of Day 2 of each period.
Subjects who signed the informed consent form will be screened for eligibility within 29 to 2 days prior to first study drug administration.
A single dose of DMF will be administered on Day 1 of each period. In the first period, FP187-GC will be administered under fasted conditions. In the second period, FP187-GC will be administered under fed conditions. Single dose administrations will be separated by a washout phase of at least 7 days.
Blood samples for determination of MMF plasma concentrations will be collected each period until 24 h after single dose administration on Day 1. The subjects will be discharged from each period after collection of the last pharmacokinetic sample in the morning of Day 2 if there are no medical objections.
A follow-up examination will be performed on Day 2 of Period 2 after all samples of that period have been collected.
The trial starts with first subjects signing informed consent and ends with the last subject undergoing last visit. The total duration of the study is estimated to be approximately 6 weeks.

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. A follow-up visit will take place directly after the last PK sample has been collected.

Study burden and risks

The study drug has been previously administered to humans and was generally well tolerated. A number of side-effects, possibly linked to administration of FP187 to healthy volunteers, were reported. These side-effects included diarrhea, abdominal pain, nausea and flushing (prickling, itching, redness and sensation of heat starting in the face but can also spread out over more parts or the whole body).

All these side effects are well known and described for all available formulations containing DMF, such as Fumaderm® (registered in Germany) or Psorinovo® (available in the Netherlands) for the treatment of psoriasis. It is also demonstrated over all these years that changes return to normal after the stop of therapy.

The dose level of 480 mg DMF as a single dose is selected on the basis of research results in animals and humans. The risk to health at these dose levels is limited but you may experience one of the above mentioned side-effects or other symptoms not previously reported. Your health will be closely monitored during the trial to minimize these risks.

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

The trial will be conducted as accurate as possible following the flow chart. Circumstances can change, for instance by reaction of the body or by new available information.

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

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 90 days 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 90 days after follow-up visit.
5. Subject has a body weight of at least 50.0 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, *-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.
12. Subjects who participated in a previous study investigating FP187 are allowed to participate in this 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 (* 500 ml) or plasma (* 100 ml) or had a comparable blood loss (approximately 500 mL) during the last 3 months prior to start of this study and subject who donated more than 1.5 L of blood during the last 10 months 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 of more than 35 g ethanol per day) or drug abuse within the last 6 months prior 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 drugs or over-the-counter medication within 2 weeks prior to the first administration (with the exception of up to 1000 mg paracetamol per day).
13. Subject who received any investigational medication within 1 month prior to the first administration or has taken part in 4 (or more) other clinical trials within 10 months 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 hepatitis B 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) [5]. 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

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-06-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	FP187-116
Generic name:	NAp

Ethics review

Approved WMO Date:	30-05-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2016
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	EUCTR2016-002098-37-NL
CCMO	NL57873.056.16