A Two-Part, Open-Label, Randomized, Placebo-Controlled, Crossover Study to Assess the Reversal of the Anticoagulant Effects of milvexian by 4-Factor Prothrombin Complex Concentrate (4F-PCC) (Part 1) and Recombinant Human Factor VIIa (rFVIIa) (Part 2) in Healthy Subjects

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON54179

Source
ToetsingOnline

Brief title
Reversal of the Anticoagulant Effects of Milvexian (JNJ-70033093)

Condition

- Embolism and thrombosis

Synonym
thromboembolic disorders

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag International NV
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Anticoagulant Effects, JNJ-70033093, Milvexian, Reversal

Outcome measures

Primary outcome

To evaluate the reversal of the anticoagulant effects of JNJ-70033093 by 4F-PCC and rFVIIa in healthy subjects as measured by changes from baseline of the coagulation testing parameters (aPTT and TGA).

Secondary outcome

To assess the safety and tolerability of 4F-PCC and rFVIIa when co-administered with milvexian to reverse its anticoagulant effects in healthy participants.

To assess the pharmacokinetics (PK) of multiple doses of milvexian at 200 mg BID on Days 4 to 7 (Part 1).

To assess the pharmacokinetics (PK) of single 100 mg and 500 mg doses of milvexian administered under fed condition on Day 1 in healthy participants (Part 2).

To assess the PK of rFVIIa in healthy participants (Part 2).

Study description

Background summary

Milvexian is a new compound that may potentially be used for the treatment of blood clots in the heart, in the blood vessels or in the brain. Milvexian is a blood thinner (an anti coagulant) that can prevent the formation of blood clots in blood vessels (so-called *thrombo-embolic* disorders). These blood clots can travel through the bloodstream and block arteries which prevents blood from delivering oxygen and nutrients to the organs. When that happens in the heart, it is called a heart attack and, in the brain, it is called a cerebral infarction (also called stroke). All these conditions may ultimately result in death or permanent disability. Milvexian aims to prevent the formation of the blood clot. It works by blocking a *blood clotting* protein (FXIa) from performing its function. Anticoagulation of all types have the potential to contribute to bleeding. In addition, there may be situations in which the anticoagulation effects may need to be reversed (eg, urgent surgery). Therefore, the availability of a drug that can reverse the effects of milvexian could be valuable in patients with life-threatening bleeding or in those requiring urgent surgery.

The drug that is used in this part of the study (Part 1) to reverse the effects of milvexian is 4F PCC. 4F PCC is available on the market as Kcentra, Beriplex, Cofact, and Octaplex. It contains 4 factors that act as *coagulants* that make blood clot again.

Study objective

The study will be performed in 2 parts, Part 1 and Part 2. Part 2 has been clinically completed. The remainder of this document concerns Part 1 only.

The purpose of Part 1 of this study is to determine the reversal of the blood thinning effects of milvexian (also called JNJ 70033093). To reverse the blood thinning effects we will test the blood clotting medicine 4F-PCC. We will determine the reversal by measuring different proteins in your blood that influence blood clotting (this is called pharmacodynamics). Milvexian has been administered to humans before. It has also been extensively tested in the laboratory and on animals. Milvexian will be tested as multiple doses of 200 mg twice daily for 3.5 days. 4F-PCC is no new drug; it is already available on the market in several dosages and formulations. 4F-PCC will be tested as a single intravenous infusion at a dose of 50 IU/kg. The reversal effects of 4F-PCC will be compared to the effects of a placebo. A placebo is a medicine without any

active ingredient.

Additionally, we will investigate how safe and well tolerated the new compound milvexian is when co administered with 4F-PCC to healthy volunteers. It will also be investigated how quickly and to what extent milvexian is absorbed and eliminated from the body (this is called pharmacokinetics).

Part 1 of this study will be performed in approximately 16 healthy male and female volunteers. Part 1 has 2 periods, Period 1 and Period 2. In each study Period, milvexian and 4F-PCC or its matching placebo will be tested. There will be an interval of 14 to 21 days between the two study periods.

Study design

Participation from screening until the follow-up visit will be approximately 116 days.

On Day 1, 2, and 3 of each period, milvexian will be given twice per day: once in the morning and once in the evening (12 hours apart). On Day 4 of each period, only a morning dose will be given. Milvexian will be given as oral capsules with 240 milliliters (mL) of noncarbonated water. The dose of milvexian that will be given each time is 200 milligram (mg). This will be given as 2 capsules of 100 mg each.

After fasting for 10 hours overnight on Day 1, 2, and 3 of each period, the volunteer will be given a standard breakfast 30 minutes before the morning dose of milvexian. the volunteer is asked to eat the entire breakfast within 20 minutes.
On Day 4 of each period, milvexian will be given without a breakfast after fasting for 10 hours overnight.

4 hours after ingestion of milvexian on Day 4, 4F-PCC or placebo will be given as an intravenous infusion (solution of the compound that will be administered directly in a blood vessel) over up to approximately 30 minutes.

There are 2 treatments in this study:
- Treatment A: 200 mg milvexian twice daily on Days 1 to 3 and a morning dose on Day 4 and intravenous infusion of 50 IU/kg* 4F-PCC on Day 4 only
- Treatment B: 200 mg milvexian twice daily on Days 1 to 3 and a morning dose on Day 4 and an intravenous infusion of placebo on Day 4 only
* This means that 50 IU of 4F-PCC will be administered per 1 kg of body weight, so the actual dose will depend on the volunteers body weight.

The volunteer will receive both Treatment A and B (one treatment in each period). The order in which the volunteer will receive Treatment A or Treatment B in each period will be determined by drawing lots.

The actual study will consist of 2 periods during each the volunteer will stay in the research center for 8 days (7 nights).
In total, the volunteer will visit the research center 4 times:
• The screening visit
• 2 visits of 8 days during each treatment period
• The follow-up visit
Additionally, there will be a follow-up phone call after leaving the research center in the second period.
There will be at least 14 days but no more than 21 days between Day 1 of each study period.

Intervention

See Study design

Study burden and risks

Possible discomforts due to procedures
Drawing blood and/or insertion of the indwelling cannula (tube in an arm vein) may be painful or cause some bruising. Insertion of a needle that delivers the reversal drug 4F-PCC to a vein in your arm may cause pain, bleeding, bruising or infection at the place where the needle goes into the skin.

In total, we will take approximately 500 milliliters (mL) of blood from the volunteer from screening to follow-up visit, including the blood samples taken to repeat tests for safety assessments. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken at once each time. Sometimes a blood test may need to be repeated. If this happens the total amount of blood drawn will be more than this.

To make a heart tracing, electrodes (small, plastic patches) will be pasted at specific locations on the volunteers arms, chest and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

A sample for the coronavirus test will be taken from the back of the volunteers nose and throat using a swab. Taking the sample only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the volunteers throat may cause the volunteer to gag. When the sample is taken from the back of the volunteers nose, the volunteer may experience a stinging sensation and the volunteers eyes may become watery.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Participants must be male or female between 18 and <55 years of age.
2. Participants must be healthy on the basis of medical history, physical examination, vital signs, ECG, and laboratory test results.
3. If a woman, must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) pregnancy test at screening and urine (β-hCG) pregnancy test on Day -1 of each study period (Part 1) or on Day -1 of Period 1 (Part 2).
4. Body mass index (weight [kg]/height^2 [m]^2) >=18.0 and <29.9 kg/m^2 body weight not less than 50 kg and not more than 100 kg.
5. After being supine for 5 minutes, systolic blood pressure between 90 and 140 mmHg, inclusive; and no higher than 90 mmHg diastolic, inclusive.

For a complete overview see the protocol

Exclusion criteria

1. If a woman, pregnant, breast-feeding or planning to become pregnant during

the study.
2. History or family history of any known illness that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study intervention to the subject or that could prevent, limit or confound the protocol specified assessments.
3. Participants with current hepatitis B infection, or hepatitis C infection, or human immunodeficiency virus type1 (HIV-1) or HIV-2 infection at study screening.
4. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity) and known allergy to the study intervention or any of the excipients of the formulations. History of allergy to or unwillingness to consume any component of high-fat breakfast menu to be provided in this study.
5. Any of the following laboratory results outside of the ranges specified below at screening or on Day -1 of Period 1, confirmed by repeat: a. Hemoglobin or hematocrit < lower limit of normal
b. Platelet count < lower limit of normal c. aPTT, or PT > ULN d. Low-density lipoprotein (LDL), High-density lipoprotein (HDL), apolipoprotein B, or lipoprotein a, outside the normal reference ranges
(at the screening visit only)

For a complete overview see the protocol

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-08-2020
Enrollment:	46
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Beriplex
Generic name:	prothrombin complex
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Milvexian
Product type:	Medicine
Brand name:	Novoseven
Generic name:	rFVIIa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	26-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2023
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	EUCTR2020-000180-24-NL
CCMO	NL73369.056.20