# A Phase 1/2 study of the dose-response in pharmacodynamics and safety of prothrombin complex concentrate Cofact in healthy subjects under vitamin K antagonist anticoagulation

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In this study we will investigate the pharmacodynamics of the compound Cofact, whereby the Cofact that will be used in this study is a modified version of the existing compound Cofact. The effect on the physiologic functions will be evaluated by…

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

## Summary

### ID

NL-OMON51966

**Source**
ToetsingOnline

**Brief title**
Dose response in PD and safety of Cofact under VKA anticoagulation

### Condition

- Other condition

**Synonym**
blood clotting, blood clotting factors

**Health condition**

Treatment of bleeding and perioperative prophylaxis

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Prothya Biosolutions BV
**Source(s) of monetary or material Support:** Pharmaceutical Industry

## Intervention

**Keyword:** Cofact, Healthy subjects, Pharmacodynamics

## Outcome measures

### Primary outcome

Establish dose-response relationship for Cofact in vitamine K antagonist (VKA)

reversal with respect to thrombin generation in subjects anticoagulated with

acenocoumarol therapy

### Secondary outcome

Kinetics of thrombin generation

Assessment of global parameters of coagulation over 14 days

To evaluate the effects of Cofact in healthy subjects receiving acenocoumarol

on biomarkers reflective of coagulation activation

To assess the safety and tolerability of Cofact in healthy subjects receiving

acenocoumarol

# Study description

## Background summary

Cofact is an existing compound that is used for the treatment of blood clotting problems.

Cofact has been on the market since 1997, and has been administered to more than 250.000 patients.
Cofact contains 4 human coagulation factors (Factors II, VII, IX, and X), and is mainly administered as a reversal therapy when patients have taken too much anticoagulants. Anticoagulants reduce the ability of the blood to form clots and these are administered, for example, after a heart attack or blood clots in the lungs (pulmonary embolism). If patients received an overdose of anticoagulants, which results in a higher risk for bleeding, Cofact can be administered to counteract this effect.

## Study objective

In this study we will investigate the pharmacodynamics of the compound Cofact, whereby the Cofact that will be used in this study is a modified version of the existing compound Cofact. The effect on the physiologic functions will be evaluated by measuring some laboratory tests. We will also investigate how safe Cofact is, and how well it is tolerated when it is used by healthy participants. In addition, we will look at the effect of Cofact on blood clotting factors in the volunteers blood.

Participants in the study will first receive the medicine acenocoumarol for 10 days. Acenocoumarol is a blood thinner, and reduces the ability of blood to clot. This way it can be investigated if Cofact normalizes blood clotting.

Traditionally, to monitor the effects of Cofact on blood clotting, the so-called INR value of blood is measured. In this study we will also investigate if another blood test (the so-called TGA test) will provide a more accurate measurement of blood clotting than the INR value. A more accurate test to monitor the normalization of blood clotting can potentially prevent any complications in patients that are treated with Cofact.

We compare the effects of Cofact with the effects of a placebo.

## Study design

The study will take a maximum of 9 weeks from the screening until the follow-up visit.

For the study it is necessary that the volunteer will have 1 short stay in the research center on Day -11 to Day -10, followed by 1 short visit on Day -5 or Day -4, and 1 stay in the research center for 1 period of 5 days (Day -2 to Day

4 for 5 nights). This will be followed by 2 short visits to the research center on Day 6 and Day 8, or Day 7 and Day 9 (at entry into the research center on Day -11, you will be asked which option you choose). The last visit (follow up visit) in the study is on Day 15 ±1 after Day 1 (Day 1 is the day when the volunteer will receive Cofact).

Acenocoumarol
While at the research center, the volunteer will be given acenocoumarol as oral tablets with 240 milliliters (mL) of (tap) water.

The volunteer will self-administer acenocoumarol for several days by mouth while they are at home (from the evening of Day -10 until the evening of Day -3).

While at home the volunteer will need to measure daily (in the morning around 8:00 hours) their blood clotting values (INR). The volunteer will have to provide this value each day to the research center before 10:00 hrs in the morning. The volunteer will be contacted by the research center staff each day before 18:00 hrs and be directed what dose of acenocoumarol they should take that evening based on the INR measurements of this day.

Cofact
The volunteer will be given Cofact or placebo (placebo only for Part A) as an intravenous infusion.

**Intervention**

Part A
Treatment Group | Day | Treatment | How often
1 | -10 to -1 |Acenocoumarol(1) | once daily
| 1 | Cofact 12.5 IU/kg(2) |
once
2 | -10 to -1 | Acenocoumarol* | once daily
| 1 | Cofact 25 IU/kg(2) |
once
3 | -10 to -1 | Acenocoumarol* | once daily
| 1 | Placebo
| once
1 The dose of acenocoumarol will depend on the volunteers INR value of that day. The first day the dose is 6 mg, the second day the dose is 4 mg and the third day the dose is 2 mg.
2 This means that the dose of Cofact will be administered per 1 kg of body weight, so the actual dose will depend on the volunteers body weight.

Part B
Treatment Group | Day | Treatment(1) | How often
1 | -10 to -1 | Acenocoumarol(2) | once daily

|1 | Cofact XX IU/kg(3) | once
1 The dose of Cofact will depend on the results of Part A. the volunteer will be told in advance what dose he will receive.
2 The dose of acenocoumarol will depend on the volunteers INR value of that day. The first day the dose is 6 mg, the second day the dose is 4 mg and the third day the dose is 2 mg.
3 This means that the dose of Cofact will be administered per 1 kg of body weight, so the actual dose will depend on the volunteers body weight.

**Study burden and risks**

Possible side effects
The study compound may cause side effects.

Cofact is already in use for the treatment of blood clotting problems but, made with the new production process, has not been given to humans yet. The following side effects are very often observed (in 1 in 10 people or more):
- Trombo-embolic complications (blood clots in a vein)
- Headache
- Elevated temperature

The following side effects are sometimes observed (in less than 1 in 100 people):
- Oversensitivity or allergic reactions

Side effects of Acenocoumarol
The main side effect of acenocoumarol is bleeding. While the risk of major bleeding is low, the volunteer needs to be aware of potential problems. The risk of bleeding is higher in elderly patients with preexisting condition, which will not be included in this study. In this study we are testing the volunteers INR daily, and by this the responsible doctor will be made aware if the volunteer risks of bleeding increases during the first 10 days of the study, while you are taking acenocoumarol.
Other side effects that have been reported when patients have taken acenocoumarol are:
- Hypersensitivity (e.g. urticaria, rash, dermatitis [inflammation of the skin] and fever)
- Decreased appetite
- Nausea
- Vomiting
- Alopecia (loss of hair)
- Vasculitis (inflammation of blood vessels)
- Liver injury
- Skin necrosis (skin death)

The following side effects are sometimes observed (in 1 in 100 people or more):
- bleeding

- nausea

Possible discomforts
Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula (a tube in a vein in the arm) can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment (bruising) of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, seating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about 500 milliliters (mL) of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn may be more than the amount indicated above.

Finger pricks
For the measurement of de INR value of the volunteer his blood, he will have, once daily for 14 days, take a drop of blood from his finger using a lancing device.

Heart tracing
To make a heart tracing, electrodes (small, plastic patches) will be placed on the volunteer his arms, chest and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

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

# Contacts

**Public**
Prothya Biosolutions BV

Plesmanlaan 125
Amsterdam 1066 CX
NL

**Scientific**
Prothya Biosolutions BV

Plesmanlaan 125
Amsterdam 1066 CX
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)

## Inclusion criteria

1. Sex: Male or female of nonchildbearing potential.
2. Age: 18 to 55 years, inclusive, at screening.
3. Body mass index (BMI):18.0 to 30.0 kg/m2, inclusive, at screening. Body weight is not less than 50 kg and not more than 100 kg.
4. Status: Healthy subjects.
5. Female subjects will be included if they are of nonchildbearing potential. Female subjects should have a documented history of tubal ligation more than 6 months prior to the onset of the study, or with a documented hysterectomy. Postmenopausal women will be included in the study if the postmenopausal status is confirmed with a history of 12 months uninterrupted spontaneous amenorrhea, or 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels >40 mIU/ml, or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
6. Male subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from first admission to the clinical research center until 90 days after the follow-up visit. Adequate contraception for the male subject (and his female partner, if she is of childbearing potential) is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, a cervical cap, or a condom. Total abstinence from heterosexual intercourse, in accordance with the lifestyle of the subject, is also acceptable.

Further criteria apply, see protocol.

### Exclusion criteria

1. Employee of PRA or the Sponsor.
2. History of relevant drug and/or food allergies.
3. Any of the following laboratory results outside of the ranges, at screening: lupus anticoagulants (LA screen) and/or anti-beta2-glycoprotein I, low levels of protein C (activity), low levels of protein S (activity), or low levels of antithrombin.
4. Abnormal aPTT or PT levels, or Fe or ferritin levels.
5. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and total bilirubin are not more than about 1.2 times the upper limit of normal at screening (per the Investigator*s discretion).

Further criteria apply, see protocol.

## Study design

### Design

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

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 12-11-2021 |
| Enrollment: | 85 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Acenocoumarol |
| Generic name: | N/A |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Cofact |
| Generic name: | N/A |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 30-09-2021 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 05-11-2021 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 17-02-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 24-02-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-04-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek |

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| | (Assen) |
| Approved WMO Date: | 02-05-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 07-06-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 08-06-2022 |
| 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 | EUCTR2021-004009-37-NL |
| CCMO | NL78895.056.21 |

# Study results

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|---|---|
| Date completed: | 09-09-2022 |
| Results posted: | 05-10-2023 |

**First publication**
21-03-2023