A phase I, open-label, single-dose, randomized, cross-over, 3 parts study to evaluate in healthy subjects the relative bioavailability of eltrombopag new capsule formulation (CPS) in comparison to the reference marketed film-coated tablets (FCT) (Part 1), the pharmacokinetic comparability of eltrombopag CPS and marketed FCT (Part 2) and the effect of food on the pharmacokinetics of eltrombopag administered as CPS (Part 3)

Published: 23-01-2020
Last updated: 08-04-2024

- To evaluate the relative bioavailability between the new eltrombopag capsule formulation (CPS) and the marketed tablet formulation (FCT) at single oral doses of 25 mg and 75 mg, in healthy subjects in the fasted state.- To evaluate the PK...

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

Summary

ID

NL-OMON49500

Source
ToetsingOnline

Brief title
Bioavailability eltrombopag CPS vs FCT

Condition

- Platelet disorders

Synonym
Low Platelet Count, thrombocytopenia

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Bioavailability, Eltrombopag, Open-label, Pharmacokinetic

Outcome measures

Primary outcome

- AUClast, AUCinf, Cmax

Tmax, Tlag, T1/2, CL/F, Vz/F

Secondary outcome

Incidence of adverse events (AEs) and severe adverse events (SAEs), changes in

vital signs, changes in electrocardiograms (ECGs), changes in laboratory

results (hematology, blood chemistry, and coagulation panel).

Study description

Background summary

The purpose of Part 1 is to investigate how the new capsule formulation of eltrombopag functions in comparison to the reference marketed film-coated

tablets of eltrombopag in healthy volunteers.
Eltrombopag is not a new compound; it is already available in the market as a tablet under various dosages.
It will be investigated how quickly and to what extent eltrombopag new capsules are absorbed and eliminated from the body compared to eltrombopag marketed tablets (this is called pharmacokinetics).

The safety of eltrombopag as an oral capsule will also be compared to the safety of eltrombopag as an oral tablet.
Eltrombopag is a compound which is on the market for the treatment of thrombocytopenia. Thrombocytopenia is a condition in which platelet levels in blood are abnormally low. Platelets are tiny blood cells that form clots to stop bleeding. Thrombocytopenia can be caused by various diseases such as chronic immune thrombocytopenia (ITP), severe aplastic anemia (SAA) and chronic hepatitis Ccaused thrombocytopenia.

Thrombocytopenia may not give any symptoms and is sometimes picked up with a blood test. Some individuals with thrombocytopenia may experience external bleeding. Examples of external bleeding are nosebleeds and/or bleeding gums.
Eltrombopag is currently on the market as a tablet. Novartis has now developed a capsule formulation of eltrombopag. This capsule formulation might overcome certain shortcoming that is related to the tablet. This shortcoming includes interference with the absorption of eltrombopag due to certain kind of foods. When the tablet formulation is given along with food with high calcium content, the absorption of eltrombopag by the intestine is decreased. The new capsule formulation is designed to overcome this shortcoming observed with the tablet formulation.
The new capsule has been tested in the laboratory. The test indicated that absorption of the capsule is better than the absorption of the tablet, also when given in combination with different kind of foods.

The purpose of Part 3 is to investigate what the effect of food and calcium is on how quickly and to what extent eltrombopag is absorbed and eliminated from the body (this is called pharmacokinetics). It will be evaluated how the pharmacokinetics of eltrombopag (capsule formulation) are affected if it is given under 4 different conditions: after fasting, after eating a low-fat/low-calorie breakfast, and after eating a high-fat/high-calorie breakfast with high or low calcium.

Furthermore, it will be investigated how safe eltrombopag is and how well it is tolerated when it is administered to healthy volunteers.

Eltrombopag is not a new compound; it is already available in the market as a tablet under various dosages.

Study objective

- To evaluate the relative bioavailability between the new eltrombopag capsule formulation (CPS) and the marketed tablet formulation (FCT) at single oral doses of 25 mg and 75 mg, in healthy subjects in the fasted state.
- To evaluate the PK comparability between the new eltrombopag CPS at the dose(s) adjusted for relative bioavailability and eltrombopag FCT at 75 mg, after single oral dose of each, in healthy subjects in the fasted state.
- To evaluate the impact of high-fat-high-calorie and low-fat-low-calorie meals, low or high in calcium content, on the rate and extent of absorption of eltrombopag CPS.
To evaluate the safety and tolerability of single oral doses of eltrombopag administered as CPS and FCT in healthy subjects under fasted conditions (Parts 1 and 2), and after high-fat-high-calorie or low-fat-low-calorie meals, low or high in calcium content, vs. fasted dosing conditions (Part 3)

Study design

The study consists of 4 periods during which the subject will stay for a minimum of 3 days (2 nights) and a maximum of 7 days (6 nights) per period. If the subject choose to stay for 3 days, you will have to come back to the research facility for short visits on the 4 subsequent days (Day 3 to Day 6). For these short visits you have to be at the research center at 10:00 h in the morning. There will be a period of 7 to 10 days without any visits between dosing in each period.

30 days after the last period or after the last visit of the last period, or from the day of early discontinuation, you will receive a phone call. This follow-up phone call will consist of questions about your wellbeing.

The volunteers will be tested for the presence of coronavirus upon admission to the research center. Until the test results are available, they will be separated from other volunteers in a separate room, and only have very limited contact with study staff. This is to avoid virus spread from potentially infected volunteers to other volunteers or to the study staff. Until the results are available, it is not known whether they are infected and can potentially infect others. The test results will be available within one hour. If the volunteer test positive for coronavirus, they cannot participate in the study.

Intervention

The study will consist of 4 periods. In total the subject will receive one single dose of 25 mg and 75 mg eltrombopag as an oral capsule, and 25 mg and 75 mg eltrombopag as an oral tablet (1 single dose per period), each single dose being separated from each other by 7 to 10 days. Every time eltrombopag will be given with 240 milliliters (mL) of (tap) water. The order in which they subject will receive eltrombopag in the different doses and formulations will be

determined by chance.

Study burden and risks

Eltrombopag may cause side effects.

The following side effects are most frequently observed (in 1 in 10 people or more):
• common cold
• feeling sick
• diarrhea
• cough

The study compound may also have side effects that are still unknown. In addition to unknown side effect, there is a (small) chance that an allergic reaction will occur. This can be caused by the study compound or the excipients.

Drawing blood and/or insertion of the indwelling cannula (tube in an arm vein) may be painful or cause some bruising.
In total, we will take about 300 milliliters (mL) of blood from the subject.
This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time.
To make a heart tracing, electrodes (small, plastic patches) will be pasted at specific locations on your 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 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 throat may cause the volunteer to gag. When the sample is taken from the back of the nose, they may experience a stinging sensation and the eyes may become watery.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male and female subjects who are 18 to 55 years of age on the day of Informed Consent signature
- Subjects in good health condition as determined by no clinically significant findings from medical history, physical examination, vital signs, and ECG, as well as laboratory values within the reference range at the local laboratory, unless deemed not clinically significant by the Investigator or designee
- Body mass index (BMI) of 18.0 to 29.9 kg/m2, with body weight greater than or equal to 50 kg for males and 45 kg for females and no more than 120 kg

Exclusion criteria

- A history or presence of clinically significant ECG abnormalities or a family history or presence of prolonged QT-interval syndrome
- Presence of hepatitis B or C virus, or human immunodeficiency virus
- Clinical evidence of renal disease or liver disease or liver injury
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs, such as gastrectomy, gastroenterosomy, bowel restriction or colecystectomy
- Administration of CYP3A4/5 inhibitors or inducers within 4 weeks prior to screening and until 2 weeks after EOT, for their potential interaction with hormonal contraceptive methods
- Consumption of any antacids, e.g., liquid antacids (e.g., Maalox, Mylanta, Amphogel, Milk of Magnesia), chewable antacids (e.g., TUMS*) during 14 days

prior the first dose of study medication and until end-of-treatment
-Not willing to avoid the following fruits and their juices: grapefruit, grapefruit hybrids, Seville oranges, pomelos, pomegranates, cranberries and star fruits from 14 days prior to the first dosing and until the end-of-treatment
- Use of any prescription or non-prescription medication (OTC) (including aspirin and non-steroidal anti-inflammatory drugs [NSAIDs]), herbal medication, dietary supplements or vitamins during 14 days prior to first dosing and until end-of-treatment

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-02-2020
Enrollment:	248
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Revolade
Generic name:	eltrombopag
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	23-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2020
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	EUCTR2019-004674-26-NL
CCMO	NL72617.056.20