A phase 1, two-part, randomized, open-label study to evaluate the relative bioavailability and food effect of test formulations of VX-152 and Ivacaftor in healthy subjects

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

Summary

ID

NL-OMON43101

Source
ToetsingOnline

Brief title
Bioavailability and Food Effect Study of VX-152 and Ivacaftor

Condition

- Respiratory disorders congenital

Synonym
Cystic Fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Cystic Fibrose, Ivacaftor, VX-152

Outcome measures

Primary outcome

Part A:

To evaluate the relative bioavailability of 3 test formulations of VX-152

relative to suspension in healthy subjects

Part B:

To evaluate the relative bioavailability of a test formulation of ivacaftor

relative to a tablet formulation in healthy subjects

Secondary outcome

Part A:

- To evaluate the safety and tolerability of single doses of 3 test

formulations of VX-152 administered to healthy subjects

- To evaluate the effect of food on the pharmacokinetics (PK) of a test

formulation of VX-152 when administered in fed relative to fasted conditions in

healthy subjects

Part B:

- To evaluate the safety and tolerability of single doses of a test formulation

of ivacaftor administered to healthy subjects

- To evaluate the effect of food on the PK of a test formulation of ivacaftor

when administered in fed relative to fasted conditions in healthy subjects

Study description

Background summary

VX 152 is a new investigational compound that may eventually be used for the treatment of cystic fibrosis (CF). CF is a genetic disorder that causes the body to produce unusually thick mucus. The thick mucus results in malfunction of organs like the lungs, pancreas and liver.

In the human body, the cystic fibrosis transmembrane conductance regulator (CFTR; this is a protein that can be found on the membrane of cells) plays an important role in the transport of salt and water in and out of cells. In CF, this protein does not work correctly or it is not produced sufficiently. As a result, the transport of salt and water in and out of cells is disturbed and mucus will become unusually thick. VX-152 is thought to improve CFTR functioning by modifying folding of the protein structure. VX 152 is in development and is not registered as a drug but has been given to humans before.

Ivacaftor, the second study compound used in this study, is approved with the brand name Kalydeco® in the U.S., the EU and some other countries for patients who have certain CF abnormalities. If you would like to know in which countries, age range, or for which genetic abnormalities Kalydeco® has been approved, ask the study doctor. In this study Ivacaftor will, in some instances, be administered in an experimental formulation that differs from the approved Kalydeco® tablet.

Study objective

The purpose of Part A is to investigate how safe the study compound VX-152 is and how well the study compound is tolerated. The study will also investigate how quickly and to what extent the compound is absorbed into and eliminated from the body (this is called pharmacokinetics). In addition, safety and pharmacokinetics of VX-152 will be compared for 4 different oral dosage forms of VX-152 (suspension, liquid filled capsules and 2 kinds of tablets) and the effect of taking 1 of the tablet doses with and without food will be investigated during this part of the study.

The purpose of Part B is to investigate how safe the study compound ivacaftor

is and how well the study compound is tolerated. The study will also investigate how quickly and to what extent the compound is absorbed into and eliminated from the body (this is called pharmacokinetics). In addition, safety and pharmacokinetics of ivacaftor will be compared for 2 different oral dosage forms (tablet and liquid filled capsule). Also the effect of taking the capsule dose with and without food will be investigated during this part of the study.

Study design

Part A:
The study will consist of 1 period during which you will stay in the clinical research center in Groningen for 22 days (21 nights).

Part B:
The study will consist of 1 period during which you will stay in the clinical research center in Groningen for 16 days (15 nights).

Intervention

Part A:
The study will consist of 1 period during which you will receive VX-152 5 times. VX-152 will be given orally as a suspension, a capsule and 2 tablet dosage forms.

Part B;
The study will consist of 1 period during which you will receive ivacaftor 3 times. Ivacaftor will be given as a tablet and a liquid filled capsule.

Study burden and risks

Part A:
All potential drugs cause adverse effects; the extent to which this occurs differs. As multiple doses of VX 152 will be administered to humans for the first time in this study, adverse effects with multiple doses of VX 152 in humans have not been previously reported. As of the date of this form single doses of up to 800 mg have been administered to healthy volunteers in another study.

VX 152 was generally well tolerated without safety concerns in these volunteers, except for an event of hemolysis (spontaneous destruction of red blood cells) in one volunteer and a possible event of milder hemolysis in a second volunteer. These volunteers were found to have a genetic condition, glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency. Volunteers with this condition may be at risk of acute hemolysis, with a small chance of kidney damage if VX-152 is administered.

To avoid inclusion of volunteers with G6PD deficiency in this study, a blood test for G6PD deficiency will be performed at screening. Furthermore, additional blood and urine samples will be taken to improve the monitoring.

Generally, VX-152 was well tolerated in rats and dogs. In rats no VX-152 related adverse reactions were observed at the dose levels tested. When VX-152 was administered to dogs, adverse effects related to VX-152 were observed at the highest dose level tested only. These adverse events included: increased incidence of diarrhea and vomiting, loss of skin elasticity, lack of appetite, and decreased activity. In addition, small body weight decreases (ie, the mean body weight of the test group decreased less than 10%) were observed.

Part B:
All potential drugs cause adverse effects; the extent to which this occurs differs. Ivacaftor has marketing authorization in a number of countries including the EU. More than 35 studies of ivacaftor have been completed or are ongoing in approximately 400 healthy adult subjects and 800 adult and pediatric subjects with CF.

Common adverse events occurring in 10% or more of CF subjects:
- headache
- upper respiratory tract infection
- nasal congestion
- oropharyngeal pain
- abdominal pain
- diarrhea
- nasopharyngitis
- rash

Less common adverse events occurring in 5% to 10% of CF subjects:
- dizziness
- bacteria in sputum
- sinus congestion
- rhinitis

A few subjects with CF receiving ivacaftor as well as placebo have shown signs of liver injury. In these cases, the liver injury was noticed as abnormalities in blood tests which were monitored as part of the study. The very high levels of these tests, called ALT and AST, led to stopping of the study compound. The levels of ALT and AST got better after the study compound was stopped. Very severe cases of liver injury can become permanent or be life-threatening. Overall, the data does not support an association between ivacaftor and ALT and AST elevations, although a possible link cannot be completely excluded based on the available data.

The study compound may contain a very small amount of lactose, a sugar found in dairy products. The amount of lactose in a single pill is roughly the same as

the amount in one teaspoon of milk. This amount of lactose is unlikely to cause symptoms in people who have lactose-intolerance.

Procedures: pain, mnor bleeding, bruising, possible infection

Contacts

Public
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US
Scientific
Vertex Pharmaceuticals

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

healthy male and female volunteers
18-55 yrs, inclusive
18.0-31.0 kg/m2, inclusive
non-smoking

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. The volunteers does not have a history of hemolysis and the blood analyses at screening are not indicative of G6PD deficiency or chronic hemolysis. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 56 days from the start of the study. In case of donating more than 0.5 liters of blood in the 56 days prior the start of this 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):	20-04-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kalydeco®
Generic name:	Ivacaftor
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-03-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2016
Application type:	First submission
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	EUCTR2016-000561-23-NL
CCMO	NL57322.056.16