A Phase 1, Randomized, Double blind, Placebo Controlled, Single and Multiple Dose Escalation Study Evaluating Safety and Pharmacokinetics of VX 152 Alone and in Combination with VX 661/Ivacaftor, and Bioavailability and Food Effect of VX 152 in Healthy Adult Subjects

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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 (...

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

Summary

ID

NL-OMON43756

Source
ToetsingOnline

Brief title
A Study to Evaluate Safety and PK of VX 152 in Healthy Adult Subjects

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 Fibrosis, VX-152

Outcome measures

Primary outcome

Part A

To evaluate the safety and tolerability of single oral ascending doses of VX

152 administered to healthy male and female subjects

Part B

To evaluate the safety and tolerability of multiple oral ascending doses of VX

152 administered for 14 days to healthy male and female subjects

Part C

To evaluate the safety and tolerability of multiple oral ascending doses of VX

152 administered in combination with VX 661/ivacaftor (triple combination [TC])

administered for 13 days to healthy male and female subjects

Part D

To evaluate the absolute bioavailability (BA) of oral VX 152 and the clearance

of VX 152 administered as an isotopically-labeled intravenous (IV) microdose to

healthy male and female subjects

Secondary outcome

Part A

To evaluate the PK of VX 152 after administration of single oral ascending doses of VX 152 to healthy male and female subjects

To evaluate the relative BA of a tablet formulation of VX 152 relative to suspension in healthy male and female subjects

To evaluate the effect of food on the PK of VX 152 when the tablet formulation is administered in fed (i.e., with a standard meal) relative to fasted conditions in healthy male and female subjects

Part B

To evaluate the PK of VX 152 after multiple oral ascending doses of VX 152 administered for 14 days to healthy male and female subjects

Part C

To evaluate the PK of VX 152 after multiple oral ascending doses of VX 152 in combination with VX 661 and ivacaftor administered for 13 days to healthy male and female subjects

To evaluate the PK of ivacaftor and metabolites (M1 ivacaftor and M6 ivacaftor) and VX 661 and metabolites (M1 661 and M2 661) after single doses and after multiple oral doses in combination with VX 152 (TC) for 13 days to healthy male and female 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 not registered as a drug and has not been given to humans before.

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 two different oral dosage forms of VX 152 (suspension and tablet) and the effect of taking the tablet dose with food will be investigated during this part of the study.
The purpose of Part B is to investigate how safe the study compound VX-152 is and how well the study compound is tolerated after multiple dosing. 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, the effects of VX-152 on lung function and on the amount of chloride in sweat will be investigated (this is called pharmacodynamics).
The purpose of Part C is to investigate how safe the study compound VX-152 is and how well the study compound is tolerated when it is administered in combination with VX-661 and ivacaftor. The study will also investigate how quickly and to what extent the study compounds (VX-152, VX-661 and ivacaftor) are absorbed into and eliminated from the body (this is called pharmacokinetics). In addition, the effects of VX-152, VX-661 and ivacaftor on lung function and the amount of chloride in sweat will be investigated (this is called pharmacodynamics).
The purpose of Part D is to investigate how safe the study compound VX-152 is to how quickly and to what extent VX-152 is absorbed, distributed, metabolized (broken down) and eliminated from the body (this is called pharmacokinetics). The compound to be administered will be labeled with deuterium, a stable isotope, and non-radioactive form of hydrogen which is used as a tracer in

human studies. This enables the investigator to trace the compound in blood, urine and feces. In addition, also VX-152 without deuterium will be administered during this study.

Study design

Part A
For all groups, except one, the study will consist of 1 period during which you will stay in the clinical research center in Zuidlaren for 6 days (5 nights).
One group is selected to stay in the clinical research center for a second consecutive period of 10 days (9 nights). This means that this group will stay in the clinical research center for a total of 16 days (15 nights).
In Group 1 only, initially two volunteers will be dosed, one will receive VX-152, and one will receive placebo. After dosing, the safety and tolerability of VX-152 in these volunteers will be closely monitored. If there are no concerns about the safety and tolerability 24 hours after dosing, then the remaining six volunteers (five will receive VX-152 and one will receive placebo) will be dosed.
In all groups, on Day 1 of the study volunteers will receive VX-152 or placebo as an oral suspension 30 minutes after the start of breakfast followed by 240 milliliters of (tap) water. You will receive a standardized breakfast which needs to be finished within 20-25 minutes. The entire breakfast must be consumed. You are not allowed to eat or drink for a minimum of 8 hours (except water) before the start of the breakfast.
All volunteers in the group that will stay in the clinical research center for a second period will receive the study compound once on Day 1 of Period 2 without a standardized breakfast and once on Day 6 of Period 2 with a standardized breakfast. The study compound will be administered as a tablet followed by 240 milliliters of (tap) water. On Day 1 you are not allowed to eat or drink (except water) for a minimum of 8 hours before you receive the study compound. On Day 1 drinking water is not permitted from 1 hour prior to until 1 hour after study compound administration. On Day 6 you will receive a standardized breakfast which will have to be finished within 20 25 minutes. The entire breakfast must be consumed. You are not allowed to eat or drink (except water) for a minimum of 8 hours before the start of the breakfast.
For all groups fasting will continue until 4 hours after administration of the study compound, at which time you will receive a lunch. You are allowed to drink water beginning 1 hour after administration of the study compound. One of the investigators will inspect your hands and mouth after the study compound intake.

Part B
The actual study will consist of 1 period during which you will stay in the clinical research center in Zuidlaren for 19 days (18 nights).
Day 1 is the first day of administration of the study compound. On Day 1 to Day 14 you will receive VX-152 or placebo as an oral suspension or as a tablet once or twice every day. A placebo is a suspension or tablet without the active

ingredient.
The initial groups will receive VX-152 or placebo as an oral suspension. Dosing with the tablet may only begin when results from Part A are available.
During the study you will receive VX-152 or placebo 30 minutes after the start of a standardized meal as an oral suspension or as a tablet followed by 240 milliliters of (tap) water. You will receive a standardized meal on all days you receive study compound. The entire meal must be consumed and has to be finished within 20-25 minutes.
If the study compound is administered once daily, then the standard meal will be breakfast. If the study compound is administered twice daily, then the standard meal will be standard breakfast and standard dinner.
On Day 1 and Day 14 you are not allowed to eat or drink for a minimum of 8 hours (except water) before start of the breakfast. Fasting on Day 1 and Day 14 will continue until at least 4 hours after administration of the study compound in the morning. During fasting you are allowed to drink water beginning 1 hour after administration of the study compound.

Part C
The actual study will consist of 1 period during which you will stay in the clinical research center in Zuidlaren for 19 days (18 nights).
During the study you will receive VX-152, VX-661, ivacaftor or matching placebo 30 minutes after the start of a meal as an oral suspension or as a tablet followed by 240 milliliters of (tap) water. You will receive a standardized meal on all days you receive study compound. The entire meal must be consumed and has to be finished within 20-25 minutes.
If the study compound is administered once daily, then the standard meal will be breakfast. If the study compound is administered twice daily, then the standard meal will be standard breakfast and standard dinner.
On Day 1, Day 2 and Day 14, you are not allowed to eat or drink for a minimum of 8 hours (except water) before start of the breakfast.
On Day 1, Day 2 and Day 14 fasting will continue until at least 4 hours after administration of the study compound in the morning. Then you will receive a lunch. You are allowed to drink water beginning 1 hour after administration of the study compound.

Part D
The actual study will consist of 1 period during which you will stay in the clinical research center in Zuidlaren for 11 days (10 nights).
Based on the results of Part A you may receive VX-152 either under fasted or under fed conditions. The unlabeled study compound will be administered as a tablet or oral suspension followed by 240 milliliters of (tap) water. The deuterium labeled VX-152 will be administered as an intravenous infusion.
When you receive VX-152 under fasted conditions, on Day 1 and Day 6 you are not allowed to eat or drink (except water) for a minimum of 8 hours before you receive the study compound. Water is allowed until 1 hour prior to study compound administration.
When you receive VX-152 under fed conditions, on Day 1 and Day 6 you will

receive a standardized breakfast which will have to be finished within 20-25 minutes. The entire breakfast must be consumed. You are not allowed to eat or drink (except water) for a minimum of 8 hours before the start of the breakfast. Water is permitted until 1 hour prior to study compound administration.
On Day 1 and Day 6 fasting will continue until at least 4 hours after administration of the study compound. Then you will receive a lunch. You are allowed to drink water beginning 1 hour after administration of the study compound.

Intervention

Part A;
In all groups you will receive a single dose of VX-152 or placebo as an oral suspension. A placebo is a suspension or tablet without the active ingredient. The group that will be selected to continue on to a second period will receive a tablet of VX 152 on Day 1 and Day 6 of Period 2.
Whether you will receive VX-152 or placebo will be determined by chance. In each group, six volunteers will receive VX-152 and two volunteers will receive placebo. Neither you nor the study doctor will know if VX-152 or placebo will be dosed; we call this *the study is blinded*. However, information on the administration of the study compound will be present in the clinical research center, in sealed envelopes, which can be opened in case of emergency.

Only the start dose of Part A, group1 is set. This is 50 mg. The following doses will be set based on the results obtained in the previous cohorts. This is applicable for all parts of the study.

Part B:
On Day 1 to Day 14 you will receive VX-152 or placebo as an oral suspension or as a tablet once or twice every day. A placebo is a suspension or tablet without the active ingredient.
Whether you will receive VX-152 or placebo will be determined by chance. In each group, six volunteers will receive VX-152 and two volunteers will receive placebo. Neither you nor the study doctor will know if VX-152 or placebo will be dosed; we call this *the study is blinded*. However, information on the administration of the study compound will be present in the clinical research center, in sealed envelopes, which can be opened in case of emergency.
The initial groups will receive VX-152 or placebo as an oral suspension. Dosing with the tablet may only begin when results from Part A are available.

Part C:
During the study you will either receive a combined treatment (with VX-661, ivacaftor and VX 152), or treatment with matching placebos only. The combined treatment starts on Day 1 with 1 tablet containing a combination of VX 661 and ivacaftor in the morning, followed by 1 tablet containing ivacaftor alone in the evening. From Day 2 to Day 14 this regimen will be continued and further

combined with doses of VX-152 either once or twice daily. The dose, dose regimen (once or twice daily) and dosage form (tablet or oral suspension) of VX 152 will be based on the results of Part A and Part B of this study.
A placebo is a suspension or tablet without the active ingredient. Whether you will receive VX 152 combined with VX-661 and ivacaftor or matching placebos (that means a placebo for each VX 152, VX 661 and ivacaftor) will be determined by chance. In each group, 6 volunteers will receive VX 152 combined with VX-661 and ivacaftor and 2 volunteers will receive matching placebos. Neither you nor the study doctor will know if VX-152, VX-661 and ivacaftor or triplicate placebo will be dosed; we call this *the study is blinded*. However, information on the administration of the study compound will be present in the clinical research center, in sealed envelopes, which can be opened in case of emergency.

Part D:
On Day 1 and Day 6 you will first receive a single oral dose of VX-152 without deuterium. VX-152 will be dosed as a tablet or as an oral suspension, depending on the results from Part A of the study. In addition, 10 minutes after receiving the oral dose you will receive deuterium labeled VX-152 via infusion (using a cannula) on both Day 1 and Day 6. Depending on results from Part A, VX-152 may be administered either after fasting for at least 8 hours or after consumption of a meal.

Study burden and risks

Procedures: pain, light bleeding, heamatoma, possibly an infection.

Single doses of up to 800 mg VX 152 or placebo were generally well tolerated without safety concerns in healthy volunteers, except for an event of hemolysis (spontaneous destruction of red blood cells) in one volunteer after a single dose of 400 mg VX-152, and a possible event of milder hemolysis in a second volunteer after a single dose of 200 mg VX 152. These volunteers were found to have a genetic condition, glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency. People with this condition are at risk of acute hemolysis, with a small chance of kidney damage if VX-152 is administered. To avoid inclusion of people 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.

Single doses of 1200 to 2000 mg VX-152 or placebo were well tolerated by about half of the volunteers but only moderately tolerated by some of the volunteers due to loss of appetite, nausea and vomiting, and/or headache. A mild increase in total and direct bilirubin was also observed in most volunteers who received single doses of 1200 to 2000 mg VX-152 or placebo.

Multiple doses of up to 400 mg VX-152 or placebo twice daily were generally well tolerated without safety concerns in healthy volunteers. Some volunteers

who received multiple doses of up to 800 mg VX-152 or placebo twice daily had mild increase in total and direct bilirubin.

Multiple doses of 800 mg VX-152 or placebo twice daily were poorly tolerated due to temporary nausea and vomiting, and high levels of blood test called ALT and AST. Increases in ALT and AST can be a sign of liver inflammation or injury. The abnormal blood tests were reversible, and the nausea and vomiting got better after the study drug was stopped.

Very severe cases of liver injury can become permanent and even be life-threatening. During the remainder of the study, the doses of study drug to be taken by the subjects will be chosen to give predicted drug levels that are substantially less than the drug levels measured in the subjects who had the adverse effects described above. Also, you will have your blood drawn every 1 * 3 days to check for liver injury. If we detect evidence of liver injury through your blood tests, we will stop your study drug.

Other than lab test changes, symptoms of liver injury are not specific and may include loss of appetite, upset stomach, tiredness, pain in the right upper belly, vomiting, dark urine, and/or yellowing of the eyes or skin. You should tell your doctor if you have any of these symptoms or anything else unusual.

Possible Risks Based Upon Chemical Profile and Animal Studies:

VX-152 has been studied in animals. VX-152 was generally well tolerated in rats and dogs. When VX-152 was administered to dogs, effects observed at the highest dose level tested included: increased diarrhea and vomiting, lack of appetite, and decreased activity. In addition, small body weight decreases were observed.

In animals treated with VX-152 by mouth, study drug that goes into the skin may absorb light and produce tissue damage. This damage might appear similar to a sunburn. Animal studies are ongoing to define whether light exposure after VX-152 treatment has effects on the skin. Until results are available, people receiving VX 152 (or placebo) as part of human studies should take appropriate measures against sun exposure or exposure to excessive UV-visible radiation.

Contacts

Public
Vertex Pharmaceuticals

Northern Avenue 50
Boston 02210
US

Scientific
Vertex Pharmaceuticals

Northern Avenue 50
Boston 02210
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

healthy male or female
18-55 y, incl.
BMI 18.0 - 31.0, and a total body weight >50 kg

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-10-2015
Enrollment:	120
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:	09-10-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	12-10-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	09-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	05-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2016
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	EUCTR2015-003084-11-NL
CCMO	NL55106.056.15