A Phase 2, Randomized, Double blind, Controlled Study to Evaluate the Safety and Efficacy of VX 440 Combination Therapy in Subjects Aged 12 Years and Older With Cystic Fibrosis

Published: 02-11-2016
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1. Primary Objectives• To evaluate the safety and tolerability of VX 440 monotherapy and VX 440 in dual and triple combination with VX-661 and IVA• To evaluate the efficacy of VX 440 monotherapy and VX 440 in dual and triple combination with VX 661…

Ethical review	Approved WMO
Status	Pending
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON45508

Source
ToetsingOnline

Brief title
VX15-440-101 / ELEVATE CF

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
fibrocystic disease of the pancreas / monogenic disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Combination Therapy, Cystic Fibrosis, Double-blind study, Phase 2

Outcome measures

Primary outcome

Primary Endpoints

• Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12 lead electrocardiograms (ECGs), vital signs, and pulse oximetry

• Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline through Day 29 (Parts 1 and 2) and through Week 12 (Part 4)

Secondary outcome

Secondary Endpoints

• Absolute change in sweat chloride concentrations from baseline through Day 29 (Parts 1 and 2) and through Week 12 (Part 4)

• Relative change in ppFEV1 from baseline through Day 29 (Parts 1 and 2) and through Week 12 (Part 4)

• Number of pulmonary exacerbations through Week 12 (Part 4)

• Time to first pulmonary exacerbation through Week 12 (Part 4)

• Absolute change in body mass index (BMI) from baseline at Week 12 (Part 4)

• Absolute change in BMI z score from baseline at Week 12 (Part 4)

• Absolute change in weight from baseline at Week 12 (Part 4)

• Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ R) respiratory

domain score from baseline at Day 29 (Parts 1 and 2) and at Week 12 (Part 4)

• PK parameters of VX 440, TEZ, M1 TEZ, IVA, and M1 IVA

Other Endpoints

• Absolute change in CFQ R non-respiratory domain scores from baseline at Day

29 (Parts 1 and 2) and at Week 12 (Part 4)

• Absolute change in inflammatory mediators from baseline at Week 12 (Part 4)

Study description

Background summary

Cystic fibrosis (CF) affects more than 70,000 children and adults worldwide and is the most common fatal genetic disease in persons of European descent. Based on its prevalence, CF qualifies as an orphan disease. CF is caused by a defect in the gene encoding the CF transmembrane conductance regulator (CFTR), an ion channel that regulates the flow of chloride and other ions in epithelia of various tissues, including lungs, pancreas and other gastrointestinal organs, and sweat glands. Decreased CFTR activity in people with CF results in multisystem pathology , beginning at birth. Despite progress in the treatment of CF with antibiotics and mucolytics, the median predicted survival age for a person with CF is approximately 40 years. More effective treatments are needed for CF.
To address this medical need, Vertex Pharmaceuticals Incorporated is developing treatment regimens that include CFTR modulators to target the underlying cause of CF: the defective CFTR protein. Two types of CFTR modulators have been developed: potentiators, which increase the channel gating activity of the CFTR protein, and correctors, which increase the quantity of CFTR at the cell surface. Because potentiators can increase the activity of CFTR protein delivered to the cell surface by correctors, CFTR potentiators and correctors are complementary therapeutic approaches.

Ivacaftor (IVA; Kalydeco®), the first CFTR modulator developed by Vertex, is an orally administered CFTR potentiator that increases the channel open

probability of CFTR protein to enhance chloride transport. Globally, Kalydeco is indicated for the treatment of CF in patients as young as 2 years who have the G551D and certain other gating mutations as well as the R117H mutation in the CFTR gene in certin regions.

Lumacaftor (LUM, VX-809) and tezacaftor (TEZ, VX-661) are orally administered first-generation CFTR correctors developed by Vertex that act directly on CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of functional F508del CFTR protein at the cell surface. F508del, the most prevalent mutation in people with CF, occurs in about 83% of CF patients of European descent and results in a decreased quantity of CFTR protein at the cell surface. Orkambi* (LUM/IVA combination therapy) is approved in the US, EU, Canada, and Australia for patients 12 years and older who are homozygous for F508del. Phase 3 studies of TEZ/IVA combination therapy are ongoing in populations that are homozygous or heterozygous for F508del.

VX 440 is a second-generation CFTR corrector that acts through a different site of the CFTR protein than LUM and TEZ. In vitro, VX 440 improves the processing and trafficking of F508del-CFTR, thereby increasing the quantity of functional F508del-CFTR protein at the cell surface. VX-440 has been studied in vitro in combination with the first generation corrector TEZ. Consistent with different mechanisms of action, the effects of VX 440 and VX 661 are additive. The activity of the CFTR protein delivered to the cell surface by VX 440, alone or in combination with TEZ, is potentiated by IVA. In human bronchial epithelial (HBE) cells derived from CF patients homozygous for F508del, the triple combination (TC) of VX 440, TEZ, and IVA increased CFTR-mediated chloride transport more than the dual combinations (VX 440 and TEZ; VX 440 and IVA; TEZ and IVA) or individual agents (VX 440; TEZ; IVA). These data, as well as the nonclinical pharmacokinetic (PK) and safety profile, support the development of VX 440 in combination with other CFTR modulators for the treatment of CF.

Study objective

1. Primary Objectives
• To evaluate the safety and tolerability of VX 440 monotherapy and VX 440 in dual and triple combination with VX-661 and IVA
• To evaluate the efficacy of VX 440 monotherapy and VX 440 in dual and triple combination with VX 661 and IVA

2. Secondary Objectives
• To evaluate the pharmacodynamic (PD) effect of VX 440 monotherapy and VX 440 in dual and triple combination with VX 661 and IVA on sweat chloride concentrations
• To evaluate the PK of VX 440 when administered alone and when administered in dual and triple combination with VX-661 and IVA
• To evaluate the PK of VX 661, IVA, and their respective metabolites when

administered with VX 440

Study design

This is a Phase 2, randomized, double blind, placebo and TEZ/IVA controlled, parallel group, multicenter study. The treatment arms and doses of VX 440, TEZ, and IVA to be evaluated are shown in the table below.
Part 1 will consist of 2 cohorts: Cohort 1A and Cohort 1B. The start of dosing of Cohort 1A and Cohort 1B will be sequential. After all Cohort 1A subjects complete the Day 15 Visit, a blinded review of all available safety and PK data will be conducted by the Vertex study team and lead investigator(s). Dosing of Cohort 1B will begin after the blinded review, if supported by safety and PK data.
Part 2 will initiate after the Cohort 1A blinded review, if supported by safety and PK data.
Part 3 will not be conducted.
Part 4 will only be initiated after Part 1 has been completed. Safety, efficacy and PK data from Part 4 will be submitted to the independent ethics committee (IEC). Screening of subjects for Part 4 will not begin without approval by the EC. Inclusion of adolescent CF subjects will only occur if Part 1 safety and efficacy data support evaluation in adolescent subjects.

Intervention

See section E4 of the ABR Form.

Study burden and risks

All potential drugs can cause adverse effects; the extent to which this occurs differs. In a previous study, single doses of up to 1600 mg VX 440 and multiple doses of up to 600 mg VX-440 twice daily for 14 days were administered to healthy volunteers. In a second study, multiple doses of up to 600 mg VX 440 twice daily combined with 100 mg tezacaftor once daily and 300 mg ivacaftor twice daily were administered to healthy volunteers, VX-440 alone or combined with the other compounds was generally well tolerated by the volunteers. During these studies, side effects reported as possibly related to study drug included: sore throat, nausea, diarrhea (loose stools), gas/flatulence, light-headed feeling, and headache. These side effects were considered either mild or moderate in intensity and usually resolved despite continued treatment. Increased levels of blood tests called bilirubin and liver enzymes (a possible sign of liver injury) have been seen in some volunteers who received VX-440 or placebo. The abnormal blood tests have been mild and reversible.
Severe cases of liver injury can become permanent and even be life-threatening. The patient will have his/her blood drawn every 1-2 weeks to check for liver injury. If we detect signs of liver injury through the blood tests, we will stop the study drug.

Other than blood 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. The patient should tell the Study Doctor or his/her regular doctor if he/she has any of these symptoms or anything else unusual.
In a study of a similar compound there was one event of hemolysis (bursting of red blood cells in the circulation that lead to anemia and brown urine) 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. Individuals with this condition may be at risk of acute hemolysis with a small chance of kidney damage when VX-440 is administered to them. To avoid inclusion of individuals with G6PD deficiency in this study, a blood test for G6PD deficiency will be performed at screening.

Tezacaftor alone, ivacaftor alone, and tezacaftor in combination with ivacaftor
To date, more than 280 subjects (106 healthy subjects and approximately 174 subjects with cystic fibrosis (CF)) have received at least 1 dose of tezacaftor either alone or taken with ivacaftor in completed or ongoing clinical studies.
No significant safety risks attributable to tezacaftor monotherapy or to tezacaftor in combination with ivacaftor have been identified in these clinical studies either in healthy subjects or in CF subjects. Overall, tezacaftor alone or in combination with ivacaftor has been well tolerated.
One healthy subject who received tezacaftor also experienced a serious adverse event of rhabdomyolysis (muscle injury), several weeks after their last dose of tezacaftor. The event was considered to be unrelated to tezacaftor.
An ongoing study is evaluating the safety of tezacaftor in combination with ivacaftor, with particular attention to potential effects on the stomach and intestines. Visual assessments of the inside of the stomach and intestines did not detect any new lymph vessel enlargement after 12-weeks of treatment with tezacaftor in combination with ivacaftor. No stomach or intestinal side effects were identified. Review of the safety data from this study has not indicated any new safety findings or concerns.
In addition, up to now, more than 35 studies of ivacaftor alone in monotherapy have been completed or are ongoing in more than 400 healthy adult subjects and more than 800 adult and pediatric subjects with CF.

Overall, the most common adverse events in studies of CF subjects who took tezacaftor, ivacaftor, or tezacaftor in combination with ivacaftor, are listed below:
Common adverse events occurring in 10% or more of CF subjects:
• Infective pulmonary exacerbation of CF (temporary worsening of lung function due to an infection or inflammation)
• Cough
• Headache
• Nausea
• Sputum increased
• Fatigue

• Upper respiratory tract infection (common cold)
• Oropharyngeal pain (sore throat)
• Nasal congestion (stuffy nose)
• Nasopharyngitis (inflammation of the nose and pharynx)
• Abdominal Pain
• Diarrhea
• Rash
Less common adverse events occurring in 5% to 10% of CF subjects:
• Dizziness (feeling faint)
• Pyrexia (fever)
• Hemoptysis (coughing up blood)
• Vomiting
• Rales (an abnormal rattling sound heard when examining unhealthy lungs)
• Bacteria in sputum
• Sinus congestion
• Rhinitis (runny nose)
In CF subjects who received tezacaftor, ivacaftor, or tezacaftor and ivacaftor, as well as placebo, a few subjects have shown signs of liver injury. In these cases, the liver injury was noticed as abnormalities in blood tests, which are monitored as part of the study which led to stopping of Study Drug and recovery of the abnormal blood tests. Very severe cases of liver injury can become permanent and even be life-threatening. While the data do not support an association between ivacaftor or tezacaftor and liver injury, a possible link cannot be excluded.
Eye examinations performed in studies involving children receiving ivacaftor, have identified several subjects with cataracts (cloudiness of the lens of the eye) present from birth, or which developed after birth. While the data do not support a link between ivacaftor and cataracts, a possible link cannot be excluded.
The Study Drug 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.
Drug Interaction Risks (medicines working with or against each other):
Almost all medicines can cause side effects. Many are mild, but some can sometimes become life threatening if they are not treated. The combination of the Study Drug and any other medications, dietary supplements, natural remedies, and vitamins could be harmful to the patient. The patient should tell the Study Doctor about every medicine, dietary supplement, natural remedy, and vitamin (or change) while the patient is in the study. There are certain herbal medications, such as St. John*s Wort, and certain fruits and fruit juices (such as grapefruit, Seville oranges, or products made from them) that the patient must not take during study. The Study Doctor will review these with the patient.

Unknown Risks:
There may be side effects that are not yet known. The patient should call the

Study Doctor if he/she thinks he/she is having any of the problems listed above or even if the patient is having problems that are not on this list.

Reproductive Risks
The patient should not become pregnant or father a baby while on this study because the Study Drug can cause serious birth defects in an unborn baby. Females should not breastfeed a baby while in this study.
All participants must have successful use of at least one study-approved method of birth control. The Study Doctor will discuss the birth control method(s) the patient currently uses. During the time that female participants are on Study Drug, they will be allowed to take birth control pills. However, the Study Drug is predicted to interfere with the ability of birth control pills to prevent pregnancy. Female participants must therefore use at least one additional form of birth control.

The details of the birth control requirements are as follows:
Male participants:
• During the period starting from first dose of study drug until 90 days after last dose of Study Drug, male participants in the study must use a male condom with all female sexual partners who are of child-bearing potential. This is to avoid exposing a possible or actual embryo or fetus to Study Drug contained in seminal fluid.

Female participants: At least 1 of the following methods must be used:
• Continuous use of a non-hormone-releasing intra-uterine device (IUD) that has been in place for at least 90 days before the first dose of Study Drug, until 90 days after the last dose of Study Drug. Hormone-releasing IUDs such as Mirena or Skyla are NOT accepted.
• Bilateral tubal ligation (or another method for which complete blockage of both of the Fallopian tubes has been documented), in place for at least 6 months before the first dose of Study Drug.
• Post-menopausal state, meaning no menstrual periods for at least 12 consecutive months, with a confirmatory lab test done at screening.
• Documented removal of uterus (hysterectomy) and/or removal of both ovaries, with or without removal of the Fallopian tubes (bilateral oophorectomy/salpingo-oophorectomy).
• Male partner has vasectomy at least 6 months before the first dose of Study Drug, with a post-vasectomy semen analysis showing that no sperm are present.
• Male partner with documented infertility; for example, has had both testicles removed (bilateral orchiectomy).
If the patient or his female partner becomes pregnant during the study he should notify the Study Doctor right away. If the patient or his female partner becomes pregnant, the patient will need to stop Study Drug immediately. The Study Doctor will ask permission from the patient or his female partner to follow the pregnancy to its outcome and until the infant is one year of age.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject (or subject*s legally appointed and authorized representative) will sign and date an informed consent form (ICF), and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects will be aged 18 years or older for Parts 1 and 2, and aged 12 years or older for Part 4, on the date of informed consent and, when appropriate, date of assent.
4. Body weight >=35 kg.
5. Sweat chloride value *60 mmol/L from test results obtained during screening. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject*s medical record may be used to establish eligibility. (It is acceptable to use a sweat

chloride value that was obtained before previous treatment with IVA, LUM/IVA, or an investigational CFTR modulator).
6. Subjects must have an eligible CFTR genotype as noted below. If the screening CFTR genotype result is not received before randomization (Parts 1 and 4) or before Day 28 (Part 2), a previous CFTR genotype laboratory report may be used to establish eligibility. Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.5).
• Part 1 and Part 4: Heterozygous for F508del with a second CFTR allele carrying an MF mutation that is not likely to respond to TEZ and/or IVA therapy (Appendix A)
• Part 2: Homozygous for F508del
7. Parts 1, 2, and 4 subjects must have an FEV1 >=40% and <=90% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])13 at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria10 for acceptability and repeatability.
8. Stable CF disease as judged by the investigator.
9. Willing to remain on a stable CF medication regimen through the planned end of treatment or, if applicable, the Safety Follow up Visit.

Exclusion criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. History of cirrhosis with portal hypertension.
3. Risk factors for Torsade de Pointes, including but not limited to, history of any of the following: familial long QT syndrome, chronic hypokalemia, heart failure, left ventricular hypertrophy, chronic bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia (ventricular or atrial fibrillation), obesity, acute neurologic events (subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, or intracranial trauma), or autonomic neuropathy.
4. History of hemolysis.
5. G6PD deficiency, defined as G6PD activity less than the lower limit of normal (LLN) or 70% of the mean of the LLN and the ULN, whichever is greater.
6. Any of the following abnormal laboratory values at screening:
• Hemoglobin <10 g/dL
• Total bilirubin >=2 × ULN
• Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), or alkaline phosphatase (ALP) >=3 × ULN
• Abnormal renal function defined as glomerular filtration rate <=50 mL/min/1.73 m2 (calculated by the Modification of Diet in Renal Disease Study Equation)14, 15 for subjects >=18 years of age and <=45 mL/min/1.73 m2 (calculated by the Counahan Barratt equation)16 for subjects aged 12 to 17 years (inclusive)
7. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before the first dose of study drug (Day 1 for Parts 1 and 4, Day 28 for Part 2).
8. Lung infection with organisms associated with a more rapid decline in pulmonary status

(e.g., Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus). For subjects who have had a history of a positive culture in the past, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
• The subject has had 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
• These 2 respiratory tract cultures were separated by at least 3 months, and 1 of them was obtained within the past 6 months.
9. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1 for Parts 1 and 4, Day 28 for Part 2).
10. A standard digital ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the subject will be excluded if the average of the 3 QTc values is >450 msec.
11. History of solid organ or hematological transplantation.
12. History or evidence of cataract or lens opacity determined to be clinically significant by the ophthalmologist or optometrist based on the ophthalmologic examination during the Screening Period. If there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the date of informed consent (or assent, when applicable), then the ophthalmologic examination does not need to be repeated during the Screening Period. This criterion does not apply to subjects with documentation of bilateral lens removal, and the ophthalmologic examination is not required for these subjects at screening.
13. History of alcohol or drug abuse in the past year, including but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
14. Ongoing or prior participation in an investigational drug study with the exception of the following:
• Ongoing or prior participation in an investigational study of TEZ/IVA, IVA, LUM/IVA, or other CFTR modulator. For Parts 1 and 4, a washout period of 28 days must elapse before Day 1. Subjects participating in Study 661-110 may have the Part 1 or Part 4 Screening Period extended by 4 weeks (Section 8.1.1.3). For Part 2, a washout period before Day -28 is not required, and subjects participating in Study 661-110 will transition directly from their prior treatment to the TEZ/IVA Run in Period providing that they meet eligibility criteria. For all parts, subjects participating in Study 661-110 may have their screening assessments performed while continuing to participate in Study 661 110.
• For prospective subjects with ongoing or prior participation in all other interventional studies, a washout period of 28 days or 5 terminal half lives, whichever is longer, must elapse before screening. The duration of the elapsed time may be longer if required by local regulations.
• Ongoing participation in a noninterventional study (including observational studies and studies requiring assessments without administration of study drug or assignment to other interventions) is permitted.
15. Use of commercially available CFTR modulator (e.g., Kalydeco, Orkambi) within 14 days before screening (Parts 1 and 4 only).
16. Use of restricted medications as defined in Table 9 1, within the specified window before the first dose of study drug (Day 1 in Parts 1 and 4, Day -28 in Part 2).
17. Pregnant or nursing females: Females of childbearing potential must have a negative pregnancy test at screening and Day 1.
18. The subject or a close relative of the subject is the investigator or a subinvestigator,

research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study. An adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that
• the adult lives independently of and does not reside with the study staff member, and
• the adult participates in the study at a site other than the site at which the family member is employed.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	25-09-2017
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	IVA (Ivacaftor, VX-770)
Generic name:	IVA (Ivacaftor, VX-770)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo
Product type:	Medicine

Brand name:	TEZ (tezacaftor, VX-661)
Generic name:	TEZ (tezacaftor, VX-661)
Product type:	Medicine
Brand name:	TEZ (tezacaftor, VX-661) and IVA (Ivacaftor, VX-770)
Generic name:	TEZ (tezacaftor, VX-661) and IVA (Ivacaftor, VX-770)
Product type:	Medicine
Brand name:	VX-440
Generic name:	VX-440

Ethics review

Approved WMO Date:	02-11-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2017
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	EUCTR2016-000454-36-NL
CCMO	NL58613.056.16