A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

Published: 18-07-2018
Last updated: 11-04-2024

Primary Objective:To evaluate the efficacy of VX-445 in triple combination (TC) with tezacaftor (TEZ) andivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for F508del and aminimal function mutation (F/MF subjects)Secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital respiratory tract disorders
Study type	Interventional

Summary

ID

NL-OMON45841

Source
ToetsingOnline

Brief title
Phase 3 Study of VX-445 CT in Heterozygous Subjects With CF (F/MF)

Condition

- Congenital respiratory tract disorders

Synonym
cystic fibrose

Research involving
Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Vertex is sponsor van dit onderzoek

Intervention

Keyword: Cystic Fibrosis, Efficacy and Safety, Phase 3 Study, VX-445 Combination Therapy

Outcome measures

Primary outcome

Primary Endpoint

Absolute change in percent predicted forced expiratory volume in 1 second

(ppFEV1) from

baseline through Week 24.

Secondary outcome

Key Secondary Endpoints

* Absolute change in ppFEV1 from baseline to Week 4

* Number of pulmonary exacerbations (PEx) through Week 24

* Absolute change in sweat chloride (SwCl) from baseline through Week 24

* Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score

from

baseline through Week 24

* Absolute change in body mass index (BMI) from baseline at Week 24

* Absolute change in SwCl from baseline at Week 4

* Absolute change in CFQ-R respiratory domain score from baseline at Week 4

Other Secondary Endpoints

* Time-to-first PEx through Week 24

* Absolute change in BMI z-score from baseline at Week 24

* Absolute change in body weight from baseline at Week 24

* Safety and tolerability assessments based on adverse events (AEs), clinical

laboratory

values, ECGs, vital signs, and pulse oximetry

* PK parameters of VX-445, TEZ, M1-TEZ, and IVA

Study description

Background summary

Cystic fibrosis (CF) is an autosomal recessive chronic disease with serious morbidities and frequent premature mortality. At present, there is no cure. CF affects approximately 70,000 individuals worldwide (approximately 30,000 in the US and 39,000 in the EU). Based on its prevalence, CF qualifies as an orphan disease.
CF is caused by decreased quantity and/or function of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein due to mutations in the CFTR gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in sweat glands and multiple organs, including the lungs, pancreas, and other gastrointestinal organs. Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years. Progressive loss of lung function is the leading cause of mortality. More effective treatments are needed for CF.
The most common disease-causing CFTR mutation, F508del, accounts for 70% of the identified alleles in people with CF, and approximately 40% of people with CF are homozygous for F508del (F/F).
Based on the understanding of the molecular defects caused by CFTR mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. Correctors facilitate the cellular processing and trafficking to increase the quantity of functional CFTR at the cell surface. Potentiators increase the channel open probability of the CFTR protein delivered to the cell surface to enhance ion transport. Depending on the amount of residual CFTR channel activity in the membrane, and the pathophysiology of that activity (reflecting the CFTR genotype of the patient and possibly other factors), both approaches

may be required.
The therapeutic activity of CFTR correctors and potentiators has been established with products that were developed by Vertex and approved for the treatment of CF: ivacaftor (IVA) monotherapy (Kalydeco®), and lumacaftor (LUM) in combination with IVA (Orkambi®). Kalydeco and Orkambi are approved to treat CF in patients with specific CFTR genotypes. A second corrector/potentiator combination, tezacaftor (TEZ)/IVA (Symdeko®) is now approved in the US. An MAA has been submitted and is under review.
VX-445 is a next-generation CFTR corrector being developed for administration in triple combination (TC) with TEZ/IVA for the treatment of CF.

The purpose of this study is to evaluate the efficacy and safety of VX-445 in TC with TEZ/IVA in subjects with CF who are heterozygous for F508del (F) and a second CFTR allele carrying a minimal function (MF) mutation that is non-responsive to TEZ, IVA, or TEZ/IVA. Patients with this genotype (F/MF) usually have severe disease and lack approved CFTR modulator therapy; previous studies with TEZ/IVA and lumacaftor (LUM)/IVA failed to demonstrate efficacy in this patient population. Due to this high unmet need, VX-445 is being developed in TC with TEZ/IVA for F/MF subjects. The potential for benefit in these patients is supported by in vitro data and clinical data in F/MF subjects; in addition, the TC of VX 445/TEZ/IVA is generally safe and well tolerated (please refer to VX-445 Investigators Brochure, v3.0 dated 20 April 2018).

Study objective

Primary Objective:
To evaluate the efficacy of VX-445 in triple combination (TC) with tezacaftor (TEZ) and
ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for F508del and a
minimal function mutation (F/MF subjects)
Secondary Objectives:
* To evaluate the safety of VX-445 in TC with TEZ and IVA
* To evaluate the pharmacodynamics (PD) of VX-445 in TC with TEZ and IVA
* To evaluate the pharmacokinetics (PK) of VX-445, TEZ, and IVA when administered in
TC

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter
study.
Approximately 360 subjects will be randomized (1:1) to the TC arm or triple placebo arm. Randomization will be stratified by
ppFEV1 determined during the Screening Period (<70 versus *70), age at the

Screening Visit (<18 versus *18 years of age), and sex (male versus female).

The total study duration is approximately 32 weeks (4 weeks for the Screening Period, 24 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).
Screening assessments may be repeated once to establish study eligibility.
The Treatment Period will be randomized, double-blind, and placebo-controlled.
It will last approximately 24 weeks (Day 1 through Week 24).
Subjects who prematurely discontinue study drug treatment will remain in the study from the time of discontinuation of study drug treatment through the last scheduled study visit and complete the assessments for all study visits.
The Safety Follow-up Visit will occur approximately 28 days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing.

Intervention

Study drug refers to VX-445/TEZ/IVA, IVA, and their matching placebos.
Active study drugs will be orally administered as 2 fixed-dose combination (FDC) film-coated
tablets (VX-445/TEZ/IVA) in the morning and as 1 film-coated IVA tablet in the evening.
Active substance: VX-445, TEZ (tezacaftor; VX-661), and IVA (ivacaftor; VX-770)
Activity: CFTR corrector, CFTR corrector, and CFTR potentiator (increased Cl* secretion)
Strength: 100-mg VX-445/50-mg TEZ/75-mg IVA FDC tablet
Active substance: IVA (ivacaftor; VX-770)
Activity: CFTR potentiator (increased Cl* secretion)
Strength: 150-mg tablet

Study burden and risks

Risks Associated with VX-445:
All drugs have the potential to cause side effects; the extent to which this occurs differs. VX-445/TEZ/IVA triple combination has been administered to subjects with cystic fibrosis. The most common complaints were cough and increase in sputum; some subjects had a rash. In a study in healthy women, the rate of rash was higher (approximately 4 out of 15) in those taking birth control pills together with VX-445/TEZ/IVA. The rashes were not serious and resolved after treatment was completed or stopped.

VX-445 has been studied in animals. VX-445 was generally well tolerated when given to dogs and rats for 28 days. Side effects in some animals included decreased body weight, decreased blood pressure, damage to the lining of the stomach, decreased numbers of young red blood cells which may cause anemia, damage to the testes and sperm, damage to the ovaries and ovarian follicles.

Each of these side effects were only seen at drug levels much higher (2 times or higher) than expected in current study.

The side effects associated with IVA alone or TEZ/IVA in combination are listed below:
To date, more than 2000 participants have received at least 1 dose of IVA alone or TEZ/IVA in combination.

Very common side effects occurring in *10% include:
* Headache;
* Throat pain,
* Upper respiratory tract infection,
* Nasal congestion,
* Abdominal pain,
* Common cold,
* Diarrhea,
* Rash

Common side effects occurring in *1 to <10% include:
* Dizziness,
* Nausea,
* Bacteria in sputum,
* Sinus congestion,
* Runny nose,
* Throat redness,

High liver enzymes (called as ALT or AST) in the blood have been observed in some participants treated with IVA or TEZ/IVA combination. The very high levels of these tests could lead to stopping of Study Drug, and these abnormal blood tests may get better after Study Drug is stopped. In some severe cases, high liver enzymes may be shown as a sign of liver injury, and can become permanent and even be life-threatening. While a link between IVA or TEZ/IVA combination and liver enzyme increase has not been established, you will have your blood drawn to check for your liver function during the study.
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 study doctor if you have any of these symptoms or anything else unusual.

Abnormality of the eye lens (cataract) has been noted in some children and adolescents treated with IVA or TEZ/IVA combination. A link between IVA or TEZ/IVA combination and cataracts is uncertain, but cannot be excluded. If you are a child or an adolescent, your study doctor may perform eye examinations prior to and during treatment with Study Drug..
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 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..

Unknown Risks:
There may be side effects that are not yet known.

Study Procedure Risks:
Blood sample collection: risk of having a bruise (a blue mark) or pain where we take the blood samples. Some people get dizzy or faint from a blood draw. Risk of infection (rare), or having bleeding, redness, or bruising at the skin puncture.
ECG: The sticky pads used for this test may cause skin irritation. Taking the sticky pads off causes discomfort similar to when taking off a band-aid.
Spirometry: You may feel the need to cough or you may feel short of breath during or after the test.
Sweat chloride test: The sweat test may cause tingling on the skin where the sticky pads are placed. In some cases, blister-like bumps may form, which will go away within 2-3 hours. There is a chance of minor skin burn. This happens in less than 1 in 50,000 people. When this happens, it is usually minor and gets better within one to two weeks with little or no scarring.

Contacts

Public
Vertex Pharmaceuticals

Van Swietenlaan 6
Utrecht 9728NZ
NL
Scientific
Vertex Pharmaceuticals

Van Swietenlaan 6
Utrecht 9728NZ
NL

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 his or her 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. Age 12 years or older, on the date of informed consent.
4. Confirmed diagnosis of CF as determined by the investigator.
5. Heterozygous for F508del and an MF mutation (F/MF genotypes, see Appendix A for eligible MF mutations). If the screening CFTR genotype result is not received before randomization, a previous CFTR genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
6. Forced expiratory volume in 1 second (FEV1) value *40% and *90% of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI]) at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria for acceptability and repeatability.
7. Stable CF disease as judged by the investigator.
8. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

Exclusion criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This
includes, but is not limited to, the following:

* Clinically significant cirrhosis with or without portal hypertension
* Solid organ or hematological transplantation.
* Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
* Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)
2. Any of the following abnormal laboratory values at screening:
* Hemoglobin <10 g/dL
* Total bilirubin *2 × ULN
* Aspartate transaminase (AST), alanine transaminase (ALT), gammaglutamyl transferase (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) for subjects *18 years of age and *45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation) for subjects aged 12 to 17 years (inclusive)
3. An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug (Day 1).
4. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus). For
subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
* The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
* The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.
5. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
6. Ongoing or prior participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if
required by local regulations.
7. Use of prohibited medications as defined in Table 9-2, within the specified window before the first dose of study drug (Day 1).
8. Pregnant or nursing females. Females of childbearing potential must have a negative pregnancy test at screening (serum test) and Day 1 (urine test).
9. 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 at that site.
However, 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:	3
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):	03-10-2018
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kalydeco
Generic name:	ivacaftor
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	not applicable
Generic name:	placebo for ivacaftor
Product type:	Medicine
Brand name:	not applicable
Generic name:	placebo for VX-445/tezacaftor/ivacaftor
Product type:	Medicine
Brand name:	not applicable
Generic name:	VX-445/tezacaftor/ivacaftor

Ethics review

Approved WMO Date:	18-07-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-09-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2018-000183-28-NL
CCMO	NL66259.041.18