A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis

Published: 09-05-2019
Last updated: 10-04-2024

Primary Objective* To evaluate the efficacy of VX-561Secondary Objectives* To evaluate the pharmacodynamic (PD) effect of VX-561* To evaluate the pharmacokinetics (PK) of VX-561, IVA, and relevant metabolites* To evaluate the safety and tolerability…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON47983

Source
ToetsingOnline

Brief title
A Study to Evaluate Efficacy and Safety of VX-561

Condition

- Other condition

Synonym
Cystic fibrosis

Health condition

Cystic fibrosis

Research involving

Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Vertex Pharmaceutical is sponsor for this study

Intervention

Keyword: Cystic Fibrosis, Phase 2, VX-561

Outcome measures

Primary outcome

Primary Endpoint

* Absolute change in percent predicted forced expiratory volume in 1 second

(ppFEV1) from baseline at Week 12

Secondary outcome

Secondary Endpoints

* Absolute change in sweat chloride concentrations from baseline at Week 12

* PK parameters of VX-561, IVA, and relevant metabolites

* Safety and tolerability, based on the assessment of adverse events (AEs),

laboratory test results, standard 12-lead ECGs, vital signs, and pulse oximetry

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 more than 70,000 individuals worldwide.1 Based on its prevalence, CF qualifies as an orphan disease.

CF is caused by reduced quantity and/or function of the 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 (GI) 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.

Based on the understanding of the molecular defects caused by these 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 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 CFTR genotype of the patient, both approaches may be required to ameliorate lung disease in patients with CF.

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®), lumacaftor (LUM) in combination with IVA (Orkambi®), and tezacaftor (TEZ) in combination with IVA (Symdeko*, Symkevi®).

IVA increases the open-channel probability of the mutated CFTR protein that has been delivered to the cell surface, thereby enhancing total chloride transport. For the most common CF-causing mutation, F508del, the combined effect of either LUM and IVA or TEZ and IVA is increased quantity and function of F508del-CFTR at the cell surface.

Phase 1 clinical studies in healthy subjects have shown that VX-561 had a reduced rate of clearance, increased exposure, greater plasma levels at 24 hours, and a longer half-life compared to IVA, thereby supporting once daily dosing (refer to VX-561 Investigator*s Brochure). In healthy subject studies to date, the safety profile of VX-561 is considered similar to IVA.

This study is being conducted to evaluate the efficacy and PD effect (i.e., change in sweat chloride) for a range of VX-561 doses to support VX-561 dose selection for future studies, including studies of VX-561 in triple combination (TC) with CFTR correctors, such as VX-121 and TEZ. Subjects will be on stable IVA treatment at baseline and will be randomized to study drug treatment groups on Day 1 (VX-561 or IVA). Change in ppFEV1 from IVA baseline is the primary endpoint. However, dose selection of VX-561 for future studies may consider the totality of data, including dose-response and exposure-response analyses for efficacy (ppFEV1) and PD (sweat chloride) endpoints.

Study objective

Primary Objective
* To evaluate the efficacy of VX-561
Secondary Objectives
* To evaluate the pharmacodynamic (PD) effect of VX-561
* To evaluate the pharmacokinetics (PK) of VX-561, IVA, and relevant metabolites
* To evaluate the safety and tolerability of VX-561

Study design

This is a Phase 2 study of VX-561 monotherapy. The study is randomized, double-blind, parallel-group, and active-controlled. The study will evaluate 4 dose levels of VX-561 in subjects with CF who have a gating mutation and were previously taking a stable dose of IVA. Randomization will be stratified by ppFEV1 value at screening (<70 versus .70).

The original protocol included 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms; both treatment arms were discontinued in the current protocol. Approximately 88 subjects were planned to enroll in 5 treatment arms (25 mg qd VX-561, 50 mg qd VX-561, 150 mg qd VX-561, 250 mg qd VX-561, and IVA 150 mg q12h) in a ratio of 1:2:2:2:1 under the original protocol. The 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms were discontinued; 44 subjects had been enrolled and randomized to the 5 treatment arms at this point. The remaining subjects planned to enroll will be randomized 2:2:1 to 3 treatment arms (250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg
q12h).

Subjects will continue their stable IVA treatment through screening, and then be randomized to study drug treatment groups on Day 1 (VX-561 or IVA). The efficacy and PD of VX-561 will be assessed after 12 weeks of randomized treatment. IVA (150 mg every 12 hours [q12h]) is included as a reference arm, but with unequal randomization to provide greater information on VX-561 dose-ranging. After the Treatment Period, a 3- to 5-day Washout Period where subjects will take no CFTR modulators is included to collect additional PK and PD data and enable a more thorough evaluation of VX-561 exposure-response relationships. Following completion of the Washout Period, subjects will resume their prior therapy with commercial IVA.

Intervention

Active substance: VX-561
Activity: CFTR potentiator (increased Cl- secretion)
Strength and route of administration: 50-mg and 25-mg VX-561 tablets for oral administration

Active substance: IVA (VX-770)
Activity: CFTR potentiator (increased Cl- secretion)
Strength and route of administration: 150-mg film-coated tablet for oral administration

Study burden and risks

All drugs have the potential to cause side effects the extent to which this occurs differs. Subjects will be monitored for possible side effects during the study. Possible risks and discomforts are described here, however, there may be other risks and side effects that are not yet known.There may or may not be a direct benefit for subjects as a result of taking part in the study. However, what is learned in this study may help in the treatment of CF or other diseases in the future, and may advance scientific knowledge.

Risks Associated with VX-561:
Side effects from IVA are listed below. VX-561 is a deuterated isotope of IVA, which means that it is structurally similar to IVA. Thus, the side effects with VX-561 are expected to be similar to those with IVA.

Possible Risks of ivacaftor:
To date, more than 1000 participants have received at least 1 dose of IVA treatment in clinical studies.
The side effects associated with IVA are listed below:

Very common side effects occurring in *10% include:
* Headache (24%)
* Throat pain (22%)
* Upper respiratory tract infection (22%)
* Nasal congestion (20%)
* Abdominal pain (16%)
* Common cold (15%)
* Diarrhoea (13%)
* Rash (13%)

Common side effects occurring in less than 10% include:

* Dizziness (9%)
* Bacteria in sputum (7%) (which may indicate an infection in your respiratory tract)
* Sinus congestion (7%)
* Runny nose (7%)
* Throat redness (5%)

High liver enzymes in the blood have been observed in some participants treated with IVA . 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 study drug and liver enzyme increase has not been established, blood will be drawn to check 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.

Abnormality of the eye lens (cataract) has been noted in some children and adolescents treated with IVA. A link between IVA and cataracts is uncertain, but 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 become life threatening if they are not treated. The combination of the study drug and any other medications, dietary supplements, natural medicines, and vitamins could be harmful. There are certain herbal medications such as St. John*s Wort, and certain fruits and fruit juices (such as grapefruit juice or products made from it) that subjects must not take during study.

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

Additional Study Risks
This study looks at a range of doses of VX-561. In this study, it is possible that the study drug does not work as well as ivacaftor, which may cause sweat chloride to be higher, lung function to be worse, and/or subjects to feel worse.

Study Procedure Risks:
Blood sample collection: Bruise or pain where blood samples are taken. Some people get dizzy or faint from a blood draw. In rare cases infection or bleeding from 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 plaster.

Spirometry: Subjects may feel the need to cough or 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

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Vertex Pharmaceuticals

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Scientific
Vertex Pharmaceuticals

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject will sign and date an informed consent form (ICF)., 2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures., 3. Subjects (males and females) aged 18 years or older on the date of informed consent., 4. Receiving IVA treatment with no interruptions for at least 28 days before screening., 5. Tolerating IVA therapy as judged by the investigator., 6. Female subjects must have a negative pregnancy test at Screening., 7. Body weight *35 kg., 8. Subjects must be able to produce a valid

(quantity-sufficient) sweat sample at screening. If the initial screening collection results in insufficient sweat volume, then the sweat chloride collection may be repeated., 9. Confirmed diagnosis of CF as determined by the investigator., 10. Has 1 of the following mutations in their CF gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. 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 enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study., 11. Subjects must have a forced expiratory volume in 1 second (FEV1) *40% and *100% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])8 at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria9 for acceptability and repeatability., 12. Stable CF disease as judged by the investigator., 13. Willing to remain on a stable CF treatment regimen (other than protocol-specified changes in CFTR modulator regimen) through 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 clinically significant cirrhosis with or without portal hypertension., 3. Any of the following abnormal laboratory values at screening:, * Hemoglobin <10 g/dL, * Total bilirubin *2 × upper limit of normal (ULN), * Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl 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)10,11 for subjects *18 years of age, 4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug., 5. 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, 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 1 within the 6 months before the date of informed consent., 6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug., 7. Standard 12-lead ECG demonstrating QTcF >450 msec at screening. If QTcF

exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject*s eligibility., 8. History of solid organ or hematological transplantation., 9. History of alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator., 10. Ongoing or prior participation in a study of an investigational treatment with the exception of the following:, * Ongoing or prior participation in an investigational study of a Vertex CFTR modulator. A washout period of 28 days must elapse before Day 1., * 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., 11. Use of prohibited medications as defined in the protocol, within the specified window before the first dose of study drug., 12. Pregnant or nursing female subjects., 13. Subject, or 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 enrolled 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:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Will not start

Enrollment:	2
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	09-05-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-09-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	07-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-003970-28-NL
CCMO	NL69639.091.19
Other	tbd