A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-F508del ELX/TEZ/IVA-responsive CFTR Mutation

Published: 23-02-2022
Last updated: 17-01-2025

To evaluate the efficacy and pharmacodynamics (PD) of ELX/TEZ/IVA

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

Summary

ID

NL-OMON51518

Source
ToetsingOnline

Brief title
Evaluation of ELX/TEZ/IVA in Subjects Without F508del Mutation

Condition

- Respiratory disorders congenital

Synonym
Cystic Fibrosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Efficacy, Phase 3, Safety

Outcome measures

Primary outcome

Absolute change from baseline in percent predicted forced expiratory volume in

1 second (ppFEV1) through Week 24

Secondary outcome

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

• Absolute change from baseline in Cystic Fibrosis Questionnaire - Revised

(CFQ-R) respiratory domain (RD) score through Week 24

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

• Absolute change from baseline in weight at Week 24

• Number of pulmonary exacerbations (PEx) through Week 24

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

laboratory values, ECGs, vital signs, and pulse oximetry

Study description

Background summary

Cystic fibrosis (CF) is a rare autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality for which there is currently no cure. CF affects more than 80,000 individuals worldwide, including more than 49,000 individuals in the EU.
CF is caused by decreased quantity and/or function of the CFTR protein due to

mutations in the CFTR gene. CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands. Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF. Progressive loss of lung function is the leading cause of mortality.
The most common disease-causing mutation is F508del: approximately 85% of individuals in the US and 80% of individuals in Europe2 have at least one F508del mutation. In the EU, patients with one F508del mutation are eligible for treatment with the CFTR modulator ELX/TEZ/IVA (Kaftrio*/Trikafta*). The ELX/TEZ/IVA regimen is the first medicine to demonstrate clinical benefit in patients with a single F508del mutation, regardless of the mutation on the second allele. The Phase 3 program in CF subjects 6 years of age and older demonstrated that treatment with ELX/TEZ/IVA results in substantial improvements in lung function, CFTR function, and nutritional status in this population, and was generally safe and well tolerated with a low rate of treatment discontinuation.
The ELX/TEZ/IVA pivotal Phase 3 program demonstrated efficacy in subjects who have at least one F508del mutation. However, more than 160 additional CFTR mutations have been shown to be responsive to ELX/TEZ/IVA in vitro. CF patients with these mutations do not currently have an indicated CFTR modulator treatment in the EU, nonetheless they are expected to derive clinical benefit from ELX/TEZ/IVA based on (1) current understanding of the biology of the CFTR mutations (2) the known mechanism by which CFTR modulators act on defective CFTR proteins that contain these mutations (3) in vitro evidence indicating responsiveness of these proteins to ELX/TEZ/IVA and (4) the established relationship between in vitro responsiveness and clinical benefit.

Study objective

To evaluate the efficacy and pharmacodynamics (PD) of ELX/TEZ/IVA

Study design

This is a Phase 3, randomized, placebo-controlled, double-blind, parallel group study. Subjects 6 years of age and older with an eligible non-F508del ELX/TEZ/IVA-responsive CFTR mutation and no exclusionary mutations may be eligible for enrollment. Eligible ELX/TEZ/IVA-responsive mutations include minimal function (MF)-like and residual function (RF)-like mutations. MF-like mutations are either (1) predicted to result in no functional CFTR protein or (2) are not responsive to IVA or TEZ/IVA. RF-like mutations result in residual CFTR function. Exclusionary mutations are already indicated for CFTR modulator treatment.
Subjects will be randomized 2:1 (ELX/TEZ/IVA group: placebo group). Randomization will be stratified based on ppFEV1 determined during the Screening Period (<70 versus >=70), age at the Screening Visit (<18 years old

versus >=18 years old) and CFTR mutation group (RF-like mutation versus no RF-like mutation).

Intervention

Active substance: ELX (VX-445)/TEZ (VX-661)/IVA (VX-770)
Activity: ELX and TEZ are CFTR correctors; IVA is a CFTR potentiator
Strength and route of administration: ELX/TEZ/IVA fixed-dose combination (FDC) tablets for oral administration at the following strengths:
• ELX 100 mg/TEZ 50 mg/IVA 75 mg
• ELX 50 mg/TEZ 25 mg/IVA 37.5 mg

Active substance: IVA (VX-770)
Activity: CFTR potentiator
Strength and route of administration: IVA tablets for oral administration at the following strengths:
• IVA 150 mg
• IVA 75 mg

Study burden and risks

Risks associated with Elexacaftor (ELX)/Tezacaftor (TEZ)/Ivacaftor (IVA) triple combination therapy (referred to as ELX/TEZ/IVA):

To date, ELX/TEZ/IVA has been administered to more than 600 clinical trial participants with cystic fibrosis age 6 years and greater. In addition, ELX has been administered alone or in combination with TEZ/IVA to approximately 200 healthy volunteers.

The side effects associated with ELX/TEZ/IVA are listed or described in the text below. For the listed side effects, the percentages of people with cystic fibrosis in a large study who experienced these side effects are shown.

• Headache (17%)
• Diarrhea (13%)
• Upper respiratory tract infection (common cold) (12%)
• Increased liver enzymes in blood (may be a sign of a liver problem) (11%)
• Rash (11%)
• Stomach ache (10%)
• Nasal congestion (9%)
• Increased blood enzyme called creatine phosphokinase (may be a sign of a muscle problem) (9%)
• Runny nose (8%)

Safety Monitoring in This Study:
In some study participants treated with ELX/TEZ/IVA triple combination therapy,

high liver enzymes in the blood have been observed. Elevated liver enzymes may be a sign of liver injury. These abnormal liver enzymes may get better after Study Drug is stopped.

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.

In severe cases, significant liver injury can potentially become permanent and even be life-threatening. In patients with advanced liver disease (for example, cirrhosis and/or portal hypertension), there is a greater risk for worsening of liver function. The worsening of liver function can lead to a need for liver transplant.

In some children or adolescents treated with IVA-containing regimens, abnormality of the eye lens (cataract) has been noted. A link between these medicines and cataracts is uncertain but cannot be excluded.
In some study participants treated with ELX/TEZ/IVA triple combination therapy, increases in blood pressure have been observed.

In some study participants treated with ELX/TEZ/IVA triple combination therapy, rash has been observed. In study participants treated with ELX/TEZ/IVA, rash was more commonly seen in women, especially those taking hormones to prevent pregnancy. In some cases, the rashes were severe, required treatment, or led to stopping of ELX/TEZ/IVA. The rashes got better after Study Drug was stopped.

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 to the participant. There are certain herbal medications such as St. John*s Wort, and certain fruits and fruit juices (such as grapefruit, or products made from them) that the participant must not take during the study.

Contacts

Public
Vertex Pharmaceuticals

Van Swietenlaan 6
Groningen 9728 NZ
NL
Scientific
Vertex Pharmaceuticals

Van Swietenlaan 6
Groningen 9728 NZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

1. Subject (or the 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 (as applicable), and other study procedures.
. For subjects < 18 years of age: as judged by the investigator, parent or legal guardian must be able to understand protocol requirements, restrictions, and instructions and the parent or legal guardian should be able to ensure that the subject will comply with and is likely to complete the study as planned.
3. Subjects (male or female) 6 years of age and older on the date of informed consent.
4. Subjects has an eligible ELX/TEZ/IVA-responsive CFTR mutation listed in Table 15-1 and none of the exclusionary mutations in Table 15-2.
5. Subject has stable CF disease, as deemed by the investigator, before randomization.

a. Forced expiratory volume in 1 second (FEV1) value >=40% and <=100% 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).
6. Subject is able to swallow tablets.

Exclusion criteria

1. History of any illness or any clinical condition that might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This may include, but is not limited to:
• History of allergy, intolerance, or hypersensitivity to any component of the investigational drug product (ELX/TEZ/IVA tablets and IVA tablets) or placebo, including excipients
• Clinically significant liver 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 clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).

3. Any of the following abnormal laboratory values at screening:
. Hemoglobin <10 g/dL
. Total bilirubin >=2 × upper limit of normal (ULN)
. AST, ALT, gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) >= 3 x 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 < 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 Day 1 (first dose of study drug).

5. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, Burkholderia cenocepacia, Burkholderia dolosa, and Mycobaterium 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, and
. 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.

6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).

7. Ongoing or prior participation in an investigational drug study within 28 days of the Screening Visit.
. A washout period of 5 terminal half-lives of the previous investigational study drug, or 28 days, whichever is longer, must elapse before the Screening Visit.
. The duration of the elapsed time may be longer if required by local regulations.

8. Pregnant and breast-feeding females. Female subjects of childbearing potential (Section 11.5.6.1) must have a negative pregnancy test at the Screening Visit and the Day 1 Visit.

9. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-3.

10. 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:	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:	Completed
Start date (anticipated):	09-05-2022
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Elexacaftor/Tezacaftor/Ivacaftor
Generic name:	Elexacaftor/Tezacaftor/Ivacaftor
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ivacaftor
Generic name:	Ivacaftor
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-02-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-05-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-03-2023
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2021-005320-38-NL
CCMO	NL79770.041.22

Study results

Date completed: 23-05-2023

Results posted: 25-03-2024

First publication
06-10-2023