A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism

Published: 09-11-2020
Last updated: 17-01-2025

To evaluate the effect of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) on glucose tolerance in CF subjects with impaired glucose tolerance (IGT) or CF related diabetes (CFRD)

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

Summary

ID

NL-OMON52358

Source
ToetsingOnline

Brief title
Study Evaluating ELX/TEZ/IVA on glucose tolerance in Subjects With CF

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 Inc. is sponsor for this study

Intervention

Keyword: Cystic Fibrosis, Phase 3b

Outcome measures

Primary outcome

Change from baseline in 2-hour blood glucose levels following an oral glucose

tolerance test (OGTT) to the average of Week 36 and Week 48

Secondary outcome

• Proportion of subjects with improvement in dysglycemia categorization (CFRD,

IGT, normal glucose tolerance [NGT]) at Week 48

• Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs),

clinical laboratory values, 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. CF affects more than 70,000 individuals worldwide1 (approximately 31,000 in the US2 and 48,000 in the EU). Based on its prevalence, CF qualifies as an orphan disease. CF is caused by decreased quantity and/or function of the 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. In the

lungs, obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure. Progressive loss of lung function is the leading cause of mortality. The most common disease causing CFTR mutation is F508del. Approximately 85% have at least 1 F508del allele. 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 CFTR at the cell surface. Potentiators increase the channel open probability (channel gating activity) of the CFTR protein delivered to the cell surface to enhance ion transport. With differing mechanisms of action, a combination of correctors and potentiators increases F508del CFTR-mediated chloride transport more than either type of modulator alone.

Study objective

To evaluate the effect of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) on glucose tolerance in CF subjects with impaired glucose tolerance (IGT) or CF related diabetes (CFRD)

Study design

This is A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism:

The study consists of 3 periods:
- Screening Period
- Treatment Period
- Follow-up Period

Screening Period: The screening period can last up to 5 weeks
Treatment Period: The treatment period can last up to 48 weeks.
Follow-up Period: The follow-up period can last up to 4 weeks. The visit will take place around 28 (±7) days after the last dose of study drug.

Intervention

Active substance: ELX (VX-445)/TEZ (VX-661)/IVA (VX-770)
Activity: CFTR correctors (ELX and TEZ) and potentiator (IVA)

Strength and route of administration: ELX 100-mg/TEZ 50-mg/IVA 75-mg fixed dose combination (FDC) tablets, oral

Active substance: IVA (VX 770)
Activity: CFTR potentiator
Strength and route of administration: 150-mg tablets, oral

Study burden and risks

To date, ELX/TEZ/IVA has been administered to more than 600 clinical trial participants with CF 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 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.

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.

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)

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. Subjects (male and female) 12 years of age or older on the date of informed consent.
4. Subjects heterozygous for F508del and an MF mutation.
a. Genotype should be confirmed at the Screening Visit.
b. If the screening CFTR genotype result is not received before the first dose of study drug, a previous CFTR genotype laboratory report may be used to establish eligibility.
c. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study.
5. Forced expiratory volume in 1 second (FEV1) value >=30% 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) and stable CF disease as judged by the investigator.
6. Willing to remain on a stable CF treatment regimen (other than CFTR modulators) through completion of study participation.
7. Abnormal glucose tolerance as determined by an OGTT, classified as either IGT (defined as 2-hour post-OGTT blood glucose level >= 140 to <200 mg/dL [>=7.77 to <11.10 mmol/L]) or CFRD (defined as either fasting hyperglycemia [blood glucose level >=126 mg/dL (>=7.00 mmol/L) after an 8-hour fast] or 2-hour post-OGTT blood glucose level >=200 mg/dL [>=11.10 mmol/L]).

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 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. Type 1 or Type 2 diabetes
3. Duration of CFRD >=5 years.
4. 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).
5. 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) 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
6. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
7. 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.
8. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
9. Ongoing or prior participation in an investigational drug study (including studies investigating ELX with or without coadministration of other study drugs) 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.
10. Use of restricted medication (including antidiabetic medication other than insulin, which must be at a dose no greater than 0.3 units/kg/day) within specified duration before the first dose of study drug.
11. BMI >=30 kg/m2 at the Screening Visit.
12. Pregnant and breast-feeding females. All female subjects regardless of childbearing potential status must have a negative pregnancy test at the

Screening Visit and the Day 1 Visit.
13. 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 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
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-03-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-11-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-12-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-07-2022
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	EUCTR2020-003170-44-NL
CCMO	NL75107.041.20

Study results

Date completed:	30-06-2022
Results posted:	27-01-2023

First publication
20-12-2022