A Phase 3b, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

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Primary Objective:To evaluate the efficacy of ELX/TEZ/IVA in subjects 6 through 11 years of age with CF, heterozygous for F508del and a MF mutation (F/MF)Secondary Objectives:• To evaluate the PD of ELX/TEZ/IVA• To evaluate the safety of ELX/TEZ/IVA...

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

Summary

ID

NL-OMON49334

Source
ToetsingOnline

Brief title
Study Evaluating ELX/TEZ/IVA in Subjects With CF and F/MF genotypes

Condition

- Respiratory disorders congenital
- Congenital respiratory tract disorders

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

Absolute change in lung clearance index2.5 (LCI2.5) from baseline through Week

24

Secondary outcome

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

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

laboratory values, standard 12 lead electrocardiograms (ECGs), vital signs,

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

Primary Objective:
To evaluate the efficacy of ELX/TEZ/IVA in subjects 6 through 11 years of age with CF, heterozygous for F508del and a MF mutation (F/MF)
Secondary Objectives:
• To evaluate the PD of ELX/TEZ/IVA
• To evaluate the safety of ELX/TEZ/IVA

Study design

This is a Phase 3b, Randomized, Placebo-Controlled Study of elexacaftor, tezacaftor and ivacaftor.

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

Screening Period:
The screening period may be up to 4 weeks.

Treatment Period:
The treatment period can last up to 24 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 corrector, CFTR corrector, and CFTR potentiator

Strength and route of administration:
• 50-mg ELX/25-mg TEZ/37.5-mg IVA fixed-dose combination (FDC) tablets for oral administration
• 100-mg ELX/50-mg TEZ/75-mg IVA FDC tablets for oral administration

Active substance: IVA (VX-770)
Activity: CFTR potentiator

Strength and route of administration:
• 75-mg IVA tablet for oral administration
• 150-mg IVA tablet for oral administration

Study Drug should be taken every 12 hours (± 2 hours). Participant will take 2 tablets in the morning and 1 tablet in the evening. The Study Drug should be taken within 30 minutes of the start of a meal or snack containing fat.

Study burden and risks

Risks associated with VX-445 (elexacaftor; ELX)/Tezacaftor (TEZ)/Ivacaftor (IVA) triple combination therapy (referred to as VX-445/TEZ/IVA):

To date, ELX/TEZ/IVA has been administered to more than 500 clinical trial participants with cystic fibrosis. In addition, LEX 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%)
• Diarrhoea (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%)

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. It is very important that participants tell their study doctor about every medicine, dietary supplement, natural remedy, and vitamin they are taking, or changes to what they are taking, while they are in the study. 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 participants must not take during study.

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

In some study participants treated with VX-445 (elexacaftor; ELX)/TEZ/IVA triple combination therapy, high liver enzymes (called ALT or AST) in the blood have been observed. These abnormal liver enzymes may get better after Study Drug is stopped. In some severe cases, high liver enzymes may be a sign of liver injury and can become permanent and even be life-threatening. The participant will have their blood drawn to check their 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.

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. The study doctor may perform eye examinations prior to and during treatment with Study Drug.

In some study participants treated with VX-445/TEZ/IVA triple combination therapy, increases in blood pressure have been observed. Blood pressure will be monitored during the study.

In some study participants treated with VX-445/TEZ/IVA triple combination therapy, rash has been observed. In study participants treated with VX-445/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 VX445-/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.

Risks from tests
• Spirometry: When the lungs are tested, participants may feel the need to cough, feel short of breath, or dizzy during or after the test.

• Blood sample collection: When participants have their blood taken with a needle, it may feel like a pinch. It will hurt for short time, and sometimes the place where the needle was put might feel sore or look bruised. Some children may experience dizziness, upset stomach, or fainting when their blood is drawn. There is a small risk of infection.

• ECG: It might hurt when the study doctor removes the sticky pads, like taking off a bandage.

• 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.

• Multiple Breath Washout: There are no known risks associated with this test. There are no known side effects to breathing pure oxygen. If participants feel uncomfortable during the test, they can remove the nose clip and mouthpiece. If this is the case, the test will be stopped, and no further testing will be performed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

• Heterozygous for the F508del mutation and a minimal function CFTR mutation (F/MF)
• Forced expiratory volume in 1 second (FEV1) value >=70% of predicted normal for age, sex, and height

Exclusion criteria

• Clinically significant cirrhosis with or without portal hypertension
• Lung infection with organisms associated with a more rapid decline in pulmonary status
• Solid organ or hematological transplantation

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:	Pending
Start date (anticipated):	03-08-2020
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ivacaftor
Generic name:	VX-770
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	n/a
Generic name:	VX-445 / TEZ / IVA

Ethics review

Approved WMO

Date:	01-05-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	28-07-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	25-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	31-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
Other	NCT04353817
EudraCT	EUCTR2019-003554-86-NL
CCMO	NL73340.078.20