A Phase 3 Open-label Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects With Non-F508del CFTR Genotypes

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This study has been transitioned to CTIS with ID 2024-515637-14-00 check the CTIS register for the current data. To evaluate the long-term safety and tolerability of elexacaftor(ELX)/tezacaftor (TEZ)/ivacaftor (IVA)

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

Summary

ID

NL-OMON51429

Source
ToetsingOnline

Brief title
Study to Evaluate ELX/TEZ/IVA Safety, Efficacy in Subjects

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: Cystic Fibrosis, Efficacy, Phase 3, Safety

Outcome measures

Primary outcome

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

values, ECGs, vital signs, and pulse oximetry

Secondary outcome

PART A ONLY:

• Absolute change from baseline in percent predicted forced expiratory

volume in 1 second (ppFEV1)

• Absolute change from baseline in sweat chloride (SwCl)

• Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised

(CFQ-R) respiratory domain (RD) score

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

• Absolute change from baseline in weight

• Number of pulmonary exacerbations (PEx)

Other endpoints

-Absolute change from baseline in BMI z-score (subjects <=20 years of

age)

-Absolute change from baseline in weight z-score (subjects <=20 years

of age)

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,1-4 including over 49,000 individuals in the EU.2
CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the
CFTR gene.5 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.6 Decreased CFTR quantity or function results in the failure to regulate chloride
transport in these tissues leading to the multisystem pathology associated with CF.7 Progressive
loss of lung function is the leading cause of mortality.8
The most common disease-causing mutation is F508del: approximately 85% of individuals in the
US1 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

This study has been transitioned to CTIS with ID 2024-515637-14-00 check the CTIS register for the current data.

To evaluate the long-term safety and tolerability of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA)

Study design

This is a Phase 3, multicenter, open-label study for subjects who complete the last
Treatment Period visit of a parent study and meet eligibility criteria.

Intervention

Investigational Drug 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 you. It is very important that you tell your study doctor about every medicine, dietary supplement, natural remedy, and vitamin (or change) while you 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 you must not take during the study.

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

Contacts

Public
Vertex Pharmaceuticals

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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. Did not withdraw consent from a parent study.
4. Part A Meets at least 1 of the following criteria:
• Completed study drug treatment in a parent study.
• Had study drug interruption(s) in a parent study, but completed study visits up to the last
scheduled visit of the Treatment Period of a parent study.
Part B: Meets at least one of the following criteria:
-Completed study frug treatment in Part A
-Had study drug interruption(s) in Part A, but completed study visits up
to the last scheduled visit of the Treatment Period of Part A
5. Willing to remain on a stable CF treatment regimen (other than CFTR modulators, through completion of study participation.

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.
2. History of drug intolerance in a parent study that would pose an additional risk to the subject.
(e.g., subjects with a history of allergy or hypersensitivity to the study drug).
3. Pregnant and nursing females. Females of childbearing potential must have a negative pregnancy test at the Day 1 Visit (in Part A and Part B) before receiving the first dose of study
drug.
4. Current participation in an investigational drug trial (other than a parent study). Participation
in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug) and screening for another
Vertex study is permitted.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-01-2023
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:	01-06-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-08-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-02-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	03-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-06-2024
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
EU-CTR	CTIS2024-515637-14-00
EudraCT	EUCTR2021-005914-33-NL
ClinicalTrials.gov	NCT05331183
CCMO	NL81015.041.22