A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No F508del Mutation

Published: 27-10-2021
Last updated: 05-04-2024

To evaluate the efficacy of VX-121/TEZ/D-IVA in CF subjects who are homozygous forF508del, heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, orhave at least 1 other TCR CFTR mutation and no F508del mutation

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

Summary

ID

NL-OMON51875

Source
ToetsingOnline

Brief title
A Phase 3 Study of VX-121 Combination Therapy 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 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

• Proportion of subjects with SwCl <60 mmol/L through Week 24

(pooled with data from VX20-121-102)

• Proportion of subjects with SwCl <30 mmol/L through Week 24

(pooled with data from VX20-121-102)

Study description

Background summary

Cystic fibrosis (CF) is an autosomal recessive genetic disease with serious morbidities and
frequent premature mortality. CF affects more than 80,000 individuals worldwide (approximately 31,000 in the US and 49,000 in the EU).1-4
CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the
CFTR gene.5 CFTR is a channel that regulates the flow of chloride and other anions across
epithelia in multiple organs and tissues, including the lungs, pancreas and other gastrointestinal
organs, and sweat glands.6 Despite progress in the treatment of CF with antibiotics and
mucolytics, the current median age at death among people with CF is approximately 30 years,
and the predicted median age of survival is approximately 47 years.1, 2 More effective treatments
are needed for CF.
The most common disease-causing mutation is F508del: approximately 85.3% of people with CF
in the US and 80.6% in Europe have at least one F508del allele.1, 2
At present CF does not have a cure. CFTR modulators (i.e., correctors and potentiators) represent
a major advancement in the treatment of CF because they are systemic therapies that target the
underlying cause of the disease and have been shown to improve CF survival by modifying the
course of disease.7, 8 The clinical testing and regulatory approval of CFTR modulators in certain
countries for the treatment of people with CF caused by specific CFTR genotypes have
established the therapeutic value of specific regimens developed by Vertex. These treatment
regimens include ivacaftor (IVA) monotherapy (Kalydeco*), lumacaftor (LUM)/IVA dual
combination therapy (Orkambi*), tezacaftor (TEZ)/IVA dual combination therapy (Symdeko*, Symkevi*), and elexacaftor (ELX)/TEZ/IVA triple combination (TC) therapy
(Trikafta*, Kaftrio*).
Deutivacaftor (D-IVA, VX-561) is a CFTR potentiator and is a deuterated isotope of IVA with a
specific pattern of 9 substituted deuteriums. In vitro data indicate similar potency of D-IVA in
human bronchial epithelial (HBE) cells relative to IVA. Nonclinical and clinical data
demonstrate a similar safety profile relative to IVA, and pharmacokinetic (PK) data support once
daily (qd) dosing (refer to VX-121/TEZ/D-IVA Investigator*s Brochure).

VX-121 is a CFTR corrector that improves the processing and trafficking of mutated CFTR in vitro, thereby increasing the quantity of functional protein at the cell surface. The effect of VX-121 was additive to the effect of TEZ. The CFTR protein delivered to the cell surface by VX-121 alone or in combination with TEZ (VX-121/TEZ) was potentiated by either IVA or D-IVA. In HBE cells derived from people homozygous for F508del (F/F-HBE) and people heterozygous for F508del and a minimal function (MF) CFTR mutation (F/MF-HBE cells) and studied in vitro, the TC of VX-121, TEZ, and IVA (VX-121/TEZ/IVA) increased CFTR chloride transport more than the dual combinations of VX-121/TEZ or VX-121/IVA under most conditions (refer to VX-121/TEZ/D-IVA Investigator*s Brochure).

Study objective

To evaluate the efficacy of VX-121/TEZ/D-IVA in CF subjects who are homozygous for F508del, heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, or have at least 1 other TCR CFTR mutation and no F508del mutation

Study design

This is a Phase 3, randomized, double-blind, ELX/TEZ/IVA-controlled, parallel-group, multicenter study.

All subjects entering the Run-in Period will receive ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h). Following completion of the Run-in Period, approximately 550 subjects will be randomized 1:1 to the VX-121/TEZ/D-IVA group or the ELX/TEZ/IVA group for the Treatment Period.

Intervention

Study drug refers to VX-121/TEZ/D-IVA, ELX/TEZ/IVA, IVA, and their matching placebos.

Active study drugs will be orally administered as either 2 fixed-dose combination (FDC)

film-coated VX-121/TEZ/D-IVA tablets in the morning, or as 2 FDC film-coated ELX/TEZ/IVA tablets in the morning and as 1 film-coated IVA tablet in the evening.

Active substance: VX-121, TEZ (VX-661), and D-IVA (VX-561)
Activity: CFTR corrector, CFTR corrector, and CFTR potentiator (increased Cl- secretion)
Strength and route of administration: 10 mg VX-121/50 mg TEZ/125 mg D-IVA; oral administration

Active substance: ELX (VX-445), TEZ (VX-661), and IVA (VX-770)
Activity: CFTR corrector, CFTR corrector, and CFTR potentiator (increased Cl- secretion)
Strength and route of administration: 100 mg ELX/50 mg TEZ/75 mg IVA; oral administration

Active substance: IVA (ivacaftor; VX-770)
Activity: CFTR potentiator (increased Cl- secretion)
Strength and route of administration: 150 mg; oral administration

Study burden and risks

All drugs have the potential to cause side effects; the extent to which this occurs differs. To date, VX-121/TEZ/D-IVA has been administered to 66 people with cystic fibrosis. In addition, VX-121 has been administered alone or in combination with TEZ/IVA or TEZ/D-IVA to 106 healthy volunteers.

The most common side effects associated with VX-121/TEZ/D-IVA are listed below. For these listed side effects, the percentages of people with cystic fibrosis who experienced these side effects are shown.

• Cough, 33%
• Increased phlegm, 28%
• Fatigue, 19%
• Headache, 18%
• Rash, 17%
• Sore throat, 16%
• Diarrhea, 15%
• Pulmonary exacerbation, 15%
• Shortness of breath, 13%
• Common cold, 12%
• Low blood sugar, 11%
• Increased blood enzyme called creatine phosphokinase (may be a sign of a muscle problem), 11%
• Nasal congestion, 10%
• Productive cough, 10%

Side effects from the combination of TEZ and ivacaftor (IVA) are listed below. D-IVA is a deuterated isotope of IVA, which means that it is structurally similar to IVA. Thus, the side effects with TEZ/D-IVA are expected to be similar to those with TEZ/IVA.

Possible Risks of IVA alone, and a combination of TEZ/IVA:

To date, more than 2000 participants have received at least 1 dose of IVA alone or TEZ/IVA in combination.

The side effects associated with IVA or TEZ/IVA are listed below:

Very common side effects occurring in >=10% include:

• Headache, 24%
• Sore throat, 22%
• Upper respiratory tract infection, 22%
• Nasal congestion, 20%
• Stomach ache, 16%
• Common cold, 15%
• Diarrhea, 13%
• Rash, 13%

Common side effects occurring in >=1 to <10% include:

• Dizziness (9%)
• Nausea (8%)
• Bacteria in phlegm (7%)
• Sinus congestion (7%)
• Runny nose (7%)
• Throat redness (5%)

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%

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.

Safety Monitoring in this Study:

In some study participants treated with ELX/TEZ/IVA, TEZ/IVA, or IVA, 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) and treated with ELX/TEZ/IVA, 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 and 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.

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. 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.

Contacts

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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)

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 aged 12 years or older, on the date of informed consent
4. Confirmed diagnosis of CF as determined by the investigator
5. Subject has one of the following genotypes: 1) homozygous for F508del; 2) heterozygous for
F508del and a gating (F/G) mutation; 3) heterozygous for F508del and a residual function
(F/RF) mutation; 4) at least 1 other TCR CFTR mutation identified as responsive to
ELX/TEZ/IVA and no F508del mutation. See Appendix A for examples of qualifying mutations. 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 (Section 9.9).
6. For subjects currently receiving Vertex CFTR modulator therapy, FEV1 value >=40% and
<=90% of predicted mean for age, sex, and height (equations of the Global Lung Function
Initiative [GLI])9 at the Screening Visit. All subjects not currently receiving Vertex CFTR
modulator therapy must have an FEV1 value >=40% and <=80% of predicted mean. Spirometry
measurements must meet American Thoracic Society/European Respiratory Society criteria10
for acceptability and repeatability.
7. Stable CF disease as judged by the investigator.
8. Willing to remain on a stable CF treatment regimen through completion of study participation.

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(s) to the subject. This
includes, but is not limited to, the following:
- Hepatic cirrhosis with portal hypertension, moderate hepatic impairment (Child Pugh
Score 7 to 9), or severe hepatic impairment (Child Pugh Score 10 to 15).
- 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. History of intolerance to study drug that would pose an additional risk to the subject in the
opinion of the investigator. (e.g., subjects with a history of liver function test [LFT]
elevations requiring treatment interruption or discontinuation, allergy or hypersensitivity to
the study drug).
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)11,12 for subjects
>=18 years of age and <=45 mL/min/1.73 m2 (calculated by the Counahan-Barratt
equation)13 for subjects aged 12 to 17 years (inclusive).
4. An acute upper or lower respiratory infection, PEx, or changes in therapy (including
antibiotics) for sinopulmonary disease within 28 days before the first dose of ELX/TEZ/IVA
in the Run-in Period (Day -28).
5. 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.
6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days

before the first dose of
ELX/TEZ/IVA in the Run-in Period (Day -28).
7. Ongoing or prior participation in a study of an investigational treatment other than a Vertex
CFTR modulator within 28 days or 5 terminal half-lives (whichever is longer) before
screening, or participation in an interventional study of a non-investigational treatment from
screening through end of study participation. The duration of the elapsed time may be longer
if required by local regulations.
8. Use of prohibited medications as defined in Table 9-2, within the specified window before
the first dose of ELX/TEZ/IVA in the Run-in Period (Day -28).
9. Pregnant or breast-feeding females. Female subjects must have a negative pregnancy test at
screening (serum test) and Run-in Period/Day -28 (urine test).
10. 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
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-04-2022
Enrollment:	30
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
Product type:	Medicine
Brand name:	VX-121/tezacaftor/deutivacaftor
Generic name:	VX-121/tezacaftor/deutivacaftor

Ethics review

Approved WMO Date:	27-10-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-12-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-03-2022
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-09-2023
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	EUCTR2021-000694-85-NL
ClinicalTrials.gov	NCT05076149
CCMO	NL78625.041.21