A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-121 Combination Therapy in Subjects With Cystic Fibrosis

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This study has been transitioned to CTIS with ID 2024-514173-22-00 check the CTIS register for the current data. Primary ObjectiveTo evaluate the long-term safety and tolerability of VNZ/TEZ/D-IVA in subjects with CFSecondary ObjectiveTo evaluate...

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

Summary

ID

NL-OMON53726

Source
ToetsingOnline

Brief title
VX20-121-104

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 of long-term treatment with VNZ/TEZ/D-IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

Secondary outcome

• Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1)

• Absolute change from baseline in sweat chloride (SwCl)

• Number of pulmonary exacerbations (PEx)

Other Endpoints

• Proportion of subjects with SwCl <60 mmol/L

• Proportion of subjects with SwCl <30 mmol/L

• Absolute change from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain (RD) score

• Absolute change in body mass index (BMI)

• Absolute change in BMI z score

• Absolute change in weight

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 symptomatic therapies, 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 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 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 and people heterozygous for F508del and a minimal function (MF) CFTR mutation (F/MF HBE cells) and studied in vitro, the triple combination (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

This study has been transitioned to CTIS with ID 2024-514173-22-00 check the CTIS register for the current data.

Primary Objective
To evaluate the long-term safety and tolerability of VNZ/TEZ/D-IVA in subjects with CF

Secondary Objective
To evaluate the long-term efficacy of VNZ/TEZ/D-IVA

Study design

This is a Phase 3, multicenter, open label study for subjects who completed the last Treatment Period visit in a parent study and meet eligibility criteria. A schematic of the study design is shown in Figure 9 1 of the protocol.
Approximately 850 subjects are expected to enroll in this study.
All subjects will receive VNZ/TEZ/D-IVA at the same dosage that was evaluated in Study 102 and Study 103. Study drug administration is described in Section 9.6 of the protocol.
Study visits and assessments to be conducted are shown in Table 3 1. All visits will occur within the windows specified.
Study drug is defined in Section 10 of the protocol.

Intervention

Active substance: VNZ/TEZ/D-IVA
Activity: CFTR corrector, CFTR corrector, and CFTR potentiator (increased Cl- secretion)
Strength:10-mg VX-121/50-mg TEZ/125-mg D-IVA
Study drug will be orally administered as fixed-dose combination (FDC) film coated tablets of VNZ/TEZ/D-IVA in the morning.

Study burden and risks

Risks Associated withVNZ/TEZ/D-IVA :

All drugs have the potential to cause side effects; the extent to which this occurs differs. To date, more than 900 clinical trial participants with cystic fibrosis ages 12 years and greater have been randomized to either VNZ/TEZ/D-IVA or elexacaftor (ELX)/TEZ/ivacaftor (IVA) treatment in two large clinical trials. More than 90 clinical trial participants with cystic fibrosis ages 6 to 11 years have received VNZ/TEZ/D-IVA in a clinical trial. In addition, VNZ has

been administered alone or in combination with TEZ/D-IVA or TEZ/IVA to approximately 200 healthy volunteers.

The most common side effects occurring in 8% or more of these cystic fibrosis trial participants are listed in the list below. For these listed side effects, the percentages of people with cystic fibrosis in a large study who experienced these side effects are shown.

• Cough, 18%
• Pulmonary exacerbation, 16%
• COVID-19 (coronavirus), 15%
• Rash, 12%
• Stomach ache, 12%
• Common cold, 11%
• Headache, 10%
• Diarrhea, 8%
• Upper respiratory tract infection, 8%

Side effects from the combination of TEZ and ivacaftor (IVA) are listed below. D-IVA is structurally similar to IVA, which means that it works similarly 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:

All drugs have the potential to cause side effects; the extent to which this occurs differs. To date, more than 2500 participants have received at least 1 dose of IVA alone or TEZ/IVA in combination in clinical studies.

The most common side effects associated with IVA or TEZ/IVA in combination are listed below. The percentages of people with cystic fibrosis who experienced these side effects are listed below.

Very common side effects occurring in 10% or more of the group include:

• Headache, 24%
• Throat pain, 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% or more to less than 10% of the group include:

• Dizziness (9%)

• Nausea (8%)
• Bacteria in sputum (which may indicate an infection in your respiratory tract)(7%)
• Sinus congestion (stuffy nose/sinuses) (7%)
• Nasal inflammation (7%)
• Throat redness (5%)

Contacts

Public
Vertex Pharmaceuticals

Leidsevaart 20
HA Haarlem 2013
NL
Scientific
Vertex Pharmaceuticals

Leidsevaart 20
HA Haarlem 2013
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. Did not withdraw consent from a parent study.
4. 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 did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of a parent study.
5. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

Exclusion criteria

1. New development of a comorbidity during the parent study that might post an additional risk in administering study drug to the subject. This includes, but is not limited to, the following:
- Hepatic cirrhosis with portal hypertension, moderate hepatic impairment, or severe hepatic impairment, that might pose an additional risk in administering study drug to the subject.
- Solid organ or hematological transplantation.
- Any other comorbidity that, in the opinion of the investigator, might post an additional risk in administering study drug to the subject.
2. Pregnant or breast-feeding females. All female subjects must have a negative pregnancy test at the Day 1 Visit before receiving the first dose of study drug.
3. History of drug intolerance in a parent study that would pose an additional risk to the subject in the opinion of the investigator. (e.g., subjects with a history of allergy or hypersensitivity to the 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.
5.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:	Recruiting
Start date (anticipated):	13-04-2023
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	VX-121/tezacaftor/deutivacaftor
Generic name:	VX-121/tezacaftor/deutivacaftor

Ethics review

Approved WMO Date:	28-09-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-12-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-01-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	17-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2024
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	CTIS2024-514173-22-00
EudraCT	EUCTR2021-000713-17-NL
ClinicalTrials.gov	NCT05076149
CCMO	NL82092.041.22