A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long term Treatment With VX 661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del CFTR Mutation

Published: 21-09-2015
Last updated: 19-04-2024

Main objective:Part ATo evaluate the long-term safety and tolerability of VX-661 in combination with ivacaftor in subjects with CF, homozygous or heterozygous for the F508del-CFTR mutation who are in the Treatment Cohort.Part B and Part CNot...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON50237

Source
ToetsingOnline

Brief title
VX14-661-110

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Cystic Fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Vextex Pharmaceuticals

Intervention

Keyword: Cystic Fibrosis, F508del-CFTR, Ivacaftor, Rollover

Outcome measures

Primary outcome

Part A

For the Treatment Cohort:

Safety and tolerability of long-term treatment of VX-661 in combination with ivacaftor based on adverse events (AEs), ophthalmologic examinations (subjects <18 years of age, clinical laboratory values (serum chemistry, hematology, coagulation, lipids, vitamins, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, and pulse oximetry

Secondary outcome

Part A

For the Treatment Cohort:

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

* Relative change from baseline in ppFEV1

* Number of pulmonary exacerbations

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

* Absolute change from baseline in BMI z score for subjects aged <20 years

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

* Absolute change from baseline in body weight

* Absolute change from baseline in body weight z-score for subjects aged <20 years

* Absolute change from baseline in height z-score for subjects aged <20 years

* Time to first pulmonary exacerbation,

* Pharmacokinetic (PK) parameters of VX 661, a VX-661 metabolite (M1 661), ivacaftor, and an ivacaftor metabolite (M1 ivacaftor)

For the Observational Cohort:

* Safety, as determined by related serious adverse events (SAEs)

Part B

* AEs

* Ophthalmologic exams (subjects < 18 years of age [age on the date of informed consent/assent in the parent study])

* Serum liver function tests (LFTs)

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

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

* Absolute change from baseline in BMI z score for subjects aged <20 years

* Number of pulmonary exacerbations

Part C

* AEs

* Ophthalmologic examinations (for subjects <18 years of age [age on date of

informed consent/assent in the parent study])

* Serum liver function tests (LFTs)

Study description

Background summary

Cystic fibrosis is an autosomal recessive genetic disease caused by a defect in the gene encoding the CF transmembrane conductance regulator (CFTR), an epithelial chloride ion (Cl*) channel activated by cyclic adenosine monophosphate-dependent protein kinase A that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. This function is defective in patients with CF due to a loss of either cell surface expression and/or function.
More than 1900 mutations in the CFTR gene have been identified. Mutations in the CFTR gene have been classified based on the molecular and functional consequence of the mutation on the CFTR protein and can be generally considered to reduce the quantity of functional CFTR protein that reaches the epithelial cell surface or reduce the function of CFTR protein located at the cell surface. CFTR gene mutations that affect the quantity of functional cell surface CFTR protein include defects that reduce CFTR protein synthesis and defects that impede the cellular processing and delivery of CFTR proteins to the cell surface. VX-661 is a compound developed by Vertex Pharmaceuticals Incorporated (Vertex) that has
been shown to have CFTR corrector properties.

Study objective

Main objective:
Part A
To evaluate the long-term safety and tolerability of VX-661 in combination with

ivacaftor in subjects with CF, homozygous or heterozygous for the F508del-CFTR mutation who are in the Treatment Cohort.

Part B and Part C
Not applicable

Secondary objectives:
Part A
Treatment Cohort
To evaluate the long-term efficacy of VX-661 in combination with ivacaftor for subjects in the Treatment Cohort.

Observational Cohort
To evaluate the post-treatment safety of VX-661 in combination with ivacaftor for subjects in the Observational Cohort.

Part B
To evaluate the long-term safety, tolerability, and efficacy of VX 661 in combination with ivacaftor in subjects with CF, homozygous or heterozygous for the F508del-CFTR mutation.

Part C
To evaluate the long-term safety and tolerability of VX-661 in combination with ivacaftor in subjects with CF, homozygous or heterozygous for the F508del-CFTR mutation.

Study design

This is a Phase 3, multicenter, open-label, rollover study in subjects with CF who are homozygous or heterozygous for the F508del-CFTR mutation and who participated in Studies 103, 106, 107, 108, 109, or 111. The study is designed to evaluate the safety and efficacy of long-term treatment of VX-661 in combination with ivacaftor.
This study consists of a Treatment Cohort and an Observational Cohort. The Treatment Cohort and the Observational Cohort will be open to enrollment in parallel.

Treatment Cohort:
Subjects who completed study drug treatment (i.e., VX-661/ivacaftor, ivacaftor monotherapy, or placebo) during the Treatment Period in a parent study (Studies 103 [Placebo-Controlled Phase or Open-Label Extension Phase], 106, 107, 108, or 109) or study drug treatment and the Safety Follow-up Visit for subjects from Study 111 who meet the eligibility criteria will be offered the opportunity to enroll in Study 110. Subjects who permanently discontinue study drug treatment or who withdrew consent during the parent study are not eligible for enrollment in the Treatment Cohort.
The Treatment Cohort will be open-label, and all subjects will receive VX-661

100 mg/ ivacaftor 150-mg FDC tablet daily (qd) in the morning and ivacaftor 150-mg tablet qd in the evening. The Treatment Period will be approximately 96 weeks.
During the course of study conduct, if VX-661 in combination with ivacaftor is approved and available for the treatment of CF in populations enrolled in Study 110, subjects with the approved CFTR genotypes may be discontinued from this rollover study at the discretion of the sponsor. If a subject is continuing onto commercially available VX-661/ivacaftor, the Early Treatment Termination Visit will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit will not be required. Alternatively, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in populations enrolled in Study 110, subjects with the relevant CFTR genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. If subjects are discontinued from the study, an Early Treatment Termination Visit should occur within 7 days of the last dose of study drug and a Safety Follow-up Visit should occur within 28 (± 7) days after the last dose of study drug.

Observational Cohort
Subjects <18 years of age (age on the date of informed consent/assent in the parent study) who received at least 4 weeks of study drug in the parent study, who are not eligible for the Treatment Cohort or who elect not to enroll in the Treatment Cohort, and meet eligibility criteria will be offered the opportunity to enroll in the Observational Cohort.
Subjects in the Observational Cohort will not receive study drug and will have regularly scheduled telephone calls for approximately 2 years after their last dose of study drug in the parent study to assess post-treatment safety of VX-661/ivacaftor combination therapy.

Intervention

Treatment Cohort:
For the Treatment Cohort, study drug will be administered for approximately 96 weeks with a Safety Follow-up Visit 28 days [± 7 days] after the last dose).

Observational Cohort:
For the Observational Cohort, maximum subject participation will be approximately 2 years.

Study burden and risks

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide and is the most common fatal genetic disease in persons of European descent. Based on the size of the population, CF qualifies as an orphan disease. Despite

progress in the treatment of CF with
antibiotics and mucolytics, the predicted median age of survival for a person with CF is in the mid-30s. Although the disease affects multiple organs, most morbidity and mortality are caused by progressive loss of lung function.
Ivacaftor (also known as VX-770) is the first CFTR modulator to show an improvement in CFTR function and clinical benefit in patients with CF. Results from several Phase 3 studies showed that ivacaftor is effective in the treatment of patients with CF who have mutations that result in gating defects as evidenced by sustained improvements in CFTR channel function (measured by reduction in sweat chloride concentration) and corresponding substantial, durable improvements in lung function, respiratory symptoms, and weight gain. Ivacaftor was also well tolerated, as evidenced by the rates and reasons for premature discontinuation and results of safety assessments.
Common adverse events in studies of CF subjects, who took VX-661, ivacaftor, or VX-661 in combination with ivacaftor are Infective pulmonary exacerbation of CF (temporary worsening of lung function due to an infection or inflammation), Cough, Headache, Nausea, Sputum increased
Fatigue, Upper respiratory tract infection (common cold), Oropharyngeal pain (sore throat), Nasal congestion (stuffy nose), Nasopharyngitis (inflammation of the nose and pharynx), Abdominal Pain, Diarrhea, Rash, Dizziness (feeling faint).

Contacts

Public
Vertex Pharmaceuticals

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US
Scientific
Vertex Pharmaceuticals

Northen Avenue 50
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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)
Elderly (65 years and older)

Inclusion criteria

Part A
Subjects entering the Treatment Cohort must meet all of the following criteria:
*Elect to enroll in the Treatment Cohort.
*Completed study drug treatment during the Treatment Period in a parent study (Studies 103, 106, 107, 108, or 109) or study drug treatment and the Safety Follow up Visit for subjects from Study 111 or study drug treatment and follow-up as specified in other Vertex studies investigating VX-661 in combination with ivacaftor.
* Willing to remain on a stable CF medication (and supplement) regimen through the Safety Follow-up Visit., Subjects re-enrolling in the treatment cohort must meet all the following criteria:
* Previously received at least 4 weeks of study drug before discontinuing Study 110 to participate in another qualified Vertex study
* Completed the last required visit of another qualified Vertex study before or during the returning visit in Part A in Study 110
* Willing to remain on a stable CF medication (and supplement) regimen through the Safety Follow-up Visit of Part A.
* Subjects who discontinue Study 110 more than once to participate in another qualified Vertex study may not re-enroll in Part A a second time., Subjects entering the Part A Observational Cohort must meet the following criteria:
* <18 years of age (age on the date of informed consent/assent in the parent study)
* Completed study drug treatment during the Treatment Period in a parent study (Studies 103, 106, 107, 108, or 109) or study drug treatment and the Safety Follow up Visit for subjects from Study 111 or study drug treatment and follow-up as specified in other Vertex studies investigating VX-661 in combination with ivacaftor, but do not elect to enroll in the Study 110 Treatment Cohort; or
* Received at least 4 weeks of study drug treatment in a parent study, but do not meet eligibility criteria for enrollment into the Treatment Cohort.
Part B
*Completed study drug treatment during the Treatment Period in Part A of VX14 661 110, Studies VX15 661 112 or VX16 661 114 or other eligible Vertex studies.
*For subjects in the middle of an approved sutdy drug interruption at the end of the Parent study or Part A, or who re-started study drug after an

interruption <4 weeks before the end of the Parent study or Part A, criteria for study drug resumption or rechallenge must be performed.
*Willing to remain on a stable CF medication (and supplement) regimen through the 96 weeks visit. Subjects re enrolling in Part B must meet all of the following criteria
*Previously received at least 4 weeks of studydrug before discontinuing Study VX661 110 to participate in another qualified Vertex study.
*Completed the last required visit of another qualified Vertex study before or during the Returning Visite in Part B.
*Willing to remain on a stable CF medication (and supplement) regimen through the 96 week visit in Part B.
Part C:
Subjects who meet all of the following inclusion criteria will be eligible for Part C.
* Signed and dated an ICF, and where appropriate, signed and dated an assent form.
* Did not withdraw consent from Part B of Study VX14-661-110.
* Able to understand and comply with protocol requirements, restrictions, and instructions, and likely to complete the study as planned, as judged by the investigator and Vertex, based in part on study compliance in the parent study and Study VX14-661-110 (Part A and B).
* Completed study drug treatment during the Treatment Period in Part B of VX14-661-110.
* For subjects in the middle of an approved study drug interruption at the end of the Part B, or who re-started study drug after an interruption <4 weeks before the end of Part B, criteria for study drug resumption must be met and safety monitoring following resumption or rechallenge must be performed.
* Willing to remain on a stable CF medication (and supplement) regimen through the 96 week visit of Study VX14-661-110 Part C.

Exclusion criteria

Part A Treatment Cohort only:
* 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 to the subject.
* Pregnant and nursing females. Females of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit (and at Returning Visit for subjects who re-enroll) and before receiving the first dose of study drug.
* Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements.
* History of drug intolerance in the parent study or other qualified Vertex study that would pose an additional risk to the subject.
* History of poor compliance with study drug and/or procedures in the parent study or other qualified Vertex study as deemed by the investigator.

* Participation in an investigational drug trial other than Studies 103, 106, 107, 108, 109, and 111, other Vertex studies investigating VX-661 in combination with ivacaftor, or other qualified study, or use of a commercially available CFTR modulator (e.g., Kalydeco).
* Previous re-enrollment in the Part A Treatment Cohort of Study 110 after participating in other qualified Vertex studie.
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 to the subject.
* Pregnant and nursing females
* Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements
* Subjects who permanently discontinue study drug treatment during the parent study or Part A
* History of drug intolerance in the parent study, Part A of study VX14-661-110, or other qualified Vertex study that would pose an additional risk to the subject in the opinion of investigator or Vertex
* History of poor compliance with study drug and/or procedures in the parent study, Part A of Study VX14-661-110, or other qualified Vertex study as deemed by the investigator
* Participation in an investigational drug trial (other than Studies VX13 661 103, VX14 661 106, VX14 661 107, VX14 661 108, VX14 661 109, VX14 661 111, VX15 661 112, VX16 661 114, Part A of Study VX14-661-110, or other eligible Vertex studies investigating VX 661 in combination with ivacaftor) or use of a commercially available CFTR modulator (e.g., Kalydeco)
* Discontinued Study VX14 661 110 (either Part A or Part B) more than once to participate in another qualified Vertex study.
Part C
Subjects who meet any of the following exclusion criteria will NOT be eligible for this study.
* 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 to the subject. For example:
* History of cirrhosis with portal hypertension, and/or history of risk factors for Torsade de Pointes (e.g., familial long QT syndrome, hypokalemia, heart failure, left ventricular hypertrophy, bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia [ventricular and atrial fibrillation], obesity, acute neurologic events [subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, and intracranial trauma], and autonomic neuropathy)
* Pregnant and nursing females. Females of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit of Part C and before receiving the first dose of study drug in Part C.
* Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements.
* Subjects who permanently discontinue study drug treatment during

the parent study or Study VX14-661-110 (Part A or Part B), including at the last visit of the Treatment Period.
* History of drug intolerance in the parent study or Study VX14-661-110 (Part A or Part B), that would pose an additional risk to the subject in the opinion of investigator or Vertex. Examples of subjects who may not be eligible for Part C include but are not limited to the following:
* Subjects with a history of allergy or hypersensitivity to the study drug
* Other severe or life-threatening reactions to the study drug in the parent study or Study VX14-661-110 (Part A or Part B).
* History of poor compliance with study drug and/or procedures in the parent study or Study VX14-661-110 (Part A or Part B) as deemed by the investigator.
* Participation in an investigational drug trial or use of a commercially available CFTR modulator (e.g., Kalydeco).
NOTE:
participation in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug), and screening for other qualified Vertex studies 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:	Recruitment stopped
Start date (anticipated):	04-12-2015
Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kalydeco
Generic name:	Ivacaftor
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Symkevi
Generic name:	Tezacaftor
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-09-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	13-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	06-12-2019
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO	

Date:	16-12-2020
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	13-01-2021
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

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	EUCTR2014-004827-29-NL
CCMO	NL54556.072.15