A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function

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To evaluate the efficacy of VX-661 in combination with ivacaftor and ivacaftormonotherapy through 8 weeks of treatment in subjects with cystic fibrosis (CF)who are heterozygous for the F508del mutation on the CF transmembraneconductance regulator (...

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

Summary

ID

NL-OMON43608

Source
ToetsingOnline

Brief title
VX14-661-108

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

Outcome measures

Primary outcome

Absolute change in percent predicted forced expiratory volume in 1 second

(FEV1) from study baseline to the average of the Week 4 and Week 8

measurements in each Treatment Period.

Secondary outcome

Key Secondary

- Relative change in percent predicted FEV1 from study baseline to the average

of the Week 4 and Week 8 measurements in each Treatment Period

- Absolute change in sweat chloride from study baseline to the average of the

Week 4 and Week 8 measurements in each Treatment Period

Secondary

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

laboratory values, standard digital electrocardiograms

(ECGs), vital signs, pulse oximetry and spirometry; from baseline to the

average of the Week 4

and Week 8 measurements in each Treatment Period

- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R)

respiratory domain score from study baseline to the average of the Week 4

and Week 8 measurements in each Treatment Period

- PK parameters of VX-661, M1-661, ivacaftor, and M1-ivacaftor through week 24

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

To evaluate the efficacy of VX-661 in combination with ivacaftor and ivacaftor monotherapy through 8 weeks of treatment in subjects with cystic fibrosis (CF) who are heterozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene and a second allele with a CFTR mutation predicted to have residual function.

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled, 2-period, 3-treatment, crossover, multicenter study in subjects aged 12 years and older with CF, heterozygous for the F508del-CFTR mutation, and a second allele with a CFTR mutation predicted to have residual function.
This study includes the following:
- Screening Period (Day *28 through Day *1)
- Treatment Period 1 (Week 1 Day 1 through Week 8 ± 5 days)
- Washout Period (Week 9 through Week 16 ± 7 days); a safety evaluation visit will be conducted at Week 12 (± 5 days).
- Treatment Period 2 (Week 17 through Week 24 ± 5 days)
- Safety Follow-up Visit (28 days ± 7 days after the last dose of study drug)
Subjects will be stratified by age at the Screening Visit (<18 versus *18 years of age), FEV1 severity determined during the Screening Visit (<70% versus *70% predicted), and type of residual function mutation on the second CFTR allele (Class V non-canonical splice mutation versus Classes II to IV residual function mutation), and then randomized (1:1:1:1:1:1) to 1 of the following 6 treatment sequences:
- Sequence 1: VX-661/ivacaftor in Treatment Period 1*washout* ivacaftor monotherapy in Treatment Period 2
- Sequence 2: ivacaftor monotherapy in Treatment Period 1*washout* VX-661/ivacaftor in Treatment Period 2
- Sequence 3: VX-661/ivacaftor in Treatment Period 1*washout* placebo in Treatment Period 2
- Sequence 4: placebo in Treatment Period 1*washout* VX-661/ivacaftor in Treatment Period 2
- Sequence 5: ivacaftor monotherapy in Treatment Period 1*washout* placebo in Treatment Period 2
- Sequence 6: placebo in Treatment Period 1*washout*ivacaftor monotherapy in Treatment Period 2
A minimum of 25% of enrolled subjects will carry a Class II to IV mutation on the second CFTR allele. Stratification of enrollment will be managed through the interactive web response system (IWRS). Enrollment into the non-canonical splice strata will be limited to no more than 75% of total enrollment.

Intervention

The first dose of the study drug will be administered after randomization on Day 1.
Clinic visits will occur on Week 1 (Day 1 of Treatment Period 1), Week 2 (± 3 days), Week 4 (± 5 days), Week 8 (± 5 days), Week 12 (± 5 days), Week 17 (Day 1 of Treatment Period 2), Week 18 (± 3 days), Weeks 20 and 24 (± 5 days), and the Safety Follow-up Visit (28 days ± 7 days after the final dose of study drug).
Subjects who prematurely discontinue study drug treatment will continue to complete all the other scheduled study visits for assessments of efficacy (spirometry, sweat chloride, and CFQ-R) and other endpoints (SF-12 and other events related to outcome [hospitalizations, pulmonary exacerbations, etc.]).

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
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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

- Subjects (males and females) will be aged 12 years or older on the date of informed consent or, where appropriate, assent.
- Heterozygous for F508del-CFTR and a second allele with a CFTR mutation predicted to have residual function. The results of the confirmatory genotype sample obtained at the Screening Visit must be

reviewed before randomization.- Forced Expiratory Volume in 1 Second (FEV1) greater than or equal to (*)40% and less than or equal to (*) 90% of predicted normal for age, sex, and height
during screening.
- Sweat chloride value *60 mmol/L from test results obtained during screening OR as documented in the subject*s medical record.
- If the sweat chloride value <60 mmol/L, there must be have documented evidence of chronic
sinopulmonary disease.
- Stable CF disease as judged by the investigator.

Exclusion criteria

- 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.
An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1
- A 12-lead electrocardiogram (ECG) demonstrating corrected QT intervals (QTc) greater than (>) 450 milliseconds (msec) at the Screening Visit.
- History of solid organ or hematological transplantation.
- History or evidence of cataract, lens opacity, Y-suture, or lamellar
rings determined to be clinically significant by the ophthalmologist
during the ophthalmologic examination during the Screening Period. If
the subject has documentation of bilateral lens removal, an
ophthalmologic examination is not required and this criterion is not
applicable.
- Ongoing or prior participation in an investigational drug study (including studies investigating VX-661, lumacaftor [VX-809], and/or ivacaftor) or use of commercially available CFTR modulator (e.g., Kalydeco) within 30 days of screening.
- Use of restricted medications or foods within the specified window before the first dose of study drug
- Pregnant and nursing females (females of childbearing potential must have a negative pregnancy test at Screening and Day 1).
- Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements
- Colonization with organisms associated with a more rapid decline in
pulmonary status

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):	01-06-2015
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Kalydeco
Generic name:	Ivacaftor
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	VRT-893661 VRT-0893661
Generic name:	VX-661

Ethics review

Approved WMO Date:	08-04-2015
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	10-07-2015

Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-10-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	17-05-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	17-02-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-10-2017
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	EUCTR2014-004788-18-NL
ClinicalTrials.gov	NCT02392234

Register	ID
CCMO	NL52602.072.15