# A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Published: 08-04-2015
Last updated: 16-04-2024

To evaluate the efficacy of VX-661 in combination with ivacaftor through 24 weeks of treatment in subjects with cystic fibrosis (CF) who are homozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene.

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

## Summary

### ID

NL-OMON42785

**Source**
ToetsingOnline

**Brief title**
VX14-661-106

### Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Congenital respiratory tract disorders

**Synonym**
Cystic Fibrosis, fibrosis cystica, mucoviscidosis

**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 baseline through Week 24

### Secondary outcome

-* Relative change in percent predicted FEV1 from baseline through Week 24

-* Number of pulmonary exacerbations through Week 24

-* Absolute change in body mass index (BMI) from baseline at Week 24

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

respiratory domain score from baseline through Week 24

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

laboratory values (i.e., hematology, serum chemistry, coagulation studies,

vitamin levels, lipid panel, and urinalysis),, standard 12-lead

electrocardiograms (ECGs), vital signs, and pulse oximetry; from screening

through 4 weeks after receiving last dose

-* Time- to- first pulmonary exacerbation through Week 24

-* Absolute change in sweat chloride from baseline through Week 24

-* Absolute change in BMI z-score from baseline at Week 24 (in subjects <20

years of age at time of screening)

-* Absolute change in body weight from baseline at Week 24

-* PK parameters of VX-661, M1-661, M2-661, 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 through 24 weeks of treatment in subjects with cystic fibrosis (CF) who are homozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene.

**Study design**

This is a Phase 3, randomized, double-blind, placebo-controlled,

parallel-group, multicenter study in subjects with CF who are homozygous for the F508del-CFTR mutation.
This study includes the following:
- Screening Period (Day *28 through Day *1)
- Treatment Period (Day 1 through Week 24 ± 5 days)
- Safety Follow-up Visit (28 ± 7 days after the final dose of study drug)
Subjects will be stratified by age at the Screening Visit (<18 versus *18 years of age), sex (male versus female), and FEV1 severity determined during the Screening Period (<70% versus *70% predicted), and then randomized (1:1) to 1 of the following 2 treatment arms:
- VX-661/ivacaftor: 100 mg VX-661 once daily (qd) + 150 mg ivacaftor every 12 hours (q12h)
- Placebo: Placebo regimen with visually matched tablets

**Intervention**

The first dose of the study drug will be administered after randomization on Day 1.
- Clinic visits will occur on Day 1, Day 15 (± 3 days), and at Weeks 4, 8, 12, 16, and 24 (± 5 days), and during the Safety Follow-up Visit (28 □±7 days after the final dose of study drug [Week 24]).
- Telephone contact will be made at Week 20 (± 5 days) to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
Subjects who prematurely discontinue study drug treatment will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, CFQ-R, sweat chloride, height, and weight), other endpoints (CFRSD, SF-12, and PSQI), 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**
Vertex Pharmaceuticals

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**Scientific**
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)
Elderly (65 years and older)

## Inclusion criteria

* Homozygous for the F508del CFTR mutation, genotype to be confirmed at the Screening Visit
* Confirmed diagnosis of CF defined as a sweat chloride value *60 mmol/L by quantitative pilocarpine iontophoresis
* FEV1 *40% and *90% of predicted normal for age, sex, and height during screening
* Stable CF disease as judged by the investigator
* Willing to remain on a stable CF medication regimen through Week 24 or, if applicable, the Safety Follow up Visit

## 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 (first dose of study drug)
* Pregnant or 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

# Study design

## Design

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| 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

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|---|---|
| Start date (anticipated): | 15-08-2015 |
| Enrollment: | 30 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Kalydeco |
| Generic name: | Ivacaftor |
| Product type: | Medicine |
| Brand name: | VRT-893661 VRT-0893661 |
| Generic name: | VX-661 |

## Ethics review

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|---|---|
| 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: | 01-07-2016 |

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|---|---|
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 20-07-2016 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Not approved Date: | 20-07-2016 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 02-08-2016 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 21-09-2016 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 25-01-2017 |
| 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) |

## 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 | EUCTR2014-004837-13-NL |
| ClinicalTrials.gov | NCT02347657 |
| CCMO | NL52592.072.15 |