# A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an A455E-CFTR Mutation

Published: 18-07-2016
Last updated: 15-04-2024

Primary ObjectiveTo evaluate the efficacy of lumacaftor/ivacaftor combination therapy (LUM/IVA) in subjects with cystic fibrosis (CF) 12 years of age and older who have at least one A455E mutation.Other Objectives* To explore the association between...

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

## Summary

### ID

NL-OMON46161

**Source**
ToetsingOnline

**Brief title**
VX15-809-111

### Condition

- Respiratory disorders congenital
- Autoimmune disorders
- Lower respiratory tract disorders (excl obstruction and infection)

**Synonym**
Mucoviscidosis

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Vertex Pharmaceuticals
**Source(s) of monetary or material Support:** Vertex Pharmaceuticals Incorporated (de sponsor) sponsort en betaalt dit onderzoek

## Intervention

**Keyword:** Crossover, Cystic, Fibrosis, Mutation

## Outcome measures

### Primary outcome

Absolute change from baseline in percent predicted forced expiratory volume in

1 second (ppFEV1) through 8 weeks of treatment.

### Secondary outcome

* Change from baseline in sweat chloride through 8 weeks of treatment.

* Change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) at

8 weeks of treatment.

* Organoid-based measurements of LUM/IVA-induced CFTR function in vitro versus

clinical outcomes.

* Change from baseline in glucose and insulin levels during the oral glucose

tolerance test (OGTT) after approximately 8 weeks of treatment.

# Study description

### Background summary

The A455E-CFTR mutation is reported to occur in less than 0.1% of patients with CF worldwide, but large regional differences in prevalence exist. In The Netherlands, it is the second most prevalent mutation, occurring in 3.6% of all

patients with CF. An especially high prevalence has been reported in the Southeast and Southwest regions of The Netherlands. Although it was initially reported that the A455E mutation is associated with mild lung disease, current clinical experience in The Netherlands shows marked differences in clinical disease severity, ranging from relatively mild to severe loss of lung function at young adulthood.

The A455E mutation results in a severe reduction of mature CFTR protein at the cell surface. In recent research, it was noted that when both F508del-CFTR and 264del-CFTR were transfected into the same cells, the expression of mature F508del-CFTR protein was increased. Similarly, when both A455E-CFTR and 264del-CFTR were transfected into the same cells, the expression of mature A455E-CFTR protein was increased. Furthermore, compounds known to be able to rescue F508del-CFTR were also able to rescue A455E-CFTR in vitro. This suggests that A455E-CFTR could be rescued by the same strategies as F508del-CFTR. These findings suggested that A455E might be a suitable candidate for LUM/IVA treatment.

A novel functional CFTR assay has been established using patient-derived intestinal stem cell cultures termed organoids. Organoids have crypt-like structures and an internal lumen lined by differentiated cells, recapitulating the in vivo tissue architecture. Intestinal CFTR is expressed at the apical membrane of the organoid. Activation of CFTR by forskolin (which increases cAMP levels) drives CFTR-dependent chloride secretion, inducing rapid, measurable swelling of organoids. In this in vitro model, organoids derived from patients with the F508del/F508del CFTR genotype display less forskolin-induced swelling than organoids derived from healthy controls. Incubation of these F508del/F508del organoids with LUM/IVA enhances forskolin-induced swelling. A similar improvement by LUM/IVA on forskolin-induced swelling is observed in A455E/F508del organoids. Based on these findings in the organoid model, it is hypothesized that LUM/IVA treatment can increase CFTR function and improve disease parameters in patients with CF who have an A455E mutation.

In this study, the clinical response of subjects with the A455E mutation to LUM/IVA will be investigated. The associations between the responses in the organoid model and the clinical response will be explored. Thus, the study will provide insights on the clinical utility of the organoid assay, potentially informing future studies in patients with very rare CFTR mutations. Also, the effect of CFTR modulation on subjects* pancreatic endocrine function, as measured by glucose levels and insulin response in the oral glucose tolerance test (OGTT), will be explored.

**Study objective**

Primary Objective
To evaluate the efficacy of lumacaftor/ivacaftor combination therapy (LUM/IVA) in subjects with cystic fibrosis (CF) 12 years of age and older who have at least one A455E mutation.
Other Objectives
* To explore the association between LUM/IVA-induced cystic fibrosis transmembrane conductance regulator (CFTR) function in in vitro organoid-based measurements and clinical response to LUM/IVA in subjects with CF 12 years of age and older who have at least one A455E mutation.
* To explore the effect of LUM/IVA on glucose tolerance and insulin secretion in subjects with CF 12 years of age and older who have at least one A455E mutation.

## Study design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, crossover study. The crossover design includes two 8-week treatment periods separated by an 8-week (± 7 days) washout period. Subjects will be randomized (1:1) to 1 of 2 treatment sequences: LUM/IVA followed by placebo or placebo followed by LUM/IVA.

## Intervention

Active substance: LUM/IVA fixed-dose combination
Activity: CFTR corrector and potentiator (chloride ion secretion)
Strength and route of administration: 200-mg lumacaftor/125-mg ivacaftor (200/125 mg) film-coated tablets for oral administration
Dosage: LUM 400 mg/IVA 250 mg every 12 hours (q12h)

The subject will receive two tablets of study drug (whether it is the placebo or the Lumacaftor/Ivacaftor Combination) in the morning and two tablets in the evening (approximately every 12 hours) every day of each Treatment Period.

## Study burden and risks

In CF subjects who received lumacaftor/ivacaftor combination treatment, some subjects have had blood tests that showed liver abnormalities. These tests, called ALT, AST, and bilirubin, led to stopping of study drug in some subjects (<1%). In these subjects, liver tests got better after study drug was stopped. Tests of patien's liver will be performed during the study.

Potential 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. The patient should tell the study doctor if he/she has any of these symptoms or anything else unusual.

In very bad cases, significant liver injury can potentially become permanent and even be life-threatening.
In patients with existing severe liver disease (cirrhosis with portal hypertension), there is a greater risk for worsening of liver function. The worsening of liver function can cause encephalopathy (confusion) or death.

Some respiratory symptoms, such as shortness of breath and/or chest tightness can occur with lumacaftor/ivacaftor combination treatment. The majority of these events began during the first week of treatment. These respiratory symptoms were more common in subjects with poor lung function. These respiratory symptoms can be serious and may lead to stopping treatment, especially in patients with poor lung function. The patient should tell the study doctor if he/she has any of these symptoms.

In a study in children 6 to 11 years old, a drop in lung function was observed during the start of lumacaftor/ivacaftor combination treatment. The biggest drop in lung function was about 8%, and was seen 4 to 6 hours after first dose on Day 1. This drop was much smaller on Day 15 and went away by Week 16 with continued treatment.

Irregular or abnormal periods have been seen in female subjects treated with lumacaftor/ivacaftor combination treatment, especially those taking hormonal contraceptives (birth-control pills). If the patient is female, hormonal contraceptives (birth control pills) will not work while she is on Study Drug.

Eye examinations performed in studies involving children receiving ivacaftor or lumacaftor/ivacaftor combination treatment have identified several subjects with cataracts (cloudiness of the lens of the eye). While the data do not support a link between ivacaftor and cataracts, a possible link cannot be excluded.

Increases in blood pressure have been observed in patients treated with lumacaftor/ivacaftor. Patien's blood pressure will be monitored periodically while he/she is in the study.
The Study Drug contains 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 5 ml of milk. This amount of lactose is unlikely to cause symptoms in people who have lactose-intolerance.

Possible Risks Based on Animal Studies:
In a study in which ivacaftor was given to newborn rats, cataracts (cloudiness of the lens of the eye) were seen. No cataracts were seen in studies of older animals (rats and dogs) dosed with ivacaftor for longer periods of time. The importance of this finding in humans is unknown.

Reproductive Risks:
De patient should not become pregnant or father a baby while on this study

because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while in this study. Patient and his partner must use a study-approved method of birth control (unless they are infertile, meaning not able to get pregnant or make a female pregnant). De patient should check with the Study Doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you are female, hormonal contraceptives (birth control pills) will not work while you are on Study Drug.
If the patient or his female partner becomes pregnant during the study he should notify the Study Doctor right away. If the patient or his female partner becomes pregnant, he will need to stop Study Drug immediately and permanently. The Study Doctor will ask to follow the pregnancy to its outcome and until the infant is one year of age. If his female partner becomes pregnant, she will be asked for permission to follow the pregnancy.
Drug Interaction Risks (medicines working with or against each other):
Almost all medicines can cause side effects. Many are mild, but some can sometimes 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. You should tell your study doctor about every medicine, dietary supplement, natural remedy, and vitamin (or change) while you are in the study.

Unknown Risks:
There may be side effects that are not yet known. De patient should call the Study Doctor if he/she thinks he/she is having any of the problems listed above or even if de patient is having problems that are not on this list. Please note that the treatment that will follow may involve risks which are currently unforeseeable to the patient and the fetus, embryo or unborn child.

Study Procedure Risks:
Blood sample collection: De patient may have a bruise (a black and blue mark) or pain where we take the blood samples. Some people get dizzy or faint from a blood draw. De patient could also get an infection (rare), or have bleeding, redness, or bruising at the skin puncture.

Spirometry: De patient may feel the need to cough or may feel short of breath during or after the test.

Eye Exam: The drops used to dilate your pupils can cause blurry vision for a few hours. They can also make it uncomfortable to be around bright lights. Patient's eye doctor will tell him/her about this.

Rectal Biopsy: De patient will feel some discomfort while the biopsy is being taken. Also during and after the biopsy, he/she may experience bloating, abdominal discomfort or passing gas for a few hours after the procedure. It is not uncommon to find a small amount of blood in your first bowel movement after your rectal biopsy.

However, the patient should contact the Study doctor if he/she experiences:
* extreme abdominal pain
* fever
* more than one bloody bowel movement, especially if bleeding is heavy or clotted
* a feeling of faintness

# Contacts

**Public**
Vertex Pharmaceuticals Incorporated (Vertex)

Northern Avenue 50
Boston MA 02210-1862
US
**Scientific**
Vertex Pharmaceuticals Incorporated (Vertex)

Northern Avenue 50
Boston MA 02210-1862
US

# 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 who meet all of the following inclusion criteria will be eligible:
1. Male or female with confirmed diagnosis of CF. The subject must have both of the

following:
o One or more characteristic phenotypic features, such as chronic cough and sputum production, persistent chest radiograph abnormalities, or airway obstruction manifested by wheezing and air trapping; or a history of CF in a sibling; or a positive newborn screening test result;
o An increased sweat chloride concentration by pilocarpine iontophoresis on two or more occasions; or identification of two CF mutations; or demonstration of abnormal nasal epithelial ion transport.
2. Age 12 years or older on the date of informed consent.
3. All subjects must have an A455E mutation on at least 1 CFTR allele.
4. Forced expiratory volume in one second (FEV1) *30% of predicted and *90% of predicted at the Screening Visit, based on the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations.
5. Stable CF disease as judged by the investigator.
6. Willing to remain on a stable medication regimen for CF from 4 weeks before Day 1 through the Follow-up Visit.
7. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
8. Subject (or subject*s legally appointed and authorized representative) will sign and date an informed consent form (ICF), and where appropriate, assent form.

## Exclusion criteria

Subjects who meet any of the following exclusion criteria will not be eligible:
1. History of any comorbidity reviewed at the Screening Visit 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:
o A history of cirrhosis with portal hypertension.
o An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (the first dose of study drug).
2. A G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H mutation on at least one CFTR allele.
3. Ongoing or prior participation in an investigational drug study (including studies investigating LUM/IVA or IVA) within 30 days before the Screening Visit.
o A washout period of 5 terminal half-lives of the previous investigational study drug or 30 days, whichever is longer, must elapse before the Screening Visit. The duration of the elapsed time may be longer if required by local regulations.
o Subjects who participated in Vertex Study VX14-661-108 may not be enrolled.
o Ongoing participation in a noninterventional study (including observational studies) is permitted.
4. Pregnant or breastfeeding.
5. Any of the following abnormal laboratory values at the Screening Visit:
* Hemoglobin <10 g/dL
* Any 2 or more of the following:

o aspartate aminotransferase (AST) *3 × upper limit of normal (ULN)
o alanine aminotransferase (ALT) *3 × ULN
o gamma-glutamyl transpeptidase (GGT) *3 × ULN
o alkaline phosphatase *3 × ULN
* ALT or AST >5 × ULN
* Bilirubin >2 × ULN
* Glomerular filtration rate *45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation).25
6. History of cataract/lens opacity, or evidence of cataract/lens opacity determined to be clinically significant by the ophthalmologist or optometrist during the ophthalmologic examination at the Screening Visit (if applicable).
7. Use of strong inhibitors or strong inducers of CYP3A, including consumption of certain herbal medications (e.g., St. John*s Wort) and certain fruit and fruit juices, within 14 days before Day 1 (the first dose of study drug).
8. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.6.5.

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 31-01-2017 |
| Enrollment: | 20 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |

| | |
|---|---|
| Brand name: | Orkambi |
| Generic name: | Lumacaftor/Ivacaftor |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 18-07-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 21-12-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 01-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 22-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 23-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 30-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 30-05-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 11-07-2017 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 03-08-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# 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 |
|---|---|
| Other | 2016-001585-29 |
| EudraCT | EUCTR2016-001585-29-NL |
| CCMO | NL57898.041.16 |

# Study results

| | |
|---|---|
| Date completed: | 04-10-2017 |
| Actual enrolment: | 20 |