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

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primary objective: To evaluate the long-term safety and tolerability of lumacaftor in combination with ivacaftor in subjects with cystic fibrosis (CF), homozygous or heterozygous for the F508del-cystic fibrosis transmembrane conductance regulator (…

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

Summary

ID

NL-OMON41659

Source
ToetsingOnline

Brief title
VX12-809-105

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: Vertex Pharmaceuticals

Intervention

Keyword: Combination Lumacaftor and Ivacaftor, CYstic Fibrosis, phase 3

Outcome measures

Primary outcome

Part A and Part B Treatment Cohorts:

Safety of long-term treatment of lumacaftor in combination with ivacaftor based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, and pulse oximetry

Part A Observational Cohort:

Not applicable.

Secondary outcome

Part A and Part B Treatment Cohorts

The following efficacy endpoints will be analyzed using baseline values in the previous study (i.e., Study VX12-809-103 [Study 103] or Study VX12-809-104 [Study 104] for Part A, and Cohort 4 of Study VX09-809-102 [Study 102] for Part B):

* Absolute change from baseline in percent predicted forced expiratory volume

in 1 second (FEV1)

* Relative change from baseline in percent predicted FEV1

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

* Number of pulmonary exacerbations starting from the previous study (Part A only)

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

* Absolute change in BMI z-score (Part A only)

* Absolute change from baseline in body weight

* Time-to-first pulmonary exacerbation including pulmonary exacerbations in the previous study (Part A only)

* Event of having at least 1 pulmonary exacerbation, including pulmonary exacerbations in the previous study (Part A only)

The following efficacy endpoints will be analyzed using baseline values in the current study (Study VX12-809-105 [Study 105]):

* Absolute change from baseline in percent predicted FEV1

* Relative change from baseline in percent predicted FEV1

* Absolute change from baseline in BMI

* Number of pulmonary exacerbations starting from the current study (Part A only)

* Absolute change from baseline in CFQ-R respiratory domain score

* Absolute change in BMI z-score (Part A only)

* Absolute change from baseline in body weight

* Time-to-first pulmonary exacerbation in the current study (Part A only)

* Event of having at least 1 pulmonary exacerbation in the current study (Part

A only)

The following efficacy endpoint will also be analyzed:

Rate of change in percent predicted FEV1

Part A Observational Cohort

Safety, as determined by serious adverse events (SAEs)

Study description

Background summary

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide1 and is the most common fatal genetic disease in persons of European descent.2 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 is caused by progressive loss of lung function.Cystic fibrosis is an autosomal recessive genetic disease caused by a defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR).

Study objective

primary objective:

To evaluate the long-term safety and tolerability of lumacaftor in combination with ivacaftor in subjects with cystic fibrosis (CF), homozygous or heterozygous for the F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation, who are in the Part A and Part B Treatment Cohorts

secondary objectives:

Part A

- To evaluate the long-term efficacy and durability of lumacaftor in combination with ivacaftor for subjects in the Part A Treatment Cohort
- To evaluate the post-treatment safety and tolerability of lumacaftor in combination with ivacaftor for subjects in the Part A Observational Cohort

Part B (patients in the Netherlands will not participate in this part)
To evaluate the long-term efficacy and durability of lumacaftor in combination with ivacaftor for subjects in the Part B Treatment Cohort

Study design

This is a Phase 3, parallel-group, multicenter, rollover study in subjects with CF who are homozygous or heterozygous for the F508del-CFTR mutation and who participated in Study 103, Study 104, or Cohort 4 of Study 102. Study 105 is designed to evaluate the safety and efficacy of long-term treatment of lumacaftor in combination with ivacaftor.

Study 105 consists of 2 parts (Part A and Part B), which will be enrolled in parallel. Part A will enroll subjects from Study 103 and Study 104. Part B will enroll subjects from Cohort 4 of Study 102.

Part A consists of a Part A Treatment Cohort and a Part A Observational Cohort, which will enroll subjects from Study 103 and Study 104. The Part A Treatment Cohort and the Part A Observational Cohort will be enrolled in parallel.

Part B (Subjects From Cohort 4 of Study 102) (patients in the Netherlands will not participate in this part)
Part B will consist of a Part B Treatment Cohort that will enroll subjects from Cohort 4 of Study 102.

Intervention

The Part A Treatment Cohort will be double-blind and will consist of 2 treatment arms:
- Treatment Arm 1: 600 mg lumacaftor once daily (qd) + 250 mg ivacaftor every 12 hours (q12h)
- Treatment Arm 2: 400 mg lumacaftor q12h + 250 mg ivacaftor q12h

Subjects who received lumacaftor in combination with ivacaftor in Study 103 or Study 104 will continue to receive the same dose and regimen of study drug in a double-blind fashion in Study 105 for 96 weeks as follows:
- Subjects who were randomized to Treatment Arm A in Study 103 or Study 104 are eligible for enrollment in Treatment Arm 1
- Subjects who were randomized to Treatment Arm B in Study 103 or Study 104 are eligible for enrollment in Treatment Arm 2
- Subjects who received placebo in Study 103 or Study 104 (Treatment Arm C in

Study 103 or Study 104) will be randomized (1:1) to 1 of the 2 double-blind treatment arms (Treatment Arm 1 or Treatment Arm 2)

Part A Observational Cohort
Subjects in the Part A 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 Study 103 or Study 104 to assess post-treatment safety of lumacaftor and ivacaftor combination therapy.

The Part B (not applicable in the Netherlands)Treatment Cohort will be open-label and will consist of 1 treatment arm:
- Treatment Arm 3: 400 mg lumacaftor q12h + 250 mg ivacaftor q12h
Subjects who received lumacaftor in combination with ivacaftor in Cohort 4 of Study 102 will be enrolled in Treatment Arm 3 and will continue to receive the same dose and regimen of study drug in Study 105 for 96 weeks as follows:
- Subjects who received active study drug in Cohort 4 of Study 102 are eligible for enrollment in Treatment Arm 3
- Subjects who received placebo in Cohort 4 of Study 102 are eligible for enrollment in Treatment Arm 3

Study burden and risks

Based on in vitro and clinical data to date, it is hypothesized that the combination of a CFTR corrector and potentiator, such as lumacaftor and ivacaftor, respectively, will optimally enhance ion transport of chloride in patients with CF, leading to meaningful improvements in lung function and other clinical outcomes. Clinical proof-of-concept demonstrating the potential for improvements in subjects with CF who are homozygous for the F508del CFTR mutation was achieved in Study 102. In Study 102, during the 28 day period of combination therapy, a significant increase in FEV1 was observed in the active treatment cohorts (600 mg qd or 400 mg q12h lumacaftor in combination with 250 mg ivacaftor q12h), while a decrease in FEV1 was observed in the placebo group. Study 105 will evaluate the long-term efficacy and safety of lumacaftor in combination with ivacaftor in CF subjects homozygous and heterozygous for the F508del-CFTR mutation.

Because lumacaftor in combination with the 250 mg q12h dose of ivacaftor is an investigational drug, there may be risks and side effects that are not yet known. The overall risk to subjects participating in this study will be minimized as much as possible. Key safety eligibility criteria, close safety monitoring of subjects, contraceptive requirements, and guidance for use of concomitant medications are included in the study protocol. In addition, all subjects will be required to complete safety follow-up visit(s) regardless of whether they complete study drug dosing.

Subjects participating in Study 105 may directly benefit from this study, although the potential benefits would not be expected to persist after the end

of the treatment period. The information gained from Study 105 will inform the development of lumacaftor in combination with ivacaftor, and demonstrate long-term efficacy and safety data to enable the submission of a marketing authorization application, which could provide an additional treatment option for patient with CF.

Based on data from nonclinical and clinical studies to date, and the potential for benefit to patients with CF from the development of this treatment, the overall risk-benefit balance for Study 105 is considered to be acceptable.

Contacts

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Scientific
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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 for this study.
1. Signed informed consent form (ICF), and where appropriate, signed assent form.
2. Subjects entering the Part A Treatment Cohort must meet both of the following criteria:
* Completed 24 weeks of study drug treatment in Study 103 or Study 104
* Subjects who had study drug interruptions, but completed study visits up to Week 24 of Study 103 or 104 are eligible. Subjects who are not taking study drug at the Week 24 Visit, including subjects that require study drug interruption to be either continued or initiated at Day 1 in Study 105, must have received Vertex approval for enrollment/randomization in the Part A Treatment Cohort.
* Elect to enroll in the Part A Treatment Cohort
Subjects entering the Part A Observational Cohort must meet the following criteria:
* Completed 24 weeks of study drug treatment in Study 103 or Study 104, but do not elect to enroll in the Part A Treatment Cohort
* Subjects who received at least 4 weeks of study drug and completed visits up to Week 24 Visit of Study 103 or 104 but are not taking study drug at the Week 24 Visit because of a drug interruption and did not receive Vertex approval for enrollment into the Part A Treatment Cohort (or elect not to enroll in the Part A Treatment Cohort).
* Subjects who permanently discontinued study drug after receiving at least 4 weeks of study drug and remained in the study from the time of discontinuation of study drug treatment through the Week 24 Visit in Study 103 or Study 104
Subjects entering the Part B Treatment Cohort must meet both of the following criteria:
* Completed 56 days of study drug treatment in Cohort 4 of Study 102
* Subjects who had study drug interruptions but completed study visits up to Day 56 are eligible. Subjects who are not taking study drug at the Day 56 Visit, including subjects that require study drug interruption to be either continued or initiated at Day 1 in Study 105,
must have received Vertex approval for enrollment/randomization in the Part B Treatment Cohort.
* Elect to enroll in the Part B Treatment Cohort
3. Willing to remain on a stable CF medication regimen through the end of study (Part A and Part B Treatment Cohorts only).
4. 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 Study 103, Study 104, and Cohort 4 of Study 102.

Exclusion criteria

Subjects who meet any of the following exclusion criteria will NOT be eligible for this study.
1. Any comorbidity or laboratory abnormality 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 (e.g., cirrhosis with portal hypertension).
2. Pregnant and nursing females. Females of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit (enrollment/randomization) and before recieving the first dose of study drug (Section 12.7.2).
3. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 12.7.7. of the protocol
4. History of drug intolerance in the prior study 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 any of the treatment arms include the following:
* Subjects with a history of allergy or hypersensitivity to the study drug
* Liver function test (LFT) abnormality during study drug treatment in the previous study (Study 103, Study 104, or Cohort 4 of Study 102) for which a clear cause was not identified.
* Other severe or life-threatening reactions to the study drug in the previous study
5. History of poor compliance with study drug and/or procedures in the previous study as deemed by the investigator.
6. Participation in an investigational drug trial (including studies investigating lumacaftor and/or ivacaftor. NOTE: participation in a noninterventional study (including observational studies and studies requiring blood collections without administration of study drug is permitted.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-03-2014
Enrollment:	28

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kalydeco
Generic name:	Ivacaftor
Product type:	Medicine
Brand name:	Lumacaftor
Generic name:	Lumacaftor

Ethics review

Approved WMO Date:	26-09-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2016
Application type:	Amendment

Review commission: METC Amsterdam UMC

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	EUCTR2013-000604-41-NL
ClinicalTrials.gov	NCT01931839
CCMO	NL45864.018.13