A Phase 2a, Two-part, Randomized, Double-blind, Placebo-controlled, Incomplete Block Crossover Study to Evaluate the Safety and Efficacy of VX-371 Solution for Inhalation With and Without Oral Ivacaftor in Subjects With Primary Ciliary Dyskinesia

Published: 28-07-2016
Last updated: 16-04-2024

Main objectivePart A: To evaluate the safety and efficacy of treatment with VX-371, administered with and without 4.2% hypertonic saline (HS) in subjects with primary ciliary dyskinesia (PCD) who are *12 years of age.Part B: To evaluate the safety...

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

Summary

ID

NL-OMON46905

Source
ToetsingOnline

Brief title
PS-G202

Condition

- Respiratory disorders congenital

Synonym
genetic condition of the cilia, Primary ciliary dyskinesia

Research involving
Human

Sponsors and support

Primary sponsor: Parion Sciences, Incorporated
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: ivacaftor, Primary Ciliary Dyskinesia, VX-371

Outcome measures

Primary outcome

Part A

* Results of safety and tolerability assessments of adverse events (AEs),

clinical laboratory values (urine, serum and plasma chemistry, and hematology),

12-lead electrocardiograms (ECGs), spirometry, vital signs, and pulse oximetry

* Absolute change in percent predicted FEV1, from study baseline after 28 days

of treatment

Part B

* Results of safety and tolerability assessments of AEs, clinical laboratory

values (urine, serum and plasma chemistry, and hematology), 12-lead ECGs,

spirometry, vital signs, and pulse oximetry

* Absolute change in ppFEV1 from study baseline and Part B baseline, after 28

days of treatment in Part B

Secondary outcome

Part A

Secondary Endpoint

* Change in QOL score as measured by the PCD Quality of Life Questionnaire (QOLPCD) and the St. George*s Respiratory Questionnaire (SGRQ) after 28 days of treatment

Other Endpoints

* Change in FEV1, FVC, FEF25%-75%, FEV1/FVC, percent predicted FVC, percent predicted FEV1/FVC, and percent predicted FEF25%-75% after 28 days of treatment
* Plasma and urine concentrations of VX-371 after 28 days of treatment

Exploratory Endpoint

* Change in sputum characteristics, which may include percent solids, inflammatory biomarkers, electrolytes, microbiology and drug concentration after 28 days of treatment

Part B:

Secondary Endpoint

* Change in QOL score as measured by the QOL-PCD and SGRQ from study baseline and Part B baseline, after 28 days of treatment in Part B

Other Endpoints

* Change in FEV1, FVC, FEF25%-75%, FEV1/FVC, ppFVC, percent predicted FEV1/FVC, and ppFEF25%-75%, from study baseline and Part B baseline, after 28 days of treatment in Part B
* Plasma and urine concentrations of VX-371

Exploratory Endpoint

* Change in sputum characteristics, which may include percent solids,

inflammatory biomarkers, electrolytes, microbiology, and drug concentration

from study baseline and Part B baseline, after 28 days of treatment in Part B

Study description

Background summary

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder characterized by various ciliary defects that result in loss of synchronous ciliary beating and ciliary propulsive function. In the ciliated airways of the lung, PCD is manifested by ineffective clearance of mucous secretions and inhaled particles, including bacteria.
Currently, there are no approved treatments for PCD and no completed, industry-sponsored, controlled clinical studies to evaluate treatments for PCD. Given the lack of demonstrated value of treatments, management of PCD patients is typically focused on clearance of airways along with prevention and treatment of airway infections. These therapies may include chest percussion, postural drainage, drugs to treat pulmonary symptoms and antibiotics (often oral). Given the importance of cough clearance in patients with PCD, the use of cough suppressants is avoided. It appears likely that the failure to clear mucus in PCD subjects reflects both the absence of cilial beat/force and the absence of normal regulation of mucus concentration.
Mucus hyperconcentration is predicted to limit the effectiveness of the 2 *backup* mechanisms for mucus clearance in PCD subjects, i.e., cough and gas-liquid pumping.
VX-371 (Parion Sciences P-1037) is a new chemical entity belonging to a family of
amiloride derivatives referred to as pyrazinoylguanidines. VX-371 is a novel ENaC inhibitor that inhibits transport of sodium through direct exofacial block of the ENaC.
It is hypothesized that the inhibition of ENaC activity with VX-371 will increase hydration of airway secretions rendering them more susceptible to cough clearance and gas-liquid pumping in subjects with PCD.

Study objective

Main objective
Part A: To evaluate the safety and efficacy of treatment with VX-371, administered with and without 4.2% hypertonic saline (HS) in subjects with

primary ciliary dyskinesia (PCD) who are *12 years of age.

Part B: To evaluate the safety and efficacy of treatment with ivacaftor and VX-371, administered with and without 4.2% HS in subjects with PCD who are *12 years of age.

Secondary objective
Part A: To evaluate the effect of VX-371, administered with and without 4.2% HS, on quality of life (QOL) in subjects with PCD who are *12 years of age.

Part B: To evaluate the effect of ivacaftor and VX-371 administered with and without 4.2% HS on QOL in subjects with PCD who are *12 years of age.

Study design

This is a Phase 2a, two-part, multicenter, randomized, double-blind, placebo-controlled, incomplete block crossover study in subjects *12 years of age with PCD.

Part A will comprise:
Treatment Period 1 -->*Washout --> Treatment Period 2

Part B will comprise:
Treatment Period 3

This study includes the following:
* Screening Period: Day of Screening Visit until Day 1 (first dose of study drug). The Screening Visit can occur Day - 38 to Day -5, relative to the first dose of study drug
* Treatment Period 1 through Treatment Period 2:
o Treatment Period 1: Day 1 (first dose of study drug) through Day 29 (28 days of treatment)
o Washout Period: Day 29 through Day 56
o Treatment Period 2: Day 57 through Day 85 (28 days of treatment)
o Optional treatment Period 3 (Part B): Day 85 through day 113 (28 days of treatment).
* Safety Follow-up Telephone Call: 28 days (+ 7 days) after the last dose of study drug

If the subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Telephone Call, approximately 28 days (+ 7 days) after their last dose of study drug.

Intervention

Treatment sequences:
Treatment sequence 1
Period 1: VX-371 in 4.2% HS
Period 2: 4.2% HS
Optional period 3: 4.2% HS + ivacaftor

Treatment sequence 2
Period 1: 2 4.2% HS
Period 2: VX-371 in 4.2% HS
Optional period 3: VX-371 in 4.2% HS + ivacaftor

Treatment sequence 3
Period 1: VX-371 in 0.17% saline (placebo)
Period 2: Placebo (0.17% saline)
Optional period 3: Placebo (0.17% saline) + ivacaftor

Treatment sequence 4
Period 1: Placebo (0.17% saline)
Period 2: VX-371 in 0.17% saline (placebo)
Optional period 3: VX-371 in 0.17% saline (placebo) + ivacaftor

Study burden and risks

In PCD, the lack of ATP release into the lumen of the airways due to dysfunctional cilia leaves ENaC uninhibited, resulting in hyperconcentration of mucus. Inhibition of ENaC by VX-371 is expected to restore hydration of the mucus in PCD patients, resulting in improved cough clearance and gas-liquid pumping of mucus. In vitro models have also shown that combining hypertonic saline (HS) with VX-371 further enhances the hydration of bronchial epithelial cells, potentially increasing the effectiveness of cough clearance and gas-liquid pumping beyond that which could be achieved with VX-371 alone. The present study is designed to evaluate the safety and efficacy of VX-371 administered with and without 4.2 % HS for 28 days to subjects with PCD who are 12 years of age and older.

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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 who meet all of the following inclusion criteria will be eligible.
1. Subject (or subject's legally appointed and authorized representative) will sign and date an informed consent form (ICF) and, where appropriate, assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions laboratory tests, contraceptive guidelines, and other study procedures.
3. Willing and able to use the nebulization device as directed by the instructions for use.
4. The subject must have evidence supportive of a PCD diagnosis, based on the following:
A. Subjects *12 to <18 years of age must meet 2 or more of the following PCD clinical criteria:
* Unexplained neonatal respiratory distress (at term birth) with need for respiratory support with CPAP and/or oxygen for >24 hours.
* Any organ laterality defect confirmed by historical chest imaging * situs inversustotalis, situs ambiguous, or heterotaxy.
* Daily, year-round wet or productive cough starting in first year of life or bronchiectasis on historical chest imaging.
* Daily, year-round nasal congestion starting in first year of life or pansinusitis on historical sinus imaging.
B. Subjects *18 years of age must have bronchiectasis on historical chest imaging.

C. All subjects must ALSO have documentation of at least 1 of the following historical tests:
* For patients with no laterality defect, nNO level, measured with a chemiluminescent NO analyzer, during plateau <77 nL/min on 2 occasions, at least 2 months apart, with CF excluded by sweat chloride or genetic testing.
* For patients with a laterality defect, nNO level, measured with a chemiluminescent NO analyzer, during plateau <77 nL/min on at least 1 occasion
* Diagnostic ciliary ultrastructural defect on transmission electron micrograph (TEM).
* 2 loss of function and/or known mutations in a single PCD-associated gene.
Prior to randomization, all subjects must have a confirmed diagnosis of PCD (including central review, as required) based on one of the following:
* 2 loss of function and/or known mutations in a single PCD-associated gene identified by the central genetic testing laboratory from the specimen obtained at the Screening Visit; previous genotype results cannot be used to determine eligibility for randomization.
* Diagnostic ciliary ultrastructural defect on transmission electron micrograph. A previously prepared TEM specimen will be reviewed centrally; a new specimen will not be obtained.
* Laterality defect that includes dextrocardia plus bronchiectasis in more than 1 lobe on historical chest imaging.
5. Subjects with ppFEV1 of *40 to <90 percentage points adjusted for age, sex, and height according to the Global Lung Function Initiative (GLI) predicted values at the Screening Visit, taken 4 hours or more after last dose of short-acting bronchodilators (*-agonists and/or anticholinergics)
6. Non-smoker for the past 90 days prior to the Screening Visit and less than a 5 pack-year lifetime history of smoking, and willing to not smoke while enrolled in the study.
7. Stable regimen of medications and chest physiotherapy for the 28 days prior to Day 1, and no anticipated need for changes during the study period (other than stopping inhaled HS).
8. If currently using daily inhaled HS, must be able to discontinue its use for the duration of the study.
9. If taking daily chronic or chronic cycling antibiotics, has been on a consistent regimen for at least 4 months prior to the Screening Visit. The cycling regimen of antibiotics can be either intermittent monotherapy (e.g., 28 days on/28 days off) or continuous alternating therapy (e.g., 28-day cycles of 2 alternating antibiotics).
10. Clinically stable (as deemed by the investigator) for at least 14 days prior to the Screening Visit with no evidence of significant new or acute respiratory exacerbations, excluding symptoms of allergic (perennial or seasonal) or non-allergic rhinitis.
11. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit. Females of childbearing potential must have a negative urine pregnancy test at the Day 1, Day 57 and Day 85 visits before receiving the first dose of study drug in each Treatment Period, respectively. Subjects of childbearing potential and who are sexually active must meet the contraception requirements outlined in Section 11.6.5.1.

Exclusion criteria

Subjects who meet any of the following exclusion criteria will not be eligible.
1. Diagnosis of CF, including at least 1 of the following:
a. Documented sweat chloride test *60 mM by quantitative pilocarpine iontophoresis

b. Abnormal nasal potential difference (NPD) test
c. 2 CF-causing mutations in the CFTR gene
2. Subjects with only 1 mutation in the CFTR gene and a sweat chloride test *60 mM by quantitative pilocarpine iontophoresis.
3. History of any organ transplantation or lung resection or chest wall surgery.
4. Significant congenital heart defects, other than a laterality defect, at the discretion of the investigator.
5. Diagnosis of Cri du chat syndrome (chromosome 5p deletion syndrome).
6. Inability to withhold short-acting bronchodilator use for 4 hours prior to clinic visit and long-acting bronchodilator use the night before the first and last clinic visit of each treatment period.
7. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This may include, but is not limited to history of clinically significant and uncontrolled adrenal, neurologic, gastrointestinal, renal, hepatic, cardiovascular (including hyper/hypotension and tachy/bradycardia), psychological, pulmonary (other than PCD), metabolic, endocrine, or hematological/coagulation disorder or disease, or scoliosis of such severity that it impacts pulmonary function or any other major disorder or disease, in the opinion of the investigator.
8. Use of diuretics (including amiloride) or renin-angiotensin antihypertensive drugs (e.g., spironolactone, angiotensin converting enzyme [ACE] and/or neural endopeptidase (NEP)-inhibitors, or angiotensin receptor blockers [ARBs]) or trimethoprim or drospirenone in the 28 days before Day 1 or anticipate need for these medications during the study.
9. Had symptoms of acute upper or lower respiratory tract infection or had an acute pulmonary exacerbation requiring treatment or was treated with systemic antibiotics for ear or sinus disease within 28 days before Day 1 (topical otic antibiotics allowed).
10. History of significant intolerance to inhaled HS, as determined by the investigator.
11. History of drug or alcohol abuse, in the opinion of the investigator.
12. Known hypersensitivity to any of the study drugs or amiloride.
13. Used ivacaftor within 28 days prior to Day 1 or anticipate need for ivacaftor during the study.
14. Pregnant and/or nursing females.
15. Any clinically significant laboratory abnormalities at the Screening Visit as judged by the investigator, or any of the following:
a. Plasma or serum potassium > upper limit of normal (ULN)
b. Abnormal renal function, defined as creatinine clearance rate <50 mL/min using the Bedside Schwartz equation (for subjects 12 to 17 years of age) or <50 mL/min using the Cockcroft-Gault equation (for subjects *18 years of age).
c. Abnormal liver function, defined as *3 × ULN for alanine aminotransferase (ALT), or aspartate aminotransferase (AST), or >2 x ULN for total bilirubin, unless accounted for by Gilbert's syndrome (benign indirect hyperbilirubinemia)
d. Hemoglobin concentration <10.0 g/dL
16. Unwilling or unable to follow the contraception guidelines as outlined in Section 11.6.5.1.
17. History of at least 2 sputum or throat swab cultures yielding B. cepacia complex or M. abscessus or M. avium within the previous 2 years.
18. Has had surgery within 3 months of Day 1 that required general anesthesia and hospitalization.

19. Has previously participated in an investigational study involving administration of any investigational compound or use of an investigational device within 28 days prior to the Screening Visit (Note: Participation in a past or concurrent observational study is acceptable).
20. Has any surgical or medical condition which in the judgment of the investigator might interfere with the absorption, distribution, metabolism, or excretion of the study drug or with safety evaluations.
21. Has any other condition or circumstances that, in the opinion of the investigator, should disqualify this subject for this study.
22. The subject or a close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved in the conduct of the study.;Additional Exclusion Criteria for Part B:
In addition to the exclusion criteria above, subjects who participate in Part B and meet any of the following exclusion criteria will not be eligible to continue into Part B.
1. Unable to swallow tablets.
2. Concomitant use of strong or moderate inhibitors or inducers of cytochrome P450 (CYP) 3A, including consumption of certain herbal medications (e.g., St. John's Wort), and grapefruit/grapefruit juice.
3. Known hypersensitivity to ivacaftor.

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):	25-04-2017
Enrollment:	15
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:	VX-371
Generic name:	VX-371

Ethics review

Approved WMO Date:	28-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-004917-26-NL
CCMO	NL57586.078.16