A Phase 3 Efficacy and Safety Study of Ataluren (PTC124 ®) in Patients with Nonsense Mutation Cystic Fibrosis

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To evaluate the ability of ataluren to improve pulmonary function relative to placeboTo determine the effect of ataluren on:1. Pulmonary symptoms2. General well-being3. Health-related Quality Life (HRQL)

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON44153

Source
ToetsingOnline

Brief title
PTC124-GD-021-CF

Condition

- Congenital and hereditary disorders NEC

Synonym
mucoviscidosis, sticky mucus disease

Research involving
Human

Sponsors and support

Primary sponsor: PTC Therapeutics, Inc.
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Ataluren, Cystic Fibrosis, PTC 124

Outcome measures

Primary outcome

Absolute change in %-predicted FEV1 at week 48, defined as the average between

the change at week 40 and that at week 48 (by spirometry).

Secondary outcome

1. Rate of pulmonary exacerbations (expanded Fuchs criteria)

2. Change from baseline in Body Mass Index (BMI)

3. Respiratory HRQL as assessed by the Cystic Fibrosis Questionnaire - Revised

(CFQ-R) respiratory domain

Study description

Background summary

There are no approved systemic therapies that address the underlying cause of CF caused by other mutations, such as premature
stop codons. New agents are therefore needed that can overcome the fundamental genetic defect
by restoring CFTR production and function.

Study objective

To evaluate the ability of ataluren to improve pulmonary function relative to placebo

To determine the effect of ataluren on:
1. Pulmonary symptoms

2. General well-being
3. Health-related Quality Life (HRQL)

Study design

It is planned that the study will enroll ~208 subjects (~184 fully evaluable) with nonsensemutation-
mediated CF who are *6 years of age and have an FEV1 *40% and *90% of predicted. Subjects will be stratified based on age, inhaled antibiotic use, and baseline FEV1, and will be
randomized in a 1:1 ratio to receive oral ataluren administered 3 times per day (TID) at respective
morning, midday, and evening doses of 10-, 10-, and 20-mg/kg or placebo. Based on the results of
a previously conducted study, patients treated with chronic inhaled aminoglycosides (including
TOBI) will not be eligible for participation [Rowe 2012]. Spirometry measurement at the
screening visit will establish patient eligibility for inclusion based on lung function. FEV1 stability
will be assessed during the approximately 4-week screening period at the conclusion of which
patients will be required to demonstrate a relative change in %-predicted FEV1 of less than 15%
when compared to the screening value. Assessments will be performed every ~8 weeks, depending
upon the outcome measure.
At the completion of blinded treatment, all compliant participants will be eligible to receive openlabel
ataluren in a separate extension study, at the same 10-, 10-, 20-mg/kg dose level.

Intervention

Dosing of study drug will be based on milligrams of drug per kilogram of subject body weight at randomization and will be calculated to allow for dosing with 1 or 2 of the 3 available sachet dose strengths (125- or 250- or 1000-mg of active drug or matching placebo).

Study burden and risks

In previous studies with ataluren adults and children with CF, the common symptoms included:
* In at least 20% of subjects: pulmonary exacerbation, cough
* Between 10% and 20% of subjects: viral upper respiratory tract infection, headache, fever (pyrexia), abdominal pain, sinusitis, vomiting, diarrhea

* In 5% to 10% of subjects: runny nose (rhinitis), productive cough, coughing blood (hemoptysis), nausea, upper abdominal pain, fatigue, common cold (nasopharyngitis), abnormal loss of weight, back pain, constipation, crackling in lungs (rales).

Contacts

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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)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

indicating that the subject (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial.
2. Age *6 years.

3. Body weight *16 kg.
4. Sweat chloride >60 mEq/L.
5. Documentation of the presence of a nonsense mutation in at least 1 allele of the CFTR gene, as determined by genotyping performed at a laboratory certified by the College of American Pathologists (CAP), or under the Clinical Laboratory Improvement Act/Amendment (CLIA), or by an equivalent organization.
6. Verification that a blood sample has been drawn for sequencing of the CFTR gene.
7. Ability to perform a valid, reproducible spirometry test using the study-specific spirometer with demonstration of an FEV1 *40% and * 90% of predicted for age, gender, and height.
8. Demonstration at Visit 2 of a valid %-predicted FEV1 within 15% of the Screening %-predicted FEV1 value.
9. Resting oxygen saturation (as measured by pulse oximetry) *92% on room air.
10. Confirmed screening laboratory values within the central laboratory ranges specified in Table 2 of the protocol.
11. In subjects who are sexually active, willingness to abstain from sexual intercourse or employ a barrier or medical method of contraception during the study drug administration and 60-day follow-up period.
12. Willingness and ability to comply with all study procedures and assessments, including scheduled visits, drug administration plan, study procedures, laboratory tests, and study restrictions.

Exclusion criteria

1. Known hypersensitivity to any of the ingredients or excipients of the study drug (polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, colloidal silica, or magnesium stearate).
2. Previous participation in the Phase 3 trial of ataluren (PTC124-GD-009-CF).
3. Any change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation, or re-initiation) in a chronic treatment/prophylaxis regimen for CF or for CF-related conditions within 4 weeks prior to screening or any change in acute therapy between screening and randomization.
4. Chronic use of inhaled or systemic tobramycin within 4 weeks to screening.
5. Exposure to another investigational drug within 4 weeks prior to screening.
6. Ongoing participation in any other therapeutic clinical trial.
7. Evidence of pulmonary exacerbation or acute upper or lower respiratory tract infection (including viral illnesses) within 3 weeks prior

to screening, or between screening and randomization.
8. Treatment with intravenous antibiotics within 3 weeks prior to screening.
9. Ongoing immunosuppressive therapy (other than corticosteroids).
10. Ongoing warfarin, phenytoin, or tolbutamide therapy.
11. History of solid organ or hematological transplantation.
12. Major complications of lung disease (including massive hemoptysis, pneumothorax, or pleural effusion) within 8 weeks prior to screening.
13. Known portal hypertension.
14. Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test.
15. Pregnancy or breast-feeding.
16. Current smoker or a smoking history of *10 pack-years (number of cigarette packs/day × number of years smoked).
17. Prior or ongoing medical condition (eg, concomitant illness, alcoholism, drug abuse, psychiatric condition), medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.

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:	Recruitment stopped
Start date (anticipated):	29-06-2015
Enrollment:	19
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PTC124
Generic name:	Ataluren

Ethics review

Approved WMO Date:	06-08-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-02-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-03-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2013-004581-34-NL
CCMO	NL49005.091.14