Treatment of Chronic Idiopathic Cough (CIC) and Chronic Cough in patients with Idiopathic Pulmonary Fibrosis (IPF) with PA101.

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The objectives of the study are as follows:*1. To assess the effectiveness of inhaled PA101 delivered via eFlow high efficiency nebulizer for treating chronic cough. Improvements in chronic cough will be assessed by measuring the change from...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Therapeutic and nontherapeutic effects (excl toxicity)
Study type	Interventional

Summary

ID

NL-OMON42283

Source
ToetsingOnline

Brief title
Protocol PA101-CC-02

Condition

- Therapeutic and nontherapeutic effects (excl toxicity)
- Upper respiratory tract disorders (excl infections)
- Lifestyle issues

Synonym
chronic cough, idiopathic pulmonary fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: PATARA PHARMA LLC
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Chronic Chough, Chronic Idiopathic Cough (CIC), Idiopathic Pulmonary Fibrosis (IPF)

Outcome measures

Primary outcome

To assess the effectiveness of inhaled PA101 delivered via eFlow® high efficiency nebulizer for treating chronic cough. Improvements in chronic cough will be assessed by measuring the change from baseline in the 24-hour objective cough count as measured by Leicester Cough Monitor (LCM).17 Other assessments will include changes in the quality of life score as measured by the Leicester Cough Questionnaire (LCQ)18 and King*s Brief Interstitial Lung Disease Questionnaire (K-BILD),19 changes in cough severity as measured by Visual Analog Scale (VAS),20 changes in pulmonary function tests (PFTs), and changes in fractional exhaled nitric oxide (FeNO) using Niox Vero®.

Secondary outcome

*To evaluate the safety and tolerability of PA101 in patients with chronic cough.

Study description

Background summary

Cough is the most common complaint for which patients seek medical attention and is the second most common reason for a general medical examination. Upper

respiratory tract infection (URTI) or the common cold is by far the most common cause of cough, but post-infectious cough, unexplained chronic cough, and cough due to pulmonary disorders such as asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and lung cancer are also common. Cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older is considered to be chronic by the American College of Chest Physicians (ACCP).

Cough results from activation of myelinated cough receptors and unmyelinated C-fibers, whose cell bodies are in the jugular and nodose ganglia. Extensive C-fiber endings are found under the airway epithelium while cough receptors endings terminate in the mucosa between the epithelium and smooth muscle. Mast cells play an important role in cough. Degranulated mast cells release mediators that activate C-fibers, causing release of Substance P, histamine, serotonin, and proteases. Substance P release results in inflammation, vasodilatation, and sensitization of nerves. In patients diagnosed with chronic nonproductive cough, bronchoalveolar lavage (BAL) showed increased numbers of inflammatory cells and airway inflammation when compared to controls. Elevated levels of mast cells were found in BAL samples in patients with chronic cough.

Identifying the underlying etiology is the most important step in the successful management of chronic cough. If, however, no cause can be identified, or if treatment of the underlying etiology fails to resolve the cough, then the cough may be treated symptomatically. In the majority of cases, symptomatic treatment consists of antitussive therapy to decrease cough frequency and severity. Antitussive treatments vary in mechanism of action. Nonspecific antitussives such as dextromethorphan and codeine appear to act in the brain stem to reduce the cough reflex. Other nonspecific antitussives, such as benzonatate, act to anesthetize respiratory passages and thus reduce the stimulus to cough. Other agents aim to decrease the volume of respiratory tract secretions and thus the need to cough. These latter antitussive agents are also used to treat certain common underlying etiologies and include antihistamines, corticosteroids, antibiotics, decongestants, and mast cell stabilizers.

Cromolyn sodium with its well-established safety profile is expected to play a therapeutic role in the treatment of chronic cough through its pleiotropic activity including direct inhibitory effect on sensory C fibers and indirect effects on mast cells mediated activity. Cromolyn sodium decreases the response to antigen challenge with a reduction in mast cell degranulation; inhibits the release of mediators such as histamine and leukotrienes (SRS-A) from the mast cells; inhibits the early and late phase airway reactions after allergen challenge; inhibits leukotriene D4-induced bronchoconstriction response; inhibits tachykinine release; attenuates human neutrophils, eosinophils and monocytes; and calcium antagonist effect. Studies also demonstrated that cromolyn sodium blocks the activation and subsequent mediator release from other inflammatory cells, including eosinophils, neutrophils, monocytes, macrophages, and lymphocytes.

Patara Pharma is developing a new inhalation formulation of cromolyn sodium (PA101) delivered via the eFlow® high efficiency nebulizer system. PA101 is a

novel inhalation solution formulation of cromolyn sodium having osmolality and pH adjusted to a physiologically well tolerable range. PA101 is preservative-free, room temperature-stable formulation optimized for improved tolerability via oral inhalation and long-term chemical stability. The eFlow nebulizer is a portable, handheld, silent, high- efficiency nebulizer with rapid delivery that can deliver a dose in less than 3 minutes. Delivering PA101 with the eFlow nebulizer system achieves higher lung deposition and systemic levels of cromolyn sodium relative to currently marketed formulations of cromolyn sodium.
PA101 via eFlow® is being investigated as a first-line maintenance therapy for the treatment of chronic cough related to chronic idiopathic cough, idiopathic pulmonary fibrosis, and lung cancer recalcitrant to currently available therapies.

Study objective

The objectives of the study are as follows:
*
1. To assess the effectiveness of inhaled PA101 delivered via eFlow high efficiency nebulizer for treating chronic cough. Improvements in chronic cough will be assessed by measuring the change from baseline in average daytime cough count as measured by Leicester Cough Monitor (LCM). Other assessments will include changes in the quality of life score as measured by the Leicester Cough Questionnaire (LCQ) and King*s Brief Interstitial Lung Disease Questionnaire (K-BILD), changes in cough severity as measured by Visual Analog Scale (VAS), changes in pulmonary function tests (PFTs), and fractional exhaled nitric oxide (FeNO) as measured by Niox Vero.
*
2. To evaluate the safety and tolerability of PA101 in patients with chronic cough.

Study design

This is a randomized, double-blind, placebo-controlled, 2-period crossover, 2-cohort, multi- center, Phase 2 study in 48 patients with chronic cough: 24 patients with idiopathic pulmonary fibrosis (IPF, Cohort 1) and 24 patients with chronic idiopathic cough (CIC, Cohort 2).

The study will consist of two treatment periods of 14 days each separated by a Washout Period of 14 days (±2 days) between Period 1 and Period 2. A Screening Visit will be conducted within 14 days before the Baseline Visit of Period 1.
The two periods will be identical except that in Period 2, patients will crossover to the alternate treatment from that received in Period 1, according to a 1:1 randomization scheme.

Each treatment period will comprise of a Baseline Visit (Visit 1: Day -1)

followed by 14 days of treatment. During the 14 days of treatment, patients will return to the clinic 4 times (Visit 2: Day 1, Visit 3: Day 7, Visit 4: Day 14 and Visit 5: Day 15) for completion of study assessments. Visits 3, 4 and 5 have a visit window of +/- 1 day. A member of the research team may be able to conduct Baseline visit (Visit 1, Day -1) and Day 14 (Visit 4) at the patient*s home; this option will be dependent on the Hospital*s policy, staff resource and at the discretion of the investigator. Assessments performed at each visit are listed below:

SCREENING VISIT (SV)
Patients will attend a SV where they will discuss the study with a member of the research team. Patients will be required to provide written informed consent if they wish to participate in the study. Patients who provide informed consent will then undergo screening procedures to determine their eligibility for participation in the study.

Screening procedures will include: medical history, physical examination (including BMI calculation), blood and urine sample for clinical safety laboratory testing, urine pregnancy test (for females), alcohol and drugs of abuse screening, vital signs (blood pressure and heart rate), ECG, cough severity by Visual Acuity Scale (VAS), cough recording and concomitant medication review. A lung function test will also be carried out at the Screening Visit if one has not been done within the last month.

Eligible patients will participate in two treatment periods separated by a washout period of 14 days. The two treatment periods will be identical except that in Period 2 patients will crossover to the alternate treatment from that received in Period 1, according to the randomization scheme.
Each treatment period will comprise of a Baseline Visit (Visit 1: Day -1) followed by 14 days of treatment. During the 14 days of treatment, patients will return to the clinic 4 times (Visit 2: Day 1, Visit 3: Day 7, Visit 4: Day 14 and Visit 5: Day 15) for completion of study assessments. Visits 3, 4 and 5 have a visit window of +/- 1 day. Assessments performed at each visit are listed below:

BASELINE VISIT (VISIT 1: DAY -1)
The day after the SV or completion of the washout period, patients will have a 24 hour cough monitor fitted to provide a baseline measurement of coughing.
VISIT 2: Day 1
Removal of the 24 hour cough monitor, medical history and eligibility review, concomitant medication review, adverse event review, vital signs, ECG, nebuliser training, cough severity and quality of life assessments (VAS and, Leicester Cough Questionnaire [LCQ])and assessment of fractional exhaled nitric oxide (FeNO) using Niox Vero®.
Blood and urine samples for clinical safety laboratory tests will be collected at this visit for treatment period 2 only.
Additionally, for patients in the IPF cohort, pulmonary function tests

(PFT)(spirometry) and the King's Brief Interstitial Lung Disease [K-BILD] questionnaire will be carried out.
At this visit in the first treatment period, the patient will be randomised to a treatment sequence. In both treatment periods the study drug will be dispensed to the patient to be taken at home, three times daily.
Vital signs and ECG will be carried out pre-dose and 30 minutes after the morning dose of the study medication is taken in the clinic. For IPF patients, PFTs will be carried out pre-dose at this visit.
VISIT 3: Day 7
The following assessments will be carried out: vital signs, ECG, VAS, LCQ, K-BILD (IPF cohort only), FeNO, concomitant and adverse event (AE) review and the 24 hour cough monitor will be fitted.
Vital signs and ECG will be carried out pre-dose and 30 minutes after the morning dose of the study medication is taken in the clinic.
VISIT 4: Day 14
24 hour cough monitor fitted and AEs reviewed. VISIT 5: Day 15
The following assessments will be carried out: blood and urine samples for clinical safety laboratory tests (treatment period 2 only), vital signs, ECG, VAS, LCQ, K-BILD (IPF cohort only), spirometry (IPF cohort only), FeNO, removal of 24 cough monitor, concomitant medication and AE review.
Vital signs and ECG will be carried out 30 minutes after the morning dose of the study medication is taken in the clinic. PFTs for patients in the IPF cohort will be completed 60 minutes post dose.
SAFETY FOLLOW UP
The safety follow up call will be carried out 7 days (+/- 2 days) after the last treatment. In this phone call, AEs will be reviewed.

Intervention

There will be two treatment periods of 14 days each, separated by 14 days without treatment. The two treatment periods will be the same, except that in Treatment Period 2, patients will crossover to the alternative treatment from that received in Treatment Period 1 (according to a 1:1 randomization schedule).

During each treatment period, patients will self administer the study drug (40 mg PA101 or placebo PA101 via an eFlow nebuliser), three times daily (i.e., 8:00am +/- 1 hour, 2:00pm +/- 1 hour and 8:00pm +/- 1 hour) for 14 consecutive days of each treatment period.

Study burden and risks

DISCOMFORT
Participants may be required to undergo procedures for this study which they ordinarily would not be subjected to, some of which the participant may find uncomfortable.
ADVERSE EVENTS

The main ethical issues posed by this study are the potential for adverse events. The full adverse event profile of the study drug has been fully explained in the Patient Information Sheet and participants will have the opportunity to discuss these with the study doctor at any time. The dose of study medication intended to be administered in this study are of a reasonable level and as such the adverse event profile should be well managed.
Sites will take every precaution to ensure the safety of study participants. Participants/carers will be provided with a contact telephone number for the site to use both during normal hours and out of hours.
IDENTIFICATION OF PREVIOUSLY UNKNOWN HEALTH PROBLEMS
There is always the possibility that tests conducted as part of the trial will identify an unknown health problem or possibility of a health problem in the participants (for example, abnormal blood laboratory results). All participants will be asked to consent to their GP being informed of their participation in the study. If any test result conducted as part of the trial is abnormal and a cause for concern, the participant and their GP will be informed. The participant will be referred to their GP for further advice.
INCONVENIENCE
Participants will attend the clinic more frequently than is required for normal routine care. The expectations and requirements of this trial are clearly indicated in the Patient Information Sheet to allow participants/carers to consider the commitment needed before they enter the trial. Should the frequency of visits or assessments conducted become too much for the participant, they are free to withdraw from the study at any time.
This study was designed according to ICH/GCP and with due thought given to potential ethical dilemmas. It is not anticipated that any significant ethical issues will now arise.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

COHORT 1: IDIOPATHIC PULMONARY FIBROSIS (IPF, Cohort 1);1. Male or female patients age 40 through 79 years, inclusive
2. Diagnosis of Idiopathic Pulmonary Fibrosis with the consensus of the multidisciplinary team based on the presence of definitive or possible usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) and after excluding alternative diagnoses, including lung diseases associated with environmental and occupational exposure, with connective tissue diseases and with drugs
3. Chronic cough present for at least 8 weeks and not responsive to current therapies
4. Daytime cough severity score on visual analogue scale > 40 mm at the Screening Visit
5. Daytime average cough count of at least 15 coughs per hour using objective cough count monitor at the Screening Visit
6. Transfer capacity for carbon monoxide corrected for hemoglobin (TLCOc) > 25% predicted value within 12 months of the Screening Visit and Forced Vital Capacity (FVC) > 50% predicted value within 1 month of the Screening Visit
7. Willingness and ability to provide written informed consent;COHORT 2: CHRONIC IDIOPATHIC COUGH (CIC, Cohort 2);1. Male or female patients age 18 through 75 years, inclusive
2. Chronic cough that has been present for at least 8 weeks
3. Diagnosis of chronic idiopathic cough (CIC) that is unresponsive to targeted treatment for identified underlying triggers (i.e., post-nasal drip, asthmatic/non-asthmatic eosinophilic bronchitis, and gastro-esophageal reflux disease)
4. Cough score on visual analogue scale of > 40 mm at the Screening Visit
5. Daytime average cough count of at least 15 coughs per hour using objective cough count monitor at the Screening Visit
6. Willingness and ability to provide written informed consent

Exclusion criteria

COHORT 1: IDIOPATHIC PULMONARY FIBROSIS (IPF, Cohort 1);1. Current or recent history of clinically significant medical condition, laboratory abnormality, or illness that could put the patient at risk or compromise the quality of the study data as determined by the investigator
2. Significant coronary artery disease (i.e., myocardial infarction within 6 months or unstable angina within 1 month of the Screening Visit)
3. An upper or lower respiratory tract infection within 4 weeks of the Screening Visit
4. Acute exacerbation of IPF within 3 months of the Screening Visit
5. Long-term daily oxygen therapy (> 10 hours/day)
6. Presence of pulmonary arterial hypertension with limitation of activity
7. History of malignancy of any organ system, treated or untreated within the past 5 years, with the exception of localized basal cell carcinoma or cervix carcinoma in situ
8. Current or recent history (previous 12 months) of excessive use or abuse of alcohol
9. Current or recent history (previous 12 months) of abusing legal drugs or use of illegal drugs or substances
10. Participation in any other investigational drug study within 4 weeks prior to the Screening Visit
11. Use of the following drugs within 2 weeks of the Screening Visit: Prednisone, narcotic antitussives, baclofen, gabapentin, inhaled corticosteroids, benzonatate, dextromethorphan, carbetapentane, H1 antihistamines, leukotriene modifiers, and cromolyn sodium
12. Females who are pregnant or breastfeeding, or if of child-bearing potential unwilling to practice acceptable means of birth control or abstinence during the study (e.g., abstinence, combination barrier and spermicide, or hormonal)
13. History of hypersensitivity or intolerance to cromolyn sodium;COHORT 2: CHRONIC IDIOPATHIC COUGH (CIC, Cohort 2);1. Current or recent history of clinically significant medical condition, laboratory abnormality, or illness that could put the patient at risk or compromise the quality of the study data as determined by the investigator
2. An upper or lower respiratory tract infection within 4 weeks of the Screening Visit
3. History of malignancy of any organ system, treated or untreated within the past 5 years, with the exception of localized basal cell carcinoma or cervix carcinoma in situ
4. Current or recent history (previous 12 months) of excessive use or abuse of alcohol
5. Current or recent history (previous 12 months) of abusing legal drugs or use of illegal drugs or substances
6. Participation in any other investigational drug study within 4 weeks prior to the Screening Visit
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9. History of hypersensitivity or intolerance to cromolyn sodium

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):	06-02-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cromolyn sodium
Generic name:	disodium cromoglycate [DSCG]
Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo

Ethics review

Approved WMO

Date:	11-12-2014
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO

Date:	06-02-2015
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2014-004025-40-NL
CCMO	NL51278.075.14