A Randomized, Double Blind, Multi Center, Parallel Group Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52 Week Treatment Period in Subjects With Moderate to Very Severe COPD

Published: 09-09-2015
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Primary Objective:* To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on the rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbationsSecondary Objectives:* To assess the effect of BGF MDI relative to GFF…

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

Summary

ID

NL-OMON47721

Source
ToetsingOnline

Brief title
PT010005 study in patients with moderate to very severe COPD

Condition

- Respiratory disorders NEC

Synonym
chronic lung disease, Chronic Obstructive Pulmonary Disease

Research involving
Human

Sponsors and support

Primary sponsor: Pearl Therapeutics, Inc
Source(s) of monetary or material Support: Pearl Therapeutics Inc

Intervention

Keyword: COPD, phase 3, PT010005

Outcome measures

Primary outcome

Rate of moderate or severe COPD exacerbations

Secondary outcome

Secondary endpoints that differ between approaches (US vs. ex-US) are indicated

in parentheses. Endpoints which are not considered

secondary for either regulatory approach have been included under other

efficacy endpoints.

- Time to first moderate or severe COPD exacerbation

- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks

- Transition Dyspnea Index (TDI) focal score over 24 weeks (ex-United States

[US] [ex-US]

- Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool

(EXACT) total score over 52 weeks (ex-US)

- Change from baseline in St. George*s Respiratory Questionnaire (SGRQ) total

score over 24 weeks (ex-US)

- Percentage of subjects achieving an minimal clinically important difference

(MCID) of 4 units or more in SGRQ total score at week 24 (US)

- Time to death (all cause)

-Rate of severe COPD exacerbations

Safety Endpoints:

* Adverse events (AEs)

* 12-lead electrocardiograms (ECGs)

* Clinical laboratory testing

* Vital sign measurements

PFT Sub-study Endpoints:

The primary PFT endpoints are:

* Change from baseline in morning pre-dose trough FEV1 at Week 24 (US) and over 24 weeks (ex-US) for the comparison of BGF MDI to GFF MDI

* FEV1 area under the curve from 0 to 4 hours (AUC0-4) at Week 24 (US) and over 24 weeks (ex-US) for the comparison of BGF MDI to BFF MDI

Other PFT endpoints include:

* Change from baseline in morning pre-dose trough FEV1 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit

* FEV1 AUC0-4 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit where measured

* Peak change from baseline in FEV1 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit where measured

* Change from baseline in morning pre-dose trough, AUC0-4, and peak change from

baseline in forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% and 75% of FVC (FEF25-75) over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit where measured

* Rate of decline in pre-dose FEV1 over 52 weeks

* Rate of decline in FEV1 AUC0-4 over 52 weeks

* Time to onset of action on Day 1

24-Hour Holter Monitoring Sub-study Endpoints (Assessed at Week 16)

Primary Endpoint:

* Change from baseline in mean heart rate averaged over 24 hours

Secondary Endpoints:

* Change from baseline in mean night-time (22:00 to 06:00) and day-time (06:00 to 22:00) heart rate

* Change from baseline in the maximum 24-hour heart rate

* Change from baseline in the minimum 24-hour heart rate

* Change from baseline in the frequency of isolated ventricular ectopic events (including a single premature ventricular contraction [PVC])

* Change from baseline in the frequency of ventricular couplets (defined as two PVCs preceded or followed by regular beats)

* Change from baseline in the frequency of ventricular runs (defined as three or more PVCs preceded or followed by regular beats)

* Incidence of sustained ventricular tachycardia (defined as PVCs lasting >30 seconds)

* Change from baseline in the frequency of isolated supraventricular ectopic

events

* Change from baseline in the frequency of supraventricular couplets

* Change from baseline in the frequency of supraventricular runs

* Incidence of atrial fibrillation with rapid ventricular response (>100 beats

per minute [bpm])

*Change from baseline in the frequency of supraventricular ectopic beats

*Incidence of withdrawal criteria being met during 24-hour Holter monitoring

Study description

Background summary

BGF MDI is a novel, fixed-dose, triple combination MDI product formulated with budesonide, glycopyrronium, and formoterol fumarate for use in subjects with COPD. As described in the GOLD COPD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life, and may further reduce exacerbations. For patients categorized in Group D (those with severe or very severe disease, many symptoms, and high risk of exacerbations), the first choice of treatment is an ICS/LABA or LAMA, with some evidence for a further reduction in exacerbations with triple therapy; however, further studies of triple therapy are needed [GOLD, 2014]. Pearl is conducting this study to evaluate the treatment effect of BGF MDI (LABA/ICS/LAMA therapy) relative to GFF MDI (LAMA/LABA therapy) and BFF MDI (ICS/LABA therapy) on the rate of moderate or severe COPD exacerbations over a 52-week treatment period in subjects with moderate to very severe COPD who have a history of COPD exacerbations.

Study objective

Primary Objective:
* To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on the rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations

Secondary Objectives:
* To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on symptoms of COPD

* To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on quality of life
* To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on all-cause mortality
* To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on COPD exacerbations

Safety Objective:
* To assess the safety of BGF MDI relative to GFF MDI and BFF MDI

The objectives for the sub-studies are:
4 Hour Pulmonary Function Test (PFT) Sub-study Objective:
* To assess the effects of BGF MDI relative to GFF MDI and BFF MDI on lung function
24-Hour Holter Monitoring Sub-study Objective:
* To evaluate the cardiovascular safety of BGF MDI relative to GFF MDI and BFF MDI as evaluated by 24-hour Holter monitoring
Health Care Resource Utilization (HCRU) Objective:
* To assess overall and COPD-specific Healthcare Resource Utilization of BGF MDI GFF MDI, and BFF MDI

Study design

This is a randomized, double-blind, multi-center, parallel group study to assess the efficacy and safety of BGF MDI 320/14.4/9.6 *g and BGF MDI 160/14.4/9.6 *g relative to GFF MDI 14.4/9.6 *g and BFF MDI 320/9.6 *g over a 52-week treatment period in approximately 8,400 subjects with moderate to very severe COPD with an increased risk of experiencing a COPD exacerbation and that remain symptomatic on the COPD Assessment Test (CAT * 10) on two or more inhaled maintenance treatments.

To be considered eligible for the study, subjects must have documented history of COPD exacerbations; subjects with a post-bronchodilator FEV1 < 50% of predicted normal must have * 1 moderate or severe COPD exacerbation in the previous 12 months. To be considered eligible for the study, subjects must have documented history of COPD exacerbations; subjects with a post-bronchodilator FEV1 * 50% of predicted normal must have * 2 moderate exacerbations or * 1 severe COPD exacerbation in the previous 12 months. In addition, post-bronchodilator FEV1 for these subjects during screening should be * 25% and * 65% of the predicted normal value calculated using appropriate reference equations.

Subjects will undergo a Screening Period of 1 to 4 weeks in duration. During the screening period subjects that are receiving an ICS/LABA will discontinue the ICS/LABA, but will continue the ICS component for the remainder of the screening period. Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for

the remainder of the screening period. All subjects will receive open-label Atrovent® hydrofluoroalkane (HFA; ipratropium bromide inhalation aerosol) administered QID for maintenance during Screening. Ventolin® HFA (albuterol sulfate inhalation aerosol) will be provided for rescue use throughout the study.

In order to allow for adequate washout of previous maintenance medications, subjects will undergo a Washout Period of at least 1 week (at least 2 weeks if taking Spiriva), but not greater than 26 days in duration prior to returning to the clinic for Visit 2. In instances where an exacerbation has occurred during the Screening Period, the Screening Period may be extended to a maximum of 10 weeks (to account for a course of oral corticosteroids of up to 2 weeks in duration and a 4-week period after treatment of the exacerbation).
Subjects who successfully complete the Screening Period will then be randomized in a 1:1:1:1 scheme to BGF MDI 320/14.4/9.6 *g BID, BGF MDI 160/14.4/9.6 *g BID, BFF MDI 320/9.6 *g BID, or GFF MDI 14.4/9.6 *g BID, respectively. Approximately 2,100 subjects will be randomized to each treatment arm. Randomization will be stratified by exacerbation history (1 or *2 moderate or severe exacerbations), post-bronchodilator FEV1 (25% to <50% predicted or 50% to 65% predicted), blood eosinophil count <150 cells per mm3 or *150 cells per mm3), and country. Enrollment will be targeted to achieve a 1:2 ratio for the blood eosinophil strata with twice as many randomized subjects in the *150 cells per mm3 category. Following randomization, subjects will enter the Treatment Period and undergo 10 additional treatment visits over 52 weeks.

Subjects who discontinue study treatment prior to Week 52 (Visit 14) will be encouraged to remain in the study to complete all remaining study visits during the 52 week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete a Treatment Discontinuation/Withdrawal Visit (refer to Table 8, and Sections 8.9 and 8.10) prior to transitioning back to regularly scheduled study visits. Subjects participating in the Holter-monitoring sub-study who discontinue from treatment will only complete regularly scheduled visits and not complete any remaining Holter sub-study assessments, however subjects participating in the PFT sub-study will continue with serial PFTs only.

Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigators discretion. For subjects recorded as Treatment Discontinuations that do not complete at least one post-treatment data collection, a telephone follow-up call is required at least 14 days after last study drug dose. These subjects will be followed for vital status at 52 weeks post randomization in accordance with the informed consent.
If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to Sections 8.9 and 8.10). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion.

A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing, a follow-up TC will not be required. These subjects will be followed for vital status at 52 weeks post randomization in accordance with the informed consent.

2 sub studies are included in the protocol:
1) 4-Hour Pulmonary Function Test Sub-study: Serial PFTs will be conducted over 4 hours in a subset of approximately 3,060 subjects (765 subjects per treatment group) at selected visits throughout the 52-week Treatment Period.
2) 24-Hour Holter Monitoring Sub-study: Holter Monitoring will be conducted over 24 hours in a subset of approximately 800 randomized (200 subjects from each treatment group) at Visit 3 (Holter Monitoring Baseline) and Visit 8 (Week 16).

Intervention

Subjects who successfully complete the Screening Period will then be randomized in a 1:1:1:1 scheme to BGF MDI 320/14.4/9.6 *g BID, BGF MDI 160/14.4/9.6 *g BID, BFF MDI 320/9.6 *g BID, or GFF MDI 14.4/9.6 *g BID, respectively. Approximately 2,100 subjects will be randomized to each treatment arm. Please also refer to table 6-1 on page 71 of the protocol

It is planned that each subject will receive study treatment for 52 weeks.

Study burden and risks

Participation in this study will last approximately 60 weeks and include approximately 6 visits to the study site (not including the 3 screening visits) and 6 telephone calls with the study site staff. The study visits will take approximately 2 * 3 hours each. the patient will also receive a telephone follow-up call from the study site 14 days after last dose of study drug.

The following procedures will be done during the different visits:

2x Reversibility testing, 1x medical history and demographics, 9x smoking status check, 1x chest imaging (if not done within 6 months of V1), 2x COPD assessment test (CAT), during all visits concomitant medication use is discussed as well as adverse events, 3x spirometry, 2x physical examination, 9x vital signs, 5x 12-lead ECG, 7x serum pregnancy test for female of childbearing potential, 5x blood drawn, 4x training on inhalation device and dose indicator, 1x ediary training and 8x ediary review, 1x vital status check. Different questionnaires will be completed:

6x BDI/TDI (baseline dyspnea index/transition dyspnea index)

6x SGRQ (St. George's respiratory questionnaire)
6x EQ-5D-5L (EuroQol 5 dimensions questionnaire)
11x HCRU (Health care resource utilization)

The most common side effects of the 3 IMPs used in this study are as follows:
BGF MDI: no very common side effects observed. Common side effects observed were:feeling of fast heart beat (palpitations), nausea, yeast infection of mouth (oral candidiasis), abnormal contraction of muscle (muscle spasms), hoarseness (dysphonia), cough.
BFF MDI: no very common side effects observed. Common side effects observed were feeling of fast heart beat (palpitations), yeast infections in the throat (Candida infections in oropharynx), headache, shakiness (tremor), mild irritation in the throat, coughing, hoarseness (dysphonia).
GFF MDI: very common side effects: none: common: dry mouth, nausea, chest pain, abnormal contraction of muscle (muscle spasms), headache, dizziness, anxiety.

Subjects that participate in 1 or 2 sub-studies will be connected to a Holter monitor for 24 hours (24-hour Holter-monitor sub-study) and/or will perform a series of 8 breathing tests (4-hour PFT sub-study)

Most common side effects for the approved medications that are used in the study:

For Atrovent® HFA (ipratropium bromide):

Very common: Inflammation and swelling of the lining of the airways (bronchitis).
Common: back pain, headache, flu (influenza) like symptoms, dizziness, indigestion (dyspepsia), dry mouth, nausea, worsening of COPD, difficulty breathing (dyspnoea), inflammation of the lining membrane in any of the hollow areas (sinuses) of the skull around the nose (sinusitis), urinary tract infection, cough, inflammation of the nose (rhinitis), upper respiratory tract infection.

For Ventolin HFA® (albuterol sulfate inhalation aerosol):
Very common: Throat irritation.
Common: upper respiratory inflammation, viral respiratory infections, cough, musculoskeletal pain.

Other risks and discomforts:
Possibility of discomfort during some of the tests and vaccinations such as:
* Blood samples: possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
* ECG: Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.
* X-Ray: The chest x-ray is one of the lowest radiation exposure medical

examinations performed today. The effective radiation dose from this procedure is about the same as the average person receives from background radiation (radiation you are exposed to in 10 days). Although all radiation is cumulative over your lifetime, small doses from x-rays should not create a significant risk to your health.
* Spirometry (Breathing Test): Performing breathing tests may cause some coughing, shortness of breath and light headedness.
* Pneumococcal and annual influenza vaccines: People who get the vaccines have very mild side effects, such as redness, swelling, or pain where the shot was given. Other rare side effects include fever, muscle aches, headaches, runny nose, sore throat, cough, and nausea.

Other risks and discomforts for the substudies:
* 24-hour Holter Monitoring: possible experience of minor local skin irritation as a result of the leads placed on the chest and body.
* 4-Hour Pulmonary function test: none

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Non-child bearing potential (ie, physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or Child bearing potential, has a negative serum pregnancy test at Visit 1, and agrees to acceptable contraceptive methods used consistently and correctly for the duration of the study.
* Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS).
* Current or former smokers with a history of at least 10 pack-years of cigarette smoking.
* Forced expiratory volume in 1 second (FEV1)/Forced vital capacity (FVC) ratio of <0.70 and FEV1 of <65% predicted normal value calculated using NHANES III reference equations (or reference norms applicable to other regions). Note: this criteria applies to subjects in the PFT sub-study only.
* Subjects with history of exacerbations. , Please refer to the study protocol for the complete inclusion criteria list.

Exclusion criteria

* Significant diseases or conditions other than COPD, which, in the opinion of the Investigator, may put the subject at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study.
* Women who are pregnant or lactating, or are planning to become pregnant during the course of the study, or women of childbearing potential who are not using an acceptable method of contraception.
* Subjects, who in the opinion of the Investigator, have a current diagnosis of asthma.
* Subjects who have been hospitalized due to poorly controlled COPD within 3 months prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 4).
* Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 4).
* Immune suppression or severe neurological disorders affecting control of the upper airway or other risk factors that in the opinion of the Investigator would put the subject at substantial risk of pneumonia.

* Subjects with a diagnosis of narrow angle glaucoma, who, in the opinion of the Investigator, have not been adequately treated.
* Subjects who have a history of hypersensitivity to *2-agonists, budesonide or any other corticosteroid components, glycopyrronium or other muscarinic anticholinergics, or any other component of the IMPs.
Please refer to the study protocol for the complete exclusion criteria list.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-02-2016
Enrollment:	126
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Budesone, Glycopyronium, and Formoterol Fumarat metered dose inhalator (BGF MDI)
Generic name:	Budesone, Glycopyronium, and Formoterol Fumarat metered dose inhalator (BGF MDI
Product type:	Medicine
Brand name:	Budesonide and Formoterol Fumarate Metered Dose inhalator (BFF MDI)
Generic name:	Budesonide and Formoterol Fumarate Metered Dose inhalator (BFF MDI)

Product type:	Medicine
Brand name:	Glycopyrronium and Formoterol Fumarate metered dose inhalator (GFF MDI)
Generic name:	Glycopyrronium and Formoterol Fumarate metered dose inhalator (GFF MDI)

Ethics review

Approved WMO Date:	09-09-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	19-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2014-005671-92-NL
ClinicalTrials.gov	NCT02465567
CCMO	NL53608.056.15