A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD.

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The aim of this study is to demonstrate that once daily treatment with tiotropium + olodaterol fixed dose combination will reduce the number of exacerbations over tiotropium 5 µg monotherapy.A secondary aim of the study is an assessment of a…

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

Summary

ID

NL-OMON44270

Source
ToetsingOnline

Brief title
DYNAGITO

Condition

- Respiratory disorders NEC

Synonym
chronic obstructive pulmonary disease, COPD

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim

Intervention

Keyword: active-controlled, COPD, exacerbations, Tiotropium-Olodatorol

Outcome measures

Primary outcome

Primary endpoint:

- Annualised rate of moderate to severe COPD exacerbation during the treatment

period (within 1 day after the last drug administration date).

Secondary outcome

Key secondary endpoint

- Time to first moderate to severe COPD exacerbation during the treatment

period (within 1 day after the last drug administration date)

Other secondary endpoints

- Annualised rate of exacerbation leading to hospitalisation during the

treatment period (within 1 day after the last drug administration date)

- Time to first COPD exacerbations leading to hospitalisation during the

treatment period (within 1 day after the last drug administration date)

- Time to all-cause mortality (within 1 day after the last drug administration date)

Other endpoints

- Time to first moderate to severe COPD exacerbation requiring treatment with systemic corticosteroids (within 1 day after the last drug administration date).
- Time to first moderate to severe COPD exacerbation requiring treatment with antibiotics (within 1 day after the last drug administration date).
- Time to first moderate to severe COPD exacerbation requiring treatment with ystemic corticosteroids and antibiotics (within 1 day after the last drug administration date).
- Annualised rate of COPD exacerbation requiring systemic corticosteroids (within 1 day after the last drug administration date).
- Annualised rate of COPD exacerbation requiring antibiotics (within 1 day after the last drug administration date).
- Annualised rate of COPD exacerbation requiring systemic corticosteroids and antibiotics (within 1 day after the last drug administration date).
- Annualised rate of all COPD exacerbation (within 1 day after the last drug administration date).
- COPD Assessment Test* (CAT) score at clinic visits

Study description

Background summary

According to the GOLD guidelines, exacerbations are important events in the course of COPD as they have major impact on the patient`s quality of life and cause an increase in symptoms and a deterioration of lung function that may take several weeks to recover from.
Moreover an exacerbation will accelerate the decline of lung function and is associated with significant mortality, especially if a hospitalisation is needed. It is without doubt, that exacerbations are associated with significant socioeconomic costs.

The benefits of tiotropium + olodaterol FDC that have been studied in the Phase III program include improvements in lung function, quality of life, dyspnea and exercise endurance time, but the benefit on exacerbations has not formally been assessed.

Study objective

The aim of this study is to demonstrate that once daily treatment with tiotropium + olodaterol fixed dose combination will reduce the number of exacerbations over tiotropium 5 µg monotherapy.

A secondary aim of the study is an assessment of a potential impact of tiotropium + olodaterol FDC on hospitalisation associated with exacerbations and survival, as compared to tiotropium 5 µg monotherapy. The latter will be included as secondary endpoints.

Study design

This is a randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD and with one or more moderate to severe COPD exacerbation during the previous 12 months.

The study is multinational and involves at least 55 participating countries. The recruitment period is approximately 12 to 14 months.

The trial consists of three consecutive study periods including the screening, the treatment and follow-up periods.

Having obtained the signed informed consent, the patient will be entered in a 2 to 7-day screening period to confirm the patient*s eligibility. At Visit 2 after a successful review of the inclusion and exclusion criteria, the patient will be randomly allocated in equal ratio to receive once daily study treatment:

i. Tiotropium + olodaterol FDC (2.5 µg / 2.5 µg per actuation) inhalation solution
ii. Tiotropium (2.5 µg / per actuation) inhalation solution (control group)
and will then enter the 52-week treatment phase. The randomised treatment period consists of 5 every 3-month clinic visits and in the interim a telephone contact will be scheduled every 6 weeks.

The treatment period will be achieved with the completion of visit 6 including the End of Treatment (EoT) information.

The patient*s trial participation will be concluded with the completion of the follow-up visit 21 days (3 weeks) after V6/EoT visit.

In Addition a sub-study will be done.
In total 854 patients will participate, with 20 patients in the Netherlands at 5 sites.

Participating sites in The Netherlands are:
* Amphia Ziekenhuis in Breda, PI dr. Djamin
* Catharina Ziekenhuis in Eindhoven, PI dr. Wielders
* Gelre Ziekenhuis in Zutphen, PI dr. Goosens
* Westfriesgasthuis in Hoorn, PI dr. Roeleveld
* ZGT Almelo in Almelo, PI dr. Sinninghe Damste

Patients will come for 2 additional visits to site; visit 0 and visit 6a.
Visit 0 will be used to inform patients and to instruct them on the requirements for the spirometry at visit 1.
At visits 2, 3, 4, 5, en 6 spirometry will be done 5 minutes before inhalation of trial medication and 1, 2 and 3 uur after inhalation. At the extra visit 6A an additional spirometry will be done at 23 hours and 55 minutes after inhalatie (at visit 6).

Intervention

Bronchodilator therapy; during 52 weeks a once daily inhalation of studymedication with the Respimat® Inhaler with one of the following treatments:
1. tiotropium + olodaterol (5 µg/5 µg) fixed dose combination inhalation solution
2. tiotropium (5 µg) inhalation solution

Patients will also undergo/ need to:
- Laboratory tests
- Completing several different patient questionnaires during study visits
- ECG
- 3- monthly telephone calls to check on health status

Patienten participating in the sub-study will have additional spirometry tests.

Study burden and risks

Tiotropium monotherapy is a well established maintenance treatment for patients with COPD across all severities. The clinical trials conducted to date have shown tiotropium + olodaterol FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population (including patients with concomitant cardiovascular diseases). The observed incremental bronchodilator response for the
combination compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient centred outcomes. Potential risks associated with administration of tiotropium include the listed (expected) adverse events for tiotropium monoproduct.

Potential risks associated with administration of the combination of tiotropium and olodaterol include the listed (expected) adverse events for tiotropium + olodaterol FDC. Women of childbearing potential may be included in clinical trials for tiotropium + olodaterol provided appropriate precautions are taken to minimize the risk of pregnancy. These precautions include pregnancy testing and use of a highly effective method of birth control. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures not to become pregnant during the period of drug exposure (which may exceed the length of study until the follow-up visit at 21 days after discontinuation of study
medication).

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

- All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions.
- All patients must have a diagnosis of chronic obstructive pulmonary disease and must meet the following spirometric criteria:
* stable airway obstruction with a post-bronchodilator FEV1< 60% of predicted normal
* and a postbronchodilator FEV1/FVC <70% documented at Visit 1
- Patients with a documented history of at least one moderate to severe COPD exacerbation in the previous 12 months requiring treatment with systemic corticosteroids and/or antibiotics and/or related hospitalization.
- Investigator should also ascertain that the patient is symptomatically stable as defined by:
* no evidence of COPD exacerbation requiring use of either antibiotics and/or steroids 4 weeks prior to visit 1,
* no evidence of change in their usual COPD medication 4 weeks prior to visit 1.
- Male or female patients, 40 years of age or older.
- Patients must be current or ex-smokers with a smoking history of more than 10 pack years.
- Patients must be able to perform all trial related procedures at the investigator discretion including:
* technically acceptable and eligible pulmonary function test (if performed at site)
* vital status follow-up in case of discontinuation until the predicted exit date (i.e.: 52 weeks from first intake of randomised treatment + 21 days).
* COPD exacerbation interview every 6 weeks in case of premature discontinuation until the predicted exit date (i.e.: 52 weeks from first intake of randomised treatment + 21 days).
- Patients must be able to inhale medication in a competent manner from the Respimat® inhaler (Appendix 10.1), and from a metered dose inhaler (MDI) in the opinion of the investigator.

Exclusion criteria

- Patients with a significant disease other than chronic obstructive pulmonary disease.
- Patients with clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis.
- Patients with a corrent documented diagnosis of asthma.;Patients with one of the following conditions:
- A diagnosis of thyrotoxicosis (due to the known class side effect profile of ß2-agonists)
- A history of myocardial infarction within 6 months of screening visit.
- Life-threatening cardiac arrhythmia.
- Known active tuberculosis.
- A malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years.
- A history of cystic fibrosis.
- Clinically relevant bronchiectasis.
- Patients with severe emphysema requiring endobronchial interventions within 6 months prior to screening
- A history of significant alcohol or drug abuse.
- Patients who have undergone thoracotomy with pulmonary resection.;- Patients being treated with any oral ß-adrenergics.
- Patients being treated with oral corticosteroid medication at unstable doses (i.e., less than six weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.
- Patients being treated with antibiotics for any reason within 4 weeks of screening visit
- Patients being treated with PDE4 inhibitors within 3 months of screening visit (e.g. roflumilast) should not be enrolled and PDE4 inhibitors should not be withdrawn for the purpose of enrolling in this study.
- Patients who have taken an investigational drug within one month or six half lives (whichever is greater) prior to screening visit.
- Patients with known hypersensitivity to ß-adrenergics drugs, anticholinergic drugs, benzalkonium chloride, disodium edentat, or any other component of the Respimat® inhalation solution delivery system.
- Pregnant or nursing women.
- Women of childbearing potential not using highly effective methods of birth control.
- Patients who have previously been randomized in this study or are currently participating in another study.
- Patients who are unable to comply with pulmonary medication restrictions prior to randomization.

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):	09-02-2015
Enrollment:	171
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Spiolto
Generic name:	tiotropium bromide+olodaterol (fixed dose combination)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Spiriva
Generic name:	Tiotropium bromide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	18-11-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	30-12-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-04-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	08-12-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2014-002275-28-NL
ClinicalTrials.gov	NCT02296138
CCMO	NL50456.060.14