The effectiveness of single dose Ultibro Breezhaler (indacaterol/glycopyrronium) by sd-DPI versus ipratropium/salbutamol by nebulizer in improving FEV1 and dyspnea during stable state of COPD

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To test our hypothesis that:The combination of the two long-acting bronchodilators indacaterol and glycopyrronium confers a superior improvement compared to nebulisation with ipratropium/salbutamol, as administered single dose in patients with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON42656

Source
ToetsingOnline

Brief title
single dose Ultibro versus ipratropium/salbutamol

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Chronic Obstructive Pulmonary Disease, COPD

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Budget Afdeling longziekten en Novartis,Novartis

Intervention

Keyword: Combivent, Nebuliser, Ultibro

Outcome measures

Primary outcome

Area under the curve (AUC) from 0 to 6 hours of FEV1 with indacaterol and glycopyrronium, compared to nebulisation with ipratropium/salbutamol.

Secondary outcome

1. Change in Borg dyspnea score at 30 min: change in Borg score at other time points, and proportion of patients reaching the MCID at all time points (15, 30, 60, 120 240 and 360 min) (1)

2. Changes in level of hyperinflation (by IC measurement), and proportion of participants reaching a difference of 100 ml.

3. Time to FEV1 increase of 100 ml

4. Peak effect of FEV1 from 0 to 6 hours

5. Time to peak of FEV1

6. FEV1 at all other time points (15, 30, 60, 120 240 and 360 min)

Study description

Background summary

Patients admitted for AECOPD are in many hospitals routinely taken of their home inhaled medication, and especially of their long-acting bronchodilators,

to be switched to 4 times daily nebulisations with ipratropium and salbutamol. Although it has been shown in many settings that nebulisations with bronchodilators in general convey no advantage over pMDI or dry powder (TH) administration, this practice prevails.(1,2). Additionally, long-acting bronchodilators have been shown to generally confer greater bronchodilation in stable state than their short counterparts, and combinations of specific long-acting bronchodilators have been shown to be more efficacious than the single constituents.(3) We believe it is likely that combined long-acting bronchodilators, are more efficacious than short acting bronchodilators per nebulizers, especially in the onset of action. If this hypothesis can be confirmed in stable state, this study will be repeated in an exacerbation state. If the study shows a positive though non-significant effect of long-acting bronchodilators, the study will also be repeated in an exacerbation state. If the trend is in favour of short-acting medication, then the study will not be repeated in the exacerbation state.

Study objective

To test our hypothesis that:
The combination of the two long-acting bronchodilators indacaterol and glycopyrronium confers a superior improvement compared to nebulisation with ipratropium/salbutamol, as administered single dose in patients with stable state COPD.

Primary objective:
The combination of the two long-acting bronchodilators indacaterol and glycopyrronium once daily confers a superior improvement in FEV1 as compared to nebulisation with ipratropium/salbutamol, both administered single dose in patients with stable state COPD.

Secondary objectives:
The combination of the two long-acting bronchodilators indacaterol and glycopyrronium once daily confers a superior reduction in dyspnea, hyperinflation (IC), FEV1 onset of action and peak effect compared to nebulisation with ipratropium/salbutamol, both administered single dose in patients with stable state COPD.

Study design

Investigator initiated, randomised, active controlled, cross-over double-blind (and therefore double-dummy), study comparing the effects of single dose indacaterol/glycopyrronium 110/50 Breezhaler® versus single dose ipratropium/salbutamol nebulisation in patients with COPD in stable state.

After inclusion long-acting bronchodilators will be washed-out for at least 7 days, and randomised to receive either Ultibro + placebo nebulization or

ipratropium/salbutamol nebulization and placebo Breezhaler first, then after a new washout period of 7 days they will receive the other treatment.

At 0 min the patient starts with Breezhaler. Nebulization starts immediately after Breezhaler has been taken. During washout patients may use reliever fenoterol/ipratropium max 4 times daily (20/50ug by PMDI and spacer, max 8 puffs per day) and they may continue any inhaled corticosteroids in a stable dose, in stable state during the study. The last dose fenoterol/ipratropium is permitted till 6 hours before the measurements.

Intervention

After inclusion long-acting bronchodilators will be washed-out for at least 7 days, and patients will be randomised to receive either Ultibro + placebo nebulization or ipratropium/salbutamol nebulization and placebo Breezhaler first. After a new washout period of at least 7 days they will receive the other treatment. During the trial they will be prescribed fenoterol/ipratropium as reliever medication.
At 0 min the patient starts with Breezhaler. Nebulization starts immediately after Breezhaler has been taken. During washout patients may use reliever fenoterol/ipratropium max 4 times daily (20/50ug by PMDI and spacer, max 8 puffs per day) and they may continue any inhaled corticosteroids in a stable dose, in stable state during the study. The last dose fenoterol/ipratropium is permitted till 6 hours before the measurements.

Study burden and risks

This study has no specific benefits for the participating patients. The study also has no major risks. Minor risks for participants after a single dosis can be throat irritation, cough, headache and dizziness, sinus tachycardia.
The combination of treatments with *2-agonist bronchodilators and anticholinergic bronchodilators have been used in daily practice for many years in many countries and they are often prescribed both in COPD. We expect that most participants have used similar medication before, Both indacaterol/glycopyrronium and ipratropium/salbutamol are approved for COPD treatment in the Netherlands.
Safety aspects regarding the replacement of long-acting bronchodilators (1-2 x daily) by short-acting (fenoterol/ipratropium 4 times daily) are deemed negligible. Many patients are still on a regimen of short-acting bronchodilators. Patients can continue all other drugs including inhaled corticosteroids. Effectively participants will have access to adequate medical treatment during the whole study.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:;1. COPD, post-bronchodilator FEV1/FVC < 70%; post-br FEV1 < 80%pred
2. Active mastery of Dutch
3. Written informed consent
4. At least 40 years old
5. Patients must be able to understand and complete protocol requirements, Instructions, and questionnaires provided in Dutch

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation

in this study:;1. Non invasive ventilation
2. Saturation by pulse oxymetry <88%
3. Documented history of asthma
4. Instable cardiac disease within 6 months.
5. Known long QTC syndrome
6. Known EGFR <30 ml/min *1,73m2
7. Exacerbations of COPD or change of medication for COPD in the last 6 weeks prior to inclusion
8. Allergic reaction or intolerance for a substance used in one of the products or atropine or atropine derived substances
9. Pregnant or lactating females.

Study design

Design

Study phase:	4
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):	02-12-2015
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Combivent
Generic name:	salbutamol/ipratropium
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Ultibro
Generic name:	indacaterol/glycopyrronium
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-10-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2015-000473-12-NL
CCMO	NL52506.042.15