A MULTINATIONAL, MULTICENTRE, RANDOMISED, OPEN-LABEL, ACTIVE-CONTROLLED, 26-WEEK, 2-ARM, PARALLEL GROUP STUDY TO EVALUATE THE NON-INFERIORITY OF FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE ADMINISTERED VIA PMDI (CHF 5993) VERSUS FIXED COMBINATION OF FLUTICASONE FUROATE PLUS VILANTEROL ADMINISTERED VIA DPI (RELVAR*) PLUS TIOTROPIUM BROMIDE (SPIRIVA®) FOR THE TREATMENT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Primary objectives To demonstrate the non-inferiority of CHF 5993 pMDI versus fixed combination of fluticasone furoate/vilanterol plus tiotropium in terms of quality of life (change from baseline in the St. George*s Respiratory Questionnaire [SGRQ]...

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

Summary

ID

NL-OMON41888

Source
ToetsingOnline

Brief title
2403/0014 COPD

Condition

- Bronchial disorders (excl neoplasms)

Synonym
COPD; airflow obstruction

Research involving
Human

Sponsors and support

Primary sponsor: Chiesi Farmaceutici
Source(s) of monetary or material Support: Chiesi Farmaceutici S.p.A

Intervention

Keyword: CHF 5993, Phase III, Pulmonary Disease (COPD)

Outcome measures

Primary outcome

Change from baseline in the SGRQ total score at Week 26.

Secondary outcome

Key secondary efficacy variable

• SGRQ response (change from baseline in total score <= -4) at Week 26.

• Change from baseline in the SGRQ total score at all the other clinic visits

and in the domain scores at all clinic visits.

• Change from baseline in pre-dose morning FEV1 at all clinic visits.

• FEV1 response (change from baseline in pre-dose morning FEV1 >= 100 ml) at Week 26.

• Change from baseline in pre-dose morning FVC at all clinic visits.

• Change from baseline to each inter-visit period and the entire treatment period in the percentage of days without nocturnal awakenings due to COPD, in the average impact of night-time COPD symptoms on sleep and in the average impact of night-time COPD symptoms on patient*s ability to get up in the morning (impacts evaluated daily on a 7-point Likert scale and averaged over inter-visit periods).

• Change from baseline to each inter-visit period and the entire treatment period in the percentage of days without intake of rescue medication and in the average use of rescue medication (number of puffs/day), distinguishing by day-time, night-time and overall intake.

• CAT score at the end of treatment

• Rate of moderate and severe COPD exacerbation over 26 weeks of treatment.

Health economic variables

• EQ-5D-3L VAS score and EQ-5D-3L index at all clinic visits

• Number of hospital admissions due to COPD and other causes

• Number of hospital days due to COPD and other causes

• Number of days in ICU due to COPD and other causes

• Number of emergency room visits due to COPD and other causes

• Number of ambulance rides to hospital due to COPD and other causes

• Number of unscheduled contacts due to COPD:

o family practitioner

o specialist outpatients setting

o specialist hospital outpatients setting

• Number of days with professional home assistance due to COPD

• Number of days with family caregivers due to COPD

• Number of days with oxygen therapy use due to COPD

• Unplanned diagnostic or instrumental tests performed due to COPD

• Lost productivity due to COPD (sick leave days from work, anticipated

retirement)

• Mortality.

Safety Assessments

• Adverse Events (AEs) and Adverse Drug Reactions (ADRs).

• Vital signs (systolic and diastolic blood pressure, pulse rate) pre-dose and

10 min post-dose at each clinic visit

• 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS pre-dose at the end

of treatment

• Standard Haematology and Blood Chemistry at the end of treatment.

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is a major public health problem
in the world [1].

COPD represents a significant cause of global morbidity and mortality, with a substantial economic impact representing a serious and disabling disease, which imposes a large burden on patients, health care systems and society, projected to become the world*s third leading cause of mortality by 2020 [2].
It is a disease characterised by airflow limitation not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to prolonged exposure to noxious particles or gases.
International guidelines [3] recommend that the main therapeutic goals, besides the prevention of disease progression, is to relieve symptoms, improve health status and prevent/treat exacerbations. Bronchodilators are the mainstay of pharmacologic therapy for chronic obstructive pulmonary disease (COPD), and are recommended by international guidelines as first-line therapy in symptomatic patients and those who demonstrate airflow limitation.
Two key classes of bronchodilators have been developed in COPD: β2-agonists and muscarinic antagonists. They are recommended in all current guidelines as appropriate treatment for first-line maintenance therapy of COPD. The twice-daily LABAs salmeterol and formoterol first became available for maintenance therapy of COPD more than 15 years ago, while the once-daily LAMA tiotropium has been available for 10 years and is the most widely prescribed maintenance monotherapy bronchodilator in COPD [4]. Inhaled bronchodilators, as monotherapy or in combination, remain the mainstay for patients in all categories [3].
Fluticasone furoate/vilanterol trifenatate (FF/VI) is a novel ICS/LABA combination being developed for once-daily (OD) administration in COPD [5].
Anticholinergic drugs, long-acting muscarinic antagonists (LAMAs), long-acting β2-agonists (LABAs) such as formoterol fumarate exhibit sustained and prolonged effects and are proven to
provide long-term improvements in lung function, quality of life, and exacerbations in patients with COPD.
Antimuscarinics are a well established class of drugs, and there is extensive experience with the use of Glycopyrrolate by injection as well as orally (Robinul®, or generic equivalents). The injectable form (given intravenously [i.v.] or intramuscularly [i.m.]) is used predominantly during preoperative anesthesia to reduce salivary, tracheobronchial and pharyngeal secretions.
Glycopyrronium Bromide (GB) is a synthetic quaternary ammonium compound that acts as a competitive antagonist of muscarinic acetylcholine receptors. Inhaled Glycopyrronium has been shown to cause prolonged bronchodilation in patients with asthma and has been found to be an effective bronchodilator in patients with COPD [6, 7]
GOLD documents highlight that, for patients uncontrolled with bronchodilator monotherapy, combination therapy is recommended. In patients with more severe disease, adding a long acting muscarinic antagonist (LAMA) to a LABA/ ICS combination is an attractive alternative considering the different molecular mechanisms of action of these drugs. Triple therapy with LABA, LAMA and ICS is widely used in clinical practice. Several clinical studies have investigated this treatment approach and showed that *triple therapy* is more effective in

terms of lung function improvement, symptoms control and health status as compared to bronchodilator monotherapy or ICS/LABA [8, 9, 10, 11].
Chiesi developed a fixed dose combination (FDC) of Beclometasone Dipropionate (BDP 100 µg/actuation) and of Formoterol Fumarate (FF 6 µg/actuation developed as a hydrofluoroalkane (HFA) pressurised metered dose inhaler (pMDI) which has been marketed under the trade name Foster® and has been approved for the indication of asthma in EU and extra-EU countries since 2006 and its efficacy and safety shown in moderate asthma patients with a greater effect on lung function and asthma control over BDP CFC alone and similar effect to that of Symbicort and Seretide. Furthermore, Foster® has being also recently approved in COPD patients.
Glycopyrronium Bromide (GB) is being developed by Chiesi as hydrofluoroalkane (HFA) pressurised metered dose inhaler (pMDI) (CHF 5259) using the same formulation as Foster®.
Chiesi is now developing a triple fixed dose combination (FDC) by combining Foster® with Glycopyrronium bromide, for COPD patients that would benefit from ICS/LABA and LAMA combined therapy. This triple fixed dose combination is named CHF 5993, or Beclometasone dipropionate/Formoterol fumarate/Glycopyrronium bromide, or BDP/FF/GB within this document.
The trial design will be optimised to demonstrate the non-inferiority of CHF 5993 pMDI versus fixed combination of fluticasone furoate/vilanterol plus tiotropium in terms of quality of life in severe very severe COPD patients after 26 weeks of treatment.
Indeed, this study has been designed to evaluate the effect of CHF 5993 pMDI on lung function parameters, patient*s health status and on clinical outcome measures, to collect data in order to assess the impact of study treatments on health economic outcomes and to assess the safety and tolerability of the study treatments.
Fluticasone furoate/vilanterol trifenatate (FF/VI) is also named Relvar® and tiotropium bromide is also named Tio or Tiotropium or Spiriva® within this document.
The choice of the Relvar and Spiriva is due to the fact that it is important to evaluate the effect of CHF5993 versus these free combination that could become in the next future the new standard of care for severe patients, also considering that both of them are once a day.
This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) current Good Clinical Practices and all other applicable laws and regulations.

Study objective

Primary objectives
To demonstrate the non-inferiority of CHF 5993 pMDI versus fixed combination of fluticasone furoate/vilanterol plus tiotropium in terms of quality of life (change from baseline in the St. George*s Respiratory Questionnaire [SGRQ] total score after 26 weeks of treatment).

Secondary objectives
To evaluate the effect of CHF 5993 pMDI on lung function parameters, patient*s health status and on clinical outcome measures.
To collect data in order to assess the impact of study treatments on health economic outcomes.
To assess the safety and tolerability of the study treatments.

Study design

This is a phase IIIb, open-label, randomised, multinational, multicentre, two-arm parallel group, active-controlled study in approximately 1142 randomised patients. Approximately 110 sites will be involved.
Throughout the study, a total of 6 clinic visits (V0 to V5) will be performed accordingly to the study flow diagram.
- A pre-screening visit (V0) will be carried out in order to fully explain the study to potential patients, to obtain the written informed consent from the patient and to instruct the patient on screening visit procedures (such as medication restrictions and fasting conditions).
- A screening visit (V1), no more than 7 days after V0 will help establishing the eligibility of patients for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, a triplicate 12-lead ECG, spirometric parameters after salbutamol, vital signs and training for the use of inhalers). This visit will be followed by a 2-week open-label run-in period where patients will receive Tiotropium 18 µg per day plus salbutamol pMDI or terbutaline DPI as rescue medication if needed.
- After the randomisation (V2), patients will be assessed after 4, 12 and 26 weeks of treatment (V3 to V5) at clinic/hospital.
- A safety follow-up phone call will be done by the investigator 1 week after the last visit or after the early discontinuation to check the status of unresolved adverse events and to record any new AEs that have occurred after the last visit as well as the related concomitant medications.
During the run-in and randomised treatment periods, patients will complete the SGRQ at all clinic visits starting from V2 and will record night-time awakenings, rescue medication use and compliance to the study medication daily on an eDiary.
AEs/SAEs and COPD exacerbations will be monitored throughout the study.
The end of the trial is defined as the last visit (follow-up call) of the last subject in the trial.

Intervention

A 2-week open-label run-in period under tiotropium followed by a 26-week open-label, randomised treatment period.

Test product dose/route/regimen
CHF 5993 pMDI: Fixed combination of beclometasone dipropionate 100 µg plus

formoterol fumarate 6 µg plus glycopyrronium bromide 12.5 µg (BDP/FF/GB) administered via pressurised metered dose inhaler (pMDI).
Dose regimen: BDP/FF/GB, 100/6/12.5 µg per inhalation, 2 inhalations bid (total daily dose: 400/24/50 µg).
Administration: pressurised metered dose inhaler (pMDI).

Reference product dose/route/regimen
Relvar® + Spiriva®: Fixed combination of fluticasone furoate 100 µg/unit dose plus vilanterol 25 µg/unit dose administered once-daily using Ellipta®, a dry powder inhaler (DPI) + Tiotropium bromide 18 µg inhalation powder, hard capsule, one capsule once daily.
Dose regimen: fluticasone furoate / vilanterol, 100/25 µg per inhalation, 1 inhalation o.d. + Tiotropium bromide 18 µg per capsule, one capsule o.d. (total daily dose: 92/22 µg + 18 µg).
Administration: ELLIPTA® (DPI) + HandiHaler® inhaler.

Study burden and risks

Chronic obstructive pulmonary disease (COPD) is a serious and disabling disease representing a major public health problem in the world. The goals of COPD treatment include alleviating symptoms, improving both health status and exercise tolerance, and reducing the future risk of exacerbations. Two key classes of bronchodilators have been developed in COPD: β2-agonists and muscarinic antagonists. They are recommended in all current guidelines [1] as appropriate treatment for first-line maintenance therapy of COPD.
GOLD guidelines [2] highlight that, for patients uncontrolled with bronchodilator monotherapy, combination therapy is recommended: Treatment with a fixed LABA / ICS combination improves lung function and symptoms, reduces the incidence of COPD exacerbations and improves health status [3][4][5][6].
In patients with more severe disease, adding a long acting muscarinic antagonist (LAMA) to a LABA/ ICS combination is an attractive alternative considering the different molecular mechanisms of action of these drugs. Several clinical studies have investigated this treatment approach and showed that *triple therapy* is more effective in terms of lung function improvement, symptoms control and health status as compared to bronchodilator monotherapy or ICS/LABA [7][8][9].
In addition to the three parallel modes of action, the possibility to increase compliance by using a single inhaler provides additional rationale for triple combination therapy. However, hitherto no triple inhaler device has been developed. Chiesi Farmaceutici S.p.A. (Parma, Italy) is developing CHF 5993 pMDI using the available fixed combination of BDP/FF (Foster®, 100/6) as the ICS/LABA platform to which glycopyrronium bromide, a drug already licensed in the treatment of COPD by inhalation (Tovanor® Breezhaler®, approved in September 2012), is added.

The Tristar trial is designed to evaluate the effect of CHF 5993 pMDI, compared to a similar reference approved treatment (fluticasone/vilanterol + tiotropium)

on lung function parameters, patient*s health status and on clinical outcome measures, to collect data in order to assess the impact of study treatments on health economic outcomes and to assess the safety and tolerability of the study treatments.
When evaluating the therapeutic potential of any compound, and β2 agonists in particular, in the COPD setting, it is considered increasingly important to evaluate a range of outcome measures in addition to FEV1 assessment. It includes the relief of clinical symptoms, enhancement of exercise tolerance and performance status, improvement of quality of life, rate of exacerbations, and possibly the inhibition of long-term disease progression [10]. The primary endpoint, change in the SGRQ total score, will allow assessment of patient*s general health status.
Approximately 850 male and female patients will be randomized in the study. The target patient population - patients with severe and very severe COPD airflow obstruction according to GOLD 2014 criteria - has the potential to benefit from the proposed treatment. The association of three components with different modes of action may benefit these difficult-to-treat patients, the ultimate goal of COPD management being the minimization of symptoms, improving health status and exercise tolerance, and preventing the future risk of exacerbations.
Women of childbearing potential will be included provided that they are using one or more reliable method of contraception. In addition, pregnancy tests will be done (serum test at screening and last study visit and urine test for the other visits) throughout the study as a precaution. In case of pregnancy, the patient will be immediately withdrawn from the study and she will be followed with due diligence until the outcome of the pregnancy is known.
During the Reproductive and Developmental Toxicity studies (section 4.3.5 of IB ref. CCD-IB-0018), no significant difference were seen in the safety profile compared to the one of the components taken separately. No concerns related to either spermatogenesis or male fertility which could be affected by any components of CHF 5993 has been raised, neither significant AEs on pregnant rats and rabbits were observed, except the exagerated pharmacological activity at higher doses. Therefore, taking also into account that the components are already in use for many years, it is considered sufficient and safe to recommend and use contraception only for included women and not for included men and for their female partners.
Non-clinical and clinical studies with the triple fixed or free pMDI combination of BDP, FF and GB support the safety and expected efficacy of their administration in this population at this dose. All three agents of the triple combination have been investigated in humans, separately or in combination with higher doses than those to be administered and showed good safety and tolerability. All observed AEs were expected with this class of drug and no cardiovascular safety issues were apparent.
The reference products tiotropium and fluticasone/vilanterol are approved for treatment of COPD. They have shown their efficacy and are corresponding to standard approved treatments for this kind of patients [11]. The doses of BDP, formoterol and glycopyrronium in CHF 5993 (400/24/50 µg), fluticasone/vilanterol (100/25 µg) and tiotropium (18 µg) are routinely

administered separately or in combination and have shown good efficacy and safety separately.
Patients will be closely monitored throughout the trial and evaluated by the Investigator.

In summary, the expected therapeutic value combined with the safety profile seen on the basis of previous studies gives an acceptable overall risk/benefit assessment for the proposed trial.

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

Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Male and female adults aged >= 40 years with written informed consent obtained prior to any study-related procedure.
2. Patients with a diagnosis of COPD at least 12 months before the screening visit (according to GOLD document updated 2014).
3. Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack years [pack-years = (number of cigarettes per day x number of years)/20].
4. A post-bronchodilator FEV1 < 50% of the predicted normal value and a post-bronchodilator FEV1/FVC < 0.7 at least 10-15 min after 4 puffs (4 x 100 µg) of salbutamol pMDI.
If this criterion is not met at screening, the test can be repeated once before randomisation.
5. A documented history of at least one exacerbation in the 12 months preceding the screening visit.
COPD exacerbation will be defined according to the following:
*A sustained worsening of the patient*s condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalization*
Also documented visits to an emergency department due to COPD exacerbation are considered acceptable to fulfil this criterion.
6. Patients under double therapy for at least 2 months prior to screening visit with either:
a. inhaled corticosteroids/long-acting β2-agonist combination (fixed or free), without regular use of short-acting muscarinic antagonist (regular use means 2 puffs 4 times per day at least) or
b. inhaled corticosteroids/long-acting muscarinic antagonist free combination, without regular use of short-acting β2-agonist (regular use means 2 puffs 4 times per day at least) or
c. Inhaled long-acting β2-agonist and inhaled long-acting muscarinic antagonist or
Patients under monotherapy with long-acting muscarinic antagonist for at least 2 months prior to screening.
7. Symptomatic patients at screening with a CAT score >=10.
8. A cooperative attitude and ability to use correctly the inhalers.
9. A cooperative attitude and ability to use correctly the daily eDiary.
At screening visit (V1), all inclusion criteria will be checked.
At randomisation visit (V2), criteria 8 and 9 will be re-checked.

Exclusion criteria

The presence of any of the following will exclude a patient from study enrolment:
1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are willing to use one or more of the following reliable methods of contraception:
a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
b. Hormonal contraception (implantable, patch, oral, injected).
c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical vaults/caps) with spermicidal foam/gel/film/cream/suppository.

d. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
Reliable contraception should be maintained throughout the study until the last study visit. *True abstinence* is acceptable only if it is in line with the preferred and usual lifestyle of the patient.
Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at screening and end of treatment, urine pregnancy test will be performed at all clinic visits except the last one.
Any postmenopausal women (physiologic menopause defined as *12 consecutive months of amenorrhea*) or women permanently sterilized (e.g. tubal occlusion, hysterectomy or bilateral salpingectomy) can be enrolled in the study.
2. Patients with a current clinical diagnosis of asthma with a physician-judged need for inhaled or oral corticosteroid therapy.
3. Patients requiring use of the following medications:
a. A course of systemic steroids longer than 3 days for COPD exacerbation in the 4 weeks prior to screening.
b. A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to screening.
c. PDE4 inhibitors in the 4 weeks prior to screening.
d. Use of antibiotics for a lower respiratory tract infection (e.g pneumonia) in the 4 weeks prior to screening.
4. COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalization during the run-in period.
5. Patients treated with non-cardio selective β-blockers in the month preceding the screening visit or during the run-in period. Those patients may enter the study after non-selective β-blockers withdrawal and/or cardio selective β-blockers intake for at least 10 days before randomization.
6. Patients treated with long-acting antihistamines unless taken at stable regimen at least 2 months prior to screening and to be maintained constant during the study, or if taken as PRN.
7. Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia.
8. Known respiratory disorders other than COPD which may impact the efficacy of the study drug according the investigator*s judgment. This can include but is not limited to *-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease.
9. Patients who have clinically significant cardiovascular condition such as, but not limited to, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, acute ischemic heart disease in the last year prior to study screening, history of sustained cardiac arrhythmias or sustained and non-sustained cardiac arrhythmias diagnosed in the last 6 months (sustained means lasting more than 30 seconds and or ending only with external action, and or leads to hemodynamic collapse; non-sustained means > 3 beats < 30 seconds, and or ending spontaneously, and or asymptomatic), impulse conduction high degree blocks, patients with Implantable Cardioverter Defribrillator (ICD).
10. Patients with atrial fibrillation (AF):
a. Paroxysmal Atrial Fibrillation
b. Persistent: AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC) within 6 months

from screening.
c. Long standing Persistent as defined by continuous atrial fibrillation diagnosed for less than 6 months with or without a rhythm control strategy.
d. Permanent: for at least 6 months with a resting ventricular rate >= 100/min controlled with a rate control strategy (i.e., selective β-blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy).
11. An abnormal and clinically significant 12-lead ECG which may impact the safety of the patient according to investigator*s judgement.
Patients whose electrocardiogram (ECG12 lead) shows QTcF >450 ms for males or QTcF >470 ms for females at screening visit are not eligible (not applicable for patient with pacemaker).
12. Medical diagnosis of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that in the opinion of the investigator would prevent use of anticholinergic agents.
13. History of hypersensitivity to anticholinergics, β2-agonist, corticosteroids or any of the excipients contained in any of the formulations used in the trial which may raise contra-indications or impact the efficacy of the study drug according to the investigator*s judgement.
14. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study drug according to investigator*s judgement.
15. Patients with hypokalaemia (serum potassium levels <3.5 mEq/L (or 3.5 mmol/L)) or uncontrolled hyperkalaemia according to investigator*s judgment.
16. Unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; significant hepatic impairment; significant renal impairment; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); uncontrolled neurological disease; uncontrolled haematological disease; uncontrolled autoimmune disorders, or other which may impact the efficacy or the safety of the study drug according to investigator*s judgment.
17. Patients with any history of malignancy likely to result in significant disability or likely to require significant medical or surgical intervention within the next six months (after V1) or with malignancy for which they are currently undergoing radiation therapy or chemotherapy.
18. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening visit.
19. Participation in another clinical trial where investigation drug was received less than 8 weeks prior to screening visit.
At screening visit (V1), all exclusion criteria will be checked except criterion 4 that will be checked at V2.
At randomisation visit (V2), criteria 4, 5, 6 will be re-checked.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-12-2015
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CHF 5993 pMDI
Generic name:	CHF 5993 pMDI
Product type:	Medicine
Brand name:	Relvar Ellipta®
Generic name:	FLUTICASONE FUROATE, VILANTEROL TRIFENATATE
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:	27-01-2015
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-09-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-12-2016
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□001487□35-NL
CCMO	NL51921.056.14