A MULTICENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED,;2-WAY CROSS-OVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF;CHF 5259 (GLYCOPYRROLATE BROMIDE) pMDI ON TOP OF QVAR® pMDI;FOR THE TREATMENT OF PATIENTS WITH UNCONTROLLED ASTHMA;ON LOW-MEDIUM DOSE OF INHALED CORTICOSTEROIDS

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The first objective is to evaluate the superiority of CHF 5259 pMDI (glycopyrrolate bromide) (50 µg total daily dose) versus placebo in terms of FEV1 AUC0-12h normalised by time on Day 42.Key Secondary objectiveTo evaluate the superiority of CHF…

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

Summary

ID

NL-OMON41903

Source
ToetsingOnline

Brief title
ELITRA

Condition

- Respiratory disorders NEC

Synonym
asthma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: bronchodilator, inhaled corticosteroid, uncontrolled asthma

Outcome measures

Primary outcome

FEV1 AUC0-12h normalised by time on Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between CHF 5259 and Placebo will be calculated with their 95% confidence intervals (CIs) and p-values.
The superiority of CHF 5259 over Placebo will be demonstrated if the lower limit of the CI for the mean difference is >0.

Secondary outcome

Change from Baseline in peak FEV1 on Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between CHF 5259 and Placebo will

be calculated with their 95% confidence intervals (CIs) and p-values.

The superiority of CHF 5259 over Placebo will be demonstrated if the lower limit of the CI for the mean difference is >0.

Secondary variables

* FEV1 AUC0-12h normalised by time on Day 1, FEV1 AUC0-3h normalised by time on Day 1 and Day 42, change from baseline in Peak FEV1 on Day 1, and change from baseline in pre-dose morning trough FEV1 on Day 42 will be analysed using the same model as for the primary variable.

In addition, descriptive statistics of FEV1 values at each time point post-dose on Day 1 and Day 42 will be provided.

* Daily (morning and evening) PEF and Daily (morning and evening) Asthma Symptoms will be averaged over the entire treatment period and analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average PEF and Asthma Symptoms during run-in or wash-out period) as a covariate.

* Average use of rescue medication (both in terms of number of puffs/day and number of times/day) will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average use of rescue medication during run-in or wash-out period) as a covariate.

* Percentage of Asthma Control Days will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (Asthma Control Days during run-in or wash-out period) as a covariate.

* Change from baseline in ACQ total score at Day 42 will be analysed using an

ANCOVA model including treatment, period and patient as fixed effects and Day 1

score as a covariate

* Change from baseline in FEV1 percentage of predicted normal value on Day 1

and Day 42, change from baseline in FVC on Day 1 and Day 42 will be analysed

using descriptive statistics.

Study description

Background summary

Inhaled Glycopyrrolate has been shown to induce prolonged bronchodilation in patients with asthma and has been found to be an effective bronchodilator in COPD.

Chiesi Farmaceutici S.p.A. is developing a Pressurized Metered Dose Inhaler (pMDI) formulation of Glycopyrrolate bromide (CHF 5259) for the treatment of patients with uncontrolled asthma.

Glycopyrrolate bromide (GB) CHF 5259 has been already assessed as single dose in a dose range of 12.5 µg to 200 µg and as multiple dose (1 week treatment) in a dose range of 25 µg to 100 µg in comparison with placebo in COPD patients. No safety risk has been raised during these studies.

Chiesi intends to develop a fixed triple dose combination of BDP/FF/GB for asthmatic patients that would benefit from ICS/LABA and LAMA combined therapy.

A significant advantage of a triple inhaler in asthma is convenience for the patient as this reduces the need for using separate inhalers that are often of a differing type and therefore need to be used differently. This is critical since most patients with poorly controlled asthma show poor adherence with regular inhaled therapy.

The study CCD-05993AB1-02 has been then designed to assess the efficacy and safety of Glycopyrrolate bromide on top of ICS on patients with uncontrolled asthma under low-medium dose of ICS.

This study will characterize the bronchodilator effect of Glycopyrrolate bromide per see, i.e. without contemporaneous exposure to any other long-acting bronchodilators, like long-acting ß-agonists, which may alter the response.

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

The first objective is to evaluate the superiority of CHF 5259 pMDI (glycopyrrolate bromide) (50 µg total daily dose) versus placebo in terms of FEV1 AUC0-12h normalised by time on Day 42.

Key Secondary objective
To evaluate the superiority of CHF 5259 pMDI (50 *g total daily dose) versus placebo in terms of peak FEV1 on Day 42.

Secondary objectives
* To evaluate the effect of CHF 5259 on other lung function parameters and on clinical outcome measures.
* To assess the safety and tolerability of study treatments.

Study design

This is a multicentre, randomised, double-blind, active-controlled, 2-way cross-over of 6 weeks, complete block, multiple dose study in asthma patients.

Intervention

The study will comprise 2 treatment groups:
* CHF 5259 (50 µg daily dose);
* the comparator placebo.
All previous treatments shall be stopped after visit 1 in accordance with the non-permitted concomitant medications list. This visit will be followed by a 2-week ± 2 days open-label run-in period where patients will receive an estimated clinical comparable dose of extrafine BDP (Qvar®) of their previous treatment. This background treatment (dose and regimen) will be maintained throughout the study.
* The investigational phase comprises 2 treatment periods of 6 weeks each, separated by a 1 week wash-out period (+ 2 days). Each treatment period comprises 2 visits: on Day 1 (day of first dosing) and Day 42 (day of last dosing) where serial spirometry of 12 hours (post-dose) will be performed.

Study burden and risks

Beschrijf de belasting en risico voor de proefpersonen in het kader van het onderzoek zoals het aantal bloedafnames, het aantal bezoeken bij de arts/onderzoeker, lichamelijk onderzoek, het aantal en soort vragenlijsten en/of dagboekjes, lichamelijk of psychisch ongemak, mogelijke schadelijke

bijwerkingen van de behandeling. Eventueel kan worden aangegeven waarom u van mening bent dat, in het licht van de belasting en/of risico*s, het uitvoeren van het onderzoek gerechtvaardigd is.
Indien het onderzoek bij minderjarige en/of wilsonbekwame proefpersonen wordt uitgevoerd en geen direct therapeutisch effect wordt beoogd, moet beschreven worden waarom belasting en risico als minimaal kunnen worden beschouwd en het onderzoek alleen kan worden uitgevoerd met deze proefpersonen (en niet met meerderjarige wilsbekwame proefpersonen) Een onderzoek is groepsgebonden als het onderzoek alleen met medewerking van de proefpersonen uit de betreffende categorie kan plaatsvinden.

Patients will attend, within 17 weeks, 6 visits at the clinic: a deciding visit, followed by visit 1 to 5.
Visits 2 to 5 will last each +/- 14 hours, due to the several measures of the lung function before and after dosing.
At each visit 1 to 5: a full physical exam, a blood sample of 10 ml, an ECG and lung function tests will be performed. Patients will also complete an asthma questionnaire. Patients are requested to be fasting before the blood sampling.
Patients will be requested to complete twice daily a diary with transmission of the peak flow measure.
Before visit 2 and visit 4, patients are requested to follow a washing period of one week, taking only the study inhaled corcticosteroid.

Contacts

Public
CROMSOURCE

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patient*s written informed consent obtained prior to any study-related procedures;2. Male or female patients aged *18 and *75 years.;3. History of asthma * 5-year and diagnosed before the age of 40 years.;4. Patients with uncontrolled asthma on low-medium doses of Inhaled Corticosteroid (ICS) (200 * 1000 *g daily dose BDP non-extrafine or estimated clinical comparable dose) at a stable dose for at least 4 weeks prior to screening. ;5. Patients with a pre-bronchodilator FEV1 *40% and <90% of their predicted normal value, after appropriate washout from bronchodilators, at screening and at the end of the run-in period.;6. Patients with a positive response to the reversibility test at screening within 30 minutes after administration of 400 *g of salbutamol pMDI, defined as *FEV1 * 12% and * 200mL over baseline.;7. Patients with uncontrolled asthma evidenced by a score at the Asthma Control Questionnaire© (ACQ) *1.5 (criterion must be met at screening and at the end of the run-in period).;8. Patients with a co-operative attitude and ability to be trained to correctly use the pMDI and the electronic peakflow meter.

Exclusion criteria

1. Inability to carry out pulmonary lung function testing, to comply with study procedures or with study treatment intake.;2. History of near fatal asthma or of a past hospitalisation for asthma in intensive care unit or of frequent exacerbations in the last year which may place the patient at risk.;3. Hospitalisation, emergency room admission or use of systemic corticosteroids for asthma exacerbation in the 4 weeks prior to screening visit or during the run-in period.;4. Lower respiratory tract infection in the 4 weeks before the screening visit or during the run-in period.;5. Patients who are in current therapy for gastroesophageal reflux disease (GERD) or patients with a medical history of GERD that leads to asthma symptoms.;6. Patients with a seasonal worsening of asthma and who cannot complete the study outside the relevant allergen season.;7. History of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, bronco-carcinoma, lung carcinoma or any other significant lung disease which may interfere with data evaluation.;8. Patients with a medical history or current diagnosis of COPD as defined by the GOLD guidelines (2014).;9. Current smokers or ex-smokers with total cumulative exposure equal or more than 10 pack-years or having stopped smoking one year or less prior to screening visit.;10. Any change in dose, schedule or formulation of ICS in the 4

weeks prior to screening visit.;11. Patient had used any of the following treatments 4 weeks before screening visit: inhaled long-acting *2-agonists (LABAs), inhaled long acting muscarinic antagonists (LAMAs), inhaled ICS/LABA fixed combinations, theophylline, leukotriene modifiers, cromolyn sodium, nedocromil sodium, systemic anticholinergics, systemic corticosteroids (12 weeks for slow release corticosteroids).;12. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are using at least one or more methods of contraception.;13. Patients who received any investigational new drug or participated in clinical study either within the last 8 weeks (or 5 half-lives for biologic products with slow elimination) before screening.;14. Patients who have clinically significant cardiovascular condition according to investigator*s judgement;15. An abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to investigator*s judgement;16. Patients whose electrocardiogram (12-lead ECG) shows QTcF >450 ms for males or QTcF >470 ms for females at screening or at randomisation visits.;17. Medical diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction that, in the opinion of the investigator, would prevent use of anticholinergic agents.;18. Unstable concurrent disease;19. Patients having received a live-attenuated virus vaccination within;two weeks prior to screening or during the run-in phase;20. Patients mentally or legally incapacitated.;21. Patients with a history of alcohol or drug abuse.;22. Patients with known intolerance/hypersensitivity or contra-indication to treatment with ß2-agonists, inhaled corticosteroids, anti-cholinergics or propellant gases/excipients.;23. Patients with major surgery in the 3 months prior to screening visit or planned surgery during the trial.;24. Patients being treated with anti-IgE antibodies.;25. Patients treated with non-potassium sparing diuretics , non-selective beta-blocking drugs quinidine, quinidine-like anti arrhythmics, or any medication with a QTc prolongation potential or a history of QTc prolongation.;26. Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants.;27. Patients who are receiving any therapy that could interfere with the study drugs according to investigator*s opinion.

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):	21-11-2014
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nvt
Generic name:	Glycopyrrolate bromide
Product type:	Medicine
Brand name:	Nvt
Generic name:	placebo Glycopyrrolate bromide

Ethics review

Approved WMO Date:	14-10-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-01-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-02-2015
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	EUCTR2014-001442-16-NL
CCMO	NL50049.060.14