Effects Of extra-fine particle HFA-becLomethasone (HFA-QVAR) Versus course particle treatment In smokers and ex-smokers with Asthma

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Objective: To perform a study comparing the efficacy of extra-fine particle HFA-QVAR 200 µg b.i.d. to an equipotent dose of course particle HFA-beclomethasone (HFA-Clenil) 400 µg b.i.d. and with coarse particle HFA-fluticasone (GSK) 250 µg in ex-...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON38937

Source
ToetsingOnline

Brief title
Effects of QVAR in smokers and ex-smokers with asthma

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Asthma, Astmatic bronchitis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Door een subsidie van TEVA Pharma,TEVA Pharma

Intervention

Keyword: Adenosine, Asthma, QVAR, Small airways

Outcome measures

Primary outcome

The primary end-parameter is the PD20 small particle adenosine. The co-primary objective (only in case of non-inferiority of QVAR on the primary objective) will be: Reduction in peripheral airways resistance (R5-R20) measured with IOS at the provocative dose of small particle adenosine causing the FEV1 to drop with 20% (PD20).

Secondary outcome

* Twice daily symptoms (including night-time symptoms) and peakflow (PEF).

* Resistance (R5, R20, R5-R20) and Reactance at 5 Herz (X5) with IOS.

* Lung function (FEF25, FEF50, FEF75, FEF25-75, PEF, FEV1, FEV1/FVC, FVC/SVC

* Body plethysmography (RV (%predicted), TLC, RV/TLC (%), FRC, FRC/TLC (%), FRC/TLC (%predicted), IC, RV/TLC %predicted).

* Peripheral blood (cell differential counts).

* Delta FVC during PD20 small particle adenosine.

* Questionnaires (Asthma Control Questionnaire (ACQ), Bronchial Hyperresponsiveness Questionnaire (BHQ), and Clinical COPD Questionnaire (CCQ).

* Multiple Breath Washout Analysis: Lung Clearance Index, Sacin and Scond before and after provocation test with AMP and small particle adenosine.

* Genome-wide mRNA and miRNA expression, and DNA methylation in epithelial

cells derived from nasal epithelial brushes.

* inflammatory cytokines and chemokines in nasal lining fluid

Study description

Background summary

Rationale: Thus far, most clinical studies investigating the effects of inhaled corticosteroids (ICS) in asthma have concentrated on non-smoking asthmatics. However, a considerable proportion of asthma patients smokes. Cigarette smoke consists of ultra-fine particles with a diameter between 0.1 and 1 µm and therefore reaches even the smallest airways.1 In line with this, it has been reported that smoking is associated with small airways dysfunction..2;3 The latter may help to explain the observation that treatment with course particle inhaled corticosteroids is less effective in smokers with asthma.4;5 Recently, extra-fine particle aerosols such as hydrofluoroalkane-beclomethasone (HFA-QVAR) have become available for the treatment of asthma, which are more likely to reach the smaller airways. Based on the above, we hypothesize that extra-fine particle treatment with HFA-QVAR will be superior in improving small airways dysfunction, especially in ex-smokers and smokers with asthma.

Study objective

Objective: To perform a study comparing the efficacy of extra-fine particle HFA-QVAR 200 µg b.i.d. to an equipotent dose of course particle HFA-beclomethasone (HFA-Clenil) 400 µg b.i.d. and with coarse particle HFA-fluticasone (GSK) 250 µg in ex-smokers and smokers with asthma.

In addition, we aim to investigate the contribution of small airways disease to the clinical expression of asthma. To this, we will assess the association between parameters of large and small airway function and symptoms. In addition, we will assess whether changes in these after the start of anti-inflammatory treatment or after treatment discontinuation are associated with changes in asthma symptoms. In addition, we will investigate whether we can identify specific gene or miRNA expression levels, SNPs, or changes in DNA methylation status that are associated with parameters of large and small airway function. Further, we will investigate the effect of treatment on nasal epithelial gene and miRNA expression profiles as well as DNA methylation status and whether there are differences between HFA-QVAR and HFA-Fluticasone or HFA-Clenil in this respect. Finally, we investigate whether discontinuation of anti-inflammatory treatment (between pre-screening (visit 1) and screening

(visit 2) induces changes nasal epithelial gene and miRNA expression profiles as well as DNA methylation status into the opposite direction.

Study design

Study design: This study will be an open-label, randomised, three-way cross-over, two-center study. 20 smokers and 20 ex-smokers with asthma will receive the following treatments for two weeks:

Intervention

There are three treatment periods of two weeks:
A: 2-week treatment with HFA-QVAR (TEVA) 200 *g b.i.d.
B: 2-week treatment with HFA-Clenil (Chiesi) 400 *g b.i.d.
C: 2-week treatment with HFA-Fluticasone (GlaxoSmithKline) 250 *g b.i.d.

Study burden and risks

*Nasal epithelium collection may cause a temporary nose bleed.
*Blood collection may cause bruising.
*All drugs may cause side effects. The inhaled corticosteroids HFA-QVAR, HFA-Clenil, and HFA-Fluticasone are medicinal products that have been on the market for many years in many countries; therefore side effects associated with each of the compounds and similar to those reported for the other inhaled corticosteroids may be expected.

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

*Males and females with a doctor*s diagnosis of asthma ;*Age between 18 and 65 years;*Current- and ex-smokers with * 5 packyears.;*Drop in FEV1 > 20% after provocation with small particle adenosine < 20 mg at visit 1.

Exclusion criteria

*An asthma exacerbation during the last 6 weeks or upper respiration tract infection during the last 4 weeks prior to inclusion in the study. ;*Severe airway obstruction at visit 1, 2, of 3, i.e. FEV1 < 50% of predicted or < 1.2 liter.;*Maintenance treatment with oral prednisolone.;*Clinically unstable concurrent disease: e.g. hyperthyroidism, diabetes mellitus or other endocrine disease; significant hepatic impairment; significant renal impairment; cardiovascular disease (e.g. coronary artery disease, hypertension, heart failure); gastrointestinal disease (e.g. active peptic ulcer); neurological disease; haematological disease; autoimmune disorders, or other which may impact the evaluation of the results of the study according to investigator*s judgement.;*Ex-smokers who have quit smoking less than 6 months prior to visit 1.;*Pregnant or lactating women. At the first visit 1, a pregnancy test (urine hCG) will be performed in all females.;*Females of childbearing potential without an efficient contraception unless they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels < 40 mIU/mL or use one or more of the following acceptable methods of contraception:;a) Surgical sterilization (e.g. bilateral tubal ligation, hysterectomy).;b) Hormonal contraception (implantable, patch, oral, injectable).;c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/cream/suppository.;d) Continuous abstinence.;Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 30 days after study drug discontinuation.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Clenil
Generic name:	HFA-belomethasone dipropionate
Product type:	Medicine
Brand name:	Flixotide
Generic name:	HFA-Fluticasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	QVAR
Generic name:	HFA-belomethasone dipropionate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-03-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-04-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-08-2013
Application type:	Amendment
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	EUCTR2012-005350-39-NL
ClinicalTrials.gov	NCT01741285
CCMO	NL42875.042.12