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# Extrafine compared to non-extrafine particle inhaled corticosteroids in smokers and ex-smokers with asthma

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ABSTRACT

*Background:* Smoking is as prevalent in asthmatics as in the general population. Asthmatic smokers benefit less from inhaled corticosteroids (ICS) than non-smoking asthmatics, possibly due to more smoking-induced small airways disease. Thus targeting small airways may be important in treating asthmatic (ex-)smokers. We hypothesized that extrafine particle ICS improve small airways function more than non-extrafine particle ICS in asthmatic (ex-)smokers.

*Methods:* We performed an open-label, randomized, three-way cross-over study comparing extrafine beclomethasone (HFA-QVAR) to non-extrafine beclomethasone (HFA-Clenil) and fluticasone (HFA-Flixotide) in 22 smokers and 21 ex-smokers with asthma (≥5 packyears).

*Results:* Improvement from baseline in $PD_{20}$ adenosine after using QVAR, Clenil or Flixotide was 1.04 ± 1.71, 1.09 ± 2.12 and 0.94 ± 1.97 doubling doses, mean ± standard deviation (SD), respectively. The change from baseline in $R_5$-$R_{20}$ at $PD_{20}$ adenosine after using QVAR, Clenil or Flixotide was −0.02 ± 0.27, 0.02 ± 0.21, and −0.02 ± 0.31 kPa $sL^{-1}$, mean ± SD, respectively. The change in $PD_{20}$ adenosine and $R_5$-$R_{20}$ at $PD_{20}$ adenosine were neither statistically significant different between QVAR and Clenil ($p = 0.86$ and $p = 0.82$) nor between QVAR and Flixotide ($p = 0.50$ and $p = 0.96$).

*Conclusion:* Similar effectiveness in improving small airways function was found for extrafine and non-extrafine particle ICS treatment for asthmatic smokers and ex-smokers.



## 1. Introduction

For many years inhaled corticosteroids (ICS) constitute the cornerstone of asthma treatment. This generally results in less symptoms, improves lung function, and reduces airway hyperresponsiveness (AHR) [1]. However, asthma patients who smoke benefit less from ICS treatment, experience worse symptoms and have more severe airflow obstruction, compared to non-smoking asthmatics [2]. Nevertheless, asthmatics smoke as often as the general population [3].

Cigarette smoke consists of particles with a diameter of 0.1–1 μm, which can affect even the smallest airways [4]. It has been shown that smoking is a strong inducer of small airways

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**Abbreviations**

| | |
|---|---|
| ACQ | asthma control questionnaire |
| AHR | airway hyperresponsiveness |
| AMP | adenosine 5′-monophosphate |
| BHQ | bronchial hyperresponsiveness questionnaire |
| BMI | body mass index |
| DPI | dry powder inhaler |
| $FEF_{25-75}$ | forced expiratory flow between 25% and 75% of FVC |
| $FEV_1$ | forced expiratory volume in 1 second |
| FRC | functional residual capacity |
| FVC | forced vital capacity |
| HFA | hydrofluoroalkane |
| ICS | inhaled corticosteroids |
| IOS | impulse oscillometry |
| LABA | long-acting $\beta_2$-agonist |
| LCI | lung clearance index |
| MBNW | multiple breath nitrogen washout |
| MMAD | median mass aerodynamic diameter |
| $PC_{20}$ AMP | provocative concentration of AMP causing a 20% drop in $FEV_1$ |
| $PD_{20}$ adenosine | provocative dose of adenosine causing a 20% drop in $FEV_1$ |
| $R_{20}$ | resistance of the respiratory system at 20 Hz |
| $R_5$ | resistance of the respiratory system at 5 Hz |
| $R_5$-$R_{20}$ | difference between the resistance of the respiratory system at 5 Hz and 20 Hz |
| RV | residual volume |
| SABA | short-acting $\beta_2$-antagonist |
| $S_{acin}$ | ventilation heterogeneity of the acinar lung zone |
| SAD | small airways disease |
| $S_{cond}$ | ventilation heterogeneity of the conductive lung zone |
| SD | standard deviation |
| TLC | total lung capacity |

disease (SAD) [5] and leads to inhomogeneous ventilation of the small airways in healthy subjects, as measured with single and multiple breath nitrogen washout tests [6]. SAD may explain the observations of earlier studies that treatment with non-extrafine particle ICS, which mainly deposit in the larger airways, is less effective in smokers with asthma, with respect to symptoms and pulmonary function improvement [3,7].

Extrafine particle ICS have a median mass aerodynamic diameter (MMAD) of ~1–1.5 μm, which can lead to an increased deposition of the drug in the most peripheral airways [8]. It has been shown that these extrafine particle ICS are effective as treatment of the small airways in non-smoking asthmatics [9–12]. For example, extrafine particle ciclesonide improves AHR to adenosine 5'-monophosphate (AMP) [10] and extrafine particle beclomethasone improves small airways resistance (difference between the resistance of the respiratory system at 5 Hz and 20 Hz ($R_5$-$R_{20}$)) to a larger extent than non-extrafine particle beclomethasone as measured with impulse oscillometry (IOS) [11]. Despite the high prevalence of smoking among asthma patients, for many years, smokers and ex-smokers have been excluded from studies investigating (extrafine particle) ICS [13]. Fortunately, smokers and ex-smokers with asthma are currently included more often. Two recent retrospective studies showed that extrafine particle ICS favored non-extrafine particle ICS with respect to asthma exacerbations and control, particularly in smokers and ex-smokers with asthma [7,14].

Provocation tests with direct stimuli such as methacholine and indirect stimuli such as AMP have been frequently used to assess the efficacy of ICS treatment [15,16]. It has been reported that the provocative concentration of AMP that induces a fall in the forced expiratory volume in 1 second ($FEV_1$) of 20% ($PC_{20}$) improves to a greater extent than $PC_{20}$ methacholine after treatment with ICS [17]. It has therefore been suggested that AMP is a more sensitive tool to monitor airway constriction and its response to ICS in asthma. However, AMP has as major drawback that a substantial part of the asthma patients is unresponsive to AMP, even after inhalation of the highest concentration (between 320 and 400 mg/mL) [16,18]. The recently developed dry powder adenosine resolves this limitation and can be administered in higher doses if needed. As an additional benefit, dry powder adenosine can be produced with different particle sizes [19]. This may imply that the response to extrafine ICS treatment reaching the small airways can be monitored more accurately with dry powder adenosine provocation than with AMP or a direct stimulus.

Since it may be particularly important to treat the small airways in smokers and ex-smokers with asthma, we hypothesized that treatment with extrafine particle ICS, hydrofluoroalkane (HFA)-beclomethasone (QVAR), would improve small airways function to a larger extent than a clinically equivalent dose of non-extrafine particle treatment (HFA-beclomethasone (Clenil) or HFA-fluticasone (Flixotide)).

## 2. Methods

### 2.1. Study design

We performed a two-center, open-label, randomized, three-way cross-over study (clinicaltrails.gov NCT01741285, approved by the ethical committee of the University Medical Center Groningen) (Fig. 1). The treatment arms consisted of two-week treatment with HFA-beclomethasone 200 μg b.i.d. (QVAR, Teva Pharmaceutical Industries Ltd.), HFA-beclomethasone 400 μg b.i.d. (Clenil Modulite, Chiesi Farmaceutici S.p.A) or HFA-fluticasone 250 μg b.i.d. (Flixotide, GlaxoSmithKline plc.) with subsequently an ICS wash-out period of three to six weeks. After the initial screening a washout period of four to six weeks was carried out for oral, inhaled, nasal, and dermal corticosteroids, long-acting $\beta_2$-agonist (LABA), long-acting anticholinergic agents, theophylline, leukotriene antagonists, and antihistamines. Throughout the study, short-acting $\beta_2$-antagonist (SABA) were permitted as rescue medication. At randomization and after each of the three treatment periods, a dry powder adenosine provocation test was performed next to pulmonary function tests and conduction of questionnaires.

### 2.2. Subjects

We included subjects between 18 and 65 years old with a doctor's diagnosis of asthma who were current- or ex-smokers (smoking cessation $\geq$ 6 months prior to the screening) with a smoking history of $\geq$5 packyears. All subjects had an $FEV_1$ > 50% predicted and $\geq$1.2 L, as well as a provocative dose of dry powder adenosine inducing a 20% fall in $FEV_1$ ($PD_{20}$) < 20 mg. Subjects were not allowed to have had an asthma exacerbation or upper airway infection for at least six weeks prior to the study and were excluded if they needed oral prednisolone at any time in the study (moderately severe exacerbation) or could not fulfill a wash-out period