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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

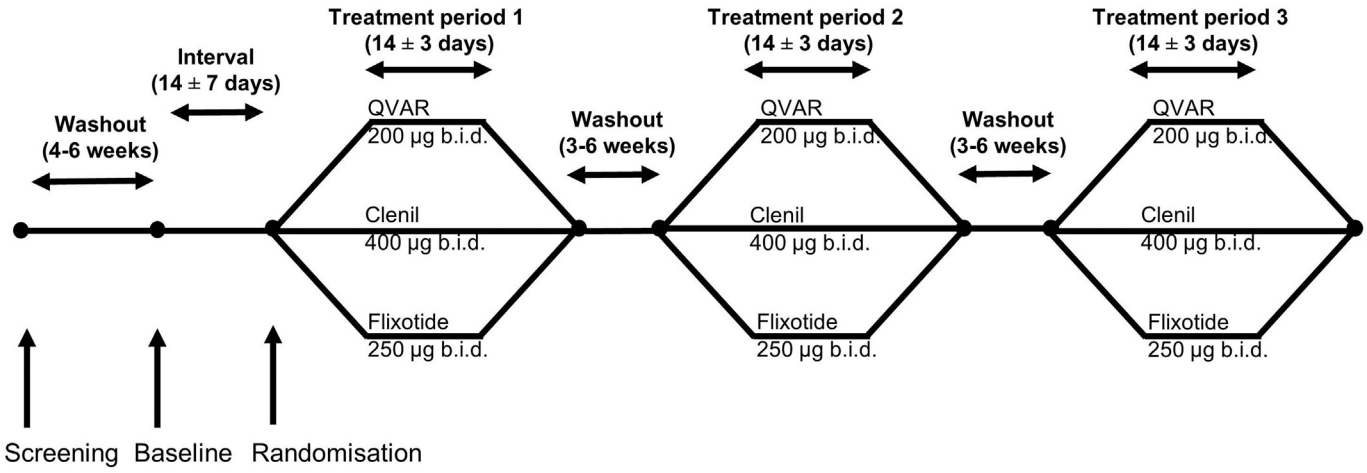


**Fig. 1.** Overview of study visits intervals.
At all visits, spirometry was measured, while the other measurements were only obtained at baseline and after each treatment period. At baseline, a coarse particle adenosine 5'-monophosphate (AMP) provocation was performed (for a parallel study). At the randomization visit, the baseline provocation with dry powder adenosine was performed, before randomization into one of the six possible study paths.

twice (mild exacerbation). Subjects were also excluded if they had clinical unstable concomitant diseases as judged by the investigators, or were pregnant or lactating.

### 2.3. Measurements

#### 2.3.1. Provocation test

Dry powder adenosine provocation was used as primary outcome. In our institution we produced dry powder adenosine with a MMAD of 2.6–2.9 μm [19,20], which is thought to be small enough to reach the small airways when inhaled at a low inspiratory flow rate [21]. The dry powder adenosine was then inhaled on inspiration from functional residual capacity (FRC) to total lung capacity (TLC) through a dry powder inhaler (DPI) guided by an inspiratory flow meter in doubling doses (0.04–80 mg), as described previously [20]. Patients were instructed to inhale at a low inspiratory flow rate (30 L/min), and hold their breath for 10 seconds at TLC, allowing better lung deposition [21]. This procedure was repeated at 3-min intervals. After each provocation step spirometry and IOS measurement were performed consecutively and the Borg dyspnea score [22] was noted. The provocation test stopped when the $FEV_1$ had dropped 20% from baseline or the highest dose (80 mg) was administered. Besides the dry powder adenosine provocation test, we performed a provocation with doubling doses of wet nebulized AMP (0.04–320 mg/ml, MMAD ~7–8 μm [23]) in the context of a parallel study to compare AMP provocation and dry powder adenosine provocation.

#### 2.3.2. Pulmonary function tests

Spirometry, body plethysmography, and IOS were performed according to international standards with the use of reference values by Quanjer et al. [24]. Multiple breath nitrogen washout (MBNW) analysis was performed with 100% pure oxygen inhalation during tidal breathing. The measurement ended when the nitrogen concentration in the exhaled gas was reduced to ≤2.5%. The acinar and conductive airways ventilation heterogeneity ($S_{acin}$ and $S_{cond}$, respectively) as well as the lung clearance index (LCI) were calculated [25]. At all visits spirometry was measured, while the other measurements were only obtained at baseline and after each treatment period. MBNW was only performed in one of the centers, due to the availability of the machine.

#### 2.3.3. Questionnaires

Subjects filled out two questionnaires at the screening visit and at each visit succeeding a treatment period. To evaluate disease control the modified six-question asthma control questionnaire (ACQ) [26] and to assess AHR the bronchial hyperresponsiveness questionnaire (BHQ) [27]. The BHQ is the overall average of a 7-point scale questionnaire assessing the severity of 15 common asthma symptoms and the reaction to 19 regularly encountered provoking stimuli. Lower scores indicate either better asthma control (ACQ) or less AHR (BHQ).

### 2.4. Statistical analyses

The co-primary outcomes were the effect of treatment on dry powder adenosine $PD_{20}$ and the $R_5$-$R_{20}$ matched to the $PD_{20}$ dry powder adenosine. The latter was calculated through linear interpolation of the $R_5$-$R_{20}$ at the second-to-last and last provocation dose, similar to the calculation of the $PD_{20}$ [28]. The secondary outcomes were the change from baseline in asthma control and (small) airways function as measured by forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25-75}$), residual volume (RV)/TLC, $R_5$-$R_{20}$, and $S_{acin}$. All variables were tested for normality of distribution and analyzed accordingly with a two-sided Student's paired *t*-test or a two-sided Wilcoxon test (IBM SPSS statistics version 22). All analyses were performed in the total study population as well as in the subpopulations of smokers and ex-smokers. For the primary outcome, we performed an intention-to-treat analysis, including subjects who participated in at least one treatment period, as well as a per-protocol analysis including only subjects who completed all treatment periods. For the secondary outcomes, only an intention-to-treat analysis was performed. The power calculation was performed on the $PD_{20}$ adenosine assuming a 0.5(±1.05) dose step detectable difference, aiming for a power of 0.8 with a two-sides alpha of 0.05.

## 3. Results

### 3.1. Study population

In total 77 subjects were screened, of which 29 did not meet the in- and exclusion criteria and 5 had withdrawn before randomization (Fig. 2). We randomized 43 subjects (22 smokers and 21 ex-

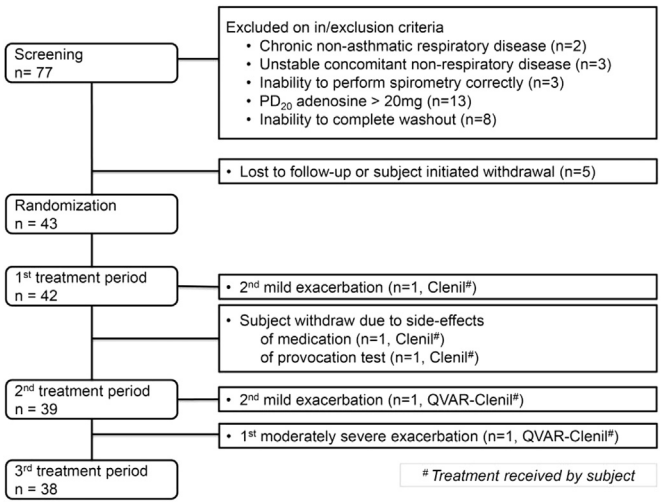


**Fig. 2.** Overview of study participation and reasons for discontinuation, with the moment the drop-out took place.
For randomized subjects is indicated which type of medication and in what order treatment was received.

smokers), but during the study five subjects dropped out. Subsequently, a total of 38 subjects (17 smokers and 21 ex-smokers) completed the study, i.e. all thee treatment periods. All subjects provided written informed consent. Table 1 shows the baseline characteristics for all randomized subjects.

### 3.2. Dry powder adenosine provocation

In the total study population, QVAR, Clenil and Flixotide improved the $PD_{20}$ dry powder adenosine to comparable extents; 1.04 (standard deviation (SD)±1.71), 1.09 (SD ± 2.12) and 0.94 (SD ± 1.97) doubling concentrations, respectively (Fig. 3a). In the current smokers improvements were 0.47 (SD ± 1.15) for QVAR, 0.52 (SD ± 1.81) for Clenil and 0.50 (SD ± 1.21) for Flixotide, while in ex-smokers improvements were 1.56 (SD ± 1.97) for QVAR, 1.62 (SD ± 2.29) for Clenil and 1.28 (SD ± 2.38) for Flixotide (Fig. 3b). The difference in improvement of the $PD_{20}$ dry powder adenosine between current- and ex-smokers was significant for QVAR, but not for Clenil or Flixotide.

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#### 3.2.1. $R_5$-$R_{20}$ at $PD_{20}$ adenosine

QVAR, Clenil and Flixotide changed the resistance of the small airways after provocation, expressed as the $R_5$-$R_{20}$ at $PD_{20}$ adenosine, to a similar extent in the total study population. Likewise, no significant difference was observed between current smokers and ex-smokers (Fig. 4).

### 3.3. Questionnaires

In the total study population, treatment with QVAR, Clenil, and Flixotide reduced the BHQ and ACQ scores equivalently, indicating less bronchial hyperresponsiveness and better asthma control. The BHQ score improved to a significantly larger extent after treatment with Flixotide than after treatment with QVAR (Table 2). In the subgroups of current smokers and ex-smokers separately, none of the treatments outperformed the others with respect to improvements in BHQ and ACQ scores.

### 3.4. Pulmonary function tests

#### 3.4.1. Spirometry

In the total population and the subgroup of ex-smokers, baseline $FEV_1$ % predicted and $FEF_{25-75}$ % predicted were significantly higher after treatment with Clenil compared to QVAR (Table 2). There were no significant differences between QVAR and Flixotide.

#### 3.4.2. IOS

In the total population, no significant differences in $R_5$, $R_{20}$ or $R_5$-$R_{20}$ changes from baseline were observed after treatment with

**Table 1**
Baseline characteristics.

| | Total | Smokers | Ex-Smokers |
|---|---|---|---|
| | n = 43 | n = 22 | n = 21 |
| Male, n (%) | 18 (41.9) | 9 (40.9) | 9 (42.9) |
| Age, Years | 44.98 (12.64) | 39.55 (12.01)[@] | 50.67 (10.84)[@] |
| Number of pack-years,# | 16.80 (11.00–24.00) | 20.00 (11.75–29.44) | 14.00 (10.00–23.00) |
| BMI, kg $m^{-2}$ | 26.54 (5.62) | 25.83 (6.14) | 27.27 (5.08) |
| $PD_{20}$ adenosine, mg + | 2.69 (3.41) | 2.38 (3.25) | 3.07 (3.66) |
| $PC_{20}$ AMP, mg $mL^{-1}$ + | 33.82 (10.48) | 18.13 (10.93) | 64.89 (8.82) |
| BHQ, points | 1.54 (1.02) | 1.93 (0.95) | 1.20 (0.96) |
| ACQ, points | 1.42 (0.91) | 1.73 (0.73) | 1.16 (0.98) |
| $FEV_1$, % predicted | 83.23 (14.47) | 82.73 (11.98) | 83.76 (16.99) |
| $FEV_1$/FVC, % | 67.48 (10.24) | 69.59 (10.84) | 65.26 (9.31) |
| $FEF_{25-75}$, % predicted | 49.02 (22.56) | 52.50 (22.22) | 45.38 (22.87) |
| RV, % predicted | 114.74 (27.57) | 113.05 (28.81) | 116.52 (26.81) |
| RV/TLC, % predicted | 102.49 (18.96) | 102.86 (17.79) | 102.10 (20.55) |
| $R_5$, kPa $sL^{-1}$ | 0.56 (0.20) | 0.57 (0.22) | 0.55 (0.18) |
| $R_{20}$, kPa $sL^{-1}$ | 0.43 (0.11) | 0.46 (0.13) | 0.40 (0.08) |
| $R_5$-$R_{20}$, kPa $sL^{-1}$ | 0.13 (0.13) | 0.11 (0.13) | 0.15 (0.13) |
| Lung clearance Index at 2.5% | 10.21 (2.06) | 9.74 (1.72) | 10.63 (2.28) |
| $S_{cond}$, $L^{-1}$ | 0.04 (0.03) | 0.04 (0.02) | 0.04 (0.03) |
| $S_{acin}$, $L^{-1}$ | 0.17 (0.09) | 0.14 (0.06)[@] | 0.20 (0.11)[@] |

Data is presented as mean with standard deviation, unless stated otherwise: # Median with Interquartile rang, + Geometric Mean with Geometric Standard deviation. [@]Significant difference between smokers and ex-smokers at baseline. Abbreviations: BMI: body mass index; $PD_{20}$ adenosine: provocative dose of adenosine causing a 20% drop in $FEV_1$; $PC_{20}$ AMP: provocative concentration of AMP causing a 20% drop in $FEV_1$; BHQ: bronchial hyperresponsiveness questionnaire; ACQ: asthma control questionnaire; $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75}$: forced expiratory flow between 25% and 75% of FVC; RV: residual volume; TLC: total lung capacity; $R_5$: resistance of the respiratory system at 5 Hz; $R_{20}$: resistance of the respiratory system at 20 Hz; $R_5$-$R_{20}$: difference between the resistance of the respiratory system at 5 Hz and 20 Hz; $S_{acin}$: ventilation heterogeneity of the acinar lung zone; $S_{cond}$: ventilation heterogeneity of the conductive lung zone.

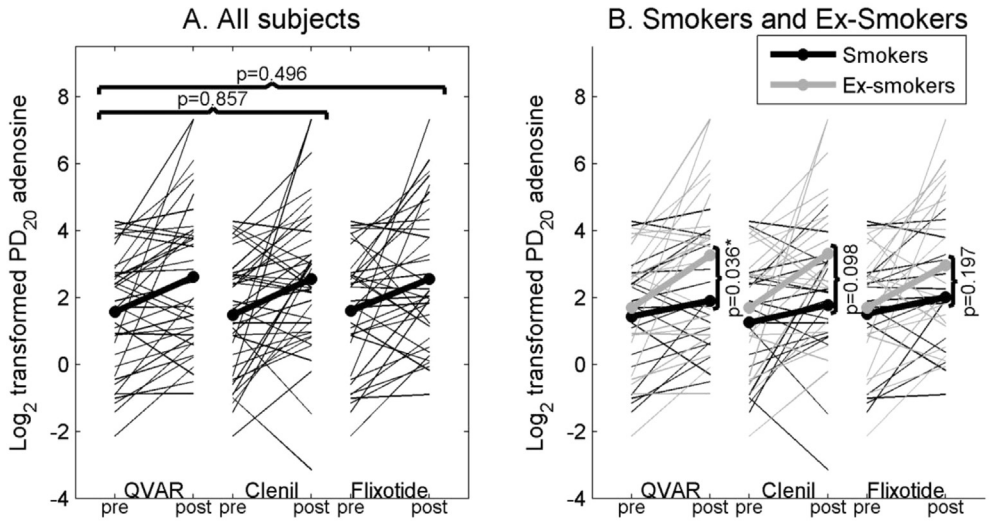


**Fig. 3.** $PD_{20}$ adenosine results of the intention-to-treat analysis.
The change in provocative dose of adenosine causing a 20% drop in forced expiratory volume in 1 s ($FEV_1$) ($PD_{20}$ adenosine) for each of the three treatments is shown. Each line depicts a subject, the bold line depicts the mean change in $PD_{20}$ adenosine in response to the treatment. A) the total population, whereas B) distinguishes smokers from ex-smokers. In the QVAR group the smokers differ significantly from the ex-smokers (*). One unit change in $log_2$ transformed $PD_{20}$ adenosine equals one dose step change.

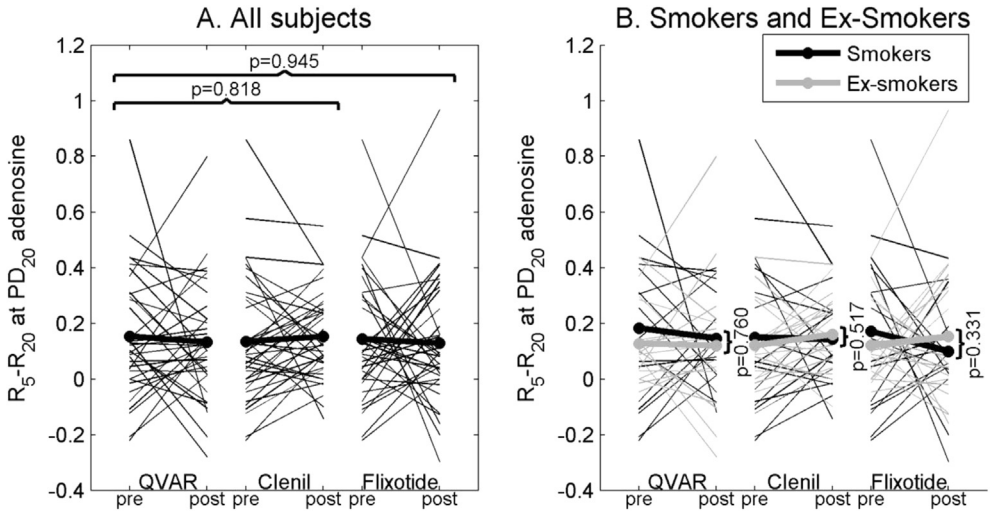


**Fig. 4.** $R_5$-$R_{20}$ at $PD_{20}$ adenosine results of the intention-to-treat analysis.
The change in the difference between the resistance of the respiratory system at 5 Hz and 20 Hz ($R_5$-$R_{20}$) at provocative dose of adenosine causing a 20% drop in forced expiratory volume in 1 second ($FEV_1$) ($PD_{20}$ adenosine for each of the three treatments is shown. Each line depicts a subject, the bold line depicts the mean of the change in $R_5$-$R_{20}$ at $PD_{20}$ in response to the treatment. A) the total population, whereas B) distinguishes smokers from ex-smokers. No significant differences were observed.

QVAR, Clenil or Flixotide (Table 2). Clenil showed a trend towards better performance than QVAR in the $R_5$ and $R_{20}$. The difference between Clenil and QVAR in the $R_5$ and $R_{20}$ was significant in the subpopulation of smokers, but not in the subpopulation of ex-smokers. The differences between treatment with QVAR and Flixotide were not-significant.

### 3.4.3. MBNW

In the total population (due to the availability of the measurement only 29 subjects) and in the subpopulations of current- and ex-smokers, all treatments performed comparably regarding changes in LCI, $S_{cond}$ and $S_{acin}$ (Table 2).

## 4. Discussion

We did not confirm our hypothesis that treatment with HFA-QVAR improves small airways function to a larger extent than treatment with HFA-Clenil or HFA-Flixotide in smokers and/or ex-smokers with asthma. The $PD_{20}$ adenosine and the $R_5$-$R_{20}$ at $PD_{20}$ adenosine changed to a similar extent after treatment with extrafine particle treatment (QVAR) compared to treatment with the same ICS in non-extrafine particle formulation (Clenil) and Flixotide.

Our results differ from those of Contoli et al. [29] who also investigated the efficacy of extrafine particle treatment in smokers with asthma. In this study, smokers and never-smokers with asthma, initially treated with non-extrafine particle ICS, were switched to an equipotent dose extrafine particle beclomethasone for a period of three months. This treatment was combined with an extrafine particle LABA in subjects who were treated with ICS/LABA prior to the study (76% of the 25 smokers and 80% of the 25 never-smokers). The extrafine particle treatment intervention

**Table 2**
Change (Δ) from baseline for the questionnaires and pulmonary function tests.

| | Total QVAR | | Total clenil | | Total flixotide | |
|---|---|---|---|---|---|---|
| | Smokers | Ex- smokers | Smokers | Ex- smokers | Smokers | Ex- smokers |
| Δ BHQ | −0.31 (0.58)# | | −0.44 (0.68) | | −0.47 (0.80)# | |
| | −0.26 (0.62) | −0.35 (0.55) | −0.45 (0.81) | −0.44 (0.55) | −0.53 (0.89) | −0.43 (0.73) |
| Δ ACQ | −0.27 (0.78) | | −0.33 (0.86) | | −0.24 (0.99) | |
| | −0.19 (0.68) | −0.33 (0.86) | −0.15 (0.93) | −0.51 (0.77)+ | −0.09 (1.23) | −0.35 (0.77) |
| Δ $FEV_1$, % predicted | 0.28 (6.14)* | | 2.0976 (5.910)* | | 0.71 (6.85) | |
| | 0.68 (7.84) | −0.10 (4.24)* | 1.40 (5.03) | 2.76 (5.38)* | 0.59 (8.21) | 0.81 (5.74) |
| ÄΔ $FEV_1$/FVC | −0.19 (3.71) | | 0.34 (3.88) | | −0.02 (4.32) | |
| | −0.66 (4.44) | 0.26 (2.90)* | −0.87 (4.18) | 1.49 (3.27)* | −0.48 (5.67) | 0.35 (2.90) |
| ÄΔ $FEF_{25-75}$, % predicted | −0.49 (9.46)* | | 2.22 (9.36)* | | 0.13 (10.14) | |
| | −1.21 (10.44) | 0.16 (8.68)* | −0.90 (9.65)$ | 5.19 (8.23)* $ | −1.12 (13.64) | 1.14 (6.23) |
| ÄΔ RV, % predicted | −0.25 (23.10) | | −1.56 (15.68) | | −5.72 (31.38) | |
| | 4.36 (27.15) | −4.43 (19.12) | −2.50 (9.93) | −0.67 (19.91) | 0.88 (13.73) | −11.07 (40.05) |
| ÄΔ RV/TLC, % predicted | 0.82 (22.83) | | −1.68 (12.78) | | −1.18 (14.28) | |
| | 4.74 (28.53) | −2.71 (16.01) | −2.80 (7.78) | −0.62 (16.32) | −0.059 (10.62) | −2.095 (16.88) |
| ÄΔ $R_5$, kPa $sL^{-1}$ | 0.01 (0.97) | | −0.02 (0.09) | | 0.01 (0.13) | |
| | 0.025 (0.09)* | 0.004 (0.10) | −0.04 (0.09)* | 0.003 (0.10) | −0.02 (0.13) | 0.03 (0.14) |
| ÄΔ $R_{20}$, kPa $sL^{-1}$ | 0.005 (0.06) | | −0.02 (0.70) | | −0.003 (0.08) | |
| | 0.01 (0.04)* | 0.001 (0.07) | −0.04 (0.06)* | 0.002 (0.08) | −0.02 (0.06) | 0.013 (0.09) |
| ÄΔ $R_5$-$R_{20}$, kPa $sL^{-1}$ | 0.01 (0.08) | | −0.002 (0.06) | | 0.01 (0.09) | |
| | 0.01 (0.09) | 0.01 (0.07) | −0.004 (0.06) | 0.000 (0.06) | −0.005 (0.10) | 0.02 (0.08) |
| ÄΔ $LCI^{X}_{2.5\%}$ | −0.44 (1.15) | | −0.35 (1.51) | | −0.69 (2.89) | |
| | −0.99 (1.49) | 0.03 (1.21) | −0.77 (1.82) | −0.03 (1.17) | −0.87 (1.75) | −0.58 (3.45) |
| ÄΔ $S_{cond}$, $L^{-1x}$ | −0.003 (0.02) | | −0.01 (0.02) | | −0.01 (0.02) | |
| | −0.01 (0.03) | −0.001 (0.02) | −0.01 (0.02) | −0.01 (0.02) | −0.003 (0.03) | −0.01 (0.02) |
| ÄΔ $S_{acin}$, $L^{-1x}$ | 0.01 (0.05) | | −0.01 (0.04) | | −0.01 (0.08) | |
| | 0.002 (0.05 | 0.01 (0.05) | 0.000 (0.04) | −0.01 (0.05) | −0.01 (0.02) | −0.01 (0.11) |

A negative value corresponds with a lower score or value after treatment.
Data is presented as means (SD). Every column shows one of the treatments, with in each parameter row first the total study population, followed by the subpopulation of smokers and ex-smokers. Comparisons were performed pairwise for each treatment arm (QVAR-Clenil, QVAR-Flixotide, and Clenil-Flixotide) in the total population as well as the subpopulations of smokers and ex-smokers.
Results are presented as mean (standard deviation). * Significant difference ($p < 0.05$) between QVAR and Clenil, # Significant difference ($p < 0.05$) between QVAR and Flixotide, $ significant difference ($p < 0.05$) between smokers and ex-smokers, +reached clinically minimal important difference for ACQ 0.5, X Due to availability of the measurement device MBNW was only performed in 29 subjects.
Abbreviations: BHQ: bronchial hyperresponsiveness questionnaire; ACQ: asthma control questionnaire; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75}$: forced expiratory flow between 25% and 75% of FVC; RV: residual volume; TLC: total lung capacity; $R_5$: resistance of the respiratory system at 5 Hz; $R_{20}$: resistance of the respiratory system at 20 Hz; $R_5$-$R_{20}$: difference between the resistance of the respiratory system at 5 Hz and 20 Hz; $LCI_{2.5\%}$: Lung clearance index at 2.5%; $S_{acin}$: ventilation heterogeneity of the acinar lung zone; $S_{cond}$: ventilation heterogeneity of the conductive lung zone.

significantly improved small airways function in smoking, but not in never-smoking asthmatics, as measured with the single breath nitrogen washout test and $R_5$-$R_{20}$ values. A possible explanation for the difference between our findings and those of Contoli et al. may be the use of (extrafine particle) LABAs in the majority of their asthma patients, while in our study LABA use was prohibited. In this context the findings of Clearie et al. are of interest [30], showing that combining a LABA with ICS treatment in smokers with asthma improved bronchial hyperresponsiveness to a greater extent than doubling the ICS dose. In agreement with this, Brusselle et al. showed that combination treatment with extrafine ICS/LABA is as effective in current- as in never-smokers with asthma in terms of improvement of $FEV_1$ and ACQ scores [31]. In line with these findings, Contoli et al. found in a subgroup analysis that the improvement in small airways function in smoking asthma patients was significantly greater following extrafine particle ICS/LABA treatment compared to ICS treatment alone.

Roche et al. [7] also reported results different from ours, in a retrospective observational study including current- and ex-smoking asthma patients. They compared extrafine to non-extrafine particle ICS treatment without additional LABA treatment. Although this was a retrospective study, with only a partial characterization of patients most of whom lacked recorded lung function and detailed information on smoking, they observed fewer exacerbations and respiratory tract infections during a period of one year in current- and ex-smokers when treated with extrafine particle compared to non-extrafine particle ICS. Obviously, we treated far too short to assess such long term effects, but rather focused on a response within the rising arm of the effect, which is at least for budesonide already detectable after one week of treatment with AMP provocation [32]. It remains possible that we would have found different results with a longer treatment period.

An unexpected finding of our study was a greater improvement in $FEV_1$ after treatment with Clenil compared to QVAR (Table 2). Since several studies showed that extrafine HFA-beclomethasone is approximately twice as effective in improving the $FEV_1$ as its predecessor chlorofluorocarbon (CFC)-beclomethasone [33,34] and because non-extrafine HFA-beclomethasone is equivalently effective to the CFC-beclomethasone [35,36], we specifically corrected for this dosage inequivalence between extrafine particle and non-extrafine particle beclomethasone in our study. However, our results make us question the validity of this 1:2 dose ratio between Clenil and QVAR. In this context, the different device properties may be important. Compared to CFC-devices, HFA-pressurized metered-dose inhalers have higher spray temperatures and lower plume velocities [37] which both contribute to a higher total lung deposition. It can be concluded that it remains difficult to investigate the effects of particle size alone in clinical studies given the differences in dose and inhaler devices. In a future study we plan to compare extrafine and non-extrafine particle ICS in exactly the same device and dose in a double-blind randomized controlled study.

Treatment with extrafine QVAR led to a statistically significantly larger improvement of the $PD_{20}$ adenosine in ex-smokers than in

current smokers (Fig. 3). It is commonly accepted that smoking is associated with a lower susceptibility to corticosteroids [38]. However, no studies so far compared current- with ex-smokers with respect to ICS treatment responsiveness in a randomized controlled trial and only three previous corticosteroid studies have included both current- and ex-smokers with asthma as separate groups to compare them to never-smokers [39–41]. These studies observed that the response to steroid treatment is significantly greater in never-smokers than in current smokers, but not significantly different between never- and ex-smokers. Taken together, our data align with previous findings that current smokers respond less to corticosteroid treatment than ex-smokers, and suggest that this difference in effect may be even more pronounced for extrafine particle treatment.

A strength of our study is the cross-over design, which guaranteed an equal distribution of patient characteristics among the three treatment groups. Our study, however, also has some limitations. Our primary aim was to investigate whether QVAR would be more effective in improving small airways function. To this end we used the $PD_{20}$ adenosine as a primary end parameter, which is based on the 20% drop in $FEV_1$, which is primarily a measure of the larger airways. To address this issue we incorporated the $R_5$-$R_{20}$ at $PD_{20}$ adenosine as a co-primary outcome, as this is assumed to be a measure of the small airways. Furthermore, we performed an open-label study, which is generally more prone to bias such, as different patient perceptions and investigator observations. Finally, it could be speculated that our sample size has been to small, even though our study has been one of the largest and most detailed, in terms of subject characterization and amount of parameters that were taken into account, randomized, cross-over studies investigating the efficacy of extrafine particle ICS. However, we consider this less likely, because we did not find any differences in the primary or secondary outcome parameters, or even observed a trend to support our hypothesis.

In conclusion, extrafine particle ICS treatment improves small airways function, measured with dry powder adenosine provocation, to the same extent as non-extrafine particle ICS treatment in current- and ex-smokers with asthma. In ex-smokers, we observed greater corticosteroid treatment responsiveness than in current smokers. We speculate that this difference in effect may be greater for extrafine particle compared to non-extrafine ICS, yet this remains to be confirmed in future studies.

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