Novel Functional Imaging of Changes in Small Airways of Patients Treated with Extrafine Beclomethasone/Formoterol

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Key Words

Asthma · Clinical trial · Extrafine beclomethasone/formoterol · Functional imaging · Small airways · High-resolution computed tomography · Computational fluid dynamics

Abstract

Background: Inhaled formulations using extrafine particles of long-acting β_2 -agonists and corticosteroids were developed to optimize asthma treatment. Findings that these combinations reach and treat smaller airways more effectively are predominantly based on general non-specific outcomes with little information on regional characteristics. **Objectives:** This study aims to assess long-term effects of extrafine beclomethasone/formoterol on small airways of asthmatic patients using novel functional imaging methods. **Methods:** Twenty-four stable asthma patients were subdivided into three groups (steroid naive, $n = 7$; partially controlled, $n = 6$; well controlled, $n = 11$). Current treatment was switched to a fixed combination of extrafine beclomethasone/formoterol (Foster[®]; Chiesi Pharmaceuticals, Parma, Italy). Patients underwent lung function evaluation and thorax high-resolution computerized tomography (HRCT) scan. Local airway resistance was obtained from computational fluid dynamics (CFD). **Results:** After 6 months, the entire

population showed improvement in pre-bronchodilation imaging parameters, including small airway volume ($p = 0.0007$), resistance ($p = 0.011$), and asthma control score ($p = 0.016$). Changes in small airway volume correlated with changes in asthma control score ($p = 0.004$). Forced expiratory volume in 1 s ($p = 0.044$) and exhaled nitric oxide ($p = 0.040$) also improved. Functional imaging provided more detail and clinical relevance compared to lung function tests, especially in the well-controlled group where only functional imaging parameters showed significant improvement, while the correlation with asthma control score remained. **Conclusions:** Extrafine beclomethasone/formoterol results in a significant reduction of small airway obstruction, detectable by functional imaging (HRCT/CFD). Changes in imaging parameters correlated significantly with clinically relevant improvements. This indicates that functional imaging is a useful tool for sensitive assessment of changes in the respiratory system after asthma treatment.

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Introduction

The prevalence of asthma continues to rise, stimulating an ongoing effort in the development of new inhaled medications to optimize the treatment of asthmatic patients.

A number of studies have supported the benefit of combining a long-acting β_2 -agonist (LABA) with inhaled corticosteroids (ICS) [1, 2]. While the LABA induces smooth muscle relaxation and hence reduced airway constriction, the ICS is predominantly used to control the airway disease and therefore reduces the number and frequency of exacerbations [3]. Combination products are typically administered using either dry powder inhalers or metered dose inhalers (MDIs). The shift from environmentally unfriendly chlorofluorocarbons to hydrofluoroalkane (HFA) propellants allows the development of HFA solution formulations. These are optimized to either achieve particle deposition patterns similar to established chlorofluorocarbon-based drug formulations (aerosol diameter size for MDIs being 3–4 μm), thus facilitating the transition to new environment-friendly pressurized MDIs (pMDIs) in the clinical setting, or to achieve extrafine drug particles able to penetrate deeper into the airways (aerosol diameter size 1–2 μm) [4]. Initial findings demonstrated that a combination of extrafine beclomethasone/formoterol (BDP/F) improved lung function with a similar efficacy compared to other non-extrafine fixed combinations. This finding is not surprising considering that the spirometric tests [i.e. forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF)] performed in these studies did not provide a comprehensive evaluation of the entire bronchial tree as they lack sufficient resolution to describe subtle changes in the small airways [5, 6]. This has prompted the need for developing new image-based [7, 8] techniques capable of detecting functional changes occurring in the more distal part of the lung following the administration of drugs able to reach and treat small airways [9–11].

Novel functional imaging (FI) methods using computational fluid dynamics (CFD) provide new opportunities to gain insights into the mode of action of newly developed inhalation compounds targeting small airways. By converting patient-specific high-resolution computed tomography (HRCT) images to detailed three-dimensional computer models of the airways, CFD allow the description of flow properties and aerosol behavior in the smaller airways (diameter 1–2 mm). By repeating measurements after an intervention, this approach yields a personalized assessment of changes in airway volume and CFD-based resistance. The method has been used in previous studies to assess morphological and flow features of large [12] and small [13] airways. A recent validation study [14] by our group demonstrated very good agreement between the HRCT/CFD method and imaging methods such as single photon emission computed tomography (SPECT). In other studies, we showed that FI

could be used to assess the acute bronchodilating effects of a LABA in asthma [15] and chronic obstructive pulmonary disease (COPD) [16].

However, a trial evaluating the long-term effects of asthma medications on the imaging parameters described above is still lacking. Therefore, this trial aims to assess whether FI can be used to describe changes occurring in the small airways of asthmatic patients following a 6-month treatment period with BDP/F (which is able to target the distal airways). Steroid-naïve patients, as well as subjects already treated with non-extrafine fixed combinations, were enrolled in this study. This allowed the assessment of whether introduction of an extrafine treatment can induce additional changes in the small airways in steroid-naïve patients and patients previously treated with non-extrafine combination therapies.

Material and Methods

Patient Selection

This study involved 24 stable asthmatic patients, as defined by the GINA guidelines (Global strategy for asthma management and prevention). Patients were subdivided into three different groups according to their treatment phenotype. The first group comprised steroid-naïve asthmatics ($n = 7$). The remaining 17 patients were already under treatment with a daily beclomethasone-equivalent dose of 500–1,000 μg at inclusion and were divided into two groups according to their level of asthma control as measured by the asthma control test (ACT) [17]: 6 were partially controlled and 11 well controlled ($n = 11$). All patients gave their informed consent and the study was approved by the Ethics Committee of the University Hospital in Antwerp.

Study Medication

Enrolled patients were switched from their current treatment [short-acting β_2 -agonist (SABA), LABA, or ICS/LABA fixed combinations] to a fixed combination of extrafine HFA solution of BDP/F (Foster®; Chiesi Pharmaceuticals, Parma, Italy) 100/6 μg , 2 inhalations twice daily, delivered via a pMDI device. The study medication has a smaller mean mass aerodynamic diameter (MMAD = 1.3–1.4 μm) compared to medications that patients were receiving before inclusion (MMAD = 2.5–4 μm).

Lung Function Tests and FI

All patients underwent full lung function evaluation and HRCT scan of the thorax at inclusion and after 6 months of treatment with the study medication. To assess only the long-term effects of the compound on pre-bronchodilation airway geometry and not the acute bronchodilator effect, all tests were performed in the morning, before the patients took their medication and following an appropriate wash-out period for short- and long-acting bronchodilators (>12 and >24 h, respectively).

Lung function tests included spirometry, full body plethysmography, exhaled nitric oxide (eNO), blood gases, and ACT questionnaire. The following parameters were considered for this study:

- FEV₁;
- Tiffeneau ratio [FEV₁/forced volume vital capacity (FVC)];
- Specific airway resistance (sRaw);
- eNO;
- ACT score.

HRCT scans were taken on a GE LightSpeed VCT scanner using a dose reduction protocol (120 kV, 10–100 mA s; noise factor 28; collimation 0.625 mm; rotation time 0.6 s, and pitch factor 1.375) resulting in an effective dose of 1–2 mSv per HRCT scan. Scan resolution was 0.5 mm² and slice increment was 0.6 mm. Scans were taken during a breath hold at two different lung levels, i.e. functional residual capacity and total lung capacity (TLC). The arms of the patients were raised above their heads. To ensure the correct lung volume, HRCT scans were respiratory volume gated during the moment of scanning using a pneumotach flow signal.

Subsequently, HRCT images were imported into Mimics, a commercial FDA-approved medical image processing software package (Materialise, Leuven, Belgium; Food and Drug Administration, K073468; CE certificate, BE 05/1191 CE01). This software package converts HRCT images into patient-specific, three-dimensional computer models of the lung lobes and the airway tree. By segmenting lung lobes at functional residual capacity and TLC, the internal airflow distribution could be derived from the relative volume change. The airway tree, i.e. intraluminal air, was evaluated at TLC level and could be segmented down to bronchi with a diameter of about 1–2 mm. Beyond this point, the HRCT resolution is insufficient to distinguish alveolar and intraluminal air. A typical airway model includes 5–10 generations, depending mainly on the disease state of the individual patient. Distal airway volumes (iVaw) could be assessed at individual airways or in different regions. Figure 1 shows a division of a segmented airway model in central airways (gray) and distal airways (red, starting at the segmental level). From previous studies it is known that BDP/F reaches both large and small airways [12]; therefore, in this study, we focused predominantly on the small airway region.

The smoothed airway models were subsequently trimmed perpendicular to the center lines at the trachea and the terminal bronchi to obtain a model that is suitable for flow simulation. Next, these models were exported to a meshing software package (TGrid 5.0; Ansys Inc., Lebanon, N.H., USA) where they were divided into discrete tetrahedral elements. After proper mesh convergence analysis, mesh size for this study was set to 4 million elements. Based on the resulting computational mesh, flow properties were obtained throughout the entire flow domain by means of Reynolds-averaged Navier-Stokes (RANS) CFD (Fluent 6.3.26; Ansys Inc.). A steady normal inspiratory flow of 25 l/min was simulated for all patients to mimic the flow properties at tidal breathing. The outflow to each lobe was adjusted iteratively for each patient to match the internal flow rate distribution obtained from the HRCT scans. Measures of resistance (iRaw) at TLC in individual airways or different regions, corresponding to the volume measurements, were obtained from CFD calculations. Resistance was defined as the total pressure drop over an airway divided by the flow rate through that airway.

Statistical Analysis

Statistical analysis was performed using Statistica 9.1 (StatSoft, Tulsa, Okla., USA). Changes in individual parameters after 6 months of treatment with the study medication were evaluated using Wilcoxon matched pairs analysis. Correlations between the

Fig. 1. Frontal view of three-dimensional reconstruction of airway structure from HRCT images showing central (gray) and distal (red) airways. The main focus in this study was on the distal (red) airways.

changes in different parameters were evaluated using Spearman correlations. Differences between the three groups of patients were assessed using Mann-Whitney U test. Sample size calculations were performed using t test for dependent samples. All statistical tests were considered significant when $p < 0.05$.

Results

Total Study Population

A total of 24 asthmatic subjects (all Caucasian, 16 females, 52.8 ± 11.9 years of age) were analyzed in this study. Medications used by the patients before enrollment are listed in table 1. The majority of patients were treated with ICS/LABA combinations delivered as fixed combinations ($n = 17$), while 2 patients were treated with LABA only. Reliever therapy consisted of the use of SABAs ($n = 5$) or a fixed combination of SABAs and muscarinic antagonists ($n = 2$) and short-acting muscarinic antagonists ($n = 1$).

Considering the entire population, a significant difference was found in all parameters except FVC, FEV₁/FVC, and sRaw after 6 months of treatment with the study medication (table 2). A significant improvement was ob-

Table 1. List of medications taken by enrolled patients before entering the study

No.	Group	ICS	LABA	LABA + ICS	SABA	SAMA
1	WC	–	–	Seretide 50/500, 2 × 1/day	–	–
2	PC	–	–	Seretide 50/500, 2 × 1/day	Ventolin PRN	–
3	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 1/day	–	–
4	SN	–	–	–	Ventolin (aerosol): 5 mg/ml, 6 drops, 3×/day	Atrovent (aerosol) 0.5 mg/ml: 0.5 mg/day
5	PC	–	–	Symbicort turbohaler 4.5/160, 2 × 2/day	–	–
6	SN	–	Oxis 4.5 µg, 2 × 2/day	–	–	–
7	WC	–	–	Seretide 50/250, 2 × 1/day	–	–
8	PC	–	–	Symbicort turbohaler 4.5/160, 2 × 1/day	–	–
9	PC	–	–	Symbicort turbohaler 4.5/160, 2 × 2/day	–	–
10	WC	–	–	Seretide 25/250, 2 × 1/day	Ventolin PRN	–
11	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 2/day	–	–
12	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 2/day	–	–
13	PC	–	–	Symbicort turbohaler 4.5/160, 2 × 2/day	–	–
14	SN	–	Foradil 12 µg, 2×/day	–	Ventolin, PRN	–
15	SN	–	–	–	Ventolin, 100 µg, 3 × 2/day	–
16	PC	–	–	Seretide 25/250, 2 × 1/day	Duovent, PRN	–
17	SN	–	–	–	–	–
18	SN	–	–	–	–	–
19	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 2/day	–	–
20	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 1/day	–	–
21	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 1/day	–	–
22	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 1/day	–	–
23	WC	–	–	Symbicort turbohaler 4.5/160, 2 × 1/day	–	–
24	SN	–	–	–	Duovent, PRN	–

WC = Well controlled; PC = partially controlled; SN = steroid naive; SAMA = short-acting muscarinic antagonist; – = not applicable. The following inhaled therapies are referenced in the table: Atrovent = ipratropium bromide; Duovent = fenoterol hydrobromide + ipratropium bromide; Foradil = formoterol fumarate dehydrate/eformoterol; Oxis = formoterol fumarate dehydrate; Seretide = salmeterol + fluticasone propionate; Symbicort = budesonide + formoterol fumarate dehydrate; Ventolin = salbutamol sulfate.

served in asthma control with an increase in the ACT score from 19.79 ± 4.46 at baseline to 21.67 ± 4.55 at the end of treatment ($p = 0.016$). FEV₁ increased from $96.3 \pm 15.72\%$ of predicted normal values to $100.1 \pm 16.8\%$ ($p = 0.044$). Significant changes were recorded also in imaging parameters with airway volume (iVaw) increasing from 8.36 ± 4.71 to 9.64 ± 5.19 cm³ ($p = 0.0007$), and CFD-based airway resistance (iRaw) decreasing from 0.082 ± 0.084 to 0.050 ± 0.030 kPa s/l ($p = 0.01$), with a maximal increase in iVaw of 11.7% of the baseline value.

Figure 2 shows that changes in iVaw and iRaw occurred predominantly in the smaller, more distal airways while changes in larger airways were less pronounced. In addition, changes in iVaw significantly correlated with changes in ACT score ($R = 0.49$, $p = 0.015$; fig. 3). At the end of treatment, a significant decrease was detected in eNO ($p = 0.040$), which showed a ~38% reduction versus baseline.

Steroid-Naive Patients

For the steroid-naive group, which included 7 asthmatic patients (baseline FEV₁ = 93.3% of predicted normal value), treatment did not result in significant changes in lung function parameters as measured by spirometry or body plethysmography (table 2). However, FI analysis showed a significant improvement in iVaw from 7.24 ± 4.23 to 9.14 ± 6.57 cm³ ($p = 0.043$) and an improvement, although not significant, in iRaw from 0.107 ± 0.112 to 0.061 ± 0.039 kPa s/l. A non-significant trend was observed also for eNO, which decreased by 50% by the end of the study. Treatment of steroid-naive patients with extrafine BDP/F resulted in significant improvement of asthma control, as shown by the increase in ACT score from 15.29 ± 5.02 to 19.29 ± 6.85 ($p = 0.018$).

Table 2. Changes in imaging and lung function parameters after 6 months of treatment with extrafine BDP/F

	Baseline		6 months		p value
	average	SD	average	SD	
Total (n = 24)					
iVaw, cm ³	8.36	4.71	9.64	5.19	0.0007*
iRaw, kPa s/l	0.082	0.084	0.050	0.030	0.011*
Δp _{tot} , Pa	34.1	35.0	20.8	12.5	0.011*
FEV ₁ , %	96.3	15.72	100.08	16.80	0.044*
FVC, l	3.82	0.99	3.85	1.01	0.584
FEV ₁ /FVC, %	70.93	6.65	72.89	6.44	0.110
eNO, ppb	44.07	54.78	27.48	29.47	0.040*
sRaw, kPa s/l	1.52	0.71	1.40	0.84	0.225
ACT score	19.79	4.46	21.67	4.55	0.016*
Steroid naïve (n = 7)					
iVaw, cm ³	7.24	4.23	9.14	6.57	0.043*
iRaw, kPa s/l	0.107	0.112	0.061	0.039	0.237
Δp _{tot} , Pa	44.6	46.7	25.4	16.3	0.237
FEV ₁ , %	93.34	17.47	99.29	19.65	0.176
FVC, l	3.78	1.06	3.79	1.18	1.000
FEV ₁ /FVC, %	69.54	7.32	73.69	7.04	0.128
eNO, ppb	61.47	75.81	30.54	26.08	0.310
sRaw, kPa s/l	1.68	0.88	1.55	1.07	0.735
ACT score	15.29	5.02	19.29	6.85	0.018*
Partially controlled (n = 6)					
iVaw, cm ³	8.53	4.37	9.86	4.42	0.116
iRaw, kPa s/l	0.09	0.11	0.047	0.033	0.173
Δp _{tot} , Pa	37.5	45.8	19.6	13.8	0.173
FEV ₁ , %	88.23	18.45	91.23	18.09	0.116
FVC, l	3.54	0.71	3.61	0.73	0.500
FEV ₁ /FVC, %	72.82	8.64	73.51	8.71	0.753
eNO, ppb	26.4	19.64	22.58	13.67	0.463
sRaw, kPa s/l	1.37	0.50	1.26	0.58	0.402
ACT score	20.33	3.14	21.67	2.80	0.463
Well controlled (n = 11)					
iVaw, cm ³	8.99	5.42	9.84	5.11	0.041*
iRaw, kPa s/l	0.061	0.035	0.044	0.023	0.062
Δp _{tot} , Pa	25.4	14.6	18.3	9.6	0.062
FEV ₁ , %	102.58	11.25	105.41	13.23	0.374
FVC, l	4.00	1.12	4.02	1.08	0.859
FEV ₁ /FVC, %	70.78	5.35	72.04	5.12	0.657
eNO, ppb	42.64	53.48	28.20	38.39	0.091
sRaw, kPa s/l	1.49	0.72	1.39	0.86	0.266
ACT score	22.36	2.01	23.18	2.99	0.214

* p < 0.05.

* p < 0.05.

Partially Controlled Patients

In the group of partially controlled patients (n = 6) no parameter changed significantly and no correlations were found between any parameters and the ACT score (table 2).

Well-Controlled Patients

The group of well-controlled patients included 11 asthmatics with a baseline ACT score of 22.4 and FEV₁ value of 102%. All patients included in this group were previously treated with ICS/LABA fixed combinations (table 1) and switching to the study medication maintained the same high level of asthma control and good lung function. However, FI showed significant improvement of iVaw from 8.99 ± 5.42 to 9.84 ± 5.11 cm³ (p = 0.041) and a clear trend in reduction of iRaw from 0.061 ± 0.035 to 0.044 ± 0.023 kPa s/l (p = 0.062). As observed in the entire population, changes in iVaw correlated with changes in ACT score (R = 0.72, p = 0.012; fig. 4). No correlation was observed between changes in FEV₁ and ACT score. Furthermore, sample size calculation indicated that a total of 359 patients would be needed to attain a significant difference with a 90% confidence interval if FEV₁ is used as an outcome parameter in a controlled (baseline vs. intervention) study in well-controlled mild asthmatics. On the other hand, when using the average change in iVaw or iRaw as outcome parameter, the required sample size is reduced to 25.

Discussion

The aim of this study was to assess whether long-term treatment with extrafine BDP/F can induce detectable changes in the distal airways of asthmatic patients who are either steroid naive or already under treatment with non-extrafine ICS/LABA fixed combinations. When considering the entire study population, the trial shows that a 6-month therapy with extrafine BDP/F results in significant improvements in pre-bronchodilation imaging parameters such as small airway volume and CFD-based resistance. Notably, a significant correlation was found between changes in small airway volume and changes in asthma control score, suggesting that reaching and treating the small airways with extrafine BDP/F translates into clinical benefits for patients.

Changes in small airway parameters can be detected by FI both in steroid-naive patients and in well-controlled patients previously treated with non-extrafine combinations. In asthmatic patients who are well controlled with non-extrafine combinations, the switch to extrafine BDP/F leads to a significant improvement in pre-bronchodilator imaged airway volume, which occurred predominantly at the level of the small airways and was more sensitive than changes in FEV₁. The observed improvement in asthma symptom scores again

Fig. 2. Changes in image-based airway volume (iVaw, left) and CFD-based airway resistance (iRaw, right) for steroid-naïve (top), partially controlled (middle), and well-controlled (bottom) asthma patients.

Fig. 3. Correlation between changes in image-based airway volume (iVaw) and change in asthma symptom score (ACT) for all patients.

Fig. 4. Correlation between changes in image-based airway volume (iVaw) and change in asthma symptom score (ACT) for well-controlled patients.

significantly correlated with the increase in imaged airway volume indicating that imaged airway volume is of clinical significance.

Overall, these findings indicate that BDP/F extrafine formulation can target areas of the lungs left untreated by larger-particle fixed combinations.

In a previous 6-month randomized controlled trial, extrafine BDP/F was compared to the combination of the same drugs (BDP + F) given as larger non-extrafine par-

ticles. The study showed that, for equivalent steroid dosages, there was no difference in the morning PEF between both preparations, but patients taking the extrafine particle combination had significantly better asthma control as a consequence of the improved lung distribution that was previously demonstrated using Krypton ventilation scan [10, 18, 19]. In other investigations, the extrafine particle combination was always comparable to either fluticasone/salmeterol [20] or budesonide/formoterol

[21] in terms of FEV₁ and PEF improvements. These findings were not surprising considering that these spirometric tests did not provide comprehensive evaluation of the entire bronchial tree as they are unable to properly reflect small airway abnormalities.

There are two main reasons why this study could be considered innovative. Firstly, the study focused on different 'treatment phenotypes' as it included steroid-naïve, partially controlled, and fully controlled patients. It did not include a typical run-in period where patients are taken off corticosteroids for a number of weeks. Secondly, this study employs a novel imaging method, combining HRCT imaging with flow simulations to investigate whether FI could describe clinically relevant changes in well-controlled patients. This would demonstrate the true clinical significance and potential added value of using extrafine particle formulations.

In the current study, virtually all parameters indicated an improvement when considering the complete population. This finding is in line with previous studies using this combination, which focused mainly on morning PEF [21, 22]. The current study expanded the knowledge by focusing on additional variables using multiple approaches, such as exhaled breath analyses and, in particular, imaging. These parameters also suggested an additional beneficial clinical effect.

The imaging parameters showed the best correlation with the changes in asthma symptoms. The clinical relevance of FI was further illustrated in the steroid-naïve group where both ACT score and iVaw changed significantly, even though the sample size was limited. Also in the larger well-controlled group the good correlation between changes in iVaw and ACT score supported the hypothesis that FI yields clinically significant results.

Additional added value of imaging lies in the enhanced sensitivity to detect clinically relevant changes. Apparently, when patients are well controlled, FEV₁ is not sensitive enough to describe additional subtle changes, and additional improvement in this parameter is difficult to detect. Imaging parameters showed further consistent improvement in airway caliber and indicated where these changes mainly occurred. It is now possible to directly observe that a dilating effect is present in both the larger and smaller airways, while this was previously only demonstrated indirectly [23].

In a similar manner to FEV₁, the ACT score appears to have limited predicting power to describe additional changes in well-controlled patients, especially considering the more subjective nature of patient-reported outcome parameters. A combination of classical lung func-

tion, patient-reported outcome parameters, and FI methods has the potential to enhance the description of the mode of action of new compounds. This could result in a reduction of the number of patients required in clinical trials as indicated by the power analysis. In addition, by performing studies in well-controlled patients it could potentially be possible to determine whether switching to a novel product has a beneficial effect on the number of exacerbations and possible decline in respiratory function.

Although this study is the largest clinical trial (n = 24) available using FI, the power in the subgroups is still limited by the small sample size. In the partially controlled group (n = 6) especially, this could have had an influence on the final findings. Future research should consider equal subgroups with a sample size of ≥10 per subgroup. The HRCT-based airway models only include airways with diameters >1 mm due to the limits of the scan resolution. This region, however, already includes 80–90% of the airway resistance [14]. Generations beyond the reconstructed parts are taken into account through the CFD boundary conditions that are derived from HRCT-based lobar expansion.

Based on the results from the current study, it would be interesting to investigate the effect of the extrafine BDP/F combination in patients with irreversible airway disease. The increased sensitivity could also assist in the assessment of anti-inflammatory compounds where classical outcome parameters alone are likely not to be sufficient.

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