Research Review™ SPEAKER SERIES

New Developments in Asthma Medication: Fostair®

Making Education Easy 2021

About the speakers

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Melbourne, Australia

Professor Bruce Thompson is Dean at the School of Health Sciences, Faculty of Health, Arts & Design, at Swinburne University. He is an Honorary Senior Research Fellow at the Alfred Hospital, and is Adjunct Professor at the Central Clinical School of Monash University. Professor Thompson is a respiratory physiologist and research academic at the NHMRC Centre of Excellence in Severe Asthma and was also previously the head of Physiology Services at the Alfred Hospital, where his group performed lung function tests on more than 11,500 patients per year. Professor Thompson is the current President of the Thoracic Society of Australia and New Zealand.

Prof. Dave Singh
Manchester, UK

Dave Singh is Professor of Clinical Pharmacology & Respiratory Medicine at the University of Manchester. He graduated from Cambridge University and then trained in clinical pharmacology and respiratory medicine in Manchester, including postgraduate research. His research interest is the development of new drugs for asthma and COPD, involving clinical trials, biomarker studies and basic mechanisms. He has over 250 publications. He is a member of the GOLD Science Committee, and the chair of the ERS airway pharmacology group. He is the medical director of the Medicines Evaluation Unit, which performs both early and late phase clinical trials.

Prof. Alberto Papi
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Alberto Papi is Professor of Respiratory Medicine at the University of Ferrara, Italy. His main research areas are airway inflammation and respiratory viral infections. Professor Papi is a member of the GOLD Science Committee, has coordinated several pivotal studies, and has authored more than 400 articles in peer-reviewed journals.

This review summarises the highlights from the Chiesi-sponsored live webinar, *New Developments in Asthma Medication* (11th November 2020), the focus of which was international experience with the Fostair®, extra-fine beclometasone dipropionate/formoterol fumarate pressurised inhalation solution. The webinar featured presentations from three international experts: 1) an introduction to the key characteristics of Fostair by Prof. Bruce Thompson (Melbourne, Australia), who also chaired the webinar; 2) an update on the assessment and impact of small airways disease in asthma by Prof. Dave Singh (Manchester, UK); and 3) a review of the clinical evidence for Fostair in the treatment of asthma by Prof. Alberto Papi (Ferrara, Italy).

Introduction to Fostair

Professor Bruce Thompson

Fostair is a fixed-dose combination of an inhaled corticosteroid (ICS) and a long-acting beta2-agonist (LABA). It contains beclometasone dipropionate (BDP, 100 µg) as the ICS plus formoterol fumarate (FF, 6 µg) as the LABA. Fostair is available as a pressurised metered dose inhaler (pMDI) in solution, which facilitates generation of extra-fine aerosol and effective lung deposition of drug.

Place in therapy

Fostair is indicated in adults (aged ≥18 years) for the regular treatment of asthma where use of an inhaled ICS/LABA is appropriate:

- Patients not adequately controlled with ICS and 'as needed' inhaled rapid-acting beta2-agonist or
- Patients already adequately controlled on both ICS and LABA.[1]

There are two treatment approaches with Fostair:

1. Maintenance therapy: taken as regular maintenance treatment with a separate as needed rapid-acting bronchodilator.[1]
2. Maintenance and reliever therapy (MART): taken as regular maintenance treatment and as needed in response to asthma symptoms.[1]

In terms of its place in established asthma guidelines, as an ICS/LABA combination therapy, Fostair is expected to be used in:

- Steps 4 and 5 specified in the GINA 2020 guidelines.[2]
- Levels 3 and 4 specified in the Australian Asthma handbook.[3]

Extra-fine particle and cloud characteristics

Of particular interest are the extra-fine particle characteristics of Fostair, which is important for how the drug is deposited within the lung. A particle dose size of <2 µm is the optimal size for homogeneous deposition across the lung, including the small airways.[4] If the particle dose size is >5 µm it has significant mass and is deposited at the back of the throat after inhalation (oropharyngeal deposition) and swallowed.[5]

The other important aspect is how the drug is delivered in terms of reducing aerosol speed and increasing aerosol cloud duration, which reduces oropharyngeal deposition,[6] and which may compensate for poor hand-breath co-ordination by the patient.[7]

Standard pMDIs generate coarse, fast-moving clouds that result in only a small fraction reaching the lung.[6] Modulite technology permits pMDIs to generate particles of optimal size and plume speed, which facilitates co-ordination of dose generation with inspiration, reduces oropharyngeal deposition, and allows particles to reach the distal airways (**Figure 1**).[6-8]

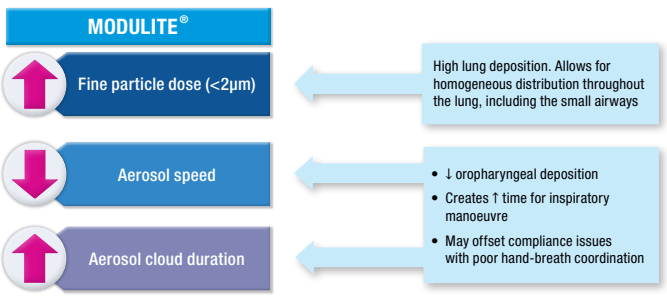

Figure 1. Extrafine aerosol delivery with the Fostair pMDI using Modulite technology.[6-8]

Take home messages

- The Fostair pMDI facilitates co-ordination of dose generation with inspiration, reduces oropharyngeal deposition, and provides a mechanism for homogeneous drug delivery to the lung.

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Rationale for treating the whole bronchial tree in asthma

Professor Dave Singh

The lungs are a branching structure starting from the trachea (generation 1) and finishing at the alveoli (generation 23) [**Figure 1**].[1] The smaller airways, defined as having an internal diameter of <2 mm,[2] are those that arise from the eighth generation onwards.[1] Small airways account for the majority of lung volume.

There is significant inflammation in both the large and small airways of asthma patients,[3] and airway remodelling occurs in the small airways in patients with mild asthma.[4]

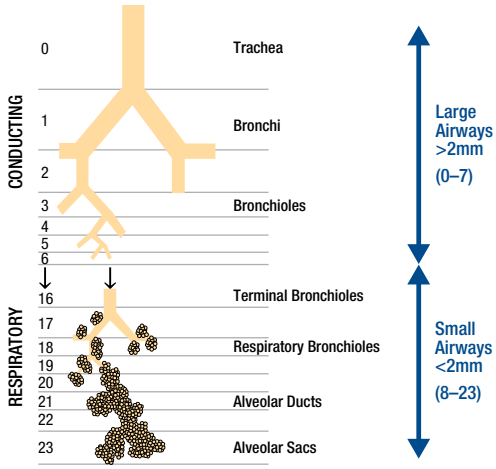


Figure 1. Branching structure of the lung.[1]

A systematic literature review of studies reporting small airways disease (SAD) using several different physiological techniques to detect SAD (most of which did not have a control group) concluded that SAD is highly prevalent in asthma, with approximately 50% of all patients with asthma having SAD.[5] However, in 2016 when the systemic review was published there were still unanswered questions relevant to daily clinical practice facing clinicians; specifically, which physiological test for SAD should I use, how many patients in my practice have SAD, and should they be treated?

These unresolved issues were addressed by the ATLANTIS study, which was published in 2019.

ATLANTIS study

The AssessmenT of smalL Airways involvemeNT In aSthma (ATLANTIS) was a 1-year prospective cohort multicentre study.[6] Among its key aims and outcomes were the following:

1. What is the best method for measuring SAD?
2. How many asthma patients have SAD?
3. What is the association of SAD with clinical outcomes?

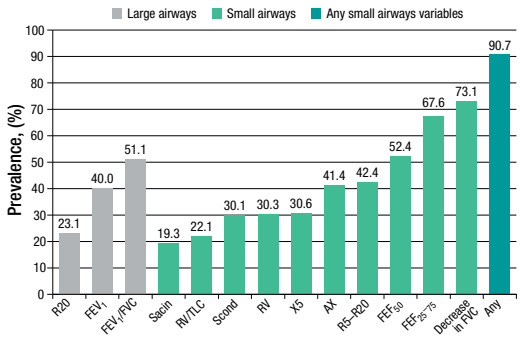
Using both physiological and imaging measurements, ATLANTIS may be the most comprehensive evaluation of SAD performed to date. Strengths of the study were the recruitment of a large group of asthma patients (n=773), representation of a wide range of asthma severities (GINA steps 1–5), inclusion of an age-matched control group (n=99), and global representation of asthma and SAD (9 countries, 4 continents, and 29 centres).

In terms of lung function testing, FEV1 is a measurement of the larger airways; impulse oscillometry measurements are R5 – R20, which indicates small airway resistance, and AX and X5, which reflect lung elasticity and compliance; FEF_{25-75} is a measure of airflow in the medium to smaller size airways; FVC and RV provide measures of air trapping; and nitrogen washout splits into S_{cond}, which is ventilation heterogeneity, and S_{acin}, which is a measure of alveolar oxygen exchange.

1. Results: cross-sectional baseline data

As asthma severity (based on GINA scale groups) increased the percentage of individuals with abnormal physiological measurements increased. Patients with severe asthma (GINA step 5) had the highest prevalence of SAD across all physiological variables.

Overall, 91% of asthma patients had some degree of SAD indicated by any abnormal physiological measure. However, the prevalence of SAD was dependent on the measure used, i.e., no single measure defines SAD (**Figure 2**). At the lower end of airways dysfunction prevalence, 30% of patients had increased RV, which is air trapping. At the higher end, 73% of patients had a decrease in FVC and 67% had an abnormal FEF_{25-75}. These differences are likely due to differences in degrees of sensitivity and specificity of the various measures. For example, rather than being due to air trapping, a reduced FVC in some individuals might be due to obesity, which suggests a lack of specificity. With RV and X5 down at 30% prevalence and the nitrogen washout measures of S_{acin} down at 19% and S_{cond} down at 30% there is a possibility that these methods lack sensitivity, i.e., are these tests truly picking up every patient with SAD.



- 90.7% of asthma participants had some degree of SAD (any abnormal physiological variable)
- Prevalence varied with the physiological measure used
- Highest prevalence was reported using FEF (68%) and decrease in FVC (73%), both probably reflect obstruction in more small-to-midsized airways
- Lowest prevalence was reported using S_{acin} measurements (19%) and RV/TLC (22%), reflecting dysfunction of the most peripheral small airways

Figure 2. The ATLANTIS study demonstrated that the prevalence of SAD depends on the physiological measure tested.[6]

Decrease in FVC was measured as the percentage decrease in FVC from baseline at PC_{20} or PD_{20}.

AX = area of reactance; **FEF25–75** = forced expiratory flow at 25–75% of FVC; **FEF50** = forced expiratory flow at 50% of FVC; **FEV1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; PC20: provocative concentration of bronchoconstrictor causing a 20% decrease in FEV1; **PD20** = provocative dose that causes a 20% decrease in FEV1 from baseline during methacholine challenge; **R5–R20** = peripheral airway resistance; **R20** = airway resistance at 20Hz; = **RV** = residual volume; **Sacin** = acinar ventilation heterogeneity; **Scond** = conducting airway ventilation heterogeneity; **TLC** = total lung capacity; **X5** = reactance at 5Hz.

To determine which physiological test should be used to measure SAD the investigators applied structural equation modelling to assess the contribution of all the physiological variables to SAD. The model determined that SAD is due to three components:

1. Abnormalities of resistance/elasticity (measured by impulse oscillometry, i.e., R5 – R20 and the compliance measurements).
2. Abnormalities in flow rate (spirometry measurements, i.e., mid-expiratory flow rates).
3. Abnormalities in gas trapping (measured by RV/TLC and FVC, i.e., lung volumes).

Therefore, because it is composed of different components, SAD can be measured by a technique that targets anyone of the three components.

Given that SAD is associated with a lack of asthma control, the investigators also determined which of the physiological measures used in ATLANTIS was most closely related to asthma control test (ACT) score. Univariate analysis revealed a positive correlation between FEV1 and ACT score (i.e., lower FEV1 = worse asthma control) and a negative correlation between impulse oscillometry variables and ACT score (i.e., higher resistance = worse asthma control). The correlation between FEV1 and ACT score ($r=0.25$, $p<0.001$) and between impulse oscillometry and ACT score (e.g., R5 – R20: $r=-0.26$, $p<0.001$) were of similar strength.

Hence, in clinical practice, if you have confidence in what FEV1 tells you about lung physiology you should also have confidence in what impulse oscillometry tells you about lung physiology.

2. Longitudinal data (1-year follow-up)

In terms of the association between asthma control and exacerbation frequency over time, the mean number of exacerbations per patient per year in the longitudinal phase of ATLANTIS was 0.32. Exacerbations over one year were significantly associated with RV/TLC ($r=0.20$, $p<0.0001$) and R5 – R20 ($r=0.22$, $p<0.0001$).

Hence, SAD as measured by RV/TLC and R5 – R20 contributes longitudinally to clinically-relevant outcomes in asthma.

Relevance of extra-fine particle formulations

When trying to target the small airways, extra-fine particles are an important consideration.

In patients with asthma receiving inhaled therapy, lung deposition of drug is influenced by both delivery device and patient factors.[7-9] Patient factors include the extent of airway obstruction and how the patient uses their inhaler. In terms of delivery device, aerosol characteristics include a range of physicochemical properties but aerosol particle size is of particular relevance because it plays an important role in avoiding the physiological barriers of the lung and targeting the drug to the appropriate lung region.[8]

How average particle diameter influences where drug is deposited in the lungs has been assessed in laboratory experiments of aerosol losses due to oropharyngeal deposition and exhalation as a function of the particle diameter.[10] As the particle size gets larger, i.e., 3–4 µm, more gets into the mouth and at about 6 µm a significant amount never gets near the lungs. As the particle size gets smaller, i.e., <1 µm, the particles are so small that they go into the lungs and out again, i.e., the exhaled fraction. Hence, the particle size for optimal lung delivery is approximately 1.25–2 µm. In this range, the most particles are deposited into the lungs and the twin problems of exhalation of drug and deposition of drug in the mouth are avoided.

The Fostair pMDI delivers a particle size of 1.5 µm,[11] which is in the 'sweet spot' for optimisation of delivery of the lung fraction.

In an open-label, single-dose, parallel-group study that assessed lung deposition and distribution of the Fostair pMDI in healthy subjects and asthma patients, lung scintigraphy techniques showed that it achieves deposition of drug throughout the bronchial tree, i.e., including the small airways (**Figure 3**).[12] The fraction of drug deposited in the lung was 34% in healthy subjects and 31% in asthma patients (**Figure 3**).

These rates are significant fractions relative to commercially-available standard pMDI inhalers that achieve lung deposition of 18% (particle size 3.5 µm) or 20% (particle size 2.0 µm).[13,14] Moreover, with the Fostair pMDI, of the fraction that goes into the lungs an additional one-third gets all the way to the small airways.

Variable	Group	
	Healthy subjects (n=8)	Asthma patients (n=8)
Lung deposition (% nominal dose)	34.0 ± 9.30 (20.00 – 43.80)	30.86 ± 8.89 (21.50 – 47.40)
Extrathoracic deposition (% nominal dose)	53.48 ± 8.95 (42.00 – 66.70)	57.64 ± 9.92 (43.50 – 69.30)

*p = 0.046 versus healthy subjects.
Results are presented as mean ± standard deviation (range)

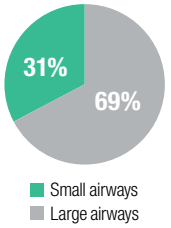


Figure 3. Extra-fine BDP/FF (Fostair pMDI) reaches the small airways and produces a high and homogenous deposition in the airways regardless of the pathophysiological condition.[12]

Take-home messages

- SAD is present across all severities of asthma, but it is especially prevalent in severe disease.
- SAD can be assessed in clinical practice using easy-to-use measures: impulse oscillometry, spirometry, and body plethysmography.
- Looking at all measurement techniques, SAD was present in 91% of the asthma population.
- Looking at individual measurement techniques, the prevalence of SAD is 30–70%.
- A reasonable compromise is to use one or two tests to capture SAD; for example, the combination of RV (for gas trapping) and impulse oscillometry.
- SAD can:
  - contribute to poorly controlled asthma.
  - be measured in clinical practice.
  - be treated with an extra-fine ICS/LABA combination.
- The Fostair pMDI delivers a particle size of 1.5 µm, which facilitates high and homogenous deposition in the airways.

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Fostair®: Scientific evidence

Professor Alberto Papi

Asthma is an inflammatory disorder that affects the entire bronchial tree from the central to the peripheral airways. In people with asthma there is presence of active inflammation and structural alterations in a large proportion of the lungs including the small airways.[1,2] Furthermore, nitrogen washout studies have demonstrated that small airways impairment is correlated with poorer asthma control and increased frequency of exacerbations.[3] These observations emphasise the importance of inhaled asthma medications reaching the peripheral airways.

Clinical evidence

Inhaled Combination Asthma Treatment vs SEretide (ICAT SE) study

ICAT SE was a multicentre, double-blind, randomised, two-arm parallel group study that compared the fixed combination of extra-fine BDP and FF (400/24 µg; Fostair) with the fixed combination of fluticasone propionate (FP) and salmeterol xinafoate [SX] (500/100 µg; Seretide) at equipotent doses.[4]

The two formulations were equivalent in terms of significantly ($p \leq 0.001$ vs baseline) improving the primary endpoint of morning PEF over 12 weeks.[4] As anticipated (due to FF being the more rapidly acting bronchodilator), Fostair was associated with significantly ($p<0.05$) faster onset of bronchodilation compared with Seretide, with the difference maintained for up to one hour post dosing.

Consistent with its extra-fine particle delivery being associated with reduced air trapping, Fostair demonstrated a statistically significantly greater improvement in FVC compared with Seretide at 12 weeks (**Figure 1**).[4] Hence, ICAT SE demonstrated the importance of medication reaching the small airways.

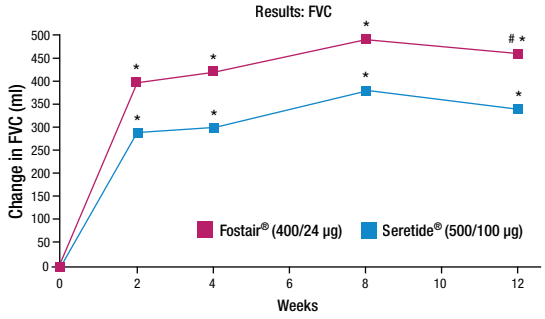

Figure 1. Significantly greater improvement in FVC after 12 weeks with Fostair versus Seretide.[4]
* p<0.001 vs baseline; # p<0.040 between treatments.

Inhaled Combination Asthma Treatment versus SYmbicort (ICAT SY) study

ICAT SY was a multicentre, double-blind, randomised, two-arm parallel group study that compared the fixed combination of extra-fine BDP and FF (400/24 µg; Fostair) with the fixed combination budesonide (BUD) and FF (800/24 µg; Symbicort).[5] The use of equipotent doses meant twice the corticosteroid dose was delivered with BUD compared with BDP. The two formulations were equivalent in terms of significantly ($p \leq 0.001$ vs baseline) improving the primary endpoint of morning PEF over 12 weeks. There were also no differences between the two formulations for improvement in asthma symptom and asthma control measurements. Hence, ICAT SY demonstrated the advantage of the extra-fine formulation in improving lung function and clinical symptoms and reducing systemic corticosteroid exposure.

Maintenance and reliver therapy (MART) strategy

A randomised double blind study compared the fixed combination of extra-fine BDP and FF (100/6 µg; Fostair) with salbutamol sulphate (SS) 100 µg as reliever strategies in asthma patients taking BDP/FF (100/6 µg; Fostair) as maintenance treatment.[6] Fostair MART significantly ($p=0.0003$) prolonged the time to first severe exacerbation by 75 days (primary endpoint) compared with Fostair plus SS. Significant reductions in the secondary endpoints of yearly rate of severe exacerbations ($p<0.0001$), hospitalisations or emergency visits ($p=0.0003$), and systemic corticosteroid use ($p<0.0001$) were also demonstrated with Fostair MART as compared with Fostair plus SS. Hence, with the MART strategy treatment efficacy can be optimised by reducing the risk of exacerbation.

Real-world evidence

It is important that the efficacy of extra-fine BDP/FF (Fostair) demonstrated in controlled clinical trials is confirmed to occur in real life, which is different from the ideal world of randomised controlled trials (RCTs).

Real patients versus those in clinical research trials

Researchers who applied patient selection criteria commonly used in RCTs to asthma patients seen at a GP practice or asthma clinic determined that only 1.3% would be enrolled in an RCT.[7] In other words, evidence-based treatment decisions for asthma patients are based on RCTs that include a small and highly selected fraction of this patient population, which calls into question whether such data can be generalised to the real-life population of patients with asthma.

Fostair real-life studies

An observational study used a cross-sectional design and asthma outpatients to compare the efficacy of extra-fine BDP/FF pMDI (Fostair) with that of ICS/LABA combinations (FP/SX [Seretide] and BUD/FF [Symbicort]) delivered via dry powder inhalers (DPI) in a real-world setting.[8] The extra-fine BDP/FF pMDI was associated with a significantly ($p=0.031$) greater proportion of patients achieving asthma control as compared with DPIs formulated with larger particles (**Figure 2**).

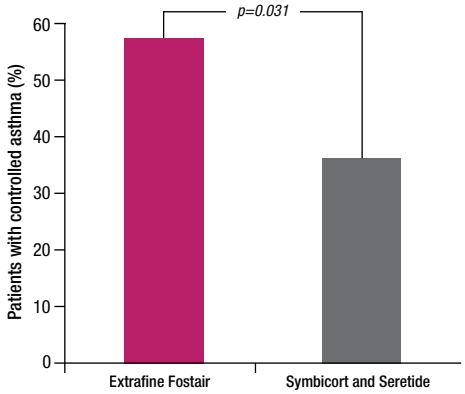

Figure 2. Real-life study that demonstrated extra-fine (<2 µm) Fostair achieves greater asthma control versus larger particle ICS/LABAs (Seretide and Symbicort).[8]

In a 1-year prospective real-life study involving adult patients with uncontrolled/partially controlled asthma, treatment with Fostair resulted in a statistically significantly higher proportion of patients with fully controlled asthma after 12 months as compared with Symbicort (**Figure 3**).[9] Furthermore, the mean daily dose of ICS administered was approximately two-fold lower for extra-fine Fostair compared with either Symbicort or Seretide. Hence, the improvement in asthma control was achieved despite the lower ICS dose.

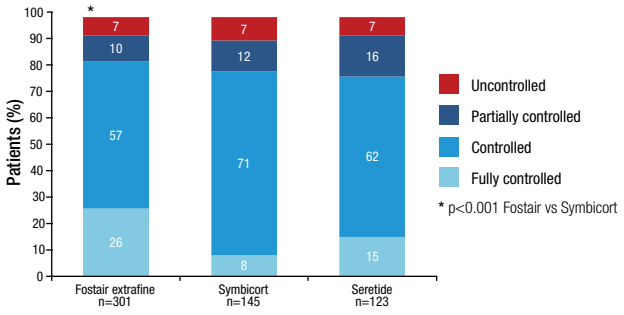

Figure 3. Evolution of asthma control over 12 months with extra-fine Fostair compared with Symbicort, and Seretitde.[9] Data are percentage of patients in each category of asthma control: fully controlled (ACT score = 25), controlled (ACT score: 24–20), partly controlled (ACT score: 19–16), and uncontrolled (ACT score ≤ 15).

Relationship between extrafine ICS and asthma control

The wider asthma population effectiveness of extra-fine ICS formulations (alone and in combination formulations) has been confirmed in a meta-analysis of observational real-life studies.[10] The analysis found that extra-fine ICS formulations have a statistically higher likelihood of achieving asthma control with lower exacerbation rates at lower prescribed doses than fine-particle ICS formulations.

Device characteristics

The effectiveness of extra-fine Fostair with lower ICS exposure is related to its ability to reach the peripheral airways.

Because pMDIs generate relatively large particles and fast-moving aerosol clouds, the fraction of dose reaching the lung is small.[11,12] These shortcomings have been addressed with the development of Modulite technology, which includes the addition of a non-volatile component to the solution formula and optimisation of the actuator orifice geometry, volume of the metered solution, and vapour pressure of the propellants. These changes result in fine particles forming a larger fraction of the delivered dose, slower aerosol speed, and longer duration of the aerosol cloud.[11,13]

Prolonged cloud duration facilitates co-ordination of actuation and inhalation and slower aerosol speed reduces deposition in the upper respiratory tract. This is important in people who have co-ordination difficulties when using inhalers, most commonly children and the elderly.

Take home messages

- Inflammation and remodelling are present throughout the bronchial tree in patients with asthma.
- SAD contributes significantly to functional impairment caused by asthma.
- Small airways are therefore an important pharmacological target.
- Extra-fine BDP/FF more effectively reaches the small airways allowing a reduction of exposure to ICS.
- RCTs have demonstrated the efficacy of extra-fine BDP/FF in improving lung function and clinical symptoms and reducing corticosteroid exposure relative to a non-extrafine ICS/LABA formulation.
- Real-world studies have demonstrated greater asthma control with extrafine BDP/FF versus non-extrafine LABA/ICS and at a lower ICS dose in real-life populations.
- The efficacy of extra-fine BDP/FF can be optimised using the MART strategy.

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