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Pragmatic evaluation of inhaled corticosteroid particle size formulations on asthma control

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Pragmatic evaluation of inhaled corticosteroid particle size formulations on asthma control

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Dr. Kuo reports personal fees and non-financial support from Pfizer, personal fees from Circassia, outside the submitted work.

Dr. Jabbal reports personal fees and non-financial support from Chiesi Pharma, personal fees and non-financial support from Pfizer, non-financial support and other from Napp, personal fees and non-financial support from AstraZeneca, non-financial support from Teva, personal fees and non-financial support from Mylan, personal fees from Boehringer Ingelheim, outside the submitted work.

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Teva had no input into study design, data analysis and interpretation, or in writing the manuscript.

Author's contributions

Dr. Kuo contributed to the acquisition, analysis, interpretation of data and drafting as well as revising the content of the final approved version of manuscript. Dr Kuo is also accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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3 Dr. Jabbal contributed to the design of the work and revising as well as approval of the final
4 version of the manuscript.
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9 Dr. Anderson contributed to the conception and design of the work and revising as well as
10 approval of the final version of the manuscript.
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15 Dr. Lipworth contributed to the conception and design of the work, acquisition, analysis and
16 interpretation of data for the work. Dr Lipworth also drafted and critically revised the content
17 as well as approval of the final version of the manuscript. He is also accountable for all aspects
18 of the work in ensuring that questions related to the accuracy or integrity of any part of the
19 work are appropriately investigated and resolved.
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Abstract**Background:**

Extra-fine particle formulations of inhaled corticosteroid (ICS) are associated with improved lung delivery.

Objectives:

A pragmatic study to assess patient reported outcomes after switching from fine to extra-fine particle ICS in persistent asthma.

Methods:

24 patients (Mean age 48 year, FEV₁ 84%, ACQ 1.67) received 4 weeks run-in with a constant dose of fine particle ICS (mean dose 710 µg), followed by switching to an equivalent dose of extra fine particle hydrofluoroalkane beclomethasone dipropionate (mean dose 355µg). Asthma control questionnaire (ACQ), the primary outcome, and mini asthma quality of life questionnaire (mAQLQ) were measured pre and post run-in (baseline) and after 4 weeks and 8 weeks of switching.

Results:

Comparing pre vs post run-in there were no differences for ACQ: 1.67 vs 1.65 or AQLQ: 5.08 vs 5.34. There were mean (95%CI) improvements ($P < 0.001$) from baseline after 8 weeks for ACQ: -0.53 (-0.83, -0.23) and AQLQ: 0.69 (0.35, 1.04), which exceeded the minimal clinically important difference (MCID) of 0.5 for both. There were also differences ($P < 0.05$) in domiciliary symptoms and reliever use. There were no significant changes at 8 weeks in lung function, FeNO or blood eosinophils.

Conclusions:

Pragmatic switching from fine to extra-fine particle ICS at half the dose was associated with clinically relevant improvements in asthma control and quality of life, but not lung function or type 2 biomarkers.

Trial Registration:

EUDRACT (2012-003923-39) and Clintrials.gov (NCT01894048)

Introduction

There are presently two hydrofluoroalkane (HFA) solution based pressurised metered dose inhaler (pMDI) formulations of inhaled beclometasone dipropionate (BDP) available in the Europe. One is a fine particle formulation with a mass median aerodynamic diameter (MMAD) of 2.9µm (Clenil Modulite, Chiesi Ltd, Manchester, UK) and the other extra-fine particle formulation with MMAD of 1.1µm (Qvar, Teva UK Ltd, Harlow, UK). The extra-fine particle HFA-BDP formulation is associated with improved total and regional lung delivery, which in turn translates in being able to use half the dose to achieve the same improvement in forced expiratory volume in 1 second (FEV₁).[1, 2]

Patient reported outcomes (PRO's) include asthma quality of life questionnaire (AQLQ) and asthma control questionnaire (ACQ), both of which have minimal clinical important difference (MCID) of 0.5.[3, 4] The cut point for ACQ between well controlled and not well controlled is 1.0.[5] We wanted to know if ACQ and AQLQ might improve after switching from fine particle to extra-fine particle ICS in a group of uncontrolled patients with ACQ>1.0. In order to evaluate this we converted patients with persistent asthma to fine particle ICS formulations comprising HFA-BDP, fluticasone propionate or budesonide over a run-in period of at least 4 weeks where the dose was kept constant, prior to switching to extra-fine particle HFA-BDP at half the dose over the subsequent 8 weeks. We elected to power the study on change in ACQ score as we use this routinely to follow control in our NHS clinic and it has also been shown to a strong predictor of future asthma exacerbations.[6, 7]

Another sensitive marker of response to ICS is airway hyper-responsiveness (AHR) using indirect acting challenge with mannitol,[8] which in turn is related to asthma exacerbations.[9] It has previously been shown that titrating the ICS dose over one year against mannitol AHR results in significantly better control compared to a reference strategy based on lung function, symptoms and reliever use.[10] Similar findings have been reported with direct acting methacholine challenge in regard to ICS titration and improved control.[11] Another study with extra-fine particle HFA-BDP at half the dose compared to fine particle CFC-BDP demonstrated

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3 a significant reduction in air trapping after methacholine challenge using high resolution
4 computerised tomography (HRCT) scanning.[12]
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7 Hence in the present pragmatic study we also measured AHR in a subgroup of patients who
8 after taking a constant dose of ICS at the end of the run-in were identified as being mannitol
9 responders at baseline. We wished to see in this subgroup if putative improvements in PRO's
10 were accompanied by commensurate changes in mannitol AHR after switching to extra-fine
11 particle HFA-BDP.
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Methods

We enrolled patients with persistent asthma aged 18-70 years, taking up steps 2, 3 or 4 of British Thoracic Society guidelines, with an ICS dose up to 2000ug/day (as fine particle HFA-BDP equivalent dose) with or without long acting β_2 adrenoceptor agonist (LABA), long acting muscarinic antagonists (LAMA), leukotriene receptor antagonist (LTRA) or theophylline. Patients were required to have FEV₁ of at least 60% predicted and an ACQ score of at least 1.0. At screening patients were requested to stop any LABA and were then converted to fine particle ICS either as HFA-BDP (Clenil Modulite pMDI, Chiesi Ltd, Manchester, UK), fluticasone propionate (GlaxoSmithKline, Uxbridge, UK) or budesonide (AstraZeneca, Luton, UK) for the subsequent step down and run-in phases. For example during the run-in after stopping LABA, patients taking fluticasone/salmeterol were converted to the same dose of fluticasone alone. The fine particle ICS dose was permitted to be halved if patients subsequently had an ACQ score <1.0, until a minimum Clenil equivalent dose of at least 200 μ g per day was reached. In other words, patients entered the subsequent run-in period with partial control – ie ACQ \geq 1. Patients were then entered into a run-in period of at least 4 weeks on a stable fine particle ICS dose and an ACQ score of at least 1.0 at the baseline visit post run-in (Figure 2). InPatients continued for the rest of the study on any other second line controllers apart from LABA.

At baseline patients were then switched to half the Clenil equivalent dose as extra-fine particle Qvar which was continued unchanged over the subsequent 8 week period.

Visits were performed pre and post run-in (baseline) and after 4 and 8 weeks of switching, where measurements were made of ACQ, mAQLQ, spirometry, impulse oscillometry, fractional exhaled nitric oxide (FeNO) and blood eosinophils.

A subgroup of patients who were identified at baseline (after run in) as being responsive to mannitol (Osmohale, Pharmaxis, Sydney, Australia) had further challenges performed at 4 and 8 weeks after switching. Mannitol sensitivity was expressed as the provocative dose required to produce a 15% fall in FEV₁ (PD15 threshold in mg) calculated by interpolation of the log linear dose response curve up to maximum cumulative dose of 635mg. Mannitol

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3 reactivity was expressed as the response dose ratio (RDR as % fall /mg) calculated by dividing
4 the maximum % fall in FEV₁ by the final mannitol dose. Data for PD15 and RDR were
5 logarithmically transformed prior to analysis.
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9 Impulse oscillometry (IOS) was measured using a Jaeger Masterscreen (Jaeger Hochberg,
10 Germany) in triplicate using a nose clip lips sealed tightly, cheeks held and with quiet tidal
11 breathing for 30s. A Superspiro spirometer (Micro Medical Ltd, Chatham, UK) was used to
12 record in triplicate according to European Respiratory Society guidelines. FeNO was
13 measured with a NIOX Mino (Aerocrine AB, Solna, Sweden) in accordance with published
14 guidelines.
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17 A domiciliary diary card was recorded for peak flow, symptoms and reliever use. Full informed
18 written consent was obtained from all patients and the study was approved by the Tayside
19 committee for medical ethics (13/ES/0064) and the study was registered at EUDRACT (2012-
20 003923-39) and Clintrials.gov (NCT01894048).
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23 **Statistical analysis**

24 The data were initially inspected to assess if they conformed to a normal distribution.
25 Outcomes which were non-normally distributed (FeNO, eosinophils, mannitol PD15 and RDR)
26 were then log transformed prior to analysis. A comparison of values for post run-in (baseline)
27 and at 4 weeks and 8 weeks after switching was performed by repeated measures analysis
28 of variance (ANOVA). Post hoc analysis was done for ACQ and mAQLQ by pairwise testing
29 using Bonferroni corrected p values. For the subgroup of mannitol responders an overall
30 ANOVA was performed but without post hoc pairwise testing to avoid confounding the alpha
31 error due to small sample size. The study was designed with at least 80% power to detect a
32 0.4 unit change in the primary outcome of ACQ at 8 weeks, assuming a standard deviation of
33 0.68, with an alpha error (two tailed) of 0.05, requiring at least 23 patients to complete per
34 protocol. Domiciliary diary card data were calculated using the rolling average values from last
35 week of the run-in while on fine particle ICS and compared to the eighth week while taking
36 extra-fine particle HFA-BDP.
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Results

The flow of participants is depicted in the CONSORT diagram (Figure 1). 24 patients completed per protocol: mean age 48 yr, FEV₁ 84% predicted, ACQ 1.67, BMI 31.1. 12 patients were atopic on skin prick testing and all were non-smokers. Mean Clenil equivalent dose was 740µg at screening (ie prior to step down) with 15 patients taking concomitant LABA, 6 on LTRA, 2 on LAMA and 1 on theophylline. During run-in there were 14 patients taking fine particle HFA-BDP, and 10 patients on either fine particle fluticasone or budesonide. 4, 5 and 15 patients were on GINA steps 2, 3, and 4 asthma treatment respectively. After step down, the mean Clenil equivalent dose was 710µg/day which was maintained unchanged throughout the run-in period. Following the run in period (ie at baseline) patients were then converted to a mean Qvar equivalent dose of 355µg/day.

There were no differences in mean values comparing pre and post run-in (Table 1) for ACQ (1.67 versus 1.65) or mAQLQ (5.08 versus 5.34). Type 2 biomarkers were significantly ($P<0.05$) reduced comparing pre and post run-in values (as mean % difference) for FeNO: -25% (95%CI -40,-7), and blood eosinophils -24% (95%CI -36,-9). There were no significant differences between pre and post run-in values for spirometry or IOS.

After switching there were significant ($P<0.001$) mean (95% confidence interval) improvements from baseline after 8 weeks for ACQ: -0.53 (95%CI -0.83, -0.23) and mAQLQ: 0.69 (95%CI 0.35, 1.04), which exceeded the MCID's of 0.5 for both (Figure 3). Individual responder analysis showed that after 8 weeks there were 11/24 (46%) who had a change in ACQ>0.5 and 11/24 (46%) who had a change in mAQLQ >0.5 (Figure 4). Individual mAQLQ domains showed significant improvements which exceeded the MCID for symptoms ($P<0.001$), emotional function ($P<0.01$), and environmental stimuli ($P<0.01$) but not for activity limitation (Figure 5). There were no significant changes in lung function, FeNO or eosinophils after switching compared to baseline (Table 2).

In the subgroup of 8/24 patients who responded to mannitol after the run-in at baseline, there were significant ($P<0.001$) overall effects on mannitol sensitivity as PD15. After switching there was a 1.59 (95%CI 0.29, 2.89) doubling dose shift in PD15 at 8 weeks (Figure 6). For mannitol

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3 reactivity as RDR the overall effect was also significant ($P < 0.05$). In this subgroup there were
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5 also significant mean improvements comparing 8 weeks versus baseline for ACQ: mean
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7 difference -0.82 (95%CI $-1.59, -0.05$), $P < 0.05$ and mAQLQ: mean difference 1.09 (95%CI $0.14,$
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9 2.05), $P < 0.05$, which exceeded the MCID's for both.
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12 Diary card data showed no significant changes in morning or evening peak expiratory flow
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14 (PEF) measurements. There were significant ($P < 0.05$) improvements in domiciliary morning
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16 and evening symptoms as well as evening reliever use after 8 weeks compared to baseline
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18 (Table 3).
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Discussion

The results of the present pragmatic study showed that in uncontrolled asthma patients taking fine particle ICS, subsequent switching to half the dose of extra-fine particle HFA-BDP resulted in significant improvements in the primary outcome of asthma control as ACQ along with asthma specific quality of life as AQLQ. The magnitude of observed changes in ACQ and AQLQ can be considered as being clinically relevant as they both exceeded their respective MCID's of 0.5.[3, 4] Responder analysis identified 46% of patients who achieved a change in ACQ and AQLQ which exceeded the MCID after 8 weeks. AQLQ domains aside from activity limitation also significantly improved by more than the MCID. Domiciliary data showed significant improvements in symptoms and reliever use. Moreover, after switching no significant changes were seen for either lung function or type 2 inflammatory biomarkers.

We originally hypothesised that improved regional lung distribution with extra-fine particle HFA-BDP [1] might lead to improved PRO's and would be reflected in commensurate changes in small airways function. We were therefore surprised to see no significant changes in impulse oscillometry (IOS) after switching, especially for R5-R20 for AX which emulate changes in small airways.[13, 14] The lack of any signal could be due to IOS being more sensitive in ICS naïve patients,[15] whereas in our study patients had been taking at least 4 weeks of fine particle ICS at a constant dose during the run-in. Indeed in a study of severe asthma where extra-fine particle HFA-BDP 400µg/day was added on top of fine particle fluticasone/salmeterol dry powder inhaler, no further changes were seen in IOS or in the alveolar fraction of exhaled nitric oxide.[16] Another possibility to explain our results is that there may have been no further room for improvement in IOS parameters after switching. Perhaps using other techniques to look at small airways such as multiple breath nitrogen washout or post challenge air trapping on HRCT,[12, 17] might have identified more subtle changes which were not detected using IOS.

A real life effectiveness study using health informatics comparing extra-fine and fine particle HFA-BDP formulations over one year observed that overall asthma control was significantly better with extra-fine particle HFA-BDP when used at a lower maintenance dose [18], although

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3 lung function was not measured. A prospective randomised controlled trial in 473 patients with
4 mean FEV₁ 84% switched patients from their existing chlorofluorocarbon (CFC) suspension
5 based fine particle BDP formulation (400-1600ug) to extra-fine particle HFA-BDP at half the
6 dose, compared to continuing on an unchanged dose of CFC-BDP, with follow up over 12
7 months.[19] The AQLQ score improved significantly with fine versus extra-fine particle BDP,
8 while there were no commensurate significant differences in lung function. The lack of any
9 significant difference in spirometry including FEF₂₅₋₇₅ after switching our study is consistent
10 with two other previous head to head trials of extra-fine and fine particle BDP formulations in
11 patients who had a baseline mean FEV₁ of 84%, which was identical to the present trial.[19,
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24 In the subgroup of mannitol responsive individuals we observed significant overall effects in
25 AHR after switching. Indeed the shift in mannitol PD15 exceeded one doubling dose which is
26 taken as being a clinically relevant improvement.[21] Notably in this subgroup the concomitant
27 changes seen in PRO's were also significant and clinically relevant. It has previously been
28 shown that dose related changes in AHR in response to ICS are more sensitive than in lung
29 function.[22, 23] As both AHR and ACQ are predictors of exacerbations,[6, 7, 9] we believe
30 that our data might suggest that switching to extra-fine particle HFA-BDP could also reduce
31 the exacerbation burden in the longer term. This is supported by two real life observational
32 studies showing better overall asthma control over a one year period of follow up when
33 comparing patients who were taking a lower maintenance dose of extra-fine particle versus
34 fine particle BDP formulations.[18, 24]
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47 It is noteworthy that FeNO and blood eosinophils were significantly reduced comparing pre
48 and post run-in values while taking a constant dose of fine particle ICS, whereas ACQ and
49 mAQLQ were not significantly altered. The reduction in FeNO and eosinophils is likely to
50 reflect the putative impact of initial improved adherence to ICS during the run-in period,[25]
51 especially for FeNO which exhibits near maximal suppression by low doses of fine particle
52 ICS.[26] The lack of any subsequent difference in either FeNO or eosinophils after switching
53 to Qvar is consistent with similar findings directly comparing half the dose of extra-fine particle
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3 BDP (100ug and 400ug/day) to fine particle BDP.[20] Although in theory concomitant use of
4 LTRA might have confounded the underlying asthmatic inflammation, this was only the case
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7 in 6 patients.
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9 We duly acknowledge the potential weaknesses of our study design. First there was no parallel
10 control arm where patients might have continued with an unchanged dose of fine particle HFA-
11 BDP after run-in, as in the study of Juniper et al.[19] Second our study was powered on ACQ,
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13 such that we may have missed smaller changes in lung function due to type 2 error, particularly
14 for IOS measurements. Third the duration of follow up after switching was relatively short at 8
15 weeks. Nonetheless in the Juniper study [19] using a much larger sample size over one year
16 there were significant improvements in AQLQ with extra-fine versus fine particle BDP which
17 were not associated with commensurate changes in lung function including FEF₂₅₋₇₅. It is also
18 possible that the observed improvements in PRO's in our patients might have occurred due
19 to progressively enhanced adherence to ICS over the 8 week switch period. However, since
20 ACQ was unchanged despite FeNO and eosinophils falling during the run in period on a
21 constant dose of ICS, we believe that patients had probably already reached a stable baseline
22 level prior to the switch occurring. Hence, we believe the subsequent improvement in ACQ
23 after switching to Qvar represents a true treatment effect consequent upon the change in
24 particle size. Finally, only a third of our patients had airway hyper-responsiveness at baseline
25 after the run in period. This may be explained by mannitol being an indirect challenge agent
26 which is more sensitive to ICS than a direct challenge using methacholine.[10, 22] In this
27 regards, we did not perform bronchial challenge at screening.
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47 In conclusion, our results show that clinically relevant changes in PRO's may be associated
48 with pragmatic switching from fine particle to extra-fine particle ICS at half the dose. Further
49 longer term trials are warranted to prospectively investigate the potential for reducing
50 exacerbations when using extra-fine particle ICS formulations in patients with uncontrolled
51 persistent asthma. As such, study might also include a parallel control arm where patient
52 continue on an unchanged dose of extra fine particle ICS.
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For Peer Review

References

1. Leach CL, Davidson PJ, Boudreau RJ, Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12: 1346-53, 998 Dec.
2. Busse W, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, Donnell D, Hannon S, Colice G, Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104: 1215-22.
3. Juniper EF, Svensson K, Mork AC, Stahl E, Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respiratory medicine* 2005;99: 553-8.
4. Juniper EF, Guyatt GH, Willan A, Griffith LE, Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47: 81-7.
5. Juniper EF, Bousquet J, Abetz L, Bateman ED, Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respiratory medicine* 2006;100: 616-21.
6. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, Chon Y, Chiou CF, Globe D, Lin SL, Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J Allergy Clin Immunol*;127: 167-72.
7. Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, Jenkins C, Humbert M, Buhl R, Harrison TW, Quirce S, O'Byrne PM, Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010;125: 600-8, 08 e1-08 e6.

- 1
2
3 8. Anderson SD, Brannan J, Spring J, Spalding N, Rodwell LT, Chan K, Gonda I,
4 Walsh A, Clark AR, A new method for bronchial-provocation testing in asthmatic
5 subjects using a dry powder of mannitol. American journal of respiratory and
6 critical care medicine 1997;156: 758-65.
7
8
9
- 10
11
12 9. Leuppi JD, Salome CM, Jenkins CR, Anderson SD, Xuan W, Marks GB, Koskela
13 H, Brannan JD, Freed R, Anderson G, Chan HK, Woolcock AJ, Predictive Markers
14 of Asthma Exacerbation during Stepwise Dose Reduction of Inhaled
15 Corticosteroids. Am J Respir Crit Care Med 2001;163: 406-12.
16
17
18
- 19
20
21 10. Lipworth BJ, Short PM, Williamson PA, Clearie KL, Fardon TC, Jackson CM,
22 A randomized primary care trial of steroid titration against mannitol in persistent
23 asthma: STAMINA trial. Chest 2012;141: 607-15.
24
25
26
27
- 28
29 11. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ,
30 Clinical control and histopathologic outcome of asthma when using airway
31 hyperresponsiveness as an additional guide to long-term treatment. The AMPUL
32 Study Group. Am J Respir Crit Care Med 1999;159: 1043-51.
33
34
35
36
- 37
38 12. Goldin JG, Tashkin DP, Kleeerup EC, Greaser LE, Haywood UM, Sayre JW,
39 Simmons MD, Suttorp M, Colice GL, Vanden Burgt JA, Aberle DR, Comparative
40 effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate
41 inhalation on small airways: assessment with functional helical thin-section
42 computed tomography. J Allergy Clin Immunol 1999;104: S258-67.
43
44
45
46
47
48
- 49
50 13. Lipworth B, Manoharan A, Anderson W, Unlocking the quiet zone: the small
51 airway asthma phenotype. The Lancet Respiratory medicine 2014;2: 497-506.
52
53
- 54
55 14. Galant SP, Komarow HD, Shin HW, Siddiqui S, Lipworth BJ, The case for
56 impulse oscillometry in the management of asthma in children and adults. Annals
57
58
59
60

- 1
2
3 of allergy, asthma & immunology : official publication of the American College of
4
5 Allergy, Asthma, & Immunology 2017;118: 664-71.
6
7
- 8 15. Yamaguchi M, Niimi A, Ueda T, Takemura M, Matsuoka H, Jinnai M, Otsuka
9
10 K, Oguma T, Takeda T, Ito I, Matsumoto H, Hirai T, Chin K, Mishima M, Effect of
11
12 inhaled corticosteroids on small airways in asthma: investigation using impulse
13
14 oscillometry. *Pulmonary Pharmacology & Therapeutics* 2009;22: 326-32.
15
16
- 17 16. Williamson PA, Short PM, Vaidyanathan S, Lipworth BJ, Inhaled and
18
19 Systemic Corticosteroid Response in Severe Asthma Assessed by Alveolar Nitric
20
21 Oxide: a randomised crossover pilot study of add-on therapy. *British Journal of*
22
23 *Clinical Pharmacology* 2012.
24
25
- 26 17. Verbanck S, Schuermans D, Vincken W, Inflammation and airway function in
27
28 the lung periphery of patients with stable asthma. *The Journal of allergy and*
29
30 *clinical immunology* 2010;125: 611-6.
31
32
- 33 18. Price D, Thomas M, Haughney J, Lewis RA, Burden A, von Ziegenweidt J,
34
35 Chisholm A, Hillyer EV, Corrigan CJ, Real-life comparison of beclometasone
36
37 dipropionate as an extrafine- or larger-particle formulation for asthma. *Respiratory*
38
39 *Medicine* 2013;107: 987-1000.
40
41
- 42 19. Juniper EF, Price DB, Stampone PA, Creemers JP, Mol SJ, Fireman P,
43
44 Clinically important improvements in asthma-specific quality of life, but no
45
46 difference in conventional clinical indexes in patients changed from conventional
47
48 beclomethasone dipropionate to approximately half the dose of extrafine
49
50 beclomethasone dipropionate. *Chest* 2002;121: 1824-32.
51
52
- 53 20. Menzies D, Nair A, Hopkinson P, McFarlane L, Lipworth BJ, Differential anti-
54
55 inflammatory effects of large and small particle size inhaled corticosteroids in
56
57 asthma. *Allergy* 2007;62: 661-7.
58
59
60

- 1
2
3 21. Currie GP, Fowler SJ, Lipworth BJ, Dose response of inhaled corticosteroids
4 on bronchial hyperresponsiveness: A meta-analysis. *Ann Allergy Asthma Immunol*
5 2003;90: 194-98.
6
7
- 8
9
10 22. Wilson AM, Lipworth BJ, Dose-response evaluation of the therapeutic index
11 for inhaled budesonide in patients with mild-to-moderate asthma. *The American*
12 *journal of medicine* 2000;108: 269-75.
13
14
- 15
16 23. Fowler SJ, Orr LC, Sims EJ, Wilson AM, Currie GP, McFarlane L, Lipworth
17 BJ, Therapeutic Ratio of Hydrofluoroalkane and Chlorofluorocarbon Formulations
18 of Fluticasone Propionate*. *Chest* 2002;122: 618-23.
19
20
- 21
22 24. Barnes N, Price D, Colice G, Chisholm A, Dorinsky P, Hillyer EV, Burden A,
23 Lee AJ, Martin RJ, Roche N, von Ziegenweidt J, Israel E, Asthma control with
24 extrafine-particle hydrofluoroalkane-beclometasone vs. large-particle
25 chlorofluorocarbon-beclometasone: a real-world observational study. *Clin Exp*
26 *Allergy* 2011;41: 1521-32.
27
28
- 29
30 25. Jabbal S, Lipworth BJ, Blood eosinophils: The forgotten man of inhaled
31 steroid dose titration. *Clinical and experimental allergy : journal of the British*
32 *Society for Allergy and Clinical Immunology* 2018;48: 93-95.
33
34
- 35
36 26. Anderson WJ, Short PM, Williamson PA, Lipworth BJ, Inhaled Corticosteroid
37 Dose Response Using Domiciliary Exhaled Nitric Oxide in Persistent Asthma The
38 FENotype Trial. *Chest* 2012;142: 1553-61.
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Table 1

	Pre run-in	Post run-in
ACQ	1.67 (0.11)	1.65 (0.08)
mAQLQ	5.08 (0.24)	5.34 (0.13)
FEV₁ (%) predicted	84 (3)	86 (3)
FEF₂₅₋₇₅ (%) predicted	49 (4)	53 (5)
AX (kPa/l)	1.95 (0.30)	1.83 (0.32)
R5 (kPa/l.s)	0.60 (0.04)	0.57 (0.03)
R5-R20 (kPa/l.s)	0.18 (0.03)	0.17 (0.03)
FeNO (ppb)	26 (4)	20 (2)*
Eos (cells/μl)	204 (33)	156 (22)**

Values are presented as means (SEM) except for FeNO and Eos which are geometric means (SEM). *p<0.05, **p<0.01.
The mean clenil equivalent dose of 710μg was maintained throughout the run in period.

Table 2

	Baseline	4 weeks	8 weeks
ACQ	1.65 (0.08)	1.35 (0.10)*	1.12 (0.12)***
mAQLQ	5.34 (0.13)	5.69 (0.18)	6.03 (0.15)***
FEV₁ (%) predicted	86 (3)	84 (2)	86 (3)
FEF₂₅₋₇₅ (%) predicted	53 (5)	52 (5)	53 (4)
AX (kPa/l)	1.83 (0.32)	1.88 (0.35)	2.09 (0.36)
R5 (kPa/l.s)	0.57 (0.03)	0.59 (0.04)	0.61 (0.04)
R5-R20 (kPa/l.s)	0.17 (0.03)	0.17 (0.03)	0.19 (0.03)
FeNO (ppb)	20 (2)	23 (3)	24 (2)
Eos (cells/μl)	156 (22)	174 (21)	179 (21)

Values are means (SEM) except for FeNO and Eos as geometric means (SEM). * p<0.05, *** p<0.001

Table 3

	Baseline	8 weeks
PEF am (l/min)	398 (27)	409 (27)
PEF pm (l/min)	393 (28)	406 (27)
Symptoms am	0.67 (0.11)	0.47 (0.12)*
Symptoms pm	0.69 (0.12)	0.48 (0.14)*
Reliever am (puffs/day)	0.63 (0.18)	0.35 (0.13)
Reliever pm (puffs/day)	0.97 (0.20)	0.52 (0.19)*

Values are presented as geometric means (SEM) except for PEF. Symptom scores are 0-3 . *p<0.05

Figure legends

Figure 1

CONSORT diagram showing participant flow through the study.

Figure 2

Protocol flow chart for the study showing initial run-in period of at least 4 weeks on fine particle ICS followed by visits at baseline (post run-in) and after 4 and 8 weeks of switching to half the dose of extra-fine particle HFA-BDP. There was a variable step down period, where in addition to stopping any LABA, patients if required halved their ICS dose at 2 weekly intervals.

Figure 3

Effects of switching from fine to extra-fine particle ICS on patient reported outcomes: asthma control questionnaire (ACQ) –the primary end point and mini asthma quality of life questionnaire (AQLQ). Data shown as means and SEM.

Figure 4

Scatter plot for ACQ and AQLQ showing individual data post run-in (baseline) on fine particle ICS and at 8 weeks after switching to extra-fine particle HFA-BDP, along with means and 95% CI.

Figure 5

Mean and SEM values for AQLQ domains after run-in at baseline on fine particle ICS and at 4 and 8 weeks after switching to extra-fine particle HFA-BDP. Data shown as means and SEM.

Figure 6

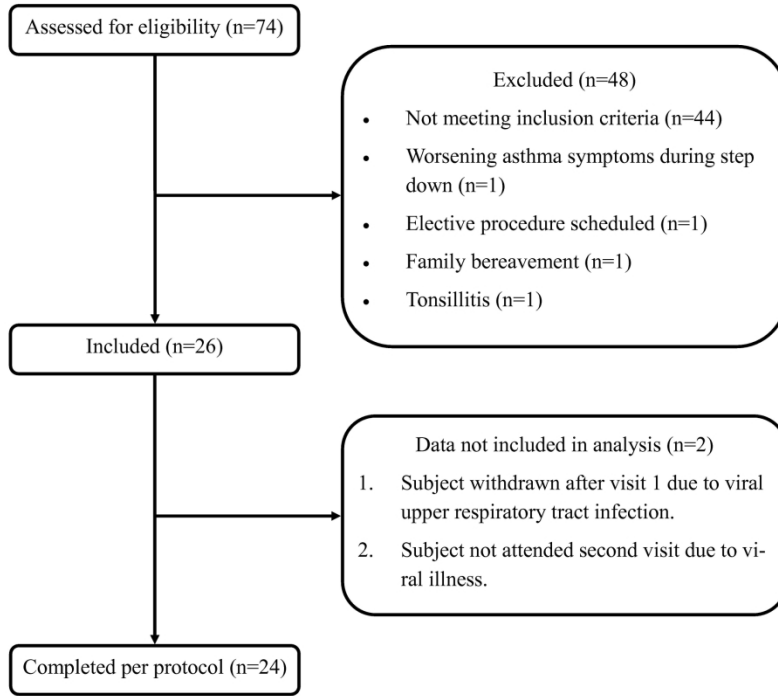
Mannitol airway hyper-responsiveness shown as sensitivity (PD15 threshold) and reactivity (response dose ratio: RDR). Values are depicted for post run-in baseline on fine particle ICS and after 4 and 8 weeks of switching to extra-fine particle HFA-BDP.

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3 Data are shown as geometric means and SEM on a log 2 scale. Overall comparisons
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5 showed $P < 0.001$ for PD15 and $P < 0.05$ for RDR.
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For Peer Review

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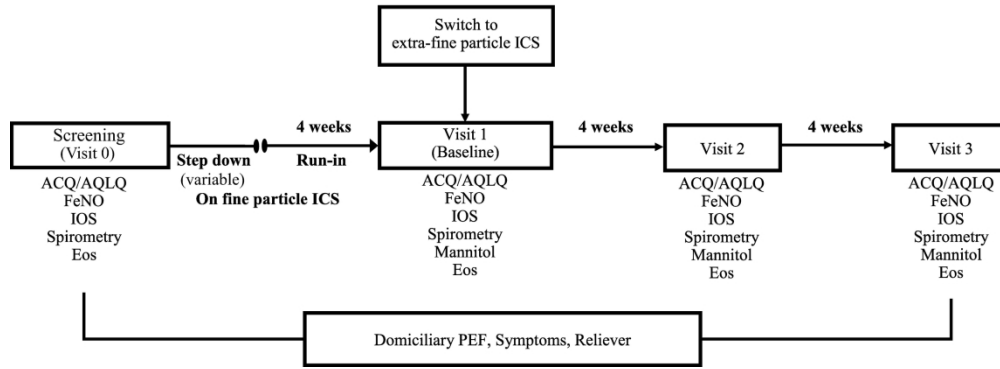
Figure 1



CONSORT diagram showing participant flow through the study.

215x279mm (300 x 300 DPI)

Figure 2

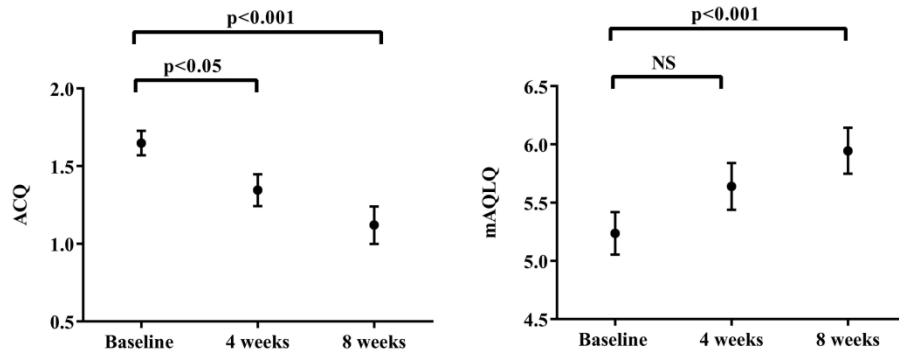


Protocol flow chart for the study showing initial run-in period of at least 4 weeks on fine particle ICS followed by visits at baseline (post run-in) and after 4 and 8 weeks of switching to half the dose of extra-fine particle HFA-BDP. There was a variable step down period, where in addition to stopping any LABA, patients if required halved their ICS dose at 2 weekly intervals.

254x113mm (300 x 300 DPI)

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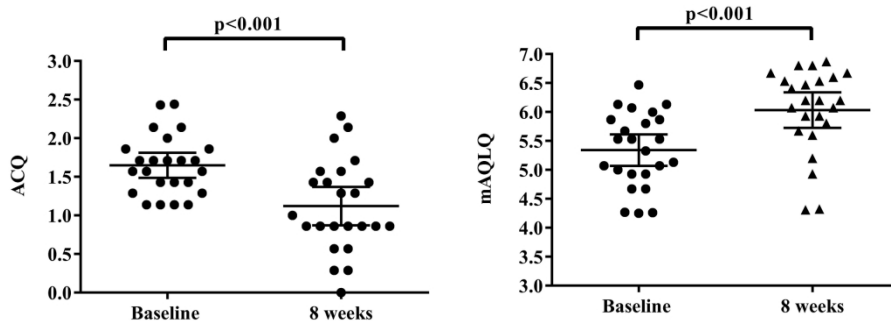
Figure 3



Effects of switching from fine to extra-fine particle ICS on patient reported outcomes: asthma control questionnaire (ACQ) –the primary end point and mini asthma quality of life questionnaire (AQLQ). Data shown as means and SEM.

218x97mm (300 x 300 DPI)

Figure 4

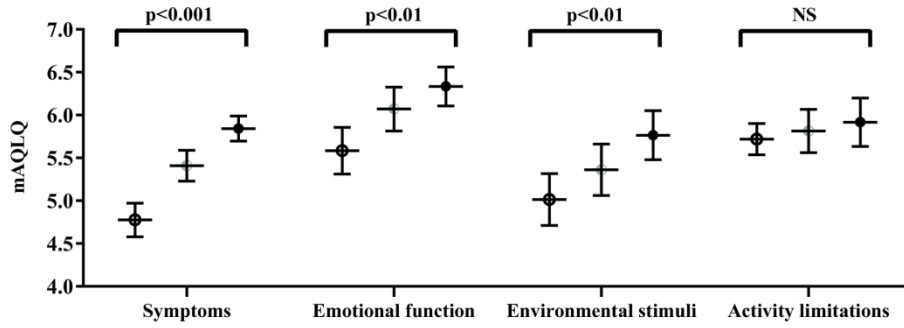


Scatter plot for ACQ and AQLQ showing individual data post run-in (baseline) on fine particle ICS and at 8 weeks after switching to extra-fine particle HFA-BDP, along with means and 95% CI.

219x93mm (300 x 300 DPI)

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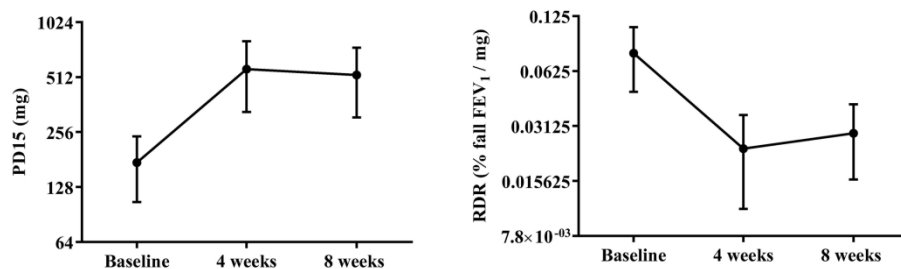
Figure 5



Mean and SEM values for AQLQ domains after run-in at baseline on fine particle ICS and at 4 and 8 weeks after switching to extra-fine particle HFA-BDP. Data shown as means and SEM.

197x84mm (300 x 300 DPI)

Figure 6



Mannitol airway hyper-responsiveness shown as sensitivity (PD15 threshold) and reactivity (response dose ratio: RDR). Values are depicted for post run-in baseline on fine particle ICS and after 4 and 8 weeks of switching to extra-fine particle HFA-BDP. Data are shown as geometric means and SEM on a log₂ scale. Overall comparisons showed $P < 0.001$ for PD15 and $P < 0.05$ for RDR.

210×78mm (300 x 300 DPI)