Pragmatic evaluation of inhaled corticosteroid particle size formulations on asthma control

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Conflict of Interest Statement

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

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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.

Dr. Jabbal contributed to the design of the work and revising as well as approval of the final version of the manuscript.

Dr. Anderson contributed to the conception and design of the work and revising as well as approval of the final version of the manuscript.

Dr. Lipworth contributed to the conception and design of the work, acquisition, analysis and interpretation of data for the work. Dr Lipworth also drafted and critically revised the content as well as approval of the final version of the manuscript. He 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.

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, FEV_1 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 dipropropionate (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 (FEV_1).[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

a significant reduction in air trapping after methacholine challenge using high resolution computerised tomography (HRCT) scanning.[12]

Hence in the present pragmatic study we also measured AHR in a subgroup of patients who after taking a constant dose of ICS at the end of the run-in were identified as being mannitol responders at baseline. We wished to see in this subgroup if putative improvements in PRO's were accompanied by commensurate changes in mannitol AHR after switching to extra-fine particle HFA-BDP.

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 FEV_1 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 200µg per day was reached. In order words, patients entered the subsequent run-in period with partial control – ie ACQ ≥ 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 FEV_1 (PD15 threshold in mg) calculated by interpolation of the log linear dose response curve up to maximum cumulative dose of 635mg. Mannitol

reactivity was expressed as the response dose ratio (RDR as % fall /mg) calculated by dividing the maximum % fall in FEV_1 by the final mannitol dose. Data for PD15 and RDR were logarithmically transformed prior to analysis.

Impulse oscillometry (IOS) was measured using a Jaeger Masterscreen (Jaeger Hochberg, Germany) in triplicate using a nose clip lips sealed tightly, cheeks held and with quiet tidal breathing for 30s. A Superspiro spirometer (Micro Medical ltd, Chatham, UK) was used to record in triplicate according to European Respiratroy Society guidelines. FeNO was measured with a NIOX Mino (Aerocrine AB, Solna, Sweden) in accordance with published guidelines.

A domiciliary diary card was recorded for peak flow, symptoms and reliever use. Full informed written consent was obtained from all patients and the study was approved by the Tayside committee for medical ethics (13/ES/0064) and the study was registered at EUDRACT (2012-003923-39) and Clintrials.gov (NCT01894048).

Statistical analysis

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

Results

The flow of participants is depicted in the CONSORT diagram (Figure 1). 24 patients completed per protocol: mean age 48 yr, FEV_1 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

reactivity as RDR the overall effect was also significant (P<0.05). In this subgroup there were also significant mean improvements comparing 8 weeks versus baseline for ACQ: mean difference -0.82 (95%CI -1.59,-0.05), P<0.05 and mAQLQ: mean difference 1.09 (95%CI 0.14, 2.05), P< 0.05, which exceeded the MCID's for both.

Diary card data showed no significant changes in morning or evening peak expiratory flow (PEF) measurements. There were significant (P<0.05) improvements in domiciliary morning and evening symptoms as well as evening reliever use after 8 weeks compared to baseline (Table 3).

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

lung function was not measured. A prospective randomised controlled trial in 473 patients with mean FEV_1 84% switched patients from their existing chlorofluorocarbon (CFC) suspension based fine particle BDP formulation (400-1600ug) to extra-fine particle HFA-BDP at half the dose, compared to continuing on an unchanged dose of CFC-BDP, with follow up over 12 months.[19] The AQLQ score improved significantly with fine versus extra-fine particle BDP, while there were no commensurate significant differences in lung function. The lack of any significant difference in spirometry including FEF_{25-75} after switching our study is consistent with two other previous head to head trials of extra-fine and fine particle BDP formulations in patients who had a baseline mean FEV_1 of 84%, which was identical to the present trial.[19, 20]

In the subgroup of mannitol responsive individuals we observed significant overall effects in AHR after switching. Indeed the shift in mannitol PD15 exceeded one doubling dose which is taken as being a clinically relevant improvement.[21] Notably in this subgroup the concomitant changes seen in PRO's were also significant and clinically relevant. It has previously been shown that dose related changes in AHR in response to ICS are more sensitive than in lung function.[22, 23] As both AHR and ACQ are predictors of exacerbations,[6, 7, 9] we believe that our data might suggest that switching to extra-fine particle HFA-BDP could also reduce the exacerbation burden in the longer term. This is supported by two real life observational studies showing better overall asthma control over a one year period of follow up when comparing patients who were taking a lower maintenance dose of extra-fine particle versus fine particle BDP formulations.[18, 24]

It is noteworthy that FeNO and blood eosinophils were significantly reduced comparing pre and post run-in values while taking a constant dose of fine particle ICS, whereas ACQ and mAQLQ were not significantly altered. The reduction in FeNO and eosinophils is likely to reflect the putative impact of initial improved adherence to ICS during the run-in period,[25] especially for FeNO which exhibits near maximal suppression by low doses of fine particle ICS.[26] The lack of any subsequent difference in either FeNO or eosinophils after switching to Qvar is consistent with similar findings directly comparing half the dose of extra-fine particle

BDP (100ug and 400ug/day) to fine particle BDP.[20] Although in theory concomitant use of LTRA might have confounded the underlying asthmatic inflammation, this was only the case in 6 patients.

We duly acknowledge the potential weaknesses of our study design. First there was no parallel control arm where patients might have continued with an unchanged dose of fine particle HFA-BDP after run-in, as in the study of Juniper et al.[19] Second our study was powered on ACQ, such that we may have missed smaller changes in lung function due to type 2 error, particularly for IOS measurements. Third the duration of follow up after switching was relatively short at 8 weeks. Nonetheless in the Juniper study [19] using a much larger sample size over one year there were significant improvements in AQLQ with extra-fine versus fine particle BDP which were not associated with commensurate changes in lung function including FEF_{25-75}. It is also possible that the observed improvements in PRO's in our patients might have occurred due to progressively enhanced adherence to ICS over the 8 week switch period. However, since ACQ was unchanged despite FeNO and eosinophils falling during the run in period on a constant dose of ICS, we believe that patients had probably already reached a stable baseline level prior to the switch occurring. Hence, we believe the subsequent improvement in ACQ after switching to Qvar represents a true treatment effect consequent upon the change in particle size. Finally, only a third of our patients had airway hyper-responsiveness at baseline after the run in period. This may be explained by mannitol being an indirect challenge agent which is more sensitive to ICS than a direct challenge using methacholine.[10, 22] In this regards, we did not perform bronchial challenge at screening.

In conclusion, our results show that clinically relevant changes in PRO's may be associated with pragmatic switching from fine particle to extra-fine particle ICS at half the dose. Further longer term trials are warranted to prospectively investigate the potential for reducing exacerbations when using extra-fine particle ICS formulations in patients with uncontrolled persistent asthma. As such, study might also include a parallel control arm where patient continue on an unchanged dose of extra fine particle ICS.

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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)
FEV_1 (%) predicted	84 (3)	86 (3)
FEF_{25-75} (%) 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)***
FEV_1 (%) predicted	86 (3)	84 (2)	86 (3)
FEF_{25-75} (%) 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

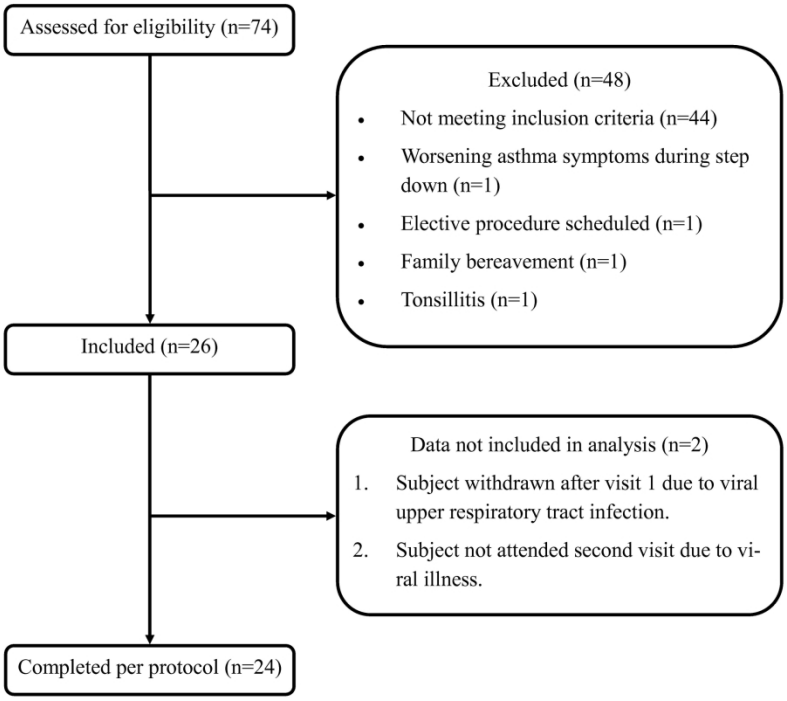
Mean and SEM values for AQLQ domains after run-in at baseline on fine particle ICS and at 4 and 8 weeks after switching to extra-fine particle HFA-BDP. Data shown as means and SEM.

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.

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

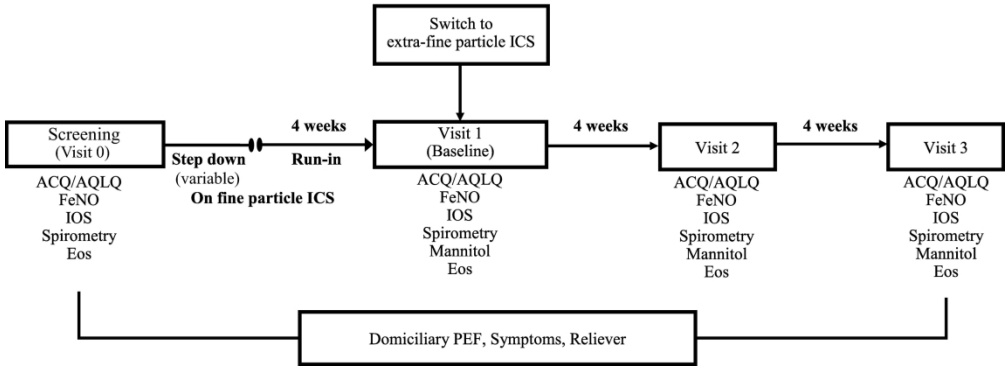
Figure 1



CONSORT diagram showing participant flow through the study.

215x279mm (300 x 300 DPI)

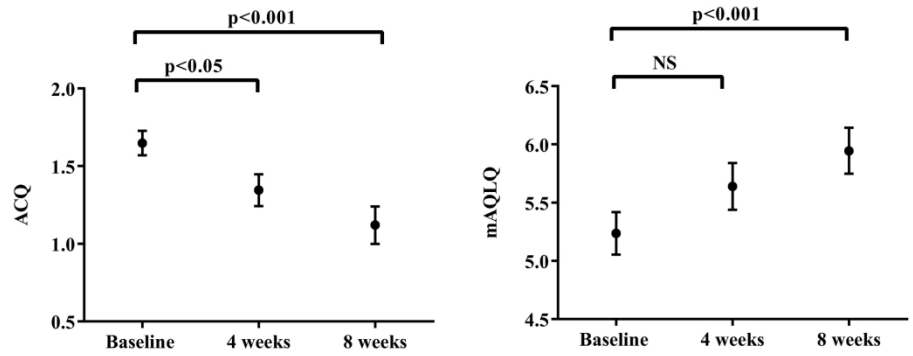
Figure 2



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)

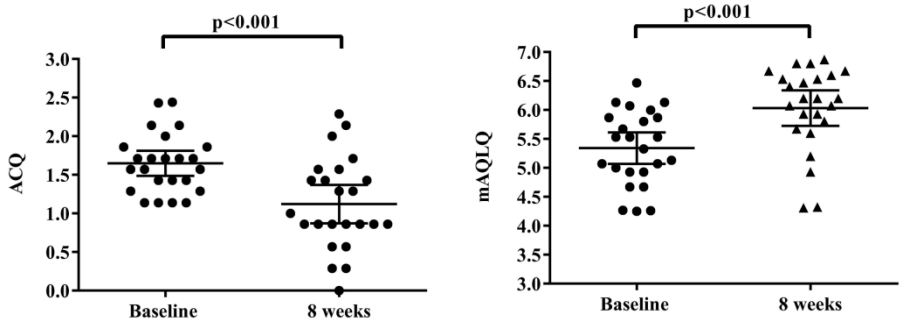
Figure 3



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)

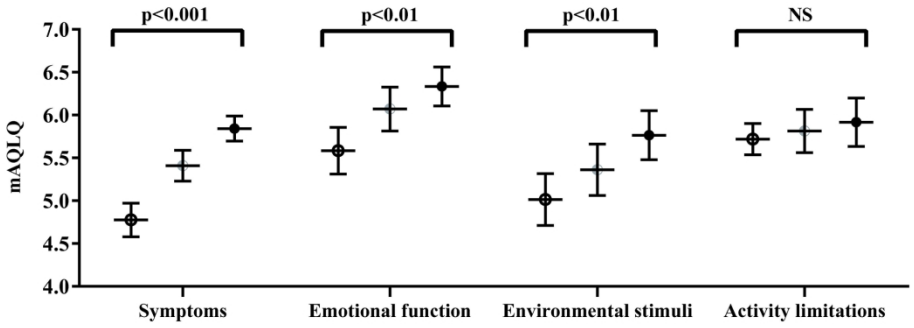
Figure 4



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)

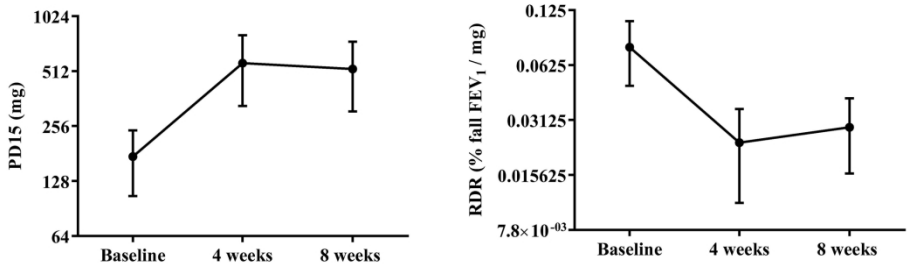
Figure 5



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 log 2 scale. Overall comparisons showed P<0.001 for PD15 and P<0.05 for RDR.

210x78mm (300 x 300 DPI)