Title: Inhaled Corticosteroids for Asthma Therapy in Young Children: does aerosol particle size matter?

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Inhaled Corticosteroids for Asthma Therapy in Young Children:

does aerosol particle size matter?

(Correspondence re van Aalderen et al, 2015 Sep-Oct; 3(5):721-731).

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To the Editor.

The Aalderen et al study published in your last issue (1) is an important addition to the pediatric asthma literature. The authors have challenged existing asthma guidelines by showing that, instead of adding long acting beta 2 agonists (LABA) to large-particle inhaled corticosteroids (ICS) as the first-line alternative for therapeutic “stepping up” when asthma is not controlled by ICS monotherapy, smaller particle ICS should be the foundation of the management of childhood asthma, since it is as effective as large particle ICS+LABA.

In their sub analysis the authors found the benefit of smaller particle ICS was particularly evident in younger children and mentioned our 2012 study that suggested such an effect (2). We would like to draw attention to an earlier study of ours (3), co-authored by international experts, that challenged the notion of lack of benefit of ICS in young children with asthma (4). We emphasized, in that article, the need to reconsider that idea and suggested that small-particle ICS “could improve the clinical outcome in infants and young children”. The present study strongly supports our previous objection to the notion, recently again seriously challenged (5), that ICS are not effective in young children.

Indeed, in our opinion, the well-designed and executed study by van Aalderen et al (1) allows four additional important clinical conclusions: 1. That asthma management in this age group can be simplified by allowing more easily taught dose adjustments with only a single small-particle MDI and is therefore likely to result in better concordance. 2. This should result in a significant reduction in health care costs by making it unnecessary to keep a combination inhaler on-hand or visit a physician to obtain a prescription for the LABA+ICS combination unit when “step-up” is required. With only a single MDI to deal with, a phone call to the pediatrician or detailed written instructions, advising patients when and how to “step-up” the dose as needed, could suffice. 3. Since the majority of the children in the study were using a VHC (although 38% were not) this raises a question that the study might be able to answer. Namely, did the non VHC users, on average, do as well as those that used a VHC? 4. Finally, since older children, capable of using a dry powder inhaler (DPI), are often switched over to that device, known to deliver ~4um particles (with an approximately 60x larger mass than the 1um MMAD of HFA 134
Beclomethasone or Ciclesonide), and requiring inhalation at very high inspiratory velocities (>60 l/min), it would be of considerable interest and therapeutic relevance to compare small (MDI generated) and large (DPI generated) particles in the management of asthma, BPD, CF and PCD, all characterized by reversible airflow obstruction, inflammation and hypersecretion and beneficial responses to ICS therapy. It would be anticipated that the much larger particles and higher inspiratory flow with the DPI would predict high oropharyngeal and lower total lung and peripheral airway deposition, thus increasing adverse effects in the upper respiratory tract and reduced efficacy.

References.


Small-particle Inhaled Corticosteroid as First-line or Step-up Controller Therapy in Childhood Asthma

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**What is already known about this topic?** Evidence from randomized controlled trials regarding asthma controller therapies for children is limited, usually short-term, and often not generalizable to general practice, where most children with asthma are managed.

**What does this article add to our knowledge?** Over 1 outcome year, small-particle inhaled corticosteroid (ICS) was more effective than standard size–particle ICS for children initiating or stepping up ICS therapy and as effective as adding a long-acting \(\beta_2\)-agonist in a fixed-dose combination inhaler.

**How does this study impact current management guidelines?** These findings challenge asthma guidelines that recommend adding a long-acting \(\beta_2\)-agonist as the first-line alternative for stepping up therapy when asthma is not controlled by ICS monotherapy.

**BACKGROUND:** Because randomized controlled trials of established pediatric asthma therapies are expensive and difficult to perform, observational studies may fill gaps in the evidence base. **OBJECTIVES:** To compare the effectiveness of representative small-particle inhaled corticosteroid (ICS) with that of standard size–particle ICS for children initiating or stepping up ICS therapy for asthma (analysis 1) and to compare the effectiveness of ICS dose step-up using small-particle ICS with adding long-acting \(\beta_2\)-agonist (LABA) to the ICS (analysis 2). **METHODS:** These historical matched cohort analyses drew on electronic medical records of children with asthma aged 5 to 11 years. Variables measured during 2 consecutive years (1 baseline year for confounder definition and 1 outcome year) included risk-domain asthma control (no hospital attendance for asthma, acute oral corticosteroids, or lower respiratory tract infection requiring antibiotics) and rate of severe exacerbations (asthma-related emergency, hospitalization, or oral corticosteroids). **RESULTS:** In the initiation population (n = 797 in each cohort), children prescribed small-particle ICS versus standard size–particle ICS experienced greater odds of asthma control (adjusted odds ratio, 1.49; 95% CI, 1.10-2.02) and lower severe exacerbation rate (adjusted rate ratio, 0.56; 95% CI, 0.35-0.88). Step-up outcomes (n = 206 in each cohort) were also significantly better for small-particle ICS, with asthma control adjusted odds ratio of 2.22 (95% CI, 1.23-4.03) and exacerbations adjusted rate ratio of 0.49 (95% CI, 0.27-0.89). The number needed to treat with small-particle ICS to achieve 1 additional child with asthma control was 17 (95% CI, 9-107) for the initiation population and 5 (95% CI, 3-78) for the step-up population. Outcomes were not significantly different for stepped-up small-particle ICS dose versus ICS/LABA combination (n = 185 in each cohort). **CONCLUSIONS:** Initiating or stepping up the ICS dose with small-particle ICS rather than with standard size–particle ICS is more effective and shows similar effectiveness to add-on LABA in childhood asthma. © 2015 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (J Allergy Clin Immunol Pract 2015;3:721-31)

**Key words:** Asthma; Childhood; Small-particle beclomethasone; Fluticasone; Inhaled corticosteroid; Long-acting \(\beta_2\)-agonist; Step-up therapy
Clinicians managing children with asthma in community settings, where most patients with asthma are seen, must rely on evidence for their therapeutic choices primarily from randomized controlled trials (RCTs). However, funding for large independent RCTs is limited; moreover, RCT results may not be widely generalizable to unselected patient populations. They exclude many children with asthma who have intermittent, milder disease and who may be most prone to exacerbations. In addition, RCTs seldom include comparisons of step-up strategies, directly compare different types or formulations of inhaled corticosteroids (ICS), or provide the long-term comparisons (>12 weeks) needed for evaluating infrequent events, such as exacerbations.1,5 Head-to-head RCTs are challenging to institute because of difficulties in unravelling the roles of corticosteroid potency, initial dose from different inhaler devices, and delivered dose to the lower airways. Moreover, recruitment into RCTs of children with poor control sufficient to justify a change in therapy is notoriously very difficult.1 Finally, the enforced adherence to prescribed medication in RCTs is difficult to duplicate in clinical practice, further limiting the applicability of RCT results.

Information from observational studies of pediatric asthma therapies can complement the limited evidence currently available. Nevertheless, the lack of randomized trials to evaluate many widespread treatment options and the potential for bias in observational studies render these data inconclusive. Therefore, the evidence for many important pediatric asthma treatment questions is derived from real-world data that were either not randomized or were not designed to assess treatment outcomes.

Real Life Ltd (RiRL, Cambridge, UK). Teva played no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The research team at RiRL designed the study, conducted the analyses, and coordinated the writing and revision of the article in collaboration with the study steering committee.

Conflicts of interest: W. M. C. van Aalderen has received travel reimbursement from Research in Real Life (RiRL); is a member of medical advisory boards of Mundipharma BV, AstraZeneca, and Teva; and received a traveling grant from Teva and a speaker’s fee from Forest. J. Grigg has received travel reimbursement from RiRL; is on the advisory boards for GlaxoSmithKline (GSK) and Novartis; and received honoraria from Novartis as a member of an advisory board for an asthma medication and received honoraria from GlaxoSmithKline for advice on an asthma medication study design. T. W. Gilburt has received travel reimbursement and medical writing support from RiRL; has received travel support to research meeting by Merck-Schering Plough; has received fees for developing questions for Pediatric Pulmonary Board exams from the American Board of Pediatrics, Pediatric Pulmonary Subboard; is on the Teva advisory board; has received research support from Teva; is a consultant for Teva, MAP Pharmaceuticals, GSK, and Merck; has received personal fees from GSK as a committee member, research advisor, advisory board member, and a subinvestigator; is on the Regeneron Pharmaceuticals research advisory board; was a subinvestigator for Altus Pharmaceuticals, Inspire Pharmaceuticals, Teva, and GSK; has received research support from the National Institute for Disease Control and Prevention, Department of Health and Human Services, National Institutes of Health University of Wisconsin-Madison Medical and Education Research Committee, Abbott Laboratories, Array Biopharma, Mylan, Forest Research Institute, F. Hoffmann-LaRoche, MedImmune, KaloBios Pharmaceuticals, Vertex Pharmaceuticals, Roxane Laboratories and CompleteWare Corporation, CF Foundation Therapeutics, and Roche-Gentech; and receives royalties from UpToDate. N. Roche has received travel reimbursement from RiRL; has received fees for speaking, organizing education and research, or consulting from Aerocrine, Nycomed, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, MEDA, MSD, Mundipharma, Novartis, Pfizer, and Teva; has received research funds from Boehringer Ingelheim, Pfizer, Novartis, and Nycomed; is on the advisory board for and has received lecture fees from Mundipharma; is on the advisory board for and has received consultancy and lecture fees from Chiesi; is on the advisory board for and has received manuscript preparation fees from Nycomed; is on the Almirall advisory board; is on the advisory board for and has received lecture fees and research support from Novartis; is on the advisory board for and has received research support from Boehringer Ingelheim; has received consultancy and lecture fees from AstraZeneca; has received lecture fees from GSK, Teva, Meda, Stallergenes, and Aerocrine; is on the advisory board for and has received lecture fees from Pfizer. E. Israel has received travel reimbursement from RiRL and Teva Specialty Pharmaceuticals; has grant support paid to his institution from Apenge, i3 Research (Biota); has received consultancy fees from Cowen & Co, Infinity Pharmaceuticals, Merck, Regeneron Pharmaceuticals, and Teva Specialty Pharmaceuticals; is on the speakers bureau and has received consultancy fees from Merck; has provided expert testimony for Campbell, Campbell, Edwards & Conroy, Ficksman & Conley, and Ryan Ryan Deluca LLP; received royalties from UpToDate; and is a Data Safety Monitoring Board member for Novartis. R. J. Martin has received travel support from RiRL; has done consultancy work and/or received travel support and/or honoraria for attendance at advisory boards for Teva, AstraZeneca, MedImmune, Boehringer Ingelheim, Throm, and Merck; has received research support from MedImmune and the National Heart, Lung, and Blood Institute; and received royalties from UpToDate. G. Colice has received travel expense reimbursement for meeting attendance and manuscript preparation from RiRL and has received speakers and consultancy fees from and is an advisory board member for Teva, MedImmune, Dey, Mylan, Novartis, and Alitair. In the past 3 years, the University of Groningen has received money for D. S. Postma regarding an unrestricted educational grant for research for AstraZeneca and Chiesi; travel to the European Respiratory Society and/or American Thoracic Society has been partially funded by AstraZeneca, Chiesi, GSK, and Nycomed; fees for consultations were given to the University of Groningen by AstraZeneca, Boeringer Ingelheim, Chiesi, GSK, Nycomed, and Teva; and money for travel and lectures in China was paid by Chiesi. D. S. Postma has received travel reimbursement from RiRL. E. V. Hillyer has received travel reimbursement and consultancy fees from RiRL; has received payment for manuscript preparation from Merck and Teva-France; and is a consultant for RiRL, A. Burden, V. Thomas, and J. von Ziegenweidt has received research support from Teva and are employed by RiRL. D. Price has received research support from Teva; is a member of the following boards for which fees were paid to RiRL: Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva; has received consultancy fees paid to RiRL from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Media, Mundipharma, Napp, Novartis, Pfizer, and Teva; has received research support for which fees were paid to RiRL from UK National Health Service, British Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Media, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, and Zentiva; has received fees (paid to RiRL) for manuscript preparation from Mundipharma and Teva; has received travel reimbursement from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva; has received funding paid to RiRL for patient enrollment or completion of research from Almirall, Chiesi, Teva, and Zentiva; has received unrestricted funding, paid to RiRL, for investigator-initiated research from Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva; has a pending patent for Phytopharmaceuticals with AKL Ltd; has shares in AKL Ltd, which produces phytopharmaceuticals; and owns 80% of RiRL Ltd and its subsidiary social enterprise Optimum Patient Care; and is peer reviewer for grant committees: Medical Research Council (2012), Efficacy and Mechanism Evaluation programme (2012), and HTA (2012). 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available from RCTs. Here, we report the results of 2 observational analyses, using routinely collected health care data, designed to evaluate the effectiveness of 1-year controller therapy for managing several clinically common situations in children with asthma.

The objective of analysis 1 was to compare outcomes in children after a first prescription or a stepped-up dose of either a small-particle ICS or a standard size–particle ICS. We chose small-particle beclomethasone and fluticasone for comparison for several reasons. These 2 ICS are the most widely used in the United States today. In previous observational studies of adults, we found that small-particle beclomethasone (ICS particles with median mass aerodynamic diameter of 1.1 μm) is prescribed for asthma at significantly lower doses, but shows effectiveness over 1 year similar to or better than that of fluticasone (median mass aerodynamic diameter, 2.4-3.2 μm, depending on formulation). Formula-tions of small-particle ICS may be particularly relevant to the treatment of children with asthma because of children’s physical size (smaller airways than those of adults), as well as the association of peripheral, small airways dysfunction with uncontrolled asthma. In adults, small-particle beclomethasone has greater and more uniform lung deposition, reaching both large and small airways, than does larger-particle ICS. In children with asthma, the lung deposition of small-particle ICS ranges from means of 37% to 55% of ex-actuator dose, depending on age and inhaler device. For young children (ages 3-7 years), 1 month’s treat-ment with small-particle beclomethasone administered using a valved holding chamber significantly decreased bronchial hyper-responsiveness. In a small study, 20 children (ages 5-14 years) with stable, moderate asthma experienced improvements in lung function after being switched from standard ICS to small-particle beclomethasone. Two small randomized comparative trials failed to demonstrate significant differences in effectiveness between small-particle beclomethasone and fluticasone for children.

The objective of our analysis 2 was to compare the effectiveness of stepping up asthma therapy by increasing the ICS dose as a small-particle ICS versus adding a long-acting β₂ agonist (LABA) to the ICS in fixed-dose combination or separate inhalers. A recent RCT and meta-analyses of previous RCTs comparing add-on LABA with increased ICS dose for children have been inconclusive or report similar outcomes with these 2 step-up strategies; however, the ICS studied were all larger-particle formulations (budesonide and fluticasone).

METHODS

Analysis and patients

These matched cohort analyses drew on anonymized clinical data (1997 through January 2011) contained in 2 UK primary care electronic databases: the General Practice Research Database, now part of the National Health Service Clinical Practice Research Datalink, and the Optimum Patient Care Research Database, previously well-described (see this article’s Online Repository at www.jaci-inpractice.org). The study was done to standards suggested for observational studies, including an independent steering committee (not remunerated for participation), use of an a priori analysis plan, and well-maintained and monitored study databases. Children’s characteristics were cross-referenced between the 2 data sets to avoid duplication.

<table>
<thead>
<tr>
<th>TABLE 1. Definitions of database-derived study outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk-domain asthma control</strong>, includes all of the following:</td>
</tr>
<tr>
<td>1. No asthma-related* hospital attendance or admission, ED attendance, out-of-hours attendance, or outpatient hospital attendance, and</td>
</tr>
<tr>
<td>2. No GP consultation for lower respiratory tract infection requiring antibiotics, and</td>
</tr>
<tr>
<td>3. No prescription for acute course of oral corticosteroids.</td>
</tr>
<tr>
<td>Overall control,† includes all of the following:</td>
</tr>
<tr>
<td>1. No asthma-related* hospital attendance or admission, ED attendance, out-of-hours attendance, or outpatient hospital attendance, and</td>
</tr>
<tr>
<td>2. No GP consultation for lower respiratory tract infection requiring antibiotics, and</td>
</tr>
<tr>
<td>3. No prescription for acute course of oral corticosteroids, and</td>
</tr>
<tr>
<td>4. Average ≤2 puffs daily dose of SABA (salbutamol ≤200 μg/d or terbutaline ≤500 μg/d)</td>
</tr>
</tbody>
</table>

Number of severe exacerbations, defined as any of the following:

1. Asthma-related* hospital attendance or admission or ED attendance, or
2. Acute course of oral corticosteroids

Number of clinical exacerbations, defined as any of the following:

1. Asthma-related* hospital attendance or admission or ED attendance, or
2. GP consultation for lower respiratory tract infection requiring antibiotics, or
3. Acute course of oral corticosteroids

Treatment stability, includes all of the following:

1. Risk-domain asthma control (see above) and
2. No additional therapy after the index date as a. increased ICS dose (by ≥50%), or
b. use of additional therapy as LABA, LTRA, or theophylline

Respiratory hospitalizations, defined as:

- hospitalizations with an asthma Read code + uncoded hospitaliza-tions occurring within a 7-d window (either side of the hospitalization date) of a lower respiratory tract Read code

Mean daily ICS dose during the baseline and the outcome year, defined as:

- number of days supply of ICS divided by 365

ED, Emergency department; LTRA, leukotriene receptor antagonist.

* Asthma-related events in the database included all events with a lower respiratory tract code, including all asthma codes and lower respiratory tract infection codes.

† Overall control was not an outcome measure in the small-particle ICS step-up vs add-on LABA comparisons (analysis 2).

For the exacerbation definitions, any criteria occurring within 2 wk of each other are counted as 1 exacerbation.

We studied 2 consecutive years of data for each eligible child, aged 5 to 11 years at the time of the index prescription: a baseline year preceding the index prescription date, included for defining potential baseline confounders, followed by an outcome year. We required a recorded asthma diagnosis in the database or evidence of active asthma, defined as 2 or more prescriptions for asthma therapy (controller or reliever) during the baseline year. In addition, during the outcome year, children had to have received at least 1 asthma prescription in addition to the index prescription. Children were excluded from the study for an ever-diagnosis of any chronic respira-tory disease other than asthma or a baseline year prescription for maintenance oral corticosteroid therapy or an ICS/LABA combi nation inhaler.

For analysis 1 comparing small-particle and standard size–particle ICS, we included children prescribed their first ICS (initiation popula-tion) or increased ICS dose (step-up population) as beclomethasone...
Matched cohorts were compared using conditional logistic regression.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Initiation population</th>
<th>Step-up population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small-particle ICS</td>
<td>Standard SP ICS</td>
</tr>
<tr>
<td>n (797)</td>
<td>455 (57.1)</td>
<td>455 (57.1)</td>
</tr>
<tr>
<td></td>
<td>124 (60.2)</td>
<td>124 (60.2)</td>
</tr>
<tr>
<td>Sex: male†</td>
<td>455 (57.1)</td>
<td>455 (57.1)</td>
</tr>
<tr>
<td>Age at index date (y), † mean ± SD</td>
<td>7.7 ± 2</td>
<td>7.7 ± 2</td>
</tr>
<tr>
<td>Recorded comorbidity†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible atopy</td>
<td>558 (70.0)</td>
<td>574 (72.0)</td>
</tr>
<tr>
<td></td>
<td>159 (77.2)</td>
<td>161 (78.2)</td>
</tr>
<tr>
<td>Rhinitis diagnosis/Rx</td>
<td>140 (17.6)</td>
<td>202 (25.3)</td>
</tr>
<tr>
<td></td>
<td>42 (20.4)</td>
<td>50 (24.3)</td>
</tr>
<tr>
<td>Eczema diagnosis/Rx</td>
<td>557 (69.9)</td>
<td>554 (69.5)</td>
</tr>
<tr>
<td></td>
<td>153 (74.3)</td>
<td>160 (77.7)</td>
</tr>
<tr>
<td>Preschool wheeze diagnosis</td>
<td>74 (13.3)</td>
<td>68 (12.1)</td>
</tr>
<tr>
<td></td>
<td>46 (30.1)</td>
<td>54 (35.1)</td>
</tr>
<tr>
<td>Preschool asthma diagnosis/Rx</td>
<td>296 (48.8)</td>
<td>293 (48.0)</td>
</tr>
<tr>
<td></td>
<td>120 (67.0)</td>
<td>128 (75.7)</td>
</tr>
<tr>
<td>Risk-domain asthma control</td>
<td>655 (82.2)</td>
<td>656 (82.3)</td>
</tr>
<tr>
<td></td>
<td>160 (77.7)</td>
<td>160 (77.7)</td>
</tr>
<tr>
<td>Overall control</td>
<td>576 (72.3)</td>
<td>579 (72.6)</td>
</tr>
<tr>
<td></td>
<td>87 (42.2)</td>
<td>87 (42.2)</td>
</tr>
<tr>
<td>Spacer device prescribed</td>
<td>232 (29.1)</td>
<td>233 (29.2)</td>
</tr>
<tr>
<td></td>
<td>88 (42.7)</td>
<td>78 (37.9)</td>
</tr>
</tbody>
</table>

Mean daily SABA dose (µg/d)†

<table>
<thead>
<tr>
<th>Value</th>
<th>Small-particle ICS</th>
<th>Standard SP ICS</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>325 (40.8)</td>
<td>325 (40.8)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>1-100</td>
<td>165 (20.7)</td>
<td>165 (20.7)</td>
<td>42 (20.4)</td>
</tr>
<tr>
<td>101-200</td>
<td>208 (26.1)</td>
<td>208 (26.1)</td>
<td>63 (30.6)</td>
</tr>
</tbody>
</table>
| 201-400                    | 84 (10.5)         | 77 (9.7)        | 66 (32.0)| 59 (28.6)| .2\<
| >400                       | 15 (1.9)          | 22 (2.8)        | 32 (15.5)| 39 (18.9) |

Median (IQR) daily ICS dose (µg/d)†

<table>
<thead>
<tr>
<th>Value</th>
<th>Small-particle ICS</th>
<th>Standard SP ICS</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>1-99</td>
<td>40 (19.4)</td>
<td>44 (21.4)</td>
<td></td>
</tr>
<tr>
<td>100-199</td>
<td>147 (71.4)</td>
<td>143 (69.4)</td>
<td>.2&lt;</td>
</tr>
<tr>
<td>≥200</td>
<td>19 (9.2)</td>
<td>19 (9.2)</td>
<td></td>
</tr>
</tbody>
</table>

Severe exacerbations†

<table>
<thead>
<tr>
<th>Value</th>
<th>Small-particle ICS</th>
<th>Standard SP ICS</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>743 (93.2)</td>
<td>743 (93.2)</td>
<td>NA</td>
</tr>
<tr>
<td>1</td>
<td>49 (6.1)</td>
<td>49 (6.1)</td>
<td>27 (13.1)</td>
</tr>
<tr>
<td>≥2</td>
<td>5 (0.6)</td>
<td>5 (0.6)</td>
<td>5 (2.4)</td>
</tr>
</tbody>
</table>

Asthma consultation and no oral corticosteroids†

<table>
<thead>
<tr>
<th>Value</th>
<th>Small-particle ICS</th>
<th>Standard SP ICS</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>400 (50.2)</td>
<td>400 (50.2)</td>
<td>64 (31.1)</td>
</tr>
<tr>
<td>1</td>
<td>297 (37.3)</td>
<td>297 (37.3)</td>
<td>75 (36.4)</td>
</tr>
<tr>
<td>2</td>
<td>82 (10.5)</td>
<td>75 (9.4)</td>
<td>45 (21.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>18 (2.3)</td>
<td>25 (3.1)</td>
<td>22 (10.7)</td>
</tr>
</tbody>
</table>

IQR, Interquartile range; NA, not applicable; Rx, therapy; standard SP, standard size—particle.

Data are presented as n (%) except otherwise indicated.

†Matching variable (year of index prescription matched ± 4 y; for details, please see this article’s Online Repository at www.jaci-inpractice.org).

‡Possible atopy was defined as any 1 or more of the following: recorded rhinitis diagnosis, rhinitis therapy, eczema diagnosis, eczema therapy. Preschool wheeze was captured through database coding; concomitant rhinitis, eczema, and preschool asthma were captured through database-coded diagnosis or therapy for same. Preschool was defined as age 1 to 3 y.

§The doses of ICS were standardized to equivalence with small-particle beclomethasone and fluticasone; thus, doses of large-particle beclomethasone and budesonide were halved.

dipropionate hydrofluorokalkane (QVAR; Teva UK Ltd, Eastbourne, East Sussex, UK), of interest to the study sponsor and the only small-particle ICS available in the United Kingdom at the time, or fluticasone propionate (hydrofluorokalkane or chlorofluorokalkane formulation; Flixotide; GlaxoSmithKline UK Ltd, Brentford, Middlesex, UK) by pressurized metered-dose inhaler (pMDI). Children in the step-up population were prescribed an ICS (any type) during the baseline year and on the index date were prescribed an increase of 50% or more in the ICS dose as either small-particle ICS or standard size—particle ICS.

For analysis 2 (step-up comparisons of small-particle ICS vs add-on LABA), eligible children prescribed ICS during the baseline year by pMDI or breath-actuated metered-dose inhaler were stepped up to 1 of 3 options: 1) an increase of 50% or more in the ICS dose as small-particle beclomethasone by pMDI or breath-actuated inhaler (ICS step-up cohort); 2) addition of LABA, with no change in the ICS dose, via fixed-dose ICS/LABA combination inhaler (ICS/LABA combination cohort) as either fluticasone propionate/salmeterol xinafoate (Seretide; GlaxoSmithKline UK Ltd, Brentford, Middlesex, UK) or budesonide/formoterol fumarate dihydrate (Symbicort; AstraZeneca Ltd, Luton, Bedfordshire, UK); or 3) addition of LABA by separate inhaler, with no change in the ICS drug, dose, or inhaler (separate ICS + LABA cohort).

**Study end points**

Composite measures to evaluate asthma-related outcomes, used in our previous studies, were defined in detail in Table I. In brief, risk-domain asthma control (asthma control) was defined as no hospital attendance for asthma, acute oral corticosteroid course, or general practice (GP) consultation for lower respiratory tract infection requiring antibiotics; the latter criterion was included because, in
practice, asthma exacerbations can be confused with lower respiratory tract infection.\textsuperscript{28,29} The definition of overall control included asthma control plus limited reliever use (daily average of \leq 2 puffs of short-acting \beta\textsubscript{2}-agonist [SABA], defined as albuterol \leq 200 \mu g/d or terbutaline \leq 500 \mu g/d, calculated as the dispensed amount divided by 365).

Severe exacerbations were defined according to American Thoracic Society/European Respiratory Society criteria (asthma-related emergency or hospitalization or oral corticosteroids).\textsuperscript{30} A second extended definition of clinical exacerbation, developed with the guidance of respiratory clinicians, included the additional criterion of a GP consultation for lower respiratory tract infection as defining an exacerbation. Another composite measure, treatment stability, was defined as risk-domain asthma control plus no treatment change (Table I).

**Statistical analysis**

Composite outcome measures and analyses were prespecified according to standard operating procedures of the research group\textsuperscript{31} (see full details in this article’s Online Repository at www.jaci-inpractice.org). The analyses were carried out using IBM SPSS Statistics version 19 (SPSS Statistics, IBM, Somers, NY), SAS versions 9.2 and 9.3 (SAS Institute, Marlow, Buckinghamshire, UK), and Microsoft Excel 2007 (Microsoft, Bellevue, Wash); statistically significant results were defined as $P < .05$.

To minimize potential confounding by baseline differences between treatment cohorts, we matched children sequentially on demographic characteristics (sex then age) and several clinically important indicators of baseline asthma severity (sequence described in this article’s Online Repository at www.jaci-inpractice.org). Children in the step-up cohorts of analysis 1 and those in analysis 2 were also matched on the last ICS dose prescribed before the index prescription. We calculated the mean daily ICS dose during baseline as the dispensed amount divided by 365, standardizing the dose to that of small-particle beclomethasone (Table I). Matching ratios were chosen to maximize patient numbers and thus statistical power for the comparisons (see this article’s Online Repository at www.jaci-inpractice.org).

We evaluated all baseline and outcome variables using summary statistics. Conditional logistic regression was used to quantify baseline differences between matched cohorts. Potential confounding factors were examined for colinearity and clinical importance to select those used as potential confounders in the regression modeling of outcomes; a detailed list is provided in this article’s Online Repository at www.jaci-inpractice.org. Variables that differed between treatment cohorts at $P < .10$ were considered as potential confounding factors, as well as baseline variables predictive of outcomes in multivariate analyses at $P < .05$.

The odds of achieving risk-domain asthma control during the outcome year were compared between matched treatment cohorts using conditional binary logistic regression models. Asthma control status was used as the dependent variable, with treatment and potential confounding factors as explanatory variables. Similar methods were used to calculate the adjusted odds ratio (adjOR) for overall control (analysis 1 only) and treatment stability. Where a significant difference was found between treatment cohorts in the primary outcome of risk-domain asthma control, we also calculated the difference in proportions achieving control between treatment cohorts (using the same conditional binary logistic regression model; with 95% CI) and the number needed to treat (NNT) for 1 additional child to achieve control (the inverse of the difference in proportions; with 95% CI) to better quantify the difference in treatment effect between cohorts. To account for multiple comparisons in the primary outcomes, a false-discovery rate controlling procedure was used (for description, see this article’s Online Repository at www.jaci-inpractice.org).\textsuperscript{32}

The total number of severe exacerbations in the outcome year was compared between treatment cohorts using a conditional
FIGURE 1. AdjORs and adjRRs comparing treatment cohorts during 1 outcome year. A, Initiation asthma therapy comparing small-particle ICS vs standard size–particle ICS (standard size–particle ICS set at odds/rate = 1.0). LRTI, Lower respiratory tract infection. Adjusted for the following confounders: *Consultation for LRTI requiring antibiotic (yes/no). †Asthma control status, number of asthma/allergy prescriptions; *LABA use (yes/no) and number of non–asthma-related consultations. ‡Rhinitis diagnosis, year of index date. §Consultation
Poison regression model to obtain an estimate of relative exacerbation rates. The model used empirical standard errors (for more conservative CI estimations), and adjustments were made for potential baseline confounders. The adjusted rate ratios (adjRRs) for clinical exacerbations and hospitalizations were calculated in a similar fashion.

For children initiating ICS, we conducted several subgroup analyses to further examine factors that could be influencing the outcomes of therapy, including spacer prescriptions and age grouped as 5 to 6 and 7 to 11 years (described in this article’s Online Repository at www.jaci-inpractice.org). For the step-up comparisons of small-particle ICS versus add-on LABA, we calculated the total β₂-agonist load (SABA + LABA) in terms of total hours of coverage (see this article’s Online Repository at www.jaci-inpractice.org).

RESULTS
Identification of children in the data sets and the results of cohort matching are depicted in Figures E1-E4 in this article’s Online Repository at www.jaci-inpractice.org.

Analysis 1: Small-particle ICS versus standard size—particle ICS as first-line or step-up ICS therapy

Initiation population. The 2 initiation cohorts were well matched at baseline for composite measures of asthma severity (Table II; see Table E1 in this article’s Online Repository at www.jaci-inpractice.org). A significant difference in median index date was minor and likely not clinically meaningful. Significantly fewer children in the small-particle ICS cohort had rhinitis or were receiving rhinitis therapy (18% vs 25% for standard size—particle ICS; P < .001); rates of possibly atopy were similar (70% vs 72%, respectively; Table II). There were significant mean ± SD differences in index date doses (167 ± 85 vs 221 ± 157 μg/d for small-particle vs standard size—particle ICS; P < .001), and fewer children in the small-particle ICS cohort were prescribed an ICS dose of 400 μg/d or more (7.4% vs 15.6% for standard size—particle ICS; see Figure E5, A, in this article’s Online Repository at www.jaci-inpractice.org).

During the outcome year (Table III), the odds of achieving risk-domain asthma control were significantly greater for children initiating small-particle ICS than for those initiating standard size—particle ICS therapy (adjOR, 1.49; 95% CI, 1.10-2.02; Figure 1, A). The adjusted difference in proportions achieving asthma control (small-particle ICS vs standard size—particle ICS) was 0.06 (95% CI, 0.01-0.11; adjusted for baseline GP consultation for lower respiratory tract infection resulting in an antibiotic prescription). The NNT to achieve 1 additional child with asthma control using small-particle ICS was 17.0 (95% CI, 9.3-107.2).

In addition, children in the small-particle ICS cohort had significantly greater odds of overall asthma control (adjOR, 1.30; 95% CI, 1.04-1.62) and significantly lower exacerbation rates (for both definitions; severe exacerbations adjRR, 0.56; 95% CI, 0.35-0.88) than did those in the standard size—particle ICS cohort, also with false-discovery rate correction. Children prescribed small-particle ICS had significantly greater odds of treatment stability, driven by significantly lower rates of therapy change (Table III; see Table E2 in this article’s Online Repository at www.jaci-inpractice.org; Figure 1, A). Respiratory-related hospitalization rates were low and comparable between treatment cohorts.

Subgroup analyses: Initiation population. A total of 465 children in the standard size—particle ICS cohort were prescribed a spacer device in the baseline and/or outcome year, but of the 465 matched children prescribed small-particle ICS, only 69% were prescribed a spacer. Outcomes for this subgroup paralleled those for the full matched initiation cohorts, with adjusted odds of asthma control significantly higher (risk-domain asthma control adjOR, 1.81; 95% CI, 1.24-2.65) and relative exacerbation rates significantly lower (severe exacerbation adjRR, 0.53; 95% CI, 0.29-0.98) for the small-particle ICS subcohort (see Table E3 in this article’s Online Repository at www.jaci-inpractice.org).

Results of unmatched subgroup analyses of children with no rhinitis or rhinitis therapy and those without exacerbations during the baseline year were consistent with the main findings (see Online Repository text and Table E3).

Results of matched cohort analyses by age group found that outcomes with small-particle ICS remained significantly better (compared with standard size—particle ICS) for 5- to 6-year-old children but were comparable with standard size—particle ICS for the 7- to 11-year-old children (Online Repository). Figure E6 (in this article’s Online Repository at www.jaci-inpractice.org) suggests greater variability in ICS response in younger children and the standard size—particle ICS cohort.

Step-up population. The 2 step-up cohorts were well matched at baseline (Table II; Table E1). Statistically significant differences in mean index date dose (224 [95% CI] vs 262 [170] μg/d for small-particle vs standard size—particle ICS; P < .001) were likely not clinically significant (Figure E5, B).
During the outcome year (Table III), children stepping up their ICS therapy as small-particle ICS had significantly greater odds of achieving risk-domain asthma control. The adjusted difference in proportions achieving asthma control (small-particle ICS vs standard size—particle ICS) was 0.21 (95% CI, 0.10-0.40; adjusted for baseline acetaminophen prescriptions and baseline lower respiratory tract-related inpatient admissions). The NNT to achieve 1 additional child with asthma control using small-particle ICS was 4.8 (95% CI, 2.5-77.8).

Children prescribed small-particle ICS had significantly lower exacerbation rates (both definitions) than did children stepping up their ICS therapy as standard size—particle ICS, as well as significantly greater odds of treatment stability (at the 5% level; Figure 1, B). Results for overall control, incorporating SABA use, were comparable for the 2 cohorts, as were lower respiratory tract-related hospitalization rates during the outcome period (Figure 1, B).

### Analysis 2: Small-particle ICS step-up versus add-on LABA in ICS/LABA combination inhaler

After 1:1 matching, statistically significant baseline differences between the ICS step-up and ICS/LABA combination cohorts were minor (Table IV; see Table E4 in this article’s Online Repository at www.jaci-inpractice.org).

Median (interquartile range) ICS doses prescribed at the index date were 200 (200-400) µg/d for the ICS step-up and 100 (100-200) µg/d for the ICS/LABA combination cohort (P < .001 for the comparison). There were no significant differences in the adjusted outcome measures between ICS step-up and ICS/LABA combination cohorts (Figure 1, C). However, for the ICS/LABA combination cohort, change in therapy was significantly more common, and the total β2-agonist coverage (LABA plus SABA) was significantly greater (Table V; see Table E5 and Figure E7, A, in this article’s Online Repository at www.jaci-inpractice.org).

The ICS step-up and separate ICS + LABA cohorts were similar after 1:2 matching (see Tables E4 and E6 in this article’s Online Repository at www.jaci-inpractice.org). The odds of treatment stability were higher for ICS step-up, but the odds of asthma control and exacerbation rates were comparable between cohorts (see Table E7 and Figure E8 in this article’s Online Repository at www.jaci-inpractice.org). Total β2-agonist coverage was greater for the separate ICS + LABA cohort (Table E5; Figure E7, B).

### DISCUSSION

The observational design of these 2 analyses provides direct comparative evidence, not currently available from RCTs, about clinically relevant outcomes using different treatment approaches to common clinical situations in children with asthma. We found that the rate of severe exacerbations among children with asthma aged 5 to 11 years prescribed small-particle ICS was significantly lower than that for children prescribed standard size—particle ICS, both for those initiating ICS (adjRR, 0.56) and for those stepping up the ICS dose (adjRR, 0.49). Moreover, the adjusted odds of the risk-domain composite measure of asthma control were significantly greater for children initiating small-particle ICS, as well as for children stepping up the dose of small-particle ICS, when compared with those for children initiating or stepping up the dose of standard size—particle ICS. The NNTs to achieve 1 additional child with asthma control using small-particle ICS were 17 and 5 for the initiation and step-up populations, respectively.

### TABLE IV. Baseline characteristics of children in the small-particle ICS step-up and combination ICS/LABA cohorts (analysis 2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICS step-up (n = 185)</th>
<th>ICS/LABA combination (n = 185)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male†</td>
<td>114 (61.6)</td>
<td>114 (61.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Age at index date (y), ‡ mean ± SD</td>
<td>8.3 ± 1.9</td>
<td>8.3 ± 1.9</td>
<td>NA</td>
</tr>
<tr>
<td>Recorded comorbidity†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible atopy</td>
<td>148 (80.0)</td>
<td>143 (77.3)</td>
<td>.54</td>
</tr>
<tr>
<td>Rhinitis diagnosis/Rx</td>
<td>48 (25.9)</td>
<td>46 (24.9)</td>
<td>.82</td>
</tr>
<tr>
<td>Eczema diagnosis/Rx</td>
<td>135 (73.0)</td>
<td>131 (70.8)</td>
<td>.66</td>
</tr>
<tr>
<td>Preschool wheeze diagnosis</td>
<td>70 (37.8)</td>
<td>62 (33.5)</td>
<td>.39</td>
</tr>
<tr>
<td>Preschool asthma diagnosis/Rx</td>
<td>94 (50.8)</td>
<td>98 (53.0)</td>
<td>.66</td>
</tr>
<tr>
<td>Risk-domain asthma control†</td>
<td>129 (69.7)</td>
<td>129 (69.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Spacer device prescribed</td>
<td>70 (37.8)</td>
<td>85 (45.9)</td>
<td>.12</td>
</tr>
<tr>
<td>Mean daily SABA dose (µg/d)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-100</td>
<td>33 (17.8)</td>
<td>24 (13.0)</td>
<td></td>
</tr>
<tr>
<td>101-200</td>
<td>58 (31.4)</td>
<td>67 (36.2)</td>
<td></td>
</tr>
<tr>
<td>201-400</td>
<td>66 (35.7)</td>
<td>66 (35.7)</td>
<td>.29</td>
</tr>
<tr>
<td>401-800</td>
<td>20 (10.8)</td>
<td>22 (11.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;800</td>
<td>8 (4.3)</td>
<td>6 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) daily ICS dose (µg/d)†</td>
<td>55 (27-110)</td>
<td>55 (27-110)</td>
<td>.26</td>
</tr>
<tr>
<td>Last ICS dose before the index date (µg/d)‡‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-50</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>51-100</td>
<td>107 (57.8)</td>
<td>107 (57.8)</td>
<td>NA</td>
</tr>
<tr>
<td>101-200</td>
<td>78 (42.2)</td>
<td>78 (42.2)</td>
<td></td>
</tr>
<tr>
<td>Severe exacerbations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>147 (79.5)</td>
<td>144 (77.8)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>27 (14.6)</td>
<td>28 (15.1)</td>
<td>.90</td>
</tr>
<tr>
<td>2</td>
<td>6 (3.2)</td>
<td>12 (6.5)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>5 (2.7)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Asthma consultation/no oral corticosteroids†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>61 (33.0)</td>
<td>61 (33.0)</td>
<td>.09</td>
</tr>
<tr>
<td>1</td>
<td>61 (33.0)</td>
<td>61 (33.0)</td>
<td>.09</td>
</tr>
<tr>
<td>2</td>
<td>37 (20.0)</td>
<td>28 (15.1)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>26 (14.1)</td>
<td>35 (18.9)</td>
<td></td>
</tr>
</tbody>
</table>

*IQR, Interquartile range; NA, not applicable; Rx, therapy; standard SP, standard size—particle. Data are presented as n (%) except otherwise indicated.

*Matched cohorts were compared using conditional logistic regression.

†Matching variable (for details, please see this article’s Online Repository at www.jaci-inpractice.org).

‡Possible atopy was defined as any 1 or more of the following: recorded rhinitis diagnosis, rhinitis therapy, eczema diagnosis, eczema therapy. Preschool wheeze was captured through database-coded diagnosis or therapy for same. Preschool was defined as age 1 to 3 y.

§The doses of ICS were standardized to equivalence with small-particle beclomethasone and fluticasone; thus, doses of large-particle beclomethasone and budesonide were halved.

In the comparison of step-up strategies in analysis 2, increasing small-particle ICS dose was comparable to adding LABA in a combination ICS/LABA inhaler with regard to both asthma control and exacerbation measures.
In analysis 1, as compared with findings in previous adult studies, greater differences were evident in outcomes favoring small-particle ICS relative to standard size—particle ICS, for both initiation and step-up cohorts. There are few other studies comparing small- and standard-size—particle ICS for children with asthma. A Cochrane analysis compared ciclesonide with other ICS for children but was inconclusive. The Cochrane analysis that compared small-particle hydrofluoroalkane-beclo-

methasone and fluticasone for children with asthma was limited because only 2 studies were found. Robroeks et al reported no difference between 12-week therapy with small-particle beclomethasone or fluticasone in either anti-inflammatory effects or clinical outcomes for 33 children with asthma in a small crossover study, although children at study start had normal lung function and generally well-controlled asthma. van Aalderen et al showed that small-particle beclomethasone and fluticasone had similar effects on lung function and overall asthma control in an 18-week ICS step-down study in 280 children aged 5 to 12 years with mild-to-moderate asthma. Neither study examined comparative effects of these 2 ICS on exacerbations in children over a 1-year period. The present analyses add to these shorter-term, smaller studies and demonstrate the value of pragmatic research for understanding asthma therapies in children.

The pattern of results according to the ICS dose during the outcome year suggests that the odds of risk-domain asthma control were better for children at lower doses of both small-particle and standard size—particle ICS (depicted in Figure E6). We found a similar pattern of results in a previous US retrospective study, whereby adults with lower medication possession ratio had better risk-domain asthma control and fewer exacerbations. We speculate that this is because adherence with ICS increases after exacerbations, as supported by previous observational studies, and that patients whose asthma is well-controlled may be less likely to take their ICS regularly.

In our subanalyses, small-particle ICS offered an advantage especially in younger children (5-6 years old vs 7-11 years old). The reason for this additional advantage is unknown, but Amirav and Newhouse have speculated that better outcomes with ICS in young children will be achieved using formulations with smaller particle size. We also found no difference from the main findings in comparative results when standard size—particle ICS was given under ideal circumstances with a spacer (the small-particle ICS subanalysis cohort was not required to have a spacer, and 31% did not). This differs from the accepted view that spacer use is necessary to achieve improved lung deposition in children prescribed a pMDI. Deposition studies in children as young as 5 to 7 years have confirmed that even without a spacer, 38% or more of a single inhalation of small-particle beclomethasone reaches the lungs. Furthermore, good lung deposition (>30%) occurs with small-particle beclomethasone even in patients who are unable to precisely coordinate inhalation and actuation of a pMDI.

In analysis 2 comparing the stepped-up dose of small-particle ICS versus adding LABA by fixed-dose combination inhaler, we found that the percentages of children meeting outcome measures improved substantially in both cohorts, without significant differences between cohorts in effectiveness. Although both UK asthma management guidelines and US drug labeling recommend the prescribing of ICS/LABA as fixed-dose combination inhalers for children and adolescent patients to ensure their adherence to concomitant therapy, we found a substantial number of children receiving ICS and LABA by separate inhalers. Of potential interest, a novel finding in this analysis was that the $\beta_2$-agonist load over the 1-year outcome period was significantly lower, and shorter-acting, in the small-particle ICS than in the ICS/LABA combination cohort.

Our findings that increasing the ICS dose for children with uncontrolled asthma can provide clinically meaningful improvement is supported by the work of Lemanske et al. In their rigorously performed, National Institutes of Health-sponsored, randomized crossover trial assessing differential responses to 3 step-up strategies for 165 children with uncontrolled asthma on low-dose fluticasone, the best response for most of the children was obtained with LABA step-up therapy; however, many children also demonstrated best response to ICS step-up. Response was measured over only 16 weeks in their study, and fluticasone was administered as the ICS. We can speculate, on the basis of the results of the present study, that more children may have demonstrated a best response to ICS step-up if a small-particle ICS had been used as the ICS. Moreover, our longer-term findings provide further information that calls into question the recommendations of UK and international asthma guidelines, which identify add-on LABA as the first-line alternative for stepping up therapy when asthma is not controlled by ICS monotherapy. Properly designed RCTs might be of help to further explore the findings reported here.
A limitation of this study is the absence of data on adverse effects of therapy, particularly growth. Information on height is not routinely available from database sources, and height measurements in daily practice are not performed using the rigorous criteria of an RCT. Although linear growth could not be measured in our study, recent RCT’s found that daily use of beclomethasone is associated with a decreased linear growth of approximately 1 cm compared with the use of intermittent ICS or leukotriene receptor antagonist; a similar pattern has been found with regular use of other ICS.40-43

An important limitation of observational studies is the possibility of unrecognized confounders. Although the matching process is designed to reduce this possibility by comparing cohorts of similar baseline asthma severity, we note that for the initiation population in analysis 1, there were fewer children with rhinitis, a factor that can influence asthma control, in the small-particle cohort than in the standard size—particle ICS cohort. However, similar proportions of children in the 2 cohorts had possible atopy, and the results of the no rhinitis subanalysis supported the main findings.

As small-particle beclomethasone is not approved for use in the United Kingdom for children younger than 12 years, it might be argued that GPs prescribing this product would be more knowledgeable about asthma. However, during the study period, similar numbers of children in the data sets were initiated on small-particle beclomethasone (4%) and fluticasone (6%). Two other observations argue against large differences between the 2 physician groups in asthma management knowledge: (1) similar (and low) proportions of children had recorded peak expiratory flow readings at baseline, and (2) socioeconomic scores were similar for practices in which small-particle beclomethasone or fluticasone was prescribed.

Strengths of the present analyses include the large numbers of children, the capture of clinically relevant outcomes over a full year for each child, and the consistency of findings across main analyses and subanalyses. We matched, in addition to sex and age, on all clinically reasonable indicators of baseline asthma severity available in the database. Because the criteria were applied sequentially, for example, first on sex and then on age, children were matched on age within the female and male groupings. We believe that this matching approach is particularly relevant to the study of children, for whom age is an important factor; in addition, it enabled us to examine subgroups of patients who might interact with outcome, for example, the youngest children with the smallest airways. This matching approach differs from the use of propensity score matching, which instead produces 2 cohorts with similar distributions of multiple covariates used to construct the propensity score but not paired patients precisely matched by age and sex.

We limited the study to a comparison of small-particle beclomethasone (the only small-particle ICS available in the United Kingdom at the time) and fluticasone, which is a larger-particle ICS that is recommended for administration at the same doses as small-particle beclomethasone.37,45,46 Thus, our conclusions are limited to the studied comparisons and are not generalizable to other ICS. Additional studies, including prospective pragmatic clinical trials, are needed to further investigate the effectiveness of other small-particle ICS, such as ciclesonide, for children with asthma.

In conclusion, we found that initiating or stepping up the dose of ICS with a small-particle ICS is significantly more effective than doing so with a standard size—particle ICS, and has similar effectiveness as add-on LABA for children with asthma treated in primary care practice. The differential effects of small-particle ICS versus standard size—particle ICS were more pronounced in children than in our previous adult studies,43,83 and more pronounced in the younger children than in the older children. We cannot identify the factors associated with the beneficial effect but speculate that this is, in part, due to smaller particle size and better ICS deposition in children with smaller airways.

References


46. Switching to CFC-free beclometasone for asthma. Drug Ther Bull 2008;46:46-8.
METHODS

Our hypothesis for analysis 1 was that asthma-related outcomes for children, as for adults, would be similar or better with small-particle ICS, even when prescribed at lower doses, than with standard size—particle ICS. Our hypothesis for analysis 2 was that increasing the dose of small-particle ICS would be an effective alternative for children with persistent asthma who require more treatment than their initial ICS therapy.

The study was done to standards suggested for observational studies, including an independent steering committee, use of an a priori analysis plan, and well-maintained and monitored study databases. The members of the steering committee are practicing physicians working in different areas of respiratory medicine who provide varied perspectives and guidance to Research in Real Life (RiRL), functioning in complete intellectual independence. The group comprises adult practitioners and pediatricians because multiple studies are being conducted in various populations. The steering committee members are not paid for their participation but are reimbursed by RiRL for travel to annual or biannual meetings to discuss multiple ongoing studies that are being conducted by RiRL. The design of the study, analyses and subanalyses, and manuscript represent consensus work of this committee, all of whom are authors on the article together with the research team at RiRL.

Although clinical trial registration was not required because this was a noninterventional study, each of the analyses was registered, as a separate study, with registered clinical trials registry numbers NCT01141439 and NCT01697722.

Data sources

The data sets we used contain anonymized primary care medical records, data entered by health care providers during patient consultations in the form of Read codes. The General Practice Research Database is a large, well-regarded, and well-validated primary care database containing anonymized medical record data from subscribing practices throughout the United Kingdom and used frequently for pharmacoepidemiological research. It forms part of the National Health Service Clinical Practice Research Datalink, the English National Health Service observational data and interventional research service. The Optimum Patient Care Research Database is a newer primary care database, established to rigorous standards, that contains anonymous patient data, including both medical records and patient-completed respiratory questionnaire results, from more than 300 primary care practices subscribing to the Optimum Patient Care respiratory review service. The value of this database information specifically for studying respiratory diseases has been documented in numerous high-quality publications.

The available data for this study spanned 1997 through January 2011 and was approved for use by the General Practice Research Database Independent Scientific Advisory Committee and, for the Optimum Patient Care Research Database, by the Trent Multi Centre Research Ethics Committee. The study protocol was approved by the Anonymised Data Ethics Protocols and Transparency Committee, the independent scientific advisory committee for Optimum Patient Care.

Patients and outcomes

Allowed ICS therapies during the baseline year for step-up cohorts included beclomethasone, budesonide, or fluticasone administered by pMDI or breath-actuated inhaler. Small-particle beclomethasone dipropionate hydrofluoroalkane (HFA) (QVAR; Teva Pharmaceuticals) is labeled for administration to both adults and children at half the daily dose of chlorofluorocarbon (CFC) or larger-particle HFA-beclomethasone (Clenil Modulite; Chiesi Ltd, Highfield, Chedale, UK) and at the same dose as HFA- or CFC-fluticasone propionate. Thus, we standardized ICS doses to small-particle beclomethasone for the analyses, using a 1:1 ratio for small-particle beclomethasone and fluticasone, and for both the latter a 1:2 dose ratio relative to budesonide and larger-particle CFC- or HFA-beclomethasone. Heights and weights were not routinely available in the data sets for all children.

Statistical analysis

For the small-particle ICS versus standard size—particle ICS comparison, the coprimary outcomes were risk-domain asthma control and the total number of severe exacerbations; for the small-particle ICS versus add-on LABA comparisons, the primary outcome was risk-domain asthma control (see Table I in the main article). We used the false-discovery rate controlling procedure of Benjamini and Liu to account for multiple comparisons in the primary outcomes. This procedure modifies the threshold (0.05) for each comparison; with 2 coprimary outcomes, the “most significant” result is required to achieve significance at the 2.5% level (P = .025) while the second result is required to achieve significance at the 5% level (P = .05).

For the patient population initiating ICS, we conducted several subanalyses to further examine factors that could be influencing the outcomes of therapy. We compared results with small-particle ICS versus standard size—particle ICS by age (5-6 years and 7-11 years); with use of a spacer for all children receiving standard size—particle ICS; for children with no rhinitis diagnosis or therapy; and according to baseline asthma severity (0 or ≥1 exacerbation during the baseline year); the latter 2 subanalyses were conducted with unmatched patient data to increase sample sizes. Patient numbers in the small-particle ICS and standard size—particle ICS step-up populations were insufficient to warrant subanalysis.

For the spacer subanalysis, we included all children in the standard size—particle ICS cohort with a spacer prescribed in baseline and/or outcome year (total of 465 children). We then compared these 465 children with their matches in the small-particle ICS cohort; of that subgroup of matched children in the small-particle ICS cohort, 69% were prescribed a spacer. (Overall, however, approximately equal numbers of the 797 children in each of the initiation cohorts were prescribed a spacer.)

For the step-up comparisons of small-particle ICS versus add-on LABA, we calculated the total β2-agonist hours of coverage (SABA + LABA). We defined albuterol 200 μg and terbutaline 500 μg as 2 puffs of SABA lasting 4 hours, whereas we defined β2-agonist coverage with LABA 2 puffs via pMDI or 1 puff via dry powder inhaler as lasting 12 hours.

Different matching ratios were evaluated, and the 1:1 ratio for the small-particle ICS versus standard size—particle ICS cohorts and the ICS dose step-up versus LABA combination cohorts and the 1:2 ratio for the ICS dose step-up versus separate ICS + LABA cohorts were chosen to maximize patient numbers and thus statistical power for the comparisons.
Matching criteria were applied sequentially as ordered below:

1. For small-particle ICS versus standard size—particle ICS initiation cohorts (analysis 1):
   a. Sex
   b. Age
   c. Mean SABA daily dose during the baseline year (0, 1-100, 101-200, >200 μg/d)
   d. Number of severe exacerbations during the baseline year (0, 1, ≥2)
   e. Number of asthma consultations without an oral corticosteroid prescription during the baseline year (0, 1, ≥2)
   f. Year of index prescription (±4 years)

2. For small-particle ICS versus standard size—particle ICS step-up cohorts (analysis 1):
   a. Sex
   b. Age
   c. Last ICS dose prescribed before the index prescription (1-100, 101-300, >300 μg/d)
   d. Number of severe exacerbations during the baseline year (0, 1, 2, ≥3)
   e. Risk-domain asthma control status during the baseline year (controlled/uncontrolled)
   f. Mean SABA daily dose during the baseline year (0, 1-200, >200 μg/d)
   g. Number of asthma consultations without an oral corticosteroid prescription during the baseline year (0, 1, ≥2)
   h. Year of index prescription (±4 years)

3. For small-particle ICS versus add-on LABA cohorts (analysis 2):
   a. Sex
   b. Age
   c. Last ICS dose prescribed before the index prescription (1-50, 51-100, 101-200, 201-300, 301-400, >400 μg/d)
   d. Mean SABA daily dose during the baseline year (0, 1-200, 201-400, >400 μg/d)
   e. Number of asthma consultations without an oral corticosteroid prescription during the baseline year (0, 1, ≥2)
   f. Risk-domain asthma control status during the baseline year (controlled/uncontrolled)

Potential confounding factors considered:

Previous research in respiratory disease has identified a range of potential confounders that can influence study outcomes. These include a range of demographic, disease severity, treatment, and comorbid factors.

Variables that differed between treatment cohorts at P < .10 were considered potential confounding factors, as well as baseline variables predictive of outcomes in multivariate analyses at P < .05. Spearman correlation coefficients were calculated between all potential confounders to determine strengths of linear relationships between variables. The correlation coefficients were considered, in conjunction with clinical interpretation, to identify pairings of variables that could present collinearity issues at the modeling stage. Scatter plots and error bars were used, if necessary, to further investigate relationships.

We fit the regression models separately for each subgroup. However, because baseline differences across treatment arms may have been different between full cohorts and subgroups, the entire modeling process was repeated separately for each subgroup to identify the unique adjustments needed for that subgroup.

Potential confounders examined, where available, at (or closest to) the relevant index date for all children:

- Age
- Sex
- Height
- Weight
- Body mass index
- Lung function as percent predicted peak flow readings before the index date

Potential confounders examined regardless of when they occurred relative to the index date:

- Date of first asthma, other respiratory and allergy-related, diagnosis (where known)
- Presence/absence of comorbid rhinitis (diagnosis ever and/or prescriptions for rhinitis therapy in the baseline/outcome year)
- Presence/absence of comorbid eczema (diagnosis ever and/or prescriptions for eczema therapy in the baseline/outcome year)
- Presence/absence of preschool wheeze (diagnosis ever)
- Presence/absence of preschool asthma (diagnosis ever and/or prescriptions for asthma therapy in the baseline/outcome year)
- Presence of gastroesophageal reflux disease (diagnosis ever and/or prescriptions for gastroesophageal reflux disease therapy in the baseline/outcome year)
- Presence of cardiac disease (diagnosis ever and/or prescriptions for cardiac drugs in the baseline/outcome year)

Potential confounders examined in the baseline year before the index date:

- Where rhinitis is present, use of nasal corticosteroids for treatment
- Other important unrelated comorbidities were expressed using the Charlson comorbidity index
- Number of asthma consultations that did not result in a prescription for an oral corticosteroid
- Number of hospital outpatient attendances where asthma was recorded as the reason for referral
- Number of hospitalizations for asthma or possibly respiratory related (a nonspecific hospitalization code and an asthma/respiratory code within a 1-week window)
- Number of asthma-related emergency department visits
- Number of prescriptions for any antibiotic where the reason for the prescription was lower respiratory tract infection
- Other medications, number of prescriptions for the following in the year before the index date:
  - Acetaminophen
  - Nonsteroidal anti-inflammatory drugs
- Number of prescriptions for any respiratory therapy (split by number of prescriptions for each)
- Number of asthma exacerbations
- Number of acute courses of oral corticosteroids
- Number of SABA prescriptions and average daily SABA dose received (calculated on the basis of the total combined dose of refilled prescriptions and averaged over 365 days)
- Average ICS daily dose during the baseline year (calculated on the basis of total combined dose of refilled prescriptions and averaged over 365 days) (step-up patients only)
- Last ICS dose prescribed before the index date (step-up patients only)
• Adherence to ICS therapy (step-up patients only)
• Spacer use/prescription
• Medication possession ratio (step-up patients only)
• Controller-to-reliever therapy ratio (step-up-population only)
• Oral candidiasis

RESULTS
Analysis 1: Small-particle ICS versus standard size—particle ICS as first-line or step-up ICS therapy
Unmatched versus matched baselines and results. For analysis 1, we found that unmatched patients prescribed small-particle ICS, as compared with standard size—particle ICS, tended to be slightly older and to have later index prescription dates; moreover, in the step-up population, those prescribed small-particle ICS had less severe asthma, with a smaller percentage experiencing multiple exacerbations during baseline (eg, 6% had ≥ 2 exacerbations vs 12% in the unmatched standard size—particle ICS cohort; other data not shown). After matching, both treatment cohorts tended to have less severe asthma than did the unmatched initiation population (eg, 82% with risk-domain asthma control vs 77% of the unmatched initiation population at baseline; other data not shown).

The pattern of unmatched results during the outcome year followed patterns for the matched cohorts, namely, better outcomes for small-particle ICS (data not shown).

Initiation population. Coprimary outcomes remained significant after having controlled the false-discovery rate at the 0.05 level.

Initiation population subanalyses. Matched cohort subanalyses by age group found that outcomes with small-particle ICS remained significantly better (compared with standard size—particle ICS) for 5- to 6-year-old children initiating ICS (n = 286 per treatment cohort) but were comparable with standard size—particle ICS for 7- to 11-year-olds (n = 511 per cohort). For 5- to 6-year-olds in the small-particle ICS cohort, the adjOR for achieving risk-domain asthma control was 2.00 (95% CI, 1.21-3.29) and for achieving overall control was 1.66 (95% CI, 1.11-2.46) compared with standard size—particle ICS; the corresponding odds ratios for 7- to 11-year-olds were 1.25 (95% CI, 0.85-1.83) and 1.19 (95% CI, 0.91-1.57). The severe exacerbation adjRR for the small-particle ICS cohort relative to the standard size—particle ICS cohort was 0.51 (0.23-1.10) and the clinical exacerbation rate ratio was 0.48 (0.30-0.77) for 5- to 6-year-olds; the corresponding adjRRs for 7- to 11-year-olds were 0.76 (0.45-1.28) and 0.87 (0.60-1.25), respectively.

Baseline asthma severity was greater among 5- to 6-year-olds initiating ICS (data not shown); therefore, we hypothesized that better outcomes with small-particle ICS in this cohort were related to baseline severity rather than age. However, the subanalysis of outcomes split by asthma severity (0 or ≥ 1 baseline exacerbations) indicated better results for children with less severe asthma (Table E3). Further exploration of results for risk-domain asthma control by outcome-year ICS dose indicated greater variation in results for 5- to 6-year-olds (compared with 7-11-year-olds) and greater variation in the standard size—particle ICS cohort (Figure E6).

Results of the subanalysis including children with no rhinitis diagnosis or prescription for nasal spray (unmatched cohorts) were reflective of the main analysis results: the odds ratios remained consistent, although with smaller patient numbers the odds ratio for risk-domain asthma control became statistically nonsignificant (Table E3).

Analysis 2: Unmatched versus matched baselines and results

For analysis 2, the unmatched ICS step-up cohort, as compared with both add-on LABA cohorts, received a lower baseline ICS dose and included more children with asthma control and fewer children with severe exacerbations during baseline (data not shown). After matching, the matched add-on LABA cohorts had (similar to the ICS step-up cohort) less severe asthma than did the unmatched cohorts (67%-70% with baseline asthma control vs 58% of the unmatched add-on LABA cohorts).

During the outcome year, a significantly greater percentage of unmatched patients in the ICS step-up cohort experienced asthma control and treatment stability as compared with both add-on LABA cohorts (data not shown). Unadjusted exacerbation results were similar for unmatched ICS step-up and ICS/LABA combination cohorts but better for the unmatched ICS step-up than for the separate ICS + LABA cohort.

Analysis 2: ICS dose step-up versus add-on LABA as separate inhaler

Several minor differences remained at baseline after 1:2 matching of the small-particle ICS dose step-up (n = 276) and separate ICS + LABA (n = 552) cohorts (Tables E4 and E6). Children in the ICS dose step-up cohort recorded fewer exacerbations during the baseline year than did children in the separate ICS + LABA cohort (Table E6).

Median (interquartile range) ICS doses prescribed at the index date were 200 µg/d (200-400 µg/d) for the ICS dose step-up and 100 µg/d (100-200 µg/d) for the separate ICS + LABA cohort (P < .001 for the comparison). Change in therapy was significantly more common, and the total β2-agonist coverage (LABA plus SABA) was significantly greater in the separate ICS + LABA cohort (Table E5). Figure E7, B, depicts coverage by time period for each cohort.

During the outcome year, children stepping up their ICS therapy with small-particle ICS had significantly higher odds of treatment stability, after adjustments for residual confounding factors, than did children remaining on the same dose but adding a separate LABA; odds of asthma control and exacerbation rates were comparable between cohorts (Figure E8; Table E7).

REFERENCES
E3. Price D, Hillyer EV, van der Molen T. Ef
c dc=100-200 g/d) for the separate ICS + LABA cohort (P < .001 for the comparison). Change in therapy was significantly more common, and the total β2-agonist coverage (LABA plus SABA) was significantly greater in the separate ICS + LABA cohort (Table E6).


Respiratory patients in the GPRD & OPCRD
n=1,540,877

Inclusion Criteria:
Patients aged 5–11 years initiating ICS as small-particle beclomethasone or fluticasone by pMDI

Patients prescribed any ICS inhalers n=705,913

Excluded:
- not aged 5–11 years and not initiating ICS as small-particle beclomethasone or fluticasone by pMDI (n=694,785)

Excluded:
- Patients not on any ICS therapy (n=834,964)
- not aged 5–11 years and not initiating ICS as small-particle beclomethasone or fluticasone by pMDI (n=694,785)

Patients aged 5–11 prescribed small-particle beclomethasone n=4237 or fluticasone n=7893

Matching criteria applied:
- same sex
- same age
- baseline mean SABA dose (0, 1–100, 101–200, >200 μg/day)
- baseline year no. severe exacerbations (0, 1, ≥2)
- baseline no. asthma consultations without oral steroid prescription (0, 1, ≥2)
- year of index date ±4 years

Eligible patients aged 5–11 with asthma initiating ICS therapy as:
SP-beclomethasone n=1025
Fluticasone n=1629

Randomize matching patients 1:1*
*Software used to randomly pick unique matched patients

Total lost on matching:
SP-beclomethasone n=100
Fluticasone n=344

Total matched patients included
1:1 uniquely matched pairs:
Small-particle beclomethasone n=797
Fluticasone n=797

Excluded:
- not registered at practice for study period (SP-BDP n=852; FP n=1432)
- prescribed FDC therapy during baseline or on index date (SP-BDP n=1221; FP n=3590)
- diagnosis of chronic respiratory disease other than asthma (FP n=1)
- no evidence of asthma (SP-BDP n=1021; FP n=1065)
- maintenance oral steroids during baseline (SP-BDP n=60; FP n=49)
- initiate ICS on multiple prescriptions (SP-BDP n=25; FP n=50)
- duplicated in GPRD or OPCRD (SP-BDP n=33; FP n=77)

Double matches lost on randomization 1:1:
SP-beclomethasone n=128
Fluticasone n=488

Patients aged 5–11 prescribed small-particle beclomethasone n=4237 or fluticasone n=7893

Excluded:
- Patients not on any ICS therapy (n=834,964)

FIGURE E1. Initiation population: patient selection and matching (analysis 1). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. FDC, Fixed-dose combination ICS/LABA; FP, fluticasone propionate; GPRD, General Practice Research Database; OPCRD, Optimum Patient Care Research Database; SP-BDP, small-particle beclomethasone dipropionate.
Respiratory patients in the GPRD & OPCRD  
\( n = 1,540,877 \)

**Inclusion Criteria:**
- Patients prescribed a ≥50% increase in ICS dose as SP-BDP or fluticasone by pMDI

**Patients prescribed any ICS inhalers**  
\( n = 706,913 \)

**Excluded:**
- no prior prescription \( (n = 29,341) \) or no current prescription \( (n = 548,082) \) for SP-BDP or fluticasone by pMDI
- prescribed lower, same, or <50% increase in ICS dose \( (n = 92,962) \)
- multiple prescriptions on the index date \( (n = 5973) \)

**Patients prescribed ≥50% dose increase of small-particle beclomethasone and/or fluticasone as single script:**  
\( n = 30,555 \)

**Matching criteria applied:**
- same sex
- same age
- last ICS dose before index date \( (1–100, 101–300, >300 \mu g/day) \)
- baseline year no. severe exacerbations \( (0, 1, 2, \geq 3) \)
- risk-domain asthma control status (controlled/uncontrolled)
- baseline mean SABA dose \( (0, 1–200, >200 \mu g/day) \)
- baseline no. asthma consultations without oral steroid prescription \( (0, 1, \geq 2) \)
- year of index date ±4 years

**Eligible patients aged 5–11 stepping up ICS therapy as:**
- Small-particle beclomethasone \( n = 294 \)
- Fluticasone \( n = 1647 \)

**Total lost on matching:**
- Small-particle beclomethasone \( n = 77 \)
- Fluticasone \( n = 1106 \)

**Randomize matching patients 1:1**
*Software used to randomly pick unique matched patients

**Total matched patients included**
- 1:1 uniquely matched pairs:
  - Small-particle beclomethasone \( n = 206 \)
  - Fluticasone \( n = 206 \)

**Double matches lost on randomization 1:1:**
- Small-particle beclomethasone \( n = 11 \)
- Fluticasone \( n = 335 \)

**Excluded:**
- not aged 5–11 years at index date \( (n = 27,223) \)
- not registered at practice for study period \( (n = 435) \)
- prescribed FDC therapy during baseline or on index date \( (n = 14) \)
- no evidence of asthma \( (n = 69) \)
- maintenance oral steroids during baseline \( (n = 89) \)
- prescribed ICS on multiple prescriptions \( (n = 575) \)
- duplicated in GPRD or OPCRD \( (n = 209) \)

*FIGURE E2. Step-up population: patient selection and matching (analysis 1). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. FDC, Fixed-dose combination ICS/LABA; FP, fluticasone propionate; GPRD, General Practice Research Database; OPCRD, Optimum Patient Care Research Database; Script, prescription; SP-BDP, small-particle beclomethasone dipropionate.*
Respiratory patients in the GPRD & OPCRD

1) SP-BDP with prior ICS script n=1,146,757
or
2) ICS script with no prior LABA n=689,076

SP-BDP dose increase n=34,509
or ICS + LABA n=240,581

ICS/LABA cohort exclusions:
- not registered at practice for study period (n=2960)
- no current asthma Rx (n=1044)
- separate LABA, ICS, or FDC or multiple scripts on IPD (n=7758)
- increased ICS dose at IPD (n=2979)
- maintenance oral steroids during baseline (n=7)
- COPD or other chronic (n=10)
- duplicated in GPRD or OPCRD (n=290)

Inclusion Criteria:
1) ≥50% ICS dose increase as SP-BDP by pMDI or BAI
or
2) LABA script as add-on or FDC

Matching criteria applied:
- same sex
- same age
- last ICS dose before index date (1–50, 51–100, 101–200, 201–300, 301–400, >400 μg/day)
- risk-domain asthma control status (controlled/uncontrolled)
- baseline mean SABA dose (0, 1–200, 201–400, >400 μg/day)
- baseline no. asthma consultations without OCS prescription (0, 1, ≥2)

Randomize matching patients 1:1*
*Software used to randomly pick unique matched patients

Total matched patients included
1:1 uniquely matched pairs:
Small-particle beclomethasone n=185
ICS/LABA combination inhaler n=185

ICS/LABA cohort key
- switch to FDC inhaler
- no change in ICS dose

SP-BDP cohort key
- no LABA inhaler baseline
- on pMDI or BAI
- on current asthma Rx
- no COPD/chronic resp

SP-BDP cohort exclusions:
- on DPI baseline (n=60)
- not registered at practice for study period (n=448)
- LABA or FDC script during baseline or on IPD (n=98)
- no current asthma Rx (n=72)
- maintenance OCS baseline (n=0)
- additional ICS dose increases (n=41)
- COPD or other (n=3)
- duplicated in GPRD or OPCRD (n=53)

Eligible patients aged 5–11 stepping up asthma therapy as:
SP-BDP increased dose n=458
ICS/LABA combination n=1440

Total lost on matching:
SP-BDP n=214
ICS/LABA n=971

Double matches lost on randomization 1:1:
SP-BDP n=55
ICS/LABA n=284

FIGURE E3. Small-particle ICS dose step-up versus add-on LABA in ICS/LABA combination inhaler: patient selection and matching (analysis 2). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. BAi, Breath-actuated inhaler; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDC, fixed-dose combination ICS/LABA; GPRD, General Practice Research Database; IPD, index prescription date; OCS, oral corticosteroid; OPCRD, Optimum Patient Care Research Database; Rx, therapy; Script, prescription; SP-BDP, small-particle beclomethasone dipropionate.
Respiratory patients in the GPRD & OPCRD

1) SP-BDP with prior ICS script \( n = 1,146,757 \)
or
2) ICS script with no prior LABA \( n = 689,076 \)

SP-BDP dose increase \( n = 34,509 \)
or
ICS + LABA \( n = 240,581 \)

Excluded \(< 5 \) or \( > 11 \) years old
-SP-BDP \( n = 33,276 \)
-ICS + LABA \( n = 224,092 \)

Separate ICS + LABA cohort exclusions:
-Add-on LABA
-No change in ICS dose

Eligible patients aged 5–11 stepping up asthma therapy as:
SP-BDP increased dose \( n = 458 \)
Separate ICS + LABA inhalers \( n = 3624 \)

Total lost on matching:
SP-BDP \( n = 65 \)
ICS/LABA \( n = 2291 \)

Randomize matching patients 1:2*
*Software used to randomly pick unique matched patients

Total matched patients included
1:2 uniquely matched pairs:
Small-particle beclomethasone \( n = 276 \)
Separate ICS + LABA inhalers \( n = 552 \)

Inclusion Criteria:
1) \( \geq 50\% \) ICS dose increase as SP-BDP by pMDI or BAI or
2) LABA script as add-on or FDC

Matching criteria applied:
-Same sex
-Same age
-Last ICS dose before index date (1–50, 51–100, 101–200, 201–300, 301–400, >400 μg/day)
-Risk-domain asthma control status (controlled/uncontrolled)
-Baseline mean SABA dose (0, 1–200, 201–400, >400 μg/day)
-Baseline no. asthma consultations without OCS prescription (0, 1, ≥ 2)

SP-BDP cohort key inclusions:
-No LABA inhaler baseline
-On pMDI or BAI
-On current asthma Rx
-No COPD/chronic resp

SP-BDP cohort exclusions:
-On DPI baseline \( n = 60 \)
-Not registered at practice for study period \( n = 448 \)
-LABA or FDC script during baseline or on IPD \( n = 98 \)
-No current asthma Rx \( n = 72 \)
-Maintenance OCS baseline \( n = 3 \)
-Additional ICS dose increases \( n = 41 \)
-COPD or other \( n = 3 \)
-Duplicated in GPRD or OPCRD \( n = 53 \)

Separate ICS + LABA cohort key inclusions:
-Add-on LABA
-No change in ICS dose

Separate ICS + LABA cohort exclusions:
-Not registered at practice for study period \( n = 2960 \)
-No current asthma Rx \( n = 1044 \)
-LABA by DPI \( n = 1226 \)
-Change to LABA pre-1998 \( n = 1318 \)
-Change in ICS dose at IPD \( n = 872 \)
-Maintenance OCS baseline \( n = 24 \)
-COPD or other chronic \( n = 20 \)
-Duplicated in GPRD or OPCRD \( n = 550 \)

FIGURE E4. Small-particle ICS dose step-up versus add-on LABA to ICS in separate inhalers: patient selection and matching (analysis 2). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. BAI, Breath-actuated inhaler; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDC, fixed-dose combination ICS/LABA; GPRD, General Practice Research Database; IPD, index prescription date; OCS, oral corticosteroid; OPCRD, Optimum Patient Care Research Database; Rx, therapy; Script, prescription; SP-BDP, small-particle beclomethasone dipropionate.
FIGURE E5. ICS dose for matched cohorts as prescribed on the index date for (A) the initiation population and (B) the step-up population. Differences in prescribed doses between small-particle ICS and standard size–particle ICS cohorts were statistically significant ($P < .001$).
FIGURE E6. Probability of achieving risk-domain asthma control during the outcome year for children in the initiation population. Probability categorized by (A) age group and (B) treatment cohort, categorized by ICS daily dose exposure (ie, prescribed ICS dose divided by 365). Standard SP, Standard size-particle.
FIGURE E7. Total β2-agonist load comparing small-particle ICS dose step-up versus add-on LABA to ICS in (A) fixed-dose combination inhaler with ICS and (B) separate inhalers. Hours covered per 24 hours. FDC, fixed-dose combination.
FIGURE E8. AdjORs and adjRRs comparing step-up with increased dose of small-particle ICS versus add-on LABA as separate inhaler with ICS. (For details of confounding factors examined, please see above in Online Repository.) LRTI, Lower respiratory tract infection; NSAIDs, nonsteroidal anti-inflammatory drugs. Adjusted for the following confounders: *Number of asthma consultations, number of acute courses of oral corticosteroids, number of antibiotic prescriptions for LRTI. †Asthma diagnosis, prescriptions for NSAIDs, number of acute courses of oral corticosteroids, number of antibiotic prescriptions for LRTI, controller-to-reliever ratio. ‡Number of asthma consultations, number of acute courses of oral corticosteroids, controller-to-reliever ratio. §Asthma diagnosis, number of primary care consultations, number of acute courses of oral corticosteroids, number of antibiotic prescriptions for LRTI, inpatient admission for lower respiratory tract-related reasons. ††Controller-to-reliever ratio, definite plus probable asthma-related hospitalizations.
### TABLE E1. More baseline characteristics of children in the small-particle ICS and standard SP ICS cohorts (analysis 1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Initiation population</th>
<th>Step-up population</th>
<th>P value*</th>
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<tbody>
<tr>
<td></td>
<td>Small-particle ICS (n = 797)</td>
<td>Standard SP ICS (n = 797)</td>
<td>P value*</td>
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<tr>
<td></td>
<td>778 (97.6)</td>
<td>786 (98.6)</td>
<td>203 (98.5)</td>
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<tr>
<td>Mean ± SD</td>
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<td>Median (IQR)</td>
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<td>17.1 (10.4-29.3)</td>
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<td>Socioeconomic score† available</td>
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<td>786 (98.6)</td>
<td>203 (98.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.4 ± 3.4</td>
<td>17.4 ± 3.7</td>
<td>17.0 ± 2.7</td>
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<tr>
<td>Years since first asthma code, median (IQR)</td>
<td>0.6 (0.0-3.8)</td>
<td>0.6 (0.0-4.0)</td>
<td>3.0 (1.4-5.3)</td>
</tr>
<tr>
<td>Database Read code for asthma</td>
<td>786 (98.6)</td>
<td>785 (98.5)</td>
<td>202 (98.1)</td>
</tr>
<tr>
<td>Patients with PEF reading at baseline</td>
<td>114 (14.3)</td>
<td>143 (17.9)</td>
<td>79 (38.3)</td>
</tr>
<tr>
<td>Mean ± SD %predicted PEF</td>
<td>101 ± 26.4</td>
<td>101 ± 29.2</td>
<td>115 ± 27.8</td>
</tr>
<tr>
<td>BMI, Body mass index; IQR, interquartile range; LRTI, lower respiratory tract infection; PEF, peak expiratory flow; standard SP, standard size—particle.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data are n (%) unless otherwise noted.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE E2. Asthma therapy during the outcome year for matched cohorts prescribed small-particle ICS or standard SP ICS for first-line or step-up therapy (analysis 1)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Initiation population</th>
<th>Step-up population</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small-particle ICS (n = 797)</td>
<td>Standard SP ICS (n = 797)</td>
<td>P value*</td>
</tr>
<tr>
<td>Spacer device prescribed</td>
<td>397 (49.8)</td>
<td>340 (42.7)</td>
<td>.004</td>
</tr>
<tr>
<td>Number of ICS inhalers, median (IQR)†</td>
<td>2 (1-4)</td>
<td>3 (2-6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Two or more ICS inhalers</td>
<td>531 (66.6)</td>
<td>621 (77.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Any prescribed change in therapy</td>
<td>89 (11.2)</td>
<td>157 (19.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Increase in ICS dose</td>
<td>57 (7.2)</td>
<td>91 (11.4)</td>
<td>.004</td>
</tr>
<tr>
<td>Any additional therapy†</td>
<td>46 (5.8)</td>
<td>87 (10.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fluticasone-salmeterol</td>
<td>13 (1.6)</td>
<td>35 (4.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Budesonide-formoterol</td>
<td>2 (0.3)</td>
<td>1 (0.1)</td>
<td>.57</td>
</tr>
<tr>
<td>LABA</td>
<td>19 (2.4)</td>
<td>39 (4.9)</td>
<td>.010</td>
</tr>
<tr>
<td>Leukotriene receptor antagonist§</td>
<td>20 (2.5)</td>
<td>26 (3.3)</td>
<td>.37</td>
</tr>
<tr>
<td>Standard SP, Standard size—particle.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data are n (%) unless otherwise noted.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†Number of ICS inhalers prescribed during the outcome year in addition to the index prescription. ICS inhaler durations ranged from 30 d (eg, for Flixotide) to 50 d (eg, for QVAR).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>§Change in therapy and additional therapy could be at any time during the outcome year, and children could have had more than 1.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡Montelukast is the only leukotriene receptor antagonist licensed in the United Kingdom.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE E3. Summary of matched spacer subanalysis and unmatched full analysis and subanalyses for the initiation population: small-particle ICS or standard SP ICS comparison

<table>
<thead>
<tr>
<th>Initiation population</th>
<th>AdjOR/RR (95% CI) for small-particle ICS relative to standard SP ICS (1.00)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Matched cohort analysis</td>
</tr>
<tr>
<td></td>
<td>Spacer subanalysis*</td>
</tr>
<tr>
<td>Sample size</td>
<td>465</td>
</tr>
<tr>
<td>Small-particle ICS</td>
<td></td>
</tr>
<tr>
<td>Standard SP ICS</td>
<td>465*</td>
</tr>
<tr>
<td>Risk-domain asthma control</td>
<td>1.81 (1.24-2.65)†</td>
</tr>
<tr>
<td>Overall asthma control</td>
<td>1.49 (1.12-2.00)‡</td>
</tr>
<tr>
<td>Treatment stability</td>
<td>1.80 (1.32-2.46)‡</td>
</tr>
<tr>
<td>Severe exacerbations</td>
<td>0.53 (0.29-0.98)#</td>
</tr>
<tr>
<td>Clinical exacerbations</td>
<td>0.55 (0.38-0.79)–</td>
</tr>
<tr>
<td>LRTI hospitalizations</td>
<td>0.71 (0.23-2.25)††</td>
</tr>
</tbody>
</table>

*All children in the standard SP ICS cohort and 319 (68.6%) children in the small-particle ICS cohort were prescribed a spacer device during baseline and/or outcome year.

**Spacer subanalysis adjusted for:**
†GP consultation for LRTI requiring antibiotics. §Number of prescriptions for asthma or allergies. ¶Baseline LABA use and number of non–asthma-related consultations.
#Mean SABA daily dose, outpatient department attendance for lower respiratory reasons, and year of index date. *GP consultation for LRTI requiring antibiotics and year of index date. ††No significant effects.

Full unmatched analysis adjusted for:
†Mean SABA daily dose, age, number of severe exacerbations. §Mean SABA daily dose, sex, asthma control status, rhinitis diagnosis and/or therapy. ¶Asthma control status, mean SABA daily dose, use of LABA. #Mean SABA daily dose, number of severe exacerbations. †-Number of severe exacerbations, oral candidiasis, age, rhinitis diagnosis and/or therapy.

No rhinitis subanalysis adjusted for:
†Age, year of index date, mean SABA daily dose, number of severe exacerbations. §Mean SABA daily dose, sex, asthma control status, rhinitis diagnosis and/or therapy. ¶Asthma control status, mean SABA daily dose, number of severe exacerbations.

0 exacerbations subanalysis adjusted for:
†Mean SABA daily dose, age, rhinitis diagnosis and/or therapy. §Asthma control status, mean SABA daily dose, sex, rhinitis diagnosis and/or therapy, asthma diagnosis.
¶Asthma control status, mean SABA daily dose. #Mean SABA daily dose, rhinitis diagnosis and/or therapy. †-Asthma control status, rhinitis diagnosis and/or therapy, number of consultations for LRTI requiring antibiotic.

≥1 exacerbations subanalysis adjusted for:
†Age. §Mean SABA daily dose. ¶No significant effects. #Sex, number of severe exacerbations, number of severe exacerbations.

IQR, Interquartile range; LRTI, lower respiratory tract infection; standard SP, standard size–particle.
**TABLE E4.** More baseline characteristics of children in the small-particle ICS step-up and add-on LABA cohorts (analysis 2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICS dose step-up vs ICS/LABA combination</th>
<th>ICS dose step-up vs separate ICS + LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²), mean ± SD†</td>
<td>BMI (kg/m²), mean ± SD†</td>
<td></td>
</tr>
<tr>
<td>Younger than 5 years, years since first asthma code,</td>
<td>3.4 (1.6-6.0)</td>
<td>3.1 (1.3-5.4)</td>
</tr>
<tr>
<td>Recorded %predicted PEF, mean ± SD</td>
<td>33 (17.8)</td>
<td>56 (20.3)</td>
</tr>
<tr>
<td>Asthma prescriptions, median (IQR)</td>
<td>4 (3-6)</td>
<td>4 (3-7)</td>
</tr>
<tr>
<td>cohorts in the small-particle ICS step-up and add-on</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA cohorts (analysis 2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE E5.** Asthma therapy during the outcome year for matched cohorts in the small-particle ICS step-up and add-on LABA cohorts (analysis 2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICS dose step-up vs ICS/LABA combination</th>
<th>ICS dose step-up vs separate ICS + LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spacer device prescribed</td>
<td>66 (35.7)</td>
<td>112 (40.6)</td>
</tr>
<tr>
<td>Three or more ICS inhalers, median (IQR)†</td>
<td>130 (70.3)</td>
<td>205 (74.3)</td>
</tr>
<tr>
<td>Median (IQR) β₂-agonist coverage (h)‡</td>
<td>2.2 (1.1-4.4)</td>
<td>2.2 (1.1-4.4)</td>
</tr>
<tr>
<td>Change in β₂-agonist coverage (h)‡</td>
<td>0.3 (–0.6 to 1.6)</td>
<td>0.5 (–0.5 to 1.6)</td>
</tr>
<tr>
<td>Any prescribed change in therapy§</td>
<td>29 (15.7)</td>
<td>44 (15.9)</td>
</tr>
<tr>
<td>Increase in ICS dose</td>
<td>5 (2.7)</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>Any additional therapy</td>
<td>28 (15.1)</td>
<td>39 (14.1)</td>
</tr>
<tr>
<td>Fluticasone-salmeterol</td>
<td>11 (5.9)</td>
<td>13 (4.7)</td>
</tr>
<tr>
<td>Budesonide-formoterol</td>
<td>2 (1.1)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Leukotriene receptor antagonist†</td>
<td>8 (4.3)</td>
<td>20 (7.2)</td>
</tr>
</tbody>
</table>

**Notes:**
- BMI, Body mass index; IQR, interquartile range; LRTI, lower respiratory tract infection; PEF, peak expiratory flow.
- Data are n (%) except otherwise indicated.
- Matched cohorts were compared using conditional logistic regression.
- Recorded data were available for BMI for 89 (48.1%) and 86 (46.5%) in ICS step-up and ICS/LABA combination cohorts, respectively, and for 127 (46.0%) and 265 (48.0%) in ICS step-up and separate ICS + LABA cohorts, respectively.
- Dry powder inhaler; IQR, interquartile range; NA, not applicable.
- Data are n (%) unless otherwise stated.
- Conditional logistic regression.
- Number of ICS or ICS/LABA inhalers prescribed during the outcome year in addition to the index prescription.
- Total β₂-agonist coverage (SABA + LABA) was calculated as SABA 2 puffs lasting 4 h plus LABA 2 puffs via pMDI or 1 puff via DPI lasting 12 h. Change was the difference between the baseline and outcome years.
- Montelukast is the only leukotriene receptor antagonist licensed in the United Kingdom.
### TABLE E6. Baseline characteristics of children comparing ICS step-up and separate ICS + LABA cohorts (analysis 2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICS dose step-up (n = 276)</th>
<th>Separate ICS + LABA (n = 552)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex: male†</strong></td>
<td>170 (61.6)</td>
<td>340 (61.6)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Age at index date (y), mean ± SD†</strong></td>
<td>7.7 ± 2.0</td>
<td>7.7 ± 2.0</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Recorded comorbidity‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible atopy</td>
<td>214 (77.5)</td>
<td>442 (80.1)</td>
<td>.39</td>
</tr>
<tr>
<td>Rhinitis diagnosis/Rx</td>
<td>61 (22.1)</td>
<td>142 (25.7)</td>
<td>.26</td>
</tr>
<tr>
<td>Eczema diagnosis/Rx</td>
<td>199 (72.1)</td>
<td>416 (75.4)</td>
<td>.32</td>
</tr>
<tr>
<td>Preschool wheeze diagnosis</td>
<td>113 (40.9)</td>
<td>249 (45.1)</td>
<td>.25</td>
</tr>
<tr>
<td>Preschool asthma diagnosis/Rx</td>
<td>147 (53.3)</td>
<td>326 (59.1)</td>
<td>.11</td>
</tr>
<tr>
<td><strong>Risk-domain asthma control†</strong></td>
<td>185 (67.0)</td>
<td>370 (67.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Spacer device prescribed</td>
<td>110 (39.9)</td>
<td>230 (41.7)</td>
<td>.61</td>
</tr>
<tr>
<td>Mean daily SABA dose (µg/d)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-100</td>
<td>50 (18.1)</td>
<td>86 (15.6)</td>
<td>.35</td>
</tr>
<tr>
<td>101-200</td>
<td>100 (36.2)</td>
<td>214 (38.8)</td>
<td>.35</td>
</tr>
<tr>
<td>201-400</td>
<td>83 (30.1)</td>
<td>166 (30.1)</td>
<td>.32</td>
</tr>
<tr>
<td>401-800</td>
<td>35 (12.7)</td>
<td>70 (12.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;800</td>
<td>8 (2.9)</td>
<td>16 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) daily ICS dose (µg/d)‡</td>
<td>55 (27-110)</td>
<td>55 (27-110)</td>
<td>.32</td>
</tr>
<tr>
<td><strong>Last ICS dose before the index date (µg/d)†‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-50</td>
<td>6 (2.2)</td>
<td>12 (2.2)</td>
<td>NA</td>
</tr>
<tr>
<td>51-100</td>
<td>195 (70.7)</td>
<td>390 (70.7)</td>
<td></td>
</tr>
<tr>
<td>101-200</td>
<td>75 (27.2)</td>
<td>147 (26.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Severe exacerbations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>215 (77.9)</td>
<td>403 (73.0)</td>
<td>.062</td>
</tr>
<tr>
<td>1</td>
<td>40 (14.5)</td>
<td>102 (18.5)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>6 (2.2)</td>
<td>17 (3.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Asthma consultation/no oral corticosteroids†‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>96 (34.8)</td>
<td>192 (34.8)</td>
<td>.34</td>
</tr>
<tr>
<td>1</td>
<td>89 (32.2)</td>
<td>178 (32.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55 (19.9)</td>
<td>99 (17.9)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>36 (13.0)</td>
<td>83 (15.0)</td>
<td></td>
</tr>
</tbody>
</table>

IQR, Interquartile range; NA, not applicable; Rx, therapy.

*Matched cohorts were compared using conditional logistic regression.

†Matching variable (please see above in Online Repository text for details).

‡Possible atopy was defined as any 1 or more of the following: recorded rhinitis diagnosis, rhinitis therapy, eczema diagnosis, eczema therapy. Preschool wheeze was captured through database coding; concomitant rhinitis, eczema, and preschool asthma were captured through database-coded diagnosis or therapy for same. Preschool was defined as age 1 to 3 y.

The doses of ICS were standardized to equivalence with small-particle beclometasone and fluticasone; thus, doses of large-particle beclometasone and budesonide were halved.

### TABLE E7. Outcome-year results for matched cohorts comparing small-particle ICS step-up and separate ICS + LABA cohorts (analysis 2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICS dose step-up (n = 276)</th>
<th>Separate ICS + LABA (n = 552)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk-domain asthma control</td>
<td>215 (77.9)</td>
<td>404 (73.2)</td>
<td></td>
</tr>
<tr>
<td>Treatment stability</td>
<td>191 (69.2)</td>
<td>303 (54.9)</td>
<td></td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>232 (84.1)</td>
<td>447 (81.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33 (12.0)</td>
<td>76 (13.8)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>11 (4.0)</td>
<td>29 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Clinical exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>218 (79.0)</td>
<td>412 (74.6)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42 (15.2)</td>
<td>97 (17.6)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>16 (5.8)</td>
<td>43 (7.8)</td>
<td></td>
</tr>
</tbody>
</table>

Disaggregated results of composite measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICS dose step-up (n = 276)</th>
<th>Separate ICS + LABA (n = 552)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 asthma-related hospitalization</td>
<td>2 (0.7)</td>
<td>2 (0.4)</td>
<td>.49</td>
</tr>
<tr>
<td>≥1 acute course of oral corticosteroids</td>
<td>42 (15.2)</td>
<td>100 (18.1)</td>
<td>.39</td>
</tr>
<tr>
<td>≥1 GP consultation for LRTI requiring antibiotic</td>
<td>26 (9.4)</td>
<td>55 (10.0)</td>
<td>.65</td>
</tr>
<tr>
<td>Mean &gt;2 puffs daily SABA</td>
<td>165 (59.8)</td>
<td>303 (54.9)</td>
<td>.37</td>
</tr>
<tr>
<td>Increase in ICS dose or additional therapy</td>
<td>44 (15.9)</td>
<td>166 (30.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

LRTI, Lower respiratory tract infection.

Data are n (%) unless otherwise stated.

*Conditional logistic regression.