Long-acting beta-agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids

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Abbreviations:

ADEPT Anonymized Data Ethics Protocols and Transparency

aOR Adjusted Odds Ratio

aRR Adjusted Rate Ratio

BTS/SIGN The British Thoracic Society and Scottish Intercollegiate Guidelines Network

CPRD Clinical Practice Research Database

FDA Food and Drug Administration

FDC Fixed Dose Combination inhaler

ICS Inhaled Corticosteroids

LABA Long Acting Beta Agonist

OCS Oral Corticosteroids

OPCRD Optimum Patient Care Research Database

NICE National Institute for Health and Care Excellence

SABA Short Acting Beta Agonist

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What is already known about this topic?

Clinical trials provide no evidence to support recommendations that children with asthma prescribed long-acting β_2-agonist (LABA) should receive treatment as a fixed-dose combination inhaler and not by addition of a separate inhaler to inhaled corticosteroids (ICS).

What does this article add to our knowledge?

In a matched cohort study, LABA treatment as a separate inhaler was associated with poorer asthma control and increased risk for exacerbation compared to fixed-dose combination inhaler.

How does this study impact current management guidelines?

These findings support British Thoracic Society, NICE asthma guideline and Food and US Drug Administration recommendations to prescribe add-on LABA as a fixed-dose combination inhaler with ICS in children

ABSTRACT

Background Adding a long-acting β_2-agonist (LABA) to inhaled corticosteroids (ICS) using a fixed-dose combination (FDC) inhaler containing ICS and LABA is the UK guideline-recommended step-up option for children aged >4 years with uncontrolled asthma on ICS monotherapy. The evidence of benefit of FDC inhalers over adding a separate LABA inhaler to ICS therapy is limited.

Objective: Our aim was to compare outcomes for FDC versus separate LABA+ICS inhalers for children by analyzing routinely-acquired clinical and prescribing data.

Methods This matched cohort study used large UK primary care databases to study children prescribed their first step-up from ICS monotherapy at 5–12 years of age as add-on LABA, either via separate LABA inhaler or FDC inhaler. A baseline year was examined to characterize patients and identify potential confounders; outcomes were examined during the subsequent year. The primary outcome was adjusted odds ratio for overall asthma control, defined as no asthma-related hospital admission, emergency room visit prescription for oral corticosteroids and ≤200 µg/day salbutamol.

Results After matching, there were 1330 children in each cohort (mean age [SD] 9 [2] years; 59% male). All measures of asthma exacerbations and control improved during the outcome year in both cohorts. In the separate ICS+LABA cohort, the odds of achieving overall asthma control were lower (adjusted odds ratio, 0.77 [95% CI 0.66-0.91] P = 0.001) compared with the FDC cohort.

Conclusion Our results demonstrate a small but significant benefit of add-on LABA therapy as FDC over separate inhaler and support current recommendations.

INTRODUCTION

Asthma is common amongst children in the UK, with an estimated 8%, or 1.1 million children, prescribed current asthma therapy.[1,2] The British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) guideline for the management of asthma recommends a stepwise approach to therapy to maintain symptom control and minimize future risk of exacerbations. Inhaled corticosteroids (ICS), prescribed at step 2 of the current BTS/SIGN guideline, are effective controller medications for most children with persistent asthma, although from 10–25% of children require additional therapy.[3-6] Adding a long-acting β_2-agonist (LABA) to ICS is the preferred step-up option (step 3) recommended by the BTS/SIGN for children ages 5–12 years with uncontrolled asthma on ICS monotherapy.[3]

Guidance from the UK National Institute for Health and Care Excellence (NICE) identifies a fixed-dose combination (FDC) inhaler containing ICS and LABA as the optimal means of adding a LABA, preferred over adding LABA as a separate inhaler,[2] but some children continue to be prescribed separates. One risk of prescribing LABA as a separate inhaler is its use without concomitant ICS therapy, and the National Review of Asthma Deaths recommended that LABA "should be prescribed with an inhaled corticosteroid in a single combination inhaler".[7]

The benefit of FDC over addition of separate LABA inhaler to ICS treatment for children with asthma is unclear. Two clinical trials, where adherence was closely monitored, found no difference in symptoms after 3[8] and 6 months'[9] treatment between groups randomized to LABA as separate inhaler or FDC. However, patient behaviours and clinical outcomes are often different in the context of a clinical trial as opposed to 'real-life' usual clinical care. One database study observed reduced need for short-acting β_2-agonist (SABA) and oral corticosteroid treatment in children treated with LABA as an FDC compared with additional inhaler,[4] but importantly there was no matching at baseline for factors known to be different between groups, including age and obesity.[10] We have recently reported that children stepped up to LABA as a separate inhaler are younger and on a lower dose of ICS compared with

those stepped up to FDC,[10] and these baseline differences might explain the apparent superiority of FDC over LABA as separate inhaler.

Rigorously conducted observational research can provide information about outcomes of asthma therapy under conditions of usual clinical practice to complement information from controlled trials.[11] Results of prior retrospective observational studies suggest that adherence and refill persistence may be better with a combination inhaler, at least among adults and adolescents.[12-14] In turn, better adherence and persistence could lead to better outcomes. The aim of this large population-based observational study was to evaluate whether outcomes differ between children with asthma stepped up to add-on LABA as separate vs. FDC inhalers. Our hypothesis was that children stepped up to separate inhalers would have increased odds for poor asthma control compared with matched children stepped up to FDC.

METHODS

Data source and permissions

In a matched cohort study, we sourced medical record and prescribing data from two large primary care databases including ~15% of children in the UK, as previously described.[10] Duplicate records from individual children were identified and removed. The Clinical Practice Research Datalink (CPRD; formerly General Practice Research Database), which is well-validated and used frequently for observational research, is the world's largest repository of anonymized longitudinal data from primary care, drawing from over 600 subscribing practices throughout the UK.[15,16] The Optimum Patient Care Research Database (OPCRD) is a quality-controlled primary care research database that contains anonymous routine medical record data and patient-completed questionnaire data from over 400 practices throughout the UK caring for approximately a half million patients with asthma.[17] Data were available from January 1990 through April 2012 for the CPRD and through December 2012 for the OPCRD.

The study was conducted to standards recommended for observational research[18] and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ref ENCEPP/SDPP/10483). Use of the data was approved in 2010 by the Independent Scientific Advisory Committee of the (then) General Practice Research Database. The OPCRD has been approved by the Trent Multi Centre Research Ethics Committee for clinical research use, and the protocol for this study was approved by the Anonymized Data Ethics Protocols and Transparency (ADEPT) committee, the independent scientific advisory committee for the OPCRD. Further background information is in the online supplementary material.

Inclusion and exclusion criteria

Inclusion criteria were: a Read code diagnosis of asthma or with ≥2 inhaler prescriptions including ≥1 for ICS in the previous 12 months (the latter comprise 2% of the study population[10]); prescribed a step-up with LABA from ICS monotherapy at 5–12 years of age; registered in the database for ≥2 sequential years, including 1 baseline year before the date of therapy step-up (the *index date*). Exclusion criteria were: cystic fibrosis or any chronic

respiratory disease other than asthma; receipt of add-on therapy (including combination inhaler) at any time prior to the index date; treatment with >7 consecutive days oral corticosteroids (OCS) during the baseline year; multiple step-up therapies on the index date; ≥50% increase or decrease in ICS dose on the index date (the latter ensured that we studied outcomes of addition of LABA independent of change in ICS).

Study Outcomes

The primary endpoint, previously described,[19-21] was overall asthma control (expressed as an adjusted odds ratio, aOR) and this includes both components of the American Thoracic Society/European Respiratory Society[22] definition of asthma control, i.e. the level of clinical asthma control (as evidenced here by short acting beta agonist use) and the risk of future adverse events (as evidenced here by a history of adverse events including hospitalisation, ED visit and receipt of OCS). Overall asthma control is defined in table 1. A prescription for antibiotics in conjunction with a respiratory consultation was included in the definition of an acute respiratory event (and absence of same in the definitions of asthma control) because in clinical practice antibiotics may be prescribed for an asthma exacerbation.[23-,25] Secondary outcomes were acute respiratory events, severe exacerbation,[26] risk-domain measure of asthma control (to give insight into risk for future exacerbation) [19-21] and treatment stability (see table 1 for definitions). Medication use during the 12 months after the index date was also compared between cohorts. Statement re coding for hospitalisation, ER and outpatients.

Calculations of medication use

We calculated the average daily doses of SABA and of ICS during the baseline and outcome years as the [number of inhalers x doses per inhaler] divided by 365 multiplied by strength (in µg). For ICS doses we used the beclomethasone dipropionate (BDP)-equivalent doses for the calculations, thus a 1:1 ratio for budesonide: BDP, 2:1 for fluticasone propionate: BDP, and 2:1 for extrafine beclomethasone (Qvar): BDP. The ICS medication possession ratio (MPR) was calculated as the number of days coverage of the drug prescribed divided by 365 multiplied by 100 and expressed as <80% (non-adherent) and ≥80% (adherent).[27,28] The separate LABA inhalers that were available during the study period contained salmeterol or

formoterol; the FDC ICS/LABA inhalers contained fluticasone-salmeterol (Seretide), budesonide-formoterol (Symbicort), and extrafine beclomethasone-formoterol (Fostair).

Statistical analyses and sample size

Children in the two treatment cohorts (separate ICS+LABA and FDC ICS/LABA) were matched sequentially 1:1 on the following criteria which were either known to differ at baseline[4]:year of index date (±3 years), age (exact year), baseline year number of severe exacerbations (0 or ≥1), prior ICS daily dose (≤150, 151–250, 251–500, or >500 µg/day), and baseline year mean daily SABA dose (0, 1–200, >200 µg/day). Bespoke software was used to randomly select unique matched patient pairs when more than one match was possible.

Data were prepared for analysis by investigating potential outliers, transforming skewed data (e.g., log transformation), and categorizing heavily skewed data; missing data were investigated for type and reason for missingness. All matched unadjusted baseline and outcome data were tabulated using summary statistics and compared using conditional logistic regression and an intention-to-treat analysis, whereby all children were included in the outcome year analyses.

The rates of adverse respiratory events and severe exacerbations during the outcome year were compared using a negative binomial regression model to estimate adjusted ratio ratios (aRR) and 95% CIs, with FDC ICS/LABA cohort as the reference cohort. General estimating equations were used to account for the correlation within matched pairs.[29] The model used empirical standard errors for more robust confidence intervals (CIs) and adjusted for potential baseline confounders.

Conditional logistic regression models were used to estimate adjusted odds ratios (aOR) and 95% CIs for the dichotomous outcomes, e.g. overall asthma control, with FDC ICS/LABA as the reference, and adjusted for potential confounding factors.

For all multivariable models, those variables that were significantly different or showed a trend towards a difference ($P < 0.10$) between the treatment cohorts at baseline were included as potential confounding factors along with any strongly predictive variables. Potential confounders examined are listed in the online supplementary material (Table S1).

195 Variables were examined for collinearity and clinical importance and were then removed in a
196 backwards stepwise procedure until all confounding variables remaining in the multivariable
197 model had $P < 0.1$ (see online supplementary material for further details).

198 No prospective power calculation was carried out since our sample size was
199 determined by the number of eligible children in CPRD and OPCRD. The analyses were
200 carried out using IBM SPSS Statistics version 21 (SPSS Statistics, IBM, Somers, NY, USA),
201 SAS version 9.3 (SAS Institute, Marlow, Buckinghamshire, UK), and Microsoft Excel 2007
202 (Microsoft, Bellevue, WA, USA); statistically significant results were defined as $P < 0.05$.

RESULTS

Patients

Overall, 1390 and 3771 children were eligible for the FDC ICS/LABA and separate ICS+LABA cohorts, respectively (see figure in supplementary file). Ninety seven percent of children had a diagnosis of asthma and 70% were from OOPCRD. After matching there were 1330 children in each cohort, of mean age (SD) 9 (2) years, and 59% were male (table 2). The two cohorts were similar in characteristics apart from the separate ICS+LABA cohort having higher dose ICS at baseline, higher annualized ICS doseand the LABA step up occurring one year earlier (i.e. 2005 versus 2006) compared to the FDC cohort, table 2 and table S3.The cohorts were well-matched for indicators of baseline asthma severity and control table 3.

Outcomes

Primary outcome

The proportion of children who achieved overall asthma control was 35% before the index data and 43% afterwards among the FDC cohort and corresponding proportions were 35% and 37% among the ICS+LABA cohort; the adjusted odds ratio (aOR) for children in the ICS+LABA cohort achieve control relative to the FDC cohort was 0.77 (0.66–0.91; $P = 0.001$), table 3, figure 1.

Secondary outcomes

The rate of acute respiratory events was greater among the ICS+LABA cohort compared to the FDC group (adjusted rate ratio [aRR] 1.21; 1.04–1.39; $P = 0.012$; table 3, figure 1). The percentage of children with ≥1 severe exacerbations was 13% during the baseline year for both cohorts and in the outcome year was 7% for the FDC cohort and 9% for the ICS+LABA cohort; the aRR for severe exacerbations among the children prescribed ICS+LABA relative to FDC was 1.31 (95% CI; 0.99–1.72; $P = 0.056$; table 3, figure 1). Relative to the FDC cohort, children in the ICS+LABA as separates cohort were at reduced odds for achieving risk-domain asthma control (aOR 0.74; 0.61–0.89; $P = 0.003$) and achieving treatment stability (aOR 0.67; 0.57–0.79; $P < 0.001$), table 3, figure 1. There were no significant differences

between cohorts for medication possession ratio being >80% or for severe exacerbations. In the follow up year there were 6 hospitalizations for asthma in each cohort (*P* = 0.99). There were 16 children in the FDC cohort and 3 in the separates cohort treated for thrush during the follow up year (*P* = 0.008, see on line supplement). Compared to the baseline year, more children in the separates cohort (29.9% in baseline year and 19.6% in follow up year) received treatment with antibiotics during the follow up year than in the FDC cohort (28.6% and 22.5% respectively, p=0.041). There was a trend which approached significance for a greater proportion of the separates cohort to receive oral corticosteroids compared to the FDC cohort during the follow up year (8.8% versus 6.5%, p=0.084) but no difference in the number with asthma-related hospital admissions and GP consultations for asthma.

Asthma prescribing during outcome year

Asthma therapy prescribed during the outcome year, as well as changes in therapy, are summarized in table 4. Children in the FDC cohort typically received one fewer SABA inhaler in the outcome year (3 versus 4, table 4) compared with the ICS+LABA as separates. Children in the FDC ICS/LABA cohort were more likely to have an increase in ICS dose compared with the ICS+LABA as separates (10% vs. 4%; *P* < 0.001) but no more likely to have LTRA added. Seventeen percent of children in the ICS+LABA as separates cohort were started on an FDC during the outcome year. The proportion of children with MPR>80% was 33% in the FDC cohort and was 31% for the ICS+LABA as separates cohort (aOR 0.87 [0.72–1.06]). During the outcome year the median daily ICS dose was 219 µg for both cohorts, 231 children in the separates cohort switched to FDC, 17 in the FDC switched to separates and LTRA treatment was started in 122 in the FDC cohort and 112 in the separates cohort.

DISCUSSION

The aim of this matched cohort study was to provide evidence to support guidelines recommending that children receiving LABA as an add-on to ICS treatment should be prescribed a fixed combination inhaler and not an additional separate LABA inhaler, as prescribing of separates remains very common in UK clinical practice despite recommendations .[2,3] The main finding was that children prescribed add-on LABA with ICS as separate inhalers had a 30% greater odds of not having controlled asthma compared with children prescribed FDC. Additionally the use of separate inhalers was associated with a 21% greater exacerbation rate compared with those who received FDC. The fact that 17% of children in the separate LABA cohort were prescribed an FDC inhaler during the outcome year suggests that prescribers may be trialing LABA as a separate, but our data suggest that the trial should be with FDC in the first instance. Our results provide additional evidence that supports guideline recommendations for LABA to be prescribed as FDC, and not as separate, inhaler..[2,3]

Although significant, the improvement in outcomes for those treated with FDC was only improved by a small degree compared with treatment with separate ICS and LABA inhalers (figure 1). We present our results as odds ratios, and the effect size is small when presented as a likelihood ratio for achieving control (0.9 for the separates cohort compared to the FDC cohort), or number needed to treat (17 children would require treatment with FDC instead of separate in order to mean one child achieved control). This small effect may be partly explained by improvement in all outcomes in both groups as the children became older. An additional factor may be that adherence was relatively poor for all participants (22-33%). Overall, relatively few children prescribed LABA in our study achieved overall asthma control (35-43%), and whilst this is partly related to the moderate severity of their disease this study highlights the burden of respiratory morbidity in children with asthma which can be at least partly improved by FDC prescription in place of ICS and LABA separates, typically one fewer SABA canister per annum.

There is little prior published work comparing outcomes with FDC versus separate inhalers for children prescribed add-on LABA yet many thousands of children are prescribed LABA each year. Outcomes were similar with FDC versus separate inhalers for children in two relatively short double-blind, double-dummy trials,[8,9] although one trial did observe a greater increase in peak expiratory flow in children receiving FDC compared with ICS+LABA as separates.[9] These studies[8,9] might have been underpowered to detect differences between two effective treatments, and additionally it is well-recognized that clinical trials recruit individuals whose disease is exceptionally stable and whose adherence behavior is not generalizable to the whole population and this potentially reduces the ability of clinical trials to detect a difference in outcome between treatment groups.[18] A recent retrospective observational database study observed that children prescribed FDC inhalers received fewer acute oral corticosteroid courses and in 2 of the 4 years studied, also less reliever medication than those prescribed separate inhalers.[4] One possible explanation for the findings of Elkout et al.[4] is that the apparent benefit of FDC is due to children receiving separates being at increased risk for adverse outcomes *per se* and our previous work confirms that younger children are more likely to be prescribed separate inhalers[10] and are also more likely to have exacerbations.[30] The present study applied a matched cohort analysis and although there were small differences between cohorts in ICS dose at baseline where any effect would minimize any benefit of step up to FDC we are able to conclude that the benefit of FDC over separates is not explained by differences at baseline.

The use of an FDC ICS/LABA inhaler has several theoretical benefits over two separate inhalers. The concurrent delivery of a bronchodilator (LABA) may provide a symptomatic benefit with use of FDC inhalers that promotes inhaler use, and thus improved adherence with treatment and increased consumption of concomitant ICS.[31,32] Other authors have hypothesized there may be a biochemical synergy between ICS and LABA with their co-deposition in the airways.[33,34] Moreover, an important advantage of combining ICS and LABA in one inhaler is the prevention of LABA use as monotherapy, which carries potential increased risk of asthma-related mortality and since 2005 is accompanied by a Food and Drug

Administration (FDA) “black box” warning in the US.[35,36] A 2010 FDA recommendation was that “a FDC product…be used to ensure compliance with concomitant therapy in pediatric and adolescent patients”.[37] Conversely, an advantage of prescribing separate inhalers is the ability to titrate ICS dose independently of the LABA.

The assumption of better LABA adherence with use of a single FDC ICS/LABA inhaler rather than two separate inhalers is generally acknowledged.[2] We found no evidence for improved ICS adherence between cohorts, in terms of refill prescription rates, but the increased number of children treated for thrush in the FDC compared to separates suggests increased adherence with ICS in the FDC cohort. Some retrospective observational studies find that FDC inhalers are associated with better adherence and refill persistence by both adults and adolescents with asthma,[12-14] but this finding is not seen in all studies. For example, in one randomized controlled trial (patient ages 16–65 years) where covert electronic monitoring was used, similar adherence was found with FDC and separate inhaler therapy.[38] In a retrospective observational study, and consistent with our findings, Elkout et al.[39] found that MPR was similar for children prescribed separate ICS+LABA inhalers and FDC LABA/ICS and it is possible that although separate ICS and LABA inhalers are issued with equal frequency, adherence with ICS is higher compared with LABA separate. Clearly more research is needed in this area but the limited data from children presented here and from adults elsewhere[38] suggest that FDC is associated with superior outcomes compared with ICS plus LABA as separates and this difference may be explained by different taking behavior, e.g. taking more separates when symptomatic.

Treatment with a “SMART” regimen has never been recommended for children in the UK, and our study cannot give insight into the potential benefits of this practice. There is evidence of reduced exacerbations in children randomized to a “SMART” regimen compared with FDC[40] but this work has not been confirmed elsewhere or incorporated into guidelines to date.

Antibiotics are not recommended for the treatment of acute asthma excerbations in any age group, but since antibiotics are commonly prescribed for childhood asthma

337 exacerbations[23-25] failure to consider antibiotic prescribing will result in missing a large number
338 of exacerbations. One study of 60 million asthma exacerbations reported that one in six
339 pediatric exacerbations were treated with antibiotics, and only 26% of those treated with
340 antibiotics received corticosteroid treatment (i.e. 12% of all exacerbations)[25] and would not be
341 identified as an exacerbation.

342 This study has several strengths. We drew on well-maintained and stable datasets
343 containing medical record information for approximately 15% of children in the UK through
344 2012. A full baseline year was used for confounder definition, and a full outcome year for
345 examining asthma-related outcomes to capture infrequent events such as exacerbations and
346 eliminate the effect of seasonal variations in allergy. A rigorous matching process was used,
347 which was informed by our previous work that identified differences between children receiving
348 LABA as separate inhaler or FDC,[10] and this resulted in two cohorts with similar demographic
349 characteristics and baseline indicators of asthma severity and control; adjustments were made
350 for minor residual confounding. We studied children receiving their first therapy step-up with
351 add-on LABA, thereby reducing potential effects of declining persistence with therapy over
352 time.[14]

353 Our study has a number of limitations. First, as in all studies of this nature the patient
354 outcomes were inferred from prescribing information which brings the benefits of a large
355 representative sample size but which cannot capture aspects of asthma control such as
356 nocturnal or exertional symptoms, however we are able to capture use of relieving medication
357 which is a valid index of asthma control. We cannot rule out the possibility of undetected
358 residual confounding in this study, although our matching and analytic methods were designed
359 to minimize this possibility. Despite matching for index data the FDC cohort was identified one
360 year after the ICS/LABA cohort, reflecting the later introduction of FDC to clinical practice
361 compared to separate LABA inhaler, but we do not believe that this difference has substantially
362 affected the outcome. Our matching ensured that the children in cohort were prescribed the
363 same ICS dose (400 µg) but we acknowledge that the separates cohort had received less ICS
364 over the previous year compared to the FDC cohort (143 versus 164 µg) and do not believe

that this difference has affected the difference seen between cohorts. Moreover, as in any observational study there was the potential for bias, for example, differential prescribing with regard to add-on LABA inhaler choice that could in turn influence outcomes. Missingness was present but was equally distributed across the two cohorts, e.g. only 60% of children had height and weight data available. The children with the most severe asthma, i.e. maintenance oral corticosteroids, were excluded from the analysis and our results cannot necessarily be extrapolated to this very small group of patients. Children with small changes in ICS dose than recommended (i.e. <50%) were also excluded from our analysis meaning that our results cannot be extrapolated to this clinical setting. We acknowledge that the definition of asthma used may have resulted in inclusion of children without asthma and exclusion of children with (unrecognized) asthma, but the aim of this study was to compare outcomes between groups of children with asthma and not outcomes between groups with and without asthma so the inclusion criteria for asthma diagnosis are not likely to affect the results. Finally, we used an intention-to-treat analysis but know that 17% of the ICS+LABA cohort received FDC during the follow up and this will underestimate the true clinical benefit of FDC over ICS+LABA.

In concluding, routinely acquired healthcare data are a valuable source for determining treatment benefits in a real world setting and complement results from clinical trials. Our results, which are based on data collected from 2660 children, provide evidence that for the whole population LABA treatment in children should be administered as an FDC and not as a separate inhaler.

Competing interests

MT. Neither MT nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years he has received speaker's honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Inglehiem, GSK, MSD, Teva. He has received honoraria for attending advisory panels with; Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Novartis. He has received sponsorship to attend international scientific meetings from: GSK, Astra Zeneca, Mundipharma. He has received funding for research projects from: GSK, Almirall. He is chief medical adviser to the charity Asthma UK, a member of the BTS SIGN Asthma guideline group and the NICE Asthma guideline group.

DP. Board Membership: Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva. Consultancy: Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva. Grants/Grants Pending: UK National Health Service, British Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, and Zentiva. Payments for lectures/speaking: Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyePharma, Takeda, and Teva. Payment for manuscript preparation: Mundipharma and Teva. Patents (planned, pending or issued): AKL Ltd

Payment for the development of educational materials: GSK, Novartis. Stock/Stock options: Shares in AKL Ltd which produces phytopharmaceuticals and owns 80% of Research in Real Life Ltd and its subsidiary social enterprise Optimum Patient Care. Payment for travel/accommodations/meeting expenses: Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva. Funding for patient enrolment or completion of research: Almirall, Chiesi, Teva, and Zentiva. Peer reviewer for grant committees: Medical Research Council

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At the time of the study analyses, AB and KR were employees of RiRL, which has conducted paid research in respiratory disease on behalf of the following organizations in the past 5 years: Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva.

ST and CM have no conflicts of interest to declare.

Contributorship

ST, CM, MT and DP conceived the idea for the analysis. KR and AB analyzed the data. EVH and ST wrote the first draft of the paper. All authors made contributions to the final paper.

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551

552 **Table 1** Definitions of database-derived study secondary outcomes. Definitions of oral
553 corticosteroid use and respiratory consultation are provided in the supplement.

Study endpoints	
Primary endpoint	
Overall asthma control. All of the following: no asthma-related hospital admission; no emergency room or outpatient attendance for asthma; no prescription for OCS or antibiotic with evidence of respiratory consultation; average daily prescribed dose of ≤200 µg/day salbutamol or ≤500 µg/day terbutaline (equivalent to ≤2 puffs daily of reliever medication).	
Secondary endpoints *(determined over 12 months)*	
Acute respiratory events	
Acute course of oral corticosteroids (with associated evidence of a respiratory consultation) or asthma-related hospitalization or emergency room attendance or antibiotic prescription with evidence of a respiratory consultation.	
Rate of severe exacerbations*	
Acute course of oral corticosteroids (with associated evidence of a respiratory consultation) or asthma-related hospitalization or emergency room attendance	
Risk-domain asthma control:	
No asthma-related hospital admission, emergency room attendance, or outpatient department attendance, ***and*** no prescription for acute course of oral corticosteroids with evidence of a respiratory consultation, ***and*** no antibiotic prescription with evidence of a respiratory consultation.	
Treatment stability:	

Risk-domain asthma control achieved (see above) ***and*** no additional therapy during the outcome year as either

a.

554

555 **Table 2 Baseline characteristics of children prescribed add-on LABA as FDC ICS/LABA inhaler or separate ICS+LABA inhalers:**

556 **matched cohorts**

Characteristic		**FDC ICS/LABA (n=1330)**	**Separate ICS + LABA (n=1330)**	**p Value for difference between cohorts**
Male sex, n (%)		780 (58.6)	779 (58.6)	0.97†
Age at index date, mean (SD)		9.4 (2.2)	9.4 (2.2)	n/a†
Weight categories‡	Not obese or overweight (i.e. <91th BMI centile)	571 (42.9)	542 (40.8)	0.11
	Overweight (i.e. 91–97th BMI centile)	118 (8.9)	111 (8.3)	
	Obese (i.e. ≥98th BMI centile)	101 (7.6)	136 (10.2)	
	Missing BMI data	540 (40.6)	541 (40.7)	
Recorded comorbidity, n (%)	Rhinitis diagnosis	295 (22.2)	333 (25.0)	0.083
	Eczema diagnosis	664 (49.9)	658 (49.5)	0.81

Year of index date, median (IQR)		2006 (2004–2008)	2005 (2003–2007)	<0.001
Year since first asthma script, median (IQR)		3 (1–5)	3 (1–6)	0.29
Median (IQR) annualized daily ICS dose, µg/d¶		143 (82–247)	164 (99–274)	0.001
ICS dose prescribed before index date, n (%)	≤150 µg/d	0 (0)	0 (0)	n/a†
	151–250 µg/d	248 (18.6)	248 (18.6)	
	251–500 µg/d	1000 (75.2)	1000 (75.2)	
	>500 µg/d	82 (6.2)	82 (6.2)	
Median ICS (IQR) ICS dose at index date (µg/d)		400 [400,400]	400 [400, 400]	n/a†
Mean daily SABA dose, n (%)¶	0 µg/d	21 (1.6)	21 (1.6)	n/a†
	≤200 µg/d	652 (49.0)	652 (49.0)	

	>200 µg/d	657 (49.4)	657 (49.4)	

†Matching variable.

‡ Cut offs for overweight and obese recommended by the Royal College of Paediatrics and Child Health.[41]

¶The doses of ICS and SABA were averaged over the baseline year using the formula [number of inhalers x doses per inhaler] divided by 365 x strength (in µg). ICS doses were standardized to equivalence with standard-particle beclomethasone; thus, the actual doses of budesonide were used, and doses of extrafine beclomethasone and fluticasone were doubled.

BMI, body mass index; CPRD, Clinical Practice Research Datalink; FDC, fixed-dose combination; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; n/a, not applicable; OPCRD, Optimum Patient Care Database; SD, standard deviation.

565 **Table 3** Study endpoints, and their components, during the baseline and outcome years. Negative binomial logistic regression models which
566 yield adjusted. Unadjusted p values are presented here. Adjusted Odds Ratio and Rate Ratio with p values are presented in figure one.

Characteristic	**Baseline year**			**Outcome year**		
	FDC ICS/LABA (n=1330)	**Separate ICS + LABA (n=1330)**	**p value for difference between groups**	**FDC ICS/LABA (n=1330)**	**Separate ICS + LABA (n=1330)**	**p value for difference between groups during the follow up years relative to baseline year without adjustment**
Achieve overall asthma control	469 (35.3)	464 (34.7)	0.59	543 (43.1)	495(37.2)	0.001
Acute respiratory events, mean (SD)	0.49 (0.84)	0.54 (0.92)	0.084	0.32 (0.71)	0.39 (0.75)	0.011

Acute respiratory events, n (%)	0	883 (66.4)	857 (64.4)		1031 (77.5)	966 (72.6)	0.003
	1	300 (22.6)	316 (23.8)		217 (16.3)	256 (19.2)	
	≥2	147 (11.1)	157 (11.8)	0.21	82 (6.2)	108 (8.1)	
Severe exacerbations, n (%)	0	1157 (87.0)	1157 (87.0)		1237 (93.0)	1205 (90.6)	0.056
	1	136 (10.2)	131 (9.8)		68 (5.1)	98 (7.4)	
	≥2	37 (2.8)	42 (3.2)	0.54†	25 (1.9)	27 (2.0)	
Achieved risk-domain asthma control, n (%)		846(65.1)	820480 (63.9)	0.21	999 (77.4)	973 (72.5)	0.003
Achieved treatment stability, n (%)		n/a	n/a	n/a	842 (65.6)	947 (56.9)	<0.001

†Matching variable. Note: severe exacerbations were matched as 0 or ≥1.

FDC, fixed-dose combination; GP, general practice; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; n/a, not applicable; SABA, short-acting β-agonist.

570 **Table 4** Asthma therapy prescribed during the outcome year

Outcome	FDC ICS/LABA (n=1330)	Separate ICS + LABA (n=1330)	p value for difference between groups
SABA inhalers, median (IQR)	3 (2–6)	4 (2–7)	<0.001
Change in therapy (any time), n (%)	244 (18.3)	326 (24.5)	<0.001
Increase in ICS dose ≥50% (any time)	133 (10.0)	58 (4.4)	<0.001

571 †The doses of ICS and SABA were averaged over the outcome year using the formula
572 [number of inhalers x doses per inhaler] divided by 365 x strength (in µg). SABA doses were
573 converted to puffs using the formula 100 µg = 1 puff. The doses of ICS were standardized to
574 equivalence with standard-particle beclomethasone; thus, the actual doses of budesonide
575 were used, and doses of extrafine beclomethasone and fluticasone were doubled.
576 FDC, fixed-dose combination; ICS, inhaled corticosteroid; IQR, interquartile range; LABA,
577 long-acting β-agonist; LTRA, leukotriene receptor antagonist; n/a, not applicable (comparison
578 not possible because of 0 or low number); SABA, short-acting β_2-agonist.
579

FIGURE LEGEND

Figure 1. Adjusted asthma-related outcome measures comparing matched treatment cohorts during 1 outcome year. adjOR/adjRR, adjusted odds ratio/rate ratio; FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist

*Adjusted for nonsteroidal anti-inflammatory drugs

†Adjusted for baseline acute respiratory events and paracetamol prescription

‡Adjusted for baseline severe exacerbations and number of asthma and non-asthma consultations

§Adjusted for paracetamol prescription

¶Adjusted for data source