Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial

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Summary

Background Evidence for management of asthma comes from closely monitored efficacy trials done in highly selected patient groups. There is a need for randomised trials that are closer to usual clinical practice.

Methods We did an open-label, randomised, controlled, two-arm effectiveness trial at 74 general practice clinics in Salford and South Manchester, UK. Patients aged 18 years or older with a general practitioner's diagnosis of symptomatic asthma and on maintenance inhaler therapy were randomly assigned to initiate treatment with a once-daily inhaled combination of either 100 µg or 200 µg fluticasone furoate with 25 µg vilanterol or optimised usual care and followed up for 12 months. The primary endpoint was the percentage of patients who achieved an asthma control test (ACT) score of 20 or greater or an increase in ACT score from baseline of 3 or greater at 24 weeks (termed responders), in patients with a baseline ACT score less than 20 (the primary effectiveness analysis population). All effectiveness analyses were done according to the intention-to-treat principle. This study is registered with ClinicalTrials.gov, number NCT01706198.

Findings Between Nov 12, 2012, and Dec 16, 2016, 4725 patients were enrolled and 4233 randomly assigned to initiate treatment with fluticasone furoate and vilanterol (n=2114) or usual care (n=2119). 1207 patients (605 assigned to usual care, 602 to fluticasone furoate and vilanterol) had a baseline ACT score greater than or equal to 20 and were thus excluded from the primary effectiveness analysis population. At week 24, the odds of being a responder were higher for patients who initiated treatment with fluticasone furoate and vilanterol than for those on usual care (977 [71%] of 1373 in the fluticasone furoate and vilanterol group *vs* 784 [56%] of 1399 in the usual care group; odds ratio [OR] 2·00 [95% CI 1·70–2·34], p<0·0001). At week 24, the adjusted mean ACT score increased by 4·4 points from baseline in patients initiated with fluticasone furoate and vilanterol, compared with 2·8 points in the usual care group (difference 1·6 [95% CI 1·3–2·0], p<0·0001). This result was consistent for the duration of the study. Pneumonia was uncommon, with no differences between groups; there was no difference in other serious adverse events between the groups.

Interpretation In patients with a general practitioner's diagnosis of symptomatic asthma and on maintenance inhaler therapy, initiation of a once-daily treatment regimen of combined fluticasone furoate and vilanterol improved asthma control without increasing the risk of serious adverse events when compared with optimised usual care.

Funding GlaxoSmithKline.

Introduction

Guidelines for routine management of asthma are mainly based on efficacy randomised controlled trials (RCTs),[1] which usually comprise patients who are selected through strict criteria and closely monitored. These efficacy RCTs are often done for registration purposes, usually excluding patients with a smoking history and comorbidities, and therefore have limited relevance to everyday clinical practice.[2] To counter this limitation, it has been proposed that integrated comparative effectiveness trials are done on more representative patients and in much less restricted environments than those of efficacy RCTs.[3]

The Salford Lung Studies[4] were set up to evaluate the effectiveness and safety of initiating the once-daily inhaled combination of fluticasone furoate and vilanterol compared with continuation of maintenance therapy (usual care) in a large, real-world population of patients with chronic obstructive pulmonary disease (COPD) and asthma in normal care settings. These studies were done in and around Salford, UK, a community mainly served by a single hospital with an established electronic health record (EHR) connecting both primary and secondary care and suitable for both safety monitoring and data collection. This setting permits unobtrusive observation of patients, both for safety monitoring and for effectiveness data collection, as part of routine clinical care. The Salford Lung Study on COPD[5] showed that, compared with continuation of usual care, initiation of the once-daily combination of fluticasone furoate and vilanterol reduced moderate and severe exacerbations. We now report the results of the Salford Lung Study on asthma, which compared the effectiveness of the fluticasone furoate and vilanterol combination versus optimised usual care on asthma control.

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See Online for appendix

Research in context

Evidence before this study

Asthma is a common chronic inflammatory airway disease. Guidelines for routine management of asthma (eg, Global Initiative for Asthma; GINA) are almost entirely based on efficacy randomised controlled trials (RCTs) in highly selected and closely monitored patient populations. However, these efficacy RCTs have limited relevance to everyday clinical practice, and there has been a call for comparative effectiveness studies to be done in more representative patients in routine care settings. We searched PubMed on Aug 23, 2017, for prospective clinical effectiveness studies of interventions to improve asthma control, using the search terms "asthma control" AND "exacerbations" AND "clinical effectiveness study" AND "Adult". We only searched for English-language publications. We identified prospective studies testing educational interventions by pharmacists and nurses, retrospective observational studies of therapeutic interventions, and efficacy RCTs. A Cochrane database systematic review on interventions to improve adherence to inhaled steroids for asthma reported that these interventions had "uncertain and inconsistent impact on clinical outcomes such as quality of life and asthma control", and had "low to moderate confidence in these findings".

Added value of this study

Results of our clinical effectiveness study show that introduction of a combination of fluticasone furoate and vilanterol in the form of a novel, once-daily, dry powder inhaler improved asthma control consistently during 1 year in patients with a general practitioner's diagnosis of asthma managed by their own primary care team.

Implications of all the available evidence

Our trial shows that initiating treatment with a once-daily combination of fluticasone furoate and vilanterol provides better asthma control than usual care in a primary care setting. Prospective clinical effectiveness studies done in routine care settings should influence future clinical guidelines.

Methods

Study design and patients

This study was a prospective, 12-month, open-label, parallel group, randomised trial done at 74 general practice clinics in Salford and South Manchester, UK. Details of the study design and the analysis have been published previously.[6]

Recruitment commenced on Nov 12, 2012, and the last visit was completed on Dec 16, 2016. We recruited patients who were 18 years or older and had a documented diagnosis of symptomatic asthma made by a general practitioner. Patients had to be taking regular maintenance inhaler therapy with inhaled corticosteroids (ICS) alone or in combination with a long-acting β-agonist (LABA). Exclusion criteria were minimal, such as a recent history of life-threatening asthma, a history of COPD, or concomitant life-threatening disease.

Patients were recruited in primary care settings, by the health-care professionals who provided their normal everyday care. All patients provided written informed consent. The study was done in accordance with the International Conference on Harmonisation, Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki 2008. The study was approved by the National Research Ethics Service Committee North West, Greater Manchester South. The protocol and analysis plan are available in the appendix.

Randomisation

At the first study visit, patients were invited to participate by providing written informed consent. At the second visit, within 1–60 days after the first visit, patients were randomly assigned by study staff at the general practitioner sites to either receive the fluticasone furoate and vilanterol combination or to continue their maintenance therapy (usual care). Participants were randomly assigned through a centralised randomisation service with stratification at the second visit according to the asthma control test (ACT) score (≥20, 16 to 19, or ≤15) and the general practitioner's intended asthma maintenance therapy after assessment including the ACT at baseline (ie, whether the GP would choose ICS or ICS/LABA as maintenance therapy in usual care).

Procedures

Participants were allocated to receive one of two treatments: the combination of fluticasone furoate and vilanterol (100 µg fluticasone furoate and 25 µg vilanterol or 200 µg fluticasone furoate and 25 µg vilanterol, according to the general practitioner's assessment) administered once daily as a dry powder through an inhaler or continuation of optimised usual care as determined by the general practitioner after baseline assessment including the ACT.

At the second visit, study staff collected the following baseline assessments: assessment of asthma control with the ACT,[7] information on disease duration, smoking status, concomitant medical history, the Asthma Quality-of-Life Questionnaire (AQLQ),[8,9] the Work Productivity and Activity Impairment Questionnaire (WPAI),[10] the EuroQoL-5 dimensions (EQ-5D)[11] questionnaire, the Medication Adherence Report Scale for Asthma (MARS-A), demographic information, and information on concomitant medications. Study staff trained patients in both treatment groups to follow the correct inhaler techniques. At weeks 12, 24, and 40, patients were contacted via telephone by a study team member who completed the ACT and assessed patients for any serious adverse events or non-serious adverse drug reactions. At 12 months, study staff met the patients to make a final

assessment of outcomes. Thus, patients had no face-to-face contact with the study team between the baseline and 12-month visits.

To preserve the real-world nature of the study, the patients' experience was kept as close to everyday clinical practice care as possible. The study's key investigators were the general practitioners and their teams, who could continuously optimise therapy according to their clinical opinion, and treatments were dispensed by community pharmacies in the usual way at the patient's request. Patients could modify their treatment and remain in the study as well as in the treatment groups to which they had been randomly assigned. Those randomly assigned to the fluticasone furoate and vilanterol group could change to any other asthma medication in addition to or instead of fluticasone furoate and vilanterol, and those on usual care could also do this but were not permitted to initiate fluticasone furoate and vilanterol. All general practitioners and pharmacy staff received ICH-GCP and study training appropriate to their roles.

Outcomes

The primary endpoint was the percentage of patients at week 24 with either an ACT score of 20 or greater or an increase in the ACT score from baseline of 3 or greater (termed responders). This endpoint was analysed in the primary effectiveness analysis population: all patients who had an ACT score less than 20 at the second visit (randomisation). The ACT is a questionnaire consisting of five questions with a 5-point scale for each,[7] which is also validated[12] for use via telephone.[13,14] The minimal clinically relevant difference is 3 points[15] and the cutoff for well-controlled asthma is 20 points or above.[1]

The secondary endpoints have been published in full[6] and are listed in the appendix (p 3). Briefly, these were ACT at weeks 12, 24, 40, and 52, all asthma-related primary and secondary care contacts, mean annual rate of severe exacerbations, (defined as any worsening of respiratory symptoms treated with systemic corticosteroids, antibiotics, or leading to hospital attendance), number of salbutamol inhalers dispensed, time to modification of initial therapy, and percentage of patients who had an increase from baseline of at least 0·5 in total AQLQ score and AQLQ environmental stimuli domain score, both at week 52. All secondary endpoints were analysed on the entire study population (ie, all randomly assigned patients who received a prescription of study medication). ACT data for secondary endpoints are presented for the primary effectiveness analysis population as per the primary endpoint analysis. Except for the ACT, other questionnaires, and demographics, data were collected in real time by use of an integrated primary and secondary care EHR, developed by NorthWest EHealth. Other effectiveness outcomes are listed in the appendix (p 4).

Safety endpoints were serious adverse events of pneumonia (defined by the pneumonia adverse event of special interest group), frequency and type of other serious adverse events, and adverse drug reactions. Adverse events of special interest were defined a priori as groups of events of interest for ICS/LABA. Because of the nature of an effectiveness study, where treatment modification is allowed to some extent, safety data are presented according to the treatment a patient was taking when they had an event. The only exception is analysis of pneumonia, which was based on randomised treatment, as requested by regulators. Safety monitoring was done by continuous real-time monitoring of patients' EHR by use of the linked NorthWest EHealth database system, and by telephone every 3 months. Serious adverse events and adverse drug reactions were continuously monitored by near-real-time data monitoring and a dedicated clinical safety team, and reported by investigators on electronic report forms. Events present at and contributing to death were recorded as fatal; cause of death was not adjudicated.

Statistical analysis

Sample size calculations were based on the primary endpoint (ACT score at 24 weeks). 2906 patients (1453 patients per treatment group) were required for the study to have 90% power to detect a relative improvement of 6% in the ACT score between the fluticasone furoate and vilanterol group and the usual care group, assuming a 50% response rate in the usual care group at 6 months. 4036 patients were required in the total population (randomisation of 2018 patients per treatment group) to have at least 2906 patients in the primary efficacy analysis population, assuming 80% of patients in the total population have an ACT score of less than 20 at baseline and a 10% dropout rate over the first 6-month period. Baseline ACT total scores of randomised patients were monitored during recruitment and additional patients were randomised to ensure a sufficient number of patients fulfilled the criteria for inclusion in the primary effectiveness analysis population. Treatment differences in ACT scores between the two treatment groups were analysed by use of logistic regression adjusting for baseline ACT total score, baseline ACT total score squared, baseline asthma therapy at randomisation (ICS or ICS/LABA), age, and sex. All effectiveness analyses were done according to the intention-to-treat principle. Subgroup analyses, where appropriate, are provided for effectiveness and safety endpoints based on baseline disease characteristics per randomisation stratification. Before the study, we sought advice on study design and analysis as well as the novel safety reporting system by use of the joint EHRs from the National Institute for Health and Care Excellence (NICE) and the Medicines & Healthcare Products Regulatory Agency in the UK. Analyses were done with SAS software, version 9.4 of the SAS system for Unix.

This study is registered with ClinicalTrials.gov, number NCT01706198.

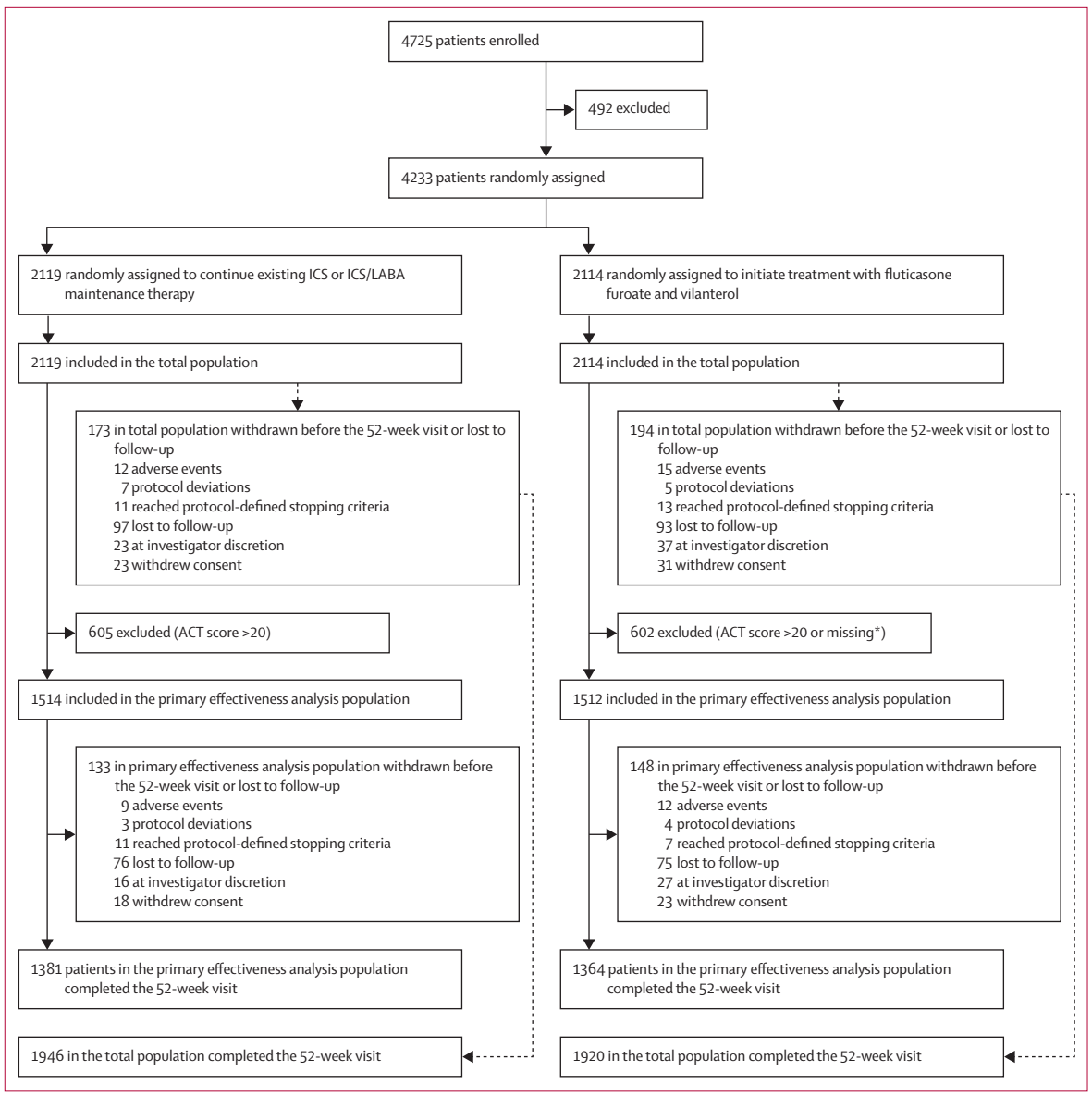

Figure 1: **Trial profile**
The total population includes all randomly assigned patients who received at least one prescription of the study medication. The primary effectiveness analysis population includes all patients in the total population who had an asthma control test (ACT) score of less than 20 at baseline. ICS=inhaled corticosteroids. LABA=long-acting β-agonist. *One patient.

Role of the funding source
The study was designed by the sponsor, GlaxoSmithKline, and the academic partners. The sponsor and NorthWest EHealth collected the data. Statistical analyses were done by a contract research organisation on behalf of, and with oversight from, employees of the sponsor. All authors had full access to the data and vouch for the accuracy and completeness of all data and analyses, and for the fidelity of the study to the protocol. The draft manuscript was written jointly by AW and JV, and all the authors worked collaboratively to prepare the final content and made the decision to submit the manuscript for publication.

Results
Between Nov 12, 2012, and Dec 16, 2016, 4725 patients were enrolled into the study, of whom 4233 were randomly assigned (2114 to initiate treatment with fluticasone furoate and vilanterol, 2119 to usual care) and comprised the total study population (figure 1). Of these, 3026 patients (71%) had an ACT score of less than 20 at baseline and comprised the primary effectiveness analysis population (1512 in the fluticasone furoate and vilanterol group, 1514 in the usual care group). 3866 (91%) patients completed the study (1920 in the fluticasone furoate and vilanterol group, 1946 in the usual care

group). After baseline assessment including the ACT, 156 (7%) of 2119 patients in the usual care group were stepped up from ICS only to ICS/LABA; subsequently, 1357 (64%) of these patients had the ICS/LABA combination as their intended asthma maintenance therapy and 762 (36%) had ICS only. In the fluticasone furoate and vilanterol group, at baseline, 1380 (65%) of 2114 patients were prescribed 100 µg fluticasone furoate plus 25 µg vilanterol once daily and 734 (35%) were prescribed 200 µg fluticasone furoate plus 25 µg vilanterol once daily.

Treatment groups were well matched for age, sex, smoking status, body-mass index, and baseline ACT score (table 1). Patients generally had a long history of asthma (≥5 years), had daytime symptoms, used rescue β-agonists more than twice weekly (1539 [73%] of 2119 in the usual care group, 1505 [71%] of 2114 in the fluticasone furoate and vilanterol group), and had woken at night with asthma in the past week. Around a third of patients had a history of severe exacerbation in the past year. Patients had substantial comorbidities, including hypertension (558 [26%] of 2119 in the usual care group, 540 [26%] of 2114 in the fluticasone furoate and vilanterol group), diabetes, and coronary artery disease (111 [5%] in the usual care group, 110 [5%] in the fluticasone furoate and vilanterol group).

In the fluticasone furoate and vilanterol group, 463 (22%) of 2114 patients modified their study medication; of these, 381 (18%) switched back to usual care. In the usual care group, 376 (18%) of 2119 patients modified their study medication, and three (<1%) switched to fluticasone furoate and vilanterol (even though this was disallowed in the protocol). More patients initiated with fluticasone furoate and vilanterol modified their treatment in the first 12 weeks of the study than did those in the usual care group (appendix p 5).

At week 24, the odds of being a responder (based on ACT score) to initiation of treatment with fluticasone furoate and vilanterol were twice the odds of being a responder with usual care in the primary effectiveness analysis population (analysed on an intention-to-treat basis); the fluticasone furoate and vilanterol group had 977 (71%) responders and 396 (29%) non-responders, whereas the usual care group had 784 (56%) responders and 615 (44%) non-responders (odds ratio [OR] 2·00 [95% CI 1·70–2·34], p<0·0001). This benefit was consistently observed across all subgroups, with no effect of baseline characteristics on the primary effectiveness analysis (appendix p 7). The odds of being a responder, based on ACT score, were similar for the total population at week 24 (analysed as on an intention-to-treat basis); the fluticasone furoate and vilanterol group had 1437 (74%) responders and 499 (26%) non-responders, whereas the usual care group had 1176 (60%) responders and 781 (40%) non-responders (OR 1·97 [95% CI 1·71–2·26], p<0·0001).

	Usual care (n=2119)	Fluticasone furoate and vilanterol (n=2114)
Age, years	50 (17)	50 (16)
Female	1241 (59%)	1257 (59%)
Body-mass index >30 kg/m²	903 (43%)	870 (42%)
Current smokers	429 (20%)	420 (20%)
Asthma control test score at baseline		
≥20	605 (29%)	601 (28%)
16–19	653 (31%)	655 (31%)
<15	861 (41%)	857 (41%)
Duration of asthma ≥5 years	1844 (87%)	1819 (86%)
Daytime symptoms more than twice per week	1926 (91%)	1904 (90%)
Nocturnal symptoms in past week	1053 (50%)	1064 (50%)
Number of exacerbations 12 months before randomisation		
0	1314 (62%)	1378 (65%)
1	501 (24%)	472 (22%)
>1	304 (14%)	264 (12%)
Comorbidities		
Any	812 (38%)	813 (38%)
Cardiac	164 (8%)	182 (9%)
Vascular	559 (26%)	540 (26%)
Diabetes	201 (9%)	205 (10%)

Data are mean (SD) or n (%).

Table 1: **Baseline characteristics of study participants**

In patients for whom the general practitioner indicated ICS as monotherapy for usual therapy, the odds of being a responder were higher for those in the fluticasone furoate and vilanterol group than for those in the usual care group at week 24 (324 [74%] responders and 116 [26%] non-responders, *vs* 259 [57%] responders and 195 [43%] non-responders; OR 2·13 [95% CI 1·60–2·83]). In patients for whom the general practitioner had found an ICS/LABA combination to be indicated for usual therapy, the odds of being a responder were also higher for those in the fluticasone furoate and vilanterol group than for those in the usual care group at week 24 (637 [70%] responders and 271 [30%] non-responders *vs* 511 [56%] responders and 405 [44%] non-responders; OR 1·95 [95% CI 1·60–2·38]).

The difference in responders (based on ACT score) between groups was consistent at 12, 24, 40, and 52 weeks for the primary effectiveness analysis population (figure 2A; appendix pp 7–9), which was independent of the intended treatment at baseline (figure 2B, 2C, appendix pp 7–9). A similar difference was seen for patients who had ACT scores of 20 or greater (appendix pp 7–9). In the primary effectiveness analysis population, the adjusted mean ACT score increased by 4·4 points from a baseline of 14·4 (SD 3·5) in the fluticasone furoate and vilanterol group compared with an increase of

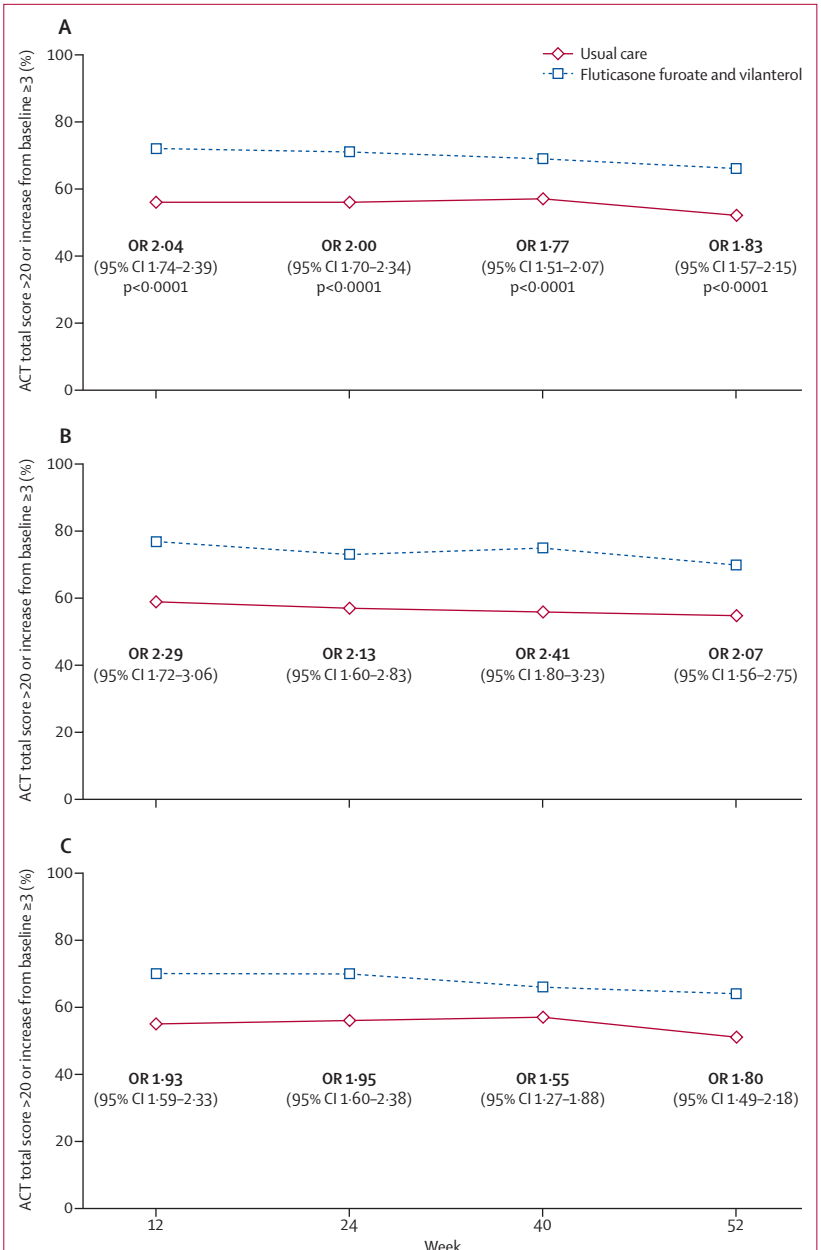

***Figure 2*: Responders according to ACT score during the study, primary effectiveness analysis population**
(A) All patients. (B) Patients for whom inhaled corticosteroids were intended as usual care. (C) patients for whom a combination of inhaled corticosteroids and a long-acting β-agonist was intended as usual care. ACT=asthma control test. OR=odds ratio.

2·8 points from 14·2 (3·5) in the usual care group (difference 1·6 [95% CI 1·3–2·0], p<0·0001) at week 24; similar results were seen at weeks 12, 40, and 52 (appendix pp 7–9).

The number of exacerbations differed according to randomised treatment (1009 exacerbations with fluticasone furoate and vilanterol *vs* 1093 with usual care). Following adjustment for the logarithm of time on treatment and baseline covariates, the adjusted annual exacerbation rate between the fluticasone furoate and vilanterol group and the usual care group did not differ significantly (0·40 *vs* 0·41; percentage reduction 2% [95% CI –9 to 12], p=0·6969). Time to first exacerbation did not differ either (figure 3).

The proportion of patients who were responders based on AQLQ total score was significantly higher in the fluticasone furoate and vilanterol group than in the usual care group at week 52 (increase from baseline of ≥0·5; OR 1·79 [95% CI 1·55–2·06], p<0·0001).

Patients initiated with fluticasone furoate and vilanterol reported a greater decrease in work impairment due to asthma on WPAI than did those continuing with usual care (–6·7% *vs* –4·0%; difference –2·8% [95% CI –4·4 to –1·1], p<0·0001) and a greater decrease in activity impairment due to asthma (–10·4% *vs* –5·9%; difference –4·5% [–5·9 to –3·2], p<0·0001)

There was no difference in the annual rate of asthma-related contacts with primary care in the total population. The annual rate of all primary care contacts in the group initiating fluticasone furoate and vilanterol versus the usual care group increased (9·7% increase [95% CI 4·6–15·0%]); there was no difference in the annual rate of all secondary health-care contacts between the two groups (1·0% decrease [–8·2 to 9·5]). The number of salbutamol inhalers prescribed was lower in the group initiated with fluticasone furoate and vilanterol than in the usual care group (7·2 *vs* 8·0; difference –0·8 [95% –1·1 to –0·5], p<0·0001).

Table 2 shows the distribution of serious adverse events based on the treatment patients were on when the event was reported. The incidence of serious adverse events of pneumonia by the treatment taken at the time (ie, taking treatment modification into account) was low, with the same number of events in both groups (table 2). When pneumonia was analysed according to randomised group, patients in the fluticasone furoate and vilanterol group had a slightly higher incidence of pneumonia than did the usual care group (23 *vs* 16; incidence ratio 1·4; 95% CI 0·8–2·7). There was no difference in the prespecified serious adverse event of special interest, time to first on-treatment pneumonia (hazard ratio 1·45 [95% CI 0·77–2·74], p=0·255).

Discussion

To our knowledge, the Salford Lung Study on asthma is the largest, randomised, comparative effectiveness study done in a population intended to represent that seen in everyday clinical practice. We found that initiation of a simple, once-daily treatment with a combination of fluticasone furoate and vilanterol was superior to usual care (optimised by the patient's general practitioner) in controlling asthma consistently over 12 months, as assessed by the ACT, without significantly increasing the risk of serious adverse events.

The fluticasone furoate and vilanterol combination has previously been shown to have efficacy in improving asthma symptoms and lung function,[16] and in reducing

the rate of asthma exacerbations[17] in conventional efficacy RCTs when compared with fluticasone furoate alone. However, this is the first time the drug combination has shown additional benefits, in terms of asthma control, when compared with optimised usual care in a broad patient population. The primary endpoint, ACT score, was chosen to reflect the effect of the treatments on patients' overall asthma control. The adjusted mean increase of 4·4 points exceeded the minimal clinically relevant difference and is clinically important, and was significantly greater than the increase observed in the usual care group, which also had treatment optimised at baseline by the general practitioner. The improvement in asthma control occurred at week 12 and was maintained for the duration of the study.

During the study design phase, the rate of severe asthma exacerbations was not considered to be a feasible primary endpoint because of the indicated infrequent occurrence of such events in a general asthma population.[6] We found no statistically significant difference in the adjusted annual rate of severe exacerbations in patients initiated with fluticasone furoate and vilanterol compared with those continuing usual care, despite the large improvement in asthma control. This finding contrasts with the results of a closely supervised multicentre efficacy RCT[18] with tight inclusion/exclusion criteria (including a history of exacerbations), which did show differences in time to first exacerbation between different as-needed interventions. There are a number of potential reasons for these observed differences.

First, we used a definition of severe exacerbations that included antibiotics as well as oral steroids, because in routine clinical care many exacerbations are treated with antibiotics (differing from American Thoracic Society/European Respiratory Society [ATS/ERS] Task Force guidelines).[19] These data support our hypothesis on treatment of exacerbations, with 452 (22%) exacerbations being treated with antibiotics alone, 405 (19%) with oral corticosteroids alone, and 1245 (59%) treated with both. In a post-hoc analysis of exacerbations treated with oral corticosteroids either alone or with antibiotics, there were fewer exacerbations with the fluticasone furoate and vilanterol combination than with usual care (775 *vs* 875), but the adjusted annual rate of exacerbations did not differ significantly (0·30 *vs* 0·32; percentage reduction 5% [95% CI –7 to 16], p=0·4206).

Second, in routine care, adherence rates are as low as 20–40%, compared with the 80–90% seen in closely monitored RCTs; therefore, small changes in adherence in routine care could improve daily asthma control without sufficiently improving exacerbation rates. A Cochrane review[20] was unable to identify an obvious impact on clinical outcomes of measures that increased adherence to inhaled corticosteroids.

Third, the significant differences seen in highly selected patients with asthma in such RCTs might be substantially diluted and not relevant to a broader population in routine care. Of the patients in the Salford COPD effectiveness study,[5] only a third would have been eligible for phase 3 RCTs of the same fluticasone furoate and vilanterol combination. Nonetheless, our data suggest that there are other important factors underlying asthma exacerbations in the everyday care setting, which are independent of asthma control and not present in a tightly controlled efficacy trial.

A significant reduction in the rate of exacerbations was seen with fluticasone furoate and vilanterol compared with fluticasone furoate alone in a phase 3 efficacy RCT[21] done for regulatory purposes, although the reduction

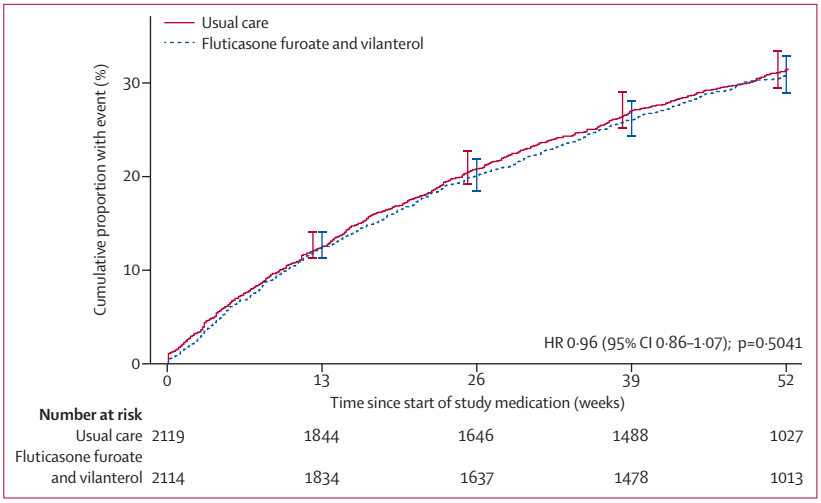

***Figure 3*: Time to first severe exacerbation, total population**
HR=hazard ratio.

	Usual care	Fluticasone furoate and vilanterol
Cardiovascular disease	69 (29·6)	42 (23·3)
Asthma and bronchospasm	40 (17·2)	24 (13·3)
Pneumonia	21 (8·4)	21 (10·7)
Lower respiratory tract infection (excluding pneumonia)	8 (3·4)	7 (3·9)
Decreased bone mineral density and associated fractures	52 (22·3)	35 (19·4)
Effects on glucose	22 (9·4)	18 (10·0)
Hypersensitivity	5 (2·1)	7 (3·9)
Effects on potassium	1 (0·4)	4 (2·2)
Corticosteroid-associated eye disease	7 (3·0)	9 (5·0)
Adrenal suppression	1 (0·4)	0
Local steroid effects	0	1 (0·6)
Tremors	0	0

Data shown for 4751 patients in the total population (according to actual treatment received at the time of event reporting), given as numbers of events with rates per 1000 patient-years in parentheses, including patients in the fluticasone furoate and vilanterol group who had modified their treatment and were receiving usual care at the time of the event.

***Table 2*: On-treatment serious adverse events of special interest**

was modest (~25%). Although the comparator was different, some comparisons can be made with the findings of the Salford asthma study. The phase 3 efficacy RCT was innovative, being powered to completion when a specific number of exacerbations had occurred in the study, and included a highly selected population that was shown to be compliant with event diaries during a run-in period. In the efficacy study, exacerbations defined as requiring steroids as per the ATS/ERS guidelines occurred at about half the frequency of the more broadly defined exacerbations in the Salford asthma study. These differences in the study design and population can clearly have a substantial effect on the outcome. Efficacy RCTs remain important in showing the efficacy and safety of a novel therapy. However, effectiveness studies will be needed to show how these treatments affect routine care.

Results of a randomised trial[22] comparing once-daily fluticasone furoate and vilanterol with twice-daily fluticasone propionate and salmeterol showed no significant differences in efficacy endpoints between treatments. However, such efficacy RCTs have subtle enrolment criteria, making them less able to differentiate potential benefits in routine care. For example, patients might be excluded for poor compliance during run-in, which could eliminate any benefit from a once-daily regimen; this benefit cannot be evaluated since double-dummy inhalers are used in all efficacy trials comparing a once-daily treatment regimen with a twice-daily regimen. Exclusion of patients with poor inhaler technique might eliminate the potential benefit in routine clinical practice from a novel inhaler that is easier to use. The tight supervision of an RCT, with emphasis on adherence and repeated inhaler training, is absent in routine care. By contrast, in the Salford Lung Studies, apart from the baseline and 12-month visits, there were no planned face-to-face visits with the study team. This difference means that subtle benefits from an improved inhaler or a once-daily regimen could occur in an effectiveness study done in a routine care setting.

The strength of this study derives from its innovative design, which aimed to maintain the scientific rigour of randomisation to an intervention versus control group while staying as close as possible to everyday clinical practice, collecting endpoints relevant to patients and health-care professionals. The study was done in a single urban area, with primary and secondary care connected through an EHR to provide integrated real-time recording, enabling collection of a study-relevant dataset for all effectiveness and safety outcomes. After randomisation, each patient was only contacted by telephone on three occasions over 12 months to complete the ACT and a safety check. All management was done by the usual health-care practitioners, with simultaneous monitoring of patients remotely done by use of the EHR for early detection of safety events. Adult patients with asthma in the Salford Lung Studies were typically older and with higher body-mass index than those usually enrolled in efficacy RCTs, with a fifth actively smoking, and a third having comorbidities that would have excluded the majority from many regulatory RCTs.[2] In common with many community surveys, these patients had unstable asthma, with 71% having a baseline ACT score less than 20, over 90% having daytime or nocturnal symptoms, or both, and 36% reporting at least one severe exacerbation in the year before the study.

Implementation of this effectiveness study was complex, involving a large multidisciplinary team and multiple collaborators. It became evident during the study that a high proportion of eligible patients entered the study because patients were approached by their own general practitioners. The study involved 74 general practice clinics, 165 community nurses, and 132 community pharmacies, and 2100 staff in study teams were trained in GCP, device technique, asthma management, and clinical study operations. The electronic patient record required significant development and validation of its outputs to provide daily safety reporting from primary care and hospital, and to provide the dataset for the overall effectiveness and safety outcomes.

Perceived weaknesses of this study might relate to the open-label design in routine care in the absence of regular face-to-face monitoring, and the consequent potential for bias. A comparative effectiveness study such as ours certainly requires careful interpretation, and in this context these features could also be seen as strengths. We did consider randomisation by practice, but believe that this would have made interpretation difficult, with additional differences because of training and education between practices. We randomised by patient, but because the study was open label this approach could potentially have introduced bias, even though all efforts were made to make the treatment experience similar for all patients by similar initial inhaler training, general practitioner prescription and collection at the usual pharmacy, and so on. Any bias might be enhanced by choosing a soft primary outcome, the ACT score, whereby patients can indicate improvement merely as a result of being switched to a novel treatment. However, the fact that the benefit was present for the entire 52-week duration of the study indicates that this was not the case.

The unblinded nature of this study is the likely reason for the large degree of modification of treatment during the first 3 months in the fluticasone furoate and vilanterol group. This modification was not due to loss of asthma control but mainly due to patients choosing to return to a long-standing treatment. Asymmetric treatment modification necessitated a new approach to analysis and interpretation of safety data, not merely based on randomisation, as done in efficacy trials where patients are maintained on their randomised medication. We have chosen to report adverse events according to treatment actually taken at the time, and therefore according to exposed risk, something we anticipate will become standard in future effectiveness RCTs.

In conclusion, patients in general practice with a diagnosis of symptomatic asthma had improved asthma control from the introduction of a simple, once-daily combination treatment of fluticasone furoate and vilanterol without having any additional risk of serious adverse events. Future effectiveness studies such as ours could influence clinical guidelines, not only for asthma and COPD but also for many other chronic diseases.

Contributors

AW and JV wrote the draft report. All authors discussed the draft and provided comments and suggestions for change. All authors have approved the final report.

Declaration of interests

AW reports personal fees from Chiesi Pharmaceuticals, GlaxoSmithKline, and Zambon outside of the submitted work. JV reports personal fees from GlaxoSmithKline during the conduct of the study, as well as personal fees from GlaxoSmithKline, Chiesi Pharmaceuticals, Boehringer Ingelheim, Novartis, and AstraZeneca outside of the submitted work. NDB has received personal fees from GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, and Novartis outside of the submitted work. JN reports grants and personal fees from GlaxoSmithKline during the conduct of the study, as well as grants from GlaxoSmithKline outside of the submitted work. JMG reports grants from GlaxoSmithKline during the conduct of the study. SM reports personal fees from GlaxoSmithKline during the conduct of the study. RJ reports personal fees and non-financial support from GlaxoSmithKline during the conduct of the study, as well as grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi Pharmaceuticals, Cipla, GlaxoSmithKline, Novartis, and Pfizer outside of the submitted work. SC, JL-F, LF, LJ, JLF, CH, HS, and DL are all employees of GlaxoSmithKline and therefore report personal fees from GlaxoSmithKline during the conduct of the study, as well as outside of the submitted work.

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