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

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Effectiveness of Fluticasone Furoate/Vilanterol in Asthma in clinical practice

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Abstract

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

Methods. In a randomised, controlled 2-arm effectiveness trial, 4233 patients with a general practitioner's diagnosis of symptomatic asthma on maintenance inhaler therapy were initiated on a once-daily inhaled combination of either 100 μg or 200 μg fluticasone furoate with 25 μg vilanterol (FF/VI) or optimized usual care (UC) and studied for 12 months. The primary endpoint was the percentage of patients who achieved an Asthma Control Test (ACT) Score of ≥20, or an increase in ACT from baseline of ≥3 at 24 weeks ("responder"), in patients with a baseline ACT <20 (primary effectiveness analysis population). Secondary endpoints included ACT at Weeks 12, 24, 40 and 52, the annual rate of severe exacerbations, and number of primary and secondary care contacts, for all randomised patients (independent of baseline ACT).

Findings. The odds of being a responder for subjects who initiated treatment with FF/VI were twice the odds of being a responder on UC (977 / 1373 (71%) responders in FF/VI group compared to 784 / 1399 (56%) in UC, OR 2·00 (1·71, 2·34) p<0·0001). Patients initiated with FF/VI improved ACT from baseline by 4·4 points compared to 2·8 in the UC group. This was consistent across the duration of the study. There was no significant difference in asthma exacerbations, or in asthma-related primary or secondary care contacts. Pneumonia was uncommon, with no differences between groups; there was no difference in other serious adverse events.

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

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The study is registered on clinicaltrials.gov as NCT01706198.

300 words

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Research in Context

Guidelines for the routine management of asthma (e.g. Global Initiative for Asthma, GINA) are almost entirely based on efficacy RCTs in highly selected and closely monitored patient populations. However these efficacy RCTs have limited relevance to everyday clinical practice, and so there has been a call for comparative effectiveness studies in more representative patients, carried out in routine care.

The Salford Lung Study on Asthma is an RCT of the clinical effectiveness of introducing the combination of Fluticasone Furoate and Vilanterol in a novel once daily dry powder inhaler, compared to usual care. The study include a broad patient population with few exclusions, managed by their own primary care team. Safety monitoring and outcome data were provided through remote monitoring with an electronic patient record.

The study showed that in these patients with a general practitioners diagnosis of asthma, FF/VI consistently improved asthma control over one year, without risk of serious events compared to usual care. In future, clinical effectiveness studies such as the Salford Studies should have a major influence for all clinical guidelines

Introduction

Guidelines for the routine management of asthma are mainly based on a large number of efficacy randomised controlled trials (RCTs) (1), usually including patients selected through strict criteria and closely monitored. These efficacy RCTs are often done for registration purposes, usually exclude patients with a smoking history as well as comorbidities and therefore have limited relevance to everyday clinical practice (2). To counter this, it has been proposed that integrated comparative effectiveness trials are carried out on more representative patients, and in much less restricted environments (3).

The Salford Lung Studies (SLS) (4) were set up to evaluate the effectiveness and safety of initiating the once-daily inhaled combination of fluticasone furoate and vilanterol (FF/VI) compared with continuing maintenance therapy (usual care) in a large, real-world population of COPD and asthma patients in conditions of normal care. The studies were conducted 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 permits the unobtrusive observation of patients, both for safety monitoring and effectiveness data collection, blended into routine clinical care. The SLS on COPD showed that initiating the combination of FF/VI given once daily reduced moderate/severe exacerbations when compared to continuing usual care (5). We now report the SLS on asthma, comparing the effectiveness of the FF/VI combination with optimised usual care (UC) on asthma control.

Methods

Details of the study design and the analysis have been published previously (6).

Patients

Recruitment commenced on 12 Nov 2012, and last visit was completed on 16 Dec 2016. We recruited patients who were 18 years or older, and had a documented diagnosis of symptomatic asthma made by a general practitioner (GP). Patients had to be taking regular maintenance inhaler therapy with inhaled corticosteroids (ICS) alone or in combination with a long-acting beta-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, by the healthcare professionals who provided their normal everyday care. All patients provided written informed consent. The study was conducted in accordance with the International Conference on Harmonisation, Good Clinical Practice (GCP) and the Declaration of Helsinki 2008. The study was approved by the National Research Ethics Service Committee North West, Greater Manchester South. The study is registered on clinicaltrials.gov (NCT01706198). Protocol and analysis plan are available in the supplementary appendix.

Study Design

This was a prospective, 12-month, open-label, parallel group, randomised trial conducted in 74 general practices in Salford and South Manchester, UK. At the first study visit, patients were offered study participation through written informed consent. Within 1–60 days after visit 1, patients were randomised to either FF/VI or to continue their maintenance therapy (Usual Care, UC). At this Visit 2, study staff collected baseline assessments, including assessment of asthma control with the Asthma Control Test (ACT)(7), information on disease duration, smoking status, concomitant medical history, and the Asthma Quality-of-Life

Questionnaire (AQLQ)(8,9), the Work Productivity and Activity Impairment Questionnaire (WPAI)(10) and the EuroQoL-5 dimensions (EQ-5D)(11) questionnaires. Participants were randomly assigned through a centralised randomisation service with stratification at this visit according to ACT score (≥20, 16 to 19, or ≤15) and the general practitioner's (GP's) intended asthma maintenance therapy after assessment including ACT at baseline; i.e., whether the GP would choose ICS or ICS/LABA as maintenance therapy in UC. Participants were allocated to one of two treatments, the combination of FF/VI (100/25 μg or 200/25 μg according to GP assessment; Relvar®/Breo®, GlaxoSmithKline) administered once daily as a dry powder through an inhaler (Ellipta®, GlaxoSmithKline) or continuation of optimised UC as determined by the GP after baseline assessment including ACT.

Study staff trained patients in both treatment groups in the correct inhaler techniques. At weeks 12, 24, and 40, the patients were contacted by telephone by a study team member who completed the ACT, and assessed any serious adverse events (SAEs) or non-serious adverse drug reactions (ADRs). 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 baseline and 12 months visits.

To preserve the real-world nature of the study, the patient experience was kept as close to everyday clinical practice care as possible. The study's key investigators were the GPs 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 arms to which they had been randomised. Those randomised to FF/VI could change to any other asthma medication, and those on usual care could also do this but were not permitted to initiate FF/VI. All GP and pharmacy staff received ICH-GCP and study training as appropriate to their roles.

Outcome Measurements

The primary endpoint was the percentage of subjects at Week 24 with either an ACT score of ≥20, or an increase from baseline of ≥3 ("responder"), analysed in all patients who had an ACT score <20 at visit 2 (randomisation), the primary effectiveness analysis (PEA) population. The ACT is a questionnaire consisting of 5 questions with a 5-point scale for each (7), which is validated (12), also for use over the telephone (13, 14). The minimal clinically relevant difference (MCD) is 3 points (15) and the cut-off point for well-controlled asthma is 20 or above (1).

The secondary endpoints were previously published in full (6) and detailed in the Supplementary Appendix. Briefly, these included 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, percentage of patients that had an increase from baseline of at least 0.5 in AQLQ(s) total score and AQLQ(s) environmental stimuli domain score. All secondary endpoints were analysed on the entire study population; i.e., all randomised patients who received a prescription of study medication. ACT data for secondary endpoints is presented for the PEA population as per the primary endpoint analysis. Except for the ACT, other questionnaires and demographics, data were collected in real-time using an integrated primary and secondary care EHR, developed by NorthWest EHealth (NWEH).

Other effectiveness outcomes are listed in the Supplementary Appendix.

Safety Evaluation

Safety endpoints included SAEs of pneumonia (defined by the pneumonia adverse event of special interest [AESI] group), frequency and type of other SAEs, and ADRs. AESIs 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 to some extent allowed, safety data are presented according to the treatment a patient was taking when experiencing an event. The only exception is an analysis of pneumonia based on randomised treatment, as requested by regulators. Safety monitoring was performed by continuous real-time monitoring of the patients' EHR using the linked NWEH database system, and by telephone every 3 months. SAEs and ADRs 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). A total of 2906 patients (1453 patients per treatment group) were required for the study to have 90% power to detect a relative improvement of 6% in ACT score between FF/VI and UC, assuming a 50% response rate in the UC group at 6 months. A total of 4036 patients were required in the total population (randomisation of 2018 patients per treatment group) in order 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 <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 (4233 in total) to ensure a sufficient number of patients satisfied their criteria for inclusion in the PEA population. Treatment differences in ACT between the two treatment arms were analysed

using logistic regression adjusting for baseline ACT total score, baseline ACT total score squared, baseline asthma therapy at randomisation (ICS or ICS/LABA), age and gender. All effectiveness analyses were intent-to-treat (ITT); more details are provided in the Supplementary Appendix. Subgroup analyses, when appropriate, are provided for effectiveness and safety endpoints based on baseline disease characteristics per randomisation stratification.Prior to the study, we sought advice from the National Institute for Health and Care Excellence, and the Medicines and Healthcare Products Regulatory Agency in the UK. The study was designed by the sponsor and the academic partners. The sponsor and NWEH collected the data. Statistical analyses were performed 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

Study Population

4725 subjects were enrolled into the study of which 4233 were randomised (FF/VI 2114, usual care 2119) and form the total study population (Fig 1). Of these, 3026 subjects (71%) had an ACT score of < 20 at baseline and formed the Primary Effectiveness Analysis (PEA) population (FF/VI 1512, usual care 1514). 3866 patients (91%) completed the study (FF/VI 1920, UC 1946). After baseline assessment including ACT, 156 patients (7%) in the UC group were stepped up from ICS only to ICS/LABA; subsequently, 1357 (64%) of subjects had ICS/LABA combination as their intended asthma maintenance therapy, and 762 (36%) ICS only. In the FF/VI group, 1380 (65%) were prescribed 100/25 μg once daily and 734 (35%) 200/25 μg at baseline.

The treatment groups were well matched for age (mean 49·8 years), gender (2498 (59%) female), smoking status (849 / 4203 (20%) current smokers), BMI (1773 / 4152 (43%) >30 kg/m^2) and baseline ACT score (≥20 1206 (28%); 16-19 1308 (31%); ≤15 1718 (41%)) (Table 1). Patients generally had a long history of asthma (3663 (87%) ≥5 years), had daytime symptoms (3830 (90%) more than twice weekly), used rescue beta-agonists frequently (3044 (72%) > twice weekly), and woke at night with asthma (2117 (50%) in the past week). Around one third of patients had a history of severe exacerbation in the last year (973 (23%) one, and 568 (13%) > one exacerbation). Subjects had significant co-morbidities (1625 (38%)), including hypertension (1098 (26%)), diabetes (406 (10%)), and coronary artery disease (221 (5%)).

In the FF/VI group, 463 patients (22%) modified their study medication, and of these 381 (18%) switched back to UC. In the UC group, 376 patients (18%) modified their study medication, and 3 subjects (<1%) switched to FF/VI (even though this was disallowed under

the protocol). More patients initiated with FF/VI modified their treatment in the first 12 weeks of the study compared to the usual care group (Table S1 and Fig S1~~2~~ Supplementary Appendix).

Primary outcome

At Week 24, the odds of being a responder on ACT score to initiation of treatment with FF/VI were twice those of UC in the PEA population (analysed as ITT); FF/VI: 977 (71%) responder/396 (29%) non-responder compared to 784 (56%) responder/615 (44%) non-responder, OR 2·00 (95% confidence interval (CI) 1·71 to 2·34) p<0·0001. The benefit was consistent across all subgroups with no impact of baseline characteristics for the PEA (Fig S2~~3~~ Supplementary Appendix). The odds of being a responder were similar for the total population (analysed as ITT); FF/VI 1437 (74%)/499 (26%) compared to 1176 (60%)/781 (40%), OR 1·97 (95% CI 1·71 to 2·26) p<0·0001 at Week 24.

When analysing those patients where the GP had found ICS as monotherapy to be indicated for usual therapy, the odds of being a responder was 324 (74%)/116 (26%) for FF/VI compared to 259 (57%)/195 (43%) for UC, OR 2·13 (95% CI 1·60 to 2·83) at Week 24. In patients where the GP had found an ICS/LABA combination to be indicated for usual therapy, the odds of being a responder was 637 (70%)/271 (30%) for FF/VI compared to 511 (56%)/405 (44%) for UC, OR 1·95 (95% CI 1·60 to 2·38) at Week 24.

Secondary Outcomes

There was a consistent difference in ACT responders between groups at 12, 24, 40, and 52 weeks for the PEA population (Fig 2a, Table S2a, Supplementary Appendix), which was independent of baseline intended treatment (Fig 2b, c and Table S2b, Supplementary

Appendix). A similar difference was seen for subjects who reached ACT scores of 20 or greater (Table S2a, Supplementary Appendix). In the PEA population, adjusted mean ACT score increased 4·4 points from a baseline of 14·4 (SD 3·5) in the FF/VI group compared to an increase of 2·8 from 14·2 (SD 3·5) in the usual care group, difference 1·6 (95% CI 1·3 to 2·0), p<0·0001) at Week 24; similar results were seen at weeks 12, 40 and 52 (Supplementary Appendix Table S3).

There was a numerical difference in exacerbations according to randomized treatment with FF/VI vs UC (1009 vs 1093). However, following adjustment for logarithm of time on treatment and baseline covariates, there was no statistically significant difference in the adjusted annual exacerbation rate between the FF/VI group vs the UC group (0·40 vs 0·41); percent reduction 2% (95% CI -9 to 12%), p=0·6969). Time to first exacerbation did not differ either *(*Fig 3).

There was a significant difference in the proportion of patients in FF/VI group vs UC who were responders on AQLQ total score (increase from baseline of ≥ 0·5; OR 1·79 (95% CI 1·55-2·06); p <0·0001).

Patients initiated with FF/VI reported a greater decrease in work impairment on WPAI compared to those continuing with UC (-6·7% vs. -4·0%, difference -2·8% (CI – 4·4 to -1·1), p<0·0001) and a greater decrease in activity impairment (-10·4% vs. -5·9%, difference -4·5% (CI -5·9 to -3·2) p<0·0001)

There was no difference in annual rate of asthma-related contacts with primary care in the total population. There was an increase in the annual rate of all primary care contacts in the group initiating FF/VI versus UC (per cent increase 9·7% (95% CI 4·6% to 15·0%)); there were no differences in all secondary healthcare contacts (per cent increase 1·0% (95% CI -

8·2 to 9.5). The number of salbutamol inhalers prescribed was lower in the group initiated with FF/VI than UC (7·2 vs. 8·0, respectively; difference -0·8 (95% -1·1 to -0·5); p<0·0001).

Safety

Table 2 shows the distribution of serious adverse events based on the treatment patients were on when the event was reported. The incidence of SAE of pneumonia by the treatment taken at the time (i.e. taking treatment modification into account) was low, with the same number of events on FF/VI and usual care (Table 2). When analysing pneumonia according to randomised group, patients in the FF/VI group had a slightly higher numerical incidence of pneumonias compared to the UC group (23 vs 16; incidence ratio 1·4; 95% CI 0·8 to 2·7). There was no difference in the pre-specified SAE of special interest, time to first on-treatment pneumonia (hazard ratio 1·45 (95% CI 0·77 to 2·74) p=0·255).

Discussion

The Salford Lung Study on asthma is the largest, randomised, comparative effectiveness study 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 GP) on asthma control consistently over 12 months, as assessed by the ACT, without significantly increasing risk of SAEs.

The FF/VI combination has previously been shown to have efficacy in improving symptoms and lung function (16), and reducing the rate of exacerbations (17) in asthma in conventional efficacy RCTs when compared to FF alone. However, this is the first time that the drug has shown additional benefits versus optimised usual care in a broad patient population in terms

of asthma control. The primary endpoint, ACT, was chosen to reflect impact of treatments on patients' overall asthma control. The adjusted mean increase of 4·4 points exceeded the MCD and is clinically important, and was significantly greater than the increase in the UC group who also had their treatment optimised at baseline by the GP. The improvement in asthma control was present from week 12 throughout the study.

During the study design phase, the rate of severe asthma exacerbations was not considered a feasible primary endpoint due to 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 FF/VI compared to continuing usual care, despite the large improvement in asthma control. This contrasts with an example of a closely supervised multi-centre 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. 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 ATS/ERS Task Force guidelines (19)). Our prediction proved correct, with 452 (22%) of 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 was a numerical difference in favour of FF/VI (775 vs 875), but there was no statistically significant difference in the adjusted annual rate of exacerbations (0·30 vs 0·32, FF/VI vs UC; percent reduction 5% (95% CI -7% to 16%), p=0·4206. Second, in routine care, adherence rates are as low as 20-40%, compared to the 80-90% seen in closely monitored RCTs, and it may be that small changes in adherence in routine care could improve daily asthma control, without having sufficient impact to improve exacerbations. Third, the

significant differences seen in highly selected asthma patients may be substantially diluted and not relevant to a broader population in routine care. Of the patients in the Salford COPD effectiveness study, only one third would have been eligible for the Phase 3 RCTs for the same FF/VI combination. In any event, our data suggest that there are other important factors underlying asthma exacerbations in the setting of everyday care, which are independent of asthma control and not present in a tightly controlled efficacy trial.

A significant reduction in exacerbations had been seen with FF/VI was compared to FF alone in a Phase 3 efficacy RCT carried out for regulatory purposes, although the reduction was modest (~25%) (20). It is interesting to compare with the Salford study, not forgetting that the comparator was different. The Efficacy RCT was innovative, in being powered to completion when a specific number of exacerbations had occurred in the study, and included a highly selected population who were 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 study. These differences in design and population can clearly make substantial differences to the outcome. Efficacy RCTs remain important in showing efficacy and safety of a novel therapy. However, effectiveness studies will be needed to show how they impact routine care.

A comparison of FF/VI once daily with fluticasone propionate/salmeterol twice daily showed no significant differences in efficacy endpoints between treatments (21). But efficacy RCTs like this have subtle enrolment criteria, which make them less able to differentiate potential benefits in routine care. For example, patients may be excluded for poor compliance during run-in, which may eliminate any benefit from a once daily regimen – which cannot be evaluated as double-dummy inhalers are used in all efficacy trials comparing a once-daily with a twice-daily treatment regimen. Exclusion of patients with poor inhaler technique,

might eliminate the potential benefit in routine clinical practice from a novel inhaler which is either easier to use. The tight supervision of an RCT with encouragement to adherence and repeated inhaler training, is absent in routine care. In contrast, in SLS, apart from the baseline and 12 month visits, there were no planned face-to-face study visits with the study team. This means that subtle benefits from improved inhaler or a once daily regimen may come into play in an effectiveness study set in routine care.

The strength of the study derives from its innovative design, which aimed to maintain scientific rigour of randomisation to an intervention versus control arm, but at the same time stay as close as possible to everyday clinical practice, collecting endpoints relevant to patients and healthcare decision-makers. It took place in a single urban area, with primary and secondary care connected through an EHR developed by NWEH to provide integrated real-time recording, enabling collection of a study-relevant dataset for all the effectiveness and safety outcomes. After randomization, the patient was only contacted by phone on three occasions over 12 months to complete the ACT and a safety check. All management was carried out by the usual carers, with simultaneous monitoring of patients remotely using the EHR for early detection of safety events. The adult asthma patients in SLS were typically older and heavier, with one fifth actively smoking, and one third having co-morbidities that would have excluded the majority from many regulatory RCTs (2). In common with many community surveys, they had unstable asthma, with 71% having a baseline ACT <20, over 90% having daytime and /or night symptoms, and 36% at least one severe exacerbation in the year prior to the study.

The implementation of this effectiveness study was complex and expensive, involving a large multidisciplinary team and multiple collaborations. It became evident that a high proportion of eligible patients entered the study because patients were approached by their own General Practitioners. The study involved 74 General Practices, 165 community nurses, and 132

community pharmacies, and 2100 staff were trained in study teams were trained in GCP, device technique, asthma management, spirometry, and clinical study operations. The EPR required significant development and validation of its outputs, in order to provide daily safety reporting from primary care and hospital, as well as provide the data set for the overall effectiveness and safety outcomes.

The perceived weakness of the study generally relates to the open label design in routine care in the absence of regular face-to-face monitoring, and consequent potential for bias. Certainly, a comparative effectiveness study like ours 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 due to training and education between practices. We randomised by patient, but because the study was open label, this could potentially have introduced bias, even though all efforts were taken to make the treatment experience similar for all patients by similar initial inhaler training, GP prescription and collection at the usual pharmacy, etc. Any bias may be enhanced by choosing a "soft" primary outcome, the ACT score, where patients may 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 weeks duration of the study indicates that this was not the case.

The un-blinded nature of the study is the likely reason for the larger degree of modifying of treatment over the first 3 months of the study in the FF/VI group. It 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 analysing and interpreting safety data, not merely based on randomisation, as 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 gained improved asthma control from the introduction of a simple once-daily combination treatment of fluticasone furoate and vilanterol without additional risk of serious adverse events. Future effectiveness studies such as ours, should influence clinical guidelines, not only for asthma and COPD but for many chronic diseases.

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525 **Table 1**

526 Baseline characteristics of study participants.

527

		Entire study population; N=4233	
		Usual care; N=2119	**FF/VI; N=2114**
Age (years; mean (SD))		50±17	50±16.
Female Sex		1241 (59%)	1257(59%)
Body Mass Index (kg/m^2) >30		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 ≥5years		1844 (87%)	1819 (86%)
Daytime Symptoms> 2 x per week		1926 (91%)	1904 (90%)
Nocturnal symptoms in last week		1053 (50%)	1064 (50%)
No. of exacerbations; 12 months prior to randomisation			
0		1314 (62%)	2692 (65%)
1		501 (24%)	973 (22%)
>1		304 (14%)	568 (12%)
Co-morbidities	Any	812 (38%)	813 (38%)

		Entire study population; N=4233	
		Usual care; N=2119	**FF/VI; N=2114**
	Cardiac	164 (8%)	182 (9%)
	Vascular	559 (26%)	540 (26%)
	Diabetes	201 (9%)	205 (10%)

528

529 Mean±standard deviation or n (%)

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531

Table 2

On treatment serious adverse events of special interest (AESI) among 4,751 patients in the total population, given as numbers with rates per 1000 subject-years in brackets *.

AESI group	**Actual treatment* Usual care**	**Actual treatment* FF/VI**
Cardiovascular disease	69 (29·6)	42 (23·3)
Asthma / 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)
Tremor	0	0

537 * includes subjects in FF/VI randomisation arm who had modified their treatment and were
538 receiving usual care at the time of the event
539 FF/VI Fluticacone furoate vilanterol combination
540

Figure legends

Figure 1

CONSORT diagram of patient flow through SLS asthma.

Figure 2

Responders according to Asthma Control Test score over the duration of the study, primary effectiveness analysis population (PEA). Figure 2A shows all subjects; Figure 2B shows those where inhaled corticosteroids was intended as usual care and Figure 2C shows those patients where a combination of inhaled corticosteroids and a long-acting beta-agonist was intended as usual care.

FF/VI fluticasone furoate/vilanterol, OR odds ratio, CI confidence interval

* Defined as Asthma Control Test score > 20 or an increase from baseline of at least 3.

Figure 3

Time to first severe exacerbation, total population

560
561 **Figure 1**
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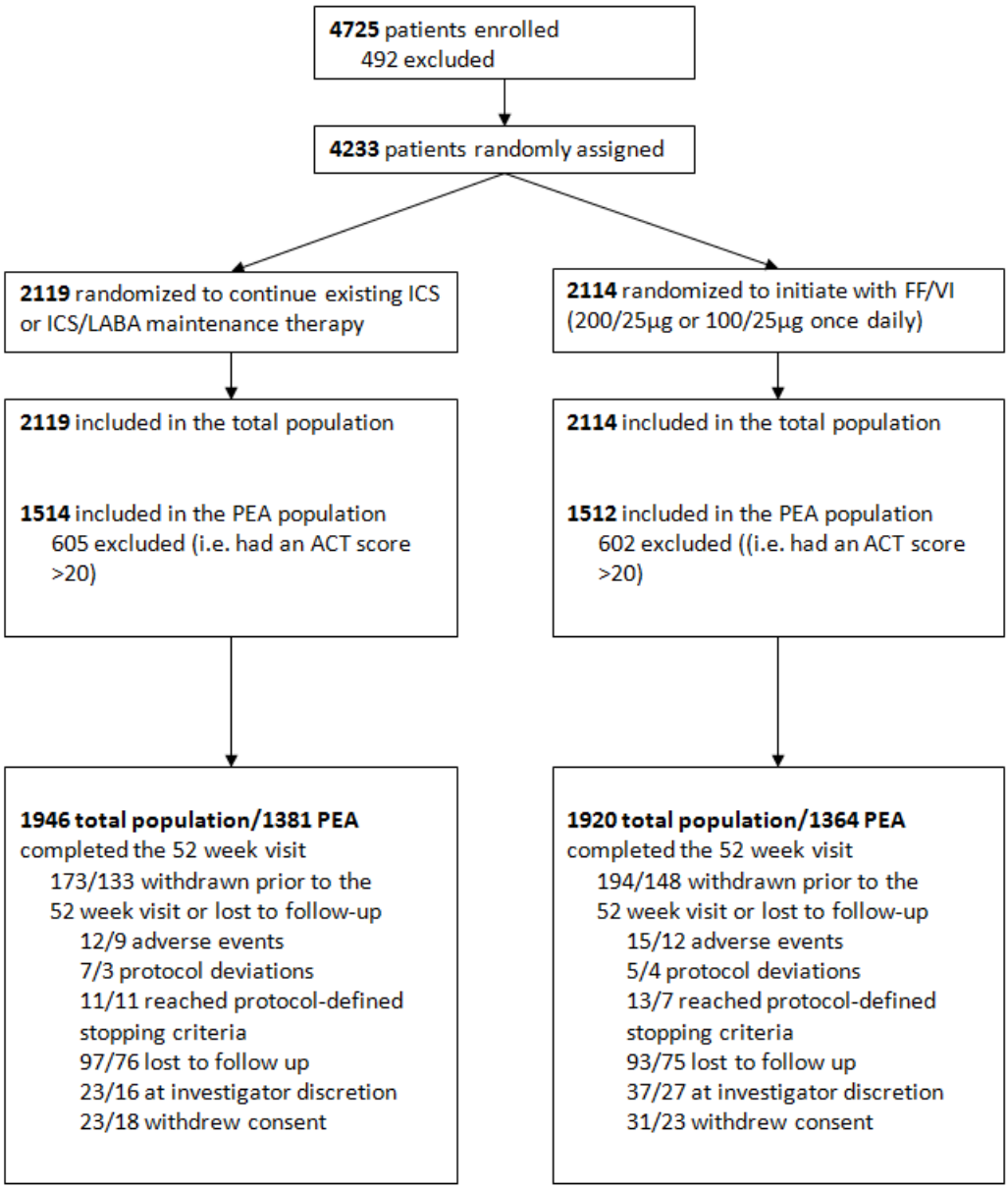
Figure. Patient flow through the SLS study



Total population: includes all randomized patients who received at least one prescription of study medication
PEA population: all patients in the total population who had an ACT score <20 at baseline

FF, fluticasone furoate; PEA, primary efficacy analysis; VI, vilanterol

563

564 **Figure 2**
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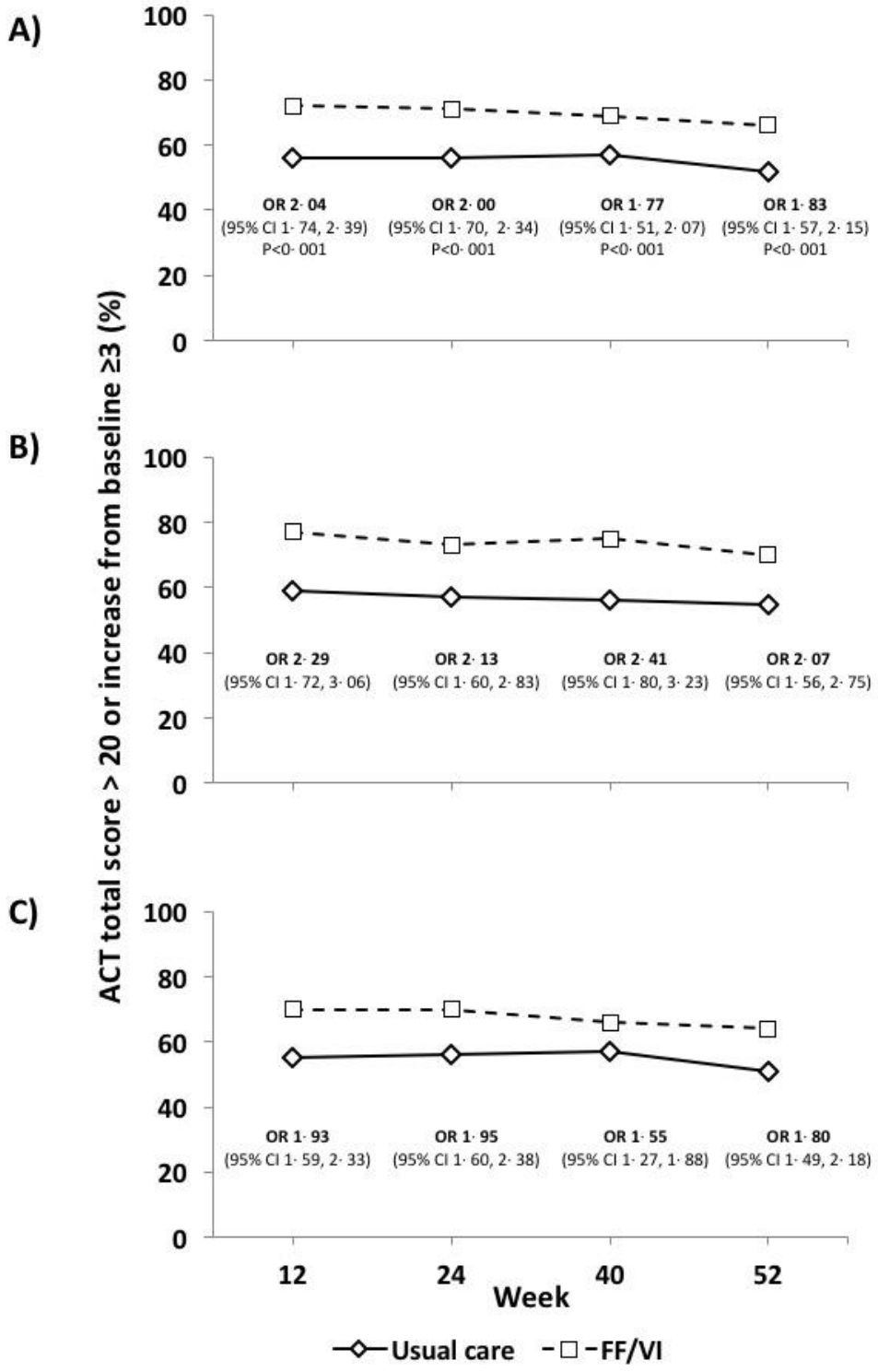

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568
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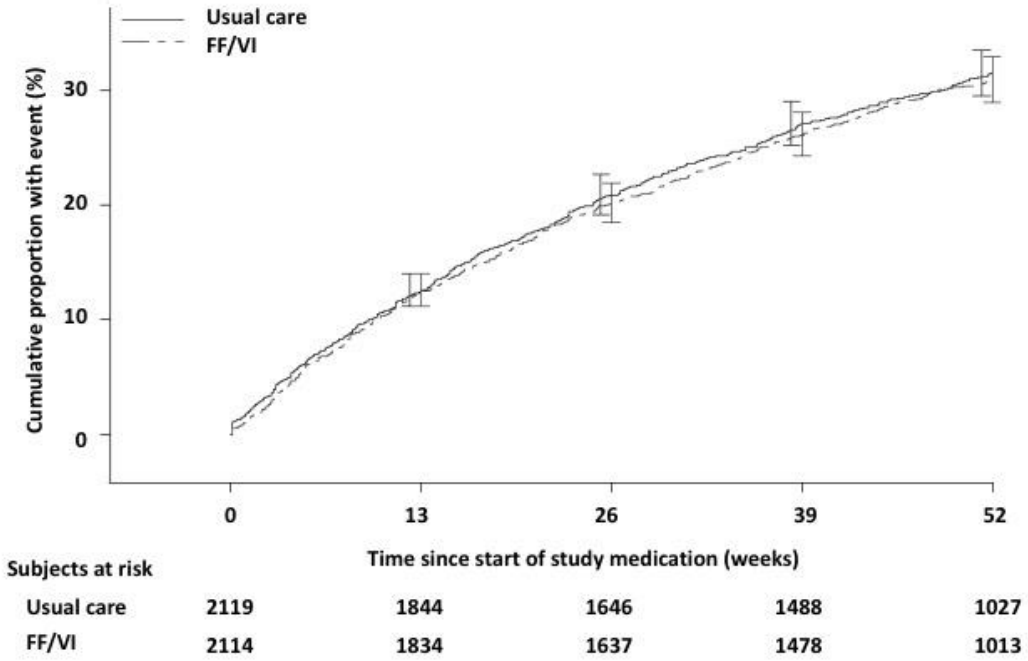
570 **Figure 3**



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