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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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8 **Effectiveness of Fluticasone Furoate/Vilanterol in Asthma**
9 **in clinical practice**

10
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68 **Abstract**

69

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

73

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

84 *Findings.* The odds of being a responder for subjects who initiated treatment with FF/VI were
85 twice the odds of being a responder on UC (977 / 1373 (71%) responders in FF/VI group
86 compared to 784 / 1399 (56%) in UC, OR 2.00 (1.71, 2.34) $p < 0.0001$). Patients initiated
87 with FF/VI improved ACT from baseline by 4.4 points compared to 2.8 in the UC group.
88 This was consistent across the duration of the study. There was no significant difference in
89 asthma exacerbations, or in asthma-related primary or secondary care contacts. Pneumonia
90 was uncommon, with no differences between groups; there was no difference in other serious
91 adverse events.

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

96 *Funding.* GlaxoSmithKline

97

98 The study is registered on clinicaltrials.gov as NCT01706198.

99 300 words

100

101 **Keywords:** Asthma control; effectiveness; exacerbations; fluticasone furoate; vilanterol;
102 combination therapy, routine care.

103

104 **Research in Context**

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

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

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

119

120

121

122 **Introduction**

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

130

131 The Salford Lung Studies (SLS) (4) were set up to evaluate the effectiveness and safety of
132 initiating the once-daily inhaled combination of fluticasone furoate and vilanterol (FF/VI)
133 compared with continuing maintenance therapy (usual care) in a large, real-world population
134 of COPD and asthma patients in conditions of normal care. The studies were conducted in
135 and around Salford, UK, a community mainly served by a single hospital with an established
136 electronic health record (EHR), connecting both primary and secondary care, and suitable for
137 both safety monitoring and data collection. This permits the unobtrusive observation of
138 patients, both for safety monitoring and effectiveness data collection, blended into routine
139 clinical care. The SLS on COPD showed that initiating the combination of FF/VI given once
140 daily reduced moderate/severe exacerbations when compared to continuing usual care (5).
141 We now report the SLS on asthma, comparing the effectiveness of the FF/VI combination
142 with optimised usual care (UC) on asthma control.

143

144

145 **Methods**

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

147 *Patients*

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

154 Patients were recruited in primary care, by the healthcare professionals who provided their
155 normal everyday care. All patients provided written informed consent. The study was
156 conducted in accordance with the International Conference on Harmonisation, Good Clinical
157 Practice (GCP) and the Declaration of Helsinki 2008. The study was approved by the
158 National Research Ethics Service Committee North West, Greater Manchester South. The
159 study is registered on clinicaltrials.gov (NCT01706198). Protocol and analysis plan are
160 available in the supplementary appendix.

161 *Study Design*

162 This was a prospective, 12-month, open-label, parallel group, randomised trial conducted in
163 74 general practices in Salford and South Manchester, UK. At the first study visit, patients
164 were offered study participation through written informed consent. Within 1–60 days after
165 visit 1, patients were randomised to either FF/VI or to continue their maintenance therapy
166 (Usual Care, UC). At this Visit 2, study staff collected baseline assessments, including
167 assessment of asthma control with the Asthma Control Test (ACT)(7), information on disease
168 duration, smoking status, concomitant medical history, and the Asthma Quality-of-Life

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

179 Study staff trained patients in both treatment groups in the correct inhaler techniques. At
180 weeks 12, 24, and 40, the patients were contacted by telephone by a study team member who
181 completed the ACT, and assessed any serious adverse events (SAEs) or non-serious adverse
182 drug reactions (ADRs). At 12 months, study staff met the patients to make a final assessment
183 of outcomes. Thus, patients had no face-to-face contact with the study team between baseline
184 and 12 months visits.

185 To preserve the real-world nature of the study, the patient experience was kept as close to
186 everyday clinical practice care as possible. The study's key investigators were the GPs and
187 their teams, who could continuously optimise therapy according to their clinical opinion, and
188 treatments were dispensed by community pharmacies in the usual way at the patient's
189 request. Patients could modify their treatment and remain in the study as well as in the
190 treatment arms to which they had been randomised. Those randomised to FF/VI could change
191 to any other asthma medication, and those on usual care could also do this but were not
192 permitted to initiate FF/VI. All GP and pharmacy staff received ICH-GCP and study training
193 as appropriate to their roles.

194 *Outcome Measurements*

195 The primary endpoint was the percentage of subjects at Week 24 with either an ACT score of
196 ≥ 20 , or an increase from baseline of ≥ 3 (“responder”), analysed in all patients who had an
197 ACT score < 20 at visit 2 (randomisation), the primary effectiveness analysis (PEA)
198 population. The ACT is a questionnaire consisting of 5 questions with a 5-point scale for
199 each (7), which is validated (12), also for use over the telephone (13, 14). The minimal
200 clinically relevant difference (MCD) is 3 points (15) and the cut-off point for well-controlled
201 asthma is 20 or above (1).

202 The secondary endpoints were previously published in full (6) and detailed in the
203 Supplementary Appendix. Briefly, these included ACT at Weeks 12, 24, 40 and 52,
204 all/asthma related primary and secondary care contacts, mean annual rate of severe
205 exacerbations, (defined as any worsening of respiratory symptoms treated with systemic
206 corticosteroids, antibiotics or leading to hospital attendance), number of salbutamol inhalers
207 dispensed, time to modification of initial therapy, percentage of patients that had an increase
208 from baseline of at least 0.5 in AQLQ(s) total score and AQLQ(s) environmental stimuli
209 domain score. All secondary endpoints were analysed on the entire study population; i.e., all
210 randomised patients who received a prescription of study medication. ACT data for
211 secondary endpoints is presented for the PEA population as per the primary endpoint
212 analysis. Except for the ACT, other questionnaires and demographics, data were collected in
213 real-time using an integrated primary and secondary care EHR, developed by NorthWest
214 EHealth (NWEH).

215 Other effectiveness outcomes are listed in the Supplementary Appendix.

216

217 *Safety Evaluation*

218 Safety endpoints included SAEs of pneumonia (defined by the pneumonia adverse event of
219 special interest [AESI] group), frequency and type of other SAEs, and ADRs. AESIs were
220 defined *a priori* as groups of events of interest for ICS/LABA. Because of the nature of an
221 effectiveness study where treatment modification is to some extent allowed, safety data are
222 presented according to the treatment a patient was taking when experiencing an event. The
223 only exception is an analysis of pneumonia based on randomised treatment, as requested by
224 regulators. Safety monitoring was performed by continuous real-time monitoring of the
225 patients' EHR using the linked NWEH database system, and by telephone every 3 months.
226 SAEs and ADRs were continuously monitored by near real-time data monitoring and a
227 dedicated clinical safety team and reported by Investigators on electronic report forms.
228 Events present at and contributing to death were recorded as fatal; cause of death was not
229 adjudicated.

230 *Statistical Analysis*

231 Sample size calculations were based on the primary endpoint (ACT Score at 24 weeks). A
232 total of 2906 patients (1453 patients per treatment group) were required for the study to have
233 90% power to detect a relative improvement of 6% in ACT score between FF/VI and UC,
234 assuming a 50% response rate in the UC group at 6 months. A total of 4036 patients were
235 required in the total population (randomisation of 2018 patients per treatment group) in order
236 to have at least 2906 patients in the primary efficacy analysis population, assuming 80% of
237 patients in the total population have an ACT score of <20 at baseline, and a 10% dropout rate
238 over the first 6-month period. Baseline ACT total scores of randomised patients were
239 monitored during recruitment and additional patients were randomised (4233 in total) to
240 ensure a sufficient number of patients satisfied their criteria for inclusion in the PEA
241 population. Treatment differences in ACT between the two treatment arms were analysed

242 using logistic regression adjusting for baseline ACT total score, baseline ACT total score
243 squared, baseline asthma therapy at randomisation (ICS or ICS/LABA), age and gender. All
244 effectiveness analyses were intent-to-treat (ITT); more details are provided in the
245 Supplementary Appendix. Subgroup analyses, when appropriate, are provided for
246 effectiveness and safety endpoints based on baseline disease characteristics per
247 randomisation stratification. Prior to the study, we sought advice from the National Institute
248 for Health and Care Excellence, and the Medicines and Healthcare Products Regulatory
249 Agency in the UK. The study was designed by the sponsor and the academic partners. The
250 sponsor and NWEH collected the data. Statistical analyses were performed by a contract
251 research organisation on behalf of, and with oversight from, employees of the sponsor. All
252 authors had full access to the data and vouch for the accuracy and completeness of all data
253 and analyses, and for the fidelity of the study to the protocol. The draft manuscript was
254 written jointly by AW and JV, and all the authors worked collaboratively to prepare the final
255 content and made the decision to submit the manuscript for publication.

256 **Results**

257 *Study Population*

258 4725 subjects were enrolled into the study of which 4233 were randomised (FF/VI 2114,
259 usual care 2119) and form the total study population (Fig 1). Of these, 3026 subjects (71%)
260 had an ACT score of < 20 at baseline and formed the Primary Effectiveness Analysis (PEA)
261 population (FF/VI 1512, usual care 1514). 3866 patients (91%) completed the study (FF/VI
262 1920, UC 1946). After baseline assessment including ACT, 156 patients (7%) in the UC
263 group were stepped up from ICS only to ICS/LABA; subsequently, 1357 (64%) of subjects
264 had ICS/LABA combination as their intended asthma maintenance therapy, and 762 (36%)
265 ICS only. In the FF/VI group, 1380 (65%) were prescribed 100/25 µg once daily and 734
266 (35%) 200/25 µg at baseline.

267 The treatment groups were well matched for age (mean 49.8 years), gender (2498 (59%)
268 female), smoking status (849 / 4203 (20%) current smokers), BMI (1773 / 4152 (43%) >30
269 kg/m²) and baseline ACT score (≥ 20 1206 (28%); 16-19 1308 (31%); ≤ 15 1718 (41%))
270 (Table 1). Patients generally had a long history of asthma (3663 (87%) ≥ 5 years), had
271 daytime symptoms (3830 (90%) more than twice weekly), used rescue beta-agonists
272 frequently (3044 (72%) > twice weekly), and woke at night with asthma (2117 (50%) in the
273 past week). Around one third of patients had a history of severe exacerbation in the last year
274 (973 (23%) one, and 568 (13%) > one exacerbation). Subjects had significant co-morbidities
275 (1625 (38%)), including hypertension (1098 (26%)), diabetes (406 (10%)), and coronary
276 artery disease (221 (5%)).

277 In the FF/VI group, 463 patients (22%) modified their study medication, and of these 381
278 (18%) switched back to UC. In the UC group, 376 patients (18%) modified their study
279 medication, and 3 subjects (<1%) switched to FF/VI (even though this was disallowed under

280 the protocol). More patients initiated with FF/VI modified their treatment in the first 12
 281 weeks of the study compared to the usual care group (Table S1 and Fig S12 Supplementary
 282 Appendix).

283

284 *Primary outcome*

285 At Week 24, the odds of being a responder on ACT score to initiation of treatment with
 286 FF/VI were twice those of UC in the PEA population (analysed as ITT); FF/VI: 977 (71%)
 287 responder/396 (29%) non-responder compared to 784 (56%) responder/615 (44%) non-
 288 responder, OR 2.00 (95% confidence interval (CI) 1.71 to 2.34) $p < 0.0001$. The benefit was
 289 consistent across all subgroups with no impact of baseline characteristics for the PEA (Fig
 290 S23 Supplementary Appendix). The odds of being a responder were similar for the total
 291 population (analysed as ITT); FF/VI 1437 (74%)/499 (26%) compared to 1176 (60%)/781
 292 (40%), OR 1.97 (95% CI 1.71 to 2.26) $p < 0.0001$ at Week 24.

293 When analysing those patients where the GP had found ICS as monotherapy to be indicated
 294 for usual therapy, the odds of being a responder was 324 (74%)/116 (26%) for FF/VI
 295 compared to 259 (57%)/195 (43%) for UC, OR 2.13 (95% CI 1.60 to 2.83) at Week 24. In
 296 patients where the GP had found an ICS/LABA combination to be indicated for usual
 297 therapy, the odds of being a responder was 637 (70%)/271 (30%) for FF/VI compared to 511
 298 (56%)/405 (44%) for UC, OR 1.95 (95% CI 1.60 to 2.38) at Week 24.

299

300 *Secondary Outcomes*

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

304 Appendix). A similar difference was seen for subjects who reached ACT scores of 20 or
305 greater (Table S2a, Supplementary Appendix). In the PEA population, adjusted mean ACT
306 score increased 4.4 points from a baseline of 14.4 (SD 3.5) in the FF/VI group compared to
307 an increase of 2.8 from 14.2 (SD 3.5) in the usual care group, difference 1.6 (95% CI 1.3 to
308 2.0), $p < 0.0001$) at Week 24; similar results were seen at weeks 12, 40 and 52
309 (Supplementary Appendix Table S3).

310 There was a numerical difference in exacerbations according to randomized treatment with
311 FF/VI vs UC (1009 vs 1093). However, following adjustment for logarithm of time on
312 treatment and baseline covariates, there was no statistically significant difference in the
313 adjusted annual exacerbation rate between the FF/VI group vs the UC group (0.40 vs 0.41);
314 percent reduction 2% (95% CI -9 to 12%), $p = 0.6969$). Time to first exacerbation did not
315 differ either (Fig 3).

316 There was a significant difference in the proportion of patients in FF/VI group vs UC who
317 were responders on AQLQ total score (increase from baseline of ≥ 0.5 ; OR 1.79 (95% CI
318 1.55-2.06); $p < 0.0001$).

319 Patients initiated with FF/VI reported a greater decrease in work impairment on WPAI
320 compared to those continuing with UC (-6.7% vs. -4.0%, difference -2.8% (CI -4.4 to -1.1),
321 $p < 0.0001$) and a greater decrease in activity impairment (-10.4% vs. -5.9%, difference -4.5%
322 (CI -5.9 to -3.2) $p < 0.0001$)

323 There was no difference in annual rate of asthma-related contacts with primary care in the
324 total population. There was an increase in the annual rate of all primary care contacts in the
325 group initiating FF/VI versus UC (per cent increase 9.7% (95% CI 4.6% to 15.0%)); there
326 were no differences in all secondary healthcare contacts (per cent increase 1.0% (95% CI -

327 8.2 to 9.5). The number of salbutamol inhalers prescribed was lower in the group initiated
328 with FF/VI than UC (7.2 vs. 8.0, respectively; difference -0.8 (95% -1.1 to -0.5); $p < 0.0001$).

329 *Safety*

330 Table 2 shows the distribution of serious adverse events based on the treatment patients were
331 on when the event was reported. The incidence of SAE of pneumonia by the treatment taken
332 at the time (i.e. taking treatment modification into account) was low, with the same number
333 of events on FF/VI and usual care (Table 2). When analysing pneumonia according to
334 randomised group, patients in the FF/VI group had a slightly higher numerical incidence of
335 pneumonias compared to the UC group (23 vs 16; incidence ratio 1.4; 95% CI 0.8 to 2.7).
336 There was no difference in the pre-specified SAE of special interest, time to first on-
337 treatment pneumonia (hazard ratio 1.45 (95% CI 0.77 to 2.74) $p = 0.255$).

338

339 **Discussion**

340 The Salford Lung Study on asthma is the largest, randomised, comparative effectiveness
341 study in a population intended to represent that seen in everyday clinical practice. We found
342 that initiation of a simple once-daily treatment with a combination of fluticasone furoate and
343 vilanterol was superior to usual care (optimised by the patient's GP) on asthma control
344 consistently over 12 months, as assessed by the ACT, without significantly increasing risk of
345 SAEs.

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

350 of asthma control. The primary endpoint, ACT, was chosen to reflect impact of treatments on
351 patients' overall asthma control. The adjusted mean increase of 4.4 points exceeded the MCD
352 and is clinically important, and was significantly greater than the increase in the UC group
353 who also had their treatment optimised at baseline by the GP. The improvement in asthma
354 control was present from week 12 throughout the study.

355 During the study design phase, the rate of severe asthma exacerbations was not considered a
356 feasible primary endpoint due to the indicated infrequent occurrence of such events in a
357 general asthma population (6). We found no statistically significant difference in the adjusted
358 annual rate of severe exacerbations in patients initiated with FF/VI compared to continuing
359 usual care, despite the large improvement in asthma control. This contrasts with an example
360 of a closely supervised multi-centre efficacy RCT (18) with tight inclusion/exclusion criteria
361 (including a history of exacerbations), which did show differences in time to first
362 exacerbation between different as-needed interventions. There are a number of potential
363 reasons. First, we used a definition of severe exacerbations that included antibiotics as well as
364 oral steroids, because in routine clinical care many exacerbations are treated with antibiotics
365 (differing from ATS/ERS Task Force guidelines (19)). Our prediction proved correct, with
366 452 (22%) of exacerbations being treated with antibiotics alone, 405 (19%) with oral
367 corticosteroids alone, and 1245 (59%) treated with both. In a post-hoc analysis of
368 exacerbations treated with oral corticosteroids either alone or with antibiotics, there was a
369 numerical difference in favour of FF/VI (775 vs 875), but there was no statistically
370 significant difference in the adjusted annual rate of exacerbations (0.30 vs 0.32, FF/VI vs
371 UC; percent reduction 5% (95% CI -7% to 16%), $p=0.4206$). Second, in routine care,
372 adherence rates are as low as 20-40%, compared to the 80-90% seen in closely monitored
373 RCTs, and it may be that small changes in adherence in routine care could improve daily
374 asthma control, without having sufficient impact to improve exacerbations. Third, the

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

381 A significant reduction in exacerbations had been seen with FF/VI was compared to FF alone
382 in a Phase 3 efficacy RCT carried out for regulatory purposes, although the reduction was
383 modest (~25%) (20). It is interesting to compare with the Salford study, not forgetting that
384 the comparator was different. The Efficacy RCT was innovative, in being powered to
385 completion when a specific number of exacerbations had occurred in the study, and included
386 a highly selected population who were shown to be compliant with event diaries during a run-
387 in period. In the efficacy study, exacerbations defined as requiring steroids as per the
388 ATS/ERS guidelines, occurred at about half the frequency of the more broadly defined
389 exacerbations in the Salford study. These differences in design and population can clearly
390 make substantial differences to the outcome. Efficacy RCTs remain important in showing
391 efficacy and safety of a novel therapy. However, effectiveness studies will be needed to show
392 how they impact routine care.

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

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

406 The strength of the study derives from its innovative design, which aimed to maintain
407 scientific rigour of randomisation to an intervention versus control arm, but at the same time
408 stay as close as possible to everyday clinical practice, collecting endpoints relevant to
409 patients and healthcare decision-makers. It took place in a single urban area, with primary
410 and secondary care connected through an EHR developed by NWEH to provide integrated
411 real-time recording, enabling collection of a study-relevant dataset for all the effectiveness
412 and safety outcomes. After randomization, the patient was only contacted by phone on three
413 occasions over 12 months to complete the ACT and a safety check. All management was
414 carried out by the usual carers, with simultaneous monitoring of patients remotely using the
415 EHR for early detection of safety events. The adult asthma patients in SLS were typically
416 older and heavier, with one fifth actively smoking, and one third having co-morbidities that
417 would have excluded the majority from many regulatory RCTs (2). In common with many
418 community surveys, they had unstable asthma, with 71% having a baseline ACT <20, over
419 90% having daytime and /or night symptoms, and 36% at least one severe exacerbation in the
420 year prior to the study.

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

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

430 The perceived weakness of the study generally relates to the open label design in routine care
431 in the absence of regular face-to-face monitoring, and consequent potential for bias.

432 Certainly, a comparative effectiveness study like ours requires careful interpretation, and in
433 this context, these features could also be seen as strengths. We did consider randomisation by
434 practice, but believe that this would have made interpretation difficult, with additional
435 differences due to training and education between practices. We randomised by patient, but
436 because the study was open label, this could potentially have introduced bias, even though all
437 efforts were taken to make the treatment experience similar for all patients by similar initial
438 inhaler training, GP prescription and collection at the usual pharmacy, etc. Any bias may be
439 enhanced by choosing a “soft” primary outcome, the ACT score, where patients may indicate
440 improvement, merely as a result of being switched to a novel treatment. However, the fact
441 that the benefit was present for the entire 52 weeks duration of the study indicates that this
442 was not the case.

443 The un-blinded nature of the study is the likely reason for the larger degree of modifying of
444 treatment over the first 3 months of the study in the FF/VI group. It was not due to loss of
445 asthma control, but mainly due to patients choosing to return to a long-standing treatment.

446 Asymmetric treatment modification necessitated a new approach to analysing and
447 interpreting safety data, not merely based on randomisation, as in efficacy trials where
448 patients are maintained on their randomised medication. We have chosen to report adverse

449 events according to treatment actually taken at the time, and therefore according to exposed
450 risk, something we anticipate will become standard in future effectiveness RCTs.

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

456

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- 523
524

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%)

The Salford Lung Study

		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 (%)

530

531

532 **Table 2**

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

535

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

536

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 Fluticasone furoate vilanterol combination
540

541 **Figure legends**

542

543 **Figure 1**

544 CONSORT diagram of patient flow through SLS asthma.

545

546 **Figure 2**

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

552

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

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

555

556 **Figure 3**

557 Time to first severe exacerbation, total population

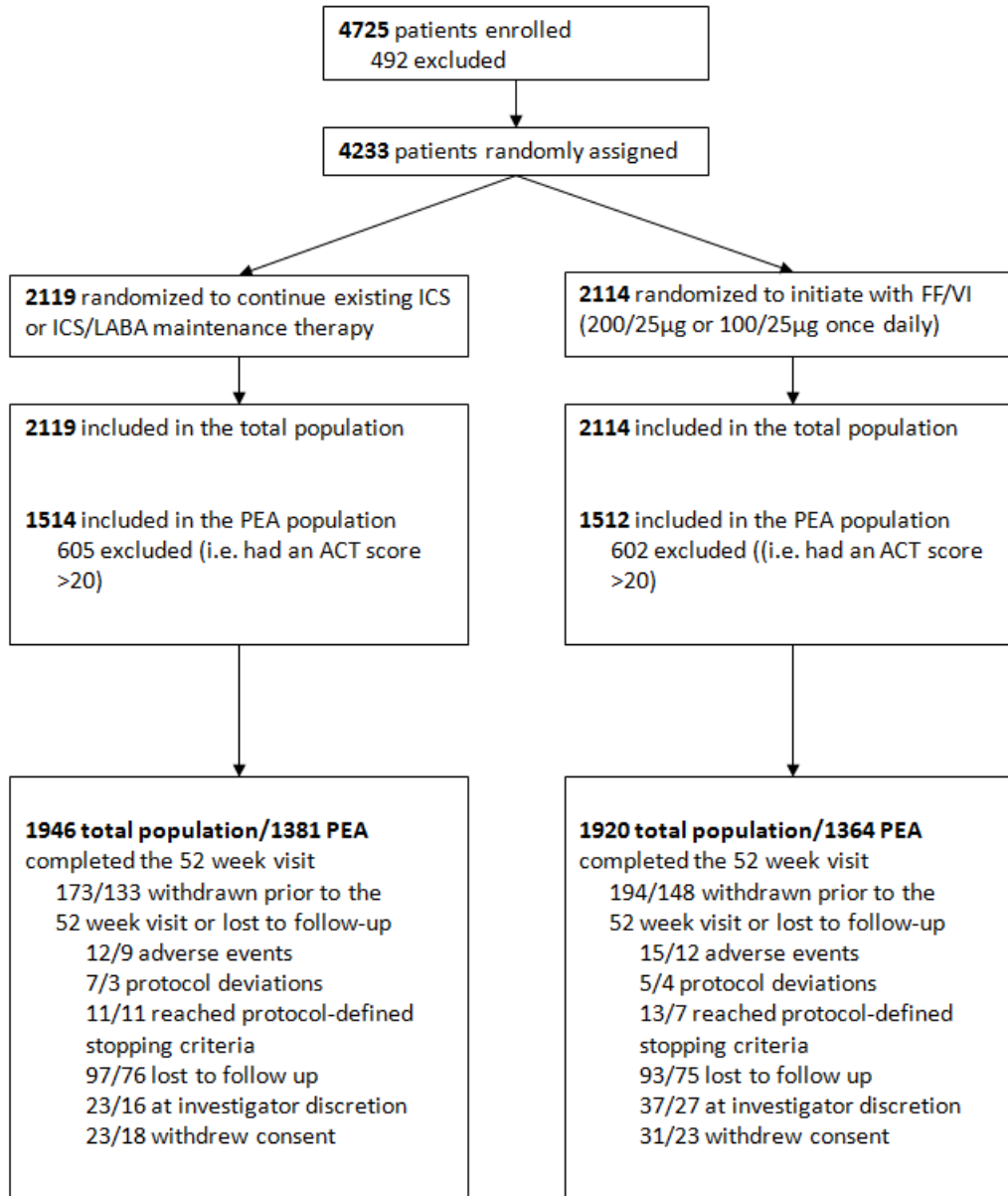
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Figure 1

Figure. Patient flow through the SLS study

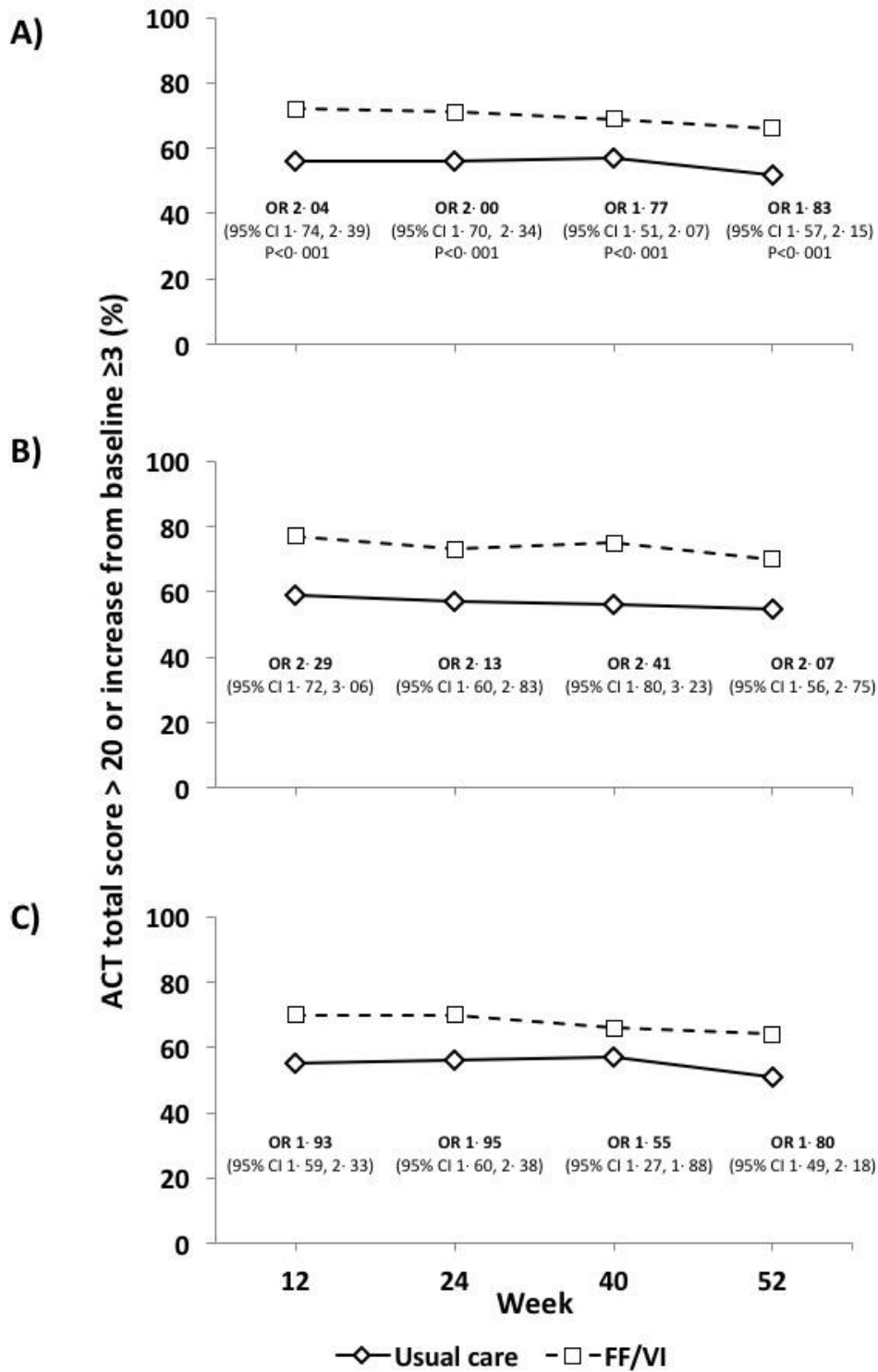


Total population: includes all randomized patients who received at least one prescription of study medication
PEA population: all patients in the total population who had an ACT score <20 at baseline

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

563

564 **Figure 2**
565

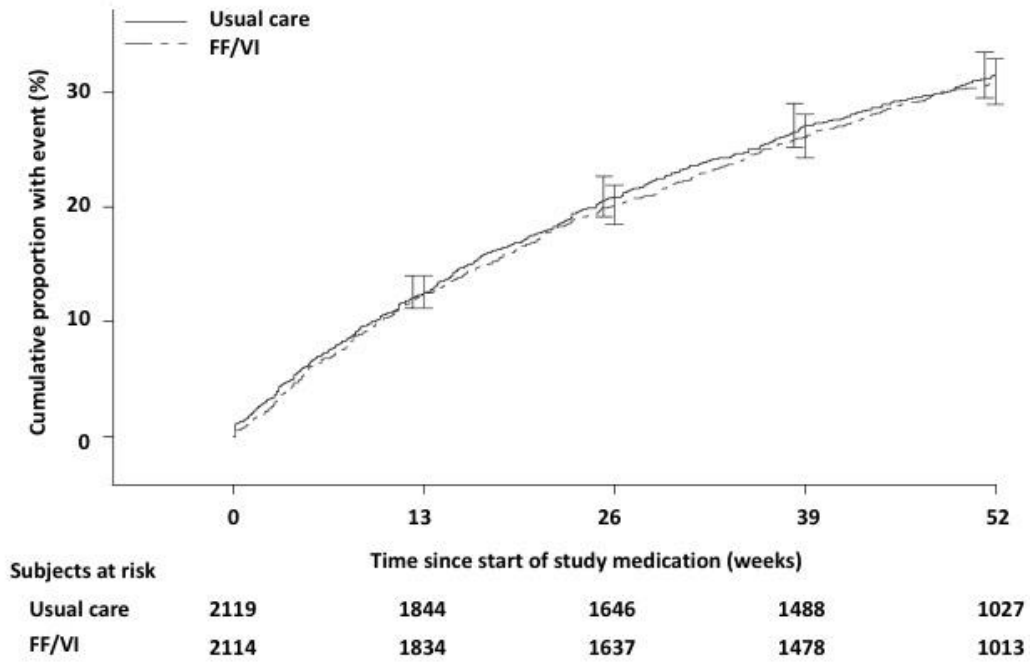


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569

570 **Figure 3**



571