Satellite Symposium : Drug treatments for severe persistent asthma

The Salford Lung Study in Asthma

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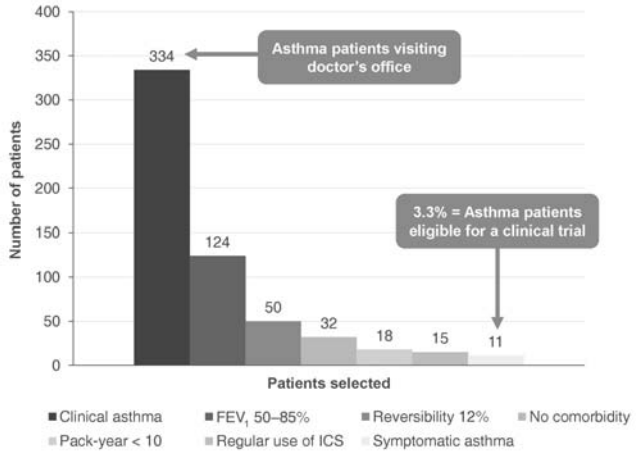
Need for studies closer to everyday clinical practice

Generalisability of studies with strict patient criteria in asthma



Common asthma patient selection criteria:

- FEV_1 50–85% of predicted
- Historical reversibility ≥ 12% last 12 months
- No significant co-morbidity
- Non-smoker; if ex-smoker, less then 10 pack-years

Adapted from: Herland K et al. *Resp Med*. 2005; 99:11–19.

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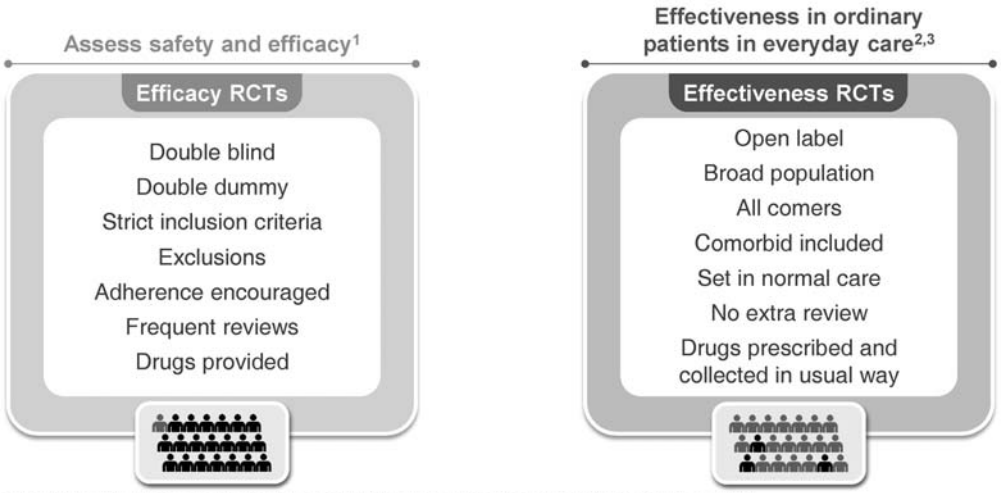
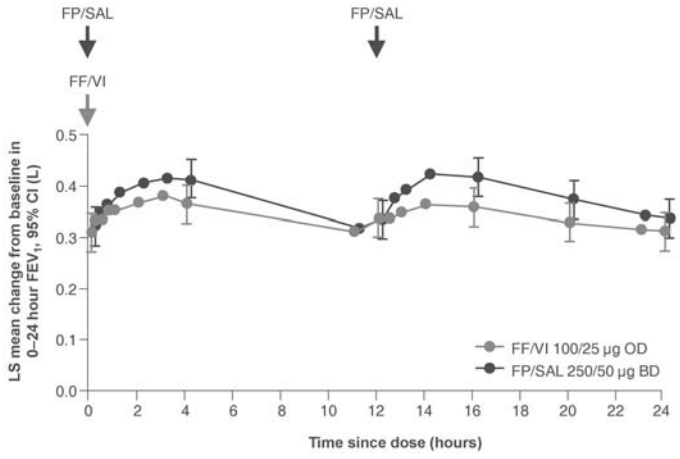
Efficacy vs. Effectiveness



ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; **RCT:** Randomised controlled trial.

1. ICH. ICH harmonised tripartite guideline: Statistical principles for clinical trials E9. 1998. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf [Accessed August 2017]; 2. Godwin M et al. *BMC Med Res Methodol*. 2003; **3**(28): 1-7; **3.** Singal AG et al. *Clin Transl Gastroenterol*. 2014; 5: e45,

The efficacy of FF/VI has been demonstrated in a comprehensive clinical development programme



Primary endpoint

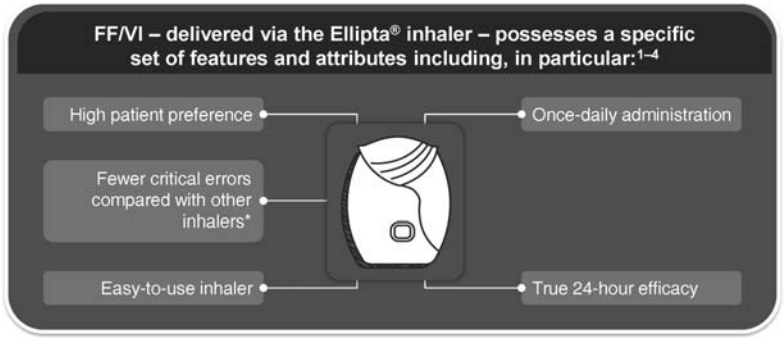
- LS mean change from baseline in serial (0–24 hour) weight mean FEV_1 at Week 24
- FF/VI vs FP/SAL (–37 mL; $P = 0.162$)

- The efficacy of FF/VI has been demonstrated in the Phase III programme
- The next step is to assess how FF/VI performs in everyday clinical practice

BD: Twice daily; **CI:** Confidence interval; **FEV_1:** Forced expiratory volume in 1 second; **FF:** Fluticasone furoate; **FP:** Fluticasone propionate; **LS:** Least square; **OD:** Once daily; **SAL:** Salmeterol; **VI:** Vilanterol.

Adapted from: Woodcock A et al. *Chest*. 2013;144:1222–1229.

The hypothesis: FF/VI has superior effectiveness in everyday asthma clinical practice compared with usual care



Based on these attributes, it is hypothesised that the true clinical value and effectiveness of FF/VI will be most evident when studied in an RCT with an open label design conducted in a normal care setting of everyday clinical practice

*Critical error: Defined as an error that was likely to result in no, or minimal (i.e., significantly reduced) medication being inhaled.[4]
FF: Fluticasone furoate; **RCT:** Randomised controlled trial; **VI:** Vilanterol.

1. Relvar 92 µg/22 µg. Summary of Product Characteristics. GlaxoSmithKline; May 2017; 2. Svedsater H et al. *npj Prim Care Resp Med.* 2014; 24:14019; 3. Sharma R et al. *Am J Respir Crit Car Med.* 2014; 189: A5693; 4. van der Palen J et al. *npj Prim Care Respir Med.* 2016; 26: 16079.

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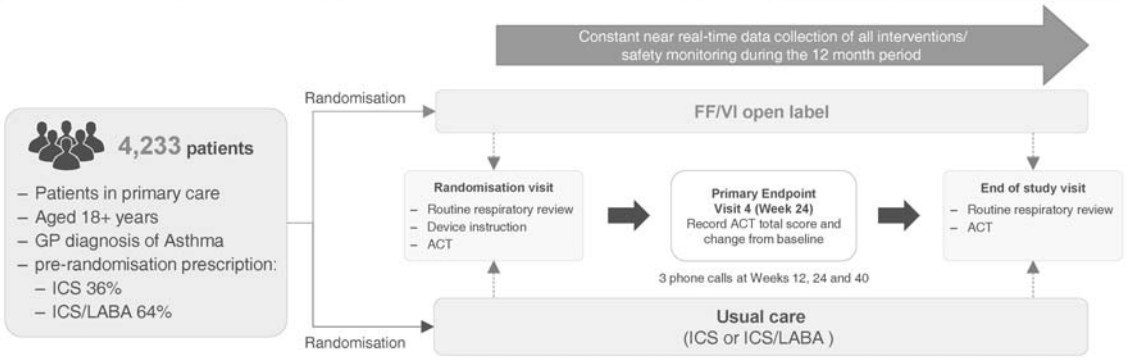
Salford Lung Study

Study design

The Question:
How effective is initiating treatment with FF/VI compared to continuing treatment with usual care

Safety Reporting:
Reporting as randomised and by actual treatment



During the 1-year treatment period, patients can have their maintenance treatment adjusted (stepping-up, stepping-down or switch) at the GP's/Investigator's discretion. Patients in the Relvar arm could switch to usual care but not vice versa

1. Bakerly ND et al. *Resp Res.* 2015; 16: 101; 2. Limb M. *BMJ.* 2015; 351: h6343; 3. New JP et al. *Thorax.* 2014; 69: 1152–1154; 4. Vestbo J et al. *NEJM.* 2016; 375: 1253-1260; 5. Woodcock et al. Lancet 2017: http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017]

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The Salford Lung Studies in Asthma & COPD

Similarities[1-3]

- Both prospective RCT effectiveness studies
- Comparing FF/VI to usual care for asthma and COPD patients
- 52 week follow up studies
- Same E-health systems used
- Broad inclusion criteria to ensure as close to everyday clinical practice as possible

Differences[1-3]

- Different patient populations
- Different primary endpoints
  - Asthma Control (as measured by ACT) compared to exacerbations in COPD

ACT: Asthma Control Test; **COPD:** Chronic obstructive pulmonary disease; **FF:** Fluticasone furoate; **VI:** Vilanterol

1. New JP et al. *Thorax.* 2014; 69: 1152–1154; 2. Woodcock A et al. *BMC Pulm Med.* 2015; 15:160; 3. Vestbo J et al. *NEJM.* 2016; 375: 1253-1260.

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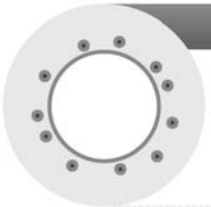
Inclusion and exclusion criteria

Inclusion criteria[1-2]

- Age ≥18 years
- Symptomatic asthma diagnosed by a GP (symptomatic in week prior to randomisation)
- Regular maintenance inhaler therapy with ICS or ICS/LABA
- Symptoms within the week prior to Visit 2
- Written consent



Exclusion criteria[1-2]

- Recent history of life-threatening asthma
- Chronic obstructive pulmonary disease or other uncontrolled / clinically significant disease
- Regular maintenance inhaler therapy with LABA only
- Chronic oral corticosteroid use
- Patient not expected to be able to complete the study

The Salford Lung Study is more generalisable than any other study conducted for FF/VI in asthma

FF: Fluticasone furoate; **GP:** General practitioner; **ICS:** Inhaled corticosteroid; **LABA:** Long-acting β_2 agonist; **VI:** Vilanterol.

1. Woodcock A, et al. *BMC Pulm Med.* 2015; 15:160; 2. ClinicalTrials.gov. NCT01706198. Available at: https://clinicaltrials.gov/ct2/show/NCT01706198 [Accessed August 2017].

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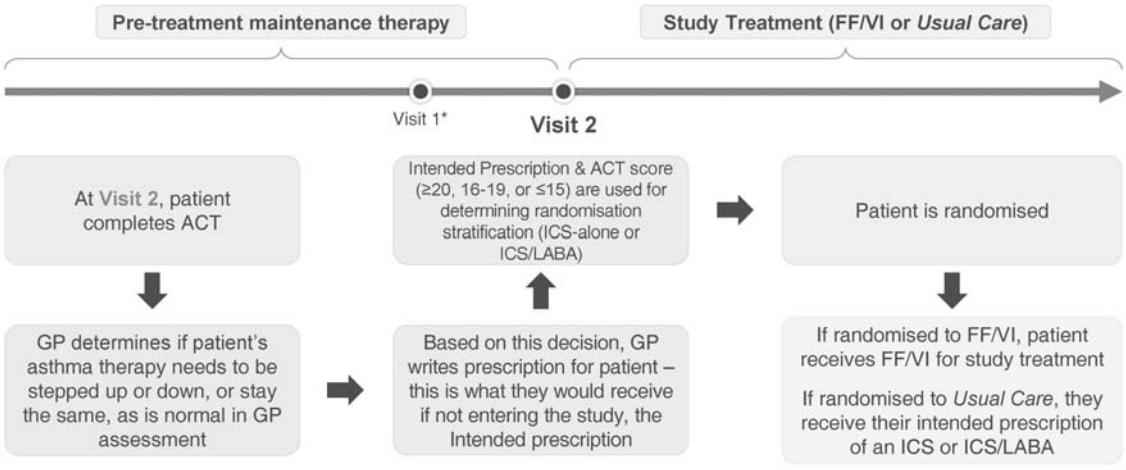
Maintenance therapy taken pre-treatment vs. Intended prescription



*Visit 1 and Visit 2 may be combined. Trade marks are owned by or licensed to the GSK group of companies.
ACT: Asthma Control Test; **FF:** Fluticasone furoate; **GP:** General practitioner; **LABA:** Long-acting β_2 agonist; **RAMOS:** Registration and Medication Ordering System; **VI:** Vilanterol.

1. Woodcock A, *et al. BMC Pulm Med.* 2015;**15**:160.

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Outcome measures

Secondary Effectiveness Endpoint

- Mean change from baseline in individual question scores for ACT at weeks 12, 24, 40 and 52
- Mean change from baseline in total score and domain scores of AQLQ(S) at weeks 24 and 52
- Percentage of patients who have an increase from baseline of ≥0.5 in AQLQ(S)
- WPAI: Asthma at week 52
- Health status using the EQ-5D at week 52
- Adherence with study medication based on analysis of medications (prescribed, dispensed and collected) during the study
- Use of the MARS-A at week 52
- Increase from baseline of ≥0.5 in AQLQ(S) refers to: Total score at week 24; individual domain scores at week 24; individual domain scores (symptoms, activity, limitations and emotional function) at week 52
- WPAI: Asthma at week 52 refers to the following categories: Percentage of work time missed due to asthma: Percentage of impairment while working due to asthma; percentage of overall work impairment due to asthma; percentage of activity impairment due to asthma

ACT: Asthma Control Test; **AQLQ(S):** Standardised Asthma Quality of Life Questionnaire; **EQ-5D:** EuroQol questionnaire; **MARS-A:** Medication Adherence Report Scale for Asthma; **WPAI:** Work Productivity and Activity Impairment Questionnaire

1. Woodcock et al. Lancet 2017; http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] online Supplement.

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Patients' profile

ITT population

		Usual Care (N = 2119)	FF/VI (N=2114)	Total (N=4233)
Age (years)	n	2119	2114	4233
	Mean (SD)	49.7 (16.69)	49.9 (16.05)	49.8 (16.37)
	≥ 50	1039 (49%)	1043 (49%)	2082 (49%)
Sex	n	2119	2114	4233
	Male	878 (41%)	857 (41%)	1735 (41%)
	Female	1241 (59%)	1257 (59%)	2498 (59%)
Smoking status	n	2105	2098	4203
	Current smoker	429 (20%)	420 (20%)	849 (20%)
	Former smoker	708 (34%)	658 (31%)	1366 (33%)
	Non smoker	968 (46%)	1020 (49%)	1988 (47%)
BMI (kg/m^2)	n	2077	2075	4152
	≤ 30	1174 (57%)	1205 (58%)	2379 (57%)
	> 30	903 (43%)	870 (42%)	1773 (43%)
ACT Total Score at Baseline	n	2119	2113	4232
	≥ 20	605 (29%)	601 (28%)	1206 (28%)
	16 to 19	653 (31%)	655 (31%)	1308 (31%)
	≤15	861 (41%)	857 (41%)	1718 (41%)

ITT: Intention to treat

1. Woodcock et al. Lancet 2017; http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017]; 2. GSK DOF RF/FFT/0058/17.

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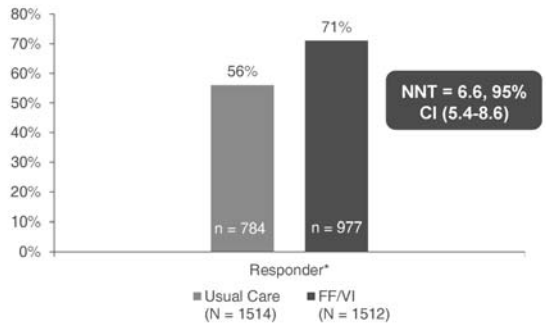
Percentage of subjects with either an ACT score of ≥20, or an increase from baseline of ≥3 at week 24

PEA Population



	Usual Care (N=1514)	FF/VI (N=1512)
n	1399	1373
Responder*	784 (56%)	977 (71%)
Non-Responder	615 (44%)	396 (29%)
FF/VI vs. Usual Care		
Adjusted Odds Ratio		2.00
95% CI		(1.71, 2.34)
P-value		<0.001

In the PEA population, the odds achieving asthma control for subjects who initiated treatment with FF/VI are twice the odds of achieving asthma control for subjects who continued treatment with Usual Care; this difference is statistically significant at the 5% level.

PEA Population: all ITT subjects who have an ACT total score of < 20 at baseline (Day 0), as recorded in the eCRF. (71% of ITT population);
* Responder is defined as an ACT total score ≥ 20 or an increase from baseline of ≥ 3.
ACT: Asthma control test; **FF:** Fluticasone furoate; **PEA:** Primary Effectiveness Analysis; **VI:** Vilanterol

1. Woodcock et al. Lancet 2017; http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017]; 2. GSK DOF RF/FFT/0058/17.

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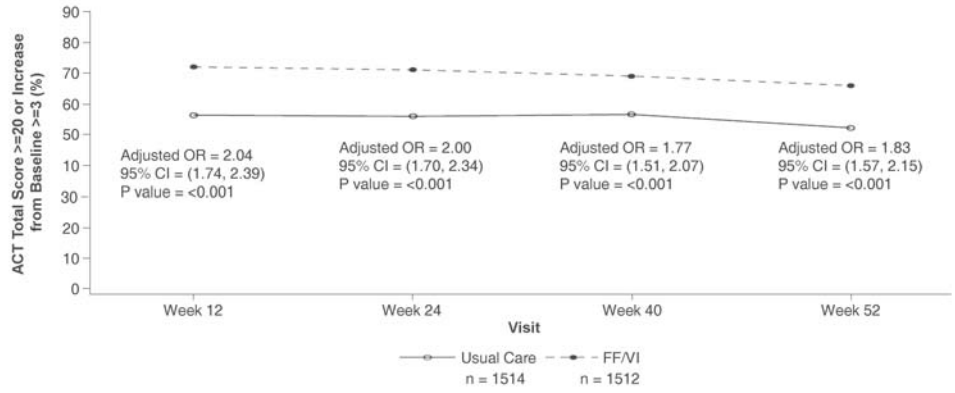
Percentage of subjects with either an ACT score of ≥20, or an increase from baseline of ≥3 across all time points

PEA Population



Primary endpoint result is consistent over time

ACT: Asthma Control Test; **OR:** Odds ratio; **PEA**: Primary Effectiveness Analysis

1 Woodcock et al. Lancet 2017: http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] 2. Woodcock et al. Lancet 2017: http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] online supplement

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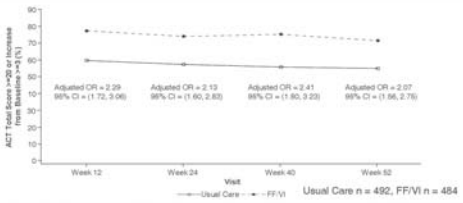
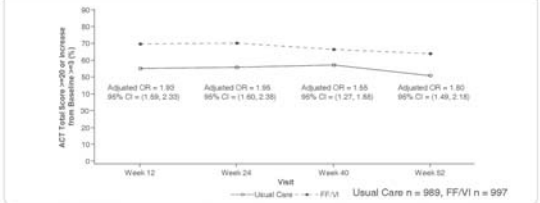
Percentage of subjects with either an ACT score of ≥20, or an increase from baseline of ≥3

PEA Population

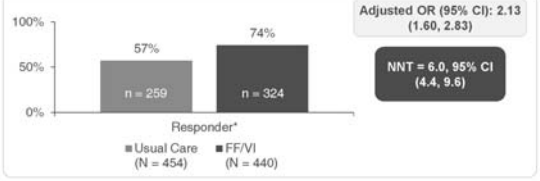
Asthma Maintenance Therapy ICS Alone Subset



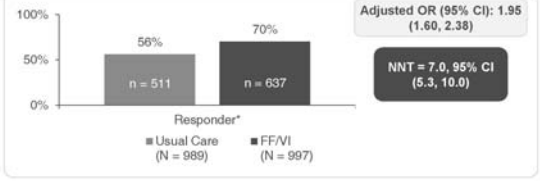
Asthma Maintenance Therapy ICS/LABA Subset



At week 24



At week 24



* Responder is defined as an ACT total score ≥ 20 or an increase from baseline of ≥ 3.
ICS: Inhaled corticosteroid; **LABA:** Long acting beta agonist; **OR:** Odds ratio; **PEA:** Primary Effectiveness Analysis

1 Woodcock et al. Lancet 2017: http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] 2. Woodcock et al. Lancet 2017: http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] online supplement

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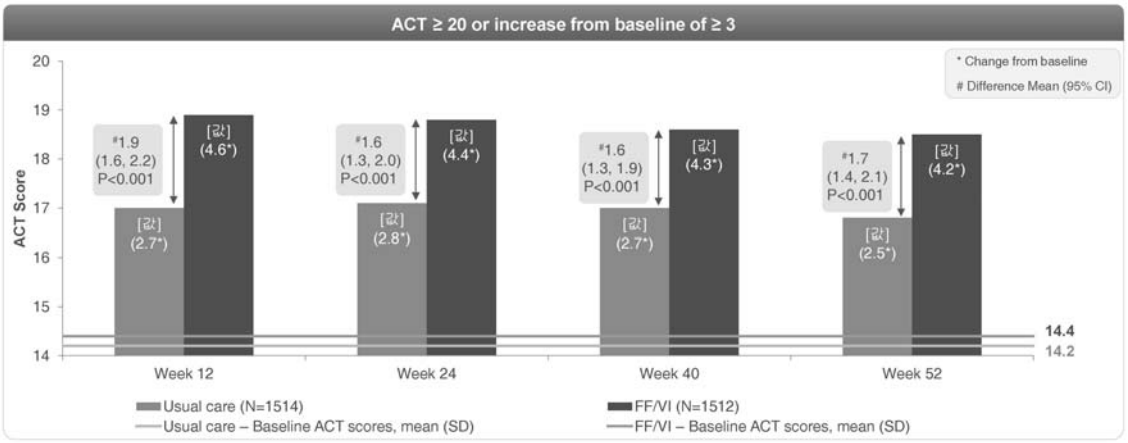
Percentage of subjects with either an ACT score of ≥20, or an increase from baseline of ≥3 across all time points

PEA Population



ACT: Asthma Control Test; **FF:** Fluticasone furoate; **PEA:** Primary Effectiveness Analysis; **UC:** Usual care; **VI:** Vilanterol

1 Woodcock et al. Lancet 2017; http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] 2. Woodcock et al. Lancet 2017; http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] online supplement

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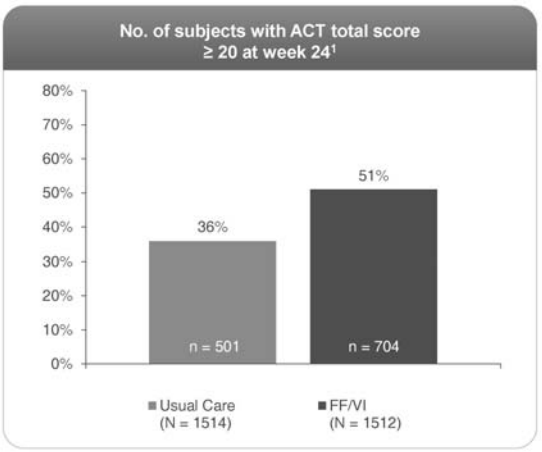
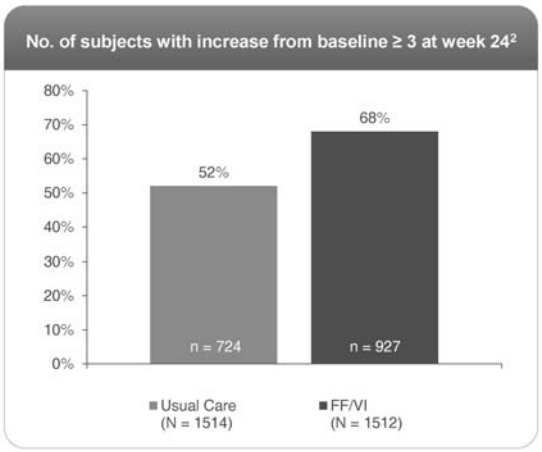
Percentage of subjects with either an ACT score of ≥20, or an increase from baseline of ≥3 at week 24

PEA Population





ACT: Asthma Control Test; **FF:** Fluticasone furoate; **PEA:** Primary Effectiveness Analysis; **VI:** Vilanterol

1. Woodcock et al. Lancet 2017; http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017] online supplement. ; 2. GSK DOF RF/FFT/0115/17.

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Effectiveness summary

- Primary endpoint demonstrated Asthma control for patients initiated on FF/VI compared to those continuing on usual care. This result was seen consistently over time and in both subsets of data
- Overall exacerbations were not different between the two arms, however:
  - The study was not powered to look at exacerbations – the small numbers and infrequent events in a non-exacerbating group makes it difficult to detect a trend
- AQLQ and WPAI in line with primary endpoint

ACT: Asthma control test; **AQLQ:** Asthma Quality of Life Questionnaire; **FP:** Fluticasone propionate; **ICS:** Inhaled corticosteroid; **LABA:** Long acting beta agonist; **SAL:** Salmeterol; **URTI:** Upper respiratory tract infections; **WPAI:** Work Productivity and Activity Impairment Questionnaire

1 Woodcock et al. Lancet 2017. http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017]

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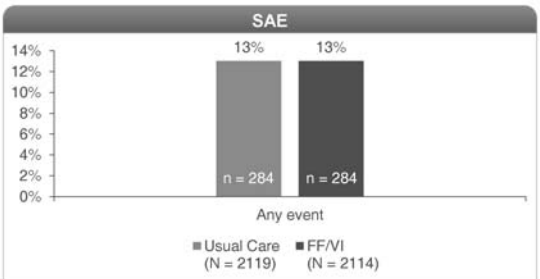
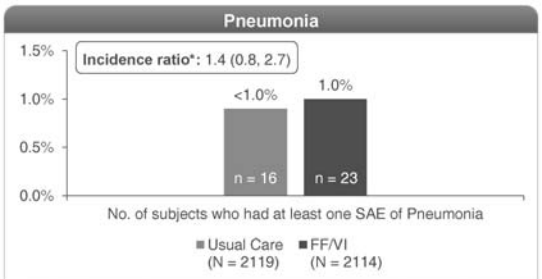
Serious adverse events (SAE) & Pneumonia special interest group

ITT Population



The incidence of serious adverse events (SAE) in the study was the same in both arms



The incidence of pneumonia, a safety endpoint of special interest, occurred infrequently in patients as randomised to the two arms of the study

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).

The non-inferiority margin for the ratio of the proportions with at least one serious SAE of pneumonia on FF/VI versus the comparator is set at 2. Non-inferiority will be demonstrated if the upper limit of the two-sided 95% confidence interval for the incidence ratio FF/VI / usual care is less than 2. * Calculated as % of subjects who had at least one SAE of pneumonia in the FF/VI group divided by the % of subjects who had at least one SAE of pneumonia in the Usual Care group. **Based on a pre-planned analyses non-inferiority by randomisation was not confirmed**
FF: Fluticasone furoate; **SAE:** Serious adverse events; **VI:** Vilanterol

1 Woodcock et al. Lancet 2017. http://dx.doi.org/10.1016/S0140-6736(17)32397-8 [Accessed: September 2017]; 2. GSK DOF RF/FFT/0058/17.

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