Clinical trial results:
A 6-month, open label, randomised, efficacy study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via the Dry Powder Inhaler Ellipta™ compared with usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler in subjects with Persistent Asthma

Summary

EudraCT number	2014-000551-81
Trial protocol	DE
Global end of trial date	20 July 2017

Results information

Result version number	v1 (current)
This version publication date	20 July 2018
First version publication date	20 July 2018

Trial information

Trial identification

Sponsor protocol code	116492

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the efficacy of fluticasone furoate (FF)/vilanterol (VI) 100 mcg/ 25 mcg or FF/VI 200 mcg/25 mcg with usual fixed combinations inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) for asthma maintenance therapy at Week 12 (Visit 4).

Protection of trial subjects:

Eligibility criteria have been incorporated into the protocol to exclude participants for whom any of the study treatments are contraindicated e.g. participants with historical or current evidence of uncontrolled or clinically significant cardiovascular disease, chronic users of systemic corticosteroids, participants with a history of life-threatening asthma, including severe and unstable asthma, and/or history of repeated severe exacerbations (3/year) and/or exacerbation in the previous 6 weeks.
The protocol requires that spirometry procedures are stopped if participants experience shortness of breath, coughing, light-headedness and/or chest tightness.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 226
Country: Number of subjects enrolled	Germany: 213
Worldwide total number of subjects	439
EEA total number of subjects	439

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1

Adults (18-64 years)	368
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 439 participants with persistent asthma were screened. The study was conducted at 63 centers in 2 countries: 43 in France and 20 in Germany from 09 July 2015 to 20 July 2017. Age value being reported for all participants is an approximate age accurate to within + or -1 year.

Pre-assignment

Screening details:

A total of 439 participants were screened for this study and 423 participants were randomized to treatment. Three of the randomized participants did not receive study treatment and were not included in the Intent-To-Treat (ITT) population.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Usual ICS/LABA

Arm description:

Eligible participants received fixed combination inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) (Fluticasone propionate [FP]/ Salmeterol [S] 250/50 micrograms [mcg] or 500/50 mcg, 1 inhalation twice daily; or Budesonide [BUD]/ Formoterol [F] 200/6 mcg or 400/12 mcg, 1 or 2 inhalations twice daily) for 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone propionate (FP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

FP 250 mcg or 500 mcg blended with lactose administered twice daily via DISKUS DPI.

Investigational medicinal product name	Salmeterol (S)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol 50 mcg blended with lactose administered twice daily via DISKUS DPI.

Investigational medicinal product name	Budesonide (BUD)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

BUD 200 mcg or 400 mcg blended with lactose administered twice daily via TURBUHALER DPI.

Investigational medicinal product name	Formoterol (F)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed

Routes of administration	Inhalation use

Dosage and administration details:

Formoterol 6 mcg or 12 mcg blended with lactose administered twice daily via TURBUHALER DPI.

Arm title	FF/VI

Arm description:

Eligible participants received Fluticasone Furoate (FF)/ Vilanterol (VI) 100 mcg/22 mcg or FF/VI 200 mcg/25 mcg 1 inhalation once daily for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Fluticasone Furoate (FF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

FF 100 mcg or 200 mcg blended with lactose administered once daily via ELLIPTA dry powder inhaler (DPI).

Investigational medicinal product name	Vilanterol (VI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

VI 25 mcg blended with lactose and magnesium stearate administered once daily via ELLIPTA DPI.

Number of subjects in period 1[1]	Usual ICS/LABA	FF/VI
Started	210	210
Completed	192	194
Not completed	18	16
Physician decision	5	1
Consent withdrawn by subject	3	3
Protocol defined stopping criteria reach	1	-
Adverse event, non-fatal	4	8
Lost to follow-up	2	2
Protocol deviation	1	2
Lack of efficacy	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 439 participants were screened, of which 12 participants were inclusion/exclusion criteria failures; remaining 4 were not randomized due to physician decision, withdrawal by subject and protocol deviation. There were 3 participants who were randomized but not included in the ITT Population because they did not receive study treatment. These 3 participants were withdrawn from the study due to physician decision, withdrawal by subject and protocol deviation.

Baseline characteristics

Reporting groups	
Reporting group title	Usual ICS/LABA
Reporting group description:	
Eligible participants received fixed combination inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) (Fluticasone propionate [FP]/ Salmeterol [S] 250/50 micrograms [mcg] or 500/50 mcg, 1 inhalation twice daily; or Budesonide [BUD]/ Formoterol [F] 200/6 mcg or 400/12 mcg, 1 or 2 inhalations twice daily) for 24 weeks.	
Reporting group title	FF/VI
Reporting group description:	
Eligible participants received Fluticasone Furoate (FF)/ Vilanterol (VI) 100 mcg/22 mcg or FF/VI 200 mcg/25 mcg 1 inhalation once daily for 24 weeks.	

Reporting group values	Usual ICS/LABA	FF/VI	Total
Number of subjects	210	210	420
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47.5	49.3	
standard deviation	± 14.99	± 14.67	-
Gender categorical Units: Subjects			
Female	124	145	269
Male	86	65	151
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	3	4	7
Asian - Central/South Asian Heritage	0	1	1
Asian - East Asian Heritage	2	0	2
Asian - South East Asian Heritage	0	1	1
Native Hawaiian Or Other Pacific Islander	1	1	2
White - Arabic/North African Heritage	8	6	14
White - White/Caucasian/European Heritage	196	196	392
Mixed White Race	0	1	1

End points

End points reporting groups

Reporting group title	Usual ICS/LABA

Reporting group description:

Eligible participants received fixed combination inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) (Fluticasone propionate [FP]/ Salmeterol [S] 250/50 micrograms [mcg] or 500/50 mcg, 1 inhalation twice daily; or Budesonide [BUD]/ Formoterol [F] 200/6 mcg or 400/12 mcg, 1 or 2 inhalations twice daily) for 24 weeks.

Reporting group title	FF/VI

Reporting group description:

Eligible participants received Fluticasone Furoate (FF)/ Vilanterol (VI) 100 mcg/22 mcg or FF/VI 200 mcg/25 mcg 1 inhalation once daily for 24 weeks.

Primary: Change from Baseline in asthma control test (ACT) total score at Week 12

End point title	Change from Baseline in asthma control test (ACT) total score at Week 12

End point description:

The ACT is a validated self-completed questionnaire consisting of 5 questions that evaluate asthma control during the past 4 weeks on a 5-point categorical scale. Total scores are calculated from the sum of the scores from the 5 questions and can range from 5 to 25, with higher scores indicating better control. An ACT total score of 5 to 19 suggests that the participant's asthma is unlikely to be well controlled, whilst a score of 20 to 25 suggests that the participant's asthma is likely to be well controlled. Baseline value was the last assessment prior to randomization (Day 0). Change from Baseline was post-dose visit value minus the Baseline value. Least square mean change is presented.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Usual ICS/LABA	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188[1]	188[2]		
Units: Scores on a Scale				
least squares mean (standard error)				
Scores on a Scale	2.8 (± 0.26)	3.6 (± 0.26)		

Notes:

[1] - ITT Population. Only those participants available at the specified time points were analyzed.

[2] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The analysis method was an MMRM adjusted for randomized treatment, visit (Week 6 and Week 12), Baseline ACT total score, randomized treatment-by-visit interaction, Baseline ACT total score-by-visit interaction, gender, age, country and participant fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Comparison groups	Usual ICS/LABA v FF/VI

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.033
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.5

Notes:

[3] - Non-inferiority of fixed combination FF/VI to usual ICS/LABA in inhalation powder was assessed assuming a non-inferiority margin of -1.5.

Secondary: Change from Baseline in ACT total score at Week 24

End point title	Change from Baseline in ACT total score at Week 24

End point description:

The ACT is a validated self-completed questionnaire consisting of 5 questions that evaluate asthma control on a 5-point categorical scale. Total scores are calculated from the sum of the scores from the 5 questions and can range from 5 to 25, with higher scores indicating better control. An ACT total score of 5 to 19 suggests that the participant's asthma is unlikely to be well controlled, whilst a score of 20 to 25 suggests that the participant's asthma is likely to be well controlled. Baseline value was the last assessment prior to randomization (Day 0). Change from Baseline was post-dose visit value minus the Baseline value. Least square mean change is presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Usual ICS/LABA	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184[4]	180[5]		
Units: Scores on a Scale				
least squares mean (standard error)				
Scores on a Scale	3.6 (± 0.25)	4.0 (± 0.25)		

Notes:

[4] - ITT Population. Only those participants available at the specified time points were analyzed.

[5] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The analysis method was an MMRM adjusted for randomized treatment, visit (Week 6, Week 12, Week 18 and Week 24), Baseline ACT total score, randomized treatment-by-visit interaction, Baseline ACT total score-by visit interaction, gender, age, country and participant fitted as a random factor. The REML estimation approach was used with a default covariance structure of unstructured.

Comparison groups	Usual ICS/LABA v FF/VI

Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 0.224
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	1.1

Notes:

[6] - Non-inferiority of fixed combination FF/VI to usual ICS/LABA in inhalation powder was assessed assuming a non-inferiority margin of -1.5.

Secondary: Percentage of participants with correct use of device, defined as not making any critical or non-critical errors, at Week 12, and at Week 24 independently of the use at Week 12

End point title	Percentage of participants with correct use of device, defined as not making any critical or non-critical errors, at Week 12, and at Week 24 independently of the use at Week 12

End point description:

Participants were asked to read the appropriate package insert for their prescribed inhaler and then the investigator (or suitably qualified designee) demonstrated the proper use of the inhaler. The participant was then asked to self-administer their first dose of study treatment under the supervision of the investigator and any critical and non-critical errors were recorded. Individual instruments for assessing correct inhaler use were provided for each of the three devices used in this study.

End point type	Secondary

End point timeframe:

Week 12 and Week 24

End point values	Usual ICS/LABA	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[7]	210[8]		
Units: Percentage of participants				
Week 12; n= 195, 197	93	94		
Week 24; n= 191, 192	96	97		

Notes:

[7] - ITT Population. Only those participants available at the specified time points were analyzed.

[8] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The analysis method was logistic regression adjusted for randomized treatment, correct use of inhaler device at Baseline, gender, age and country.

Comparison groups	FF/VI v Usual ICS/LABA

Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82 [9]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	2.62

Notes:

[9] - Week 12

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The analysis method was logistic regression adjusted for randomized treatment, correct use of inhaler device at Baseline, gender, age and country.

Comparison groups	FF/VI v Usual ICS/LABA
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.566 [10]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	4.6

Notes:

[10] - Week 24

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse drug reactions were collected from start of study treatment up to Week 24

Adverse event reporting additional description:

On-treatment SAEs and non-serious adverse drug reactions were collected for the Safety Population comprised of all enrolled participants who received at least one dose of study medication (either FF/VI or usual ICS/LABA) and considered as-treated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	FF/VI

Reporting group description:

Eligible participants received Fluticasone FF/Vilanterol VI 100 mcg/22 mcg or FF/VI 200 mcg/25 mcg 1 inhalation once daily for 24 weeks.

Reporting group title	Usual ICS/LABA

Reporting group description:

Eligible participants received fixed combination ICS/LABA (FP/S 250/50 mcg or 500/50 mcg, 1 inhalation twice daily; or BUD/F 200/6 mcg or 400/12 mcg, 1 or 2 inhalations twice daily) for 24 weeks.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious adverse events above 5% threshold.

Serious adverse events	FF/VI	Usual ICS/LABA	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 209 (1.44%)	4 / 210 (1.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Varicose vein ruptured			
subjects affected / exposed	1 / 209 (0.48%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 209 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 209 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexa uteri pain			
subjects affected / exposed	1 / 209 (0.48%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 209 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 209 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian abscess			
subjects affected / exposed	1 / 209 (0.48%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	FF/VI	Usual ICS/LABA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 209 (0.00%)	0 / 210 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2015	This protocol amendment has been created to correct mistakes in the wording of the inhaler errors questionnaires for the Ellipta®, Diskus® and Turbuhaler inhalers, which are included in Section 7.3.1 of the protocol. All references to 'Type A errors' and 'overall errors' within the protocol, have been changed to 'critical' and 'non-critical' errors, respectively, for consistency with the inhaler errors questionnaire worksheets. Storage condition instructions for Seretide® (fluticasone propionate/salmeterol) in Section 6.7 have been amended. The wording for the recommended number of spirometry efforts has been revised. New text has been included with regards to investigational product malfunction in Section 6.8. The secondary medical monitor contact information has been revised to include a new study physician. Other minor corrections and edits have been made.
28 April 2016	This amendment has been written primarily to allow the addition of a new country/countries to the study. This includes: • Removing reference to France unless specifically required • Amending text to make language more applicable to participating countries • Updating the number of sites • Defining permitted 'usual ICS/LABA combinations' The endpoint associated with Inhaler Correct Use has been further defined. The objective and associated endpoint of adherence with study medication has been amended to compliance with study medication. Mepolizumab (Nucala®) has been added as a prohibited medication at screening and during the study. The option to rescreen a participant following approval by the medical monitor has been added. The section describing planned dose adjustments has been updated to clarify that dose increases are permitted but switching between treatments is not permitted, in accordance with the intention of the protocol. It has been clarified that GSK will not provide treatment following the study. The T&E table has been updated to reflect that Screening, Visit 6 and Withdrawal Visit should be logged on RAMOS NG. This was previously omitted in error. The description of the Per Protocol Population has been updated to reflect terminology now used as standard at GSK. Other minor corrections and edits have been made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported