Clinical trial results:
A Randomised, Double-Blind, Placebo-Controlled, Cross-Over, Single-Centre Study to Investigate the Acute Lung Deflation Effects of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25mcg Once Daily on Cardiac Biventricular Function and Arterial Stiffness in Adults with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2012-000927-42
Trial protocol	GB
Global end of trial date	08 August 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	18 April 2015

Trial information

Trial identification

Sponsor protocol code	HZC116601

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01691885
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	23 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2014
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 test the hypothesis that lung hyperinflation contributes to cardiac dysfunction in COPD and that treatment of lung deflation with Fluticasone Furoate/Vilanterol (FF/VI) Inhalation Powder 100/25 mcg administered once daily (QD) will result in the reversal of this cardiac dysfunction compared with placebo. This will be assessed by measures of right and left global and regional systolic and diastolic cardiac function as assessed using a 30 minute CMR.

Protection of trial subjects:

There were no specific measures other than using the baseline scan as the comparator against which treatment response were compared for both treatment periods, rather than adding another MRI scan at Contact/Visit 4. This reduced the number of visits to the hospital and reduced the number of MRI scans required, also limiting inconvenience to the participants. Subjects who were unable to tolerate the confined conditions of the scanner without claustrophobia were excluded from participating. Routine blood test were performed at screening and randomisation. Spirometry and plethysmography was supervised by a trained respiratory technician.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2012
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	United Kingdom: 96
Worldwide total number of subjects	96
EEA total number of subjects	96

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)	0

Adults (18-64 years)	36
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At Visit 1a, participants who met the eligibility criteria stopped their respiratory medication in preparation for their lung volume assessment at screening Visit 1b. At Visit 1b, participants entered a 7(plus or minus 3) day Run-in Period. Overall study duration, following Screening to Follow-up, was 36 days up to a maximum of 54 days.

Period 1

Period 1 title	Treatment Period 1(7-14 days)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo then FF/VI

Arm description:

Participants entering Treatment Period 1 received matching placebo once daily (QD), each morning via a dry powder inhaler (DPI) for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period participants entered Treatment Period 2 and received Fluticasone Furoate/Vilanterol (FF/VI) 100/25 micrograms (µg), QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

one inhalation each morning via dry powder inhaler

Investigational medicinal product name	FF/VI
Investigational medicinal product code	
Other name	Relvar (A combination product)
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Once a day – AM only. 100mcg/25mcg (FF/VI- combination product)

Arm title	FF/VI then Placebo

Arm description:

Participants entering Treatment Period 1 received FF/VI 100/25 µg QD, each morning via a DPI for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period, participants entered Treatment Period 2 and received matching placebo QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

one inhalation each morning via dry powder inhaler

Investigational medicinal product name	FF/VI
Investigational medicinal product code	
Other name	Relvar (A combination product)
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Once a day – AM only. 100mcg/25mcg (FF/VI- combination product)

Number of subjects in period 1[1]	Placebo then FF/VI	FF/VI then Placebo
Started	22	23
Completed	21	22
Not completed	1	1
Adverse event, non-fatal	1	1

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: Of the 96 total enrolled participants, only 45 were randomized to study treatment. These 45 participants comprised the Modified Intent to Treat and per Protocol populations for analysis.

Period 2

Period 2 title	Washout Period (7-9 days)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo then FF/VI

Arm description:

Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	FF/VI then Placebo

Arm description:

Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Placebo then FF/VI	FF/VI then Placebo
Started	21	22
Completed	21	21
Not completed	0	1
Adverse event, non-fatal	-	1

Period 3

Period 3 title	Treatment Period 2 (7-14 days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo then FF/VI

Arm description:

Participants entering Treatment Period 1 received matching placebo once daily (QD), each morning via a dry powder inhaler (DPI) for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period participants entered Treatment Period 2 and received FF/VI 100/25 micrograms (µg), QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

one inhalation each morning via dry powder inhaler

Investigational medicinal product name	FF/VI
Investigational medicinal product code	
Other name	Relvar (A combination product)
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Once a day – AM only. 100mcg/25mcg (FF/VI- combination product)

Arm title	FF/VI then Placebo

Arm description:

Participants entering Treatment Period 1 received FF/VI 100/25 µg QD, each morning via a DPI for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period, participants entered Treatment Period 2 and received matching placebo QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
one inhalation each morning via dry powder inhaler

Investigational medicinal product name	FF/VI
Investigational medicinal product code	
Other name	Relvar (A combination product)
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
Once a day – AM only. 100mcg/25mcg (FF/VI- combination product)

Number of subjects in period 3	Placebo then FF/VI	FF/VI then Placebo
Started	21	21
Completed	21	21

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period 1(7-14 days)

Reporting group description:

All participants received placebo or FF/VI 100/25 µg in either of the two treatment periods QD, each morning from a DPI. Treatment periods lasted 7 days up to a maximum of 14 days for each period. The two treatments were separated by a wash out period of 7 days, up to a maximum of 9 days. Participants were provided salbutamol/ ipratropium bromide (administered via a MDI or nebules) to be used as needed throughout the study.

Reporting group values	Treatment Period 1(7-14 days)	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 64.4 ± 8.95	 -	
Gender categorical Units: Subjects			
Female Male	17 28	17 28	
Race, Customized Units: Subjects			
African American/African Heritage White - White/Caucasian/European Heritage	6 39	6 39	

End points

End points reporting groups

Reporting group title	Placebo then FF/VI

Reporting group description:

Participants entering Treatment Period 1 received matching placebo once daily (QD), each morning via a dry powder inhaler (DPI) for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period participants entered Treatment Period 2 and received Fluticasone Furoate/Vilanterol (FF/VI) 100/25 micrograms (µg), QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Reporting group title	FF/VI then Placebo

Reporting group description:

Participants entering Treatment Period 1 received FF/VI 100/25 µg QD, each morning via a DPI for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period, participants entered Treatment Period 2 and received matching placebo QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Reporting group title	Placebo then FF/VI

Reporting group description:

Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days.

Reporting group title	FF/VI then Placebo

Reporting group description:

Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days.

Reporting group title	Placebo then FF/VI

Reporting group description:

Participants entering Treatment Period 1 received matching placebo once daily (QD), each morning via a dry powder inhaler (DPI) for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period participants entered Treatment Period 2 and received FF/VI 100/25 micrograms (µg), QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Reporting group title	FF/VI then Placebo

Reporting group description:

Participants entering Treatment Period 1 received FF/VI 100/25 µg QD, each morning via a DPI for a period of 7 days, up to a maximum of 14 days. Following Treatment Period 1, participants entered a washout period for 7 days, up to a maximum of 9 days. Following the washout period, participants entered Treatment Period 2 and received matching placebo QD, each morning via a DPI for 7 days, up to a maximum of 14 days.

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received matching placebo once daily (QD), each morning via a dry powder inhaler (DPI) for a period of 7 days, up to a maximum of 14 days during one of the two Treatment Periods. Participants that received placebo in Treatment Period 1, crossed over after the washout period to receive FF/VI 100/25 µg during Treatment Period 2. Participants that received FF/VI 100/25 µg during Treatment Period 1, crossed over after the washout period to receive placebo during Treatment Period 2.

Subject analysis set title	FF/VI
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received FF/VI 100/25 µg QD, each morning via a DPI for a period of 7 days, up to a maximum of 14 days during one of the two Treatment Periods. Participants that received FF/VI 100/25 µg in Treatment Period 1, crossed over after the washout period to receive placebo during Treatment Period 2. Participants that received placebo during Treatment Period 1, crossed over after the washout period to receive FF/VI 100/25 µg during Treatment Period 2.

Primary: Mean change from Baseline in right ventricular end diastolic volume index (RVEDVI) at the end of the Overall Treatment Period

End point title	Mean change from Baseline in right ventricular end diastolic volume index (RVEDVI) at the end of the Overall Treatment Period

End point description:

RVEDVI is a measure of the volume of blood in the right ventricle at the end of diastole, normalized over body surface area and was measured using Cardiac Magnetic Resonance (CMR) imaging. RVEDVI is calculated as the right ventricular end diastolic volume (RDEDV) divided by the body surface area (BSA). The change from Baseline in RVEDVI was analyzed using a mixed model analysis with period, treatment group, and Baseline RVEDVI fitted as fixed effects and participants fitted as a random effect. The Baseline is defined as the assessment performed pre-dose at Day 1 of Treatment Period 1. The change from Baseline is calculated as the RVEDVI value at the end of each treatment period minus the Baseline value. The Per Protocol (PP) Population was comprised of all participants in the modified intent-to-treat (mITT) Population not identified as having deviations considered to impact the primary efficacy analysis.

End point type	Primary

End point timeframe:

Baseline and end of Treatment Period

End point values	Placebo	FF/VI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[1]	43[2]		
Units: Milliliter per meter square (mL/m^2)				
least squares mean (standard error)	-0.47 (± 1.393)	5.35 (± 1.365)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The statistical analysis shows that 41 participants received placebo (in either treatment period 1 or treatment period 2) and 43 participants received FF/VI (in either treatment period 1 or treatment period 2). In a cross over study each participant acts as their own control and therefore appear in both treatment groups, unless withdrawn. Therefore, the comparison groups total should be 45, not 84 as automatically totalled by the database.

Comparison groups	Placebo v FF/VI
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.74
upper limit	8.91

Notes:

[3] - Analysis was performed using an ANCOVA model with covariates of treatment, baseline, period and subject as a random effect.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On treatment serious adverse events (SAEs) were collected from the signing of informed consent and non-serious adverse events (AEs) were collected from the start of study treatment (randomization) and up to the end of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo once daily (QD), each morning via a dry powder inhaler (DPI) for a period of 7 days, up to a maximum of 14 days during one of the two Treatment Periods. Participants that received placebo in Treatment Period 1, crossed over after the washout period to receive FF/VI 100/25 µg during Treatment Period 2. Participants that received FF/VI 100/25 µg during Treatment Period 1, crossed over after the washout period to receive placebo during Treatment Period 2. Participants were provided salbutamol/ ipratropium bromide (administered via a MDI or nebules) to be used as needed throughout the study.

Reporting group title	FF/VI

Reporting group description:

Participants received FF/VI 100/25 µg QD, each morning via a DPI for a period of 7 days, up to a maximum of 14 days during one of the two Treatment Periods. Participants that received FF/VI 100/25 µg in Treatment Period 1, crossed over after the washout period to receive placebo during Treatment Period 2. Participants that received placebo during Treatment Period 1, crossed over after the washout period to receive FF/VI 100/25 µg during Treatment Period 2. Participants were provided salbutamol/ ipratropium bromide (administered via a MDI or nebules) to be used as needed throughout the study.

Serious adverse events	Placebo	FF/VI	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo	FF/VI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 43 (4.65%)	2 / 44 (4.55%)	
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	2 / 44 (4.55%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2013	Allow subject screening to occur over two separate screening visits Allow an extension of the screening period window to permit subjects to be included following an exacerbation Change to medication inclusion criteria Clarification to the time related to washout of medications Addition of lung function endpoints Correction of minor typographical errors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported