Clinical trial results:
A randomised double-blind, parallel group, dose-ranging study to evaluate the efficacy and safety of three different total daily doses of fluticasone propionate inhaled from a new dry powder inhaler in subjects with severe persistent asthma requiring oral corticosteroid therapy

Summary

EudraCT number	2011-005030-19
Trial protocol	GB DE HU PL BG ES
Global end of trial date	31 October 2013

Results information

Result version number	v1 (current)
This version publication date	22 July 2016
First version publication date	22 July 2016

Trial information

Trial identification

Sponsor protocol code	VR506/2/004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01720069
WHO universal trial number (UTN)	-
Other trial identifiers	IND number : 107310

Notes:

Sponsors

Sponsor organisation name	Vectura Limited
Sponsor organisation address	1 Prospect West, Chippenham, United Kingdom,
Public contact	Clinical Trials Information, Vectura Limited, +44 1249667700, clinical.enquiries@vectura.com
Scientific contact	Clinical Trials Information, Vectura Limited, +44 1249667700, clinical.enquiries@vectura.com

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	31 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy and dose-response relationship, using oral corticosteroid (OCS) modulation, of 3 different total daily doses of Fluticasone Propionate Inhalation Powder taken using a twice daily regimen from nDPI for 16 weeks in subjects with severe persistent asthma requiring OCS therapy, i.e. Step 5 treatment as defined by modified Global Initiative for Asthma (GINA) guidelines (GINA 2011).

Protection of trial subjects:

There are no specific measures for protection of patients.

Background therapy:

Evidence for comparator: -

Actual start date of recruitment	29 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	Romania: 49
Country: Number of subjects enrolled	Ukraine: 47
Worldwide total number of subjects	196
EEA total number of subjects	139

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	195
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period covered 29 October 2012 to 31 October 2013. Subjects were screened at 61 sites in 8 countries: Bulgaria, Germany, Hungary, Poland, Romania, Ukraine, United Kingdom (UK) and United States of America (USA).

Pre-assignment

Screening details:

Subjects were screened at 61 sites in 8 countries: Bulgaria, Germany, Hungary, Poland, Romania, Ukraine, UK & US.
Total of 285 subjects were screened of whom 197 from 56 sites were randomised. 1 subject in Romania was randomised, not treated. So only 196 were treated . 88 subjects failed screening, 35 discontinued during treatment period.

Period 1

Period 1 title	Randomisation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Double-blind conditions were secured by the identical appearance of 3 strengths of the Test Product. Due to the coded labelling of the IMPs, neither site personnel nor subject knew which treatment was being administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test product 1

Arm description:

Fluticasone Propionate Inhalation Powder 50ug

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

Dosage and administration details:

50ug Inhalation Powder per actuation. Self administered twice daily

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

Dosage and administration details:

50ug Inhalation Powder per actuation. Self administered twice daily

Arm title	Test Product 2

Arm description:

Fluticasone Propionate Inhalation Powder 250ug

Arm type	Experimental

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

Dosage and administration details:

250ug Inhalation Powder per actuation. Self administered twice daily

Arm title	Test Product 3

Arm description:

Fluticasone Propionate Inhalation Powder 500ug

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

Dosage and administration details:

500ug Inhalation Powder per actuation. Self administered twice daily

Number of subjects in period 1	Test product 1	Test Product 2	Test Product 3
Started	62	71	63
Completed	57	56	48
Not completed	5	15	15
Consent withdrawn by subject	-	2	1
Non-compliance on using e-diary	-	-	1
Asthma exacerbation	-	4	-
Adverse event, non-fatal	-	-	1
OCS bursts occured, discontinued in line with IWRS	1	-	-
Could not use e-diary correctly	-	1	1
Treatment period withdrawal criteria met	4	8	9
Lost to follow-up	-	-	1
Randomised without baseline values	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Test product 1
Reporting group description: Fluticasone Propionate Inhalation Powder 50ug	
Reporting group title	Test Product 2
Reporting group description: Fluticasone Propionate Inhalation Powder 250ug	
Reporting group title	Test Product 3
Reporting group description: Fluticasone Propionate Inhalation Powder 500ug	

Reporting group values	Test product 1	Test Product 2	Test Product 3
Number of subjects	62	71	63
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Adolescents (12-17 years)	0	1	0
Children (2-11 years)	0	0	0
Adults (18-64 years)	62	70	63
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	40	45	42
Male	22	26	21
Ethnic group Units: Subjects			
White	60	70	62
Black or African American	2	0	1
Other	0	1	0
Country Units: Subjects			
Bulgaria	6	7	6
Germany	4	3	3
Hungary	3	3	4
Poland	15	18	16
Romania	16	17	16
Ukraine	15	18	14
UK	1	1	0
US	2	4	4

Reporting group values	Total		

Number of subjects	196		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Adolescents (12-17 years)	1		
Children (2-11 years)	0		
Adults (18-64 years)	195		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	127		
Male	69		
Ethnic group Units: Subjects			
White	192		
Black or African American	3		
Other	1		
Country Units: Subjects			
Bulgaria	19		
Germany	10		
Hungary	10		
Poland	49		
Romania	49		
Ukraine	47		
UK	2		
US	10		

End points

End points reporting groups	
Reporting group title	Test product 1
Reporting group description: Fluticasone Propionate Inhalation Powder 50ug	
Reporting group title	Test Product 2
Reporting group description: Fluticasone Propionate Inhalation Powder 250ug	
Reporting group title	Test Product 3
Reporting group description: Fluticasone Propionate Inhalation Powder 500ug	

Primary: Prednisone/Prednisolone Dose for Analysis (PDA)	
End point title	Prednisone/Prednisolone Dose for Analysis (PDA)
End point description:	
End point type	Primary
End point timeframe: 16 weeks	

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: mg				
arithmetic mean (standard deviation)	4.55 (± 6.85)	4.31 (± 7.38)	3.97 (± 6.21)	

Statistical analyses

Statistical analysis title	Prednisone/Prednisolone Dose for Analysis (PDA)
Comparison groups	Test product 1 v Test Product 2 v Test Product 3
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Secondary: In-clinic morning pre-dose FEV1	
End point title	In-clinic morning pre-dose FEV1

End point description:

This secondary endpoint measures the mean change in the in-clinic morning pre-dose FEV1 from baseline to end of study. FEV1 is measured in Litres (L).

End point type	Secondary

End point timeframe:

16 weeks

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: FEV1				
arithmetic mean (standard deviation)	0.06 (± 0.4)	0.02 (± 0.31)	0.06 (± 0.35)	

Statistical analyses

Statistical analysis title	In-clinic morning pre-dose FEV1

Statistical analysis description:

FEV1 is measured in Litres (L)

Comparison groups	Test Product 2 v Test Product 3 v Test product 1
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Secondary: ACQ-5 total score

End point title	ACQ-5 total score

End point description:

To measure the change from baseline to end of study in ACQ-5 mean total score

End point type	Secondary

End point timeframe:

16 weeks

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: ACQ-5 Mean total score				
arithmetic mean (standard deviation)	-0.67 (± 0.98)	-0.77 (± 1.15)	-0.39 (± 0.89)	

Statistical analyses

Statistical analysis title	ACQ-5 Total Score
Comparison groups	Test product 1 v Test Product 2 v Test Product 3
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Secondary: Weekly average morning pre-dose PEF	
End point title	Weekly average morning pre-dose PEF
End point description: To measure the change from baseline to end of study in the weekly mean morning pre-dose PEF.	
End point type	Secondary
End point timeframe: 16 weeks	

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: L/min				
arithmetic mean (standard deviation)	2 (± 45.7)	20.1 (± 51.7)	6.1 (± 53.5)	

Statistical analyses

Statistical analysis title	Weekly average morning pre-dose PEF
Comparison groups	Test product 1 v Test Product 2 v Test Product 3
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Secondary: Weekly average asthma night-time symptom score	
End point title	Weekly average asthma night-time symptom score

End point description:

To measure the change from baseline to end of study for the weekly mean asthma night time symptom score .

End point type	Secondary

End point timeframe:

16 weeks

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: Symptom score				
arithmetic mean (standard deviation)	-0.3 (± 1)	-0.6 (± 1)	-0.2 (± 1)	

Statistical analyses

Statistical analysis title	Weekly average asthma night-time symptom score
Comparison groups	Test product 1 v Test Product 2 v Test Product 3
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Secondary: Withdrawals due to worsening of asthma	
End point title	Withdrawals due to worsening of asthma

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: Number of patient withdrawals	4	11	8	

Statistical analyses

Statistical analysis title	Number of withdrawals due to worsening of asthma
Statistical analysis description: Arm 1 versus Arm 2	
Comparison groups	Test product 1 v Test Product 2
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Number of withdrawals due to worsening of asthma
Statistical analysis description: Arm 1 versus Arm 3	
Comparison groups	Test product 1 v Test Product 3
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Number of withdrawals due to worsening of asthma
Statistical analysis description: Arm 2 and Arm 3	
Comparison groups	Test Product 2 v Test Product 3
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Secondary: Proportion of subjects stopping oral corticosteroid (OCS) treatment	
End point title	Proportion of subjects stopping oral corticosteroid (OCS) treatment
End point description:	
End point type	Secondary
End point timeframe: 16 weeks	

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: Number of subjects stopping OCS	29	23	24	

Statistical analyses

Statistical analysis title	Proportion of subjects stopping OCS Arm 1 v Arm 2
Comparison groups	Test Product 2 v Test product 1
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Proportion of subjects stopping OCS Arm 1 v Arm 3
Comparison groups	Test Product 3 v Test product 1
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Proportion of subjects stopping OCS Arm 2 v Arm 3
Comparison groups	Test Product 2 v Test Product 3
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Secondary: Number of Subjects with Asthma Exacerbations

End point title	Number of Subjects with Asthma Exacerbations

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: Number of subjects with Exacerbations	11	26	10	

Statistical analyses

Statistical analysis title	Number of Subjects with Asthma Exacerbations
Comparison groups	Test Product 2 v Test product 1
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact

Statistical analysis title	Number of Subjects with Asthma Exacerbations
Comparison groups	Test product 1 v Test Product 3
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Number of Subjects with Asthma Exacerbations
Comparison groups	Test Product 2 v Test Product 3
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact

Secondary: Proportion subjects achieving asthma control OCS dose

End point title	Proportion subjects achieving asthma control OCS dose

End point description:

End point type	Secondary

End point timeframe: 16 weeks

End point values	Test product 1	Test Product 2	Test Product 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	63	
Units: Subjects achieving asthma control	47	43	42	

Statistical analyses

Statistical analysis title	Proportion subjects achieving asthma control
Statistical analysis description: Proportion subjects achieving asthma control OCS dose	
Comparison groups	Test Product 2 v Test product 1
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Proportion subjects achieving asthma control
Statistical analysis description: Proportion subjects achieving asthma control OCS dose	
Comparison groups	Test Product 3 v Test product 1
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Proportion subjects achieving asthma control
Statistical analysis description: Proportion subjects achieving asthma control OCS dose	
Comparison groups	Test Product 2 v Test Product 3

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 16 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14
Reporting groups	
Reporting group title	Test Product 1
Reporting group description: -	
Reporting group title	Test Product 2
Reporting group description: -	
Reporting group title	Test Product 3
Reporting group description: -	

Serious adverse events	Test Product 1	Test Product 2	Test Product 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 71 (0.00%)	0 / 63 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Test Product 1	Test Product 2	Test Product 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 62 (33.87%)	33 / 71 (46.48%)	25 / 63 (39.68%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 62 (3.23%)	4 / 71 (5.63%)	1 / 63 (1.59%)
occurrences (all)	3	4	1
Dizziness			
subjects affected / exposed	0 / 62 (0.00%)	2 / 71 (2.82%)	0 / 63 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	12 / 62 (19.35%)	26 / 71 (36.62%)	12 / 63 (19.05%)
occurrences (all)	15	35	16
Oropharyngeal pain			
subjects affected / exposed	2 / 62 (3.23%)	0 / 71 (0.00%)	2 / 63 (3.17%)
occurrences (all)	2	0	2
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 71 (0.00%)	2 / 63 (3.17%)
occurrences (all)	0	0	3
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 62 (1.61%)	1 / 71 (1.41%)	2 / 63 (3.17%)
occurrences (all)	2	1	3
Acute sinusitis			
subjects affected / exposed	0 / 62 (0.00%)	3 / 71 (4.23%)	1 / 63 (1.59%)
occurrences (all)	0	4	1
Oral candidiasis			
subjects affected / exposed	2 / 62 (3.23%)	0 / 71 (0.00%)	0 / 63 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	2 / 62 (3.23%)	0 / 71 (0.00%)	1 / 63 (1.59%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2012	The reasons for the amendment are as follows: "Risk/Benefit Assessment" section amended to include justification of doses, in order to provide information on the reasons for the selection of the proposed doses to be used in the study; Removal of inclusion criterion requiring subjects to have a documented history of airway inflammation indicated by an elevated blood eosinophil count. On review of the literature, the presence of raised levels of eosinophils in the blood was not considered to be an adequate predictor of either airway inflammation or steroid responsive asthma, so this criterion did not offer a useful selection criterion to predict response but would have reduced the eligible population. Addition of acetaminophen as well as paracetamol in concomitant medication list as clinics in the US are taking part in this study; Correction to Figure 1; Correction to in clinic FEV1 withdrawal criterion to ensure consistency with inclusion criteria; Correction to albuterol/salbutamol use withdrawal criterion; Increased number of study sites; Clarification that patients are invited to return to the study clinic for end-of-study assessments; References added to support additional information provided in "Risk/Benefit Assessment".
05 October 2012	To clarify and make consistent information regarding prednisone/prednisolone dose reductions and escalations throughout the protocol and appendices.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported