Clinical trial results:
STUDY COMPARING BRONCHODILATOR EFFICACY OF TWO DRY POWDER INHALERS, BUDESONIDE/FORMOTEROL EASYHALER AND SYMBICORT TURBUHALER; A RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY, MULTICENTRE, SINGLE DOSE, CROSSOVER STUDY IN ASTHMATIC SUBJECTS

Summary

EudraCT number	2014-002705-38
Trial protocol	HU BG
Global end of trial date	12 June 2015

Results information

Result version number	v1 (current)
This version publication date	19 June 2016
First version publication date	19 June 2016

Trial information

Trial identification

Sponsor protocol code	3103013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02308098
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Orion Corporation
Sponsor organisation address	Orionintie 1, Espoo, Finland, 02200
Public contact	clinicaltrials@orionpharma.com, Orion Corporation Orion Pharma, +358 104261, clinicaltrials@orionpharma.com
Scientific contact	clinicaltrials@orionpharma.com, Orion Corporation Orion Pharma, +358 104261, clinicaltrials@orionpharma.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	12 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2015
Global end of trial reached?	Yes
Global end of trial date	12 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to confirm equivalent bronchodilator efficacy of the test product (Budesonide/formoterol Easyhaler) compared to the reference product (Symbicort Turbuhaler).

Protection of trial subjects:

Safety parameters: (vital signs, 12-lead electrocardiograms, laboratory variables) were assessed, physical examinations were done, and adverse events were recorded.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2014
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	Bulgaria: 48
Country: Number of subjects enrolled	Hungary: 24
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	62
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Investigators recruited asthmatic patients from their clinics.

Pre-assignment

Screening details:

Documented diagnosis of asthma for more than 6 months. Prebronchodilator FEV1 45-90 % of predicted value.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Budesonide/formoterol Easyhaler 9/320 ug one inhalation
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Budesonide/formoterol Easyhaler 9/320 ug dry powder inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: One inhalation as a single dose	
Arm title	Budesonide/formoterol Easyhaler 9/320 ug four inhalations
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Budesonide/formoterol Easyhaler 9/320 ug dry powder inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: Four inhalations as a single dose	
Arm title	Symbicort Turbuhaler 9/320 ug one inhalation
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Symbicort Turbuhaler 9/320 ug dry powder inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: One inhalation as a single dose	
Arm title	Symbicort Turbuhaler 9/320 ug four inhalations

Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Symbicort Turbuhaler 9/320 ug dry powder inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Four inhalations as a single dose

Number of subjects in period 1	Budesonide/formoterol Easyhaler 9/320 ug one inhalation	Budesonide/formoterol Easyhaler 9/320 ug four inhalations	Symbicort Turbuhaler 9/320 ug one inhalation
Started	72	72	72
Completed	67	67	67
Not completed	5	5	5
Lack of reproducibility of spirometry	1	1	1
Lost to follow-up	2	2	2
Protocol deviation	2	2	2

Number of subjects in period 1	Symbicort Turbuhaler 9/320 ug four inhalations
Started	72
Completed	67
Not completed	5
Lack of reproducibility of spirometry	1
Lost to follow-up	2
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
Adults (18-64 years)	62	62	
Adults (65-84 years)	10	10	
Gender categorical Units: Subjects			
Female	46	46	
Male	26	26	

End points

End points reporting groups

Reporting group title	Budesonide/formoterol Easyhaler 9/320 ug one inhalation
Reporting group description: -	
Reporting group title	Budesonide/formoterol Easyhaler 9/320 ug four inhalations
Reporting group description: -	
Reporting group title	Symbicort Turbuhaler 9/320 ug one inhalation
Reporting group description: -	
Reporting group title	Symbicort Turbuhaler 9/320 ug four inhalations
Reporting group description: -	

Primary: Average FEV1 between doses

End point title	Average FEV1 between doses
End point description:	
End point type	Primary
End point timeframe:	
0-12 h after dosing	

End point values	Budesonide/formoterol Easyhaler 9/320 ug one inhalation	Budesonide/formoterol Easyhaler 9/320 ug four inhalations	Symbicort Turbuhaler 9/320 ug one inhalation	Symbicort Turbuhaler 9/320 ug four inhalations
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[1]	53[2]	53[3]	53[4]
Units: litre(s)				
least squares mean (confidence interval 95%)	2.324 (2.287 to 2.36)	2.411 (2.374 to 2.447)	2.332 (2.295 to 2.368)	2.419 (2.382 to 2.455)

Notes:

[1] - PP population

[2] - PP population

[3] - PP population

[4] - PP population

Statistical analyses

Statistical analysis title	General linear model
Comparison groups	Budesonide/formoterol Easyhaler 9/320 ug one inhalation v Budesonide/formoterol Easyhaler 9/320 ug four inhalations v Symbicort Turbuhaler 9/320 ug one inhalation v Symbicort Turbuhaler 9/320 ug four inhalations

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Primary: Average FEV1 within doses

End point title	Average FEV1 within doses

End point description:

End point type	Primary

End point timeframe:

0-12 hours after dosing

End point values	Budesonide/formoterol Easyhaler 9/320 ug one inhalation	Budesonide/formoterol Easyhaler 9/320 ug four inhalations	Symbicort Turbuhaler 9/320 ug one inhalation	Symbicort Turbuhaler 9/320 ug four inhalations
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[5]	53[6]	53[7]	53[8]
Units: litre(s)				
least squares mean (confidence interval 95%)	2.334 (2.292 to 2.376)	2.401 (2.359 to 2.44)	2.321 (2.279 to 2.364)	2.429 (2.387 to 2.471)

Notes:

[5] - PP population

[6] - PP population

[7] - PP population

[8] - PP population

Statistical analyses

Statistical analysis title	General linear model
Comparison groups	Budesonide/formoterol Easyhaler 9/320 ug one inhalation v Symbicort Turbuhaler 9/320 ug one inhalation
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.073

Primary: Average FEV1 within doses 2

End point title	Average FEV1 within doses 2[9]

End point description:

End point type	Primary

End point timeframe:

0-12 hours after dosing

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparisons within doses by definition does not include all the arms.

End point values	Budesonide/formoterol Easyhaler 9/320 ug four inhalations	Symbicort Turbuhaler 9/320 ug four inhalations		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[10]	53[11]		
Units: litre(s)				
least squares mean (confidence interval 95%)	2.401 (2.359 to 2.443)	2.429 (2.387 to 2.471)		

Notes:

[10] - PP population

[11] - PP population

Statistical analyses

Statistical analysis title	General linear model
Comparison groups	Symbicort Turbuhaler 9/320 ug four inhalations v Budesonide/formoterol Easyhaler 9/320 ug four inhalations
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	-0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.087
upper limit	0.032

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From screening to end of study visit.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Budesonide/formoterol Easyhaler 9/320 ug one inhalation
Reporting group description: -	
Reporting group title	Budesonide/formoterol Easyhaler 9/320 ug four inhalations
Reporting group description: -	
Reporting group title	Symbicort Turbuhaler 9/320 ug one inhalation
Reporting group description: -	
Reporting group title	Symbicort Turbuhaler 9/320 ug four inhalations
Reporting group description: -	

Serious adverse events	Budesonide/formoterol Easyhaler 9/320 ug one inhalation	Budesonide/formoterol Easyhaler 9/320 ug four inhalations	Symbicort Turbuhaler 9/320 ug one inhalation
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	0 / 70 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Symbicort Turbuhaler 9/320 ug four inhalations		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 68 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Budesonide/formoterol Easyhaler 9/320 ug one inhalation	Budesonide/formoterol Easyhaler 9/320 ug four inhalations	Symbicort Turbuhaler 9/320 ug one inhalation
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 68 (2.94%)	1 / 70 (1.43%)	3 / 70 (4.29%)

Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 70 (0.00%) 0	1 / 70 (1.43%) 1
General disorders and administration site conditions Product taste abnormal subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	1 / 70 (1.43%) 1	0 / 70 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Dysphonia subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 70 (1.43%) 1	0 / 70 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 70 (0.00%) 0	2 / 70 (2.86%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	0 / 70 (0.00%) 0	0 / 70 (0.00%) 0
Infections and infestations Viral infection subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 70 (0.00%) 0	0 / 70 (0.00%) 0

Non-serious adverse events	Symbicort Turbuhaler 9/320 ug four inhalations		
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 68 (2.94%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0		
General disorders and administration site conditions Product taste abnormal subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		
Respiratory, thoracic and mediastinal disorders			

Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0 0 / 68 (0.00%) 0 0 / 68 (0.00%) 0		
Infections and infestations Viral infection subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported