Clinical trial results:
A Double Blind, Double Dummy, Randomized, Two Way Cross-Over Study To Compare The Effects Of Z7200 And Symbicort® Turbohaler On Functional Respiratory Imaging Parameters In Asthmatic Patients

Summary

EudraCT number	2014-002151-26
Trial protocol	BE
Global end of trial date	28 November 2014

Results information

Result version number	v1 (current)
This version publication date	23 March 2016
First version publication date	23 March 2016
Summary attachment (see zip file)	Study Results Synopsis (Z7200K02 CSR synopsis_final2_2Oct2015 No PW.pdf)

Trial information

Trial identification

Sponsor protocol code	Z7200K02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02227394
WHO universal trial number (UTN)	-
Other trial identifiers	CRO protocol code number: FLUI-2014-125

Notes:

Sponsors

Sponsor organisation name	Zambon SpA
Sponsor organisation address	via Lillo Del Duca 10, Bresso, Italy, 20091
Public contact	Clinical Development, R&D Open Innovation Zambon SpA, +39 02.665241, clinicaltrials@zambongroup.com
Scientific contact	Clinical Development, R&D Open Innovation Zambon SpA, +39 02.665241, clinicaltrials@zambongroup.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	02 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of the products under investigation on Functional Respiratory Imaging (FRI)
parameters and evaluate the particle deposition with Computational Fluid Dynamics (CFD) in comparison to a reference product.

Protection of trial subjects:

Salbutamol MDI was supplied as rescue medication at screening/enrolment visit and could have been used until 6 hours before the first study procedure.
The use of concomitant inhalation drugs was maintained constant throughout the study.
Patients who were on combination therapy were switched to ICS on the evening before the dosing days (Visits 2 and 3).

Background therapy: -

Evidence for comparator:

The comparator is a product available on the market in EU (Symbicort Turbohaler, DPI) with the same active ingredients but at a different dose level.

Actual start date of recruitment	25 August 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	Belgium: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	13
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects are recruited at the clinic

Pre-assignment

Screening details:

Only patients who met all inclusion criteria and none of the exclusion criteria were enrolled in the study and entered the run-in period of 7 (minimum) to 31 (maximum) days . Bronchodilator therapy was washed out before dosing.

Period 1

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

Blinding implementation details:

A double dummy technique was implemented.
Patients were to receive a single dose consisting of 2 inhalations of either the test product or the reference product, according to the assigned treatment sequence, in the presence of the Investigator or authorized site personnel. In addition, patients were to receive 2 inhalations with matching placebo to the alternate treatment as a dummy inhaler to achieve double-blinding.

Arms

Arm title	Treatment period
Arm description: -	
Arm type	Cross-over experimental
Investigational medicinal product name	Z7200
Investigational medicinal product code	
Other name	Formoterol/budesonide combination product
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Two inhalations by using dedicated RS-01 device

Investigational medicinal product name	Symbicort
Investigational medicinal product code	
Other name	Formoterol/budesonide combination product
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Two inhalations by using multidose Turbohaler (Dry Powder Inhaler)

Number of subjects in period 1	Treatment period
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
from 18 to 80 years	20	20	
Age continuous Units: years			
arithmetic mean	58.5		
standard deviation	± 11.6	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	12	12	
FEV1% predicted Units: Percentage			
arithmetic mean	96.79		
standard deviation	± 22.82	-	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

all randomized patients who received at least one dose of study drug

Subject analysis set title	pre dose Z7200
Subject analysis set type	Per protocol

Subject analysis set description:

all randomized patients who had correct Z7200 administration, without any major protocol deviations that could possibly have influenced the assessment of the product effect

Subject analysis set title	pre- dose SYMBICORT
Subject analysis set type	Per protocol

Subject analysis set description:

all randomized patients who had correct Symbicort administration, without any major protocol

deviations that could possibly have influenced the assessment of the product effect

Subject analysis set title	post- dose Z7200
Subject analysis set type	Per protocol

Subject analysis set description:

all randomized patients who had correct Z7200 administration, without any major protocol deviations that could possibly have influenced the assessment of the product effect

Subject analysis set title	Post-dose Symbicort
Subject analysis set type	Per protocol

Subject analysis set description:

all randomized patients who had correct Symbicort administration, without any major protocol deviations that could possibly have influenced the assessment of the product effect

Reporting group values	Safety population	pre dose Z7200	pre- dose SYMBICORT
Number of subjects	20	20	20
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
from 18 to 80 years	20	20	
Age continuous			
Units: years			
arithmetic mean	58.5	58.5	
standard deviation	± 11.6	± 11.6	±
Gender categorical			
Units: Subjects			
Female	8	8	
Male	12	12	
FEV1% predicted			
Units: Percentage			
arithmetic mean	96.79	96.79	
standard deviation	± 22.82	± 22.82	±

Reporting group values	post- dose Z7200	Post-dose Symbicort	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over from 18 to 80 years			
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			
FEV1% predicted Units: Percentage arithmetic mean standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Treatment period
Reporting group description: -	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: all randomized patients who received at least one dose of study drug	
Subject analysis set title	pre dose Z7200
Subject analysis set type	Per protocol
Subject analysis set description: all randomized patients who had correct Z7200 administration, without any major protocol deviations that could possibly have influenced the assessment of the product effect	
Subject analysis set title	pre- dose SYMBICORT
Subject analysis set type	Per protocol
Subject analysis set description: all randomized patients who had correct Symbicort administration, without any major protocol deviations that could possibly have influenced the assessment of the product effect	
Subject analysis set title	post- dose Z7200
Subject analysis set type	Per protocol
Subject analysis set description: all randomized patients who had correct Z7200 administration, without any major protocol deviations that could possibly have influenced the assessment of the product effect	
Subject analysis set title	Post-dose Symbicort
Subject analysis set type	Per protocol
Subject analysis set description: all randomized patients who had correct Symbicort administration, without any major protocol deviations that could possibly have influenced the assessment of the product effect	

Primary: Imaged Based Total Airway Volume (iVaw)

End point title	Imaged Based Total Airway Volume (iVaw)
End point description:	
End point type	Primary
End point timeframe: Pre and post-dose	

End point values	pre dose Z7200	pre- dose SYMBICORT	post- dose Z7200	Post-dose Symbicort
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	20	20
Units: millilitre(s)				
arithmetic mean (standard deviation)	49.03 (± 13.23)	48.58 (± 13.43)	51.1 (± 12.74)	50.83 (± 13.48)

Statistical analyses

Statistical analysis title	iVaw post-dose differences
Statistical analysis description: change in pre and post dose value are compared in the statistical analysis (difference test vs reference)	
Comparison groups	Post-dose Symbicort v post- dose Z7200
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.59
Method	t-test, 2-sided

Primary: Imaged Based Total Airway Resistance (iRaw)

End point title	Imaged Based Total Airway Resistance (iRaw)
End point description:	
End point type	Primary
End point timeframe: pre and post-dose	

End point values	pre dose Z7200	pre- dose SYMBICORT	post- dose Z7200	Post-dose Symbicort
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	20	20
Units: kPa/L				
arithmetic mean (standard deviation)	0.034 (± 0.016)	0.037 (± 0.022)	0.025 (± 0.011)	0.026 (± 0.009)

Statistical analyses

Statistical analysis title	iRaw post-dose differences
Statistical analysis description: change from pre-dose test vs reference difference	
Comparison groups	post- dose Z7200 v Post-dose Symbicort
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.75
Method	t-test, 2-sided

Primary: Lung dose of Budesonide

End point title	Lung dose of Budesonide

End point description: dosimetry simulation per inhalation of test vs reference (1 puff)	
End point type	Primary
End point timeframe: post-dose	

End point values	post- dose Z7200	Post-dose Symbicort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: microgram(s)/dose				
arithmetic mean (standard deviation)	45.05 (± 6.66)	36.35 (± 12.94)		

Statistical analyses

Statistical analysis title	Dosimetry comparison budesonide
Comparison groups	post- dose Z7200 v Post-dose Symbicort
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.018
Method	t-test, 2-sided

Primary: Lung dose of formoterol

End point title	Lung dose of formoterol
End point description: Dosimetry simulation of test vs reference per inhalation (1 puff)	
End point type	Primary
End point timeframe: post-dose	

End point values	post- dose Z7200	Post-dose Symbicort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: microgram(s)/dose				
arithmetic mean (standard deviation)	1.26 (± 0.18)	0.88 (± 0.34)		

Statistical analyses

Statistical analysis title	Dosimetry comparison formoterol
Comparison groups	Post-dose Symbicort v post- dose Z7200
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided

Secondary: VAS dyspnea (pre 6MWT)

End point title	VAS dyspnea (pre 6MWT)

End point description:

The VAS dyspnea was completed using an analogue scale from "very much worse" to "very much improved". Rating was measured using a ruler in cm from the indication "unchanged"

End point type	Secondary

End point timeframe:

before the exercise test (6 minutes walking test)

End point values	post- dose Z7200	Post-dose Symbicort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: percentage	19	8		

Statistical analyses

Statistical analysis title	VAS dyspnea pre 6MWT difference

Statistical analysis description:

VAS dyspnea measured after inhalation of test and reference before exercise test

Comparison groups	post- dose Z7200 v Post-dose Symbicort
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.034
Method	t-test, 2-sided

Secondary: VAS dyspnea (post 6MWT)

End point title	VAS dyspnea (post 6MWT)

End point description:

The VAS dyspnea was completed using an analogue scale from "very much worse" to "very much improved" . Rating was measured using a ruler in cm from the indication "unchanged"

End point type	Secondary
End point timeframe: post exercise test (6MWT)	

End point values	post- dose Z7200	Post-dose Symbicort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: percentage	21	16		

Statistical analyses

Statistical analysis title	VAS dyspnea post 6MWT difference
Comparison groups	Post-dose Symbicort v post- dose Z7200
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.43
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: All AEs were collected and reported from signature of informed consent form up to Visit 4. Adverse events that occurred before the first dosing with study drugs were defined as pre-treatment AEs.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	safety population
Reporting group description: all subjects randomized with at least one dose of test or reference administered.	

Serious adverse events	safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (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	safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	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