Clinical trial results:
A Randomized, Double Blind, Single Dose, Crossover Study, in Subjects with Mild to Moderate Asthma, to Compare the Pharmacodynamic (Bronchodilator) Responses of 12.5/250 µg and 50/250 µg Salmeterol / Fluticasone Propionate (SAL/FP) Delivered Via a Novel Dry Powder Inhaler Device PulmoJet® Versus the Seretide Diskus® 50/250

Summary

EudraCT number	2014-005047-40
Trial protocol	DE GB BG
Global end of trial date	25 August 2015

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	SIT001-12

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis
Sponsor organisation address	de Montfleury 3, Vernier, Switzerland,
Public contact	Michael Klein, Zentiva Inhalationsprodukte GmbH Staffelseestr. 4 81477 Munich, +49 89710502130, michael.klein@zentiva.de
Scientific contact	Michael Klein, Zentiva Inhalationsprodukte GmbH Staffelseestr. 4 81477 Munich, +49 89710502130, michael.klein@zentiva.de

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	14 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the therapeutic non-inferiority of the bronchodilator responses (area under the time curve of forced expiratory volume in 1 second [AUC-FEV1]) over 12 hours of the salmeterol component (50 µg) of a novel SAL/FP combination dry powder inhaler product (PulmoJet 50 µg/250 µg SAL/FP; test) with the respective mid-strength of the European reference product (Seretide Diskus; reference).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 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	United Kingdom: 107
Country: Number of subjects enrolled	Bulgaria: 22
Country: Number of subjects enrolled	Germany: 111
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	13
Adults (18-64 years)	227

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 sites in 3 countries. A total of 240 subjects (227 adults and 13 adolescents) enrolled in the study.

Pre-assignment

Screening details:

From 240 subjects enrolled in the study, 124 subjects (112 adults and 12 adolescents) met the entry criteria, and 123 subjects (111 adults and 12 adolescents) were randomly assigned. One subject was randomized in error and immediately discontinued prior to receiving study drug.

Pre-assignment period milestones

Number of subjects started	240
Number of subjects completed	122

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 4
Reason: Number of subjects	Failed Inclusion/Exclusion Criterion: 112
Reason: Number of subjects	randomised in error: 1
Reason: Number of subjects	Physician decision: 1

Period 1

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

Arms

Arm title	Test 2

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PulmoJet 50/250 SAL/FP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Single-dose, Dose per inhalation SAL: 50 µg, FP: 250 µg

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

Dosage and administration details:

Lactose Monohydrate, Single-dose

Number of subjects in period 1[1]	Test 2
Started	122
Completed	117
Not completed	5
Meet the Stopping Criteria: Stability	4
Lost to follow-up	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: A total of 240 subjects (227 adults and 13 adolescents) enrolled in the study, 124 subjects (112 adults and 12 adolescents) met the entry
criteria, and 123 subjects (111 adults and 12 adolescents) were randomly assigned. One subject was randomized in error and immediately discontinued prior to receiving study drug. The remaining 122 randomised subjects received Treatment. Treatment B was set as baseline period.

Period 2

Period 2 title	Treatment A
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Arm title	Test 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PulmoJet 12.5/250 SAL/FP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Single-dose, Dose per inhalation SAL: 12.5 µg, FP: 250 µg

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

Dosage and administration details:

Lactose Monohydrate, Single-dose

Number of subjects in period 2	Test 1
Started	117
Completed	117

Period 3	
Period 3 title	Treatment C
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Arm title	Reference
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Seretide Diskus 50/250 SAL/FP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Single-dose, Dose per inhalation SAL: 50 µg, FP: 250 µg

Investigational medicinal product name	PulmoJet SAL/FP Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Lactose Monohydrate, Single-dose

Number of subjects in period 3	Reference
Started	117
Completed	117

Baseline characteristics

Reporting groups	
Reporting group title	Treatment B

Reporting group description: -

Reporting group values	Treatment B	Total	
Number of subjects	122	122	
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	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	38.3		
standard deviation	± 13.2	-	
Gender categorical Units: Subjects			
Female	37	37	
Male	85	85	

End points

End points reporting groups	
Reporting group title	Test 2
Reporting group description: -	
Reporting group title	Test 1
Reporting group description: -	
Reporting group title	Reference
Reporting group description: -	

Primary: baseline-adjusted positive-shifted FEV1-AUC0-12	
End point title	baseline-adjusted positive-shifted FEV1-AUC0-12
End point description:	
End point type	Primary
End point timeframe: after each dosing	

End point values	Test 2	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: L•h				
arithmetic mean (standard deviation)	9.244 (± 4.354)	8.478 (± 4.063)		

Statistical analyses

Statistical analysis title	bronchodilator response B/C
Comparison groups	Reference v Test 2
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2706
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.16
Variability estimate	Standard deviation

Secondary: Duration of Bronchodilatation

End point title	Duration of Bronchodilatation
End point description:	
End point type	Secondary
End point timeframe: after every dosing	

End point values	Test 2	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: hour				
arithmetic mean (standard deviation)	7.27 (± 5.043)	6.3 (± 5.089)		

Statistical analyses

Statistical analysis title	Duration of Bronchodilatation B/C
Comparison groups	Test 2 v Reference
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0125
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.62
Variability estimate	Standard deviation

Secondary: Maximum Spirometry (FEV1)

End point title	Maximum Spirometry (FEV1)
End point description:	
End point type	Secondary
End point timeframe: after every dosing	

End point values	Test 2	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: Liters				
arithmetic mean (standard deviation)	3.366 (± 0.84563)	3.2963 (± 0.8187)		

Statistical analyses

Statistical analysis title	Maximum FEV1 B/C
Comparison groups	Test 2 v Reference
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.1
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit regardless of seriousness or relationship to investigational product

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Test 2
Reporting group description: -	
Reporting group title	Test 1
Reporting group description: -	
Reporting group title	Reference

Reporting group description: -

Serious adverse events	Test 2	Test 1	Reference
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)	0 / 117 (0.00%)	0 / 117 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Test 2	Test 1	Reference
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 117 (20.51%)	28 / 117 (23.93%)	27 / 117 (23.08%)
Investigations			
Investigations			
subjects affected / exposed	1 / 117 (0.85%)	1 / 117 (0.85%)	2 / 117 (1.71%)
occurrences (all)	1	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 117 (9.40%)	15 / 117 (12.82%)	10 / 117 (8.55%)
occurrences (all)	16	15	13
Eye disorders			

Conjunctivitis allergic			
subjects affected / exposed	2 / 117 (1.71%)	0 / 117 (0.00%)	0 / 117 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Gastrointestinal Disorders			
subjects affected / exposed	5 / 117 (4.27%)	6 / 117 (5.13%)	2 / 117 (1.71%)
occurrences (all)	7	7	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 117 (0.85%)	2 / 117 (1.71%)	1 / 117 (0.85%)
occurrences (all)	1	2	1
Respiratory, thoracic and mediastinal disorders			
Respiratory, Thoracic and Mediastinal Disorders			
subjects affected / exposed	3 / 117 (2.56%)	3 / 117 (2.56%)	7 / 117 (5.98%)
occurrences (all)	3	3	7
Skin and subcutaneous tissue disorders			
Skin and Subcutaneous Tissue Disorders			
subjects affected / exposed	1 / 117 (0.85%)	1 / 117 (0.85%)	1 / 117 (0.85%)
occurrences (all)	1	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 117 (0.00%)	5 / 117 (4.27%)
occurrences (all)	0	0	5
Rhinitis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 117 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	0	2

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