

**Clinical trial results:**

**A pharmacokinetic and pharmacodynamic, randomised, single dose, cross-over, partially blinded study to compare the systemic exposure and the efficacy of a fixed-dose combination of Budesonide-Salmeterol DPI capsule 75-25 g, Budesonide-Salmeterol DPI capsule 75-12.5 g, Budesonide-Salmeterol DPI capsule 75-6.25 g delivered by the Axahaler® versus Serevent® Diskus® 50 g + Pulmicort® Turbohaler® 100µg co-administration in asthmatic children**

**Summary**

EudraCT number	2017-003330-91
Trial protocol	BG
Global end of trial date	30 September 2018

**Results information**

Result version number	v1 (current)
This version publication date	11 April 2019
First version publication date	11 April 2019

**Trial information****Trial identification**

Sponsor protocol code	BUSAL-II-17-1
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**Additional study identifiers**

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

Notes:

**Sponsors**

Sponsor organisation name	Laboratoires SMB S.A.
Sponsor organisation address	26-28 rue de la pastorale, Brussels, Belgium,
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Scientific contact	TREMEGE Mickaël, Laboratoires SMB S.A., 32 (0)2411 48 28, DptClinique@smb.be

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	07 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2018
Global end of trial reached?	Yes
Global end of trial date	30 September 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the non-inferiority between budesonide-salmeterol DPI capsule 75/25µg and Serevent® Diskus® 50 µg + Pulmicort® Turbohaler® 100µg co-administration by measurement of the bronchodilating effect

To assess and compare the systemic exposure of budesonide after administration of the two study products (budesonide-salmeterol DPI capsule 75/25µg versus Serevent® Diskus® 50 µg + Pulmicort® Turbohaler® 100µg co-administration) in asthmatic children aged from 6 to 11 years old, inclusive.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practices (GCP), including International Conference on Harmonization (ICH) Guidelines, Directive 2001/20/EC of the European Parliament and the most recent version of the declaration of Helsinki (64th WMA General Assembly, Fortaleza, October 2013).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2018
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
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	48
Adolescents (12-17 years)	0

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

## Subject disposition

### Recruitment

Recruitment details:

The patients will be screened within 3 weeks prior to the randomization visit. Following all screening procedures, patients who satisfy all of the preliminary inclusion/exclusion criteria will be randomised in the study.

### Pre-assignment

Screening details:

signed informed consent form by his/her parents

Demographic data

Asthma history

Medical history and physical examination

Vital signs/ECG

Review of prior and conco

Measurement of pulmonary function/reversibility test

Lab tests

Review IC/EC

### Period 1

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

Blinding implementation details:

This is a partly blinded study. Indeed, as the double blind is not feasible due to the impossibility to obtain placebo from the reference products (Serevent® and Pulmicort®), the blind was maintained only for the two lower doses of the budesonide/salmeterol combination. The randomization procedure is applied in the study design to minimize the bias possibility as the investigator will not be able to predict the next treatment option for the sequential patient randomization in the trial

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	BUSAL 75/25µg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Budesonide/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

one capsule a day by inhalation via the Axahaler®, containing 75µg of budesonide and salmeterol

<b>Arm title</b>	BUSAL 75/12.5µg
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Budesonide/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

one capsule a day by inhalation via the Axahaler®, containing budesonide and salmeterol

<b>Arm title</b>	BUSAL 75/6.25µg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Budesonide/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

one capsule a day by inhalation via the Axahaler®, containing 75µg of budesonide and salmeterol

<b>Arm title</b>	Serevent/pulmicort50/100µg
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Budesonide/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

SEREVENT® DISKUS® 50µg, one inhalation via the Diskus®, each inhalation containing 50µg of salmeterol

PULMICORT® TURBOHALER® 100µg, one inhalation taken by inhalation via the turbohaler®, each inhalation containing 100µg of budesonide

<b>Number of subjects in period 1</b>	BUSAL 75/25µg	BUSAL 75/12.5µg	BUSAL 75/6.25µg
Started	48	48	48
Completed	45	45	45
Not completed	3	3	3
Consent withdrawn by subject	2	2	2
Subject failed to demonstrate FEV1 stability	1	1	1

<b>Number of subjects in period 1</b>	Serevent/pulmicort50/100µg
Started	48
Completed	45
Not completed	3
Consent withdrawn by subject	2
Subject failed to demonstrate FEV1 stability	1

## Baseline characteristics

### Reporting groups

Reporting group title	Study phase
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Reporting group description: -

Reporting group values	Study phase	Total	
Number of subjects	48	48	
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)	48	48	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	9.30		
standard deviation	± 1.72	-	
Gender categorical			
Units: Subjects			
Female	27	27	
Male	21	21	

## End points

### End points reporting groups

Reporting group title	BUSAL 75/25µg
Reporting group description: -	
Reporting group title	BUSAL 75/12.5µg
Reporting group description: -	
Reporting group title	BUSAL 75/6.25µg
Reporting group description: -	
Reporting group title	Serevent/pulmicort50/100µg
Reporting group description: -	

### Primary: FEV1 AUC0-12h

End point title	FEV1 AUC0-12h
End point description:	
End point type	Primary
End point timeframe:	
Clinical assessments should always start in the morning between 07:00 and 10:00 a.m. with study treatment administration done at the same time as the first administration done at Visit 2. Pulmonary function tests will be performed at all visits	

End point values	BUSAL 75/25µg	BUSAL 75/12.5µg	BUSAL 75/6.25µg	Serevent/pulmicort50/100µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	45	45	45
Units: L/sec*h				
arithmetic mean (standard deviation)	2.72 (± 1.09)	2.23 (± 1.12)	2.09 (± 1.09)	2.64 (± 1.42)

### Statistical analyses

Statistical analysis title	Non-inferiority analysis
Comparison groups	BUSAL 75/25µg v Serevent/pulmicort50/100µg
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0068 <sup>[1]</sup>
Method	t-test, 1-sided
Parameter estimate	ratio Test/reference
Point estimate	1.08

Confidence interval	
level	95 %
sides	1-sided
lower limit	0.93

Notes:

[1] - Since the lower bound of the 95% CI of the ratio was over the non-inferiority threshold (0.90), the null hypothesis of inferiority was rejected. Therefore BUSAL75-25 µg was demonstrated to be non-inferior to Serevent 50 µg + Pulmicort 100 µg.

### Primary: Cmax

End point title	Cmax <sup>[2]</sup>
End point description:	

End point type	Primary
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End point timeframe:

The blood sampling were performed at various timepoints only after administration of BUSAL 75/25µg and Serevent/pulmicort 50/100µg.

Notes:

[2] - 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 objective was to assess and compare the systemic exposure of budesonide after administration of the two study products (budesonide-salmeterol DPI capsule 75/25µg versus Serevent® Diskus® 50 µg + Pulmicort® Turbohaler® 100µg co-administration). Therefore, only these two treatments were compared.

End point values	BUSAL 75/25µg	Serevent/pulmicort50/100µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: pg/ml				
arithmetic mean (standard deviation)	229.67 (± 94.08)	145.43 (± 64.52)		

### Statistical analyses

Statistical analysis title	Bioequivalence test
Comparison groups	BUSAL 75/25µg v Serevent/pulmicort50/100µg
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	1.65
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.45
upper limit	1.89

### Primary: AUCt

End point title	AUCt <sup>[3]</sup>
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End point description:

End point type	Primary
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End point timeframe:

The blood samplings were performed at various timepoints on peridos where BUSAL 75/25µg and Serevent/pulmicort were administered.

Notes:

[3] - 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 objective was to assess and compare the systemic exposure of budesonide after administration of the two study products (budesonide-salmeterol DPI capsule 75/25µg versus Serevent® Diskus® 50 µg + Pulmicort® Turbohaler® 100µg co-administration). Therefore, only these two treatments were compared.

End point values	BUSAL 75/25µg	Serevent/pulmicort50/100µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: pg/ml*min				
arithmetic mean (standard deviation)	32347.27 (± 9414.34)	22627.58 (± 9862.86)		

## Statistical analyses

Statistical analysis title	bioequivalence test
Comparison groups	BUSAL 75/25µg v Serevent/pulmicort50/100µg
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	1.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.32
upper limit	1.7

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Safety profile will be compared using:

- Adverse events
- Physical examination
- Vital signs
- 12 lead ECG
- Tremor
- Serum glucose and potassium measurements

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

### Reporting groups

Reporting group title	BUSAL 75/25µg
Reporting group description: -	
Reporting group title	BUSAL 75/12.5µg
Reporting group description: -	
Reporting group title	BUSAL 75/6.25µg
Reporting group description: -	
Reporting group title	Serevent/Pulmicort 50/100µg
Reporting group description: -	

Serious adverse events	BUSAL 75/25µg	BUSAL 75/12.5µg	BUSAL 75/6.25µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 48 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Serevent/Pulmicort 50/100µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	BUSAL 75/25µg	BUSAL 75/12.5µg	BUSAL 75/6.25µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 48 (0.00%)

<b>Non-serious adverse events</b>	Serevent/Pulmicort 50/100µg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)		

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Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events superior to the frequency threshold were reported in this study.

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported