CONFIDENTIAL

CLINICAL REPORT SUMMARY

1 TITLE PAGE

Clinical Report No.: Final version

Protocol No.: BUSAL-III-08-1
EudraCT No.: 2008-004833-70

Date of Issue: March 15th, 2010

Study Title: **A PHASE III, RANDOMIZED, PARALLEL GROUP, OPEN STUDY TO COMPARE THE THERAPEUTIC EFFICACY AND SAFETY OF SMB BUDESONIDE-SALMETEROL DPI CAPSULE 150/25 µG BID DELIVERED BY THE AXAHALER® VERSUS SYMBICORT® TURBUHALER® 200/12 µG BID OVER 12 WEEKS IN MODERATE TO SEVERE PERSISTENT ASTHMATIC PATIENTS.**

Drug Name: SMB BUDESONIDE-SALMETEROL Dry Powder inhaler 150/25 µg

Indication / Purpose: Reversible airway obstruction

Methodology: Multicentre, randomized, parallel group, non-inferiority, open study.

Drug Development Phase: III

Country: Bulgaria, Romania, Macedonia and Serbia

Coordinating Investigators:

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First Patient First Visit: February 13th, 2009

Last Patient Last Visit: August 6th, 2009

Sponsor Signatory:

Laboratoires SMB S.A.
Rue de la Pastorale, 26-28
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2 SYNOPSIS

Name of Sponsor/Company: Laboratoires SMB S.A.	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: To be determined		
Name of Active Ingredient: Budesonide 150 µg/ Salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

Title of Study:

A PHASE III, RANDOMISED, PARALLEL GROUP, OPEN STUDY TO COMPARE THE THERAPEUTIC EFFICACY AND SAFETY OF SMB BUDESONIDE-SALMETEROL DPI CAPSULE 150/25 µG BID DELIVERED BY THE AXAHALER® VERSUS SYMBICORT® TURBUHALER® 200/12 µG BID OVER 12 WEEKS IN MODERATE TO SEVERE PERSISTENT ASTHMATIC PATIENTS.

Study Center/Investigator:

22 investigational centres were planned in Bulgaria, Romania, Macedonia and Serbia. Back-up sites were initiated, and finally 25 and 1 satellite sites were activated.

26 out of the 26 centers were active and selected at least one patient (7 in Bulgaria, 9 in Romania, 4 in Macedonia and 6 in Serbia). 24 of these 26 centers enrolled at least one patient: 7 in Bulgaria, 7 in Romania, 4 in Macedonia and 6 in Serbia.

Publication (Reference):

NA.

Study Period:	**Phase of Development:**
February 13th, 2009 (First Patient First Visit) - August 6th, 2009 (Last Patient Last Visit).	Phase III

Objectives:

The study aimed:

1) to compare the therapeutic efficacy in a non-inferiority model of 12 weeks course of SMB Budesonide-Salmeterol DPI capsule 150/25 µg delivered by Axahaler®, taken BID, versus Symbicort® Turbuhaler® 200/12 µg BID, taken by inhalation, in patients with moderate to severe persistent asthma.

2) to compare the safety of SMB Budesonide-Salmeterol DPI capsule 150/25 µg taken BID versus Symbicort® Turbuhaler® 200/12 µg BID taken by inhalation, in patients with moderate to severe persistent asthma over 12 weeks.

Methodology:

This was a randomised, parallel group, non-inferiority, open-label multicenter study.

The planned duration of the study was 14 weeks per patient:

- a 2-week screening/run-in period during which patients were all treated with Budesonide (Pulmicort® Turbuhaler®, 800 µg/d) and placebo via Axahaler®. Patients were trained about using placebo during the run-in period.
- a 12-week open-label treatment period during which patients were treated either with SMB Budesonide-Salmeterol DPI capsule 150/25 µg BID or Symbicort® Turbuhaler® 200/12 µg BID.

5 visits were planned for each patient :

- V1 - Screening visit (W-2)
- V2 - Randomization (W1±2 days)
- V3 - 3 weeks (21 days) after randomization (±3 days)
- V4 - 6 weeks (42 days) after randomization (±3 days)
- V5 - Final visit, 12 weeks (84 days) after randomization (±3 days)

Inhaled Salbutamol (max. 1600 µg/d) was permitted as rescue medication at any time of the study but at least 6 hours prior to performing the pulmonary function test.

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Number of Patients (Planned, Entered, Randomized and Analysed):

Planned: an estimated total of 300 patients to be screened in order to obtain 216 included patients and a per-protocol subset of 196 patients (98 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 98 patients in the Symbicort® Turbuhaler® 200/12 µg group).

Selected: 329 patients.

Randomized: 229 patients (115 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 114 patients in the Symbicort® Turbuhaler® 200/12 µg group).

Safety analysis (treated patients) : 229 patients (115 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 114 patients in the Symbicort® Turbuhaler® 200/12 µg group).

ITT efficacy analysis: 222 patients (113 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 109 patients in the Symbicort® Turbuhaler® 200/12 µg group).

PP analysis: 216 patients (109 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 107 patients in the Symbicort® Turbuhaler® 200/12 µg group).

Diagnosis and Main Criteria for Inclusion:

Men or women, aged from 18 to 65 years old, with a diagnosis of moderate to severe persistent asthma for a minimum of 6 months duration with FEV_1 range of 50-80 % predicted at screening and baseline, at least 12 % in FEV_1 and 200 mL reversibility to 4 puffs of Salbutamol 100 µg and having asthma symptoms partly controlled or uncontrolled according to the GINA guidelines.

Patients were excluded from participating in the study if they received oral or parental corticosteroids in the past 8 weeks or were hospitalized for an asthma exacerbation or a related disorder in the past 3 months before screening visit.

Test Product, Dose and Mode of Administration:

- Investigational medicinal product: **SMB Budesonide-Salmeterol DPI 150/25 µg**, one capsule, taken twice a day by inhalation via the Axahaler®, containing 150 µg of Budesonide and 25 µg of Salmeterol (equivalent to 36.3 µg of Salmeterol xinafoate).
- Reference therapy: **Symbicort® Turbuhaler® 100/6 µg**, two inhalations taken twice a day via the Turbuhaler®, containing 100 µg of Budesonide and 6 µg of Formoterol.

Duration of Treatment:

During the 2-week run-in period, patients inhaled Budesonide (Pulmicort® Turbuhaler®, 800 µg/d) and placebo (via Axahaler®).

During the 12-week open-label treatment period, patients inhaled either SMB Budesonide-Salmeterol DPI 150/25 µg BID or Symbicort® Turbuhaler® 200/12 µg BID .

Criteria for Evaluation:

Primary efficacy assessment:

- Mean change over the weeks from baseline to W12 in morning pre-dose peak expiratory flow (PEF).

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Criteria for Evaluation:

Secondary efficacy assessment (Pulmonary Function Test was performed at each visit before study drug intake at least 12 hours after the previous dose):

- Mean change over the weeks from baseline to W12 in evening pre-dose PEF
- Mean change over the weeks from baseline to W12 in FEV_1
- Mean change over the weeks from baseline to W12 in FEV_1 % of predicted
- Mean change over the weeks from baseline to W12 in Forced Vital Capacity (FVC)
- Mean change over the weeks from baseline to W12 in asthma symptoms score
- Mean change over the weeks from baseline to W12 in sleep disturbance score (subset of the asthma symptom score)
- Number of asthma exacerbations
- Number of bronchodilator rescue inhalations

Safety assessment:

- Adverse events (AEs)
- Withdrawals or drop-out rate due to AEs
- Physical examination
- Vital signs
- 12-lead ECG
- Laboratory data

Statistical Methods:

The statistical analysis was realized using the 9.1. SAS software (SAS Institute, Cary, NC, USA).

Handling of missing data:

Missing efficacy data were replaced using the LOCF method (i.e. the last available evaluation under treatment will be carried out forward to W12).

Definitions:

Baseline value: for parameters assessed every day, baseline was defined as the mean of the 5 last days with available results within 10 days before randomization; for FEV_1, FEV_1% of predicted and FVC parameters, the baseline was defined as the value at randomization visit (V2).

Endpoint value: for parameters assessed every day, week 12 was defined as the mean of the 5 last days with available results within 10 days before Visit 5 (week12); for FEV1, FEV1% of predicted and FVC parameters, the endpoint value was defined as the value at Visit 5 (week12). Same rules were applied for calculation of W3 and W6 values.

Descriptive statistics:

Continuous variables were described in each group by the number of documented patients, mean, standard deviation, range, median and amount of missing data.

Binary and categorical variables were described in each group by the frequency and percentage of each modality as well as amount of missing data.

Efficacy analysis:

Given the non-inferiority design, both the PP and the ITT sets were used for a robust interpretation of the efficacy analysis.

The analysis of covariance (ANCOVA) with factors for treatment, site within country, age, sex, and baseline value was used on efficacy parameters to compare the two treatments (Budesonide-Salmeterol 150/25 µg vs Symbicort® 100/6 µg, significance level $p<0.05$). Two-sided 95% adjusted confidence interval (CI) were calculated for the mean difference of LSmeans between treatments for each efficacy parameter between baseline and W12. To demonstrate the non-inferiority, CI had to be above the non-inferiority margin, - 20 L/min, for both the PP and the ITT analysis set.

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Safety analysis:

The number and frequency of patients experiencing a specific adverse event and the number of AEs were tabulated by group, system organ class, and preferred term.

Evolution of vital signs and ECGs during the efficacy period (from V2 to V5) was analyzed by ANOVA for repeated measurements.

Laboratory data were described at V1, V3, V4 and V5 per treatment group. For each parameter and for each treatment group, change from baseline to V5 was provided. A Student's t-test for paired series was performed in order to test if the change observed between V5 and baseline was significantly different from 0 (= no change) in each treatment group. Moreover an analysis of covariance adjusted on baseline was performed to test the difference at V5 between treatment groups.

Summary - Conclusions:

Efficacy conclusions:

The analysis was carried out on an ITT subset including 222 patients divided into 2 well-balanced treatment groups: 113 patients received Budesonide-Salmeterol 150/25 µg, 109 patients received Symbicort® 200/12 µg. All treatments were administered twice a day by inhalation (once in the morning and once in the evening) for 12 weeks. The compliance was very good in both groups.

The main efficacy criteria was the pre-dose morning PEF that significantly increased in both groups over the study. The lower bound of the two-sided 95% confidence interval for effect size was -2.93 L/min, a value far upper of the lower limit of not inferiority set in the protocol (-20 L/min). ITT analysis and PP analysis gave consistent results.

Secondary efficacy parameters included evening PEF, pulmonary function test results, scores for asthma symptoms and use of rescue medications. Results for evening PEF were consistent with those obtained for morning PEF. Lower bound of the two-sided 95% confidence interval for effect size was -6.56 L/min. FEV1 and FVC significantly increased in both groups without difference between groups. Need for rescue medications was significantly and similarly reduced in both groups. Details in table below.

Table 1. Summary of evolution of pulmonary function parameters and use of rescue medication between baseline and W12 endpoint in ITT population

	BUSAL 150/25 µg N=113		Symbicort® 200/12 µg N=109		Effect size 95% CI	p for effect size
Parameters	lsmeans±SE endpoint-baseline	p-value for lsmeans	lsmeans±SE endpoint-baseline	p-value for lsmeans		
Morning PEF (L/min)	37.97±6.89	<0.0001	25.77±6.61	<0.0001	12.19 [-2.93 ; 27.32]	0.11
Evening PEF (L/min)	25.77±6.81	<0.0001	17.32±6.53	0.003	8.45 [-6.56 ; 23.45]	0.27
FEV_1 (L/sec)	0.26±0.05	<0.0001	0.24±0.04	<0.0001	0.02 [-0.08 ; 0.12]	0.72
FEV_1 (% predicted)	8.44±1.51	<0.0001	7.75±1.45	<0.0001	0.69 [-2.66 ; 4.04]	0.46
FVC (L)	0.29±0.06	<0.0001	0.22±0.06	<0.0001	0.08 [-0.05 ; 0.21]	0.24
Daily number of rescue medication inhalations	-1.17±0.20	<0.0001	-1.14±0.19	<0.0001	-0.03 [-0.47 ; 0.42]	0.91
% of days with rescue medication	-31.71± 4.90	<0.0001	-25.75±4.80	<0.0001	-5.96 [-17.38 ; 5.46]	0.30

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Asthma symptoms decreased from baseline to W12 endpoint in both groups. There were no differences between the groups at W12 end-point.

Table 2. Evolution of asthma evaluation scores from baseline to W12 endpoint in ITT population

		ITT population N=222		p CMH
		BUSAL 150/25 µg N=113	Symbicort® 200/12 µg N=109	
Score for cough	N m±SD [min - max ; med]	113 -0.34±0.59 [-2.50 - 1.20 ; -0.20]	109 -0.27±0.50 [-2.30 - 1.20 ; -0.10]	0.27
Score for shortness of breath	N m±SD [min - max ; med]	113 -0.32±0.57 [-2.50 - 1.20 ; -0.20]	109 -0.23±0.54 [-2.00 - 1.60 ; -0.10]	0.13
Score for wheezing	N m±SD [min - max ; med]	113 -0.22±0.60 [-2.60 - 1.60 ; 0.00]	109 -0.20±0.54 [-2.00 - 1.60 ; 0.00]	0.49
Asthma symptoms score	N m±SD [min - max ; med]	113 -0.86±1.61 [-7.50 - 3.00 ; -0.40]	109 -0.73±1.51 [-6.00 - 4.60 ; -0.3]	0.34
Sleep disturbance score	N m±SD [min - max ; med]	113 -0.34±0.60 [-2.60 - 1.10 ; -0.20]	109 -0.26±0.51 [-2.00 - 1.50 ; -0.10]	0.30
Total asthma symptoms score	N m±SD [min - max ; med]	113 -1.21±2.15 [-10.10 - 3.80 ; -0.70]	109 -1.00±1.96 [-8.00 - 6.10 ; -0.50]	0.31

These results were confirmed by the PP analysis.

Globally the study demonstrated that Budesonide-Salmeterol 150/25µg is a potent combination for the treatment of moderate to severe persistent asthma, reducing symptoms and improving lung function tests. Budesonide-Salmeterol 150/25µg can be considered to be not inferior to Symbicort® on pre-dose morning PEF improvement in these patients.

Safety conclusions:

Safety evaluation was conducted in all randomized patients having taken at least one unit of the study drug. 115 patients from the Budesonide-salmeterol group and 114 patients form the Symbicort® group were involved in the safety analysis.

Patients randomized in the Budesonide-Salmeterol group received a mean nominal daily dose of 276.80±29.24 µg/d of Budesonide and mean nominal daily dose of 46.13±4.87 µg/d of Salmeterol; patients randomized in the Symbicort® group received a mean nominal daily dose 379.37±66.91 µg/d of Budesonide and a mean nominal daily dose of 22.76±4.01 µg/d of Formoterol.

From W-2 to W0, twenty-three (23) adverse events were reported by 17 of the 254 patients who entered the run-in period. 4 patients discontinued the trial during the run-in period due to an AE. Three of them reported an asthma exacerbation.
During the treatment period (from W0 to W12), 82 AEs were reported by 47 of the 115 patients treated with Budesonide-Salmeterol 150/25 µg(40.87 %) and 133 AEs were reported by 53 of the 114 patients treated with Symbicort® 200/12 µg (46.49 %). Few AEs were judged treatment-related: 9 in the Budesonide-Salmeterol group (reported by 7 patients) and 5 in the Symbicort® group (reported by 5 patients). No AE of severe intensity occurred the during treatment period. One emergent SAE was reported concerning a woman treated with Symbicort® who became pregnant during the treatment period.

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Three patients, all of whom treated with Symbicort® 200/12 µg, discontinued the study due to an AE: one patient for asthma exacerbation, one patient for angioedema and one patient for pregnancy. No AE led to drug discontinuation in the Budesonide-Salmeterol group.

Fifty five asthma exacerbations occurred during the treatment period : 17 exacerbations -all of mild intensity- were reported by 10 patients treated with Budesonide-Salmeterol and 38 exacerbations -36 of mild intensity and 2 of moderate intensity- were reported by 15 patients treated with Symbicort. These AEs were not related to study treatment.

Clinically relevant changes in laboratory values or vital signs were noticed in 5 patients. 2 in the Budesonide-Salmeterol group: hypokalaemia (treatment related) and diabetes mellitus (but blood glucose level was out of range at entry) and 3 in the Symbicort® group: hypokalaemia (treatment related), hyperbilirubinemia (not treatment related - reported as medical history at entry) and elevations of liver enzymes at W12 (not treatment related).

Therefore, Budesonide-Salmeterol appeared to be well tolerated and offers a safety profile expected in combination with long acting bêta$_2$ agonist and glucocorticoid.