C O N F I D E N T I A L

CLINICAL REPORT SUMMARY

1. TITLE PAGE

Clinical Report No.:	Final version	**Protocol No.:**	BUSAL-II-10-2
		EudraCT No.:	2010-020794-16
Date of Issue:	August 26th, 2011		
Study Title:	**A PHASE II, RANDOMISED, PARTIALLY-BLINDED, CROSS OVER STUDY TO EVALUATE THE SYSTEMIC EFFECT OF TWO DOSES OF THE SMB BUDESONIDE-SALMETEROL DPI FIXED-DOSE COMBINATION CAPSULE (300/25 µG BID AND 150/25 µG BID) DELIVERED BY THE AXAHALER® VERSUS PULMICORT® TURBOHALER® 400 µG BID AND SEREVENT® DISKUS® 50 µG BID VERSUS PLACEBO IN MILD PERSISTENT ASTHMATIC PATIENTS.**		
Drug Name:	Budesonide (budesonide) -Salmeterol (salmeterol xinafoate)		
Indication / Purpose:	Reversible airway obstruction		
Methodology:	Randomized, cross-over, partially-blinded		
Drug Development Phase:	Phase II		
Country:	Bulgaria		
Coordinating Investigator:	Assoc. Prof. Todor Popov, PhD UMHAT "Sv. Ivan Rilski" Clinic for Professional Diseases 13, Urvich Str., 3-rd Floor 1612 Sofia, Bulgaria		
First Patient First Visit:	October 20th, 2010		
Last Patient Last Visit:	March 25th, 2011		
Sponsor Signatory:	Laboratoires SMB S.A. Rue de la Pastorale 26-28 1080 Brussels, Belgium		

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 Ingredients: - Budesonide 300 µg / Salmeterol 25 µg fixed dose combination - Budesonide 150 µg / Salmeterol 25 µg fixed dose combination		

Title of Study:

A PHASE II, RANDOMISED, PARTIALLY-BLINDED, CROSS OVER STUDY TO EVALUATE THE SYSTEMIC EFFECT OF TWO DOSES OF THE SMB BUDESONIDE-SALMETEROL DPI FIXED-DOSE COMBINATION CAPSULE (300/25 µG BID AND 150/25 µG BID) DELIVERED BY THE AXAHALER® VERSUS PULMICORT® TURBOHALER® 400 µG BID AND SEREVENT® DISKUS® 50 µG BID VERSUS PLACEBO IN MILD PERSISTENT ASTHMATIC PATIENTS.

Study Center/Investigator:

One site in Bulgaria.

Publication (Reference):

NA

Study Period:	**Phase of Development:**
First Patient First Visit: 20/10/2010 Last Patient Last Visit: 25/03/2011	Phase II

Objectives:

- To compare the systemic effect of two doses of SMB Budesonide-Salmeterol DPI capsule (300/25 µg BID and 150/25 µg BID) versus Pulmicort® Turbohaler® 400 µg BID and Serevent® Diskus® 50 µg BID versus placebo by the measurement of 24-hour plasma and urinary cortisol.
- To assess and compare the safety of the tests versus reference products.

Methodology:

Randomised, cross-over, partially-blinded study.

Number of Patients (Planned, Consented, Randomized and Analyzed):

Planned: 40 patients included, 30 patients completed.

Included: 49 patients screened, 40 patients randomised.

Treated: 40 patients treated (at least one treatment intake for at least one treatment period).

Completed *(per treatment group)*: BUSAL 300/25 µg: N=39; BUSAL 150/25 µg: N=39; placebo: N=38; Pulmicort® Turbohaler® + Serevent® Diskus®: N=39.

Analyzed:

- 40 patients were involved in the safety analysis. Considering the cross-over study design, 39 patients were analysed in the BUSAL 300/25 µg group, 39 patients were analysed in the BUSAL 150/25 µg group, 38 patients were analysed in the placebo group and 39 patients were analysed in the Pulmicort® Turbohaler® + Serevent® Diskus® group.
- The same number of patients was included in the ITT efficacy subset.
- In the PP subset, 2 patients were excluded from the analysis in the BUSAL 150/25 µg group and 1 patient was excluded in the placebo group.

Diagnosis and Main Criteria for Inclusion:

Male and female patients 18 to 70 years old, with a diagnosis of mild persistent asthma for a minimum of 3 months with $FEV_1 \geq 80\%$ predicted, at least 12% and 200 mL FEV_1 reversibility to 4 puffs of Salbutamol 100 µg. Patients should be corticosteroid naïve and should not have received oral, parenteral or inhaled steroids in the preceding 3 months.

Test Products, Doses and Mode of Administration:

Budesonide-Salmeterol DPI 300/25 µg, one capsule taken twice a day by inhalation via the Axahaler®, containing 300 µg of Budesonide and 25 µg of Salmeterol (equivalent to 36.3 µg of salmeterol xinafoate).

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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 Products, Doses and Mode of Administration:

Pulmicort® Turbohaler® 400 µg, two inhalations twice a day via the Turbohaler®, each containing 200 µg of Budesonide; co-administered with Serevent® Diskus®.

Serevent® Diskus® 50 µg, one inhalation twice a day via the Diskus®, each containing 50 µg of Salmeterol; co-administered with Pulmicort® Turbohaler®.

Placebo DPI, one inhalation twice a day via the Axahaler®, containing lactose monohydrate and lactose anhydrous.

Duration of Treatment:

After being screened for the study, the patients were randomised to enter the cross-over study during which they received each treatment for 10 days separated by wash-out periods of at least 21 days. After the screening visit and inclusion in the study, the patients remained in the study for a total duration of approximately 110 days.

Criteria for Evaluation:

Primary endpoint:

- Change from baseline in the area under the curve (AUC) of 24-hour plasma cortisol (mean change from baseline to day 11 of each period).

Other safety parameters:

- Change from baseline in the Cmax of 24-hour plasma cortisol (mean change from baseline to day 11 of each period),
- Change from baseline in the concentration of urinary cortisol over 24 hours (mean change from baseline to day 11 of each period),
- Adverse events (including asthma exacerbations),
- Physical examination,
- Vital signs,
- Laboratory data,
- 12-lead ECG data,
- Withdrawals or drop-out rate.

Statistical Methods:

The ITT and PP sets were used for the analysis in this equivalence trial.

The objective was to demonstrate that Budesonide-Salmeterol DPI 300/25 µg BID and Pulmicort® Turbohaler® 400 µg BID coadministered with Serevent® Diskus® 50 µg BID were equivalent regarding the decrease in the 24-hour AUC of plasma cortisol after a 10-day treatment. AUC_{0-24h} values were calculated using the trapezoidal rule for numerical integration. A mixed model with treatment, period and baseline predosing as fixed effects and patient as random effect was built, no interaction term was added in the model. The carry over effect was not tested given that the wash out time between each treatment period was 21 days. Tests were two-sided with an α risk adjusted to 0.0085 for each of the 6 contrasts according to the Bonferroni inequality. For the main analysis the limit of the 99.15% CI was compared to the equivalence margins, concluding to equivalence if the bounds of the CI were included in the interval [-20%; +20%].

The secondary outcomes were analysed with the same model.

Other safety parameters were described for each treatment group.

The statistical analysis was performed using SAS/STAT software version 9.1. of the SAS system for Windows.

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Summary - Conclusions:

40 patients entered the study and received at least one dose of one study drug. 39 patients completed the treatment period with BUSAL 300/25µg, 39 patients completed the treatment period with BUSAL 150/25 µg, 38 patients completed the treatment period with placebo and 39 patients completed the treatment period with Pulmicort® Turbohaler® + Serevent® Diskus®. They were involved in the intent-to-treat efficacy analysis.

Efficacy Results:

24-hour AUC for plasma cortisol remained stable in the placebo group while it decreased in all active treatment groups. Effect size was significant for BUSAL 300/25 µg (p=0.0001).

Equivalence in cortisol suppression has been demonstrated between all active treatments. Indeed, the 99.15% CI was included in the [-20% ; +20%] equivalence margin defined in the protocol for all three pairwise comparisons. BUSAL 300/25 µg and BUSAL 150/25 µg were equivalent to the comparator Pulmicort® Turbohaler® 400 µg + Serevent® Diskus® 50 µg ([-17.31% - 4.87%] and [-10.21% - 12.11%]). Equivalence was also demonstrated between the two doses of BUSAL (300/25 µg and 150/25 µg) (CI [-18.29% - 3.94%]).

24-hour urinary cortisol decreased with Pulmicort® Turbohaler® 400 µg + Serevent® Diskus® 50 µg only but without reaching significance (p=0.0125). Based on the evaluation of 24-hour urinary cortisol, no significant difference has been observed between:

- BUSAL 300/25 µg (and 150/25 µg) and Pulmicort® Turbohaler® 400 µg + Serevent® Diskus® 50 µg,
- BUSAL 300/25 µg (and 150/25 µg) and the placebo,
- The two doses of the BUSAL combination.

Cortisol Cmax at D11 was unchanged in all groups when compared to baseline.

All these results were confirmed by the PP analysis.

Safety Results:

Study treatments appeared to be well tolerated after 11 days of treatment. 45 emergent AEs were reported over the 4 treatment periods:

- 15 AEs with BUSAL 300/25 µg,
- 12 AEs with BUSAL 150/25 µg,
- 10 AEs with placebo,
- 8 AEs with Pulmicort® Turbohaler® 400 µg and Serevent® Diskus® 50 µg.

Thirty-four (34) AEs were judged related to study treatment.

All AEs were of mild to moderate intensity and were mostly hypertension (19 AEs) and headache (16 episodes). There was no trend toward the occurrence of specific AEs in any treatment groups.

One patient withdrew from the study during the BUSAL 300/25 µg period further to an episode of acute viral infection not related to study treatment. No treatment-related AE led to study discontinuation and no serious or specific AE occurred during the study.

None clinically relevant difference was noticed in haematology and biochemistry between groups over the study. Vital signs remained stable during the study. No clinically significant abnormality of ECG was reported in any treatment group.