1. TITLE PAGE

CLINICAL STUDY REPORT SUMMARY

SPONSOR	:	Laboratoires SMB S.A.
ADDRESS	:	Rue de la Pastorale, 26-28 B-1080 Bruxelles, BELGIUM ☏ : +32.2.411.48.28 🖷 : +32.2.411.28.28
INVESTIGATIONAL PRODUCT	:	BUDESONIDE-SALMETEROL Dry Powder Inhaler 300/25 µg
CODE PRODUCT	:	BUSAL
STUDY CODE	:	BUSAL-III-05-1
TITLE	:	A Phase III, Randomized, Parallel Group Study to Compare the Therapeutic Efficacy of SMB BUDESONIDE-SALMETEROL DPI Capsule 300/25 µg BID Delivered by the AXAHALER® Versus SERETIDE® DISKUS® 500/50 µg (Fluticasone Propionate 500 µg/Salmeterol 50 µg) BID Over 12 Weeks and to Evaluate the Safety of SMB BUDESONIDE-SALMETEROL DPI 300/25 µg Over an Additional Period of 12 Weeks in Moderate to Severe Persistent Asthmatic Patients.
STUDY INITIATION	:	11 July 2006
STUDY TERMINATION	:	14 March 2008
INDICATION	:	Reversible airway obstructions
CLINICAL PHASE	:	Phase III
SPONSOR'S OFFICER	:	Monte Coffiner M.D.
CONTACT DETAILS	:	Rue de la Pastorale, 26-28 B-1080 Brussels, Belgium ☏ : +32.2.411.48.28 🖷 : +32.2.411.28.28
CO-ORDINATING INVESTIGATOR	:	Prof Piotr Kuna Uniwersytecki Szpital Kliniczny Nr 1 im. N. Barlickiego Ul. Kopcinskiego 22, 90-153 Lodz, Poland
RESEARCH ORGANISATION	:	Encorium Oy/Ltd. (Headquarters) Keilaranta 16, 5th floor FIN-02150 Espoo, FINLAND
GCP STATEMENT	:	The study described within this report was conducted in accordance with Good Clinical Practice (including the archiving of essential documents).
DOCUMENT ID	:	CSRS BUSAL-III-05-1
VERSION/DATE	:	Version 1, Final 11 August 2008

2. SYNOPSIS

Name of Sponsor/Company Laboratoires SMB SA	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use Only)
Name of Finished Product To be determined	**Volume:** **Page:**	
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

Protocol Number: Busal-III-05-1

Study Title: A Phase III, Randomized, Parallel Group Study to Compare the Therapeutic Efficacy of SMB BUDESONIDE-SALMETEROL DPI Capsule 300/25 µg BID Delivered by the AXAHALER® Versus SERETIDE® DISKUS® 500/50 µg (Fluticasone Propionate 500 µg/Salmeterol 50 µg) BID Over 12 Weeks and to Evaluate the Safety of SMB BUDESONIDE-SALMETEROL DPI 300/25 µg Over an Additional Period of 12 Weeks in Moderate to Severe Persistent Asthmatic Patients.

Investigators and study centers: The study was conducted at 28 centers in Estonia, Finland, Poland, and Romania. The Principal Investigator was Prof Piotr Kuna of Uniwersytecki Szpital Kliniczny, Lodz, Poland.

Publication (reference): None at the time of this report.

Phase of Development:	**Studied period (years)**
III	First patient enrolled: 11 July 2006 Last patient last visit: 14 March 2008

Objectives:

- To compare the therapeutic efficacy, in a non-inferiority model, of a 12-week course of BUDESONIDE-SALMETEROL dry powder inhaler (DPI) capsule 300/25 µg (BUSAL 300/25 µg), taken twice daily, versus SERETIDE® DISKUS® 500/50 µg taken twice daily by inhalation, in patients with moderate to severe persistent asthma.
- To compare the safety of BUSAL 300/25 µg taken twice daily by inhalation versus SERETIDE® DISKUS® 500/50 µg taken twice daily by inhalation in patients with moderate to severe persistent asthma over 12 weeks.
- To evaluate the safety of a 24-week course of BUSAL 300/25 µg taken twice daily by inhalation, in patients with moderate to severe persistent asthma.

Methodology:

This was a randomized, non-inferiority, parallel group, open-label, multicenter study. Patients were screened at Visit 1. Eligible patients who gave their informed consent entered a 2-week run-in phase during which patients inhaled beclometasone dipropionate 200 µg twice daily plus placebo, and baseline data were collected. Patients were randomized at Visit 2 to 12-weeks active treatment with BUSAL 300/25 µg (75% of patients), or SERETIDE® DISKUS® 500/50 µg (25% of patients). Patients attended the clinic for interim visits after 3 weeks (Visit 3) and 6 weeks (Visit 4) of treatment. Patients in the SERETIDE® DISKUS® 500/50 µg group completed the study at Week 12.

Patients in the BUSAL 300/25 µg group continued the study for a further 12 weeks treatment and safety assessments. They attended the clinic for an interim visit 18 weeks after randomization (Visit 6) and completed the study after a total of 24 weeks treatment (Visit 7).

Number of patients (planned and analyzed):

It was planned that a total of 600 patients would be screened and 500 patients would be included in the study: 375 patients in the BUSAL 300/25 µg group and 125 patients in the SERETIDE® DISKUS® 500/50 µg group

Name of Sponsor/Company Laboratoires SMB SA	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use Only)
Name of Finished Product To be determined	**Volume:** **Page:**	
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

to obtain 460 completed patients for the efficacy phase and 300 completed patients for the safety phase.

At the end of the study, 810 patients were screened, 492 patients were randomized and 342 patients completed the study. The Safety Population included 489 patients (372 patients in the BUSAL 300/25 µg group and 117 patients in the SERETIDE® DISKUS® 500/50 µg group; the Intent-To-Treat (ITT) population included 473 patients (357 patients in the BUSAL 300/25 µg group and 116 patients in the SERETIDE® DISKUS® 500/50 µg group; and the Per Protocol (PP) population included 436 patients (333 patients in the BUSAL 300/25 µg group and 103 patients in the SERETIDE® DISKUS® 500/50 µg group).

Diagnosis and main criteria for inclusion:
Male and female patients aged 18 to 70 years, with a diagnosis of moderate to severe persistent asthma for a minimum of 3 months duration, with forced expiratory volume in 1 second (FEV_1) range of 50-80% of predicted, at least 12% FEV_1 reversibility to 4 puffs of salbutamol 100 µg. Patients were excluded if they received oral or parenteral steroids in the previous 8 weeks or were hospitalized for a related disorder in the previous 3 months.

Investigational product, dose and mode of administration, batch number:
BUSAL 300/25 µg, containing budesonide 300 µg and salmeterol 25 µg (equivalent to 36.3 µg of salmeterol xinafoate).

One capsule inhaled twice daily via an AXAHALER®.

Batch numbers: 14B06, 04F07 and 06F07

Duration of treatment:
Patients randomized to the BUSAL 300/25 µg group took active treatment for 24 weeks while patients in the SERETIDE® DISKUS® 500/50 µg group took active treatment for 12 weeks.

During the run-in phase, patients inhaled beclometasone dipropionate 100 µg, 2 puffs twice daily from a Qvar® Autohaler (batch number GGI011B), plus placebo (batch number 25A06), 1 capsule inhaled twice daily via an AXAHALER®.

Comparative product, dose and mode of administration, batch number:
SERETIDE® DISKUS® 500/50 µg containing fluticasone propionate 500 µg and salmeterol 50 µg (equivalent to 72.6 µg of salmeterol xinafoate).

The contents of 1 blister inhaled twice daily using a Diskus®.

Batch numbers: 0693, 0777 and 091

Criteria for evaluation:
Efficacy Assessments:
Primary efficacy variable:

- Mean change from baseline to Week 12 in morning peak expiratory flow (PEF).

Name of Sponsor/Company Laboratoires SMB SA	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product To be determined		
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

Secondary efficacy variables:

- Mean change over the weeks from baseline to Week 12 in evening PEF.
- Mean change over the weeks from baseline to Week 12 in FEV_1.
- Mean change over the weeks from baseline to Week 12 in FEV_1% of predicted.
- Mean change over the weeks from baseline to Week 12 in forced vital capacity (FVC).
- Change from baseline in asthma symptoms score averaged over the weeks from baseline to Week 12.
- Mean·change from baseline in sleep disturbance score (subset of the asthma symptom score) averaged over the weeks from baseline to Week 12.
- Number of asthma exacerbations.
- Number of doses (inhalations) of bronchodilator rescue medication.

Safety variables:

- Adverse events.
- Physical examination.
- Vital signs.
- Laboratory data.
- Withdrawals or drop-out rate.

Statistical methods:

For the primary efficacy variable, mean change in morning PEF from baseline to Week 12 was analyzed using analysis of covariance (ANCOVA) with fixed factors of treatment, center within country, age and gender and using baseline mean morning PEF as covariates. To estimate the treatment effect, the mean difference between treatments and 95% confidence interval (CI) was calculated. Non-inferiority could be concluded if the lower limit of the 95% CI was greater than –15 L/min for both the PP and ITT populations.

FEV_1 (highest FEV_1 and FEV_1 percent of predicted normal), and FVC values were log-transformed at each visit and analyzed by ANCOVA with the log-transformed baseline value used as covariate. Weekly asthma symptoms score and weekly sleep disturbance score from baseline to Week 12 were analyzed using Cochran-Mantel-Haenszel [CMH] statistic with rank-scores and center as stratification factor.

Other efficacy variables and safety data were summarized using appropriate summary statistics. All data were listed.

Name of Sponsor/Company Laboratoires SMB SA	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use Only)
Name of Finished Product To be determined	**Volume:**	
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule	**Page:**	

Summary/Conclusions

Disposition/Demographics:

At the end of the study, 584 patients had entered the run-in period and 489 patients were randomized and took study medication: 372 patients in the BUSAL 300/25 µg group and 117 patients in the SERETIDE® DISKUS® 500/50 µg group. 351 (94.4%) patients in the BUSAL 300/25 µg group and 109 (94.0%) patients in the SERETIDE® DISKUS® 500/50 µg group completed the 12-week efficacy phase of the study.

Mean age was approximately 46.5 years and ranged between 18 and 69 years in both groups. There were more females than males: 220 (61.6%) females in the BUSAL 300/25 µg group and 75 (64.7%) females in the SERETIDE® DISKUS® 500/50 µg group. All patients were Caucasian.

Efficacy results:

Primary efficacy variable

In the ITT population, morning PEF values increased over the weeks after baseline and were significantly ($p<0.001$) higher than baseline in both treatment groups at every post-baseline week (Table S1). At Week 12, the mean difference between the groups was –2.5 L/min and the 95% CI was [–13.4 ; 8.5] L/min ($p=0.660$).

The results of the PP population were similar to the results of the ITT population (Table S2). In the PP population, morning PEF values increased over the weeks after baseline and were significantly ($p<0.001$) higher than baseline in both treatment groups at every post-baseline week. At Week 12, the mean difference between the groups was –0.8 L/min and the 95% CI was [–12.2 ; 10.5] L/min ($p=0.887$).

Since the lower limit of the 95% CI was greater than –15 L/min in both the ITT and PP populations, non-inferiority between BUSAL 300/25 µg and SERETIDE® DISKUS® 500/50 µg was demonstrated.

Table S1: Mean Morning PEF Values: ITT Population

Mean morning PEF values (L/min)	BUSAL 300/25 µg (N=356)		SERETIDE® DISKUS® 500/50 µg (N=116)			
	mean	(SD)	mean	(SD)	95% CI	p-value
Baseline	338.3	(99.3)	336.5	110.2		
Change from baseline to:						
Visit 3 (Week 3)	30.6	(44.1)	28.8	(39.7)	[-7.4 ; 10.2]	0.755
Visit 4 (Week 6)	34.8	(46.7)	33.8	(42.0)	[-8.2 ; 10.2]	0.837
Visit 5 (Week 12)	39.0	(52.4)	40.4	(56.5)	[-13.4 ; 8.5]	0.660
Visit 6 (Week 18)	40.1	(55.6)	Not applicable			
Visit 7 (Week 24)	42.7	(54.8)	Not applicable			

Name of Sponsor/Company Laboratoires SMB SA	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product To be determined	**Volume:** **Page:**	
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

Table S2: Mean Morning PEF Values: PP Population

Mean morning PEF values (L/min)	BUSAL 300/25 µg (N=333)		SERETIDE® DISKUS® 500/50 µg (N=106)			
	mean	(SD)	mean	(SD)	95% CI	p-value
Baseline	338.8	(99.6)	334.9	109.5		
Change from baseline to:						
Visit 3 (Week 3)	30.4	(45.0)	29.5	(41.2)	[-8.4 ; 10.6]	0.828
Visit 4 (Week 6)	35.1	(47.3)	33.4	(43.5)	[-7.2 ; 12.2]	0.612
Visit 5 (Week 12)	39.4	(53.0)	40.2	(57.8)	[-12.2 ; 10.5]	0.887
Visit 6 (Week 18)	40.4	(56.1)	Not applicable			
Visit 7 (Week 24)	43.0	(55.5)	Not applicable			

Secondary efficacy variables (ITT population)

Evening PEF

Evening PEF values at baseline were (mean [SD]) 350.0 (99.4) L/min in the BUSAL 300/25 µg group and 347.5 (113.2) L/min in the SERETIDE® DISKUS® 500/50 µg group (Table S3). There was no difference between these values (t-test p=0.835). Evening PEF values increased over the weeks after baseline and were significantly (p<0.001) higher than baseline in both treatment groups at every post-baseline week. The mean (SD) changes from baseline to Week 12 in evening PEF values were 35.2 (48.8) L/min in the BUSAL 300/25 µg group and 35.8 (51.8) L/min in the SERETIDE® DISKUS® 500/50 µg group. The mean difference between the groups at Week 12 was -1.5 L/min and the 95% CI was [–11.6 ; 8.7] L/min, and was not statistically significant (p=0.775). The results of the PP population were similar to the results of the ITT population.

Table S3: Mean Evening PEF Values: ITT Population

Mean evening PEF values (L/min)	BUSAL 300/25 µg (N=356)		SERETIDE® DISKUS® 500/50 µg (N=116)			
	mean	(SD)	mean	(SD)	95% CI	p-value
Baseline	350.0	(99.4)	347.5	(113.2)		
Change from baseline to Week 12	35.2	(48.8)	35.8	(51.8)	[-11.6 ; 8.7]	0.775

Name of Sponsor/Company Laboratoires SMB SA	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product To be determined		
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

Spirometry variables (ITT Population)

Highest FEV_1 values at baseline were (median [range]) 1.95 (0.94–3.68) L/sec in the BUSAL 300/25 µg group and 1.87 (1.08–3.36) L/sec in the SERETIDE® DISKUS® 500/50 µg group (Table S4). The median (range) changes from baseline to Week 12 in highest FEV_1 values were 0.36 (-0.39–2.23) L/sec in the BUSAL 300/25 µg group and 0.42 (-0.58–2.02) L/sec in the SERETIDE® DISKUS® 500/50 µg group. The ratio of means was 0.98 (95% CI: [0.95 ; 1.02]) and the mean difference between the groups was –0.02 (95%CI:
[-0.06 ; 0.01]). This was not statistically significant (p=0.259).

Percent of predicted FEV_1 values at baseline were (median [range]) 66.80 (50.40–83.10)% in the BUSAL 300/25 µg group and 67.15 (51.90–80.00)% in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in predicted FEV_1 values were 12.30 (-14.70–59.20)% in the BUSAL 300/25 µg group and 15.95 (-14.20–58.10)% in the SERETIDE® DISKUS® 500/50 µg group. The ratio of means was 0.98 (95% CI: [0.95 ; 1.02]) and the mean difference between the groups was –0.02 (95%CI: [-0.05 ; 0.02]). This was not statistically significant (p=0.273).

Highest FVC values at baseline were (median [range]) 3.02 (1.71–6.18) L in the BUSAL 300/25 µg group and 2.99 (1.80–5.49) L in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in highest FVC values were 0.33 (-1.01–2.74) L in the BUSAL 300/25 µg group and 0.32 (-0.93–2.87) L in the SERETIDE® DISKUS® 500/50 µg group. The ratio of means was 1.00 (95% CI: [0.97 ; 1.03] and the mean difference between the groups was 0.00 (95%CI: [-0.03 ; 0.03]). This was not statistically significant (p=0.854).

The results of the PP population were similar to the results of the ITT population for the above parameters.

Table S4: Spirometry Variables (ITT Population)

Spirometry variables	BUSAL 300/25 µg		SERETIDE® DISKUS® 500/50 µg			
	(N=356)		(N=116)		Ratio	
	median	(range)	median	(range)	95% CI	p-value
Highest FEV_1 (L/sec)						
Baseline	1.95	(0.94–3.68)	1.87	(1.08–3.36)	0.98	
Change from baseline to Week 12	0.36	(-0.39–2.23)	0.42	(-0.58–2.02)	[0.95 ; 1.02]	0.259
Percent of predicted FEV_1 (%)						
Baseline	66.80	(50.40–83.10)	67.15	(51.90–80.00)	0.98	
Change from baseline to Week 12	12.30	(-14.70–59.20)	15.95	(-14.20–58.10)	[0.95 ; 1.02]	0.273
Highest FVC (L)						
Baseline	3.02	(1.71–6.18)	2.99	(1.80–5.49)	1.00	
Change from baseline to Week 12	0.33	(-1.01–2.74)	0.32	(-0.93–2.87)	[0.97 ; 1.03]	0.854

Name of Sponsor/Company Laboratoires SMB SA	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use Only)
Name of Finished Product To be determined	**Volume:** **Page:**	
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

Asthma symptom scores (ITT Population)

Weekly asthma symptoms score values at baseline were (median [range]) 1.63 (0.0–9.0) in the BUSAL 300/25 µg group and 1.40 (0.0–6.5) in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in weekly asthma symptoms score values were –0.50 (-8.4–4.0) in the BUSAL 300/25 µg group and –0.58 (-4.7–4.7) in the SERETIDE® DISKUS® 500/50 µg group. The medians (distribution free CIs) for the differences were -0.50 [-0.60 ; -0.40] in the BUSAL 300/25 µg group and -0.58 [-0.70 ; -0.43] in the SERETIDE® DISKUS® 500/50 µg group and was not statistically significant (p=0.528).

Sleep disturbance score values at baseline were (median [range]) 0.00 (0.0–3.3) in the BUSAL 300/25 µg group and 0.00 (0.0–3.2) in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in sleep disturbance score values were 0.00 (-2.0–2.4) in the BUSAL 300/25 µg group and 0.00 (-2.6–2.0) in the SERETIDE® DISKUS® 500/50 µg group. The medians (distribution free CIs) for the differences were 0 [0 ; 0] in both treatment groups and was not statistically significant (p=0.151).

Weekly total symptoms scores at baseline were (median [range]) were 2.00 (0.0–11.0) in the BUSAL 300/25 µg group and 1.63 (0.0–9.7) in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in weekly total asthma symptoms score values were –0.60 (-9.4–2.9) in the BUSAL 300/25 µg group and –0.65 (-6.8–5.5) in the SERETIDE® DISKUS® 500/50 µg group. The medians (distribution free CIs) for the differences were –0.60 [-0.80 ; -0.47] in the BUSAL 300/25 µg group and -0.65 [-1.00 ; -0.40] in the SERETIDE® DISKUS® 500/50 µg group and was not statistically significant (p=0.793).

Wheezing scores at baseline were (median [range]) 0.40 (0.0–3.0) in the BUSAL 300/25 µg group and 0.30 (0.0–2.7) in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in wheezing score values were 0.00 (-3.0–1.4) in the BUSAL 300/25 µg group and –0.10 (-2.0–2.1) in the SERETIDE® DISKUS® 500/50 µg group. The medians (distribution free CIs) for the differences were 0.00 [-0.10 ; 0.00] in the BUSAL 300/25 µg group and -0.10 [-0.20 ; 0.00] in the SERETIDE® DISKUS® 500/50 µg group and was not statistically significant (p=0.705).

Cough scores at baseline were (median [range]) 0.50 (0.0–3.0) in the BUSAL 300/25 µg group and 0.40 (0.0–2.3) in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in cough score values were -0.10 (-3.0–2.0) in the BUSAL 300/25 µg group and –0.10 (-2.1–3.0) in the SERETIDE® DISKUS® 500/50 µg group.. The medians (distribution free CIs) for the differences were –0.10 [-0.20 ; 0.00] in both treatment groups and was not statistically significant (p=0.423).

Shortness of breath scores at baseline were (median [range]) 0.80 (0.0–2.8) in the BUSAL 300/25 µg group and 0.50 (0.0–2.1) in the SERETIDE® DISKUS® 500/50 µg group. The median (range) changes from baseline to Week 12 in shortness of breath score values were -0.20 (-2.2–2.0) in the BUSAL 300/25 µg group and –0.20 (-1.6–2.6) in the SERETIDE® DISKUS® 500/50 µg group. The medians (distribution free CIs) for the differences were -0.20 [-0.20 ; -0.10] in the BUSAL 300/25 µg group and -0.20 [-0.30 ; -0.10] in the SERETIDE® DISKUS® 500/50 µg group and was not statistically significant (p=0.363).

The results of the PP population were similar to the results of the ITT population for the above parameters.

Name of Sponsor/Company Laboratoires SMB SA	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use Only)
Name of Finished Product To be determined	**Volume:**	
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule	**Page:**	

For all of the above secondary efficacy variables, except for sleep disturbance scores, the values on treatment showed a statistically significant ($p<0.05$) improvement compared with baseline at every post-baseline visit and at every week (if measured). Sleep disturbance score values were lower on treatment compared with baseline, and were significantly ($p<0.001$) lower than baseline in both treatment groups at every post-baseline visit in the BUSAL 300/25 µg group only. In the SERETIDE® DISKUS® 500/50 µg group, mean sleep disturbance scores were not statistically significantly different from baseline at Weeks 1–5 and 8 ($p>0.05$) but were statistically significantly different at Weeks 6, 7 and 9–12 ($p<0.05$).

Use of rescue medication at baseline was (median [range]) 5.0 (0–64) inhalations/week in the BUSAL 300/25 µg group and 5.0 (0–59) inhalations/week in the SERETIDE® DISKUS® 500/50 µg group. Use of rescue medication was lower on treatment compared with baseline throughout the study. The median (range) change from baseline to Week 12 in number of puffs of rescue medication was –2.0 (-54–23) inhalations/week in the BUSAL 300/25 µg group and –3.0 (-40–19) inhalations/week in the SERETIDE® DISKUS® 500/50 µg group. The medians (distribution free CIs) for the differences were 0.0 [0.0 ; 1.0] in both treatment groups and was not statistically significant ($p=0.191$).

A total of 8 patients reported asthma exacerbations during the efficacy phase of the study: 7 (2.0%) patients in the BUSAL 300/25 µg group and 1 (0.9%) patient in the SERETIDE® DISKUS® 500/50 µg group. Six (1.7%) additional patients in the BUSAL 300/25 µg group reported asthma exacerbations during the safety phase of the study.

The results of the PP population were similar to the results of the ITT population for the above parameters.

Safety results:

The two treatment groups were balanced in terms of the overall incidence of AEs during the efficacy phase of the study. In the BUSAL 300/25 µg group, 76 (20.4%) patients experienced a total of 91 AEs, compared with 30 (25.6%) patients in the SERETIDE® DISKUS® 500/50 µg group experiencing 38 AEs. During the full 24-week treatment period for patients who were randomized to the BUSAL 300/25 µg group, the incidence of AEs in this group was 146 AEs experienced by 108 (29.0%) patients.

During the efficacy phase of the study, the most common System Organ Classes with AEs were Infections and Infestations (52 [14.0%] patients in the BUSAL 300/25 µg group and 19 [16.2%] patients in the SERETIDE® DISKUS® 500/50 µg group), followed by Respiratory, Thoracic and Mediastinal Disorders (4 [1.1%] patients in the BUSAL 300/25 µg group and 6 [5.1%] patients in the SERETIDE® DISKUS® 500/50 µg group). The most common Preferred Terms were nasopharyngitis (12 [3.2%] patients in the BUSAL 300/25 µg group, 3 [2.6%] patients in the SERETIDE® DISKUS® 500/50 µg group) followed by pharyngitis (12 [3.2%] patients in the BUSAL 300/25 µg group, 1 [0.9%] patient in the SERETIDE® DISKUS® 500/50 µg group).

For patients in the BUSAL 300/25 µg group, during the full 24-week safety period, the most common Preferred Terms remained nasopharyngitis and pharyngitis, both of which occurred in 20 (5.4%) patients.

Most AEs were mild or moderate. Three (0.8%) patients in the BUSAL 300/25 µg group had severe AEs: ear infection, muscle spasms and dysphonia. No patients in the SERETIDE® DISKUS® 500/50 µg group had

Name of Sponsor/Company Laboratoires SMB SA	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product To be determined	**Volume:** **Page:**	
Name of Active Ingredient Budesonide 300 µg/ salmeterol 25 µg fixed dose combination, inhalation powder, hard capsule		

any severe AEs.

Treatment-related AEs during the efficacy phase of the study occurred in 11 (3.0%) patients in the BUSAL 300/25 µg group and 8 (6.8%) patients in the SERETIDE® DISKUS® 500/50 µg group. The most common treatment-related AEs during the first 12 weeks of the study were dysphonia (3 [0.8%] patients in the BUSAL 300/25 µg group and 4 [3.4%] patients in the SERETIDE® DISKUS® 500/50 µg group) followed by oral candidiasis (2 [0.5%] patients in the BUSAL 300/25 µg group and 2 [1.7%] patients in the SERETIDE® DISKUS® 500/50 µg group). All of the other treatment-related AEs were single episodes. This was confirmed over the additional 12-week safety phase under BUSAL 300/25 µg.

Four SAEs occurred during the study. One patient was hospitalized during the run-in phase because of a mild upper respiratory tract infection. In the BUSAL 300/25 µg group, 1 patient was hospitalized because of acute peritonsillitis and, in the SERETIDE® DISKUS® 500/50 µg group, 1 patient was hospitalized to treat foot and humerus fractures. None of the SAEs were treatment-related and all of these patients recovered and completed the study.

Four patients, all in the BUSAL 300/25 µg group, were withdrawn because of AEs. Severe dysphonia was considered by the investigator to be possibly related to study medication; the other AEs that led to permanent withdrawal (viral infection, diabetes mellitus and hepatitis C virus) were not related.

There were no findings in laboratory safety variables, vitals signs or ECG to suggest a trend or any unexpected safety concerns.

Conclusions:

- BUSAL 300/25 µg is non-inferior to SERETIDE® DISKUS® 500/50 µg in terms of morning PEF in patients with moderate to severe persistent asthma.
- For the secondary efficacy variables: evening PEF, FEV_1, FEV_1 percent of predicted, FVC, asthma symptoms scores and use of rescue medication, treatment with BUSAL 300/25 µg and SERETIDE® DISKUS® 500/50 µg both similarly improved the symptoms of asthma throughout the study. There were no statistically significant differences between the two treatments for any of the secondary efficacy variables.
- The safety of BUSAL 300/25 µg was similar to that of SERETIDE® DISKUS® 500/50 µg over 12 weeks. BUSAL 300/25 µg 300/25 µg was safe and well tolerated over the treatment period of 24 weeks.
- The AE profile of the investigational product was as expected for an inhaled fixed-dose combination of a corticosteroid and long-acting β_2-agonist.

Date of the report: 11 August 2008