2.0 SYNOPSIS

Name of Company: AstraZeneca, LP		**(For National Authority Use only)**
Name of Finished Product: Pulmicort Respules®	**Volume:**	
Name of Active Ingredient: budesonide	**Page:**	

Title of Study: A Safety and Efficacy Study of Two Dosage Levels of Pulmicort® Respules™ (budesonide inhalation suspension, 0.5 or 1.0 mg/day) versus Placebo in Infants Between the Ages of Six and Twelve Months with Mild to Moderate Asthma

Study Centers: Multiple centers in the United States and its territories

Publication (reference): None

Studied Period (years): (date of first enrollment) September 23, 2000 (date of last completed) June 30, 2002	**Phase of development:** IV

Objectives: The primary objective of this study was to evaluate the safety of once-daily administration of PULMICORT RESPULES (0.5 mg and 1.0 mg) compared with placebo for the treatment of mild to moderate asthma or recurrent or persistent wheezing in infants between the ages of 6 and 12 months. The secondary objective of this study was to evaluate the efficacy of PULMICORT RESPULES and placebo by comparing nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, and patient discontinuations, and physician's global assessment of each patient's asthma status.

Methodology: A 12-week, multicenter, randomized, double-blind, placebo-controlled study. Throughout this document, PULMICORT RESPULES will be referred to by the generic name, Budesonide Inhalation Suspension (BIS).

Number of Patients (Planned and Analyzed):
Planned: It was planned to randomize 144 patients in order to obtain 90 patients completing the study (including at least 60 who received active treatment), and 72 patients evaluable for the assessment of adrenal function (including at least 48 who received active treatment).
Randomized: 141 (total), 48 (BIS 0.5 mg), 44 (BIS 1.0 mg), 49 (placebo)
Evaluable for Analysis of Adrenal Function: 82 (total), 33 (BIS 0.5 mg), 17 (BIS 1.0 mg), 32 (placebo)
Analyzed for Efficacy: 136 (total), 46 (BIS 0.5 mg), 43 (BIS 1.0 mg), 47 (placebo)
Analyzed for Safety: 141 (total), 48 (BIS 0.5 mg), 44 (BIS 1.0 mg), 49 (placebo)

Diagnosis and Main Criteria for Inclusion: Male and female patients between the ages of 6 and 12 months who had not reached their first birthday and who were diagnosed with asthma or have demonstrated, historically, signs and symptoms of asthma (at least 2 episodes of persistent/recurrent wheezing), who may have benefited from inhaled anti-inflammatory therapy, and who had a caregiver willing and able to comply with protocol procedures were eligible for enrollment.

Test Product, Dose and Mode of Administration, Batch or Lot Number:
PULMICORT RESPULES (budesonide), 0.25 or 0.5 mg/mL once daily (qd), inhaled via nebulizer, batch (lot numbers): 0.25 mg/mL AM-328 (AM 127), AM-535 (BK 128) and AM-696 (DA 129); 0.5 mg/mL AM-328 (AM 155), AM-535 (BK 156) and AM-696 (DA 157).

Duration of Treatment:
12 weeks.

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
Placebo, qd, inhaled via nebulizer, batch (lot numbers) AM-328 (AM 24), AM-535 (BK 25) and AM-696 (DA 27).
Cortrosyn, 0.125 mg, intravenous injection, lot numbers 2360100731, 2460401731, and 2470501731.

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Criteria for Evaluation:

Safety: Safety was assessed by changes in adrenal function (plasma and urine cortisol), incidence and severity of adverse events, changes in clinical laboratory parameters (hematology, blood chemistry), body weight and length, vital signs (pulse rate, blood pressure), physical examinations, and oropharyngeal and nasal fungal cultures. A 1-hour plasma post-cosyntropin stimulation value of less than 500 nmol/L was considered subnormal.

Efficacy: Efficacy was assessed by nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, patient discontinuations, and investigators' global assessment of each patient's asthma status.

Statistical Methods:

Adrenal Function: The primary endpoint in this study was the assessment of adrenal function. This was assessed as the mean change from baseline at Week 12 in ACTH-simulated minus basal plasma cortisol levels for plasma samples, and as the mean change from baseline at Week 12 in urine cortisol levels for urine samples. The primary variable was analyzed using an analysis of covariance (ANCOVA) with treatment as the main effect and baseline as the covariate. The Wilcoxon Rank Sum test was applied to these data to support the results of the parametric analysis. Additional analyses were conducted to evaluate if the effect of treatment differed across the different age groups studied.

Adrenal function was also assessed using basal pre-stimulated cortisol levels, 1-hour ACTH-stimulated cortisol levels, and the ACTH-stimulated minus basal plasma cortisol levels at Week 12 and last observed value carried forward (LOCF). Tabular and graphical summaries of individual patient shifts from baseline were also presented, defining ACTH-stimulated plasma values less than 500 nmol/L as subnormal. The variables for change from baseline were analyzed using ANCOVA with treatment as the main effect and baseline as the covariate. The end-of-study values were analyzed using analysis of variance (ANOVA) with treatment as the main effect and baseline as the covariate. The end-of-study values were analyzed using ANOVA with treatment as the main effect.

Summaries of the change from baseline at Week 12 in urinary cortisol levels were also assessed.

Efficacy Variables: The assessment of efficacy included the change from baseline in nighttime and daytime symptom scores, the percentage of symptom-free days, the percentage of days when breakthrough medication was not needed, withdrawal and treatment failure rates, and the physician’s global assessment of each patient’s asthma symptoms and their ability to manage their asthma. Changes from baseline were analyzed using an ANCOVA model with treatment as the main effect and baseline as the covariate. Continuous data with no baseline assessment were analyzed using ANOVA with treatment as the main effect. The investigator’s global assessment variables were analyzed using the Mantel-Haenszel test statistic.

Other Safety Variables: Safety was also assessed by review of the incidence and severity of adverse events and the summary of changes from baseline in the vital signs, physical exams, and routine laboratory tests over the study period.

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SUMMARY – CONCLUSIONS

PATIENT DISPOSITION:

A total of 141 pediatric patients were randomized into the study to receive BIS 0.5 mg (N=48), BIS 1.0 mg (N=44), or placebo (N=49). Within each treatment group, approximately one-half of the randomized patients (51% to 57%) were less than 9 months of age. The demographic and baseline characteristics of randomized patients were comparable among the 3 treatment groups. Of the 141 patients randomized to treatment, 117 (83%) completed the study, including 75 who received BIS (40 in 0.5 mg group; 35 in 1.0 mg group) and 42 who received placebo.

ADRENAL FUNCTION RESULTS:

Eighty-two patients were evaluable for the analysis of adrenal function (plasma or urine cortisol), 50 (61%) who received active treatment (33 in the BIS 0.5 mg group; 17 in the BIS 1.0 mg group) and 32 (39%) who received placebo. Within each treatment group, approximately one-half of the evaluable patients were < 9 months of age (15/33=46% in BIS 0.5 mg group; 10/17=59% in BIS 1.0 mg group; and 18/32=56% in placebo group). At both baseline and at the end of the study, plasma cortisol values increased from basal levels following cosyntropin (ACTH) stimulation in all treatment groups. In the evaluable population, the mean changes from baseline in the ACTH-stimulated minus basal plasma cortisol levels were similar among the 3 treatment groups, with no apparent decreases in cortisol levels resulting from active treatment (see Table S1). Although there was a suggestion of a dose-related trend in the mean change from baseline in plasma cortisol levels among a subset of patients with normal adrenal function at baseline and who did not take any disallowed medications, due to the variability of these data, meaningful conclusions cannot be drawn.

A shift from a baseline post-ACTH stimulation plasma cortisol value of ≥ 500 nmol/L to a Week 12 post-ACTH stimulation plasma cortisol value of < 500 nmol/L was evident for 7 patients (4, 2, and 1 in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups, respectively) and the majority of values in these patients were near the cut-off value of < 500 nmol/L. Six patients (5 in BIS 0.5 mg group; 1 in placebo group) were evaluable for analysis of urinary cortisol data. No patient in the BIS 0.5 mg group had a subnormal urine cortisol value at Week 12 (defined as a reduction of at least 50% from baseline). The mean changes from baseline to Week 12 in urinary cortisol values are provided in Table S2.

Table S1. Summary of change from baseline in mean plasma cortisol values (nmol/L) (Evaluable Population)

Variable	Change from baseline, Adjusted mean (SE)	95% CI (versus placebo)	ANCOVA p-value	Wilcoxon Rank Sum p-value
Plasma cortisol (pre-stimulation)				
Placebo (N=31)	-17.8 (22.0)			
0.5 mg BIS (N=28)	-6.3 (23.0)	-51.9, 75.0	0.718	0.671
1.0 mg BIS (N=17)	20.4 (29.7)	-36.0, 112.5	0.307	0.168
Plasma cortisol (post-stimulation)				
Placebo (N=31)	5.61 (30.4)			
0.5 mg BIS (N=28)	30.0 (31.9)	-63.5, 112.2	0.582	0.891
1.0 mg BIS (N=17)	24.8 (41.0)	-82.6, 121.0	0.708	0.940
Plasma cortisol (post- minus pre-stimulation)				
Placebo (N=31)	19.8 (36.1)			
0.5 mg BIS (N=28)	37.9 (38.0)	-86.6, 122.7	0.732	0.832
1.0 mg BIS (N=17)	8.4 (48.8)	-133, 109.8	0.852	0.140

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Table S2. Summary of change from baseline in urinary cortisol values (µg/g Creat) (Evaluable Population)

Treatment Group	N	Baseline Mean (SE)		Visit 6 Mean (SE)		Change from Baseline (SE)	
BIS 0.5 mg	5	16.3	(3.79)	68.5	(33.58)	52.2	(34.55)
Placebo	1	62.6		17.8		-44.8	

EFFICACY RESULTS:

Treatment with BIS resulted in a greater reduction in daytime and nighttime asthma symptoms compared with placebo. Some improvements were also observed in the active treatment groups compared with placebo for the other efficacy variables (physician's global assessment of symptom control, breakthrough medication use, treatment failure, and patient discontinuation) but these differences did not reach statistical significance.

OTHER SAFETY RESULTS:

The safety and tolerability profile of BIS in pediatric patients 6 to 12 months of age with mild to moderate asthma was comparable to that of placebo. The overall incidence of adverse events was 90%, 98%, and 88% in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups, respectively. The most frequent adverse events reported in this study reflected symptoms common to a pediatric population with asthma and included respiratory infection, otitis media, fever, rhinitis, and vomiting. The majority (99%) of adverse events were mild to moderate in severity. Three patients discontinued treatment prematurely due to an adverse event, 1 in 0.5 mg BIS (facial and neck rash), and 2 in 1.0 mg BIS (aggravated asthma and pneumonia). The 2 patients in the BIS 1.0 mg group were hospitalized and were also classified as serious adverse events. Three additional patients in the BIS 0.5 mg group experienced serious adverse events (aggravated asthma, respiratory infection, and viral infection). With the exception of the facial and neck rashes in the BIS 0.5 mg group, none of the serious or treatment-limiting adverse events were considered by the investigator to be treatment-related. No discontinuation due to adverse events or serious adverse event occurred in the placebo group. There were no deaths in the study. No unexpected treatment-related changes were observed in laboratory tests, vital signs, or physical findings.