MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA #20-929	**TRADE NAME:**	Pulmicort Respules
APPLICANT/SPONSOR:	AstraZeneca	**USAN NAME:**	Budesonide Inhalation suspension
MEDICAL OFFICER:	Curtis J Rosebraugh MD, MPH		
TEAM LEADER:	Lydia Gilbert-McClain, MD	**CATEGORY:**	Corticosteroid
DUE DATE:		**ROUTE:**	Inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
30 Aug 2002	03 Sept 2002	sNDA	
14 Dec 1998			Written Request for Pediatric Studies in infants between the ages of 6 and 12 months

RELATED APPLICATIONS

Document Date	Application Type	Comments
8 Aug 2000	NDA 20-929	Approval date for Pulmicort Respules

REVIEW SUMMARY: The primary objective of this study was to evaluate the safety of once-daily administration of Pulmicort Respules (0.5 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 primary safety variable was assessment of adrenal function as assessed by the mean change from baseline at Week 12 in basal and 1-hour post adrenocorticotropic hormone (ACTH) stimulated cortisol levels or changes in urinary cortisol excretion. Secondary objectives included evaluating body length changes and evaluating the efficacy of Pulmicort Respules and placebo by comparing nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, and subject discontinuations, and physician's global assessment of each subject's asthma status.

The results of this study do not indicate a population mean suppressive effect on adrenal function in subjects aged 6 to 12 months with once-daily dosages of 0.5 or 1.0 mg BIS, although there may be individual subjects with increased sensitivity and possible adrenal suppression. The safety profile of BIS was comparable to that already existing in labeling except for higher percentages of Tooth disorder, Nervousness, Pneumonia, and Urticaria in the BIS group compared to placebo. A dose–dependent decrease in growth velocity was seen in the BIS groups compared to placebo which suggests that at these doses the drug may have systemic effects.

This submission fulfills the requirements of the Written Request and this application is approvable with need for label revisions to gain full approval.

OUTSTANDING ISSUES: See Above

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	**SAFE TO PROCEED**	___	**CLINICAL HOLD**	
NDA/SUPPLEMENTS:	___	**FILEABLE**	___	**NOT FILEABLE**	
	___	**APPROVAL**	X	**APPROVABLE**	___ **NOT APPROVABLE**
OTHER ACTION:					

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1. ABBREVIATIONS

BIS- Budesonide Inhalation Suspension (generic name for Pulmicort Respules)

ITT-Intent to Treat

ACTH-adrenocorticotropic hormone

LOCF- last observed value carried forward

ANCOVA-analysis of covariance

sNDA-Supplemental New Drug Application

CLINICAL REVIEW OF SNDA #20-929

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

This supplemental NDA has been submitted in accordance with the December 14, 1998 Written Request as a supplement to the already approved drug product Pulmicort Respules®. The sponsor is not seeking changes in the INDICATIONS section of the labeling. Rather, the sponsor is requesting changes to the CLINICAL PHARMACOLOGY, Pharmacodynamics, and PRECAUTIONS, Pediatric Use label sections. The study report submitted in this application completes the requirements of the Written Request and this application is approvable based on appropriate revision of the proposed labeling changes.

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

Not Applicable

2. SUMMARY OF CLINICAL FINDINGS

2.1. Background and Administrative Issues

Pulmicort Respules for nebulization was approved August 8, 2000 for use in asthmatic patients 12 months to 8 years of age. As part of a Written Request issued December 14, 1999, the sponsor has submitted this sNDA reporting additional safety information on the use of Pulmicort Respules in subjects 6 months to 12 months in age.

2.2. Brief Overview of Clinical Program

The primary objective of this study was to evaluate the safety of once-daily administration of Pulmicort Respules (0.5 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 primary safety variable was assessment of adrenal function as assessed by the mean change from baseline at Week 12 in basal and 1-hour post adrenocorticotropic hormone (ACTH) stimulated cortisol levels or changes in urinary cortisol excretion. Secondary objectives included evaluation of body length changes and evaluating the efficacy of Pulmicort Respules and placebo by comparing nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, and subject discontinuations, and physician's global assessment of each subject's asthma status.

2.3. Efficacy

Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores,

daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days, number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study.

In general the Budesonide Inhalation Suspension (BIS) treatment groups demonstrated greater improvement trends of mean values (not statistically significant) in subjective parameters (AM & PM symptom scores, Symptom-free days, investigator global assessment), but not in the objective parameters (Withdrawals, breakthrough medication use) with the exception of treatment failures which occurred less frequently in the active treatment groups 15 % and 18% for BIS 0.5 mg and BIS 1.0 mg respectively) compared to placebo (22%). Definitive efficacy conclusions can not be made from these results. Approximately twice the percentage of subjects randomized to the BIS 0.5 mg treatment group (29%) had prior corticosteroid use compared to the BIS 1.0 mg and placebo groups (16% and 14% respectively) suggesting that subjects in the BIS 0.5 mg group were sicker and more likely to have treatment failures. The results of the asthma symptom score also suggest a more favorable response in the BIS 0.5 mg group compared with the BIS 1.0 mg group.

2.4. Safety

The primary safety variable was adrenal function as determined by plasma cortisol levels (pre- and 1-hour post- ACTH) and overnight urinary free cortisol levels at Visits 2 (randomization) and 6 (Week 12). Subnormal adrenal function by plasma cortisol levels was defined as a post-ACTH plasma cortisol value less than 500 nmol/L at either Visit 2 or Visit 6. Urinary cortisol excretion was measured as the (b) (4) cortisol levels from overnight timed urine samples. Subjects who did not undergo the cosyntropin stimulation test were to provide timed urine samples. Other secondary safety variables included the incidence and severity of adverse events, changes from baseline in hematology and chemistry laboratory, body length/height and body weight and oropharyngeal and nasal fungal cultures.

Body length was measured (b) (4)

The mean values of the three different groups did not indicate any difference in adrenal responsiveness of the populations to the ACTH stimulation test. Using a combination of the serum and urine analysis groups, there were seven subjects that had subnormal responses to adrenal stimulation with six in the BIS group and one in the placebo group. In the serum analysis group, there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response (as pre-defined as a post-ACTH infusion level >500 nmol/L) to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals within those populations that may have increased sensitivity to exogenous corticosteroid than the group mean and this sensitivity must be kept in mind by practicing physicians when approaching therapy for the individual patient. It is

also important to note that the BIS 1.0 mg group only contained data from 17 subjects of the 29 originally randomized (compared to 28 for the BIS 0.5mg and 31 for the placebo groups) which could introduce a considerable bias if the excluded subjects did not reflect the group mean.

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The data from this aspect of adrenal evaluation has a great deal of variability and questionable validity of the single placebo comparator and as such should not be used to make any HPA function conclusions for labeling purposes.

Overall Mean body length increases were 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. There appears to be dose ordering growth suppression. In order to see if there was a possible drop-out bias, the biostatistics reviewer, Dr. Jim Gebert investigated growth for an "evaluable group" consisting of subjects that had all data points and completed the study. This group demonstrated the same trend with mean body length increases of 3.3 cm, 3.5 cm and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. While this is not statistically significant (p=0.2861 BIS 1.0 mg vs. placebo) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an expected effect of corticosteroids. This finding should be reflected in the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into an erroneous sense of security that because they are giving a corticosteroid by inhalation there will not be systemic effects. There was no relationship between mean body length and abnormal responses to ACTH stimulation.

Three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event. Adverse events of Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria were reported more frequently in the active treatment arms compared to placebo and except for pharyngitis are not presently in the Label for PULMICORT Respules.

2.5. Dosing

The Pulmicort Respules product is currently approved at dosages of 0.5 mg – 1 mg total daily dose in patients 12 months to 8 years of age. The sponsors studied Pulmicort Respules 0.5 mg and 1 mg once a day in this study.

2.6. Special Populations

This study was performed in infants 6 months to 12 months in age. Overall, most subjects were Caucasian (70%) and male (62%).

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Trade Name:	Pulmicort Respules™
Drug Class:	Corticosteroid
Indication:	Pulmicort Respules is already approved for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age. The sponsor is not seeking additions to the INDICATIONS section of the label.
Dose/regimens/Age Groups:	The dosages used in this study of infants 6 to months of age were 0.5 mg and 1.0 mg once a day.

1.2. State of Armamentarium for Indication(s)

Budesonide Inhalation Solution (Pulmicort Respules®) is the only inhaled corticosteroid formulated for nebulization in the U.S. It is the only corticosteroid approved for asthma in patients down to 1 year of age.

1.3. Important Milestones in Product Development

14 Dec 1998: Written Request

8 Aug 2000: Approval of NDA 20-929 for Pulmicort Respules

03 Sept 2002: CDER stamp date for sNDA

1.4. Other Relevant Information

Not Applicable

1.5. Important Issues with Pharmacologically Related Agents

Not Applicable

2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

2.1. Chemistry, Manufacturing and Controls

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

2.2. Animal Pharmacology and Toxicology

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

2.3. Microbiology

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

2.4. Statistics

Not Applicable

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Cross-referenced to review NDA 20-929 dated 8 Aug 2000.

3.2. Pharmacodynamics

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

Sources of data were this sNDA submission dated August 30, 2002 with a CDER stamp date of September 03, 2002.

4.2. Overview of Clinical Trials

There was one clinical trial submitted in this package titled: Study #SD-004-0732: "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". This was a 12-week, multicenter, randomized, double-blind, placebo-controlled study of 2 doses of Pulmicort Respules (Budesonide Inhalation Suspension referred to further as BIS 0.5 mg and 1.0 mg) and placebo. It was planned that 144 subjects would be randomized throughout approximately 50 clinical sites to obtain 90 subjects completing the study.

4.3. Postmarketing Experience

There have been no adverse marketing experiences with this product.

4.4. Literature Review

The following literature was reviewed during the course of this application:

Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. NEJM. 2000; 343(15):1064-1069.

Wohl MEB, Majzoub JA. Asthma, steroids, and growth. NEJM 2000; 343(15): 1113

Simons FER. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. NEJM. 1997; 337(23):1659-1665

The Childhood Asthma Management Program Research Group. NEJM. 2000; 343(15):1054-1063

Purucker M, Malozowski S. Letter to Editor. NEJM. 2001; 344(8):607

Ilowite J. Letter to Editor. NEJM. 2001; 344(8):607

Skoner DP. Growth effects of asthma and asthma therapy. Curr Opin Pulm Med. 2002; 8(1):45-9

Brand PL. Inhaled corticosteroids reduce growth. Or do they? Eur Respir J. 2001; 17(2):287-94

Carson SH, Taeusch HW Jr, Avery ME. Inhibition of lung cell division after hydrocortisone injection into fetal rabbits. J Appl Physiol 1973; 34:660-663

Massaro GD, Massaro D. Formation of alveoli in rats: postnatal effect of prenatal dexamethasone. Am Physiol 1992; 263:L37-L41

Muglia LJ, Bae DS, Brown TT, et al. Proliferation and differentiation defects during lung development in corticotrophin-releasing hormone-deficient mice. Am J Respir Cell Mol Biol 1999; 20:181-188

5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

Assessment of this NDA was initiated with a review of the sponsor's overall clinical program for this drug. Minutes of meetings and teleconferences with the sponsor were reviewed, as well as notes from previous reviewers. Financial disclosure statements were reviewed. A literature review on inhaled corticosteroids and growth in children was performed. Input was obtained from other disciplines, especially statistics and biopharmaceutics. Medical officer comments are written in Italics. References to pages in the application are in square brackets [ ].

5.2. Materials Consulted and Documentation

Not applicable

5.3. Data Quality and Integrity

The quality and integrity of the data was intact.

5.4. Ethical Standards

Ethical standards were maintained throughout the study and were reviewed and agreed upon prior to study initiation by all local IRB reviewing bodies at each participating site.

5.5. Financial Disclosure

As required by 21 CFR part 54, the sponsor submitted financial disclosure information for all investigators participating in the study. Three investigators responded positively to having a financial interest. (b) (6) responded to having Significant Equity Interests in AstraZeneca LP. (b) (6) was listed as the primary investigator at center (b) (6), and enrolled 9 patients in the study. (b) (6), the primary investigator at Center # 47, also responded postively to having Significant Equity interests (b) (6) enrolled (b) (6) (b) (6) into the trial. (b) (6) also at Center (b) (6), enrolled (b) (6) patients in the study and responded positively to receiving significant payments from AstraZeneca LP. In total therefore,12 (8%) of the 141 randomized subjects were enrolled at centers with investigators with financial interests in AstraZeneca. This number should not have a significant impact on the interpretation of the safety results.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

Efficacy evaluation was not a primary outcome in this study and no efficacy conclusions will be reflected in the label. Efficacy was evaluated by examination of asthma symptom scores (AM and PM), physician's global assessments, withdrawal/treatment failure, use of breakthrough medication, percentage of symptom-free days, and investigator's global assessment of each subject's asthma status at the end of the study. In general the BIS treatment groups demonstrated greater improvement trends of mean values in AM and PM symptom scores, symptom-free days, and investigator global assessment. For the "Harder" (objective) endpoints in the study -withdrawal rates, treatment failure and use of breakthrough medication, only treatment failures showed a favorable response in the active treatment groups compared to placebo. The sponsor asserts that assessing efficacy in this population is difficult, since there are no standard methods for measurement of lung function and only few objective parameters. In general the BIS treatment groups demonstrated mean trends of greater improvement in the subjective parameters listed above, but not in the objective parameters (except for treatment failures) and not to the extent that any definitive conclusions can be made.

Reviewer Comment: This reviewer is struck by the somewhat "Harder" endpoints of withdrawal rates and breakthrough medication use being essentially equivalent. This would indicate that the placebo group had an equivalent outcome to the active treatment group. This conclusion must be somewhat tempered by the fact that some subjects in the placebo group received additional/breakthrough inhaled corticosteroids other than BIS. Having said that however, it does give caution to clinicians to carefully access whether infant patients do need inhaled steroids or not for wheezing that may or may not be asthma. There are animal studies that give cause for concern about the use of inhaled steroids in infants. In babies, the number of branching structures of airways and conducting vessels are complete in early gestation, while alveoli increase by a factor of six after birth, mostly in the first two years (Wohl and Majzoub)[1]. In glucocorticoid-deficient mice, the administration of corticosteroids during a period of alveolar development results in decrease lung-cell mass and the presence of too few abnormally large alveoli (Muglia, Bae, Brown)[2],(Carson, Taeusch and Avery)[3], (Massaro and Massaro)[4]. Therefore, the long-term consequence of steroid use in this age population on subsequent lung/organ development is unknown and was not part of this study's design. Clinicians should therefore be judicious in their use of steroid inhalation

[1] Wohl MEB, Majzoub JA. Asthma, steroids, and growth. NEJM 2000; 343 (15): 1113

[2] Muglia LJ, Base DS, Brown TT, et.al. Proliferation and differentiation defects during lung development in corticotrophin-releasing hormone-deficient mice. Am J Respir Cell Mol Biol 1999; 20: 181-188

[3] Carson SH, Taeusch HW Jr, Avery ME. Inhibition of lung cell division after hydrocortisone injection into fetal rabbits. J Appl physiol 1973; 34:660-663

[4] Massaro GD, Massaro D. Formation of alveoli in rats: pstnatal effect of prenatal dexamethasone. Am Physiol 1992: 263: L37 – L41

therapy especially when there are studies like the present one that do not demonstrate better outcome measures than placebo by "Harder" objective endpoints.

6.2. General Approach to the Efficacy Review

This application includes one study for efficacy review and therefore only the results of this study were reviewed. The efficacy endpoints in this study are supportive only for the listed age categories.

6.3. Summary of Trials by Indication

Not Applicable

6.3.1. Studies for Indication #1

Not Applicable

6.3.2. Studies for Indication #2

Not Applicable

6.4. Efficacy Discussion and Conclusions

AM and PM Symptom Scores: The BIS 0.5 mg group had a greater mean improvement than placebo for AM and PM symptom scores whereas the BIS 1.0 mg group was indistinguishable from placebo. Both active treatment groups experienced a greater mean number of symptom free days compared to placebo (BIS 0.5=11.3 mean days, BIS 1.0=5.8 mean days) but did not achieve statistical significance.

Physician Global Assessments: Physician global assessments rated asthma symptomatology as a "Great Deal Better" or "Somewhat Better" for 90% and 85% of subjects in the BIS 0.5 mg and BIS 1.0 mg groups, respectively, compared with 67% of placebo-treated subjects.

Withdrawals: There were no significant differences in withdrawal rates of the ITT population between groups during the double-blind period with 7 (14.6%), 8 (18.2%) and 7 (14.3%) of subjects withdrawing from the BIS 0.5 mg, BIS 1.0 mg and Placebo groups respectively.

Treatment Failure: Treatment failure was defined as the use of an additional asthma/breakthrough maintenance therapy for uncontrolled asthma symptoms or the use of prednisone for an asthma exacerbation. Treatment failure occurred in 7 (14.6%), 8 (18.2%) and 11 (22.4%) subjects in the BIS 0.5 mg, BIS 1.0 mg and placebo groups respectively. It is interesting to note that under the summary of prior medication use [Vol. 001/Pg 224], total glucocorticoid use was 29.2%, 15.9% and 14.3% for the BIS 0.5 mg, BIS 1.0mg and placebo groups respectively indicating that almost twice as many subjects with prior corticosteroid use were randomized into the BIS 0.5 mg group.

Reviewer Comment: *This may indicate that the subjects in the BIS 0.5 mg group were sicker on average.*

Breakthrough Medication Use: The percentage of total days on study treatment without use of breakthrough medication was not statistically significant for either of the BIS dosage groups compared with placebo (72.8, 76.6 and 72.3 days for placebo, 0.5 mg, and 1.0 mg groups respectively.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

The primary purpose of this study was to evaluate the effects of BIS 0.5 mg and 1.0 mg on adrenal function in a 6 to 12 month of age population with wheezing. Adrenal function was assessed before and at the end of the 12-week treatment period by measuring changes in plasma cortisol levels in response to the 1-hour cosyntropin (ACTH) stimulation test or by changes in urinary free cortisol excretion obtained from overnight timed urine samples. The mean values of the three different groups did not indicate any difference in adrenal responsiveness of the populations to the ACTH stimulation test. However, there were seven subjects that had subnormal responses to adrenal stimulation with six in the BIS group and one in the placebo group (the one subject in the placebo group is probably a labeling error). There were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response (as pre-defined as a post-ACTH infusion level >500 nmol/L) to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals within those populations that may have increased sensitive to exogenous corticosteroid than the group mean and this sensitivity must be kept in mind by practicing physicians when approaching therapy for the individual patient. It is also important to note that the BIS 1.0 mg group only contained 17 subjects (compared to 28 for the BIS 0.5mg and 31 for the placebo groups) which could introduce a considerable bias if the excluded subjects did not reflect the group mean.

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The data from this aspect of adrenal evaluation has a great deal of variability and questionable validity of the single placebo comparator and as such should not be used to make any HPA function conclusions for labeling purposes. Regarding adverse events, three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event. Adverse events of Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria occurred in higher percentages in the active treatment arms compared to placebo and are not presently contained in the Label for the Respules. (b) (4)

While there did not seem to group mean differences in adrenal suppression, the same cannot be said of Body Length changes. Overall Mean body length increases were 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. There appears to be dose ordering growth suppression. In order to see if there was a possible drop-out bias, Dr. Gebert investigated growth for an “evaluable group” consisting of subjects that had all data points and completed the study. This group demonstrated the same trend with mean changes of 3.3 cm, 3.5 cm and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. While this is not statistically significant (p=0.2861 BIS 1.0 mg vs. placebo) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an expected effect of corticosteroids. This effect should be placed in the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be

lulled into an erroneous false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences.

7.2. Methods and Content (Materials Utilized in Review)

A literature review on growth velocity in pediatric subjects receiving inhaled corticosteroids was performed. Safety information from the study was reviewed

7.3. Description of Patient Exposure

A total of 101 subjects had basal and ACTH-stimulated plasma cortisol values at baseline (33, 29, and 39 in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively).

7.4. Safety Findings from Clinical Studies

7.4.1.1. Safety Outcomes

7.4.1.1.1. ACTH-stimulated plasma cortisol

A total of 101 subjects had basal and ACTH-stimulated plasma cortisol values at baseline (33, 29, and 39 in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively). The mean basal and ACTH-stimulated plasma cortisol values at baseline averaged 244.7 nmol/L and 631.4 nmol/L across all treatment groups, respectively. The mean change from baseline to Visit 6 in ACTH-stimulated minus basal plasma cortisol levels did not indicate apparent suppression as monitored by mean values. [vol. 001/Pg. 093]

<u>Reviewer Comment:</u> Note that data from only 17 subjects (compared to 29 at baseline) was collected at the final visit.

Study SD-004-0732: Summary of change from Baseline in Mean Plasma Cortisol Values (nmol/L) at Week 12 (Evaluable Population[a])

Parameter	Treatment Group	N	Baseline Mean	Visit 6 Mean (SE)	Change from Baseline Mean (SE)	Change from Baseline Adjusted Mean (SE)[b]	Adjusted Mean Difference from Placebo (SE)[b]	95% CI	ANCOVA P-Value	Wilcoxon P-Value
Plasma Cortisol (Pre-Stimulation)	Placebo	31	268	234 (24.5)	-33.3 (26.4)	-17.8 (22.0)				
	BIS 0.5 mg	28	233	231 (25.8)	-2.3 (20.8)	-6.3 (23.0)	11.6 (31.8)	-51.9, 75.0	0.718	0.671
	BIS 1.0 mg	17	202	244 (32.1)	42.2 (44.8)	20.4 (29.7)	38.3 (37.2)	-36.0, 112.5	0.307	0.168
Plasma Cortisol (Post-Stimulation)	Placebo	31	647	650 (31.6)	2.8 (32.0)	5.6 (30.4)				
	BIS 0.5 mg	28	646	674 (40.0)	27.9 (41.0)	30.0 (31.9)	24.4 (44.1)	-63.5, 112.2	0.582	0.891
	BIS 1.0 mg	17	627	661 (33.4)	33.5 (46.7)	24.8 (41.0)	19.2 (51.1)	-82.6, 121.0	0.708	0.940
Plasma cortisol (Post-Minus Pre-Stimulation)	Placebo	31	379	415 (38.4)	36.1 (48.9)	19.8 (36.1)				
	BIS 0.5 mg	28	412	443 (43.7)	30.2 (44.3)	37.9 (38.0)	18.0 (52.5)	-86.6, 122.7	0.732	0.832
	BIS 1.0 mg	17	426	417 (37.0)	-8.7 (62.6)	8.4 (48.8)	-11.4 (60.8)	-133, 109.8	0.852	0.140

[i]ncluded subjects with a baseline plasma cortisol value ≥500 nmol/L and who did not receive a steroid within the 4 weeks prior to final cortisol testing

[b] Mean adjusted for baseline

<u>Reviewer Comment:</u> Noted that the BIS 1.0 mg group only contained 17 subjects which could introduce a considerable bias if the excluded subjects did not reflect the mean report.

Few subjects had shifts from a baseline post-ACTH-stimulation plasma cortisol value ≥ 500 nmol/L to a Week 12 post-ACTH plasma cortisol value of < 500 nmol/L (4 (14%), 2 (12%), and 1 (3%) in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively. For 5 of the 7 subjects with a subnormal ACTH-stimulated plasma cortisol value at Week 12 the end-of-treatment post-ACTH-stimulated plasma cortisol value was below the cut-off value of 500 nmol/L (18 µg/dL)(values of (b) (4) all exposed to BIS 0.5mg and (b) (4) both exposed to BIS 1.0mg). For the remaining 2 subjects (BIS 0.5 and Placebo) the post-stimulation value was very low, 155nmol/L and 109 nmol/L (pre-stimulation values were (b) (4) The sponsor speculates that these low values may be due to sampling or labeling errors.

Reviewer Comment: While the mean values of the three different groups did not indicate any difference in adrenal responsiveness of the populations, there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response to cosyntropin. This may indicate that, while the general patient population may not have adrenal suppression, there are individuals that may have increased sensitivity to exogenous corticosteroid suppression and this must be kept in mind by practicing physicians when treating individual patients.

7.4.1.1.2. Urinary Cortisol

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The mean change from baseline at Week 12 was 52.2 ug/g (b) (4) among subjects in the BIS 0.5 mg group compared to a –44.8 mean change for the placebo subject. See table below. [Vol. 001/Pg. 102]

Study SD-004-0732: Urinary Cortisol Data (Evaluable Population)

Treatment Group	Sex/Age	Race	Urinary Cortisol Value (ug/g (b) (4)	
			Visit 2	Visit 6
BIS 0.5 mg	F/6	Caucasian	13.7	10.0
BIS 0.5 mg	M/11	Caucasian	21.0	34.8
BIS 0.5 mg	M/9	Black	5.9	181.6
BIS 0.5 mg	F/7	Caucasian	12.9	8.1
BIS 0.5 mg	M/8	Caucasian	28.1	108.0
Placebo	F/6	Black	62.6	17.8

Review Comment: The data from this aspect of adrenal evaluation has a great deal of variability as demonstrated by the subject on Placebo who had a minus mean change which would fulfill the criteria for abnormal response. Since there is not a placebo control group and because of the wide range of variability (perhaps reflecting the difficulty in collecting proper urine samples in this age group) this data should not be used to make any HPA function conclusions for labeling purposes.

Frequency of Adverse Events with discrepancies between active arms and placebo are listed in the table below. [vol. 001/pgs 112-114]

Study SD-004-0732: Frequency of Adverse Events with discrepancy reporting of BIS compared to placebo			
	BIS 0.5 mg (N=48)	BIS 1.0 mg (N=44)	Placebo (N=49)
Otitis Media	23 (47.9%)	12 (27.3%)	20 (40.8%)
Fever	12 (25.0%)	10 (22.7%)	17 (34.7%)
Asthma Aggravated	4 (8.3%)	4 (9.1%)	8 (16.3%)
Tooth Disorder	**6 (12.5%)**	**7 (15.9%)**	**2 (4.1%)**
Coughing	4 (8.3%)	2 (4.5%)	6 (12.2%)
Conjunctivitis	7 (14.6%)	0. (0.0%)	4 (8.2%)
Pharyngitis	**7 (14.6%)**	**0 (0.0%)**	**2 (4.1%)**
Rhonchi	1 (2.1%)	1 (2.3%)	6 (12.2%)
Dermatitis Fungal	2 (4.2%)	2 (4.5%)	4 (8.2%)
Nervousness	**3 (6.3%)**	**1 (2.3%)**	**0 (0.0%)**
Pneumonia	**2 (4.2%)**	**1 (2.3%)**	**0 (0.0%)**
Urticaria	**1 (2.1%)**	**1 (2.3%)**	**0 (0.0%)**
Lymphadenopathy	0 (0.0%)	0 (0.0%)	2 (4.1%)
Dysphonia	1 (2.1%)	0 (0.0%)	0 (0.0%)

Three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event.

<u>Reviewer Comment:</u> Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria are not presently in the Label (b) (4) *Noted is the lower frequency of Asthma aggravation, rhonchi, dermatitis fungal and lymphadenopathy in the active treatment group compared to placebo..*

7.4.1.1.3. Body Length

The protocol for body length measurement is in Vol. 003/pg 065 (b) (4)

(b) (4)

Mean body length increased across visits in all 3 treatment groups, although mean body length in the BIS 1.0 mg group increased less from Week 8 to Week 12 compared with the other treatment groups. The mean changes in body length for the ITT group are in the table below. [vol.001/pg 216][Vol.002/pg. 231-232]

Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in ITT Group			
	BIS 1.0 mg N=43	BIS 0.5 mg N=47	Placebo N=47
Mean Baseline (cm)	71.0	70.2	70.9
Mean Last Visit (cm)	74.1	73.5	74.4
Mean Change (cm)	3.1	3.3	3.5

Review Comment: The sponsor's value for Mean body length increase are 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. Although we have not reproduced the same numbers, the trend is the same and reveals dose ordering.

This table may not be an accurate reflection of growth changes due to drop-outs. The biostatistics reviewer, Dr. Jim Gebert developed an "evaluable group" of subjects that completed the study and had complete data. This table is below.

Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in Evaluable Group			
	BIS 1.0 mg N=35	BIS 0.5 mg N=39	Placebo N=42
Mean Baseline (cm)	70.8	70.9	70.6
Mean Last Visit (cm)	74.1	74.4	74.3
Mean Change (cm)	3.3	3.5	3.7

By this analysis we again have dose ordering in reduction of growth velocity. It may be instructive to review growth per visit in the evaluable group presented in the table below.

Study SD-004-0732: Mean Body Length Change per Visit (Evaluable Group)						
	BIS 1.0 mg (cm) N=41	**Δ BIS 1.0 mg from previous Visit (cm)**	**BIS 0.5 mg (cm) N=43**	**Δ BIS 0.5 mg from previous Visit (cm)**	**Placebo (cm) N=38**	**Δ Placebo from previous Visit (cm)**
Visit 3 (2 wks) Δ from baseline	0.63		0.44		0.61	
Visit 4 – Visit 3		0.80		0.61		0.60
Visit 4 (4 wks) Δ from baseline	1.43		1.05		1.21	
Visit 5 – visit 4		1.09		1.11		1.14
Visit 5 (8 wks) Δ from baseline	2.52		2.16		2.35	
Visit 6 – Visit 5		0.7		1.30		1.31
Visit 6 (12 wks) Δ from baseline	**3.22**		**3.46**		**3.66**	

As the Sponsor has noted, the BIS 1.0 mg group had less of an increase from Visit 5 to Visit 6 compared to the other groups. However, there is again dose ordering and as the dose of BIS increases total growth over the 12 week study decreases. While this is not statistically significant (p=0.2861 BIS 1.0 mg vs. placebo on change from baseline) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an effect that is expected from corticosteroids. The overall difference in total growth between the placebo and BIS 1.0 group is **0.44 cm**.

Study SD-004-0732: Mean Body Length Change per Visit for subjects 6mo to <9mo (Evaluable Group)						
	BIS 1.0 mg (cm) N=21	**Δ BIS 1.0 mg from previous Visit (cm)**	**BIS 0.5 mg (cm) N=21**	**Δ BIS 0.5 mg from previous Visit (cm)**	**Placebo (cm) N=21**	**Δ Placebo from previous Visit (cm)**
Visit 3 (2 wks) Δ from baseline	0.50		0.45		0.85	
Visit 4 – Visit 3		1.00		0.58		0.55
Visit 4 (4 wks) Δ from baseline	1.50		1.03		1.40	
Visit 5 – visit 4		0.90		1.08		1.23
Visit 5 (8 wks) Δ from baseline	2.40		2.11		2.63	
Visit 6 – Visit 5		1.23		1.23		1.29
Visit 6 (12 wks) Δ from baseline	**3.18**		**3.34**		**3.92**	

From the above results, it appears that decrease in growth velocity occurs in a dose related fashion. The magnitude of difference between placebo and BIS 1.0 is greater in this age group than for the data regarding all combined age groups. This might be expected as the greatest amount of growth velocity in 6mo to 12 mo old infants would occur in the 6 to < 9 mo old subgroup compared to the 9 to 12 mo group. The overall difference in growth between the placebo and BIS 1.0 mg group is **0.74 cm**.

Study SD-004-0732: Mean Body Length Change per Visit for subjects 9mo to 12mo (Evaluable Group)						
	BIS 1.0 mg (cm) N=21	**Δ BIS 1.0 mg from previous Visit (cm)**	**BIS 0.5 mg (cm) N=21**	**Δ BIS 0.5 mg from previous Visit (cm)**	**Placebo (cm) N=21**	**Δ Placebo from previous Visit (cm)**
Visit 3 (2 wks) Δ from baseline	0.81		0.43		0.37	
Visit 4 – Visit 3		0.50		0.65		0.65
Visit 4 (4 wks) Δ from baseline	1.31		1.08		1.02	
Visit 5 – visit 4		1.38		1.13		1.04
Visit 5 (8 wks) Δ from baseline	2.69		2.21		2.06	
Visit 6 – Visit 5		0.60		1.40		1.35
Visit 6 (12 wks) Δ from baseline	**3.29**		**3.61**		**3.41**	

This stratified age group does not have a clear dose related suppression of growth velocity. However, this age grouping would have less total growth compared to the 6 mo to < 9 mo age group and therefore would not be as sensitive to possible corticosteroid suppressing effects. The difference between the placebo and BIS 1.0 mg group is **0.12 cm**.

Reviewer Comment: *Decreased growth velocity in infants receiving corticosteroid agents is expected and consideration should be given to placing this information into the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into a false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences. If the present rate of growth differential would be sustained the BIS 1.0 mg group would have approximately 1.8 cm less growth over a year which is consistent with the literature on reduced growth velocity and gives more credibility to these results.*

7.5. Miscellaneous Studies

Not applicable

7.6. Literature Review of Safety

See heading 7.3.

7.7. Postmarketing Surveillance – If Applicable

Not Applicable

7.8. Safety Update – If Available

Not Applicable

7.9. Drug Withdrawal, Abuse, and Overdose Experience

None

7.10. Adequacy of Safety Testing

The safety study gives data pertinent to the short-term adverse effects of use of inhaled corticosteroids. This study does not give any information on the possible long-term effects of corticosteroid use, particularly on organ (lung) maturation and function. It would be useful if studies could be performed on long-term effects of inhaled steroids use in infants on lung functions and development, particularly in this age group where alveoli development is possibly vulnerable. However, for purposes of the Written Request, the sponsor has performed the negotiated study.

7.11. Labeling, Safety Issues, and Postmarketing Commitments

Please refer to section 10.3 for safety labeling issues. Again, it should be noted that there are animal studies demonstrating that the administration of corticosteroids during a period of alveolar development results in decrease lung-cell mass and the presence of too few abnormally large alveoli (Muglia, Bae, Brown)(Carson, Taeusch and Avery)(Massaro and Massaro). It is also known that in babies alveoli increase by a factor of six after birth,

mostly in the first two years (Wohl and Majzoub). Therefore, the long-term consequence of steroid use in this age population on subsequent lung/organ development is unknown and it would probably benefit society and public health if studies are designed and conducted to answer this question.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The dosages used in the active treatment arms of this study were BIS 0.5 mg and BIS 1.0 mg once a day. Pulmicort Respules are presently approved at a starting dose of 0.25 mg once daily and total daily doses of 0.5 or 1 mg depending on the patient population.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Gender, Age, Race, or Ethnicity Efficacy and Safety Analyses and Adequacy of Investigation

The sponsor has done an adequate safety evaluation of Gender in this submission. The population studied for this submission was mainly Caucasian.

9.2. Pediatric Program

The sponsor has fulfilled the requirements of a pediatric program in patients aged 6 months to 8 years of age.

9.3. Comments on Data Available or Needed in Other Populations (Such as Renal or Hepatic Compromised Patients, Use in Pregnancy)

There is a great deal of information available in the literature regarding the use of budesonide in other populations.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

The results of this study do not indicate a population mean suppressive effect on adrenal function in subjects aged 6 to 12 months with once-daily dosages of 0.5 or 1.0 mg BIS, however, there may be individual subjects with increased sensitivity and possible adrenal suppression. The safety profile of BIS was generally comparable to the safety profile in the approved label except for higher percentages of Tooth disorder, Nervousness, Pneumonia and Urticaria in the BIS group compared to placebo. A dose -dependent decrease in growth velocity was seen in the BIS groups compared to placebo. Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores, daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days, number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study. The BIS treatment groups demonstrated trends of greater mean reduction in subjective parameters, with no clear advantage in the objective parameters, and not to the extent that any efficacy conclusions could be made.

10.2. Recommendations on Approvability

The sponsor is not seeking new indications in the label. This submission has fulfilled the requirements of the Written Request and is approvable with need for label revisions to gain full approval.

10.3. Labeling

Under heading "PRECAUTIONS", subheading Pediatric Use, (b) (4) Also the labeling should reflect that, while there was no difference in mean cosyntropin simulation values, 6 subjects in the treatment group and one in the placebo group had abnormal (low cortisol secretion) cosyntropin responses at the end of the 12 week study. This section should also reflect that there might be dose-ordered growth velocity suppression (b) (4)

Under the heading "CLINICAL PHARMACOLOGY", subheading Pharmacodynamics, the double-lined addition beginning "A 12-week study…." Should be amended to reflect the number of patients who actually had an evaluation of serum cortisol levels post-ACTH stimulation at baseline and Week 12 and the finding that 6 subjects in the Pulmicort Respules group and one subject in the placebo group had a subnormal

(<500 nmol/L)response.

Conclusions and Recommendations

APPENDIX

11. DETAILED STUDY REVIEWS

11.1. Study #SD-004-0732: "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"

11.1.1. Protocol

11.1.1.1. Investigators and Centers

This was a multicenter clinical study employing 55 centers in the United States. One hundred and forty one subjects were randomized into this study.

11.1.1.2. Objective/Rationale

The primary objective of this study was to evaluate the safety of once-daily administration of Pulmicort Respules (0.5 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 primary safety variable was assessment of adrenal function as assessed as the mean change from baseline at Week 12 in basal and 1-hour post adrenocorticotropic hormone (ACTH) stimulated cortisol levels or changes in urinary cortical excretion. Secondary objectives included evaluating the efficacy of Pulmicort Respules and placebo by comparing nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, and subject discontinuations, and physician's global assessment of each subject's asthma status.

11.1.1.3. Overall Design

A 12-week, multicenter, randomized, double-blind, placebo-controlled study of 2 doses of Pulmicort Respules (Budesonide Inhalation Suspension referred to further as BIS) (0.5 mg and 1.0 mg) and placebo. It was planned that 144 subjects would be randomized throughout approximately 50 clinical sites to obtain 90 subjects completing the study.

11.1.1.4. Study Population

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 defined as at least 2 episodes of persistent/recurrent wheezing, who may have benefited from inhaled anti-inflammatory therapy.

11.1.1.5. Inclusion Criteria

1. Male or Female between the ages of 6 and 12 months.
2. Diagnosed with asthma by historical signs and symptoms (consisting of at least 2 episodes of persistent or recurrent wheezing).

3. Agree to basal cortisol specimens drawn in the morning at Visits 2 and 6 and post-ACTH specimens
4. Normal baseline electrocardiogram (ECG) on file if being treated with propulsid (cisapride) for gastroesophageal reflux disease.
5. Asthma symptoms scores (nighttime or daytime; score of 1, 2, 3) on 3 or more of the last 7 days prior to Visit 2. Asthma scale:

0= None; no symptoms

1= Mild symptoms; awareness of asthma symptoms and/or signs that are easily tolerated

2= Moderate symptoms; asthma symptoms and/or signs with some discomfort, causing some interference of daily activities (daytime) or sleep (nighttime)

3= Severe symptoms; incapacitating asthma symptoms and/or signs, with inability to perform daily activities (daytime) or sleep (nighttime)

Reviewer note: These symptoms scores seemed more geared toward self reporting which is not possible in this population. Therefore limited conclusions may be made based on this system.

11.1.1.6. Exclusion Criteria

1. Diagnosed with severe asthma
2. History of assisted ventilation
3. Having a functioning tracheostomy
4. Require chronic or intermittent oxygen therapy
5. Severe GERD
6. Severe chronic lung disease which may lead to hypoxia (Note: subjects with mild cystic fibrosis or bronchopulmonary dysplasia who were normoxic and demonstrated reversible airway disease could be considered for study entry)
7. Severe immunodeficiencies disease
8. HIV positive
9. Hospitalized for pulmonary disease or respiratory infection within the past 4 weeks
10. Born less than 32 weeks of gestation
11. Failure-to-thrive within past 2 months
12. Treatment with systemic steroids within past 4 weeks
13. Endocrine abnormality
14. Receiving treatment with any of the following medications: systemic steroids, inhaled steroids including intranasal steroids, slow-release oral beta2 agonists, long-acting

Appendix,

inhaled beta2 agonists or 5-lipoxygenase and leukotriene antagonists (anticholinergics and metaproterenol were allowed during baseline although anticholinergics were not allowed following randomization. After randomization the use of oral prednisone or prednisolone was permitted. If the duration exceeded 10 days, the patient was to be discontinued)

11.1.1.7. Study Procedures

This study included 6 visits.

Visit 1 was a screening visit with review of exclusion/inclusion criteria and began a 2-week washout period during which chronic asthma medications were stopped.

Visit 2 was a randomization visit that included review of exclusion/inclusion criteria, obtaining physical examination, laboratory evaluation, oropharyngeal and nasal fungal cultures and cortisol specimens. Subjects undergoing plasma cortisol testing also received an intravenous (IV) infusion of cosyntropin 0.125 mg and a second plasma cortisol sample was obtained 60 minutes after infusion. Subjects were then assigned according to stratified randomization schedule to treatment arms. Each treatment was administered using a Pari LC-Plus™ nebulizer connected to a Pari Master compressor with a face mask or mouthpiece manufactured by (b) (4). The face mask was to cover the child's nose and mouth.

Visits 3, 4, and 5 were double-blind treatment visits and were scheduled after 2 weeks (Visit 3), 4 weeks (Visit 4), 8 weeks (Visit 5), and 12 weeks (visit 6). At each visit, diary cards were collected and a brief physical examination including measurement of body length and weight was performed. Visit 5 included distribution of urinary cortisol collecting equipment for collection of urine during the last week.

Visit 6 was the final visit and occurred at Week 12. Diary cards were collected and a complete physical examination was performed. For subjects undergoing plasma cortisol testing, a basal cortisol sample was obtained and the 1-hour cosyntropin stimulation test was repeated. Investigators completed a 5-point global assessment of efficacy. See table below [Vol. 001/Pg 049].

Appendix,

Study SD-004-0732: Study Summary/Flow Chart						
	Baseline	Double-blind Week				
Week Number	-2 ± 1	0	2	4	8	12
Visit Number	1	2	3	4	5	6
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical & Surgical Histories	X					
Complete Physical Examination	X					X
Brief Physical Examination		X	X	X	X	
Vital Signs, including Length and Weight	X	X	X	X	X	X
Randomization		X				
Hematology, Blood Chemistry		X				X
Oropharyngeal & Nasal Fungal Cultures		X				X
Cortisol Specimens (blood) or (urine)		X				X
Dispense Study Drug & Instructions on dosing		X	X	X	X	
Drug Accountability			X	X	X	X
Instruct Parent/Guardian in Diary Completion	X	X	X	X	X	
Collect and review Diary Entries		X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X
Review Use of Concomitant Medications	X	X	X	X	X	X
Physician's Global Assessment						X

11.1.1.8. Efficacy Parameters

Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores, daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days (see scale under inclusion criteria), number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study.

Investigator Global Assessment:

1 = a great deal better

2 = somewhat better

Appendix,

3 = unchanged

4 = somewhat worse

5 = a great deal worse

11.1.1.9. Safety Evaluations

The primary safety variable was adrenal function as determined by plasma cortisol levels (pre- and 1-hour post- ACTH) and overnight urinary free cortisol levels at Visits 2 and 6. Subnormal adrenal function by plasma cortisol levels was defined as a post-ACTH plasma cortisol value less than 500 nmol/L at either Visit 2 or Visit 6. Urinary cortisol excretion was measured as the (b) (4) and also as total free cortisol levels from overnight timed urine samples. Subjects who did not undergo the cosyntropin stimulation test were to provide timed urine samples. Other secondary safety variables included the incidence and severity of adverse events, changes from baseline in hematology and chemistry laboratory, body length/height and body weight and oropharyngeal and nasal fungal cultures.

Body length was measured with the subject on (b) (4)

11.1.1.10. Statistical Plan

The sponsor's state that this study was designed to address whether BIS is safe compared to placebo and differs from placebo in terms of improvement of asthma/wheezing. All statistical comparisons were carried out as two-sided tests. The Intent-to-treat (ITT) population was all subjects who were randomized and received at least one dose of study medication and had one observation taken. The "Evaluable" population is all subjects with at least a pre- and post-cosyntropin stimulation sample obtained before and at the end of treatment or urine samples obtained before and at the end of treatment.

The last observed value carried forward (LOCF) was used for analysis and summary of plasma and urinary cortisol and for the investigator's global assessment of asthma status. Only observed data were summarized for the remaining efficacy safety analyses.

The primary variable was analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect and baseline as the covariate. The p-value from the Wilcoxon Rank Sum test is also provided for this analysis.

For efficacy variables, the change from baseline in nighttime and daytime symptom scores were analyzed using an ANCOVA with treatment as the main effect and baseline as the covariate. Investigator's global assessment were analyzed using Mantel-Haenszel test.

The sponsor states that sample size calculations were not based upon strict statistical criteria but rather on pediatric exclusivity guidance from the FDA that approximately half of the subjects were to be between the 6 and 9 months of age and the other half were to be between

9 and 12 months of age with at least 90 completing subjects, at least 60 of whom had to be in the active treatment groups.

11.1.2. Results

11.1.2.1. Subject Disposition

A total of 216 subjects were screened. There were 75 screening failures. A total of 141 pediatric patients were randomized into the study to receive Pulmicort Respules (48 to BIS 0.5 mg, 44 to BIS 1.0 mg and 49 to placebo).

Study SD-004-0732: Summary of Subject Disposition

Parameter	BID 0.5mg N=48	BIS 1.0 mg N=44	Placebo N=49	Total N=141
Total Randomized	48	44	49	141
Age strata				
6 to < 9 months	26	25	25	
9 to <12 months	22	19	24	
Completed Study	40 (83.3%)	35 (79.5%)	42 (85.7%)	117 (83.0%)
Discontinued Study	8 (16.7%)	9 (20.5%)	7 (14.3%)	24 (17.0%)
Reason for Discontinuation[a]				
Lost to follow-up	4 (50.0%)	2 (22.2%)	2 (28.6%)	8 (33.3%)
Other[b]	3 (37.5%)	2 (22.2%)	3 (42.9%)	8 (33.3%)
Consent withdrawn	0	3 (33.3%)	2 (28.6%)	5 (20.8%)
Adverse event	1 (12.5%)	2 (22.2%)	0	3 (12.5%)
Treatment failure	0	0	0	0

[a] Percentages based on number discontinuing in each treatment group

[b] Other included noncompliance, doctor's choice, moving

<u>Reviewer Comment:</u> It is interesting to note that a higher percentage of subjects in the placebo group completed the study than in either active treatment group. Adverse events as a reason for stopping the study were limited to the active treatment groups and appeared dose related.

The sponsor's state that only a total of 82 pediatric subjects (33 in the BIS 0.5 mg group, 17 in the BIS 1.0 mg group and 32 in the placebo group) were considered evaluable for the

analyses of adrenal function due to inability to obtain plasma cortisol levels as the result of unsuccessful blood draws [Vol. 001/Pg 086].

11.1.2.2. Demographics

Overall, most subjects were Caucasian (99, 70%) and male (87, 62%). With the exception of a higher proportion of males vs. females among subjects aged 9 to < 12 months compared with younger subjects in the BIS 0.5 mg group (82% vs. 18%), demographic characteristics were comparable across treatment groups and age strata [Vol.001/pg. 088].

11.1.2.3. Efficacy Endpoint Outcomes

Efficacy was evaluated by examination of asthma symptom scores (AM and PM), physician's global assessments, withdrawal/treatment failure, and the use of breakthrough medication.

<u>Reviewer comment:</u> Symptom scores and global assessments are "soft" endpoints and should only be used to look for signals of concern. Withdrawal rates and use of breakthrough medication may give a better indication of effectiveness.

These results are presented in the following tables.

Appendix,

Study SD-004-0732: Summary of Mean Change from Baseline in AM and PM Asthma Symptom Scores (ITT Population)									
Parameter	Treatment Group	N	Baseline Mean	Week 1-12 Mean (SE)	Baseline change Adjusted Mean (SE)[a]	Difference from Placebo (SE)[a]	95% CI	ANCOVA P-Value	Wilcoxon P-Value
Daytime Score (Week 1-12)	Placebo	46	1.20	0.8 (0.1)	0.4 (0.1)				
	BIS 0.5 mg	45	1.28	0.6 (0.1)	0.6 (0.1)	-0.2 (0.1)	-0.4, 0.0	0.060	0.040
	BIS 1.0 mg	43	1.10	0.7 (0.1)	0.4 (0.1)	-0.0 (0.1)	-0.2, 0.1	0.634	0.853
Nighttime Score (Week 1-12)	Placebo	46	1.21	0.8 (0.1)	0.4 (0.1)				
	BIS .5 mg	45	1.24	0.6 (0.1)	0.6 (0.1)	-0.2 (0.1)	-0.4, -0.0	0.047	0.173
	BIS 1.0 mg	43	1.08	0.7 (0.1)	0.5 (0.1)	-0.1 (0.1)	-0.3, 0.1	0.447	0.944
[a] Mean adjusted for baseline									

The BIS 0.5 mg group had a greater change from baseline compared to the placebo group, but the 95% CI included 0. It would appear that the BIS 0.1 mg group was less symptomatic than the placebo group at baseline so it is not unexpected that there would less opportunity for an effect size difference to be realized.

Appendix,

Study SD-004-0732: Summary of Percentage of Symptom-Free Days (ITT Population)							
Treatment Group	N	Mean (SE)	Adjusted Mean (SE)	Placebo Difference Mean (SE)	95% CI	ANOVA P-Value	Wilcoxon P-Value
Placebo	47	37.5 (4.4)	37.5 (4.8)				
BIS 0.5 mg	46	48.9 (4.9)	48.8 (4.9)	11.3 (6.8)	-2.3, 24.8	0.102	0.081
BIS 1.0 mg	43	43.4 (5.5)	43.4 (5.0)	5.8 (7.0)	-7.9, 19.6	0.403	0.372

Both active treatment groups experienced a greater mean number of symptom free days compared to placebo.

For the ITT population, physician global assessments rated asthma symptomatology as a "Great Deal Better" or "Somewhat Better" for 90% and 85% of subjects in the BIS 0.5 mg and BIS 1.0 mg groups, respectively, compared with 67% of placebo-treated subjects.

There were no significant differences in withdrawal rates of the ITT population between groups during the double-blind period with 7 (14.6%), 8 (18.2%) and 7 (14.3%) of subjects withdrawing from the BIS 0.5 mg, BIS 1.0 mg and Placebo groups respectively.

Treatment failure was defined as the use of an additional asthma/breakthrough maintenance therapy for uncontrolled asthma symptoms or the use of prednisone for an asthma exacerbation. Treatment failure occurred for 7 (14.6%), 8 (18.2%) and 11 (22.4%) of subjects in the BIS 0.5 mg, BIS 1.0 mg and placebo groups respectively. It is interesting to note that under the summary of prior medication use [Vol. 001/Pg 224], total glucocorticoid use was 29.2%, 15.9% and 14.3% for the BIS 0.5 mg, BIS 1.0mg and placebo groups respectively indicating that almost twice as many subjects with prior corticosteroid use were randomized into the BIS 0.5 mg group.

The percentage of total days on study treatment without use of breakthrough medication was not statistically significant for either of the BIS dosage groups compared with placebo (72.8, 76.6 and 72.3 days for placebo, 0.5 mg, and 1.0 mg groups respectively.

11.1.2.4. Safety Outcomes

11.1.2.4.1. ACTH-stimulated plasma cortisol

A total of 101 subjects had basal and ACTH-stimulated plasma cortisol values at baseline (33, 29, and 39 in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively). The mean basal and ACTH-stimulated plasma cortisol values at baseline averaged 244.7 nmol/L and 631.4 nmol/L across all treatment groups, respectively. The mean change from baseline to

Visit 6 in ACTH-stimulated minus basal plasma cortisol levels did not indicate apparent suppression as monitored by mean values. [vol. 001/Pg. 093]

Appendix,

Study SD-004-0732: Summary of change from Baseline in Mean Plasma Cortisol Values (nmol/L) at Week 12 (Evaluable Population[a])

Parameter	Treatment Group	N	Baseline Mean	Visit 6 Mean (SE)	Change from Baseline Mean (SE)	Change from Baseline Adjusted Mean (SE)[b]	Adjusted Mean Difference from Placebo (SE)[b]	95% CI	ANCOVA P-Value	Wilcoxon P-Value
Plasma Cortisol (Pre-Stimulation)	Placebo	31	268	234 (24.5)	-33.3 (26.4)	-17.8 (22.0)				
	BIS 0.5 mg	28	233	231 (25.8)	-2.3 (20.8)	-6.3 (23.0)	11.6 (31.8)	-51.9, 75.0	0.718	0.671
	BIS 1.0 mg	17	202	244 (32.1)	42.2 (44.8)	20.4 (29.7)	38.3 (37.2)	-36.0, 112.5	0.307	0.168
Plasma Cortisol (Post-Stimulation)	Placebo	31	647	650 (31.6)	2.8 (32.0)	5.6 (30.4)				
	BIS 0.5 mg	28	646	674 (40.0)	27.9 (41.0)	30.0 (31.9)	24.4 (44.1)	-63.5, 112.2	0.582	0.891
	BIS 1.0 mg	17	627	661 (33.4)	33.5 (46.7)	24.8 (41.0)	19.2 (51.1)	-82.6, 121.0	0.708	0.940
Plasma cortisol (Post-Minus Pre-Stimulation)	Placebo	31	379	415 (38.4)	36.1 (48.9)	19.8 (36.1)				
	BIS 0.5 mg	28	412	443 (43.7)	30.2 (44.3)	37.9 (38.0)	18.0 (52.5)	-86.6, 122.7	0.732	0.832
	BIS 1.0 mg	17	426	417 (37.0)	-8.7 (62.6)	8.4 (48.8)	-11.4 (60.8)	-133, 109.8	0.852	0.140

[i]ncluded subjects with a baseline plasma cortisol value ≥500 nmol/L and who did not receive a steroid within the 4 weeks prior to final cortisol testing

[b] Mean adjusted for baseline

<u>Reviewer Comment:</u> Noted that the BIS 1.0 mg group only contained 17 subjects which could introduce a considerable bias if the excluded subjects did not reflect the mean report.

Appendix,

Few subjects had shifts from a baseline post-ACTH-stimulation plasma cortisol value ≥ 500 nmol/L to a Week 12 post-ACTH plasma cortisol value of < 500 nmol/L (4 (14%), 2 (12%), and 1 (3%) in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively. For 5 of the 7 subjects with a subnormal ACTH-stimulated plasma cortisol value at Week 12 the end-of-treatment post-ACTH-stimulated plasma cortisol value was near the cut-off value of 500 nmol/L (18 µg/dL)(values of (b) (4) all exposed to BIS 0.5mg (b) (4) both exposed to BIS 1.0mg). For the remaining 2 subjects (BIS 0.5 and Placebo) the post-stimulation value was low, 155nmol/L and 109 nmol/L (pre-stimulation values were (b) (4) nmol/L (b) (4) nmol/L. The sponsor speculates that the discrepancy may be due to sampling or labeling errors.

Reviewer Comment: The mean values of the three different group did not indicate any difference in adrenal responsiveness of the populations while there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals that may have increased sensitive to exogenous corticosteroid suppression and must be kept in mind by practicing physicians when approaching individual patients.

11.1.2.4.2. Urinary Cortisol

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The mean change from baseline at Week 12 was 52.2 ug/g (b) (4) among subjects in the BIS 0.5 mg group compared to a –44.8 mean change for the placebo subject. See table below. [Vol. 001/Pg. 102]

Study SD-004-0732: Urinary Cortisol Data (Evaluable Population)

Treatment Group	Sex/Age	Race	Urinary Cortisol Value (ug/g (b) (4)	
			Visit 2	Visit 6
BIS 0.5 mg	F/6	Caucasian	13.7	10.0
BIS 0.5 mg	M/11	Caucasian	21.0	34.8
BIS 0.5 mg	M/9	Black	5.9	181.6
BIS 0.5 mg	F/7	Caucasian	12.9	8.1
BIS 0.5 mg	M/8	Caucasian	28.1	108.0
Placebo	F/6	Black	62.6	17.8

Review Comment: The data from this aspect of adrenal evaluation has a great deal of variability as demonstrated by the Placebo group's minus mean change which would fulfill the criteria for abnormal response. Therefore since there is not a placebo control and because of wide range of variability (perhaps reflecting the difficulty collecting proper urine samples in this age group) this data should not be used to make any HPA function conclusions for labeling purposes.

Appendix,

Frequency of Adverse Events with discrepancies between active arms and placebo are listed in the table below. [vol. 001/pgs 112-114]

Study SD-004-0732: Frequency of Adverse Events with discrepancy reporting of BIS compared to placebo			
	BIS 0.5 mg (N=48)	BIS 1.0 mg (N=44)	Placebo (N=49)
Otitis Media	23 (47.9%)	12 (27.3%)	20 (40.8%)
Fever	12 (25.0%)	10 (22.7%)	17 (34.7%)
Asthma Aggravated	4 (8.3%)	4 (9.1%)	8 (16.3%)
Tooth Disorder	**6 (12.5%)**	**7 (15.9%)**	**2 (4.1%)**
Coughing	4 (8.3%)	2 (4.5%)	6 (12.2%)
Conjunctivitis	7 (14.6%)	0. (0.0%)	4 (8.2%)
Pharyngitis	**7 (14.6%)**	**0 (0.0%)**	**2 (4.1%)**
Rhonchi	1 (2.1%)	1 (2.3%)	6 (12.2%)
Dermatitis Fungal	2 (4.2%)	2 (4.5%)	4 (8.2%)
Nervousness	**3 (6.3%)**	**1 (2.3%)**	**0 (0.0%)**
Pneumonia	**2 (4.2%)**	**1 (2.3%)**	**0 (0.0%)**
Urticaria	**1 (2.1%)**	**1 (2.3%)**	**0 (0.0%)**
Lymphadenopathy	0 (0.0%)	0 (0.0%)	2 (4.1%)
Dysphonia	1 (2.1%)	0 (0.0%)	0 (0.0%)

Three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event.

Reviewer Comment: Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria are not presently in the Label and [redacted] (b) (4) *Noted is the favorable effect of active treatment with regard to Asthma aggravation, rhonchi, dermatitis fungal and lymphadenopathy.*

11.1.2.4.3. Body Length

The protocol for body length measurement is in Vol. 003/pg 065. [redacted] (b) (4)

Appendix,

(b) (4)

[redacted]

Mean body length increased across visits in all 3 treatment groups, although mean body length in the BIS 1.0 mg group increased less from Week 8 to Week 12 compared with the other treatment groups. The mean changes in body length for the ITT group are in the table below. [vol.001/pg 216][Vol.002/pg. 231-232]

Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in ITT Group			
	BIS 1.0 mg N=43	BIS 0.5 mg N=47	Placebo N=47
Mean Baseline (cm)	71.0	70.2	70.9
Mean Last Visit (cm)	74.1	73.5	74.4
Mean Change (cm)	3.1	3.3	3.5

Review Comment: The sponsor's value for Mean body length increase are 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. Although we have not reproduced the same numbers, the trend is the same and reveals dose ordering.

This table may not be an accurate reflection of growth changes due to drop-outs. Dr. Gebert has developed an evaluable group of subjects that completed the study and had complete data. This table is below.

Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in Evaluable Group			
	BIS 1.0 mg N=35	BIS 0.5 mg N=39	Placebo N=42
Mean Baseline (cm)	70.8	70.9	70.6
Mean Last Visit (cm)	74.1	74.4	74.3
Mean Change (cm)	3.3	3.5	3.7

By this analysis we again have dose ordering in reduction of growth velocity. It may be instructive to review growth per visit in the evaluable group presented in the table below.

Appendix,

Study SD-004-0732: Mean Body Length Change per Visit (Evaluable Group)						
	BIS 1.0 mg (cm) N=41	**Δ BIS 1.0 mg from previous Visit (cm)**	**BIS 0.5 mg (cm) N=43**	**Δ BIS 0.5 mg from previous Visit (cm)**	**Placebo (cm) N=38**	**Δ Placebo from previous Visit (cm)**
Visit 3 (2 wks) Δ from baseline	0.63		0.44		0.61	
Visit 4 – Visit 3		0.80		0.61		0.60
Visit 4 (4 wks) Δ from baseline	1.43		1.05		1.21	
Visit 5 – visit 4		1.09		1.11		1.14
Visit 5 (8 wks) Δ from baseline	2.52		2.16		2.35	
Visit 6 – Visit 5		0.7		1.30		1.31
Visit 6 (12 wks) Δ from baseline	**3.22**		**3.46**		**3.66**	

As the Sponsor has noted, the BIS 1.0 mg group had less of an increase from Visit 5 to Visit 6 compared to the other groups. However, there is again dose ordering and as the dose of BIS increases total growth over the 12 week study decreases. While this is not statistically significant (p=0.2861 BIS 1.0 mg vs. placebo on change from baseline) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an effect that is expected from corticosteroids. The overall difference in total growth between the placebo and BIS 1.0 group is **0.44 cm**.

Appendix,

Study SD-004-0732: Mean Body Length Change per Visit 6mo to <9mo (Evaluable Group)						
	BIS 1.0 mg (cm) N=21	**Δ BIS 1.0 mg from previous Visit (cm)**	**BIS 0.5 mg (cm) N=21**	**Δ BIS 0.5 mg from previous Visit (cm)**	**Placebo (cm) N=21**	**Δ Placebo from previous Visit (cm)**
Visit 3 (2 wks) Δ from baseline	0.50		0.45		0.85	
Visit 4 – Visit 3		1.00		0.58		0.55
Visit 4 (4 wks) Δ from baseline	1.50		1.03		1.40	
Visit 5 – visit 4		0.90		1.08		1.23
Visit 5 (8 wks) Δ from baseline	2.40		2.11		2.63	
Visit 6 – Visit 5		1.23		1.23		1.29
Visit 6 (12 wks) Δ from baseline	**3.18**		**3.34**		**3.92**	

From the above results, it appears that decrease in growth velocity occurs in a dose related fashion. The magnitude of difference between placebo and BIS 1.0 is greater in this age group than in the over study results presented in the table above. This might be expected as the greatest amount of growth velocity in 6mo to 12 mo old infants would occur in the 6 to < 9 mo old subgroup compared to the 9 to 12 mo group. The overall difference in growth between the placebo and BIS 1.0 mg group is **0.74 cm**.

Appendix,

Study SD-004-0732: Mean Body Length Change per Visit 9mo to 12mo (Evaluable Group)						
	BIS 1.0 mg (cm) N=21	**Δ BIS 1.0 mg from previous Visit (cm)**	**BIS 0.5 mg (cm) N=21**	**Δ BIS 0.5 mg from previous Visit (cm)**	**Placebo (cm) N=21**	**Δ Placebo from previous Visit (cm)**
Visit 3 (2 wks) Δ from baseline	0.81		0.43		0.37	
Visit 4 – Visit 3		0.50		0.65		0.65
Visit 4 (4 wks) Δ from baseline	1.31		1.08		1.02	
Visit 5 – visit 4		1.38		1.13		1.04
Visit 5 (8 wks) Δ from baseline	2.69		2.21		2.06	
Visit 6 – Visit 5		0.60		1.40		1.35
Visit 6 (12 wks) Δ from baseline	**3.29**		**3.61**		**3.41**	

This stratified age group does not have a clear dose related suppression of growth velocity. However, this age grouping would have less total growth compared to the 6 mo to < 9 mo age group and therefore would not be as sensitive to possible corticosteroid suppressing effects. The difference between the placebo and BIS 1.0 mg group is **0.12 cm**.

Appendix,

Reviewer Comment: This effect is expected and consideration should be given to placing this information into the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into an erroneous false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences. If the present rate of growth differential would be sustained the BIS 1.0 mg group would have approximately 1.8 cm less growth over a year which is consistent with the literature on reduced growth velocity and gives more credibility to these results.

11.1.3. Discussion and Conclusions

The primary purpose of this study was to evaluate the effects of BIS 0.5 mg and 1.0 mg on adrenal function in a 6 to 12 month of age population with wheezing. Adrenal function was assessed before and at the end of the 12-week treatment period by measuring changes in plasma cortisol levels in response to the 1-hour cosyntropin (ACTH) stimulation test or by changes in urinary free cortisol excretion obtained from overnight timed urine samples. The mean values of the three different group did not indicate any difference in adrenal responsiveness of the populations to the ACTH stimulation test. However, there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response (as pre-defined as a post-ACTH infusion level >500 nmol/L) to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals within those populations that may have increased sensitive to exogenous corticosteroid than the group mean and this sensitivity must be kept in mind by practicing physicians when approaching therapy for the individual patient. It is also important to note that the BIS 1.0 mg group only contained 17 subjects (compared to 28 for the BIS 0.5mg and 31 for the placebo groups) which could introduce a considerable bias if the excluded subjects did not reflect the group mean.

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The data from this aspect of adrenal evaluation has a great deal of variability and questionable validity of the single placebo comparator and as such should not be used to make any HPA function conclusions for labeling purposes.

Regarding adverse events, three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event. Tooth disorder, Nervousness, Pneumonia and Urticaria occurred in higher percentages in the active treatment group compared to placebo and are not presently contained in the Label for the Respules. (b) (4)

While there did not seem to group mean differences in adrenal suppression, the same cannot be said of Body Length changes. While mean body length increased across visits in all 3 treatment groups in the ITT group, the BIS 1.0 mg group increased less from Week 8 to Week 12 compared with the other treatment groups. Overall Mean body length increases were 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. There appears to be dose ordering growth suppression. In order to see if there was a possible drop-out bias, Dr. Gebert investigated growth for an "evaluable group" consisting of subjects that

had all data points and completed the study. However, this group demonstrated the same trend with mean changes of 3.3 cm, 3.5 cm and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. While this is not statistically significant (p=0.2861 BIS 1.0 mg vs. placebo on change from baseline) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an expected effect of corticosteroids. This effect should be placed in the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into an erroneous false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences.

I agree with the sponsor's that assessing efficacy in this population is difficult, since there are no standard methods for measurement of lung function and few objective parameters. The sponsor is not making any label claims of efficacy based on this study. Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores, daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days (see scale under inclusion criteria), number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study. The BIS treatment groups demonstrated trends of greater mean reductions in subjective parameters, less so in objective parameters, such that no efficacy conclusions could be made.

In conclusion, the results of this study do not indicate a population mean suppressive effect on adrenal function in subjects aged 6 to 12 months with once-daily dosages of 0.5 or 1.0 mg BIS, although there may be individual subjects with increased sensitivity and possible adrenal suppression. The safety profile of BIS was comparable to that of placebo or is already existing in labeling except for higher percentages of Tooth disorder, Nervousness, Pneumonia and Urticaria in the BIS group compared to placebo. Dose proportional growth velocity retardation was seen in the BIS groups compared to placebo. The clinical relevance of this is unknown.

12. DETAILED LABELING CHANGES OR REVISED DRUG LABEL

Under heading "PRECAUTIONS", subheading Pediatric Use, (b) (4) . Also the labeling should reflect that, while there was no difference in mean cosyntropin simulation values, 6 subjects in the treatment group and one in the placebo group had abnormal (low cortisol secretion) cosyntropin responses at the end of the 12 week study. This section should also reflect that there might be dose-ordered growth velocity suppression (b) (4)

Appendix,

Under the heading “CLINICAL PHARMACOLOGY”, subheading Pharmacodynamics, the double-lined addition beginning “A 12-week study….” Should be amended to reflect the number of patients who actually had an evaluation of serum cortisol levels post-ACTH stimulation at baseline and Week 12 and the finding that 6 subjects in the Pulmicort Respules group and one subject in the placebo group had a subnormal

(<500 nmol/L)response.

Citations

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