# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-929**

# MEDICAL REVIEW

Trout

AUG - 4 2000

# MEDICAL OFFICER REVIEW

## Division of Pulmonary and Allergy Drug Products (HFD-570)

| | | | |
|---|---|---|---|
| **APPLICATION #:** | NDA # 20-929 | **APPLICATION TYPE:** | NDA Amendment |
| **SPONSOR:** | AstraZeneca | **PRODUCT/PROPRIETARY NAME:** | Pulmicort Respules |
| **INDICATION:** | Asthma | **USAN / Established Name:** | Budeonide |
| **CATEGORY OF DRUG:** | Corticosteroid | **ROUTE OF ADMINISTRATION:** | Orally inhaled |
| **MEDICAL REVIEWER:** | M.Purucker, MD, PhD | **REVIEW DATE:** | 4 August 2000 |

### SUBMISSIONS REVIEWED IN THIS DOCUMENT

| Document Date: | Document ID #: | Submission type/Comments: |
|---|---|---|
| 9 February 2000 | NDA 20-929<br>N 000 AZ | Response to approvable letter of 11 February 1999 ; Due date 9 August 2000 |
| 2 June 2000 | NDA 20-929<br>N 000 SU | Safety Update, covering the period 1 March 1998 through 29 February 2000 |

### RELATED APPLICATIONS

| Document Date: | Document ID #: | Comments: |
|---|---|---|
| 20 November 1997 | NDA #20-929 | Original NDA; Priority review completed 20 May1998. |

Overview of Application/Review: The first submission incorporates the Sponsor's response to the 15 deficiencies outlined in the approvable letter of 11 February 1999, the last five of which were clinical deficiencies:

1. CLINICAL PHARMACOLOGY: Claims of minimal impact on the HPA axis.
2. CLINICAL TRIALS:
   - A. Inclusion of a dose or patient group in the label not included in the indications sought in this application.
   - B. Claims of uniform efficacy across doses and patient groups.
3. PRECAUTIONS/ADVERSE REACTIONS: Failure to include the class label on pediatric growth suppression.
4. WARNINGS: Failure to enclose within a black box the warning that acute adrenal insufficiency may occur during withdrawal of systemic corticosteroids.
5. DOSAGE AND ADMINISTRATION:
   - A. Failure to include the information that Pulmicort Respules should not be mixed with other medications during administration.
   - B. Failure to include the option of changing to twice daily administration of the same nominal dose if once daily administration inadequately controls symptoms.

With regard to the first submission, the sponsor has adequately addressed the deficiencies identified as 4 and 5-A, above. The deficiencies identified as 1, 2-A, 2-B, 3, and 5-B have not been adequately addressed by the sponsor's proposed wording in the product label.

The second submission is the Safety Update. There were no new or unexpected safety concerns identified.

The application is approvable.

Outstanding Issues: The sponsor should modify the labeling in the following sections:

1) The Pharmacodynamics subsection of the CLINICAL PHARMACOLOGY Section.
2) The CLINICAL TRIALS Section.
3) The General and Pediatric Use subsections of PRECAUTIONS and the ADVERSE REACTIONS Section.
4) The DOSAGE AND ADMINISTRATION Section.

**Recommended Regulatory Action:** **N drive location:**

**NDA:** ___X___ **Approvable** _____ **Not Approvable**

**Signed: Medical Reviewer:** /S/ **Date:** 4 Aug. 00

**Division Director:** _____ **Date:** 8/4/00

## A. LABELING REVIEW

1. **CLINICAL PHARMACOLOGY** Section, **Pharmacodynamics** Subsection:
   In response to Comments 11a and 11b of the Approvable Letter dated 11 February 1999, the sponsor has deleted the paragraph beginning with " ——————— ——————— ." (paragraph 2 on Page 5 of the resubmission). This paragraph did not accurately reflect the data because it implied that children receiving Pulmicort Respules had no more HPA-axis suppression in the short-term (12-weeks) or long-term (52-weeks) analyses than did children receiving conventional asthma therapy.
   - The sponsor has replaced the deleted paragraph 2 with three new paragraphs containing much of the same information as the old one. In addition, the sponsor has added disclaimers that are irrelevant, and has juxtaposed data from different age groups, treatment durations, and assays of HPA axis function that leave the reader confused.
   - **Recommendations:** The sponsor should incorporate the labeling that has been revised to accurately reflect the data. The last sentence of paragraph 3, all of paragraph 4, and the first three lines of paragraph 1 on page 6 should be deleted. Information about the dose-related increase in HPA-axis suppression that can be seen in infants[1] and in older children,[2] the latter by using a more sensitive measurement tool (urinary cortisol excretion), should be included.

   *[1] Pooled data for infants age 6 – 24 months from 3 pivotal trials; see Clinical Review, first NDA submission: Table 10.2.1.10B*
   *[2] Supportive study 04-2188; see Clinical Review, first NDA submission: Table 10.3.3.4.1*

2. **CLINICAL TRIALS** Section:
   In response to Comments 12a, 12b, and 12c of the Approvable Letter of 11 February 1999, the sponsor has deleted the first three paragraphs under CLINICAL TRIALS beginning with ——————— (paragraphs 1, 2, and 3 under "CLINICAL TRIALS" beginning on page 6 of the resubmission). These paragraphs implied that Pulmicort Respules were clinically efficacious at all doses and across ethnic groups and did not accurately reflect the data.

   The sponsor has also rewritten the three subsections entitled "Patients Not Receiving Inhaled Corticosteroid Therapy", "Patients Previously Maintained on Inhaled Corticosteroids", and "Patients Receiving Once Daily Or Twice Daily Dosing" (under the CLINICAL TRIALS Section on pages 8, 9, and 10 of the resubmission). These subsections had included data from children ——————— an age range not encompassed by the proposed labeling, and therefore required numerical corrections.
   - The sponsor has made the appropriate corrections to each of the subsections contained in CLINICAL TRIALS. However, the initial paragraphs introducing this section still fail to accurately reflect the data. At least part of the problem is the sponsor's failure to clearly explain the design of these studies, particularly as it pertains to clinical endpoints and dosing schedules.
   - **Recommendations:** The sponsor should incorporate the labeling that has been

revised to accurately reflect the data and the indicated age range for this product. At the end of the first paragraph under CLINICAL TRIALS, a sentence has been added to clarify the following: 1) The Daytime symptom score and Nighttime symptom score were co-primary endpoints for each of the three studies and 2) Not all of the five possible dosing regimens of the three strengths of Pulmicort Respules were tested in each of the three clinical trials. These clarifications help the reader to judge the strength of evidence supporting the efficacy of each of the five proposed doses/dosing schedules.[3]

[3] *Data from Table 9.2.1.4.1.1, p.146, MO review of original submission.*

- The subsection entitled "Patients Receiving Once Daily or Twice Daily Dosing" does not adequately compare the two dosing schedules. While the evidence supports the efficacy of the same nominal dose of Pulmicort Respules administered on either a once daily or twice daily schedule, the weight of evidence by all measures is stronger for twice daily dosing.
  - **Recommendations:** The sponsor should incorporate the labeling that has been revised to accurately reflect the data.

3. **PRECAUTIONS and ADVERSE REACTIONS** Sections:
The sponsor has adequately addressed comments 13 and 14 of the Approvable Letter of 11 February 1999 by placing the bolded paragraphs into a black box and by including the new class labeling for corticosteroids with regard to growth in children.

Minor modifications in the text of the "growth class label" and its position within the "General" and "Pediatric Use" subsection should be made (see revised label).

4. **DOSAGE AND ADMINISTRATION** Section:
The sponsor has adequately addressed comment 15 of the Approvable letter as it pertains to not mixing Pulmicort Respules with any other medications during administration via jet nebulizer.

The response regarding once daily compared to twice daily administration of the same nominal dose of Pulmicort Respules is inadequate. Specifically, it is recommended that [redacted] The option of [redacted] has been deleted from the current version of the label. (See Subsection "Patients not receiving systemic (oral) corticosteroids.")

Although a head-to-head comparison of the efficacy of once daily compared to the same nominal dose of Pulmicort Respules administered on a twice daily schedule was not a pre-specified endpoint, the data do not support these schedules as being interchangeable. In general, 0.25 mg of Pulmicort Respules administered BID was numerically superior to 0.5 mg administered as a single daily dose (Four of four co-primary endpoints were significant in two clinical trials for 0.25 mg BID compared to one out of two in one clinical trial for 0.5 mg QD; change from baseline in $FEV_1$ was

significant in two of two trials for 0.25 mg BID compared to one of two for 0.5 mg QD).[4] A similar statement can be made for the comparison of 0.5 mg BID compared to 1.0 mg given as a single daily dose (Three of four co-primary endpoints were significant in two clinical trials for 0.50 mg BID compared to one of four in two clinical trials for 1.0 mg QD).[4] These data favor a BID schedule for dosing Pulmicort Respules over the same nominal dose administered once daily.

In selecting a dosing schedule for Pulmicort Respules, it is important to take into consideration the mean treatment effect, as measured by controlled clinical trials, and the potential for the individual patient to respond better to an alternative dosing schedule. In particular, twice daily compared to once daily administration of the same nominal dose may be far more efficacious for an individual patient. It is noteworthy that published guidelines[5] recommend downward titration of inhaled corticosteroids the lowest dose effective in controlling a patient's symptoms. Accepted practice would therefore support testing a BID dosing schedule of the same nominal dose before increasing the total daily dose to be administered once daily.
**Recommendations**: The sponsor should incorporate the changes indicated in the label.

*[4] Data from Table 9.2.1.4.1.1, p.146, MO review of original submission.*
*[5] National Heart, Lung, and Blood Institute; "Guidelines for the Diagnosis and Management of Asthma: NAEPP 2"; National Institutes of Health pub no 97-4051, Bethesda, MD, USA, 1997.*

## B. SAFETY UPDATE

The safety update was submitted 2 June 2000 and covers clinical activity in the NDA over the period from 1 March 1998 through 29 February 2000. The update is contained within a single volume and includes abbreviated reports of 25 completed or ongoing studies of Pulmicort Respules conducted internationally or within the US. Three of this total are US studies conducted for the indication of persistent asthma and considered to be open-label extensions of the pivotal trials submitted at the time of NDA filing. These trials have been kept open for purposes of gathering additional safety data and to provide for "compassionate use" of the drug product by enrollees from earlier trials, in anticipation of future approval. These three trials account for a total of 898 patients.

There are 22 non-US studies accounting for an additional 1696 patients. Seven trials have been completed or are underway for the indication of persistent asthma, one trial is considered a "compassionate use" program, and fourteen are for respiratory conditions other than asthma, including acute bronchiolitis and RDS.

With regard to safety information, the submission identified 213 new serious adverse events (SAEs) reported over the two-year time frame. There were 49 dropouts due to adverse events (DAEs), and one death. Twenty-one (21) of the DAEs were reported from the three US trials. There was one report of growth suppression. Overall, none of these AEs would be considered as signals of new or unexpected safety problems not previously

identified for this drug product. From a clinical standpoint, therefore, the NDA remains approvable.

*CC:* *NDA 20-929/Division file/HFD-570*
*Trout/PM/HFD-570*
*Purucker/MO/HFD-570*

APPEARS THIS WAY
ON ORIGINAL

# MEDICAL OFFICER REVIEW

## DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

| | | | |
|---|---|---|---|
| **APPLICATION #:** | **N20-929** | **APPLICATION TYPE:** | **NDA Resubmission** |
| **SPONSOR:** | **Astra Pharmaceuticals** | **PROPRIETARY NAME:** | **Pulmicort Respules** |
| **CATEGORY OF DRUG:** | **Corticosteroid** | **USAN / Established Name:** | **Budesonide** |
| | | **ROUTE:** | **Oral Inhalation** |
| **MEDICAL REVIEWER:** | **Shan C. Chu, MD** | **REVIEW DATE:** | **02-03-99** |

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

| Document Date: | CDER Stamp Date: | Submission Type: | Comments: |
|---|---|---|---|
| 11-18-97 | 11-20-97 | Full NDA application | |
| 03-12-98 | 03-16-98 | 120-day safety update | |
| 06-22-98 | 06-23-98 | IND 44,535 Information amendment | Complete reports 04-3072B and 04-3100B |
| 08-07-98 | 08-11-98 | NDA resubmission | |

**RELATED APPLICATIONS (if applicable)**

| Document Date: | APPLICATION Type: | Comments: |
|---|---|---|
| | NDA 20-233 | Rhinocort Nasal Inhaler |
| | NDA 20-441 | Pulmicort Turbuhaler |
| | NDA 20-746 | Rhinocort Aqua Nasal Spray |

**Overview of Application/Review:** The sponsor originally submitted this NDA on November 18, 1997 and sought approval of Pulmicort Respules in doses of 0.25, 0.5, [redacted] once or twice daily for the treatment of asthma in children aged [redacted] to 8 years. Because of CMC issues the product was not approved. In the Agency's approvable letter issued on May 20, 1998, the sponsor was informed that there were not sufficient data to support the approval of the product for [redacted]. On August 7, 1998, the sponsor resubmitted the NDA which included final reports of two long-tern clinical studies (04-3072B and 04-3100B), updated ISS and labeling as well as new CMC and toxicology information. In this NDA resubmission, the sponsor is not in pursuit of the product labeling for [redacted]. Overall, the new data provided in this submission do not raise new safety or efficacy concerns other than those mentioned in the original review. The safety data of three pivotal studies excluding patients under one year of age or those randomized to 1.0 mg BID treatment are similar to that including these patients. The data of three completed U.S. long-term, open-label studies (04-3069B, 04-3072B, 04-3100B) demonstrated the following: 1. Pulmicort Respules at total daily doses of 0 to 1.0 mg was generally well tolerated for a period of 52 weeks in patients aged 1-8 years. 2. A measurable HPA-axis suppression was observed in both treatment groups and patients on Pulmicort Respules had more HPA-axis suppression than those on conventional therapy (including inhaled steroids other than Pulmicort Respules). 3. Study 04-3069B demonstrated that administration of Pulmicort Respules at total daily dose up to 1 mg for one year was associated with a statistically significant decrease (0.84 cm/year) in growth velocity in inhaled steroid naïve asthmatic children, compared to non-steroidal treatment. Studies 04-3072B and 04-3100B showed no growth inhibition for Pulmicort Respules, but were flawed in design.

**Outstanding Issues:** 1. A number of statements in the labeling need to be modified or removed. 2. Several CMC issues have to be resolved.

**Recommended Regulatory Action:**

**NDAs:**

**Efficacy / Label Supp.:** ___X___ **Approvable** _____ **Not Approvable**

**Signed:** **Medical Reviewer:** _ /S/ **Date:** 2/3/1999

**Medical Team Leader:** _____ **Date:** 2/3/99

CC: HFD-570/NDA File
HFD-570/Division File
HFD-570/Chu/~~Meyer~~/Elashoff/Vogel/Kim

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# 1. NOTE TO READERS

Square brackets are used throughout this review to include references to volumes and pages of the original NDA submitted on 11/18/1997 (shown as [vol:page-page]), NDA resubmission submitted on 8/7/1998 (shown as [8/7/1998; vol:page-page]), and IND 44,535 information amendment (submitted on 6/22/1998) which contains complete reports of Studies 04-3072B and 04-3100B (shown as [IND 44,535; 6/22/1998; vol:page-page]). Parentheses are used to include references to sections, tables, or figures in the review of original NDA and this review.

# 2. GLOSSARY OF ABBREVIATIONS USED

| | |
|---|---|
| ACTH: | adrenocorticotropic hormone; |
| ADRAC: | Adverse Drug Reaction Advisory Committee; |
| AE: | adverse event; |
| ANOVA: | analysis of variance; |
| APT: | all patients treated; |
| ATC: | Anatomical Therapeutical Chemical (classification system); |
| AUC: | area under the curve; |
| BID: | twice a day; |
| CI: | confidence interval; |
| CDER: | Center for Drug Evaluation and Research; |
| CRA: | clinical research associate; |
| CRF: | case report form; |
| CV: | coefficient of variation; |
| FDA: | Food & Drug Administration (USA); |
| $FEF_{25-75\%}$ (L/sec): | forced expiratory flow during the middle half of the forced vital capacity (liters per second); |
| $FEV_1$ (L): | forced expiratory volume in one second (liters); |
| FVC (L): | forced vital capacity (liters); |
| GCS: | glucocorticosteroid; |
| HPA-axis: | hypothalamic pituitary adrenal-axis; |
| IRB: | Institutional Review Board; |
| IND: | Investigational New Drug application; |
| ISE: | integrated summary of efficacy; |
| ISS: | integrated summary of safety; |
| L: | liter; |
| LVCF: | last value carried forward; |
| MED: | minimal effective dose; |
| NIH: | (U.S.) National Institutes of Health; |
| NDA: | New Drug Application; |
| NOS: | not otherwise specified; |
| PEF (L/min): | peak expiratory flow (liters per minute); |
| PFT: | pulmonary function test; |
| pMDI: | pressurized metered dose inhaler; |
| p.r.n.: | as the occasion requires; |
| p-value: | probability value; |

| | |
|---|---|
| QD: | once a day; |
| QOD: | once every other day; |
| SAE: | serious adverse event; |
| SD: | standard deviation; |
| SEM: | standard error of the mean; |
| WHO: | World Health Organization. |

# 3. CONDUCT OF THE REVIEW

The original NDA was thoroughly reviewed previously (May 5, 1998). The documents used for the current review consists of the following:

1. Medical officer's copy of NDA 20-929 resubmission (August 7, 1998) in 8 volumes (15.1-2, 5-10).
2. Information amendment to IND 44,535 submitted in 21 volume on June 22, 1998.

The main new clinical data in the NDA resubmission and the information amendment to IND 44,535 were provided in final reports of two multicenter, randomized, open-label, 52-week studies, which were reviewed first. Then, the updated Integrated Summary of Safety and the revised proposed labeling were reviewed and an overall assessment of the NDA resubmission was concluded and recommendations made.

Most of the tables and figures in this review were taken from the sponsor's report, many with modification. Some tables were made using the data from tabulations in the NDA.

# 4. BACKGROUND

Budesonide is a corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In the original NDA submission (November 18, 1997), the sponsor sought approval of Pulmicort Respules (budesonide inhalation suspension) in doses of 0.25, 0.5, and [redacted] once or twice daily for the treatment of asthma in children aged [redacted] to 8 years. Because of several CMC issues the product was not approved. In the Agency's approvable letter issued on May 20, 1998, the sponsor was informed that there were not sufficient data to support the approval of Pulmicort Respules [redacted]

On August 7, 1998, the sponsor resubmitted NDA which included responses for each of the items outlined in the Agency's approval letter, final reports of two long-tern clinical studies (04-3072B and 04-3100B), updated Integrated Summary of Safety and revised labeling as well as new CMC and toxicology information. In agreement with the Agency's position, the sponsor is not in pursuit of the product labeling [redacted] in this NDA resubmission.

## 4.1 Proposed Indications and Dosage

[8/7/1998; 2:8, 20]

Pulmicort Respules is indicated for the maintenance treatment of asthma and as prophylactic therapy in children [redacted] 12 months to 8 years. Pulmicort Respules is not indicated for the relief of acute bronchospasm.

The Proposed dosage is detailed in the following table. In symptomatic children (2 years or less) not responding to non-steroidal therapy, a starting dose of 0.25 mg daily of Pulmicort Respules may be considered.

**Table 4.1:** The Recommended Starting Dose and Highest Recommended Dose.

| Previous Therapy | Recommended Starting Dose | Highest Recommended Dose |
|---|---|---|
| **Bronchodilators alone** | 0.5 mg total daily dose administered as a single or divided dose | 0.5 mg total daily dose |
| **Inhaled Corticosteroids** | 0.5 mg total daily dose administered as a single or divided dose | 1.0 mg total daily dose |
| **Oral Corticosteroids** | [redacted] | 1.0 mg total daily dose |

# 5. CLINICAL STUDIES

## 5.1 Study 04-3072B: A 52-Week Open-Label Safety and Efficacy Study of Budesonide (Pulmicort) Nebulizing Suspension Compared to Conventional Asthma Therapy in Children with Asthma Aged Eight Years and Younger.

### *5.1.1 Objectives*

[IND 44,535; 6/22/1998; 1:15-6]

This multicenter, randomized, open-label, active-controlled study was preceded by a randomized, double-blind, placebo-controlled, parallel treatment phase (Study 04-3072) that assess the efficacy and safety of budesonide nebulizing suspension, 0.25, 0.5, and 1.0 mg BID compared to placebo in 178 children aged 4-8 years with persistent asthma not well-controlled on inhaled GCS therapies. The primary objective of this study was to assess the long-term safety of the lowest individual maintenance dose of budesonide nebulizing suspension when administered for a period of up to 52 weeks, as compared to conventional asthma therapy.

#### 5.1.1.1 Safety Variables

- Reported adverse events (AEs).
- Pre- and post-ACTH-stimulation effects on HPA-axis function in a subset of patients.
- Changes in physical examinations, vital signs, and clinical laboratory tests (including oropharyngeal fungal cultures).
- Changes in body length/height (stadiometry).
- Changes in skeletal age.

#### 5.1.1.2 Efficacy Variables

- Mean changes from baseline in nighttime and daytime asthma symptom scores over the 52-week treatment phase.
- Patient outcome, including the proportion of patients who discontinued from the study for any reason and the proportion of patients who discontinued due to worsening asthma.
- The proportion of patients who took oral prednisone and the average daily amount of prednisone used for asthma deteriorations.
- The number of days breakthrough medication (short-term inhaled bronchodilator) was used.
- Spirometry variables ($FEV_1$, $FEF_{25-75\%}$ and FVC) performed at clinic.
- PEF measured daily in the morning and evening.

*Reviewer's Comments: It is always difficult in assessing subjective efficacy endpoints in an open-label study without bias. The dose-titration design in an open-label trial also complicates the interpretation of all efficacy variables, subjective or objective.*

### *5.1.2 Design*

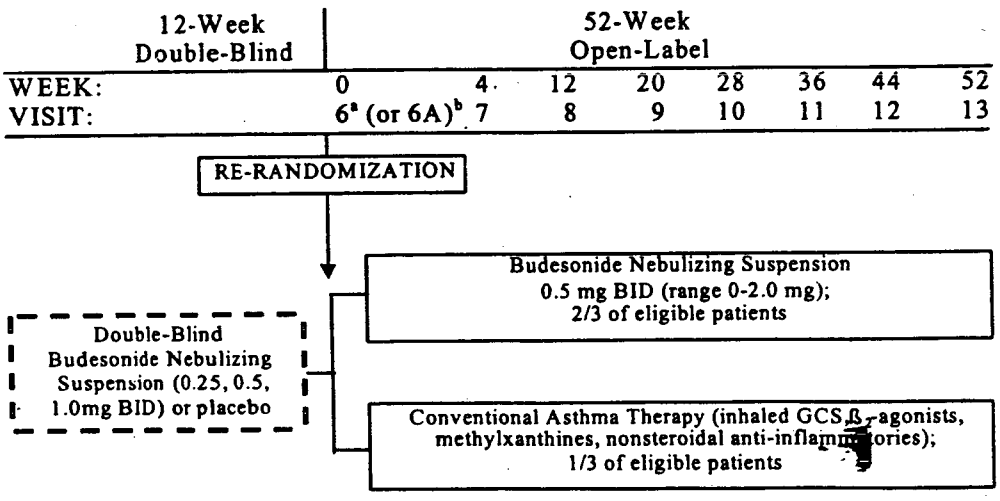
[IND 44,535; 6/22/1998; 1:16-8]

This was a multicenter, randomized, open-label, active-controlled, parallel-group study. A total of 91 patients were randomized at 14 centers located throughout the USA. Due to amendments of the study protocol, these patients can be divided to 2 groups: (A) 53.8% of patients entered the open-label phase immediately after they had successfully completed the 12-week, double-blind treatment phase of Study 04-3072 or had discontinued due to worsening of asthma requiring oral corticosteroids. There was no washout period between the double-blind and the open-label treatment phases. (B) 46.2% of patients (49.2% of patients in the budesonide group; 40.0% of patients in the conventional asthma therapy group) entered the open-label phase after they had already completed the double-blind treatment phase or had discontinued due to worsening of asthma requiring oral corticosteroids for various periods of time, and thus had a time lapse between the end of the double-blind phase and the beginning of the open-label phase, during which they were treated with conventional asthma medications (including inhaled corticosteroids) per the judgment of their physicians.

Two-thirds of the eligible patients were randomized to budesonide nebulizing suspension. These patients started the open-label treatment phase with 0.5 mg budesonide BID with attempts made at every visit to reduce the dose to 0.25 mg BID, followed by 0.25 mg QD in the morning, followed by 0.25 mg every other day in the morning, followed by no budesonide treatment, as judged by the investigator. During asthma exacerbations, the patients were to be stabilized by increasing the dose of the breakthrough medications and/or by increasing the dose of budesonide nebulizing suspension (to a maximum dose of 1.0 mg BID), followed by intermittent courses of oral prednisone as needed.

One-third of the eligible patients were randomized to conventional asthma therapy. These patients were treated with inhaled glucocorticosteroids, $\beta_2$-agonists, methylxanthines, and/or nonsteroidal anti-inflammatory agents (e.g., cromolyn sodium), as judged by the investigator. During asthma exacerbations, the patients were to be stabilized by combining the therapeutic agents mentioned above, followed by intermittent courses of oral prednisone as needed.

**Figure 5.1.2.** Open-Label Study Design. [IND 44,535; 6/22/1998; 1:17]




[a] Re-randomization into open-label for patients who just completed or discontinued the double-blind phase; baseline for open-label.
[b] Re-randomization into open-label for patients who had already completed or discontinued the double-blind phase for various periods of time; new baseline for open-label.

## Table 5.1.2. Schedule of Open-Label Visits and Procedures. [IND 44,535; 6/22/1998; 1:18]

| OPEN-LABEL WEEK NUMBER: | 0 | 0 | 4 | 12 | 20 | 28 | 36 | 44 | 52 |
|---|---|---|---|---|---|---|---|---|---|
| VISIT NUMBER: | 6[a] | 6A[b] | 7 | 8 | 9 | 10 | 11 | 12 | 13[c] |

[a] Re-randomization into open-label for patients who prospectively completed or discontinued the double-blind phase; baseline for open-label.

[b] Re-randomization into open-label for patients who had already completed or discontinued the double-blind phase for various periods of time; new baseline for open-label.

[c] Final visit of open-label.

| CLINICAL ASSESSMENTS: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Open-Label Informed Consent Form | X | X | | | | | | | |
| Updated Medical History | | X | | | | | | | |
| Comprehensive Physical Examination with Vital Signs | X | X[d] | | | | | | | X |
| Brief Physical Examination with Vital Signs | | X[d] | X | X | X | X | X | X | |
| Left Hand-Wrist X-Ray | X | X[e] | | | | | | | X |
| Body Height (Stadiometry), Weight | X | X | X | X | X | X | X | X | X |
| Pulmonary Function Test[f] | X | X | X | X | X | X | X | X | X |

[d] Patients with a ≤14 day window between double-blind and Visit 6A only needed a brief physical examination with vital signs.

[e] If not done within the previous 30 days.

[f] $FEV_{1.0}$, FVC, $FEF_{25-75\%}$.

| LABORATORY ASSESSMENTS: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Hematology, Blood Chemistry | X | X[g] | | X | | X | | | X |
| Urinalysis | X | X[g] | | X | | X | | | X |
| Basal & Post-ACTH Cortisol Levels[h] | X | X[g] | | | | | | | X |
| Oropharyngeal and/or Nasal Fungal Cultures[i] | X | X[g] | | | | | | | X |

[g] Patients with a ≤ 30-day window between double-blind and Visit 6A did not need to perform laboratory assessments at this visit.

[h] Consenting patients only.

[i] Repeated as judged necessary by the investigator.

| OTHER: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Review Adverse Events | X | X | X | X | X | X | X | X | X |
| Review Daily Diaries (asthma symptoms, use of breakthrough medications, PEF) | X | | X | X | X | X | X | X | X |
| Return Study Drug/Assess Compliance | X | | X | X | X | X | X | X | |
| Practice and/or Review Inhalation Technique, PEF Technique, Use/Care of Equipment | X | X | X | X | X | X | X | X | |
| Dispense Study Drug/ Nebulizing Equipment | X | X | X | X | X | X | X | X | |
| Dispense New Diaries | X | X | X | X | X | X | X | X | |

## *5.1.3 Protocol*

### 5.1.3.1 Selection of Study Population

[IND 44,535; 6/22/1998; 1:19]

#### *5.1.3.1.1 Inclusion Criteria*

1. Amendment #1: The patient prospectively completed the 12-week double-blind phase of the study (Study 04-3072), or discontinued from the double-blind treatment phase because of the need for oral corticosteroids for worsening airways disease.
   Amendment #2: The patient had already completed the 12-week double-blind phase of the study (Study 04-3072), or had been discontinued from the double-blind treatment phase because of the need for oral corticosteroids for worsening airways disease prior to Amendment #1.
2. The patient's health would not be compromised by participating in the study, per the judgment of the investigator.

#### *5.1.3.1.2 Exclusion Criteria*

There were no exclusion criteria for this phase of the study.

### 5.1.3.2 Study Drugs

[IND 44,535; 6/22/1998; 1:21]

Same as those in Study 04-3072 except different batch numbers (Original review: Section 8.3.3.2).

### 5.1.3.3 Concomitant Treatments

[IND 44,535; 6/22/1998; 1:25]

The following medications were not allowed:

- Long-acting inhaled $\beta_2$-agonists
- Astemizole
- Over-the-counter asthma medications

The following were allowed with the appropriate restrictions (e.g., prior to PFT):

- Asthma medication: Patients randomized to conventional asthma therapy could have been treated with inhaled GCS, short-acting $\beta_2$-agonists, methylxanthines, and/or inhaled nonsteroidal anti-inflammatory agents (e.g., cromolyn sodium), as judged necessary by the investigator.
- Oral corticosteroids: Intermittent courses of oral prednisone were allowed for the control of asthma exacerbations, as judged by the investigator.

Other medications considered necessary for the patient's welfare were permitted at the discretion of the investigator.

### 5.1.3.4 Efficacy Measurements and Variables

[IND 44,535; 6/22/1998; 1:24-29]

Apart from using a different schedule, the procedures of efficacy measurements in this study were the same as those in Study 04-3072 (Original review: Sections 8.3.3.4).

#### 5.1.3.5 Safety Measurements and Variables

[IND 44,535; 6/22/1998; 1:24-29]

Apart from using a different schedule, the procedures of safety measurements in this study were the same as those in Study 04-3072 (Original review: Section 8.3.3.5) except the following modifications and/or addition:

- Left hand-wrist x-rays were taken at Visits 6 (or 6A) and Visit 13

#### 5.1.3.6 Adverse Events (AEs)

[IND 44,535; 6/22/1998; 1:29-32]

Same as those in Study 04-3072 (Original review: Section 8.3.3.6).

#### 5.1.3.7 Treatment and Measurement Discontinuation

[IND 44,535; 6/22/1998; 1:20]

Same as those in Study 04-3072 (Original review: Section 8.3.3.7).

#### 5.1.3.8 Statistical Analysis

[IND 44,535; 6/22/1998; 1:33-38]

Same as those in Study 04-3069B (Original review: Sections 8.4.3.8) except the modifications and/or addition described in Section 5.1.3.8.1.

##### *5.1.3.8.1 Statistical Methods: Safety Variables*

Changes in skeletal age over the one year open-label extension treatment phase was assessed by computing differences between skeletal maturity indicators (external and internal [medullary cavity] diameters and cortical thickness of the mid-shaft of the second metacarpal from hand-wrist x-rays) and chronological age (years). Summary statistics were reported for observed mean skeletal ages and differences between observed and chronological mean years for the budesonide and conventional asthma therapy groups at Week 52.

### *5.1.4 Results*

#### 5.1.4.1 Patient Disposition

[IND 44,535; 6/22/1998; 1:38-40]

The distribution of the patients by their previous double-blind treatment assignment and the disposition of patients enrolled into the open-label treatment phase of the study are summarized in the following tables. The proportion of patients who discontinued from the study in the conventional asthma therapy group was the same as that for the budesonide group (13% for both treatment groups). The Kaplan-Meier estimate of the time to discontinuation from the study therapy showed that the discontinuation rates were similar for both treatment groups (p=0.676, log rank test).

**Table 5.1.4.1A.** Distribution of Randomized Patients by Their Previous Double-Blind Treatment Assignment. [IND 44,535; 6/22/1998; 1:70]

| Previous Double-Blind Treatment | Open-Label Treatment | | Total |
|---|---|---|---|
| | Conventional Asthma Therapy | Budesonide Nebulizing Suspension | |
| | (n=30) | (n=61) | (n=91) |
| Placebo | 7 (23%) | 13 (21%) | 20 (22%) |
| Budesonide Nebulizing Suspension: | | | |
| 0.25 mg BID | 12 (40%) | 13 (21%) | 25 (27%) |
| 0.5 mg BID | 5 (17%) | 17 (28%) | 22 (24%) |
| 1.0 mg BID | 6 (20%) | 18 (30%) | 24 (26%) |

*Reviewer's Comments: Higher proportion of patients in the budesonide group (58%) received higher dose of budesonide (0.5 mg or 1.0 mg BID) compared to the conventional asthma therapy group (37%).*

**Table 5.1.4.1B.** Summary of Patient Deposition. [IND 44,535; 6/22/1998; 1:72-3]

| Patient Disposition | Open-Label Treatment | |
|---|---|---|
| | Conventional Asthma Therapy | Budesonide Nebulizing Suspension |
| Randomized | 30 | 61 |
| Completed Open-Label Treatment | 26 (87%) | 53 (87%) |
| Total No. Patients Discontinued: | 4 (13%) | 8 (13%) |
| Worsening Asthma[1] | 0 (0%) | 0 (0%) |
| Adverse Event | 0 (0%) | 1 (2%) |
| Use of Medication Excluded by Protocol[2] | 0 (0%) | 1 (2%) |
| Non-Compliance w/Study Procedures | 1 (3%) | 2 (3%) |
| Withdrew Consent | 3 (10%) | 3 (5%) |
| Lost to Follow-up | 0 (0%) | 1 (2%) |
| Evaluated for Efficacy Analyses | 30 | 61 |
| Evaluated for Safety | 30 | 61 |

[1] Includes patients who were discontinued due to lack of therapeutic effect or disease deterioration, and patients who received drugs for asthma not permitted by the protocol.
[2] Non-permitted medications for indications other than asthma.

### 5.1.4.2 Demographic and Other Open-Label Baseline Characteristics

[IND 44,535; 6/22/1998; 1:41-2, 76-7]

The basic demographic characteristics and the proportion of patients who had discontinued the double-blind phase of the study prior to entering the open-label phase were similar for

the two treatment groups. The mean age, weight, and height of the conventional therapy group were slightly higher than those of the budesonide group.

**Table 5.1.4.2.** Demographic and Baseline Characteristics.

| Variable | Open-Label Treatment | |
|---|---|---|
| | Conventional Asthma Therapy | Budesonide Nebulizing Suspension |
| n | 30 | 61 |
| Gender: | | |
| Male | 18 (60.0%) | 39 (63.9%) |
| Female | 12 (40.0%) | 22 (36.1%) |
| Age (months): | | |
| Mean ± SD | 85.5±15.5 | 82.1±14.8 |
| Range | 57-112 | 53-110 |
| Race: | | |
| Caucasian | 24 (80.0%) | 53 (86.9%) |
| Black | 4 (13.3%) | 7 (11.5%) |
| Hispanic | 2 (6.7%) | 1 (1.6%) |
| Weight; Mean ± SD: | | |
| Pounds | 59.2±17.6 | 57.5±15.2 |
| Kilograms | 26.8±8.0 (n=29) | 26.1±6.9 |
| Height (cm); Mean ± SD | 124.6±11.0 (n=29) | 123.3±10.1 (n=56) |
| Double-Blind Phase: | | |
| Completion | 26 (86.7%) | 53 (86.9%) |
| Discontinuation | 4 (13.3%) | 8 (13.1%) |

Data source: [IND 44,535; 6/22/1998; 1:41-2, 76-7]

### 5.1.4.2.1 *Baseline Asthma Symptom Scores, Pulmonary Function Test Data, and Breakthrough Medication Use*

[IND 44,535; 6/22/1998; 1:42-3]

The mean baseline (last 14 days of double-blind therapy) nighttime asthma symptom scores, daytime asthma symptom scores, and number of days use of breakthrough medication for the patients in the conventional asthma therapy group were higher compared to the budesonide group.

**Table 5.1.4.2.1.** Baseline Lung Function, Asthma Symptom Scores, and Number of Days Use of Breakthrough Medication. [IND 44,535; 6/22/1998; 1:78-80].

| Variable | Open-Label Treatment | |
|---|---|---|
| | **Conventional Asthma Therapy (n=30)** | **Budesonide Nebulizing Suspension (n=61)** |
| Nighttime Asthma Symptom Scores: | | |
| Mean±SD | 0.82±0.67 (n=26) | 0.64±0.57 (n=59) |
| Daytime Asthma Symptom Scores: | | |
| Mean±SD | 0.92±0.65 (n=26) | 0.71±0.55 (n=59) |
| $FEV_1$ (L/sec): | 1.26±0.34 | 1.30±0.39 |
| % predicted $FEV_1$: | 83.48±19.17 | 87.01±19.52 |
| Morning PEF (L/min): | 177.8±54.5 (n=26) | 185.1±58.2 (n=59) |
| Evening PEF (L/min): | 180.2±55.0 (n=26) | 188.2±60.0 (n=59) |
| Number of Days Use of Breakthrough Medication: | | |
| Mean±SD | 8.0±9.4 (n=26) | 5.9±7.3 (n=59) |

*Reviewer's Comments: The fact that lower proportion of patients in the conventional asthma therapy group (37%) received higher dose of budesonide (0.5 mg or 1.0 mg BID) than that in the budesonide group (58%) during double-blind phase (Section 5.1.4.1) might explain why patients in the conventional therapy group had higher asthma symptom scores, slightly worse pulmonary function, and higher number of days use of breakthrough medication at baseline. This also confounds the interpretation of comparative growth data.*

### 5.1.4.2.2 *Baseline (Visit 6 of Visit 6A) Physical Examination*

[IND 44,535; 6/22/1998; 1:44, 81-2]

In general, the treatment groups were similar with respect to general physical condition at baseline. Forty-five percent of patients had abnormal findings in the nasal examination categories; 57% in the conventional therapy group and 39% in the budesonide group.

### 5.1.4.2.3 *Medications Taken During Open-Label*

[IND 44,535; 6/22/1998; 1:44-6]

#### 5.1.4.2.3.1 Asthma Medications

***Study Medications; General:*** The mean number of days on study therapy for the patients on budesonide (347±70 days) was slightly higher than that for those on conventional therapy (322±125 days).

**Table 5.1.4.2.3.1.** Duration of Exposure (Days) to Open-Label Treatment. [IND 44,535; 6/22/1998; 1:125]

| Duration of Treatment (Days) | Budesonide Nebulizing Suspension[1] | Conventional Asthma Therapy |
|---|---|---|
| N | 59 | 30 |
| Mean±SD | 347±70 | 322±125 |
| Median | 364 | 365 |
| Minimum | 26 | 1 |
| Maximum | 398 | 418 |

[1] One budesonide patient was lost to follow-up and the other one refused to use a nebulizer.

***Study Medications; Budesonide Nebulizing Suspension:***
The mean total daily dose of budesonide nebulizing suspension was between 0.88 mg and 1.0 mg over the course of the study. Thirty-nine (63.9%) patients were titrated down and up; 11(18.0%) were titrated down and stayed below the initial dose; 5 (8.2%) were titrated up and stayed up; 6 (9.8%) remained on the initial 0.5 mg BID dose. [IND 44,535; 6/22/1998; 1:84]

***Study Medications; Conventional Asthma Therapy Medications:*** In patients randomized to the conventional asthma therapy group, the therapies used were beclomethasone (43%), albuterol (30%), cromolyn sodium (23%), triamcinolone (23%), fluticasone (7%), flunisolide (3%), sodium chloride (3%), theophylline (3%) and other (7%). [IND 44,535; 6/22/1998; 1:85]

***Added Asthma Medications (Concomitant asthma medications):*** Among asthma medications added during the open-label treatment phase (i.e., not budesonide or conventional asthma therapy assigned by the investigator) not including prednisone, albuterol was the medication used by the greatest number of patients (81%), followed by beclomethasone (18%), cromolyn sodium (13%) and triamcinolone (8%). Albuterol could have been added on as maintenance therapy in addition to being used already as breakthrough medication, and that the distinction between the two uses was not always clear. [IND 44,535; 6/22/1998; 1:86]

For patients with a time lapse between the double-blind phase and the open-label phase, beclomethasone was the steroid asthma medication used by the greatest number of patients (32%) between Visits 6 and 6A. No significant difference in the use of steroid asthma medications between the 2 treatment groups during this period. [IND 44,535; 6/22/1998; 1:94]

## 5.1.4.2.3.2 Non-Asthma Medications

***Concomitant non-asthma medications:*** In general, the use of concomitant non-asthma medications was similar between treatment groups. Drug classes mentioned most frequently were nasal preparations (76%), dermatologic preparations (74%), systemic

antibacterials (69%), systemic antihistamines (52%), analgesics (46%), and cough and cold preparations (25%). [IND 44,535; 6/22/1998; 1:87-93]

*Reviewer's Comments: 1. Systemic antibacterials, systemic antihistamines, or antiinflammatory and antirheumatic products were used more frequently in the budesonide group (74%, 57%, and 18%, respectively) compared to those in the conventional therapy group (60%, 40%, and 3%, respectively). The effect of this on the results of efficacy and safety endpoints is uncertain. 2. Psycholeptics were used more frequently in the budesonide group (8%) than in the conventional therapy group (0%).* [IND 44,535; 6/22/1998; 1:88] *This might be treatment related since psychiatric disorders were also reported more frequently in the budesonide group* (Sections 5.1.4.5.2.2).

### 5.1.4.3 Measurements of Treatment Compliance

[IND 44,535; 6/22/1998; 1:46; 3:6.1-6.2]

In the budesonide treatment group, the proportion of patients who achieved ≥80% compliance with respect to administration of study drug was 87-97% and the compliance with respect to study requirements was 84-95%. In the conventional therapy group, the compliance with respect to administration of study drug was not assessed and the compliance with respect to study requirements was 80-87%.

### 5.1.4.4 Efficacy Analysis

[IND 44,535; 6/22/1998; 1:46-9]

#### *5.1.4.4.1 Asthma Symptoms and Prednisone Use*

The mean changes of nighttime and daytime asthma symptom scores from baseline (last 14 days of double-blind) to the last observation were similar between the two treatment groups.

A slightly higher percent of patients from the conventional therapy group (63%) required the use of oral prednisone compared to the budesonide group (56%). The mean and median total daily doses of oral prednisone used by patients in the conventional asthma therapy group were also higher compared to the budesonide group.

**Table 5.1.4.4.1.** Mean Changes From Baseline (Last 14 Days Of Double-Blind) to the Last Observation in Asthma Symptom Scores (Scale Of 0-3) and Oral Prednisone Use.

| Variable | Open-Label Treatment | |
|---|---|---|
| | Conventional Asthma Therapy (n=30) | Budesonide Nebulizing Suspension (n=61) |
| Asthma Symptom Score:[1] | | |
| Mean Change from Baseline | | |
| Nighttime | -0.02 | -0.02 |
| 95% CI | -0.27, 0.23 | -0.19, 0.15 |
| (n) | (26) | (59) |
| Daytime | -0.04 | -0.03 |
| 95% CI | -0.30, 0.21 | -0.21, 0.14 |
| (n) | (26) | (59) |
| Prednisone Use:[2] | | |
| Number (%) of Patients that Used Oral Prednisone During the Study: | | |
| No | 11 (37%) | 27 (44%) |
| Yes | 19 (63%) | 34 (56%) |
| Average Total Daily Amount Used (mg): | | |
| Mean±SD | 1.40±2.71 | 0.65±0.93 |
| Median | 0.52 | 0.26 |

[1] Data sources: [IND 44,535; 6/22/1998; 1:97]
[2] Data sources: [IND 44,535; 6/22/1998; 1:101-2]

*Reviewer's Comments: Compared to the budesonide group, a higher proportion of patients used oral prednisone and there was higher average total daily amount used in the conventional therapy group. This confounds the interpretation of comparative growth data.*

### 5.1.4.4.2 *Breakthrough Medication Use*

No consistent differences were observed in the mean changes from baseline (last 14 days of double-blind) to the last open-label observation in the number of days use of breakthrough medication and the number of nebulizations (nebulizer)/day and puffs (pMDI)/day of breakthrough medication. These results should be interpreted with caution since albuterol could have been used as maintenance therapy in addition to being used as breakthrough medication, and the distinction between the two uses was not always clear.

**Table 5.1.4.4.2.** Mean Changes from Baseline (Last 14 Days of Double-Blind) to the Last Observation in the Use of Breakthrough Medication. [IND 44,535; 6/22/1998; 1:98-100]

| Variable | Open-Label Treatment | |
|---|---|---|
| | Conventional Asthma Therapy | Budesonide Nebulizing Suspension |
| Use of Breakthrough Medication: | | |
| Mean Change from Baseline | | |
| Days | 0.2 | -1.1 |
| 95% CI | -2.0, 2.4 | -2.7, 0.4 |
| (n) | (26) | (59) |
| Nebulizations (of Nebulizer)/day | -0.37 | -0.02 |
| 95% CI | -1.1, 0.3 | -0.3, 0.3 |
| (n) | (7) | (25) |
| Puffs (of pMDI)/day | 0.31 | -0.24 |
| 95% CI | -0.4, 1.0 | -0.8, 0.3 |
| (n) | (17) | (31) |

### 5.1.4.4.3 *Morning and Evening PEFs*

Both treatment groups showed similar improvements, with the 95% CIs overlapping between the two treatment groups.

**Table 5.1.4.4.3.** Mean Changes from Baseline (Last 14 Days of Double-Blind) to the Last Observation in Morning and Evening PEFs. [IND 44,535; 6/22/1998; 1:103, 107]

| Variable | Open-Label Treatment | |
|---|---|---|
| | Conventional Asthma Therapy | Budesonide Nebulizing Suspension |
| PEF (L/min): | | |
| Mean Change from Baseline | | |
| Morning | 12.9 | 7.1 |
| 95% CI | -14.5, 40.3 | -11.7, 25.8 |
| (n) | (26) | (59) |
| Evening | 13.5 | 8.9 |
| 95% CI | -14.4, 41.4 | -10.3, 28.0 |
| (n) | (26) | (59) |

### 5.1.4.4.4 *$FEV_1$, FVC and corresponding $FEF_{25-75\%}$*

Improvement in $FEV_1$, FVC and corresponding $FEF_{25-75\%}$ was observed in both groups. The increases in these parameters were numerically higher in the conventional therapy group compared to the budesonide group throughout the treatment period.

**Table 5.1.4.4.4.** Mean Changes From Baseline (Last Visit of Double-Blind) to the Last Observation in $FEV_1$, FVC and Corresponding $FEF_{25-75\%}$. [IND 44,535; 6/22/1998; 1:104-6]

| Variable | Open-Label Treatment | |
|---|---|---|
| | Conventional Asthma Therapy | Budesonide Nebulizing Suspension |
| Spirometry: | | |
| Mean Change from Baseline | | |
| $FEV_1$ (L/min) | 0.15 | 0.10 |
| 95% CI | 0.00, 0.31 | -0.01, 0.21 |
| (n) | (27) | (60) |
| FVC (L/min) | 0.19 | 0.10 |
| 95% CI | -0.01, 0.38 | -0.04, 0.23 |
| (n) | (27) | (60) |
| $FEF_{25-75\%}$ | 0.14 | 0.06 |
| 95% CI | -0.09, 0.37 | -0.10, 0.22 |
| (n) | (27) | (60) |

## 5.1.4.5 Safety Analysis

[IND 44,535; 6/22/1998; 1:49-66]

### *5.1.4.5.1 Extent of Exposure*

See Section 5.1.4.2.3.1.

### *5.1.4.5.2 Adverse Events*

[IND 44,535; 6/22/1998; 1:49-57]

#### 5.1.4.5.2.1 Brief Summary of Adverse Events

There were no deaths reported during the study. A total of 9 serious AEs (SAEs) in 8 patients (4 SAEs in 3 (10%) patients in the conventional therapy group; 5 SAEs in 5 (8%) patients in the budesonide group) were reported (Table 5.1.4.5.2.4). One patient was discontinued from the study due to an AE (budesonide treatment: hyperkinesia). The AE was judged by the investigator to be of possible relationship to study treatment. The patient recovered completely.

The percentages of reported severe AEs were similar for both treatment groups (20% for conventional therapy; 21% for budesonide). After adjusting for the length of time in the study there were no statistically significant differences in the frequency of reported AEs.

#### 5.1.4.5.2.2 Display of All Adverse Events

A total of 82 (90%) patients experienced adverse events during the open-label phase, including 58 (95%) in the budesonide group and 24 (80%) in the conventional therapy group.

**Table 5.1.4.5.2.2.A.** Summary of Reported Adverse Events. [IND 44,535; 6/22/1998; 1:56, 131-4]

| | Budesonide Nebulizing Suspension (n=61) | Conventional Asthma Therapy (n=30) |
|---|---|---|
| No. of Patients with ≥1 AE | 58 (95%) | 24 (80%) |
| No. of Patients with ≥1 SAE | 5 (8%) | 3 (10%) |
| No. of Patients Who Discontinued from the Study Due to an AE | 1 (2%) | 0 (0%) |

The most frequently reported AEs included respiratory infection (46%), sinusitis (31%), pharyngitis (27%), and fever (22%). After adjusting for the length of time in the study there were no statistically significant differences in the frequency of reported AEs between the two treatment groups. (Table 5.1.4.5.2.2.B)

*Reviewer's Comments: 1. The AEs with a frequency ≥3% and a relative risk >2 (the budesonide group versus the conventional therapy group) included bronchitis, pneumonia, coughing, varicella, vomiting, nausea, hyperkinesia, dyspnonia, earache, conjunctivitis, and lymphadenopathy. The significance of these observations is not clear. 2. Psychiatric disorders were reported slightly more frequently in the budesonide group (anorexia, emotional liability, insomnia, nervousness, and unusual behavior, 2% for each) than in the conventional therapy group (apathy, 3%).* [IND 44,535; 6/22/1998; 1:133]



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**Table 5.1.4.5.2.2B.** Summary of Most Frequently Reported AEs (≥3% of Patients in Any Treatment Group) that Began During Open-Label Treatment with Relative Risks (From Proportional Hazards Model) and 95% Confidence Interval, and Adjusted for Length of Time (Per 12 Patient-Months) in the Study.

| Body System/AE [1] | Incidence of AEs Beginning in Open-Label | | | | | Frequency per 12 Pt-Months | |
|---|---|---|---|---|---|---|---|
| | Conv. Asthma Therapy (n=30) | Budesonide Nebulizing Suspension (n=61) | Total (n=91) | Relative Risk | 95% Confidence Interval | Conv. Asthma Therapy | Budesonide Nebulizing Suspension |
| **Respiratory System Disorders** | | | | | | | |
| Respiratory Infection | 12 (40%) | 30 (49%) | 42 (46%) | 1.274 | (0.65, 2.49) | 0.5 | 0.5 |
| Sinusitis | 9 (30%) | 19 (31%) | 28 (31%) | 0.997 | (0.45, 2.20) | 0.3 | 0.3 |
| Pharyngitis | 6 (20%) | 19 (31%) | 25 (27%) | 1.644 | (0.66, 4.12) | 0.2 | 0.3 |
| Rhinitis | 5 (17%) | 9 (15%) | 14 (15%) | 0.840 | (0.28, 2.51) | 0.2 | 0.2 |
| Bronchitis | 2 (7%) | 9 (15%) | 11 (12%) | 2.182 | (0.47, 10.1) | 0.1 | 0.2 |
| Pneumonia | 1 (3%) | 8 (13%) | 9 (10%) | 3.917 | (0.49, 31.3) | 0.0 | 0.1 |
| Coughing | 1 (3%) | 6 (10%) | 7 (8%) | 2.764 | (0.33, 22.9) | 0.0 | 0.1 |
| Stridor | 2 (7%) | 3 (5%) | 5 (5%) | 0.688 | (0.11, 4.12) | 0.1 | 0.1 |
| Bronchospasm | 3 (10%) | 2 (3%) | 5 (5%) | 0.477 | (0.07, 3.39) | 0.1 | 0.0 |
| **Body as a Whole** | | | | | | | |
| Fever | 6 (20%) | 14 (23%) | 20 (22%) | 1.051 | (0.40, 2.77) | 0.2 | 0.2 |
| Accident and/or Injury | 4 (13%) | 7 (11%) | 11 (12%) | 1.007 | (0.29 3.47) | 0.2 | 0.1 |
| Pain | 3 (10%) | 3 (5%) | 6 (7%) | 0.450 | (0.09, 2.23) | 0.1 | 0.1 |
| Flu-Like Disorder | 1 (3%) | 4 (7%) | 5 (5%) | 1.350 | (0.14, 12.9) | 0.0 | 0.1 |
| Chest Pain | 1 (3%) | 2 (3%) | 3 (3%) | 0.928 | (0.08, 10.2) | 0.0 | 0.0 |
| Allergic Reaction | 1 (3%) | 1 (2%) | 2 (2%) | 0.491 | (0.03, 7.85) | 0.0 | 0.0 |

Continued on next page.

| Body System/AE [1] | Incidence of AEs Beginning in Open-Label | | | | | Frequency per 12 Pt-Months | |
|---|---|---|---|---|---|---|---|
| | Conv. Asthma Therapy (n=30) | Budesonide Nebulizing Suspension (n=61) | Total (n=91) | Relative Risk | 95% Confidence Interval | Conv. Asthma Therapy | Budesonide Nebulizing Suspension |
| **Resistance Mechanism Disorders** | | | | | | | |
| Otitis Media | 4 (13%) | 12 (20%) | 16 (18%) | 1.412 | (0.46, 4.38) | 0.2 | 0.2 |
| Moniliasis | 2 (7%) | 6 (10%) | 8 (9%) | 1.411 | (0.28, 6.99) | 0.1 | 0.1 |
| Infection Viral | 2 (7%) | 2 (3%) | 4 (4%) | 0.944 | (0.09, 10.4) | 0.1 | 0.0 |
| Varicella | 0 (0%) | 3 (5%) | 3 (3%) | $> 10^6$ | (0.00, . . 0) | 0.0 | 0.1 |
| Ear Infection External | 1 (3%) | 1 (2%) | 2 (2%) | 0.482 | (0.03, 7.71) | 0.0 | 0.0 |
| Infection | 1 (3%) | 0 (0%) | 1 (1%) | 0.000 | (0.00, 0.00) | 0.0 | 0.0 |
| Infection Bacterial | 1 (3%) | 0 (0%) | 1 (1%) | 0.000 | (0.00, . . 0) | 0.0 | 0.0 |
| **Gastrointestinal System Disorders** | | | | | | | |
| Vomiting | 2 (7%) | 9 (15%) | 11 (12%) | 2.101 | (0.45, 9.73) | 0.1 | 0.2 |
| Abdominal Pain | 2 (7%) | 6 (10%) | 8 (9%) | 1.381 | (0.28, 6.85) | 0.1 | 0.1 |
| Gastroenteritis | 2 (7%) | 3 (5%) | 5 (5%) | 0.779 | (0.13, 4.67) | 0.1 | 0.1 |
| Nausea | 0 (0%) | 3 (5%) | 3 (3%) | $> 10^6$ | (0.00, . . 0) | 0.0 | 0.1 |
| Diarrhea | 2 (7%) | 0 (0%) | 2 (2%) | 0.000 | (0.00, . . 0) | 0.1 | 0.0 |
| **Skin & Appendages Disorders** | | | | | | | |
| Eczema | 1 (3%) | 2 (3%) | 3 (3%) | 0.928 | (0.08, 10.2) | 0.0 | 0.0 |
| Urticaria | 2 (7%) | 1 (2%) | 3 (3%) | 0.241 | (0.02, 2.66) | 0.1 | 0.0 |
| Rash Pustular | 1 (3%) | 1 (2%) | 2 (2%) | 0.477 | (0.03, 7.63) | 0.0 | 0.0 |
| **Central & Peripheral Nervous Sys. Disorder** | | | | | | | |
| Headache | 7 (23%) | 11 (18%) | 18 (20%) | 0.682 | (0.26, 1.76) | 0.3 | 0.2 |
| Hyperkinesia | 0 (0%) | 3 (5%) | 3 (3%) | $> 10^6$ | (0.00, . . 0) | 0.0 | 0.1 |
| Dysphonia | 0 (0%) | 2 (3%) | 2 (2%) | $> 10^6$ | (0.00, . . 0) | 0.0 | 0.0 |

Continued on next page.

| Body System/AE [1] | Incidence of AEs Beginning in Open-Label | | | | | Frequency per 12 Pt-Months | |
|---|---|---|---|---|---|---|---|
| | Conv. Asthma Therapy (n=30) | Budesonide Nebulizing Suspension (n=61) | Total (n=91) | Relative Risk | 95% Confidence Interval | Conv. Asthma Therapy | Budesonide Nebulizing Suspension |
| **Hearing & Vestibular Disorders** | | | | | | | |
| Ear Ache | 0 (0%) | 3 (5%) | 3 (3%) | $> 10^6$ | (0.00, . . 0) | 0.0 | 0.1 |
| Ear or Hearing Symptoms NOS | 1 (3%) | 2 (3%) | 3 (3%) | 0.934 | (0.08, 10.3) | 0.0 | 0.0 |
| Ear Infection NOS | 2 (7%) | 1 (2%) | 3 (3%) | 0.219 | (0.02, 2.42) | 0.1 | 0.0 |
| **Vision Disorders** | | | | | | | |
| Conjunctivitis | 0 (0%) | 5 (8%) | 5 (5%) | $> 10^6$ | (0.00, . . 0) | 0.0 | 0.1 |
| Eye Pain | 1 (3%) | 0 (0%) | 1 (1%) | 0.000 | (0.00, . . 0) | 0.0 | 0.0 |
| **White Cell and Res Disorders** | | | | | | | |
| Lymphadenopathy | 0 (0%) | 2 (3%) | 2 (2%) | $> 10^6$ | (0.00, . . 0) | 0.0 | 0.0 |
| **Platelet, Bleeding & Clotting Disorders** | | | | | | | |
| Purpura | 1 (3%) | 2 (3%) | 3 (3%) | 0.922 | (0.08, 10.1) | 0.0 | 0.0 |
| **Psychiatric Disorders** | | | | | | | |
| Apathy | 1 (3%) | 0 (0%) | 1 (1%) | 0.000 | (0.00, . . 0) | 0.0 | 0.0 |
| **Musculo-Skeletal System Disorders** | | | | | | | |
| Fracture | 1 (3%) | 0 (0%) | 1 (1%) | 0.000 | (0.00, . . 0) | 0.0 | 0.0 |

[1] Data sour[redacted] [IND 44,535; 6/22/1998; 1:131-7]

### 5.1.4.5.2.3 Analysis of Adverse Events

The incidence of all AEs considered by the investigator to be possibly or probably related to treatment was higher in the budesonide group (n=12, 20%) compared to the conventional therapy group (n=0). Moniliasis was reported in 6 (10%) and dysphonia in 2 (3%) in patients on budesonide. The incidence of all other AEs considered by the investigator to be possibly or probably related to treatment was <3% (i.e., one patient) in the budesonide treatment group. [IND 44,535; 6/22/1998; 1:138]

*Reviewer's Comments: In patients on budesonide, the possibly or probably treatment-related AEs included psychiatric disorders, e.g., emotional lability (2%), insomnia (2%), and nervousness (2%).*

### 5.1.4.5.2.4 Serious Adverse Events

There were no deaths reported during this study. A total of 9 SAEs in 8 patients were reported (4 events in 3 patients (10%) in the conventional therapy group; 5 events in 5 (8%) patients in the budesonide group).

**Table 5.1.4.5.2.4.** Summary of Serious Adverse Events.[1]

| Patient Number | Adverse Event[2] | Causality: Investigator's Assessment |
|---|---|---|
| **Budesonide Nebulizing Suspension:** | | |
| 02-0154 | Sinusitis/completely recovered. | Unlikely |
| 05-0220 | Sinusitis/completely recovered. | Unlikely |
| 08-0338 | Bronchospasm/completely recovered. | Unlikely |
| 13-0129 | Bronchospasm/completely recovered. | Unlikely |
| 17-0402 | Pneumonia/completely recovered. | Unlikely |
| **Conventional Asthma Therapy:** | | |
| 05-0212 | Bronchospasm/completely recovered.<br>Bronchospasm/completely recovered. | Unlikely<br>Unlikely |
| 12-0263 | Bronchospasm/completely recovered. | Unlikely |
| 13-0130 | Bronchospasm/completely recovered. | Unlikely |

[1] Data sources: [IND 44,535; 6/22/1998; 1:142, 149-53]
[2] WHO preferred term.

### 5.1.4.5.2.5 Discontinuations Due to Adverse Events

One patient was discontinued from the open-label treatment phase due to an AE (budesonide nebulizing suspension: hyperkinesia) judged by the investigator to be of possible relationship to study treatment. The patient recovered completely. [IND 44,535; 6/22/1998; 1:142, 154]

### 5.1.4.5.2.6 Adverse Events of Severe Intensity

The incidence of severe AEs was 21% in the budesonide group and 20% in the conventional therapy group. Sinusitis was the most frequently reported severe AE with an incidence of 7% in both groups. Bronchospasm occurred in 3% of the patients on budesonide and 7% of the patients on conventional therapy. Respiratory infection occurred in 5% of the patients on budesonide and 0% of the patients on conventional therapy. All severe AEs were judged by the investigators to be unlikely causally-related to treatment. [IND 44,535; 6/22/1998; 1:142, 143-6]

### 5.1.4.5.3 *Assessment of HPA-Axis*

[IND 44,535; 6/22/1998; 1:59-61, 186-91]

The total number of patients assessed for plasma cortisol levels was small (n=22): 14 in the budesonide group and 8 in the conventional therapy group. Therefore, these results have to be interpreted with caution.

There were no significant differences between the conventional therapy group and the budesonide group in adjusted mean changes in ACTH-stimulated cortisol levels from baseline. However, the percent of patients showing a shift in ACTH-stimulation tests from normal responsiveness at baseline to abnormal responsiveness at Week 52 was higher in the budesonide group (45%, 5 patients) than that in the conventional therapy group (25%, 2 patients).

*Reviewer's Comments: In both the conventional therapy (including inhaled steroids) group and the budesonide group, the basal cortisol levels and the mean increase in cortisol levels after ACTH-stimulation were decreased at Week 52 compared to the baseline, suggesting a measurable systemic effect of inhaled corticosteroids.*

**Table 5.1.4.5.3.A.** Summary Results of ACTH-Stimulation Tests for Patients Who Completed One Year of Open-Label Treatment.[1]

| Variable | | Open-Label Treatment | |
|---|---|---|---|
| | | Conventional Asthma Therapy | Budesonide Nebulizing Suspension |
| Cortisol Levels (nmol/L) | | | |
| All patients: | | | |
| Basal: | Baseline | 323 | 246 |
| | Week 52 | 288 | 230 |
| | | (n=8) | (n=14) |
| ACTH-Stimulated: | Baseline | 630 | 580 |
| | Week 52 | 495 | 426 |
| | | (n=8) | (n=14) |
| Male Patients: | | | |
| Basal: | Baseline | 240 | 190 |
| | Week 52 | 224 | 231 |
| | | (n=3) | (n=9) |
| ACTH-Stimulated: | Baseline | 584 | 614 |
| | Week 52 | 516 | 434 |
| | | (n=3) | (n=9) |
| Female Patients: | | | |
| Basal: | Baseline | 373 | 347 |
| | Week 52 | 326 | 227 |
| | | (n=5) | (n=5) |
| ACTH-Stimulated: | Baseline | 657 | 519 |
| | Week 52 | 482 | 412 |
| | | (n=5) | (n=5) |
| Adjusted Mean Changes in ACTH-Stimulated Cortisol Levels from Baseline[2] (p-value vs. conventional asthma therapy) | | | |
| All Patients | | -115.0 (-253, 24)[3] | -96.2 (-187, -6) (p=0.772) |
| Male Patients | | -57.5 (-288, 174) | -91.1 (-182, 0) (p=0.643) |
| Female Patients | | -172.0 (-377, 33) | -82.8 (-258, 92) (p=0.384) |

[1] Data source: [IND 44,535; 6/22/1998; 1:186]
[2] Means adjusted for Center Effect.
[3] 95% confidence interval.

### 5.1.4.5.6 *Assessment Of Oral Fungal Cultures*

[IND 44,535; 6/22/1998; 1:61, 192-4]

The incidence of clinically significant abnormalities in oral fungal cultures in the budesonide groups (8%) was higher than that of the conventional therapy group (3%). In the budesonide group the incidence of moderat and heavy growth of oral fungal cultures at Week 52 (43%) was higher than that at baseline (28%). In the conventional therapy group the incidences at Week 52 (20%) and at baseline (17%) were similar.

### 5.1.4.5.7 *Assessment of Body Length/Height (Stadiometry)*

[IND 44,535; 6/22/1998; 1:61-5, 195-207]

Either as a whole group or stratified by gender, the mean measured growth velocity (cm/year) of patients on conventional therapy was numerically smaller than that of patients on budesonide (0.71, 0.64 and 0.85 cm/year for all patients, male patients, and female patients, respectively).

**Table 5.1.4.5.7A.** Summary of Mean Measured Growth Velocity (cm/year) over One Year (Week 0 to Week 52) for Patients Who Completed One Year of Open-Label Treatment.[1]

| Stratification Group | Treatment Group | n | Mean Measured Growth Velocity[2] |
|---|---|---|---|
| All Patients | Budesonide | 47 | 5.68±1.71 |
| | Conventional | 25 | 4.97±2.00 |
| Male Patients | Budesonide | 32 | 5.64±1.72 |
| | Conventional | 14 | 5.00±2.03 |
| Female Patients | Budesonide | 15 | 5.78±1.73 |
| | Conventional | 11 | 4.93±2.05 |

[1] 7 patients were excluded from the analysis of growth (6 budesonide patients and 1conventional asthma therapy patient). These patients had either been taking Pulmicort Turbuhaler or Rhinocort for long periods of time at high doses before the beginning of open-label, or had great variations in height data which were judged to be unreliable.

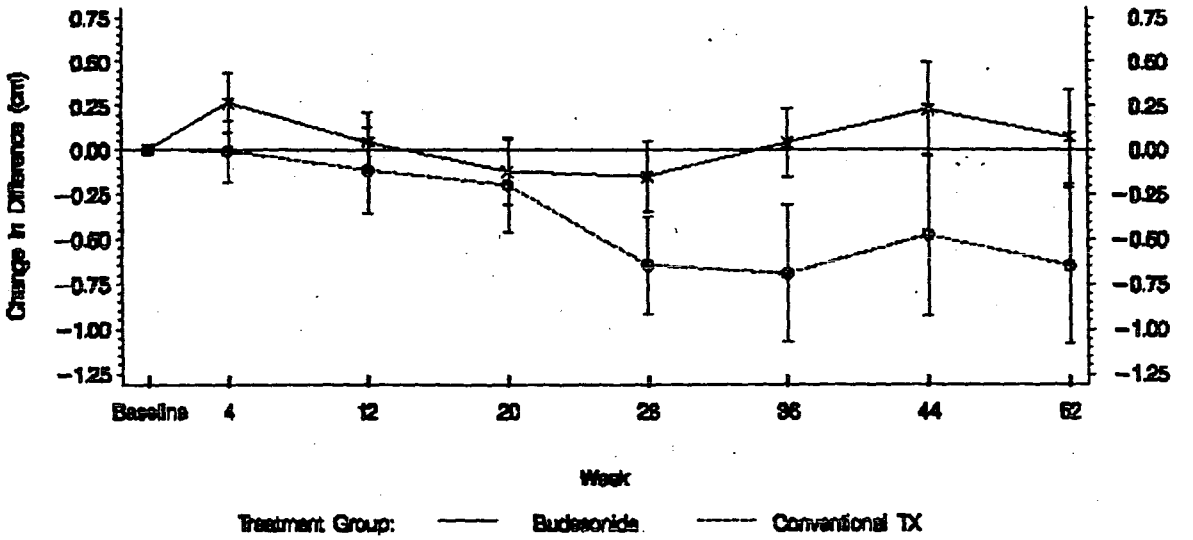
[2] The differences between 2 treatment groups were not statistically different (all patients, p=0.197; males, p=0.926; females, p=0.337).

Data source: [IND 44,535; 6/22/1998; 1:206]

A similar result was observed in the mean changes from baseline in the difference between observed heights and standard median height (50$^{th}$ percentile based on data from the U.S. National Center for Health Statistics) for all the patients who completed the open-label treatment phase (Figure 5.1.4.5.7). Both treatment groups were taller compared to the standard median height at the start and throughout the study. The budesonide group began the study with a lower mean observed height compared to the conventional therapy group (123.56 cm vs. 125.45 cm, respectively). At subsequent visits, the mean differences from the standard median height fluctuated slightly for the

patients on budesonide (ranging between 2.09 to 2.51 cm), and decreased for the patients on conventional therapy (1.34 cm at Week 0 and 0.69 cm at Week 52).

**Figure 5.1.4.5.7.** The Mean (±Standard Error) Changes from Baseline in the Difference between Observed Heights and Standard Median Height for all the Patients Who Completed One Year of Open-Label Treatment. [IND 44,535; 6/22/1998; 1:63]




The shifting patterns in observed height relative to standard 50th percentile height from baseline to Week 52 were similar in both groups. Of patients whose heights were less than standard 50th percentile height at baseline, the proportion of patients shifting to above 50th percentile at Week 52 was higher in the budesonide group (5/12, 29.4%) compared to the conventional therapy group (1/12, 8.3%).

**Table 5.1.4.5.7B.** Shifts in Observed Height Relative to Standard 50th Percentile Height from Baseline to Week 52 for All Patients Who Completed One Year of Open-Label Treatment.

| Parameter | Baseline | Week 52 | | | |
|---|---|---|---|---|---|
| | | Conventional Asthma Therapy | | Budesonide Nebulizing Suspension | |
| | | Below | Above | Below | Above |
| Observed Height[1] | Below | 11 (91.7%) | 1 (8.3%) | 12 (70.6%) | 5 (29.4%) |
| | Above | 2 (15.4%) | 11 (84.6%) | 2 (6.7%) | 28 (93.3%) |

[1] Relative to the standard 50th percentile height based on data from the U.S. National Center for Health Statistics for age and gender.
Data source: [IND 44,535; 6/22/1998; 1:204]

*Reviewer's Comments: There were problems in the growth study design; these included the following: 1. Treatments were not blinded. 2. Baseline growth velocity for an appropriate period of time (e.g. 6 months) was not assessed. 3. Re-randomization between double-blind (12-week) and*

*open-label (52-week) phases without washout period. 4. Significant portion of patients had various intervals between the end of double-blind phase and the beginning of open-label phase. 5. Patient's asthma symptoms and signs at baseline were not well balanced between the two treatment groups. 6. The high proportion of patients on inhaled steroids in the conventional therapy group. 7. The disproportionate use of oral steroids for acute asthma exacerbations. Thence, it's hard to interpret the growth data and the significance of these data is uncertain.*

*Both the proportion of patients who used oral prednisone and the average total daily amount used in the conventional therapy group (63% and 1.40 mg/day, respectively) were higher compared to the budesonide group (56% and 0.65 mg/day, respectively). In addition, the mean age and height were slightly higher in the conventional therapy group. At baseline, the control of asthma was poorer (higher asthma symptom scores, slightly worse pulmonary function, and higher number of days use of breakthrough medication) in the conventional therapy group. All these might explain, at least partially, why the mean measured growth velocity of the conventional therapy group was smaller than that of the budesonide group.*

### 5.1.4.5.8 Assessment of Skeletal Age

[IND 44,535; 6/22/1998; 1:65-6, 209]

At both baseline and Week 52, the mean differences between measured skeletal age and chronological age (measured skeletal age - chronological age) in the budesonide group were larger than (or the same as) those in the conventional therapy group. In the conventional therapy group, the mean differences between measured skeletal age and chronological age were decreased at Week 52 compared to the baseline.

**Table 5.1.4.5.8.** Summary of Mean Differences Between Skeletal Age and Chronological Age (in Years) Over One Year (Week 0 to Week 52) for Patients Who Completed One Year of Open-Label Treatment.

| Stratification Group | Treatment Group | Time Interval | n | Mean Difference[1] |
|---|---|---|---|---|
| All Patients | Budesonide | Baseline | 49 | 0.10±1.03 |
| | | Week 52 | 48 | 0.13±1.14 |
| | Conventional | Baseline | 26 | 0.05±0.91 |
| | | Week 52 | 24 | -0.09±0.97 |
| Female Patients | Budesonide | Baseline | 16 | 0.42±1.07 |
| | | Week 52 | 15 | 0.79±0.09 |
| | Conventional | Baseline | 12 | 0.18±1.16 |
| | | Week 52 | 12 | 0.12±1.13 |
| Male Patients | Budesonide | Baseline | 33 | -0.06±1.00 |
| | | Week 52 | 33 | -0.17±1.08 |
| | Conventional | Baseline | 14 | -0.06±0.67 |
| | | Week 52 | 12 | -0.30±0.76 |

[1] Measured skeletal age minus chronological age.
Data source: [IND 44,535; 6/22/1998; 1:209]

### 5.1.5 Conclusions and Comments of Study Results

This was a randomized, open-label, active-controlled, 52-week extension of a previous 12-week, randomized, double-blind, placebo-controlled study to assess the long-term safety in asthmatic children aged 4-8 years whose asthma was controlled with titrated doses budesonide nebulizing suspension or conventional asthma therapies (that could have included inhaled GCS, $\beta_2$-agonists, methylxanthines and non-steroidal anti-inflammatories).

The results demonstrated that patients on budesonide and those on conventional asthma therapy had similar improvements in most efficacy variables. Between the two treatment groups, no statistically significant difference was observed in the mean changes from baseline in any efficacy variable. The increases in morning PEF, $FEV_1$, FVC and $FEF_{25-75\%}$ were numerically higher in the conventional asthma therapy group compared to the budesonide group. The proportion of patients that used oral prednisone and the average total daily amount used were also higher in the conventional therapy group. (Table 5.1.5)

In general, the safety evaluations did not reveal apparent difference between the two treatment groups in reported adverse events or regular clinical laboratory tests. After adjusting for length of time in the study, there were no obviously significant differences in the type, incidence, or severity of AEs between treatment groups. However, the relative risks of bronchitis, pneumonia, coughing, varicella, vomiting, nausea, hyperkinesia, dyspnonia, earache, conjunctivitis, and lymphadenopathy was higher (>2) in the budesonide group compared to the conventional asthma therapy group. The significance of these observations is not clear. Of note, psychiatric disorders and use of psycholeptics were reported more frequently in the budesonide group than in the conventional therapy group. The incidence of clinically significant abnormalities in oral cavity fungal cultures was numerically higher in the budesonide groups (8%) compared to the conventional asthma therapy group (3%). Importantly, in both treatment groups the basal cortisol levels and the mean increase in cortisol levels after ACTH-stimulation were decreased at Week 52 compared to the baseline, suggesting a measurable systemic effect of inhaled corticosteroids. When assessed categorically, more patients became abnormal for this test in the budesonide group than in the conventional therapy group, despite many in the conventional therapy group receiving inhaled corticosteroids.

In this study, the growth velocity of patients on conventional asthmatic therapy was numerically (0.71 cm/year) smaller than that of patients on budesonide. These data are hard to interpret due to problems in the study design; these included the following: 1. Treatments were not blinded. 2. Baseline growth velocity of each patient was not assessed. 3. Re-randomization between double-blind and open-label phases without washout period. 4. Significant portion of patients had various intervals between the end of double-blind phase and the beginning of open-label phase. 5. Patient's asthma symptoms and signs at baseline were not well balanced between the two treatment groups. 6. The high proportion of patients on inhaled steroids in the conventional therapy group. 7. The disproportionate use of oral steroids for acute asthma exacerbations. Thence, the significance of these data is uncertain. Both the proportion of patients who used oral steroids and the average total daily amount

used were higher in the conventional therapy group (63% and 1.40 mg/day, respectively) compared to the budesonide group (56% and 0.65 mg/day, respectively). In addition, the mean age and height were slightly higher in the conventional therapy group. At baseline, the control of asthma was poorer (higher asthma symptom scores, slightly worse pulmonary function, and higher number of days use of breakthrough medication) in the conventional therapy group. All these might explain, at least partially, why the mean measured growth velocity was smaller in the conventional therapy group.