AstraZeneca

**Clinical Study Report**

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|---|---|
| Drug substance: | Budesonide |
| Edition No.: | Final |
| Study code: | DX-RES-2103 |
| Date: | 13 January 2006 |

# An evaluation of the effectiveness of PULMICORT RESPULES® (budesonide inhalation suspension) versus SINGULAIR® (montelukast sodium) in children 2 to 8 years old with asthma requiring controller therapy

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|---|---|
| **Study dates:** | First subject enrolled: 16 October 2002<br>Last subject completed: 2 February 2005 |
| **Phase of development:** | Phase IV |
| **International Coordinating Investigator:** | Not applicable |

This study was performed in compliance with Good Clinical Practice.

| | | | |
|---|---|---|---|
| Drug product: | PULMICORT RESPULES | **SYNOPSIS** | |
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# An evaluation of the effectiveness of PULMICORT RESPULES® (budesonide inhalation suspension) versus SINGULAIR® (montelukast sodium) in children 2 to 8 years old with asthma requiring controller therapy

**International coordinating investigator (not applicable)**

**Study centers**

This study was initiated at 70 centers across the United States, with subjects enrolled at 58 centers and randomized to treatment at only 55 centers.

**Publications**

None at report time.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First subject enrolled** | 16 October 2002 | Phase IV |
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**Objectives**

**Primary:** To compare the effectiveness of 0.5-mg PULMICORT RESPULES once daily to 4- or 5-mg SINGULAIR (tablets) once daily in children between 2 and 8 years of age, inclusive, who have symptoms of asthma requiring controller therapy.[1]
**Secondary:** To compare the safety and effectiveness of 0.5-mg PULMICORT RESPULES once daily to 4- or 5-mg SINGULAIR tablets once daily in children between 2 and 8 years of age, inclusive, who have symptoms of asthma by assessing 20 secondary endpoints, including 3 additional time-to-event endpoints, 2 corresponding event-rate endpoints, 14 change from baseline endpoints for a range of disease-related variables, and the endpoint of percentage of asthma-free days (AFD) (see *Efficacy and Pharmacokinetics* for details).

[1] Long-term medication used to prevent asthma attacks.

## Study design

This study was a 1-year, open-label, randomized, active-controlled, multicenter pediatric study, comprising a 3- to 21-day qualification run-in period, a 52-week treatment period, and a safety follow-up contact (by telephone) 2 weeks after the last visit. Qualified children were stratified by age (2 to 5 years or 6 to 8 years) and randomized to daily evening treatment with either PULMICORT RESPULES or SINGULAIR chewable tablets. During the 52-week treatment period, subjects who met protocol-defined criteria for subacute mild worsening of asthma received *step-up therapy* with PULMICORT RESPULES (regardless of assigned randomized treatment), and subjects who met protocol-defined criteria for having acute severe asthma exacerbation received a 3- to 10-day course of oral steroids. There was no limit to the number of times subjects could receive step-up therapy or a course of oral steroids.

At study entry (Visit 1), caregivers received electronic diaries, which were used to record and transmit the following information on a daily basis: morning and evening peak flow rates, daytime and nighttime asthma symptom scores, nighttime awakenings due to asthma, intake of study medication during the previous night (Administration of study medication was recorded after randomization.) and rescue medication use during the day and at night because of asthma-related awakenings. Data were stored in a centralized database that was accessed by study personnel on an ongoing basis.

## Target subject population and sample size

Children aged 2 through 8 years, with asthma symptoms requiring controller therapy, were enrolled. Primary eligibility at screening was based on subjects having (a) 3 or more episodes of wheezing that lasted more than 1 day and affected sleep in the year prior to screening or (b) symptoms of mild persistent asthma as defined by the National Heart, Lung, and Blood Institute (NHLBI, 2002 guidelines). Primary eligibility for assignment to randomized therapy (and further study participation) was based on subjects having both a recorded cumulative asthma symptom score (daytime plus nighttime) of 2 or more and a need for rescue medication on at least 3 of 7 consecutive days during the run-in period.

The planned sample size for the study was calculated for 80% power to detect a difference between PULMICORT RESPULES and SINGULAIR of at least 10% in the time to first addition of step-up therapy or oral steroids. On the basis of a 2-sided test with a 0.05 level of significance and an estimated rate at which subjects treated with PULMICORT RESPULES would require additional therapy (12.5% based on data from Study DX-RES-2000), the calculated sample size was 176 subjects per treatment group. To ensure an adequate number of evaluable subjects, an estimated 380 subjects (190 per treatment group) were sought for enrollment.

## Investigational product and active control agent: dosage, mode of administration, and batch numbers

Each PULMICORT RESPULES ampule provided 0.5 mg of budesonide in a 2-ml sterile suspension. After nebulization with a jet nebulizer, each 0.5-mg dose was inhaled (mouthpiece or facemask). Subjects randomized to treatment with PULMICORT RESPULES (Batch numbers: 206033, 304159, 304051, and 402800) inhaled the contents of 1 ampule every evening. Subjects who received PULMICORT RESPULES as step-up therapy (Batch numbers: 206033, 304100, 304051, 308212, and 401001) inhaled 0.5 mg every morning for 14 days, regardless of evening treatment. SINGULAIR chewable tablets, providing 4 or 5 mg of montelukast per tablet, served as the active control agent for the study. Tablets were supplied as the commercially

available product (Batch numbers: M3835, N4646, N5235, and N4446 [4-mg tablets] and M3851, N4521, and N5325 [5-mg tablets]). Subjects randomized to treatment with SINGULAIR took 1 tablet every evening: 4 mg if 2 to 5 years old, inclusive, and 5 mg if 6 to 8 years old, inclusive.
Subjects who required a course of oral steroids for acute severe exacerbation of asthma took prednisone, prednisolone, or methylprednisolone at a starting dose of 1 to 2 mg/kg, not to exceed 60 mg/kg, with tapering off permitted as appropriate.
AstraZeneca did not provide rescue medication or oral steroids.

**Duration of treatment**

Once randomized, subjects were treated for up to 52 weeks. During the treatment period, subjects and caregivers were scheduled for 7 clinic visits (Visits 2 through 8); during these visits, subjects underwent lung function testing, and caregivers completed quality-of-life (QOL) questionnaires, as outlined in the study plan.

**Criteria for evaluation (main variables)**

**Efficacy and pharmacokinetics**

- Primary variable: Time to 1st additional asthma medication (either step-up therapy or oral steroids) measured at 52 weeks

- Secondary variables:

  0 Time to 1st additional asthma medication measured at 12 weeks and 26 weeks

  1 Time to 1st acute severe exacerbation (as measured by the need for oral steroids), both measured at 12 weeks, 26 weeks, and 52 weeks

  2 Rates (numbers of events per period) of subacute mild exacerbations and acute severe exacerbations, both measured at 52 weeks

  3 Change from baseline in mean daily use of rescue medication and percentage of rescue-medication-free days, rescue-medication-free nights, and rescue-medication-free 24-hours, each measured at 12 weeks, 26 weeks, and 52 weeks

  4 Change from baseline in forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and forced expiratory flow for the middle 50% of FVC ($FEF_{25\%-75\%}$) measured at 12 weeks, 26 weeks, 52 weeks, and last on-treatment visit in all children able to perform spirometry maneuvers[2]

[2]As a pilot study within the main study, 18 investigational sites were preselected to use impulse oscillometry (IOS) for all enrolled subjects to measure airway resistance during normal tidal breathing. Data from these assessments were considered exploratory.

5 Change from baseline in mean daily morning and evening measurements of peak flow measured at 12 weeks, 26 weeks, and 52 weeks in all children able to perform peak flow maneuvers

6 Change from baseline in mean day and nighttime symptom scores and percentage of symptom-free days, symptom-free nights, and symptom-free 24-hours, each measured at 12 weeks, 26 weeks, and 52 weeks

7 Percentage of asthma-free days (AFD) measured at 12 weeks, 26 weeks, and 52 weeks. (An AFD was defined as a 24-hour period in which there were no day or nighttime asthma symptoms and no use of rescue medication.)

Pharmacokinetics variables were not evaluated in this study.

**Quality of life and health economics**

Health-related quality of life (HRQOL) was evaluated using the following questionnaires that were self-administered by each subject's caregiver: Child Health Questionnaire Parent Form-50 (CHQ-PF50); Children's Health Survey for Asthma (CHSA); Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ); and the Caregiver's Global Assessment. Additionally, each subject's physician responded to the Physician's Global Assessment questionnaire. The following HRQOL endpoints were considered: change from baseline in domain scores from the CHQ-PF50 and CHSA at 12 and 26 weeks or at last visit; change from baseline in total score for PACQLQ at 12 and 26 weeks or at last visit; and comparisons of 12- and 52-week global assessments (by caregivers and physicians) between treatments (PULMICORT RESPULES versus Singulair).
The following direct medical-resource utilization variables were evaluated every 2 weeks in terms of number of events due to asthma: hospitalizations; days hospitalized among subjects hospitalized; emergency room visits; urgent care visits; unscheduled healthcare provider visits; and unscheduled healthcare provider phone calls. Additionally, oral and parenteral steroid use and additional asthma medication use were recorded at each scheduled visit, and rescue medication use was recorded daily. Several indirect economic variables were documented as well, including child days lost from school/camp/day care/play group; caregiver days with interrupted activity, excluding sleep; caregiver days of lost work; and caregiver nights of interrupted sleep—all in terms of number of occurrences due to asthma.

**Safety**

Safety was measured relative to stadiometric (height) measurements, incidence and severity of adverse events (AEs), incidence of AEs described as drug related, incidence of serious adverse events (SAEs), changes in vital signs, physical examination findings, concomitant medication use, and incidence of early withdrawal (study discontinuation) because of AEs or other events that fulfilled withdrawal criteria.

**Statistical methods**

Time-to-event analyses were used to test for differences between PULMICORT RESPULES and SINGULAIR for times to 1$^{st}$ additional asthma medication. The analysis of continuous efficacy and quality of life (QOL) variables used a 2-way analysis of covariance (ANCOVA) model, with treatment group as the independent variable of interest, age group (2 to 5 years old or 6 to 8 years old) as the stratification factor, and

baseline value (variable specific) as the covariate. The treatment group least squares mean (with standard deviation) and the 95% confidence interval were determined for comparisons between PULMICORT RESPULES and SINGULAIR. Two-sided p-values for treatment-group comparisons at the significance level of 0.05 were determined for all significance testing. Health economic variables related to direct and indirect medical-resource utilization were summarized without formal statistical analysis. Results of airway resistance testing by means of impulse oscillometry were considered exploratory and thus were summarized without a formal statistical analysis.
Safety variables were summarized descriptively and without formal statistical analysis.

## Subject population

Baseline demographics and disease characteristics for subjects are presented in Table S1.

**Table S1 Baseline demographics and disease characteristics: safety analysis set**

| | n (%) | | |
|---|---|---|---|
| | **PULM RESP** | **Singulair** | **Total** |
| **Demographic characteristic** | **(N=197)** | **(N=197)** | **(N=394)** |
| Sex | | | |
| Female | 75 (38.1) | 79 (40.1) | 154 (39.1) |
| Male | 122 (61.9) | 118 (59.9) | 240 (60.9) |
| Race | | | |
| Caucasian | 162 (82.2) | 164 (83.2) | 326 (82.7) |
| Black | 27 (13.7) | 29 (14.7) | 56 (14.2) |
| Oriental | 3 (1.5) | 3 (1.5) | 6 (1.5) |
| Other | 5 (2.5) | 1 (0.5) | 6 (1.5) |
| Age group | | | |
| 0 to 1 year | 2 (1.0) | 0 | 2 (0.5) |
| 2 to 5 years | 129 (65.5) | 126 (64.0) | 255 (64.7) |
| 6 to 8 years | 66 (33.5) | 71 (36.0) | 137 (34.8) |
| Age (years) | | | |
| Mean (SD) | 4.62 (1.97) | 4.73 (1.94) | 4.67 (1.95) |
| Range | 1 to 8 | 2 to 8 | 1 to 8 |
| Average asthma score AM | | | |
| Mean (SD) | 1.30 (0.5) | 1.30 (0.45) | 1.30 (0.48) |
| Range | 0 to 2.76 | 0.29 to 2.67 | 0 to 2.76 |
| Average asthma score PM | | | |
| Mean (SD) | 1.24 (0.52) | 1.17 (0.54) | 1.20 (0.53) |
| Range | 0 to 2.85 | 0 to 3.00 | 0 to 3.00 |
| Average rescue medication use (24 hr) | | | |
| Mean (SD) | 1.69 (1.37) | 1.75 (1.33) | 1.72 (1.35) |

**Table S1 Baseline demographics and disease characteristics: safety analysis set**

| | n (%) | | |
|---|---|---|---|
| **Demographic characteristic** | **PULM RESP (N=197)** | **Singulair (N=197)** | **Total (N=394)** |
| Range | 0 to 9.33 | 0.15 to 7 | 0 to 9.33 |
| Mean ICS daily dose taken prior to treatment (µg) | 310.5 | 392.08 | 352.12 |
| Subjects who used ICS Prior to Treatment | 25 (12.7) | 24 (12.2) | 49 (12.4) |
| Subjects who used LABA Prior to Treatment | 6 (3.0) | 4 (2.0) | 10 (2.5) |

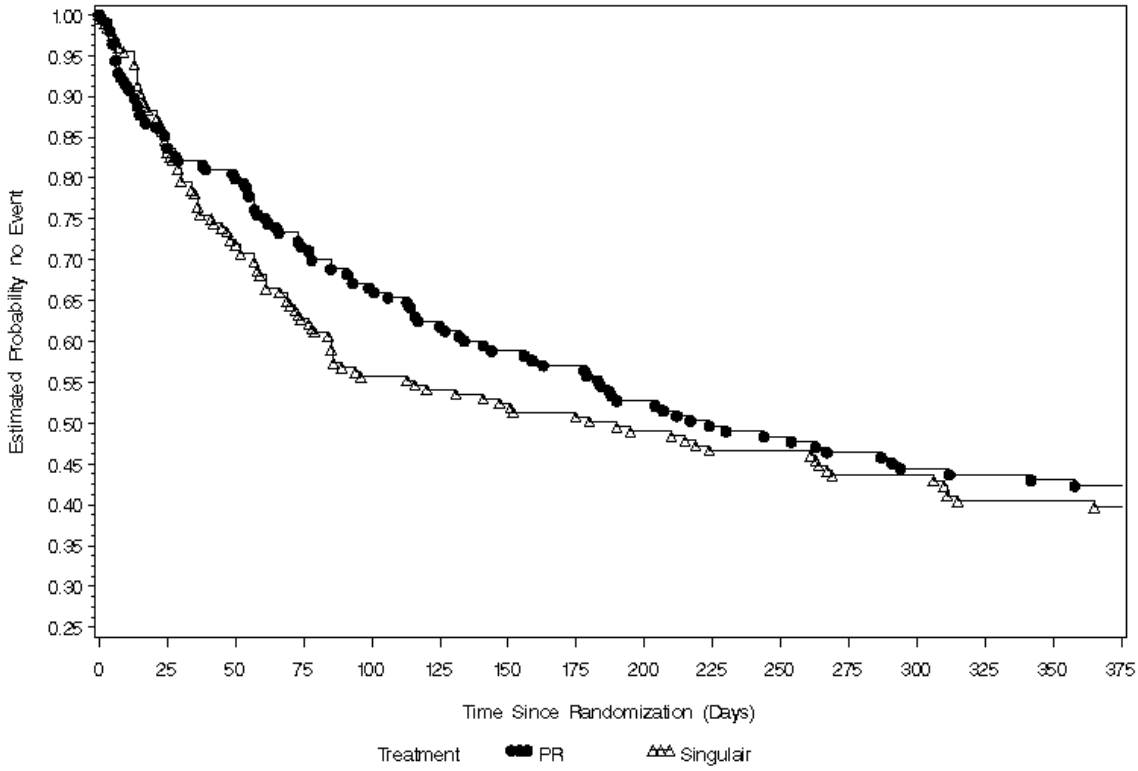
ICS Inhaled corticosteroid; LABA Long-acting beta agonist; PULM RESP PULMICORT RESPULES

The characteristics of the population of asthmatic subjects enrolled in this study were consistent across both treatment groups and adequately representative of the target pediatric patient population with mild persistent asthma.
Subjects in the treatment groups were comparable for all pre-study variables and adhered to the study protocol to similar degrees during the study. Subjects generally complied with their study medication regimen as assessed by their daily diary entries. Concomitant medication use was consistent across treatment groups and typical for this patient population.

## Efficacy and pharmacokinetic results

Figure S1 shows the Kaplan-Meier plot of time to 1st additional asthma medication at 52 weeks in both PULMICORT RESPULES and Singulair subjects while Table S2 shows the survival analysis based on time to use of first additional asthma medication at 52 weeks.

**Figure S1 Kaplan-Meier plot of time to 1st additional asthma medication at 52 weeks**




PR PULMICORT RESPULES

**Table S2 Survival analysis based on time to use of first additional asthma medication at 52 weeks: Efficacy Analysis Set**

| | n (%) of subjects with at least 1 course of step-up or OCS therapy | | |
|---|---|---|---|
| | **PULM RESP (N=196)** | **Singulair (N=197)** | **Total (N=393)** |
| | 102 (52.0) | 112 (56.9) | 214 (54.5) |
| **PULM RESP vs Singulair** | | | |
| Log-Rank Test p=0.285 | | | |

OCS Oral corticosteroid; PULM RESP PULMICORT RESPULES

Analysis of the primary efficacy variable of time to 1st additional asthma medication, in the form of either step-up PULMICORT RESPULES or oral steroids, at 52 weeks provided results indicating:

- The time to first use of additional asthma medication, step-up or OCS therapy, was similar between the PULMICORT RESPULES and Singulair subjects with no statistically significant differences between the treatment groups at one year.

The analysis of secondary variables provided the following results:

- The time to first use of additional asthma medicine was notably greater at 12 weeks (unadjusted p-value=0.050) and numerically greater at 26 weeks (unadjusted p-value=0.146) for the PULMICORT RESPULES group compared to the Singulair group.

- The total number of courses of additional asthma medication over 52 weeks (step-up or OCS) was notably reduced for subjects on PULMICORT RESPULES compared to those on Singulair (unadjusted p-value= 0.034).

- There were nominally statistically significant improvements from baseline in the PULMICORT RESPULES group compared to the Singulair group at 12 weeks for both AM PEF (difference=7.0 L/min, unadjusted p-value=0.007) and PM PEF (difference= 7.4 L/min, unadjusted p-value=0.005).

- Physicians reported a nominally statistically significant greater improvement in control of asthma symptoms and in their ability to manage their subject's asthma compared to baseline in PULMICORT RESPULES subjects compared to Singulair subjects at Week 12 (unadjusted p-value=0.001 and p-value=0.0164, respectively), weeks 1 through 12 (unadjusted p-value=0.001 and p-value=0.0142, respectively), and at the end of treatment (unadjusted p-value=0.0171 and p-value=0.0075, respectively).

- Caregivers reported a nominally statistically significant greater improvement in their ability to manage the subject's asthma symptoms and in their child's health compared to baseline in PULMICORT RESPULES subjects compared to Singulair subjects at Week 12 (unadjusted p value=0.0139 and p-value=0.0024, respectively), at weeks 1 through 12 (unadjusted p value=0.0126 and p-value=0.0027, respectively), and at the end of treatment (unadjusted p-value=0. 067 and p-value=0. 0524, respectively).

- For the CHSA results, a nominally statistically significant greater improvement in the subject's emotional health compared to baseline was observed in Singulair subjects compared to PULMICORT RESPULES subjects at week 12 (unadjusted p-value<0.001), weeks 1 through 12 (unadjusted p-value<0.001), and at the end of treatment (unadjusted p-value<0.001). This difference was predominately driven by questions pertaining to the subjects' frustration with having to rely on asthma treatments.

- Other efficacy variables generally demonstrated a numerical difference favoring PULMICORT RESPULES.

## Safety results

Table S3 presents a categorical overview of AEs by treatment group.

**Table S3 Number (%) of subjects who had adverse events in any category and number of adverse events per category, by treatment group: Safety Analysis Set**

| Category | Treatment | | |
|---|---|---|---|
| | PULM RESP (n=197) | Singulair (n=197) | Total (n=394) |
| **Subjects, number (%)[a]** | | | |
| With any adverse event (AE) | 154 (78.2%) | 167 (84.8%) | 321 (81.5%) |
| With serious AEs (SAEs) | 4 (2.0%) | 8 (4.1%) | 12 (3.0%) |
| SAEs leading to death | 0 | 0 | 0 |
| SAEs not leading to death | 4 (2.0%) | 8 (4.1%) | 12 (3.0%) |
| With AEs that led to withdrawal (DAEs) | 2 (1.0%) | 5 (2.5%) | 7 (1.8%) |
| With other significant AEs | 0 | 0 | 0 |
| **Events, number[b]** | | | |
| All AEs | 707 | 809 | 1516 |
| Intensity: Mild | 424 | 491 | 915 |
| Intensity: Moderate | 263 | 265 | 528 |
| Intensity: Severe | 20 | 53 | 73 |
| Intensity: Not Recorded | 0 | 0 | 0 |
| SAEs | 5 | 10 | 15 |
| Drug-related AEs | 2 | 5 | 7 |
| Other significant AEs | 0 | 0 | 0 |

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Events are counted by individual occurrence, therefore multiple occurrences of the same adverse event all get counted.

AE Adverse event; SAE Serious adverse event; DAE Adverse event caused subject to discontinue study.

Of 395 subjects randomized to treatment, 394 were included in the safety analysis set: 197 were treated with PULMICORT RESPULES and 197 were treated with Singulair. A slightly higher percentage of subjects in the Singulair group compared to the PULMICORT RESPULES group completed the study. Exposure to study medication among the Singulair subjects was slightly higher than that for PULMICORT RESPULES subjects.

Of the 394 subjects in the safety analysis set, 321 (81.5%) reported AEs: 154 (78.2%) treated with PULMICORT RESPULES and 167 (84.8%) treated with Singulair. There were 4 subjects with SAEs in the PULMICORT RESPULES treatment group and 8 subjects with SAEs in the Singulair treatment group. There were 2 DAEs reported in subjects treated with PULMICORT RESPULES and 5 DAEs reported in subjects treated with Singulair. No deaths or OAEs occurred during this study.

There were no clinically important vital sign or physical examination findings in either the PULMICORT RESPULES or Singulair treatment groups.

**Date of the report**

13 January 2006