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Drug product:	PULMICORT RESPULES®	**SYNOPSIS**	
Drug substance(s):	Budesonide		
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A Randomized, Partly Blinded, Multicenter, Parallel Study Comparing the Efficacy and Safety of PULMICORT RESPULES® (budesonide inhalation suspension) at 0.5 mg qd, 1.0 mg qd, 1.0 mg bid, 2.0 mg bid and PULMICORT TURBUHALER® (budesonide) at 400 mcg bid in Adolescents (12 Years of Age and Older) and Adults with Moderate to Severe Asthma

International co-ordinating investigator

None.

Study center(s)

This study was initiated at 80 centers in the United States, 70 of whom randomized subjects.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	8 May 2003	Phase III
Last subject completed	4 January 2005	

Objectives

The primary objective of this study was to compare the efficacy of PULMICORT RESPULES®[1] at 0.5 mg once daily (qd) and 2.0 mg twice daily (bid) in subjects with moderate to severe asthma 12 years of age and older. The primary variable is the change from baseline in forced expiratory volume at 1 second (FEV_1) at the end of treatment.
Secondary objectives were to compare the efficacy and safety of PULMICORT RESPULES at 0.5 mg qd with 1.0 mg qd and 1.0 mg bid and to assess the steady state pharmacokinetics of PULMICORT RESPULES at doses of 0.5 mg qd, 1.0 mg qd, 1.0 mg

[1] PULMICORT RESPULES is a trademark of the AstraZeneca group of companies.

bid, 2.0 mg bid and PULMICORT TURBUHALER®[2] at 400 μg bid, in asthmatic subjects 12 years and older. PULMICORT TURBUHALER at 400 μg bid was included as an active reference for the comparison of efficacy and safety.

Study design

This was a 12-week, randomized, partly blinded, parallel-group study. The study was divided into 3 phases: a 14- to 21-day run-in period, a 12-week partly blinded treatment period, and a 2-week safety follow-up period. All asthma medications, including inhaled corticosteroids (ICS), were discontinued at the end of the run-in period for the duration of the study. Rescue medication use (albuterol) was allowed during the randomized treatment period. A subset of approximately 24 subjects per treatment group was targeted for inclusion in the pharmacokinetic (PK) analyses. Blood sampling was collected before and for up 720 minutes after drug administration at Visit 3.

Target subject population and sample size

Male or female subjects 12 years of age and older with moderate to severe asthma as defined by daily requirements of ICS (received for at least 30 days prior to Visit 1) and a FEV_1 of 45% to 90% of predicted normal at screening and FEV_1 of 45% to 85% of predicted normal at Visit 2 were eligible for inclusion in this study. Demonstration of reversibility of FEV_1 of ≥12% was required at Visits 1 or 2.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Each Respules ampule contained 0.25 mg/mL in 2.0 mL of budesonide nebulizing suspension. Respules ampules were provided using batch numbers PN10017395, PN10018356, PN10018585, PN10018357, PN10022548, PN10024315, and PN10024495. Matching placebo Respules ampules, containing excipients only, were provided using batch numbers PN10017395, PN10018356, PN10018585, PN10018357, PN10022548, PN10024315, and PN10024495. Batch numbers for PULMICORT TURBUHALER 400 μg bid, delivered as 200 μg per inhalation, were BN2000044360, BN2000047078, and BN2000054268.
Albuterol, delivered by pMDI, was used as rescue medication on an as-needed basis, during both the run-in and randomized treatment periods. Commercially available albuterol (90 μg/actuation) was provided by AstraZeneca.

Duration of treatment

12 weeks

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: The primary variable was the change from baseline FEV_1 to the last FEV_1 value recorded at the end of treatment.

- Key secondary variables included the change from baseline in FEV_1, forced vital capacity (FVC) and forced expiratory flow expired during the middle half of exhalation ($FEF_{25-75\%}$) at each visit and to the treatment period average;

[2] PULMICORT TURBUHALER is a trademark of the AstraZeneca group of companies.

percentage of symptom-free days, symptom-free nights, symptom-free 24-hour periods, awakening free nights, rescue medication free 24-hour periods, and asthma control days at each 2-week interval (ie, biweekly), at the end of treatment (last 2 weeks of the treatment period), and averaged over the treatment period; change from baseline in mean daily morning and evening peak expiratory flow (PEF), mean daytime and nighttime asthma symptom scores, and total rescue medication use biweekly, at the end of treatment (last 2 weeks of the treatment period), and averaged over the treatment period; and incidence of predefined asthma events and time to predefined asthma events over the treatment period.

- Pharmacokinetic parameters included area under the curve (AUC), AUC_{0-t}, maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life ($T_{1/2}$), and mean residence time (MRT).

Safety

Safety was measured relative to the incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to study discontinuation (DAEs), and other significant AEs (OAEs) and changes from baseline in clinical laboratory test results, vital signs, and physical examination findings.

Statistical methods

The efficacy analysis set (EAS) included data from all randomized subjects who took at least 1 dose of study medication and provided data after randomization for at least 1 efficacy variable. For the primary analysis, FEV_1 was analyzed as a change from baseline (Visit 2) to the final treatment period value using an analysis of covariance (ANCOVA) model with treatment and center as study factors and baseline FEV_1 as a covariate using a last observation carried forward (LOCF) approach. To maintain the experiment-wise Type I error rate at no greater than 5%, a step-down approach to hypothesis testing among treatment groups (closed test procedure) and the interpretation of p-values was taken. The primary inferential statistical comparison was between the PULMICORT RESPULES 0.5 mg qd and 2.0 mg bid groups. For comparisons involving the PULMICORT TURBUHALER group, no inferential statistical testing was done, but rather 2-sided 95% confidence intervals (CI) on differences with each of the PULMICORT RESPULES groups. For all secondary variables, nominal p-values for all pairwise comparisons were presented with the primary comparison being between the 0.5 mg qd and 2.0 mg bid PULMICORT RESPULES groups. The proportion of subjects with a predefined asthma event was compared between treatment groups using Fisher's exact test, and time to a predefined asthma event analyzed using a log-rank test for treatment pairs. For all diary variables, changes from baseline were compared among treatment groups using an ANCOVA model with change from baseline as the dependent variable, treatment and center as main effects, and baseline as the covariate.

Pharmacokinetic parameters (AUC, C_{max} and AUC_{0-t}) were compared between treatment regimens using a multiplicative ANOVA model with single factor treatment, and 90% 2-sided CI were constructed for the differences between the 2 PULMICORT RESPULES bid groups, the 2 PULMICORT RESPULES qd groups, and the PULMICORT RESPULES 1.0 mg bid and PULMICORT TURBUHALER groups.

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Subject population

A total of 760 subjects were randomized at 70 centers to 1 of 5 treatment groups, with the number of subjects well balanced across treatment groups. One subject was enrolled at 2 study centers and randomized to receive PULMICORT RESPULES 1.0 mg bid at both centers. Data from both treatment exposures were excluded from all analyses. Thus, the all randomized population includes a total of 758 subjects. All subjects who took at least 1 dose of study medication were included in the safety analysis set. In addition, all treated subjects who contributed data for at least 1 efficacy endpoint were included in the EAS. A total of 93 subjects had at least 1 protocol deviation that prompted exclusion from the PP analysis set. Demographic and baseline characteristics of the EAS were generally similar across treatment groups. Within each treatment group, approximately two-thirds of subjects were female (58.4% to 66.0%) and most subjects (81.3%) were Caucasian. Across all randomized subjects, the mean age was 40.6 years and most subjects were between 17 and 64 years of age (88.0%). The mean FEV_1 as a percent of predicted normal ranged from 69.6% to 71.2% in the 5 treatment groups and mean baseline FEV_1 was 2.33 L across all subjects. Mean daytime and nighttime asthma symptom scores during the 7-day period immediately preceding randomization ranged from 1.02 to 1.11 and from 0.82 to 0.92 among the 5 treatment groups, respectively. With the exception of 1 subject in the PULMICORT RESPULES 1.0 mg bid group, all subjects received an ICS medication during the 14- to 21-day run-in period, the most common of which was fluticasone propionate, used by approximately three-quarters of subjects in each treatment group at an average daily dose of 508.0 to 560.7 µg/day.

The proportion of subjects who discontinued treatment prematurely was lowest in the PULMICORT TURBUHALER (21.3%) and PULMICORT RESPULES 0.5 mg qd (26.2%) groups and ranged from 32.0% to 39.5% among the remaining 3 groups. The most common reason for discontinuation was development of study-specific discontinuation criteria (16.2%) and the proportion of subjects discontinuing for this reason was generally comparable between the 5 treatment groups. A higher percentage of subjects in the PULMICORT RESPULES 1.0 mg bid and 2.0 mg bid groups (9.4% and 15.6%) compared with the other 3 groups (1.9% to 5.4%) discontinued the study prematurely because they were not willing to continue.

Efficacy and pharmacokinetic results

The primary analysis of predose FEV_1 was based on the change from baseline to the last value during the randomized treatment period in the EAS. As seen in Table S1, the primary treatment group comparison between the PULMICORT RESPULES 0.5 mg qd and 2.0 mg bid groups was not statistically significant for the primary variable (p=0.834). In addition, no statistically significant differences in adjusted mean changes from baseline at any timepoint were observed for any of the PFT variables (FEV_1, FVC, $FEF_{25-75\%}$) between the 2.0 mg bid and 0.5 mg qd groups (p>0.05).

Table S1 Change from baseline at end of treatment (LOCF) in FEV_1 (efficacy analysis set)

	Treatment group				
FEV_1 (%)	**PRESP 0.5 mg qd**	**PRESP 1.0 mg qd**	**PRESP 1.0 mg bid**	**PRESP 2.0 mg bid**	**PTBH 400 µg bid**
N	140	135	145	129	151

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Table S1 Change from baseline at end of treatment (LOCF) in FEV_1 (efficacy analysis set)

	Treatment group				
FEV_1 (%)	**PRESP 0.5 mg qd**	**PRESP 1.0 mg qd**	**PRESP 1.0 mg bid**	**PRESP 2.0 mg bid**	**PTBH 400 µg bid**
Baseline, Mean (SE)	2.37 (0.05)	2.30 (0.05)	2.32 (0.05)	2.30 (0.06)	2.35 (0.05)
Adjusted mean change (SE) from BL	0.02 (0.03)	0.01 (0.03)	0.08 (0.03)	0.01 (0.03)	0.12 (0.03)
Adjusted change from BL vs PRESP 0.5 mg qd, p-value	--	0.899	0.122	0.834	--
Adjusted change from BL vs PTBH 400 µg bid, 95% CI	0.03, 0.18	-0.19, -0.03	-0.12, 0.03	-0.19, -0.03	--

bid twice daily; BL baseline; CI confidence interval; FEV_1 forced expiratory volume in the 1st second; LOCF last observation carried forward; PRESP PULMICORT RESPULES; qd once daily; PTBH PULMICORT TURBUHALER; SE standard error.

In each of the PULMICORT RESPULES treatment groups, mean increases from baseline at the end of treatment were observed in the percentage of symptom-free days, symptom-free nights, symptom-free 24-hour periods, rescue medication free 24-hour periods, and asthma control days, with the largest mean increases observed for the PULMICORT RESPULES 2.0 mg bid group. Small mean reductions in daytime and nighttime asthma symptom scores and rescue medication use, and mean increases in morning and evening PEF were seen in all treatment groups at the end of treatment. None of the comparisons between the PULMICORT RESPULES 0.5 mg qd and 2.0 mg bid groups were statistically significant ($p>0.05$) for any of the secondary efficacy variables. The proportion of subjects with a predefined asthma event was generally comparable among the PULMICORT RESPULES (17.5% to 21.8%) and PULMICORT TURBUHALER (17.4%) groups.

Among the 4 PULMICORT RESPULES groups, systemic exposure to budesonide increased with increasing daily dose, although the increase was slightly less than dose proportional with a doubling of the dose within the qd (0.5 vs. 1.0 mg) and bid (1.0 vs. 2.0 mg) regimens. The systemic exposure (AUC) to budesonide following dosing with PULMICORT RESPULES 1.0 mg bid was approximately 12% greater than that observed following PULMICORT TURBUHALER 400 µg bid.

Safety results

During the randomized treatment period, the overall percentage of subjects with at least 1 AE was lower in the PULMICORT RESPULES 0.5 mg qd and 2.0 mg bid groups (45.0% and 44.9%, respectively) compared with the PULMICORT RESPULES 1.0 mg qd (53.7%), 1.0 mg bid (55.0%), and PULMICORT TURBUHALER (51.0%) groups. Across all treatment groups, the majority of AEs were mild to moderate in intensity, and the most commonly reported AEs were upper respiratory tract infection, headache, and nasopharyngitis. No dose-related pattern was observed among the PULMICORT RESPULES groups with respect to the incidence of common AEs. The overall incidence of drug-related AEs as judged by the investigator was 6.6% during the randomized treatment period.

No subject died or experienced an OAE and few (0.8%) had an SAE. Similar proportions of subjects in the 4 PULMICORT RESPULES groups discontinued treatment prematurely due to an AE. The majority of DAEs were mild to moderate in intensity, and approximately one-half were judged by the investigator to be unrelated to study medication. No subject in the PULMICORT TURBUHALER 400 μg bid group discontinued treatment prematurely due to an AE. No clinically meaningful changes from baseline were noted for any laboratory or vital sign parameter for any treatment group and no new safety concerns were identified.

Date of the report

19 October 2005