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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00174733
Drug substance(s):	ciclesonide	**Study Code:**	EFC6163 (XRP1526B/3030)
		Date:	27 March 2007

Title of the study:	A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of ciclesonide metered-dose inhaler at a daily dose of 160 µg administered for 12 weeks either in a once-daily regimen in the morning (160 µg q.d. AM) or in a twice-daily regimen (80 µg b.i.d.) in adults and adolescents with mild to moderate persistent asthma treated previously with inhaled corticosteroids.
Investigator(s):	Andrew Pedinoff, MD Princeton Center for Clinical Research - Skillman, NJ, USA
Study center(s):	38 centers in the United States of America
Publications:	None
Study period: Date first patient/subject enrolled: 15 July 2005 Date last patient/subject completed: 3 February 2006	**Phase of development:** Phase III
Objectives:	**Primary objective**: To investigate the efficacy of ciclesonide, compared to placebo, at a daily dose of 160 µg administered for 12 weeks either in a once-daily regimen in the morning (160 µg q.d. AM) or in a twice-daily regimen (80 µg b.i.d.) in adults and adolescents with mild to moderate persistent asthma treated previously with inhaled corticosteroids (ICS). **Secondary objective**: To investigate the safety of ciclesonide, compared to placebo, at a daily dose of 160 µg administered for 12 weeks either in a once-daily regimen in the morning (160 µg q.d. AM) or in a twice-daily regimen (80 µg b.i.d.) in adults and adolescents with mild to moderate persistent asthma treated previously with ICS.
Methodology:	Randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of ciclesonide metered-dose inhaler (MDI) at a daily dose of 160 µg administered for 12 weeks either in a once-daily regimen in the morning (160 µg q.d. AM) or in a twice-daily regimen (80 µg b.i.d.) in adults and adolescents with mild to moderate persistent asthma treated previously with ICS.
Number of patients/subjects:	Planned: 447 (149 in each of the 3 treatment groups) Randomized: 456 Treated: 456

Diagnosis and criteria for inclusion:	Males or females ≥12 years of age, with a history of persistent bronchial asthma for ≥6 months prior to screening, documented use of ICS monotherapy for ≥1 month prior to screening or documented use of ICS/long-acting β_2-agonist (LABA) combination therapy for ≥1 month prior to screening; at screening and immediately prior to randomization, forced expiratory volume in 1 second (FEV_1) of ≥60% to ≤90% of predicted normal (patients previously on ICS monotherapy) or FEV_1 of ≥70% to ≤95% of predicted normal (patients previously on ICS/LABA combination therapy). During a 7- to 14-day screening period, patients continued to take their usual ICS monotherapy (ie, ≤440 µg/day fluticasone propionate or equivalent) or their usual ICS/long-acting β_2-agonist (LABA) combination therapy (ie, ≤200/100 µg/day Advair® [fluticasone propionate/salmeterol]).
Investigational product: Dose: Administration:	Ciclesonide MDI 160 µg/day 160 µg q.d. in the morning or 80 µg b.i.d. (ie, in the morning and in the evening)
Duration of treatment: 12 weeks	**Duration of observation:** 14 weeks
Reference therapy: Dose: Administration:	Placebo ciclesonide MDI NA b.i.d.
Criteria for evaluation: Efficacy:	**Primary efficacy data**: FEV_1 (centralized spirometry) **Key secondary efficacy data**: morning peak expiratory flow (AM PEF), albuterol use, and total asthma symptom score **Additional efficacy data**: rate of and time to withdrawal due to lack of efficacy or asthma exacerbation, rate of and time to withdrawal due to any reason, evening peak expiratory flow (PM PEF), and nighttime awakenings due to asthma requiring treatment with albuterol, forced vital capacity (FVC), forced mid-expiratory flow ($FEF_{25-75\%}$), asthma control (based on diary entries for AM and PM asthma symptom score, nighttime awakenings, and number of albuterol puffs)
Safety:	Adverse events, standard clinical laboratory, vital signs, and physical examinations
Statistical methods:	**Efficacy**: The primary efficacy analysis was an intent-to-treat (ITT) analysis of covariance (ANCOVA) of the change in FEV_1 from baseline to Week 12 (Visit 10, or early termination, using the last observation carried forward (LOCF) method), with factors for treatment, pooled center, and gender, and with baseline value (FEV_1 on Day 1) and age as covariates. To adjust for multiplicity, a closed testing procedure was used. Both ciclesonide treatment groups were compared with placebo, each at the 2-sided 0.05 level of significance.

Statistical methods (cont'd):

The key secondary efficacy endpoints were the changes from baseline to Week 12 or early termination (LOCF) in AM PEF, albuterol use, and total asthma symptom score. For analyses of the key secondary efficacy endpoints, for the purpose of claiming formal statistical significance, the type 1 error rate was controlled at the pairwise comparison level. Ciclesonide MDI treatment groups that tested statistically significant vs placebo MDI for the primary endpoint were each tested at the 0.025 (1-sided) level of significance for the secondary efficacy endpoints in a sequential manner, starting with AM PEF. If the comparison was statistically significant, then the comparison was tested for albuterol use, followed by total asthma symptom score. Even if a comparison for 1 of the key secondary endpoints was not statistically significant, the results of the subsequent comparisons for the key secondary endpoints are presented for descriptive purposes.

Assuming a standard deviation for the change from baseline to Week 12 in FEV_1 of 0.45 L (based on previous ciclesonide MDI studies), a sample size of 149 patients in each treatment group was required to provide 90% power to detect a difference of 0.17 L for a pairwise treatment comparison, using a t-test and a 2-sided 0.05 level of significance.

Safety: Safety variables (adverse events, standard laboratory safety, vital signs) were summarized using descriptive statistics.

Summary:

Data sets analyzed:

The numbers of patients in each analysis population were comparable across treatment groups, as summarized in the table below.

Data sets analyzed

	Number (%) of patients			
		Ciclesonide MDI		
Population	**Placebo MDI**	**160 µg q.d. AM**	**80 µg b.i.d.**	**Overall**
Randomized	152 (100.0)	152 (100.0)	152 (100.0)	456 (100.0)
Safety	152 (100.0)	152 (100.0)	152 (100.0)	456 (100.0)
ITT	147 (96.7)	150 (98.7)	149 (98.0)	446 (97.8)
Per-protocol	142 (93.4)	147 (96.7)	149 (98.0)	438 (96.1)

Efficacy results:

In the ITT population, both dosing regimens of ciclesonide MDI (160 µg q.d. AM and 80 µg b.i.d.) provided overall better asthma control compared to placebo MDI, as summarized for the primary and key secondary efficacy variables in the table below.

Summary of treatment differences of ciclesonide MDI versus placebo MDI at Week 12 (LOCF) - ITT population

Variable	**Treatment difference at Week 12 (LOCF) versus placebo MDI (LS mean [95% CI] *P* value)**	
	Cic MDI 160 µg q.d. AM	**Cic MDI 80 µg b.i.d.**
Primary efficacy variable		
FEV_1 (L)	0.14 (0.06; 0.22) 0.0006	0.19 (0.11; 0.27) <0.0001
Key secondary efficacy variables		
AM PEF (L/min)	7.05 (-0.76; 14.86) 0.0769	8.39 (0.60; 16.19) 0.0349
Albuterol use (puffs/day)	-0.60 (-0.91; -0.28) 0.0002	-0.64 (-0.95; -0.33) <0.0001
Total asthma symptom score (0-8 scale)	-0.38 (-0.60; -0.15) 0.0010	-0.37 (-0.60; -0.15) 0.0011

Cic = ciclesonide; LS = least squares; CI = confidence interval

Efficacy results (cont'd):

Both ciclesonide MDI regimens (q.d. AM and b.i.d.) provided significantly better asthma control compared to placebo MDI in terms of change in FEV_1 from baseline to Week 12 (LOCF). A treatment difference in FEV_1 between both ciclesonide MDI groups and placebo MDI was observed as early as Week 1 and was maintained throughout the 12-week treatment period. Consistency of treatment effect was seen across the subgroups of gender, age, race, baseline FEV_1 percent predicted and pooled center, as assessed by treatment by subgroup statistical interaction tests.

Both ciclesonide MDI regimens provided better asthma control compared to placebo MDI for 2 of the 3 key secondary efficacy variables (change from baseline to Week 12 [LOCF] in albuterol use and total asthma symptom score). For AM PEF, however, the treatment difference between the ciclesonide MDI 160 µg q.d. AM group and placebo MDI (7.05 L/min) was not statistically significant (*P*=0.0769) (Thus, based on the sequential testing algorithm, formal statistical significance cannot be claimed for ciclesonide MDI 160 µg q.d. AM vs. placebo for albuterol use and total asthma symptom score).

A higher percentage of patients was withdrawn from the study due to lack of efficacy or asthma exacerbation in the placebo MDI group (21.8%) than in both ciclesonide MDI groups (160 q.d. AM: 5.3%; 80 µg b.i.d.: 4.0%).

Results from additional secondary variables (including PM PEF, nighttime awakenings due to asthma requiring treatment with albuterol, FVC, $FEF_{25-75\%}$, percentages of asthma-controlled days, symptom-free days, and nights with nighttime awakenings during the 12-week treatment period) were generally consistent with those of the primary and key secondary endpoints in terms of better asthma control with ciclesonide MDI.

Overall, in patients with mild to moderate asthma treated previously with either ICS monotherapy or ICS/LABA combination therapy, ciclesonide MDI 160 µg q.d. AM and 80 µg b.i.d. treatments were both able to provide maintenance treatment of asthma, with clinically and statistically significant improvements versus placebo in FEV_1. Consistent with the results for the primary endpoint, the findings from key secondary efficacy endpoints and the additional efficacy endpoints favored the ciclesonide groups over placebo.

Safety results:

A summary of treatment-emergent adverse events (TEAEs) by treatment group is presented in the table below.

	Number (%) of patients			
		Ciclesonide MDI		
TEAE categories	**Placebo MDI (N=152)**	**160 µg q.d. AM (N=152)**	**80 µg b.i.d. (N=152)**	**Total (N=304)**
All TEAEs	84 (55.3)	88 (57.9)	79 (52.0)	167 (54.9)
All possibly related TEAEs	13 (8.6)	5 (3.3)	2 (1.3)	7 (2.3)
Serious TEAEs	1 (0.7)	0 (0.0)	3 (2.0)	3 (1.0)
Possibly related serious TEAEs	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Permanent discontinuation of study medication due to TEAE	24 (15.8)	7 (4.6)	8 (5.3)	15 (4.9)

MDI = metered-dose inhaler.

Safety results (cont'd):	The safety profiles for ciclesonide MDI administered at a daily dose of 160 µg either as 160 µg q.d. AM or as 80 µg b.i.d. were generally comparable to the safety profile of placebo MDI. The percentage of patients who experienced at least 1 TEAE was comparable across treatment groups (placebo MDI: 55.3%; ciclesonide MDI 160 µg q.d. AM: 57.9%; ciclesonide MDI 80 µg b.i.d.: 52.0%). The frequencies of individual TEAEs were generally comparable across treatment groups except for asthma (more frequent in the placebo MDI group [17.8%] than in the ciclesonide MDI groups [160 µg q.d. AM: 4.6%; 80 µg b.i.d.: 3.3%]) and nasopharyngitis (more frequent in the ciclesonide MDI groups [160 µg q.d. AM: 12.5%; 80 µg b.i.d.: 9.2%] than in the placebo MDI group [5.9%]). The most frequent TEAEs (occurring in at least 6 patients [ie, at least 2% of patients] in the total ciclesonide MDI group) were nasopharyngitis, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, asthma, headache, cough, gastroenteritis viral, and nasal congestion. There were no deaths. Four serious TEAEs were reported by 4 patients in this study (placebo MDI: 1 patient with asthma; ciclesonide MDI 160 µg q.d. AM: 0 patients; ciclesonide MDI 80 µg b.i.d.: 1 patient with post procedural complication [after hernia repair], 1 patient with breast cancer in situ, and 1 patient with anemia). One of these serious TEAEs (asthma in the placebo MDI group) was considered by the investigator to be possibly related to study medication. The percentage of patients who had a TEAE leading to permanent discontinuation of study medication was higher in the placebo MDI group (15.8%) than in both ciclesonide MDI groups (160 µg q.d. AM: 4.6%; 80 µg b.i.d.: 5.3%), which was mostly accounted for by cases of asthma. The frequencies of local oropharyngeal TEAEs were comparable between the treatment groups. There were no signals of concern in any of the clinical laboratory data or in any of the vital signs or physical examination data.
Date of full report:	18 December 2006