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Sponsor / Company: sanofi-aventis	**Study Identifier:** NCT00174720
Drug substance(s): ciclesonide	**Study code:** EFC6164 (XRP1526B/3031)

Title of the study:

A multinational, 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 either in a once-daily in the morning regimen (160 µg q.d. AM) for 16 weeks or in a 160 µg q.d. AM regimen for 12 weeks preceded by a twice-daily regimen (80 µg b.i.d.) for 4 weeks, or in an 80 µg b.i.d. regimen for 16 weeks, in adults and adolescents with mild to moderate persistent asthma not treated with steroids

Study center(s): 139 centers in 11 countries (United States of America, Mexico, Puerto Rico, Costa Rica, Brazil, Chile, Poland, Russian Federation, Estonia, Latvia, Israel)

Study period:

Date first patient enrolled: 21-Sep-2005

Date last patient completed: 05-Feb-2007

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 16 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.), or in a 160 µg q.d. AM regimen for 12 weeks preceded by a twice-daily regimen (80 µg b.i.d.) for 4 weeks in adults and adolescents with mild to moderate persistent asthma not treated 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.), or in a 160 µg q.d. AM regimen for 12 weeks preceded by a twice-daily regimen (80 µg b.i.d.) for 4 weeks in adults and adolescents with mild to moderate persistent asthma not treated with ICS.

Methodology: randomized, double-blind, placebo-controlled, parallel-group study

Number of patients: Planned: 700; Randomized: 708; Treated: 700
Evaluated for efficacy: 691 (intent-to-treat), 671 (per-protocol); Evaluated for safety: 700

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; at screening and immediately prior to randomization, after an albuterol withhold of at least 6 hours, forced expiratory volume in 1 second (FEV_1) of ≥60% and ≤85% of predicted normal and a morning peak expiratory flow (AM PEF) of ≤95% of predicted normal; asthma therapy limited to bronchodilators alone for at least 1 month prior to screening.

Investigational product: ciclesonide metered-dose inhaler (MDI)

Dose: 160 µg/day
Administration:
- 160 µg q.d. in the morning for 16 weeks, or
- 80 µg b.i.d. (ie, in the morning and in the evening) for 4 weeks, followed by 160 µg q.d. in the morning for 12 weeks, or
- 80 µg b.i.d. (ie, in the morning and in the evening) for 16 weeks

Duration of treatment: 7- to 14-day screening period, 16-week double-blind treatment period

Duration of observation: Up to 20 weeks (including the 7- to 14-day screening period, the 16-week double-blind treatment period, and the 14-day follow-up period)

Reference therapy: placebo ciclesonide MDI
Dose: NA
Administration: b.i.d.

Criteria for evaluation:

Efficacy:

Primary efficacy data: Forced expiratory volume in 1 second (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), 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 scores, 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 intention-to-treat (ITT) analysis of covariance of the change in FEV_1 from baseline to the average of the Week 12 and 16 measurements, with factors for treatment, pooled center, and gender, and with baseline value (FEV_1 on Day 1) and age as covariates. The statistical comparison between the ciclesonide MDI treatment regimens and placebo MDI was performed in a stepwise fashion to control the Type I error, in the following order:

1. Ciclesonide MDI 80 µg b.i.d. was compared against placebo at $\alpha = 0.05$ (2-sided). If this test was statistically significant, it was concluded that ciclesonide MDI 80 µg b.i.d. was efficacious. Statistical testing then proceeded to Step 2.

2. The average of the ciclesonide MDI 160 µg q.d. AM and ciclesonide MDI 80 µg b.i.d./160 µg q.d. AM groups was compared against placebo at $\alpha = 0.05$ (2-sided). If this test was statistically significant, statistical testing then proceeded to Step 3. This step was included to ensure a closed testing procedure.

3. The ciclesonide MDI 160 µg q.d. AM group and the ciclesonide MDI 80 µg b.i.d./160 µg q.d. AM groups were compared against placebo, each at $\alpha = 0.05$ (2-sided).

The key secondary efficacy endpoints were the changes in AM PEF, albuterol use, and total asthma symptom score from baseline to Week 16 or early termination (using the last observation carried forward [LOCF] approach). To adjust for the presence of multiple key secondary efficacy endpoints, for the purpose of claiming formal statistical significance, the Type I error rate was controlled within each pairwise comparison. Ciclesonide MDI treatment groups that were statistically significant versus placebo MDI for the primary endpoint were each tested at the $\alpha = 0.025$ (1-sided) level of significance for the key 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.

Assuming a standard deviation of 0.43 L for a change from baseline to Week 12 in FEV_1 in steroid- naïve patients (based on previous ciclesonide MDI studies), a sample size of 175 patients in each treatment group was required to provide approximately 80% power to detect a difference of 0.13 L for a pairwise treatment comparison, using a t-test and a 2-sided significance level of $\alpha = 0.05$.

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

Summary:

Study population:

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 (µg)			
Population	Placebo MDI	160 q.d. AM	80 b.i.d./ 160 q.d. AM	80 b.i.d.	Overall
Randomized	178 (100.0)	178 (100.0)	177 (100.0)	175 (100.0)	708 (100.0)
Safety	178 (100.0)	176 (98.9)	173 (97.7)	173 (98.9)	700 (98.9)
ITT	177 (99.4)	173 (97.2)	171 (96.6)	170 (97.1)	691 (97.6)
Per-protocol	168 (94.4)	170 (95.5)	167 (94.4)	166 (94.9)	671 (94.8)

MDI = metered-dose inhaler; b.i.d. = twice daily; q.d. = once daily; ITT = intent-to-treat

Efficacy results:

In the ITT population, all 3 dosing regimens of ciclesonide MDI (160 µg q.d. AM, 80 µg b.i.d. switched to 160 µg q.d. AM, and 80 µg b.i.d.) showed statistically significant improvements compared to placebo MDI in the primary and in 2 of the 3 key secondary efficacy variables, as summarized in the table below.

Summary of treatment differences of ciclesonide MDI versus placebo MDI - ITT population

Variable	Treatment difference versus placebo MDI [LS mean (95% CI) p-value]		
	Cic MDI 160 µg q.d. AM	Cic MDI 80 µg b.i.d./ 160 µg q.d. AM	Cic MDI 80 µg b.i.d.
Primary efficacy endpoint: Change from baseline to the average of Weeks 12 and 16			
FEV_1 (L)	0.12 (0.05; 0.20) 0.0021	0.13 (0.05; 0.20) 0.0016	0.24 (0.16; 0.32) <0.0001
Key secondary efficacy endpoints: Change from baseline to Week 16 (LOCF)			
AM PEF (L/min)	23.32 (10.08; 36.53) 0.0006	30.71 (17.70; 43.71) <0.0001	36.16 (23.13; 49.20) <0.0001
Albuterol use (puffs/day)	-0.41 (-0.73; -0.09) 0.0116	-0.60 (-0.92; -0.28) 0.0002	-0.73 (-1.04; -0.41) <0.0001
Total asthma symptom score (0-8 scale)	-0.27 (-0.57; 0.03) 0.0781	-0.32 (-0.62; -0.03) 0.0325	-0.57 (-0.87; -0.27) 0.0002

Cic = ciclesonide; LS = least squares; CI = confidence interval; MDI = metered-dose inhaler; b.i.d. = twice daily; q.d. = once daily; ITT = intent-to-treat

All 3 ciclesonide MDI regimens showed statistically significant improvements compared to placebo MDI in terms of change in FEV_1 from baseline to the average of Weeks 12 and 16. A treatment difference in FEV_1 between all 3 ciclesonide MDI groups and placebo MDI was observed by Week 2 and was maintained throughout the 16-week treatment period. Consistency of treatment effect was seen across the subgroups of gender, age group, race, baseline FEV_1 percent predicted and pooled center, as assessed by treatment by subgroup statistical interaction tests.

All 3 ciclesonide MDI groups showed statistically significant improvements compared to placebo MDI in 2 of the 3 key secondary efficacy variables (change from baseline to Week 16 [LOCF] in AM PEF and albuterol use). For total asthma symptom score, the treatment difference between the ciclesonide MDI 160 µg q.d. AM group and placebo MDI was not statistically significant.

Efficacy results (cont'd):

A higher percentage of patients was withdrawn due to lack of efficacy or asthma exacerbation in the placebo MDI group (13.0%) compared with the ciclesonide MDI groups (2.3% to 6.4%). Results from additional secondary efficacy 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 16-week treatment period) were generally consistent with those of the primary and key secondary endpoints in terms of greater improvements with ciclesonide MDI.

Overall, in patients with mild to moderate asthma previously treated with inhaled bronchodilators alone, all 3 ciclesonide MDI regimens (160 µg q.d. AM, 80 µg b.i.d switched to 160 µg q.d. AM, and 80 µg b.i.d.) were able to provide significant improvements versus placebo in FEV_1. Consistent with the results for the primary endpoint, the analyses of key secondary efficacy endpoints and additional efficacy endpoints showed improvements with all 3 ciclesonide MDI regimens compared to placebo MDI.

Safety results:

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

	Number (%) of patients				
		Ciclesonide MDI (µg)			
TEAE categories	Placebo MDI (N=178)	160 q.d. AM (N=176)	80 b.i.d./ 160 q.d. AM (N=173)	80 b.i.d. (N=173)	Total (N=522)
All TEAEs	102 (57.3)	93 (52.8)	100 (57.8)	96 (55.5)	289 (55.4)
All possibly related TEAEs	12 (6.7)	9 (5.1)	6 (3.5)	6 (3.5)	21 (4.0)
Serious TEAEs	1 (0.6)	2 (1.1)	2 (1.2)	3 (1.7)	7 (1.3)
Possibly related serious TEAEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Permanent discontinuation due to TEAE	22 (12.4)	14 (8.0)	8 (4.6)	4 (2.3)	26 (5.0)

MDI = metered-dose inhaler; b.i.d. = twice daily; q.d. = once daily; TEAE = treatment-emergent adverse event; N = population size

The safety profiles for ciclesonide MDI administered at a daily dose of 160 µg either as 160 µg q.d. AM, as 80 µg b.i.d., or as an 80 µg b.i.d./160 µg q.d. AM switch regimen were generally comparable to the safety profile of placebo MDI. The percentage of patients who experienced at least 1 TEAE, as well as the percentages of the individual TEAEs, were generally comparable across treatment groups, except for asthma and nasal congestion (both more frequent in the placebo MDI group than in the ciclesonide MDI groups) as well as influenza and sinusitis (both more frequent in the ciclesonide MDI groups than in the placebo MDI group). The most frequent TEAEs were asthma, nasopharyngitis, headache, upper respiratory tract infection, influenza, pharyngolaryngeal pain, and sinusitis.

There were no deaths in this study. Nine serious TEAEs were reported by 8 patients (placebo MDI: 1 patient with asthma and viral pneumonia; ciclesonide MDI 160 µg q.d. AM: 1 patient each with staphylococcal infection and renal colic; ciclesonide MDI 80 µg b.i.d./160 µg q.d. AM: 1 patient each with acute cholangitis and pneumonia; ciclesonide MDI 80 µg b.i.d.: 1 patient each with chest pain, lower respiratory tract infection, and nephrolithiasis). None of these serious TEAEs was considered by the Investigator to be possibly related to study medication.

The frequency of TEAEs leading to permanent discontinuation of study medication was higher in the placebo MDI group (12.4%) than in the ciclesonide MDI groups (2.3% to 8.0%), which was mostly accounted for by TEAEs 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.

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