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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00174746
Drug substance(s):	ciclesonide	**Study Code:**	DFI6153 (AVE2635A/2001)
		Date:	31 January 2007

Title of the study:	A placebo- and active-controlled (ciclesonide metered-dose inhaler), randomized, parallel-group, dose-range finding study of ciclesonide administered by dry powder inhaler (Ultrahaler®) in adult and adolescent patients with persistent asthma.
Investigator(s):	David I. Bernstein, MD, Bernstein Clinical Research Center, LLC, Cincinnati, OH 45231, USA
Study center(s):	66 centers in the United States of America (USA)
Publications:	None
Study period: Date first patient/subject enrolled: 21/Feb/2005 Date last patient/subject completed: 28/Nov/2005	**Phase of development:** Phase II
Objectives:	**Primary objective:** To investigate the efficacy and safety of ciclesonide administered twice daily by dry powder inhaler (DPI) (Ultrahaler) at doses of 160 to 1280 µg/day (80 to 640 µg twice daily) in patients with moderate to severe persistent asthma. **Secondary objectives:** To investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of ciclesonide DPI at doses of 160 to 1280 µg/day (80 to 640 µg twice daily) compared to open-label ciclesonide metered-dose inhaler (MDI) administered as 640 µg/day (320 µg twice daily).
Methodology:	Placebo- and active-controlled, randomized, parallel-group, dose-range finding study of ciclesonide administered by DPI at doses of 160 to 1280 µg/day (80 to 640 µg twice daily) for 6 weeks to adult and adolescent patients with moderate to severe persistent asthma. Patients were treated with fluticasone propionate (88 µg/day) during the screening period.
Number of patients: **Evaluated:**	Planned: 1146 (191 in each of the 6 treatment groups) Randomized: 1145 Treated: 1142 Efficacy: 1115 (modified intent-to-treat), 1076 (per-protocol) Safety: 1142 PK-PD stratum: 155
Diagnosis and criteria for inclusion:	Males or females ≥12 years of age, with a history of persistent bronchial asthma for ≥6 months before screening, documented use of an inhaled corticosteroid (ICS) for ≥1 month before screening; forced expiratory volume in one second (FEV_1) ≥40% of predicted normal at screening, FEV_1 ≥40% and ≤80% of predicted normal at randomization.

Investigational product: Dose: Administration:	Ciclesonide DPI (Ultrahaler) 160, 320, 640, and 1280 µg/day 80, 160, 320, and 640 µg twice daily
Duration of treatment: 6 weeks	**Duration of observation:** 8 weeks
Reference therapy I: (placebo control) Dose: Administration:	Placebo ciclesonide DPI (Ultrahaler) NA twice daily
Reference therapy II: (ative control) Dose: Administration:	Ciclesonide MDI 640 µg/day 320 µg twice daily
Criteria for evaluation: Efficacy/ Pharmacodynamics:	**Primary efficacy data:** FEV_1. **Key secondary efficacy data:** morning peak expiratory flow (AM PEF), albuterol use, and total asthma symptom score. **Other secondary efficacy data:** nocturnal awakenings, evening PEF (PM PEF), forced vital capacity (FVC), forced mid-expiratory flow ($FEF_{25-75\%}$), rate of withdrawal due to lack of efficacy or asthma exacerbation, time to withdrawal due to lack of efficacy or asthma exacerbation, AM and PM asthma symptom score, asthma control (ie, percentage of days on which a patient perceived asthma control, based on diary entries for AM and PM asthma symptom score, nocturnal awakenings, and number of albuterol puffs).
Safety:	Adverse events reported by the patient or noted by the Investigator, standard hematology and serum chemistry, hypothalamic-pituitary-adrenal (HPA) axis function (serum cortisol [before and after cosyntropin stimulation] and 24-hour urinary cortisol), vital signs, and physical examinations.
Pharmacokinetics:	PK parameters calculated from the serum concentration-time profiles of ciclesonide and its active M1 metabolite: maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the concentration-time curve (AUC) between time 0 and the last quantifiable serum concentration or the last sampling timepoint (AUC(0-last)), AUC during the dosing interval (12 hours) (AUC(0-τ), terminal half-life ($t_{1/2}$), apparent oral clearance at steady state (CL/F_{ss}).
Pharmacokinetic sampling times and bioanalytical methods:	Serum concentrations of ciclesonide and M1 on Day 1 (Week 0, Visit 3), and predose and at 0.5, 1, 2, 4, 6, 8, and 10 hours after dosing on Day 28 ± 2 (Week 4, Visit 5); an additional sample was taken at the end of the treatment period on Day 42 ± 2 (Week 6, Visit 6) to check for compliance. Serum concentrations of ciclesonide and M1 were determined by a validated high-performance liquid chromatography/mass spectrometry (HPLC/MS) assay with lower limits of quantification of 25 ng/L for ciclesonide and 10.3 ng/L for M1.

Statistical methods:

Efficacy: The primary efficacy analysis was an analysis of covariance (ANCOVA) of the change from baseline to Week 6 or early termination (last observation carried forward [LOCF]) in FEV_1, with factors for treatment, pooled center, and gender, and baseline value (FEV_1 on Day 1 [Week 0, Visit 3]) and age as covariates. The primary comparisons were performed between ciclesonide DPI doses and placebo DPI, using a step-down procedure starting with the highest ciclesonide DPI dose of 1280 µg/day. All other pairwise comparisons were provided for descriptive purposes. Two-sided 95% confidence intervals were constructed to obtain estimates of mean differences. Comparisons of the ciclesonide MDI dose with ciclesonide DPI doses were provided for descriptive purposes only. The key secondary efficacy variables (AM PEF, albuterol use, total asthma symptom score) were analyzed as change from baseline to Week 6 (LOCF) using the ANCOVA model described above for the primary efficacy analysis.

Assuming a standard deviation of 0.45 L (based on a previous ciclesonide MDI study), a sample size of 191 patients in each treatment group was required to provide 90% power to detect a difference of 0.15 L for any pairwise 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. In addition, the change from baseline to Week 6 (LOCF) in serum cortisol (before and after cosyntropin stimulation) and 24-hour urinary cortisol were each analyzed by an ANCOVA with the baseline level as the covariate.

Pharmacokinetics: Steady-state PK variables of ciclesonide and its active M1 metabolite on Day 28 ± 2 (Week 4, Visit 5) were calculated by non-compartmental methods and were summarized using descriptive statistics. PK/PD relationships were not assessed.

Summary:

Data sets analyzed:

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

Data sets analyzed

	Number (%) of patients						
		Ciclesonide DPI (µg/day)				CIC-MDI	
Population	**Pla DPI**	**160**	**320**	**640**	**1280**	**640 [a]**	**Total**
Randomized	192 (100.0)	192 (100.0)	190 (100.0)	190 (100.0)	191 (100.0)	190 (100.0)	1145 (100.0)
Safety	192 (100.0)	191 (99.5)	190 (100.0)	189 (99.5)	190 (99.5)	190 (100.0)	1142 (99.7)
mITT	186 (96.9)	189 (98.4)	184 (96.8)	186 (97.9)	184 (96.3)	186 (97.9)	1115 (97.4)
Per-protocol (evaluable)	182 (94.8)	185 (96.4)	178 (93.7)	182 (95.8)	172 (90.1)	177 (93.2)	1076 (94.0)
PK-PD stratum	25 (13.0)	27 (14.1)	26 (13.7)	26 (13.7)	25 (13.1)	26 (13.7)	155 (13.5)

Pla = Placebo DPI = dry powder inhaler; MDI = metered-dose inhaler.

[a] Ciclesonide MDI 640 µg/day

Summary (cont'd):

Efficacy/ Pharmacodynamic results:

The efficacy analyses (modified intent-to-treat [mITT] population) showed that, compared to placebo DPI, all ciclesonide DPI dose groups (and the ciclesonide MDI-640 group) had clinically and statistically significant improvements for the primary and key secondary efficacy variables as well as nocturnal awakenings, as summarized in the table below.

Summary of treatment differences at Week 6 of ciclesonide DPI versus placebo DPI – modified intent-to-treat population

	Treatment difference at Week 6 (LOCF) versus placebo DPI (LS mean, 95% CI, *P* value)			
Variable	**CIC-DPI 160**	**CIC-DPI 320**	**CIC-DPI 640**	**CIC-DPI 1280**
Primary efficacy variable				
FEV_1 (L)	0.25 (0.16 ; 0.34) < 0.0001	0.25 (0.16 ; 0.33) < 0.0001	0.25 (0.16 ; 0.34) < 0.0001	0.30 (0.22 ; 0.39) < 0.0001
Key secondary efficacy variables				
AM PEF (L/min)	23.2 (14.4; 32.0) < 0.0001	30.0 (21.2; 38.9) < 0.0001	28.8 (20.0; 37.6) < 0.0001	25.1 (16.2; 34.0) < 0.0001
Albuterol use (puffs/day)	- 1.11 (-1.44; -0.78) < 0.0001	- 1.30 (-1.64; -0.97) < 0.0001	- 1.19 (-1.52; -0.86) < 0.0001	- 1.42 (-1.76; -1.09) < 0.0001
Total asthma symptom score (0-8 scale)	- 0.62 (-0.82; -0.42) < 0.0001	- 0.76 (-0.96; -0.55) < 0.0001	- 0.77 (-0.98; -0.57) < 0.0001	- 0.87 (-1.07; -0.66) < 0.0001
Other secondary efficacy variables				
Nocturnal awakenings (nights/week)[a]	-0.51 (-1.20; 0.18) 0.1465	-0.72 (-1.40; -0.04) 0.0392	-1.11 (-1.79; -0.42) 0.0016	-1.27 (-1.95; -0.59) 0.0003

LS = least squares; CI = confidence interval; CIC-DPI = ciclesonide DPI (doses in µg/day); FEV_1 = forced expiratory volume in 1 second; AM PEF = morning peak expiratory flow.

[a] Restricted to patients with at least 1 night/week of awakening at baseline (N = 65 to 74 per group).

For the primary efficacy analysis, all ciclesonide DPI groups showed significantly greater improvements from baseline in FEV_1 compared to placebo DPI for the mITT and per-protocol populations (P <0.0001 for all comparisons). Although no dose-ordering was observed, the highest dose of ciclesonide DPI (1280 µg/day) showed a greater improvement in FEV_1 compared to placebo DPI (0.30 L) than the other ciclesonide DPI doses (each 0.25 L). A post-hoc analysis of FEV_1 percent predicted by gender revealed no significant interaction between treatment group and gender. In patients with severe asthma (ie, baseline FEV_1 percent predicted ≤60%) notably greater improvements were seen in the ciclesonide DPI–1280 group (0.32 L) than in the ciclesonide DPI-160, -320, and –640 groups (0.11, 0.13, and 0.12 L, respectively).

Among the key secondary efficacy analyses, the improvements in asthma symptom scores in the ciclesonide DPI groups compared to placebo DPI were dose-ordered, and the improvements in albuterol use compared to placebo DPI were highest in the ciclesonide DPI-1280 group and lowest in the ciclesonide DPI-160 group.

There was also dose-ordering in the improvements in the number of nights with nocturnal awakenings in the ciclesonide DPI groups compared to placebo DPI (only patients with at least 1 night per week with nocturnal awakenings at baseline), although the difference between the ciclesonide DPI-160 group and placebo DPI was not statistically significant.

Summary (cont'd):	A higher percentage of patients discontinued due to lack of efficacy or asthma exacerbation in the placebo DPI group (21.5%) compared to all ciclesonide DPI groups (1.6% to 4.2%), but with no dose-ordering in the percentage of patients who discontinued for these reasons. There was a significant difference across treatment groups in the time to withdrawal due to lack of efficacy or asthma exacerbation. The improvements in asthma control (defined as the percentage of days on which a patient perceived asthma control, based on diary entries for AM and PM asthma symptom score, nocturnal awakenings, and number of albuterol puffs) from baseline to post-baseline were comparable among the ciclesonide DPI groups (between 11.2% and 14.6% of days, with no evidence of dose-ordering); no improvement in asthma control was observed in the placebo DPI group. Taken together, the analyses of the primary and secondary efficacy variables provide robust evidence that all doses of ciclesonide DPI (ie, 160 to 1280 µg/day [80 to 640 µg twice daily]) were effective in the treatment of moderate to severe persistent asthma, as compared to placebo DPI.
Safety results:	The safety profiles for ciclesonide DPI at doses of 160 to 1280 µg/day (80 to 640 µg twice daily) and ciclesonide MDI at a dose of 640 µg/day (320 µg twice daily) were generally comparable to the profile for placebo DPI, as indicated by the following observations: • The overall percentage of patients with treatment-emergent adverse events (TEAEs) was higher in the placebo DPI group (43.8%) than in the ciclesonide DPI groups (total ciclesonide DPI: 37.5%; ranging from 33.5% to 42.1%, without dose-ordering) and the ciclesonide MDI-640 group (33.2%). The most frequent TEAEs (occurring in at least 1% of the total ciclesonide DPI group) were headache, upper respiratory tract infection, asthma, pharyngolaryngeal pain, nasopharyngitis, sinusitis and back pain. The frequencies of individual TEAEs were generally comparable across treatment groups except for asthma, which was more frequent in the placebo DPI group (14.6%) than in the ciclesonide DPI groups (2.6% to 3.7%) or in the ciclesonide MDI-640 group (1.6%). • Three serious TEAEs were reported by 3 patients (1 patient with anaphylactoid reaction in the placebo DPI group, 1 patient with hypersensitivity in the ciclesonide DPI-160 group, and 1 patient with B-cell lymphoma in the ciclesonide DPI-1280 group). The hypersensitivity was considered by the Investigator to be possibly related to study medication. There were no deaths. • The percentage of patients who had a TEAE leading to permanent discontinuation of study medication was higher in the placebo DPI group (11.5%) than in the ciclesonide DPI (ranging from 3.2% to 6.8%) and ciclesonide MDI-640 (2.6%) groups, which was mostly accounted for by cases of asthma. • The frequency of local oropharyngeal TEAEs in the ciclesonide groups was low and generally comparable to the placebo DPI group. • There were no signals of concern in any of the clinical laboratory data (including changes in serum and urinary free cortisol levels as indicators of HPA-axis function) or in any of the vital signs or physical examination data.

Summary (cont'd): Pharmacokinetic results:	The C_{max} and AUC of the active M1 metabolite showed a trend of dose-proportional increases across the ciclesonide DPI groups. The mean exposure values in the ciclesonide MDI-640 group were approximately 3 times higher than in the ciclesonide DPI-640 group.
Date of full report:	23 August 2006