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Sponsor / Company: sanofi-aventis **Drug substance(s):** Ciclesonide	**Study Identifier:** **Study code:** EFC6161 (XRP1526B/3028)
Title of the study: A multicenter, randomized, open-label, parallel-group study to assess the accuracy, functionality, and reliability of the Trudell™ dose counter in subjects with mild-to-moderate persistent asthma treated for 15 or 30 days with ciclesonide metered-dose inhaler administered at a daily dose of 160 µg once daily Note: For purposes of this clinical study report, the Trudell device integrated with the ciclesonide MDI will henceforth be referred to as a dose indicator and not as a dose counter.	
Study center(s): 15 centers in the United States of America (USA)	
Study period: Date first patient enrolled: 18 November 2005 Date last patient completed: 03 March 2006	
Phase of development: Device functionality study	
Objectives: **Primary objective:** To evaluate the accuracy, functionality, and reliability of the Trudell dose indicator in patients with mild-to-moderate asthma treated with ciclesonide 160 µg/day (ex-actuator) for 15 or 30 days, taken as 4 puffs in the morning using the metered-dose inhaler (MDI) fitted with an integrated Trudell dose indicator **Secondary objective:** To assess the safety of ciclesonide administered using the MDI fitted with an integrated Trudell dose indicator	
Methodology: Randomized, open-label, parallel-group study to assess the accuracy, functionality, and reliability of the Trudell dose indicator device. After screening at Visit 1 (Day 1), patients were randomized in a ratio of 4:1 to 30- or 15-day open-label treatment with ciclesonide 160 µg/day (ex-actuator), taken as 4 puffs in the morning using the MDI with an integrated Trudell dose indicator. There were 3 study visits for the 15-day group (on Days 1, 8, and 15) and 5 study visits for the 30-day group (on Days 1, 8, 15, 22, and 30).	
Number of subjects/patients: Planned: 125 (30-day group: 100; 15-day group: 25); randomized: 125; treated: 125 Evaluated for efficacy: 125; evaluated for safety: 125	

Diagnosis and criteria for inclusion:

Males or females 4 years of age and older (including approximately 10% of patients between 4 and 11 years of age and approximately 10% of patients ≥65 years of age) with a history of mild-to-moderate persistent asthma (as defined by the National Asthma Education and Prevention Program -NAEPP- Guidelines); forced expiratory volume in 1 second (FEV_1) ≥60% of predicted at Visit 1 (screening); reversibility of FEV_1 of at least 12% (relative to the pre-bronchodilator value in L) and ≥0.2 L after inhalation of 180 µg albuterol (ex-actuator), or documented history of reversibility of FEV_1 by at least 12% and ≥0.2 L within 1 year before screening

Investigational product: Ciclesonide hydrofluoroalkane (HFA)-MDI

Dose: 160 µg total daily dose (ex-actuator)

Administration: 4 puffs in the morning (40 µg per puff), administered for 15 or 30 consecutive days

Duration of treatment: 15 or 30 days

Duration of observation: 4 weeks (15-day group); 6 weeks (30-day group)

Reference therapy: Not applicable

Criteria for evaluation:

Efficacy: Accuracy, functionality, and reliability of the Trudell dose indicator were assessed by the following endpoints:

Primary endpoints included the following:

- Ratio (in percent) of correct advances of the dose indicator out of expected advances, where a correct advance was defined as one when the number of puffs between the 2 advances was within the range of 8 to 12 puffs (i.e., ±20% of 10 puffs);
- Number and percentage of devices with actuation consistency at the end of study, where actuation consistency was defined as a Trudell count within ±20% of the diary count;
- Number and percentage of devices with major discrepancies, where a major discrepancy was defined as a discrepancy of more than 20 puffs between the Trudell count and the diary count at the end of the study.

Secondary endpoints included the following:

- Consistency between the Trudell dose count and the canister weight count: The percentage of patients for whom there was agreement between the 2 counts (i.e., Trudell count was within ± 20% of the canister weight count) was summarized for each group at the end of the study;
- Functionality of the dose indicators that reached zero, assessed as the percentage of dose indicators that ceased to make a clicking sound upon further actuation after reaching zero (30-day group only);
- Number and percentage of patients with a particular response for each question in the patient satisfaction survey.

Safety: Adverse events, vital signs, and physical examinations.

Statistical methods:

Efficacy: Summary statistics were provided for all variables. No formal hypothesis testing or comparisons between the treatment groups were performed.

Safety: Safety variables (adverse events, vital signs, physical examinations) were summarized using descriptive statistics.

Summary:

A total of 125 patients were randomized and treated (15-day group: 25 patients; 30-day group: 100 patients). All randomized and treated patients were included in the safety and intent-to-treat (ITT) populations.

Efficacy results:

Overall, 120 of the 125 devices evaluated (96.0%) showed actuation consistency between the Trudell count assessed by the center staff and the diary count at the end of the study (i.e., the Trudell count was within ±20% of the diary count). Five (4.0%) devices were identified as not achieving actuation consistency between the Trudell count and the diary count, and these 5 devices also had a major discrepancy of >20 puffs between the 2 counts. On the basis of these data, 4 of these 5 devices were presumed to have a device malfunctioning problem resulting in undercounting. However, no damage or malfunction was detected in the manufacturer's investigations of these 4 devices. All 125 MDIs were returned to the Sponsor at the end of the study, and 73 of these were forwarded to the manufacturer for further investigation. As reported by the manufacturer, none of these 73 devices were found to be defective or damaged.

The results of the secondary analyses of actuation consistency (between the Trudell count and the canister weight count) were consistent with the results of the primary analysis.

The results of the patient satisfaction survey indicated that patients' acceptance of the Trudell dose indicator was high. Most patients reported that the device was easy to use and that it provided accurate and reliable guidance on their use of study medication.

Safety results:

A summary of treatment-emergent adverse events (TEAEs) is presented below.

	Number (%) of patients		
TEAE categories	**15-day group (N=25)**	**30-day group (N=100)**	**Overall (N=125)**
All TEAEs	4 (16.0)	25 (25.0)	29 (23.2)
All possibly related TEAEs	1 (4.0)	1 (1.0)	2 (1.6)
Serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation of study medication due to TEAE	0 (0.0)	3 (3.0)	3 (2.4)

The safety profile of ciclesonide MDI at a dose of 160 µg once daily in the morning for 15 and 30 days was consistent with that observed in previous clinical studies with ciclesonide, as indicated by the following observations:

- Overall, 4 patients (16.0%) in the 15-day group and 25 patients (25.0%) in the 30-day group experienced at least 1 TEAE. The 2 system organ classes with the highest frequency of patients with TEAEs were infections and infestations and respiratory, thoracic, and mediastinal disorders. The most frequent TEAEs were nasopharyngitis, asthma, and (viral) upper respiratory tract infection. All other TEAEs (except for pharyngolaryngeal pain and influenza) were single occurrences mostly in the 30-day group. TEAEs were mild or moderate in intensity in all patients except 1. Two patients (1 in each treatment group) had possibly related TEAEs (asthma, chest pain);
- There were no deaths or serious TEAEs during this study;
- Three patients in the 30-day group had a TEAE leading to discontinuation of study medication (1 each of chest pain, upper respiratory tract infection, and heart rate increased);
- The frequency of local oropharyngeal TEAEs was low (no cases of oropharyngeal candidiasis, oral candidiasis and pharyngitis; pharyngolaryngeal pain and dysphonia in 2 patients [1.6%] and 1 patient [0.8%], respectively);
- There were no signals of concern for ciclesonide MDI in the vital signs and physical examination data.

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