These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis	**Study Identifier:** NCT00254956
Drug substance(s): ciclesonide	**Study code:** SFY6160 (XRP1526B/3027)

Title of the study:

A multicenter, multinational, randomized, double-blind, parallel group study of the effects of ciclesonide HFA-MDI 640 µg/day and beclomethasone HFA-MDI 640 µg/day on lens opacification in adult subjects with moderate to severe persistent asthma.

Study center(s): Multinational: 102 sites in the USA, 7 sites in Poland and 10 sites in South Africa.

Study period:

Date first patient enrolled: 19 January 2004

Date last patient completed: 21 June 2005

Phase of development: Phase III

Objectives:

Primary:

To demonstrate the non-inferiority of ciclesonide-hydrofluoroalkane (HFA) compared to beclomethasone-HFA in the occurrence of a Class I lens event for nuclear opalescence, cortical, or posterior subcapsular lens opacification within 12 months. Lens events were determined by the occurrence of a protocol-specified change in lens opacification using the Lens Opacities Classification System III (LOCS III) for grading lens opacities, or the occurrence of cataract surgery.

Secondary:

To compare ciclesonide-HFA and beclomethasone-HFA with respect to the following endpoints:

- Change from baseline to Month 12 in LOCS III grade for (a) nuclear opalescence, (b) cortical opacity, and (c) posterior subcapsular opacity;
- Occurrence within 12 months in either eye of a Class II lens event, or cataract surgery;
- Occurrence within 12 months in either eye of a Class III lens event, or cataract surgery;
- Change from baseline to Month 12 in Best-Corrected Visual Acuity (BCVA);
- Change from baseline to Month 12 in intraocular pressure (mmHg).

Methodology:

This was a multicenter, multinational, active-controlled, double-blind, randomized (1:1) parallel-group study of the effects of inhaled ciclesonide-HFA 640 µg/day and beclomethasone-HFA 640 µg/day (both delivered by means of a Metered-Dose Inhaler, MDI) on lens opacification in adult subjects with moderate to severe persistent asthma. The study consisted of a 1- to 14-day screening phase during which subject eligibility was determined, followed by a 12-month double-blind treatment period. Lens opacification was evaluated by slit-lamp examination performed after pupillary dilation to at least 6.0 mm before randomization and after 4 months, 8 months, and 12 months of treatment, using the LOCS III system for grading lens opacities. BCVA and intraocular pressure were measured at each eye examination visit. An Independent Data Monitoring Committee (IDMC) was constituted to monitor safety throughout the double-blind treatment period.

Number of patients: Planned: 1500 subjects (750 in each treatment group) Randomized: 1568 Treated: 1552

Diagnosis and criteria for inclusion:

Males or non-pregnant, non-lactating females 18 years of age and older, with a history of moderate to severe persistent asthma for a duration of at least 2 months prior to screening, a Forced Expiratory Volume in one second (FEV_1) value of ≥ 40% and ≤ 85% of predicted at screening, documented use of inhaled corticosteroid therapy at any dose for at least one month prior to screening, and non-smoker for at least the past year and less than a 10 pack-year smoking history if a previous smoker.

Investigational product:

Dose: Ciclesonide 134a-HFA (MDI): 640 µg/day (ex-actuator)

Administration: 4 actuations twice daily (b.i.d.) (80 µg/actuation)

Duration of treatment: 12 months

Duration of observation: 2 weeks of screening + 12 months of treatment

Reference therapy:

Dose: Beclomethasone 134a-HFA (MDI): 640 µg/day (ex-actuator)

Administration: 4 actuations b.i.d. (80 µg/actuation)

Criteria for evaluation:

Efficacy:

- Ophthalmologic data

  Lens opacification assessed by slit-lamp examinations, using LOCS III classification for grading lens opacities. Lens events (occurring at any time within the 12 months since baseline in either eye) were defined as follows:
  Class I: increase from baseline in LOCS III grade of ≥ 0.5 (nuclear opalescence), or ≥ 0.8 (cortical), or ≥ 0.5 (posterior subcapsular), or cataract surgery since baseline,
  Class II: increase from baseline in LOCS III grade of ≥ 0.9 (nuclear opalescence), ≥ 1.5 (cortical), or ≥ 0.9 (posterior subcapsular), or cataract surgery since baseline,
  Sustained Class II: a Class II lens event observed at any timepoint with presence of a Class I lens event in the same eye at the next timepoint. If the Class II lens event was observed only at the last examination done, then it should be also a Class I lens event in the same eye at the timepoint immediately preceding the last one,
  Class III: LOCS III grade of ≥ 2.0 for any type of opacity (nuclear opalescence, cortical, or posterior subcapsular) and increase from baseline in LOCS III grade of ≥ 0.9 (nuclear opalescence), ≥ 1.5 (cortical), or ≥ 0.9 (posterior subcapsular), or cataract surgery since baseline.
  BCVA;

  Intraocular pressure (tonometry).

- Pulmonary function data (maintenance of asthma control)
  Maintenance of asthma control was assessed on the basis of pulmonary function: FEV_1 and FEV_1 percent predicted.

Safety:

Safety data included adverse events reported by the subject or noted by the investigator, clinical laboratory safety (blood chemistry, hematology, urinalysis), vital signs, weight, and physical examination.

Statistical methods:

The primary analysis for the primary endpoint of the Class I lens event was the comparison for non-inferiority between treatment (ciclesonide-HFA) and control (beclomethasone-HFA) of the proportion of subjects with a Class I lens event within 12 months using the modified intent-to-treat (mITT) population (i.e. randomized patients with at least one dose of study medication, a valid pre-treatment and at least one valid post-treatment LOCS III measurement, or patient with a post-treatment cataract surgery until 14 days after the last study dose administration). In order to assess the consistency of results, the analyses were also performed for the per-protocol population.

The proportion of subjects with the primary endpoint of a Class I lens event in a treatment group was estimated by the life-table estimate of the event at Month 12. A life-table method that managed withdrawals with their actual fractions of completion for the interval of withdrawal was used. Three time intervals (in days) were defined: [0, 120], [121, 240] and [241, 360].

Non-inferiority of ciclesonide-HFA versus the control (beclomethasone-HFA) was demonstrated if the upper bound of the one-sided 97.5% confidence interval of the risk ratio was less than the non-inferiority bound NIB (see below).
If non-inferiority was demonstrated, then superiority of ciclesonide-HFA over control (beclomethasone-HFA) was to be subsequently tested by comparing the upper bound of the one-sided 97.5% confidence interval to one. By closure principle, this stepwise approach to the multiple hypotheses maintained the experimentwise error rate at $\alpha = 5\%$.
The NIB was defined as a function of the control event rate for p_C ranging from 2% to 12%:

$NIB = (1.63 - \sqrt{p_C}) * \exp(\sqrt{(1/(80\ p_C))})$.

This function ensured that the risk ratio would not be greater than 1.5 with 503 subjects per group, which was acceptable from a clinical perspective.
Blinded review of the data indicated a higher rate of events than expected. Therefore the NIB function defined in the protocol was extended to a higher range, maintaining a decreasing functional form, with a minimum of 1.333, which occurred when the estimated control event rate was 30% or higher. This insured a maximum sample risk ratio for non-inferiority higher than 1 and sufficient power for high rates of events.

Class II, sustained Class II, and Class III lens events were events of increasing severity compared with the primary Class I lens events. These endpoints were analyzed in the mITT population, using the same methodology as the primary endpoint of Class I lens event. The primary analysis approach for these secondary endpoints was the confidence interval of the risk ratio of the event rate within 12 months. Two-sided 95% confidence intervals for the risk ratio were constructed using the life-table estimates in the same manner as for the primary endpoint. However, these secondary endpoints were not tested for non-inferiority.

Summary:

Population studied:

A total of 1568 subjects were randomized, all but 16 of whom received at least one dose of double-blind study medication. The disposition of randomized subjects is shown in the table below:

Subject disposition (randomized subjects)

	Number (%) of subjects		
Disposition status	CIC-HFA (N = 785)	BDP-HFA (N = 783)	Overall (N = 1568)
Subjects randomized	785 (100%)	783 (100%)	1568 (100%)
Subjects treated	776 (98.9%)	776 (99.1%)	1552 (99.0%)
Completed the study	672 (85.6%)	682 (87.1%)	1354 (86.4%)
Discontinued from the study	113 (14.4%)	101 (12.9%)	214 (13.6%)
Safety	776 (98.9%)	776 (99.1%)	1552 (99.0%)
Modified intent-to-treat	743 (94.6%)	742 (94.8%)	1485 (94.7%)
Per-protocol	673 (85.7%)	676 (86.3%)	1349 (86.0%)

BDP = beclomethasone; CIC = ciclesonide.

Summary:

Population studied (cont'd):

The most common reasons for discontinuation in both treatment groups were "Did not wish to continue" (ciclesonide-HFA: 33 subjects, 4.2%; beclomethasone-HFA: 32 subjects, 4.1%) and "Adverse event" (ciclesonide-HFA: 29 subjects, 3.7%; beclomethasone-HFA: 22 subjects, 2.8%), with comparable rates for both reasons in both treatment groups. Only 8 randomized subjects discontinued due to lack of efficacy (ciclesonide-HFA: 5 subjects, 0.6%; beclomethasone-HFA: 3 subjects, 0.4%).

At screening, the mean subject age was 43.1 years, and, as intended by stratification of the randomization procedure, nearly twice as many subjects were ≥ 40 years (62.4%) than < 40 years (37.6%). The majority of subjects were female (60.1%), white (83.5%), and enrolled in the United States (84.6%). The mean subject weight was 83.4 kg. The majority of subjects (76.8%) had never smoked. The overall mean duration of asthma was 22.1 years, and all subjects had prior corticosteroid use. There were no relevant differences between the 2 treatment groups in any of the demographic characteristics at screening.

All baseline ophthalmologic characteristics were comparable between the 2 treatment groups. For each type of opacity, the mean LOCS III grades were identical in both treatment groups for each eye (nuclear opalescence: 1.4; cortical: 0.4; posterior subcapsular: 0.2). The mean BCVA values were also identical in both treatment groups for each eye (87 letters). The mean median intraocular pressure was comparable for both treatment groups for each eye (ciclesonide-HFA: left eye 14.8 mmHg, right eye 14.6 mmHg; beclomethasone-HFA: left eye 14.8 mmHg, right eye 14.7 mmHg).

Efficacy results:

Ophthalmologic endpoints

The incidence rates of lens events (life-table estimates) were either comparable between the 2 treatment groups, or were slightly lower in the ciclesonide-HFA group than in the beclomethasone-HFA group, for all classes of lens event (see table below) and for all types of lens opacity.

Summary of the analysis of life table estimates for lens event rates (mITT population)

Parameter	CIC-HFA (N=743)	BDP-HFA (N=742)	Risk Ratio (RR)	Upper bound of 95% confidence interval of RR	Prespecified non-inferiority bound
Class I lens event	36.1%	38.4%	0.940	1.077	1.333
Class II lens event	14.0%	16.4%	0.857	1.097	1.615
Sustained Class II lens event	9.4%	11.5%	0.821	1.118	1.796
Class III lens event	8.1%	9.2%	0.885	1.245	1.921

Proportions of subjects with lens events (expressed as percent) calculated from life table estimates.
Risk ratio calculated as ratio of ciclesonide-HFA to beclomethasone-HFA.

Efficacy results (cont'd):

In the primary analysis of Class I lens events by life table estimates for the mITT population, ciclesonide-HFA 640 µg/day was non-inferior ($p < 0.0001$) to beclomethasone-HFA 640 µg/day. The estimated relative risk ratio of ciclesonide-HFA to beclomethasone-HFA for Class I lens events was less than 1 (0.940), and the upper bound of the one-sided 97.5% confidence interval (1.077) was lower than the prespecified NIB of 1.333, thereby satisfying the criterion of non-inferiority. The analysis of Class I lens events by life table estimates for the per-protocol population also showed that ciclesonide-HFA was non-inferior ($p < 0.0001$) to beclomethasone-HFA.

As shown in the table above, similar conclusions could be drawn from the analyses on the pre-defined secondary endpoints of Class II, sustained Class II, and Class III lens events. Only one subject, in the beclomethasone-HFA group, had cataract surgery during the conduct of the study.

For all types of opacity, a large percentage of subjects had either no change in LOCS III grade or a decrease in LOCS III grade for the maximum change from baseline. This was particularly the case for posterior subcapsular opacities, for which the maximum on-treatment LOCS III values were either the same or less than baseline for approximately 75% of the subjects. An exploratory analysis of "negative" lens events (defined as changes of the same magnitude for each type of opacity as defined for the lens events in the primary and key secondary endpoints, but in the opposite direction) showed that the frequencies of observed negative Class I, negative Class II, and negative sustained Class II lens events in either eye during the study were each comparable in the 2 treatment groups, and were each as common as "positive" Class I lens events.

Observed "negative" lens events in either eye during the study (mITT population)

	Number (%) of subjects	
	CIC-HFA (N = 743)	BDP-HFA (N = 742)
Negative Class I events	230 (31.0%)	248 (33.4%)
Negative Class II events	94 (12.7%)	102 (13.7%)
Negative sustained Class II events	62 (8.3%)	64 (8.6%)

Mean maximum changes (least square means) from baseline in LOCS III grade during the study in either eye were comparable in the 2 treatment groups for each type of opacity (nuclear opalescence - ciclesonide-HFA: 0.22; beclomethasone-HFA: 0.23; cortical - ciclesonide-HFA: 0.14; beclomethasone-HFA: 0.16; posterior subcapsular - ciclesonide-HFA: 0.06; beclomethasone-HFA: 0.05). These magnitudes of change were low, detecting very small changes in opacification (and not cataracts). For each type of opacity, the mean change from baseline at Month 12 in LOCS III grade was lower than for the corresponding maximum change from baseline in LOCS III grade during the study. These changes were still comparable between the 2 treatment groups.

No clinically relevant differences between ciclesonide-HFA and beclomethasone -HFA were identified when the life-table estimates for lens event rates were analyzed by subgroups of age, gender, or country.
Changes from baseline in BCVA score and median intraocular pressure were comparable between the ciclesonide-HFA and beclomethasone-HFA groups, and were not clinically relevant.

Maintenance of asthma control

Asthma control, as measured by FEV_1, was maintained between randomization and end of study in both treatment groups. Only 8 subjects discontinued study medication due to lack of efficacy (ciclesonide-HFA: 5 subjects, 0.6%; beclomethasone-HFA: 3 subjects, 0.4%). Consistent with the low level of discontinuation due to lack of efficacy, only 12 subjects had a treatment-emergent adverse event (TEAE) of asthma leading to discontinuation of study medication. Although 11 of these subjects were in the ciclesonide-HFA group, there was no obvious reason for this imbalance in the absence of other signals for lack of maintenance of asthma control in the ciclesonide-HFA group. In addition to the comparable maintenance of asthma control in the 2 treatment groups, both groups were also highly comparable regarding the frequencies of subjects reporting asthma as a TEAE, as a serious TEAE, as a severe TEAE, and as a possibly related TEAE.

Safety results:

The safety profile for ciclesonide-HFA in this study was generally comparable to the profile for beclomethasone-HFA, as indicated by the following:

- The percentage of subjects with TEAEs was comparable in the ciclesonide-HFA and beclomethasone-HFA groups (83.5% and 85.6%, respectively); the most common TEAE in the ciclesonide-HFA group was nasopharyngitis (20.9%, compared to 17.5% in the beclomethasone-HFA group), and the most common TEAE in the beclomethasone-HFA group was upper respiratory tract infection (19.1%, compared to 19.5% in the ciclesonide-HFA group). Other common TEAEs included sinusitis, asthma, and headache, all of which had a frequency of > 10% in both treatment groups. The frequencies of individual TEAEs were generally comparable between the 2 treatment groups. The majority of TEAEs were mild or moderate in intensity, and there was a comparable frequency of severe TEAEs in the ciclesonide-HFA (13.5%) and beclomethasone-HFA (14.9%) groups.
- A total of 83 subjects had serious adverse events, 77 of whom had serious TEAEs (i.e. events that occurred during the on-treatment period): ciclesonide-HFA: 31 subjects, 4.0%; beclomethasone-HFA: 46 subjects, 5.9%. Two of these 83 subjects had serious adverse events that resulted in death (a case of acute myocardial infarction in the ciclesonide-HFA group, and a case of completed suicide in the beclomethasone-HFA group); neither event was considered by the investigator to be related to study medication.
- The most frequent TEAE leading to permanent discontinuation of study medication was asthma, which occurred more frequently in the ciclesonide-HFA group (11 subjects, 1.4%) than in the beclomethasone-HFA group (1 subject, 0.1%); there was no obvious reason for this imbalance in the absence of other signals for lack of maintenance of asthma control in the ciclesonide-HFA group. In addition to the comparable maintenance of asthma control in the 2 treatment groups, both groups were also highly comparable regarding the frequencies of subjects reporting asthma as a TEAE, as a serious TEAE, as a severe TEAE, and as a possibly related TEAE.
- There was no sign of ocular toxicity associated with ciclesonide-HFA over beclomethasone-HFA.
- There were no signals of concern in any of the clinical laboratory data or in any of the vital signs or physical examination data.

Issue date: 03-March-2008