

3 Study # XRP1526B/3027

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

3.1 Protocol

3.1.1 Administrative

Enrollment Dates: January 19, 2004 – June 21, 2005
Screening Centers: 102 centers in the USA, 7 in Poland and 10 in S. Africa
Sponsor's medical expert:
CRO:

3.1.2. Objective/Rationale

The primary objective of the study was to demonstrate the non-inferiority of ciclesonide compared to beclomethasone-HFA in the occurrence of a Class I lens event for nuclear opalescence, cortical, and posterior subcapsular lens opacification within 12 months. Lens event outcomes were determined by the occurrence of a protocol-specified change in lens opacification using the LOCS III method for grading lens opacities, or the occurrence of cataract surgery.

The secondary objective of the study was to compare ciclesonide to beclomethasone for changes in various subscores of the LOCS III.

3.1.3. Study Design

This was a multinational, multi-center, randomized, double-blind, active-controlled, parallel group study of the effects of ciclesonide-HFA 640 mcg daily and beclomethasone 640 mcg daily on lens opacification in adults with moderate to severe persistent asthma. Eligible subjects were enrolled into a 1 to 14-day screening period after which they were randomized (1:1) to receive either ciclesonide or beclomethasone by inhalation. They were treated for 12 months and seen in follow-up at 4, 8, and 12 months after initiation of treatment. At each visit a slit-lamp examination was performed to grade lens opacities. Visual acuity, intraocular pressure and pulmonary function were also assessed at each visit. Throughout the treatment period the subjects maintained a diary indicating how much study medication they took every day.

Reviewer: Although it is logical that the subjects would have continued their maintenance ICS during the run-in period, this is not specified in the protocol.

3.1.3.2 Protocol Amendments

Protocol Amendment 1 (May 19, 2004) stipulated that the number of clinical centers would be reduced from 200 to 125. It also increased the sample size from 1200 to 1500.

Protocol Amendment 2 (November 20, 2004) stated that all subjects in the modified intent-to-treat (ITT) population were to be analyzed according to the treatment randomized to unless there was a drug dispensing error. If the subject received the incorrect **drug under the study staff's** direction, they were to be returned to the correct arm as soon as possible. The order of the ophthalmology examinations was specified and the ophthalmologist was instructed not to review the previous LOCS III assessments.

Protocol Amendment 3 (June 28, 2005) was implemented due to an unexpectedly high incidence of Class I events. The non-inferiority bound (NIB) was originally chosen to detect infrequent events. Therefore, the sponsor adjusted the original NIB for event rates $\geq 30\%$ to a constant value of 1.333. This bound allowed the conclusion of non-inferiority if the number of Class I lens events with test treatment was not more than a third larger than that of the control treatment.

Reviewer: Protocol Amendment 3 was submitted to the Agency for review. The Agency did not accept the logic for the change in NIB and reported to the Applicant that the NIB should be no higher than 1.11 (See FDA Statistics Review for details).

3.1.4. Study Population

Inclusion Criteria

- Males and females 18 years or older
- Moderate to severe persistent asthma of at least 2 months prior to Screening
- At Screening, forced expiratory volume in one second (FEV₁) $\geq 40\%$ and $\leq 85\%$ of predicted
- Documented use of ICS therapy at any dose for at least one month prior to Screening
- Ability to demonstrate acceptable oral inhaler technique
- Non-smoker for at least the past year and less than a 10 pack-year total smoking history
- Written informed consent agreement.

Exclusion Criteria

- History of prior cataract surgery in either eye
- Evidence of congenital cortical cataract
- LOCS III criteria
 - Inability to grade opacities in either eye with LOCS III at the baseline
 - Inability to dilate pupils to at least 6.0 mm
 - Nuclear opalescence with a LOCS III grade ≥ 4 in either eye at the baseline
 - Cortical lens opacities with a LOCS III grade ≥ 3 in either eye at the baseline
 - Posterior subcapsular lens opacities with a LOCS III grade ≥ 2 in either eye at the baseline

- Elevated intraocular pressure requiring treatment
- BCVA less than 74 letters (equivalent to vision worse than 20/30) in either eye at baseline
- Females who were pregnant, lactating or had a positive pregnancy test at screening
- More than one in-patient hospitalization in the past year for asthma exacerbation
- More than 2 bursts of oral steroids per year for each of the past 2 years prior to Screening
- Chronic use of oral, injectable, or topical steroids except for ICSs for any condition. Topical corticosteroids designated as having a mild potency by the Stoughton-Cornell Scale or the European Guideline for levels of corticosteroid activity were allowed
- Any chronic condition likely to require treatment with oral or systemic corticosteroids other than asthma
- Topical ocular steroid treatment within 3 months prior to Screening
- Chronic or recurrent inflammatory disease in either eye likely to result in visual abnormalities or require treatment with ocular steroids
- History of drug or alcohol abuse
- Any clinically significant medical condition that would interfere with **the subject's ability** to participate in and comply with the study protocol
- Subject was the investigator or any sub-investigator, research assistant, pharmacist, study Staff or relative thereof directly involved in the conduct of the study
- Hypersensitivity to the investigational products
- Treated with any investigational drug/product within 30 days prior to Visit 1 (Screening).

Withdrawal Criteria

Subjects could be withdrawn if any of the following occurred:

- At their own request
- In the investigators opinion continued participation in the study would be detrimental to the subject
- In the event of a protocol deviation at the discretion of the Investigator or the Sponsor

Subjects had to be withdrawn if any of the following occurred:

- Poor compliance defined as failure to take medication or to come to clinic visits
- Exacerbation of asthma requiring >2 courses of systemic corticosteroids
- Pregnancy
- Cataract surgery

3.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Ciclesonide MDI-HFA 320 mcg BID (4 puffs 80 mcg BID)

- Beclomethasone-HFA MDI 320 mg BID (4 puffs 80 mcg BID)

Reviewer: The dosing regimen may have been determined by the lack of availability of a higher strength formulation of beclomethasone. However, requiring 4 puffs rather than 2 of 160, might tend to decrease compliance.

Compliance was assessed by the patient's notation in the diary that the medication was taken. The number of inhalers returned was also compared to the number dispensed. At 35 selected sites blood was collected for ciclesonide and des-ciclesonide levels as an exploratory way of measuring compliance. The intent was to collect serum samples on at least 375 randomized subjects.

Concomitant medications were supposed to have been kept to a minimum during randomized treatment. The following concomitant medications were permitted throughout the study:

- Intranasal corticosteroids: up to 1 month if absolutely necessary for severe allergic rhinosinusitis
- Systemic corticosteroids: up to 2 bursts for the treatment of acute asthma. If a third course was required the subject had to be withdrawn
 - Recommended dose of prednisone was 60 mg as a single dose for 3 days followed by a 10 mg/day taper over the next 5 days
 - The decision to initiate or continue the course for >8 days was left to the investigator, but should be discussed with sponsor
 - Systemic corticosteroids for other conditions were allowed if absolutely necessary
- Mild-potency topical corticosteroids
- β_2 -agonists, long and short-acting
- Leukotriene receptor antagonists
- Xanthine derivatives
- Cromolyn
- Anticholinergic agents

The following concomitant medications were prohibited from screening onward:

- Non-study ICS
- Chronic use of otic or ophthalmic preparations containing corticosteroids

Ophthalmologic Examination

Ophthalmologic examinations were performed at baseline, and month 4, 8, and 12. The same ophthalmologist was to perform the examinations on each subject; if this was impossible, a trained and certified examiner was to be substituted. The examination consisted of the following procedures performed in the order listed:

- Manifest refraction
- Visual acuity of each eye

- Intraocular pressure measured by tonometry.
- Slit lamp examination for Lens grading: LOC III
 - Nuclear opalescence
 - Nuclear color
 - Cortical lens opacity
 - Posterior subcapsular lens opacity

To assure consistency, the examiners were trained at baseline and recertified twice during the trial. Recertification required 70% correct answers on a certification examination.

Other Safety Variables

Adverse events, routine hematology and chemistry blood tests, and urinalysis for glucose and protein were performed at baseline and at month 4 and 12. Serum for ciclesonide and des-ciclesonide was collected at selected centers at baseline and month 4 and 12. Physical examinations and vital signs completed the safety evaluation.

Efficacy Evaluation

Efficacy was not the primary objective of the study but pulmonary function was monitored with spirometry. The forced vital capacity was obtained following the 1994 ATS standards at baseline and at all follow-up visits.

Schedule of Events

The timing of the various examinations is summarized in Table 44.

Table 44. Summary of Events

Study Day	Screen	Random	Treatment Period				
	-1 to -14	0	1	60	120	180-300	365
Visit number	1		2	3	4	5,6,7	8
Informed consent	X						
Randomization		X					
Medical history	X						
Physical examination	X				X		X
Review medication	X		X	X	X	X	X
Spirometry	X		X	X	X	X	X
Ophthalmology exam*	X				X	X**	X
Laboratory tests	X				X		X
Issue & Review Diary	X		X	X	X	X	X
Adverse event review			X	X	X	X	X
Dispense appropriate medications			X	X	X	X	X

*Ophthalmologic exam consists of refraction, visual acuity, IOP, and slit lamp examination

**Only performed at visit 6 (month 8)

3.1.6 Analysis

Primary Variable

The primary efficacy evaluation was based on the ophthalmologic examination. Lens opacification was assessed by slit lamp examinations using the LOCS III classification. The primary endpoint was the occurrence of a Class I lens event within 12 months. A Class I lens event was defined as any of the following events in either eye:

- Increase from baseline in LOCS III grade of ≥ 0.5 (nuclear opalescence), or ≥ 0.8 (cortical) or ≥ 0.5 (posterior subcapsular)
- Cataract surgery since baseline

If a subject had any of the events listed above during the 12 months of treatment they were classified as having the event for analysis purposes. This was true even if the event was not observed at a later date.

Key secondary variables

LOCS III lens events

- Occurrence of a Class II lens event. A Class II lens event is defined as any of the following events in either eye:
 - Increase from baseline in LOCS III grade of ≥ 0.9 (nuclear opalescence), ≥ 1.5 (cortical), or ≥ 0.9 (posterior subcapsular),
 - Cataract surgery
- A sustained Class II lens event is defined as a Class II lens event observed at any time point with presence of a Class I lens event in the same eye at the next time point. If the Class II lens event was observed only at the last examination, then there should also be a Class I lens event in the same eye at the time point immediately preceding the last one.
- Occurrence within 12 months in either eye of a Class III lens event. A Class III lens event is defined as any of the following events in either eye
 - 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),
 - Cataract surgery.

Change in LOCS III grade from baseline

- Maximum increase in LOCS III grade during the study for (a) nuclear opalescence, (b) cortical opacity, and (c) posterior subcapsular opacity by eye and in either eye
- Change from baseline to each timepoint in LOCS III grade for (a) nuclear opalescence, (b) cortical opacity, and (c) posterior subcapsular opacity. The change from baseline was derived by eye and for the highest value in either eye for each subject.

Other secondary variables

- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.5 (nuclear opalescence) in either eye
- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.8 (cortical) in either eye

- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.5 (posterior subcapsular) in either eye

Best-corrected visual acuity score

The BCVA score was calculated as the sum of the number of letters read correctly at the 4-meter distance plus 30 added if 20 or more letters were read correctly. If fewer than 20 letters were read, the score was the sum of the number of letters read correctly at the 4-meter distance plus the number of letters read at the 1-meter distance.

The following endpoints were reported:

- Change from baseline to each time-point in BCVA, derived by eye and for the lowest value in either eye for each subject;
- Change from baseline to the lowest on-study visual acuity by eye and in either eye.

Intraocular pressure

Two measurements were made and a third measurement was to be done if the first 2 measures differed by more than 2 mmHg. The median of the 2 or 3 measurements became the intraocular pressure determination. The median was calculated as the mean (midpoint) of the 2 measurements or was the middle value when the 3 measurements are arranged in ascending or descending order.

The following endpoints were reported:

- Change from baseline to each time-point in median intraocular pressure (mmHg), derived by eye and for the highest value in either eye for each subject;
- Change from baseline to the highest median intraocular pressure (mmHg) on-study by eye and in either eye.

Other events

Negative lens events were recorded when the LOS III readings decreased

A non-reversing event was one that was present at two visits

Pulmonary Function Variables

The following endpoints were reported:

- Change in post-bronchodilator FEV₁ (L) from baseline to Month 4, Month 8, Month 12 and end of study, where the end of study time point was the last available time point under treatment derived using the last observation carried forward (LOCF) principle
- Percent change in post-bronchodilator FEV₁ from baseline to Month 4, Month 8, Month 12 and end of study
- Change in post-bronchodilator FEV₁ percent predicted from baseline to Month 4, Month 8, Month 12 and end of study
- Change in post-bronchodilator FVC (L) from baseline to Month 4, Month 8, Month 12 and end of study.

3.1.6.1 Statistical Analysis Plan

Sample Size

This study was an assessment of non-inferiority of ciclesonide-HFA compared with beclomethasone-HFA for the primary endpoint of Class I lens event. Non-inferiority was demonstrated if the upper bound of the one-sided 97.5% confidence interval of the risk ratio was less than the NIB. Sample size was computed using the following expression based on the Taylor series expansion of the variance of the logarithm of the risk ratio (1).

$$\text{var}(\log_e(p_T / p_C)) \approx \frac{1}{n} \left(\frac{1}{R} + 1 \right) - \frac{2}{n}$$

A LOCS III-based Class I lens event rate of approximately 8% was anticipated in the control group. No data were available in the intended study population. The event rate was extrapolated from the finding of a 3% lens event rate (defined using a larger change in lens opacity) in subjects of 40 to 49 years of age in the Age-Related Eye Disease Study (AREDS)(2). Using the criteria described above in subjects whose mean age was approximately 65 years was anticipated to increase the rate to approximately 8% within 12 months. As specified in the protocol, approximately 503 subjects were required per treatment group to achieve 90% power for non-inferiority based on a one-sided 97.5% confidence interval of the risk ratio. The anticipated drop out rate was increased based on observations from an earlier long-term study [XRP1526B-323/324LT] completed after the original protocol for the cataract study had been written. Therefore Protocol Amendment 1 was required to increase the sample size. It was therefore planned to randomize 1500 subjects into 2 treatment groups (750 subjects per group), assuming a discontinuation rate of 30%.

Study Populations

The modified intention to treat (mITT) population included all randomized subjects who received medication and who had at least 1 valid post treatment LOC III measurement.

A LOCS III measurement was deemed valid (each eye evaluated separately) if:

- The diameter of the pupil was at least equal to 6 mm (with or without eye dilatation)
- The LOCS III grade was within the valid range for nuclear opalescence (0.1 to 6.9) and for cortical or posterior subcapsular opacities (0.1 to 5.9)
- The examination was done by a certified ophthalmologist according to the list of valid certification numbers for that site
- The post-baseline LOCS III measurements were done at least after one month following exposure to the study drug and within 14 days from the end of study treatment period

The per-protocol (PP) population consisted of all the subjects in the mITT population who did not have an important protocol deviation. The determination about the presence of an important protocol deviation was made for each subject prior to breaking the blind.

The list of major protocol violations includes the following events prior to treatment:

Prior to Screening

- No documented use of ICS therapy for asthma at any dose for at least 21 days during the month prior to Screening;
- History of prior cataract surgery in either eye
- Nuclear opalescence with a LOCS III grade ≥ 4 in either eye at the screening slit-lamp examination
- Cortical lens opacities with a LOCS III grade ≥ 3 in either eye at the screening slit-lamp examination
- Posterior subcapsular lens opacities with a LOCS III grade ≥ 2 in either eye at the screening slit-lamp examination
- Elevated intraocular pressure (> 25 mmHg) requiring treatment for glaucoma (ATC S01E) at Screening
- BCVA score of less than 72 letters in either eye at Screening
- Treatment with more than 2 bursts of oral (prednisolone 60 mg/day for 3 days) or injectable (one shot of injectable equivalent to one burst of oral) steroids per year for each of the past 2 years prior to Screening
- Topical ocular steroid treatment within 3 months prior to Screening unless agreed with the sponsor
- Chronic use of oral steroids except ICSs for any condition.

During Treatment

- Use of non-study medication ICSs for more than 14 days prior to an eye examination (i.e., between 2 consecutive visits);
- Use of any ocular steroid at any time during the treatment period for more than 14 days;
- Use of intranasal corticosteroids continuously for more than one month;
- Subject received more than 2 bursts of oral (prednisolone 60 mg/day for 3 days) or injectable (one shot of injectable equivalent to one burst of oral) steroids during the 12-month treatment period;
- Overall compliance to study medication was less than 70%;
- Less than 4 months on study medication.

Statistical Analysis

Analysis of the primary endpoint was determined by the life-table estimate of the event at Month 12 using the mITT population. Since the number of subjects who completed the study with no event was expected to be high, the cumulative probability of failure in the standard life-table estimate would have been an overestimate. Therefore an alternative method, which managed withdrawals with their actual fractions of completion for the interval of withdrawal was used. Three time intervals were defined as 0 to 120, 121 to 240, and 241 to 360 days. Non-inferiority of ciclesonide-HFA versus the control (beclomethasone-HFA) was demonstrated if the upper bound of the one-sided 97.5% confidence interval was less than the NIB (see section below). If non-inferiority was demonstrated, then superiority of ciclesonide-HFA over control was to be subsequently tested by comparing the upper bound of the one-sided 97.5% confidence interval to one.

If non-inferiority of ciclesonide-HFA versus the control was demonstrated for the primary endpoint of Class I lens events, then non-inferiority of ciclesonide-HFA based on Class II, sustained Class II, and Class III lens events was also assessed using a one-sided 97.5% confidence interval for each type of event.

Subjects who withdrew prior to study completion without a Class I lens event were considered censored for this analysis. Since the withdrawal of subjects before the occurrence of a Class I lens event was expected to be unrelated to lens opacification, it was assumed that the censoring for the primary endpoint of Class I lens events was non-informative. Any event occurring after 390 days was censored for the analysis. Subjects with an early termination visit within the first 30 days after first intake of study medication were censored regardless of the outcome of the LOCS III examination.

Non-inferiority bound

The NIB was defined as a function of the control event rate for pc ranging from 2% to 12%:

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

This function insured that the risk ratio would not be greater than 1.5 with 503 subjects per group, which the Applicant accepted as clinically relevant. Blinded review of the data indicated a higher rate of events than expected. Therefore the NIB function defined in the study protocol was extended to a higher range, maintaining a decreasing functional form, with a minimum of 1.333. The NIB was then the maximum of 1.333 and the value obtained by the function. The NIB could not be less than 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.

Reviewer: The above analysis was not agreed upon by the Agency (See FDA Statistical Review for details). The ophthalmology consult felt that the NIB should be no higher than 1.11.

Pooling of Centers

For statistical analysis, centers with less than 3 subjects per treatment group were pooled. Centers were ordered within country (USA, Poland, and S Africa) by number of subjects. Starting with the smallest enrollers, centers were added sequentially until the pooled group contained at least 3 subjects per treatment group. For statistical purposes the pooled groups were considered single centers.

3.2. Results

3.2.1. Study Population

Disposition

A total of 2032 subjects were screened and 464 failed, resulting in randomization of 1568 subjects (785 to ciclesonide 320 mcg BID (C320) and 783 to budesonide (BDP). Of those enrolled, 1552 subjects received treatment and were included in the safety population (Table 45). Of those who were randomized and treated, 743 C320 and 742 BDP subjects had valid ophthalmologic examinations and were included in the mITT population. This represented 94.7% of the randomized population. The per-protocol (PP) population (those without major protocol violations) consisted of 673 C320 and 676 BDP subjects (86% of those randomized).

Of the 1552 subjects who were randomized and treated, 1354 (86.4% of those randomized) completed the course of treatment. Withdrawal was equivalent in the two treatment groups (14.4% in the C320 group and 12.9% in the BDP subjects). Differing from the short term efficacy trials, but similar to other long-term follow-up studies, the most common cause of withdrawal was patient request (4.2 and 4.1% of the C320 and BDP subjects, respectively). Adverse reactions were the second most common indication for withdrawal (3.7, and 2.8% in the C320 and BDP subjects, respectively). Loss to follow-up accounted for 1.7% of those randomized and lack of efficacy was reported as a reason for withdrawal in only 0.5% if those randomized,

Table 45. Disposition of Subjects in Study 3027

	C320	BPD	Overall
Randomized	785	783	1568
Treated	776 (98.9)	776 (99.1)	1552 (99.0)
Discontinued	113 (14.4)	101 (12.9)	214 (13.64)
Reason for discontinuation:			
Did not wish to continue	33 (4.2)	32 (4.1)	65 (4.1)
Adverse event	29 (3.7)	22 (2.8)	51 (3.3)
Lost to follow-up	16 (2.0)	10 (1.3)	26 (1.7)
Protocol violation	15 (1.9)	21 (2.7)	36 (2.3)
Lack of efficacy	5 (0.6)	3 (0.4)	8 (0.5)
Death	1 (0.1)	1 (0.1)	2 (0.1)
Other	14 (1.8)	12 (1.5)	26 (1.7)

Reviewer: The drop-out was approximately ½ of the 30% expected and used to calculate the sample size.

Of the 1568 subjects randomized, 36 (2.3%) subjects were withdrawn for major protocol violations. The number withdrawn for protocol violations was greater in the BDP group (2.7% compared with 1.9% of the C320 subjects). However, the number of subjects in the mITT population who took some form of prohibited corticosteroid was greater in the C320 group (49) than in the BDP group (33) and fewer of the C320 subjects (17) than the BDP subjects (23)

failed to take study medication as prescribed. Overall, the subjects in the mITT who were treated with ciclesonide had a higher exposure to corticosteroids than did the BDP subjects. All of the subjects with concomitant steroid exposure or with failure to take study medication as prescribed were excluded from the PP population.

Reviewer: Text Table 11 (pg 113 of the study report) lists the protocol violations that were present in the mITT population, not protocol violations that led to exclusion. This is concluded from an analysis of datasheet ASV.xpt. Most of the subjects excluded from the mITT were excluded because of lack of a valid post-treatment ophthalmology examination.

Demographics

Of the 1485 subjects in the mITT population 39.9% were male and the mean age (Range) was 43.1 (18 - 80) years (Table 46). More than 60% were over 40 years of age, and 130 (63 in the C320 group and 67 in the BDP group) were over 60 years of age. The predominant racial group was White (83.5% compared with 8.8% Black and 7.7% Other). Most of the subjects (76.8%) were never smokers and the US was the site of enrollment of 84.6% of the subjects.

Table 46. Demographic Characteristics of the ITT Population

	C320	BDP	Overall
Total ITT Population	743	742	1485
Gender, % M	(40.0)	(39.8)	(39.9)
Age, mean (SD)	42.9 (12.9)	43.3 (12.6)	43.1 (12.8)
≥40 years, N (%)	460 (61.9)	466 (62.8)	926 (62.4)
Race, %			
White	83.0	84.0	83.5
Black	9.2	8.5	8.8
Other	7.8	7.5	7.7
Smoking History			
Never	76.6	77.0	76.8
Region, %			
USA	84.7	84.6	84.6
Poland	6.5	6.2	6.3
South Africa	8.9	9.2	9.0

The baseline ophthalmologic values (Table 47) were almost identical in the two treatment groups. The range of values for intraocular pressure were somewhat smaller for the BDP subjects (8.0 – 24.0) than for the C320 subjects (6.0 – 30.0), but the means were very close (14.8 and 14.6 for the right and left eyes in the C320 subjects and 4.8 and 14.7 in the right and left eyes of the BDP subjects).

Table 47. Baseline values for ophthalmologic examinations

Treatment	C320 (N=743)		BDP (N=742)	
	R	L	R	L
Nuclear opalescence*	1.4 (0.9) 0.1 - 3.8	1.4 (0.9) 0.1 - 3.8	1.4 (0.9) 0.1 - 3.7	1.4 (0.9) 0.1 - 3.7

Cortical opacity*	0.4 (0.6) 0.1 - 3.2	0.4 (0.5) 0.1 - 3.1	0.4 (0.6) 0.1 - 2.9	0.4 (0.5) 0.1 - 2.9
Posterior subcapsular opacity*	0.2 (0.2) 0.1 - 1.8	0.2 (0.2) 0.1 - 2.0	0.2 (0.2) 0.1 - 1.9	0.2 (0.2) 0.1 - 2.0
Visual Acuity	87.0 (4.7) 58 - 100	86.9 (4.9) 65 - 99	87.0 (4.8) 66 - 99	87.0 (4.9) 64 - 99
Intraocular pressure	14.8 (3.0) 6.0 - 30.0	14.6 (3.0) 6.5 - 28.0	14.8 (2.8) 8.0 - 22.5	14.7 (2.8) 8.0 - 24.0

* Part of LOC III examination

The mean (SD) duration of asthma was 21.7 (13.8) years (Table 48), and all of the subjects had used an inhaled corticosteroid within 90 days of enrollment. Short acting selective β -adrenergic agonists were the second most frequently used medication (88.4 and 90.2% of the C320 and BDP subjects, respectively). The mean (SD) FEV₁ was 2.4 (0.6) L and the mean (SD) FEV₁ percent predicted was 71.7 (10.6) percent.

Table 48. Characteristics of Asthma – ITT Population

	C320	BDP	Overall
Total	743	742	1485
Duration			
Years, mean (SD)	21.9 (15.5)	22.3 (14.7)	22.1 (15.1)
Range	0.3 - 63.8	0.2 - 64.0	0.2 - 64.0
FEV ₁			
Mean Absolute, ml (SD)	2.4 (0.6)	2.4 (0.6)	2.4 (0.6)
Range	0.5 - 4.3	0.8 - 4.3	0.5 - 4.3
FEV ₁			
Mean % predicted, % (SD)	71.7 (10.7)	71.6 (10.6)	71.7 (10.6)
Range	41.0 - 90.2	40.3 - 87.1	40.3 - 90.2

Compliance with Treatment

As assessed by diary recordings, more than 88% of the subjects had a compliance of at least 90%. In a subset of 255 subjects treated with ciclesonide, blood levels of ciclesonide and des-ciclesonide were measured to further assess compliance. As can be seen in Table 49, none of the subjects had the parent compound (ciclesonide) or the metabolite (des-ciclesonide) in their blood at screening. At month 4 and 12, 88 to 89% of the subjects had measurable levels of des-ciclesonide and 26 to 29% had measurable levels of ciclesonide. Subjects who terminated early had a lower incidence of positive blood levels for both ciclesonide (0%) and the metabolite (57.1%).

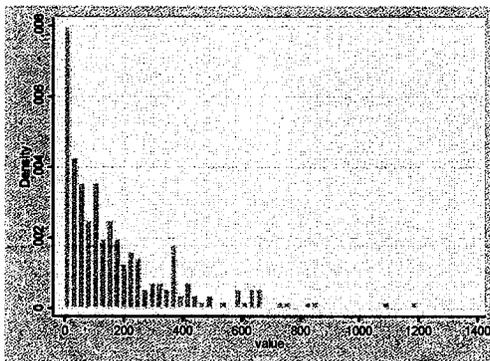
Table 49. Blood Levels of Ciclesonide and its Active Metabolite

Visit / Status	n/N (%) of subjects	
	Ciclesonide (pg/mL) (N = 255)	des-ciclesonide (pg/mL) (N = 255)
Screening		
Absence	242/242 (100%)	242/242 (100%)
Presence	0/242 (0%)	0/242 (0%)
Month 4		
Absence	168/236 (71.2%)	25/236 (10.6%)
Presence	68/236 (28.8%)	211/236 (89.4%)
Month 12		
Absence	173/235 (73.6%)	28/235 (11.9%)
Presence	62/235 (26.4%)	207/235 (88.1%)
Early termination		
Absence	7/7 (100%)	3/7 (42.9%)
Presence	0/7 (0%)	4/7 (57.1%)
Overall		
Absence	348/478 (72.8%)	56/478 (11.7%)
Presence	130/478 (27.2%)	422/478 (88.3%)

Note: 11 subjects among the 255 subjects to be sampled had no serum concentration measurement at any visit.

The actual values of the blood levels varied widely (Figure 8). For instance, the endpoint value for the metabolite ranged from 10.4 to 1200 pg/mL (0.01 to 1.2 ng/mL) and the value for ciclesonide ranged from 25.4 to 1180 pg/mL. For the RM1 metabolite at Month 12, 75% of the measurable levels were >57.9 pg/mL and 50% were higher than 130 pg/mL (104/235 = 44.3% of the total population sampled).

Figure 8. Blood Levels of RM1 After 12 Months of Treatment



Reviewer: In the study report there is no mention of the time the samples were taken or the relationship of the blood draw to the daily study medication. The values, therefore, are random samples taken during chronic treatment and are not directly comparable to the Cmax values reported in previous studies. However, in study 41/2003 the geometric mean Cmax, obtained after treatment with a single dose of 400 mcg (320 mcg ex-actuator) was 0.313 ng/mL

3.2.2. Efficacy Results

Primary Efficacy Outcome

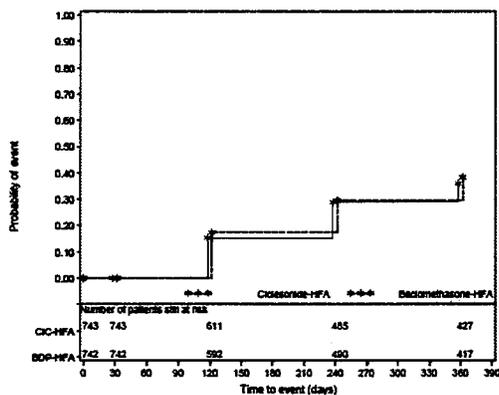
By the life-table analysis, the incidence of Class I ophthalmology events was slightly lower (36.1%) in the ciclesonide-treated subjects than in the BDP-treated subjects (38.4%). The risk ratio (95% CI) comparing ciclesonide to BDP was 0.94 (0.82, 1.08) and the p-value for non-inferiority was <0.0001 (Table 50). The results of the per-protocol analysis were supportive. If subjects with major protocol violations were excluded, the risk ratio (95% CI) was 0.926 (0.803, 1.068). As part of a further sensitivity analysis, the risk was also calculated assuming that all drop-outs as had the event. In this instance the risk ratio (95% CI) was 0.971 (0.864, 1.091).

Table 50 . Analysis of Class I Lens Events in the mITT Population by Life-table Estimate

	N	% of Subjects with Class I event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320	743	36.1 (1.82)	0.94	0.82, 1.08	1.33	<0.0001
BDP	742	38.4 (1.83)				

The development of Class I changes in the mITT population are shown graphically in Figure 9.

Figure 9. Development of Class I events



No important subgroup interactions were noted.

Secondary efficacy outcome measures

Class II events are more severe and they were less common than Class I events. Of the subjects treated with ciclesonide, 14.0% showed Class II changes compared with 16.4% of the subjects treated with BPD. Similarly, sustained Class II (See Section 3.1.6 Key Secondary Events for definition) events were reported in 9.4% of the ciclesonide and 11.5% of the BDP-treated subjects (Table 51).

Table 51. Change in Class II Lens Events

	N	% of Subjects with Class II event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320	743	14.0 (1.31)	0.86	0.67, 1.10	1.62	<0.0001
BDP	742	16.4 (1.39)				
	N	% of Subjects with sustained Class II event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320	743	9.4 (1.11)	0.821	0.60, 1.12	1.796	<0.0001
BDP	742	11.5 (1.20)				

Class III events were reported for 57 (7.7%) of the C320 subjects and 65 (8.8%) of the BDP-treated subjects. The only subject who had cataract surgery during the course of the trial was in the BDP group.

The LOCS III classification is made up of a combination of three evaluations: nuclear opalescence, cortical opacity, and posterior subcapsular opacity (PSC). While all may affect vision, the PSC changes are most characteristic of the changes induced with corticosteroid treatment. As shown in Table 52 the percentage of subjects with Class I, II, and III events was consistently lower in the C320-treated subjects compared to the BDP subjects, but the percentage with the Class I, II, and III changes in the sub-score for PSC opacity was consistently higher for the C320 subjects. If this represents a corticosteroid treatment-related event the small differences could become clinically meaningful over years of treatment.

Table 52. Number (%) of Subjects by LOCS III Classification and Treatment group

Type of lens event	Observed proportions: Number (%) of subjects		Life table estimates: Percent of subjects ± SE	
	CIC-HFA (N = 743)	BDP-HFA (N = 742)	CIC-HFA (N = 743)	BDP-HFA (N = 742)
Class I	255 (34.3%)	273 (36.8%)	36.1 ± 1.8	38.4 ± 1.8
Nuclear opalescence	210 (28.3%)	227 (30.6%)	29.7 ± 1.7	32.0 ± 1.8
Cortical opacity	60 (8.1%)	66 (8.9%)	8.5 ± 1.1	9.3 ± 1.1
Posterior subcapsular opacity	20 (2.7%)	17 (2.3%)	2.8 ± 0.6	2.4 ± 0.6
Class II	99 (13.3%)	117 (15.8%)	14.0 ± 1.3	16.4 ± 1.4
Nuclear opalescence	82 (11.0%)	103 (13.9%)	11.7 ± 1.2	14.5 ± 1.3
Cortical opacity	14 (1.9%)	13 (1.8%)	2.0 ± 0.5	1.8 ± 0.5
Posterior subcapsular opacity	10 (1.3%)	6 (0.8%)	1.4 ± 0.4	0.8 ± 0.3
Sustained Class II	66 (8.9%)	81 (10.9%)	9.4 ± 1.1	11.5 ± 1.2
Nuclear opalescence	55 (7.4%)	71 (9.6%)	7.9 ± 1.0	10.1 ± 1.1
Cortical opacity ^a	6 (0.8%)	9 (1.2%)	0.8 ± 0.3	1.2 ± 0.4
Posterior subcapsular opacity ^a	5 (0.7%)	1 (0.1%)	0.7 ± 0.3	0.1 ± 0.1
Class III	57 (7.7%)	65 (8.8%)	8.1 ± 1.0	9.2 ± 1.1
Nuclear opalescence	44 (5.9%)	54 (7.3%)	6.3 ± 0.9	7.6 ± 1.0
Cortical opacity	12 (1.6%)	11 (1.5%)	1.7 ± 0.5	1.6 ± 0.5
Posterior subcapsular opacity ^a	7 (0.9%)	4 (0.5%)	0.9 ± 0.4	0.5 ± 0.3

BDP = beclomethasone; CIC = ciclesonide.

NC = estimates not calculated because at least one treatment group had less than 10 events.

^a Life table estimates were obtained using the standard life table method if there were fewer than 10 events in each treatment group because the modified method requires 10 or more events in at least one treatment group to provide robust estimates.

In addition to the categorical analysis, the mean cataract grade was compared among the treatment groups. The differences between the two treatment groups are small, but the pattern shown in the categorical analysis is repeated: Cataract size was smaller for the C320 subjects for nuclear and cortical opacities, but the PSC opacities were slightly larger compared to BPD treatment (Table 53).

Table 53 Mean changes in LOCS III Scores

Treatment	N	Baseline mean	Change from baseline	Ciclesonide-HFA vs. beclomethasone-HFA	
			LS mean ± SE (LOCS III grade)	LS mean ± SE	2-sided 95% CI
Nuclear opalescence					
Ciclesonide-HFA	743	1.33	0.22 ± 0.019	-0.016 ± 0.020	-0.056, 0.024
Beclomethasone-HFA	742	1.36	0.23 ± 0.018		
Cortical					
Ciclesonide-HFA	743	0.36	0.14 ± 0.018	-0.018 ± 0.020	-0.057, 0.021
Beclomethasone-HFA	742	0.35	0.16 ± 0.017		
Posterior subcapsular					
Ciclesonide-HFA	743	0.14	0.06 ± 0.009	0.018 ± 0.010	-0.001, 0.037
Beclomethasone-HFA	742	0.15	0.05 ± 0.009		

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; N = mITT population; SE = standard error. Ciclesonide-HFA vs. beclomethasone-HFA is calculated as ciclesonide-HFA minus beclomethasone-HFA.

In the application, the argument is put forward that the distribution of size change was similar in the two treatment groups. In Table 54, the changes are grouped into decrease, no change, and three degrees of increase, and the point is made that most of the subjects had no change or a decrease.

Table 54. Distribution of Change in LOCS III Grade

Variable	Number (%) of subjects	
	Ciclesonide-HFA (N = 743)	Beclomethasone-HFA (N=742)
Nuclear opalescence		
Decrease	121 (16.3%)	145 (19.5%)
No change	151 (20.3%)	123 (16.6%)
Increase by 0.1 to 0.4	261 (35.1%)	247 (33.3%)
Increase by 0.5 to 0.8	128 (17.2%)	124 (16.7%)
Increase by ≥ 0.9	82 (11.0%)	103 (13.9%)
Cortical		
Decrease	48 (6.5%)	49 (6.6%)
No change	343 (46.2%)	320 (43.1%)
Increase by 0.1 to 0.7	292 (39.3%)	307 (41.4%)
Increase by 0.8 to 1.4	46 (6.2%)	53 (7.1%)
Increase by ≥ 1.5	14 (1.9%)	13 (1.8%)
Posterior subcapsular		
Decrease	16 (2.2%)	26 (3.5%)
No change	542 (72.9%)	550 (74.1%)
Increase by 0.1 to 0.4	165 (22.2%)	149 (20.1%)
Increase by 0.5 to 0.8	10 (1.3%)	11 (1.5%)
Increase by ≥ 0.9	10 (1.3%)	6 (0.8%)

The 2 highest categories of increase for each type of opacity together correspond to the Class I lens event criteria, and the highest categories correspond to the Class II lens event criteria.

Reviewer: The distributions in Table actually show that there were a higher proportion of subjects with large increases in PSC in the C320 group (10 [1.3%]) compared to the subjects treated with BDP (6 [0.8%]). The absolute numbers are small, but the proportion suggests that almost twice as many subjects treated with C320 developed these changes compared to the BDP group. Confirming the trend is the increased number of subjects in the BDP group whose opacities decreased (26 [3.5%]) compared to the subjects treated with ciclesonide (16 [2.2%]). Finally, an LOCS III score of 2 or greater is often taken as the cutoff for clinically significant cataracts []. This criterion was satisfied by 11 ciclesonide and 4 beclomethasone subjects at the end of the study. All of these subjects had baseline values of less than 1.4 and all had an increase of at least 1.4 over the course of the study. The results of the primary and supportive secondary analysis are quite consistent. While the overall LOCS III grade was lower in the subjects treated with C320, the scores for the change in PSC were slightly higher in the C320-treated subjects.

In a sub-set analysis, it is stated that the changes in LOCS III were equivalent in all of the age groups. Table 29 in the study report, reproduced here as table 55, shows the proportion of subjects, divided into age groups of 40 and less and over 40 years of age, with Class I, II, III, and sustained Class II events. The proportion with events is slightly higher in the older age groups for all of the categories other than Class III events, but the incidence in the BDP group was higher than that in the subjects treated with C320 in both age groups.

Table 55. Summary of LOCS III by Age (2 groups)

Type of lens event	Percent of subjects ± SE			
	< 40 years		≥ 40 years	
	CIC-HFA (N= 283)	BDP-HFA (N= 276)	CIC-HFA (N= 460)	BDP-HFA (N=466)
Class I lens event	31.1 ± 2.9	31.7 ± 2.9	39.1 ± 2.3	42.3 ± 2.3
Class II lens event	12.2 ± 2.0	14.8 ± 2.2	15.2 ± 1.7	17.3 ± 1.8
Sustained Class II lens event	8.7 ± 1.7	11.5 ± 2.0	9.9 ± 1.4	11.5 ± 1.5
Class III lens event	3.1 ± 1.1	4.2 ± 1.2	1.1 ± 1.5	1.2 ± 1.5

CIC = ciclesonide; BDP = beclomethasone. SE = standard error.

Reviewer: Of note, all of the subjects who had an LOS III grade for PSC of 2 or greater were 40 years of age or older. On the other hand, a cutoff of 40 years of age may underestimate the ability of ICS to potentiate the development of cataracts in older subjects. If the age groups are <40, 40 to 60, and >60 years, it appears that subjects over 60 years of age developed all classes of cataracts at a higher rate when treated with ciclesonide than during treatment with beclomethasone (Table 56). The difference in treatment was most marked for Class II and III events where 25 and 22% of the ciclesonide-treated subjects, respectively, reported events compared with 17.5% of the BDP-treated subjects for both classes of events. If the incidence of PSC is examined separately, the differences are even more dramatic. The mean change in PSC grade in the over 60 age group was 0.184 compared to 0.111 (a 65% increase) in the BDP group (Table 57). Unfortunately, the over 60 age-group was not well represented in the sample. There were only 130 subjects (67 and 63 in the C320 and BDP groups, respectively) over 60 years of

age compared with over 300 in each treatment group who were 40 to 60 years of age and almost 300 in each treatment group less than 40 years of age. Despite the small number of subjects over 60 this finding is of concern since this is the age group most predisposed to develop cataracts.

Table 56. Number of Subjects by LOCS III Scores and Age-group (3 groups)

	<i>Ciclesonide</i>		<i>BDP</i>	
	<i>N</i>	<i>N (%) Positive</i>	<i>N</i>	<i>N (%) Positive</i>
<i>Class I</i>				
<i>Overall</i>	743	255 (34.3)	742	273 (36.8)
<i><40 years</i>	308	89 (28.9)	298	93 (31.2)
<i>40 – 60 years</i>	368	130 (35.3)	381	147 (38.6)
<i>> 60 years</i>	67	36 (53.7)	63	33 (52.4)
<i>Class II</i>				
<i>Overall</i>	743	99 (13.3)	742	117 (15.7)
<i><40 years</i>	308	36 (11.7)	298	43 (14.4)
<i>40 – 60 years</i>	368	46 (12.5)	381	63 (16.5)
<i>> 60 years</i>	67	17 (25.4)	63	11 (17.5)
<i>Class III</i>				
<i>Overall</i>	743	57 (7.7)	742	65 (8.8)
<i><40 years</i>	308	8 (2.6)	298	13 (4.4)
<i>40 – 60 years</i>	368	34 (9.2)	381	41 (10.8)
<i>> 60 years</i>	67	15 (22.4)	63	11 (17.5)

Table 57. Mean Change in PSC Grade by Age*

<i>Age in years</i>	<i>N</i>	<i>Ciclesonide</i>	<i>BDP</i>
<i>< 40</i>	606	0.040	0.024
<i>40 – 60</i>	749	0.049	0.043
<i>> 60</i>	130	0.184	0.111

* Taken from datasets AEF01.xpt through AEF010.xpt

The differences between men and women were small and not clinically meaningful. There was some variability when comparing geographic region (Table 58) but for the most part, the incidence in the C320 group was lower than in the BDP treated subjects. There was a relatively low incidence of Class I events in South Africa for both treatment groups and of Class III events in Poland. In South Africa, sustained Class II and Class III events were more common in the Ciclesonide-treated subjects.

Table 58. LOCS III Scores by Geographic Region

Type of lens event	Percent of subjects ± SE					
	United States		Poland		South Africa	
	CIC-HFA (N= 629)	BDP-HFA (N= 628)	CIC-HFA (N= 48)	BDP-HFA (N= 46)	CIC-HFA (N= 66)	BDP-HFA (N= 68)
Class I lens event	37.4 ± 2.0	39.5 ± 2.0	32.6 ± 7.0	41.8 ± 7.6	26.5 ± 5.6	25.8 ± 5.5
Class II lens event	15.0 ± 1.5	17.2 ± 1.5	6.3 ± 3.6	9.3 ± 4.5	10.8 ± 3.9	13.9 ± 4.3
Sustained Class II lens event	9.5 ± 1.2	11.7 ± 1.3	6.3 ± 3.6	9.3 ± 4.5	10.8 ± 3.9	10.7 ± 3.9
Class III lens event	8.4 ± 1.1	9.6 ± 1.2	2.1 ± 2.1	4.7 ± 3.3	9.4 ± 3.7	7.6 ± 3.3

CIC = ciclesonide; BDP = beclomethasone. SE = standard error.

Source: Table T - 62, pg. 484, Table T - 72, pg. 496, Table T - 82, pg. 507, Table T - 92, pg. 518

An analysis performed on subgroups defined by baseline category of opacities showed similar changes in the two treatment groups when the absolute increase in mean area of opacities was compared. However, this analysis also showed a larger increase in PSC for most categories compared to BDP.

Other Ophthalmologic Variables

The LS mean (SE) decrease in visual acuity was 2.65 (0.15) for ciclesonide-treated subjects and 2.96 (0.15) for subjects treated with beclomethasone. The mean (SD) increase in intraocular pressure was 1.48 (2.25) and 1.64 (2.18) mm Hg in the ciclesonide and BDP-treated subjects, respectively. The median change was 1.5 mm Hg in **both groups with a range of - 6.0 to 16.0** mm Hg in the ciclesonide group and -5.5 to 9.0 mm Hg in the BDP group.

Asthma Control

Post-bronchodilator pulmonary function was obtained at baseline and at each follow-up visit. The analyses were performed on the subjects who were in the study at the time of measurement. Improvement in function was seen in both treatment groups, but it was very small and the difference between C320 and BDP was inconsequential (Table 59).

Table 59. Pulmonary Function After 12 months of Treatment with C320 and BDP

Parameter Treatment	N	Baseline mean	Change from baseline LS mean \pm SE	Difference vs. beclomethasone-HFA	
				LS mean \pm SE	2-sided 95% CI
FEV₁ (L)					
Ciclesonide-HFA	739	2.68	0.06 \pm 0.014	-0.013 \pm 0.015	-0.043, 0.017
Beclomethasone-HFA	740	2.71	0.08 \pm 0.013		
FEV₁ percent predicted					
Ciclesonide-HFA	739	79.4	1.14 \pm 0.401	-0.624 \pm 0.445	-1.497, 0.249
Beclomethasone-HFA	740	80.5	1.76 \pm 0.396		
Percent change in FEV₁ ^a					
Ciclesonide-HFA	739	2.68	3.14 \pm 0.572	-0.862 \pm 0.642	-2.121, 0.396
Beclomethasone-HFA	740	2.71	4.00 \pm 0.569		

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; N = mITT population; SE = standard error.

^a FEV₁ at baseline measured in liters.

Differences vs. beclomethasone-HFA are calculated as ciclesonide-HFA minus beclomethasone-HFA.

Source: Table T - 142, pg. 595; Table T - 148, pg. 607; Table T - 145, pg. 600

3.2.3. Safety

3.2.3.1 Exposure

The total safety population included 1552 individuals, 776 in each treatment group. Exposure to study medication was comparable in the two treatment groups. The mean (SD) exposure was 337.7 (68.7) and 339.4 (68.1) days in the C320 and BDP-treated subjects, respectively. The respective ranges were 10 to 380 and 18 to 386 days.

3.2.3.2 Adverse Events

Overall Assessment of Adverse Events

The overall incidence of AEs was slightly lower in the C320 group than in those treated with BDP (Table 60). The incidence of serious AEs and AEs leading to withdrawal was low, however serious AEs were more common in the BPD group (5.9% compared to 4.0% in the C320 group) whereas AEs leading to withdrawal were more common in the C320 group (3.6% compared to 2.6% in the BDP group). There was one death in each treatment group. Neither was considered by the investigator to be treatment related (See below for details).

Table 60. Overall Summary of Adverse Events.

	C320	BDP	Total
N	776	776	1552
All AEs	648 (83.5)	664 (85.6)	1312 (84.5)
Serious AEs	31 (4.0)	46 (5.9)	77 (5.0)
AEs leading to withdrawal	23 (3.6)	20 (2.6)	43 (2.8)
Deaths	1 (0.1)	1 (0.1)	2 (0.1)

Grouped by MedDRA SOC, the most common adverse events were in the Infections and infestations category (65.2 and 66.6% in the C320 and BDP groups, respectively) followed by Respiratory, Thoracic and Mediastinal disorders (31.3 and 27.3%, respectively) and Musculoskeletal and Connective Tissue Disorders (21.3 and 18.0%, respectively). Gastrointestinal Disorders, Nervous System Disorders, Injury, Poisoning, and Procedural Complications affected 15 to 17% of the subjects in both treatment groups. Eye Disorders were reported in 11% of both treatment groups and Skin, General, Psychiatric, Investigations were reported in 4 to 8%.

Listed by MedDRA preferred term, the most common events were Nasopharyngitis, Upper respiratory tract infection, Sinusitis, Asthma, and Headache (Table 61). Nasopharyngitis was reported in 3.4% more subjects treated with C320 than in subjects treated with BDP while Lower Respiratory Tract Infection and Candidiasis were reported more frequently in the BDP group (2.5 and 4.9% difference, respectively). Most of the other events occurred with similar frequency in the two groups (difference <2%), although Pain in extremity and Arthralgia were almost twice as frequent in the C320 group as in the BDP subjects. This corresponds to the elevated level of Connective Tissue Disorders seen in the listing of AEs by SOC.

Table 61. AEs Occurring in 3% or more subjects in any treatment group, by system organ class and Selected preferred terms

SOC and Preferred Term	C320	BDP
N	776	776
All AEs	648 (83.5)	664 (85.6)
Nasopharyngitis	162 (20.9)	136 (17.5)
Upper Respiratory Tract Infection	151 (19.5)	148 (19.1)
Sinusitis	114 (14.7)	108 (13.9)
Asthma	96 (12.4)	100 (12.9)
Headache	81 (10.4)	81 (10.4)
Influenza	60 (7.7)	63 (8.1)
Bronchitis	51 (6.6)	62 (8.0)
Pharyngolaryngeal pain	42 (5.4)	51 (6.6)
Cough	44 (5.7)	43 (5.5)
Back pain	41 (5.3)	53 (6.8)
Diarrhea	35 (4.5)	24 (3.1)
Arthralgia	32 (4.1)	17 (2.2)
Urinary Tract Infection	30 (3.9)	16 (2.1)
Viral upper respiratory tract infection	30 (3.9)	24 (3.1)
Pain in extremity	27 (3.5)	15 (1.9)
Gastroenteritis viral	25 (3.2)	19 (2.4)
Sinus headache	18 (2.3)	25 (3.2)

Nausea	16 (2.1)	25 (3.2)
Lower Respiratory Tract infection	12 (1.5)	31 (4.0)
Oral candidiasis	11 (1.4)	49 (6.3)

Tabulating oropharyngeal adverse events separately, resulted in a balance of events in the two treatment groups (Table 62). Oral candidiasis, oropharyngeal candidiasis and Pharyngolaryngeal pain were more common during BDP treatment while Pharyngitis and Dysphonia were more common during C320 treatment.

Table 62. Oropharyngeal Adverse Events

SOC and Preferred Term	C320	BDP
N	776	776
Oral candidiasis	1.4	6.3
Oropharyngeal candidiasis	0.1	0.4
Pharyngitis	2.6	1.8
Pharyngolaryngeal pain	5.4	6.6
Dysphonia	2.2	1.5

The incidence of AEs classified as Mild and Moderate was approximately equal with > 10% classified as severe. There were 105 (13.5%) events classified as severe in the C320 group and 116 (14.9%) were classified as severe in the BDP group.

Alert Terms

The following description occurs on page 151 of the study report:

“Ophthalmologic findings considered by the ophthalmologist to be clinically relevant were defined in the clinical study protocol as alert terms. These alert term events were subject to expedited reporting to the sponsor’s Pharmacovigilance department for blinded review while the study was still being conducted. The alert term events recorded in the Pharmacovigilance database consisted of diagnoses and symptoms, and therefore do not correspond directly with the TEAE reporting in the clinical database. The alert term events were not recorded in the CRF and were therefore not entered into the clinical database.”

The section further states that while there were more of these events in the C320 treatment group, some of the events were increased in the BPD group. Conjunctivitis, eye pain, migraine, conjunctivitis allergic, and eye infection more common in the C320 group and vitreous floaters, chalazion, blepharitis, and pinguecula more common in the BPD group. Referring to the reference tables (*Listing C.3.2– 19 and C.3.2– 20*) the total tally of events appears to be 216 for ciclesonide and 172 for BDP.

Serious Adverse Events and Events Leading to Withdrawal

One subject died in each of the treatment groups. A 54 year old obese female who was randomized to ciclesonide and who had a strong family history of myocardial infarction but no personal history of chest pain, hypertension or diabetes was admitted to the hospital

unresponsive and cyanotic. She died later in the **day and the autopsy attributed death to “acute coronary insufficiency due to marked atherosclerotic cardiovascular disease, resulting in fatal myocardial infarction.”** One 31 year old male completed treatment with BDP and 19 days later committed suicide.

Serious adverse events were reported for 31 (4.0%) of the C320 subjects and for 46 (5.9%) of the BPD subjects. The most common events were asthma (5 [0.6%] and 4 [0.5%] in the C320 and BPD subjects, respectively), lobar pneumonia (3 [0.4%] and 1 [.1%], respectively) and nephrolithiasis (2 [0.2%] and 0, respectively). All of the other events occurred in 1 or fewer individuals. If all forms of pneumonia are combined (lobar pneumonia, bronchopneumonia, pneumonia, and pneumonia primary atypical) then there were 6 (0.8%) cases of pneumonia in the C320 group compared to 2 (0.3%) in the BPD group.

Four subjects (1 C320 and 3 BPD) were assessed by the treating physician as sustaining a severe AE that was possibly related to treatment. The C320 subject was a 47 year-old male who had a retinal hemorrhage diagnosed on day 263 of treatment during a routine follow-up ophthalmologic examination. On day 271 the study medication was discontinued due to the onset of the third asthma exacerbation. Of the subjects treated with BDP, one developed significant hypertension and extrasystoles during treatment, one had an elevation in transaminases and one developed a cataract that was treated with surgery. The subject with the elevated transaminases was also taking arthrotec (combination of diclofenac and misoprostol), simvastatin, and zafirlukast. The transaminases remained elevated a week after stopping BPD, but decreased after stopping the other medication.

Withdrawal from treatment due to an adverse event occurred infrequently (28 [3.6%] and 20 [2.6%] of the C320 and BPD subjects, respectively). The excess withdrawals in the C320 group were classified as asthma (11 [1.4%] and 1 [0.1%] in the C320 and BPD groups respectively), dysphonia (2 [0.3%] and 0, respectively) and hypertension (2 [0.3%] and 0 respectively). One subject in each treatment group was withdrawn due to pneumonia/bronchopneumonia but 5 subjects were withdrawn from the BPD group due to an eye complaint compared to 2 in the C320 group. A total of 47 subjects (26 [3.4%] and 21 [2.7%] of the C320 and BPD groups, respectively) had study treatment withheld temporarily due to an adverse event.

Overdosage

A 58 year-old female took 16 puffs bid of C320 on one day and 12 puffs bid on another day. No adverse effects were reported.

3.2.3.6 Laboratory Results

The mean baseline, 4-month and 12-month values for all hematology and routine safety chemistry analyses were within the normal range.

Individual shifts in laboratory values and highly abnormal values were unusual. The eosinophil counts tended to increase over the year of treatment and this trend was more prominent in the

C320 group. Of the subjects who were normal at baseline, none was low at the end of the study and 15 (1.9%) of the C320 and 5 (0.6%) of the BPD subjects had values at the end of the study that were over the laboratory normal value. Similarly, 13/750 (1.7%) of the C320 and 7/748 (0.9%) of the BPD subjects had absolute eosinophil counts that increased more than the predefined abnormal amount (PCA) of 0.37 GG/L. The clinically important level for an increase in absolute eosinophil count was $> 1.0 \times 10^3 \text{ mm}^3$ and this occurred in three C320 subject and no BPD subjects. A clinically important increase in glucose was taken as $> 12.8 \text{ mmol/L}$ and this occurred in one C320 subject and 3 BPD subjects. An increase of $> 5.5 \text{ mmol/L}$ was taken as the PCA for serum potassium and this occurred in 4 BPD subjects. The greatest increase was 5.7 mmol/L.

Abnormal laboratory values were reported as adverse events for 26 (3.4%) of the C320 and 30 (3.9%) of the BPD subjects (Table 63). Other than the subject with elevated transaminase (described above) the events were all considered mild to moderate and none resulted in termination of therapy.

Table 63. Abnormal Laboratory Results

SOC and Preferred Term	C320	BDP
N	776	776
All Laboratory results reported as AEs	26 (3.4)	30 (3.9)
Blood uric acid increased	4 (0.5)	1 (0.1)
Blood glucose increased	3 (0.4)	1 (0.1)
Alanine aminotransferase increased	2 (0.3)	3 (0.4)
Aspartate aminotransferase increased	2 (0.3)	3 (0.4)
Blood alkaline phosphatase increased	2 (0.3)	0
Hypokalemia	2 (0.3)	1 (0.1)
Blood cholesterol increased	1 (0.1)	2 (0.3)
Hypercholesterolemia	1 (0.1)	2 (0.3)
Oral candidiasis	0	3 (0.4)
Diabetes mellitus	0	1 (0.1)
Hematuria	0	2 (0.3)
White blood cell increased	0	3 (0.4)

Visual Acuity

During the conduct of the study, the DSMB requested heightened follow-up of subjects with changes in visual acuity (VA). Reports were submitted to the board for any subject with a 10-letter change in visual acuity along with the investigators assessment of cause. Of the 7 subjects with a fall in VA, three in the C320 and 2 in the BPD group had associated lens opacities.

3.2.3.7 Physical Examination including Vital Signs.

The mean values for vital signs were within the normal range in both treatment groups. Physical examinations included abnormalities in 30% of the subjects at 4 and 12 months in both treatment groups. However, in only 8% of the subjects had a normal exam at baseline and an abnormal exam at the end of the study.

Mean values for baseline and Week 12 vital signs were comparable across the treatment groups. Changes during treatment were uncommon and clinically insignificant.

3.2.3.3 Pregnancy

Fifteen pregnancies were reported during the course of the study. Of these 5 were females taking C320 and 5 were females taking BPD. In addition 3 female partners of male subjects in the C320 group and 2 female partners of males in the BPD group became pregnant. None of the subjects in the C320 group had a negative outcome. One BPD subject had a cesarean section at 40 weeks of gestation and at an unknown time after that reported **that the baby's left kidney was larger than the right kidney**. The baby was jaundiced at birth. No medical confirmation of this event was reported. There was, in addition, one spontaneous abortion at 20 weeks in the BPD group.

3.3 Summary and Discussion

This study was designed to compare the development of cataracts in adults treated with ciclesonide 320 mcg BID to adults treated with beclomethasone 320 mcg BID. Treatment lasted for 12 months and the outcomes were careful measurements of lens opacities using the LOCS III scoring system. The primary outcome, the difference in the proportions of subjects developing Class I (the smallest) changes, was consistently slightly smaller in the ciclesonide-treated subjects when compared to subjects treated with BDP. On the other hand the LOCS III scoring system is made up of three components. It assesses opacities in the nucleus, the cortical, and the posterior subcapsular region. Opacification of the PSC region is more typical of the reaction to corticosteroid treatment than in opacification of the other two regions. While the differences in treatment were quantitatively small, the mean increase in PSC score was larger in the C320-treated subjects compared to the BDP subjects. Also, in subjects over 60 years of age, the increase in Class of lens opacities was greater in the C320 subjects. Therefore, while the overall evaluation of lens opacities using the LOS III grading system showed fewer increases for the ciclesonide-treated subjects compared with subjects treated with BPD, some of the sub-group analysis suggest that the risk for lens opacification during treatment with inhaled ciclesonide is not inconsequential,

4 Study # XRP1526B/343

A PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO CONTROLLED, NONINFERIORITY STUDY ASSESSING THE EFFECTS OF CICLESONIDE METERED DOSE INHALER 50 µG/DAY AND 200 µG/DAY (EX-VALVE) ADMINISTERED ONCE DAILY ON GROWTH IN CHILDREN WITH MILD PERSISTENT ASTHMA

4.1 Protocol

4.1.1 Administrative

Enrollment Dates: **December 29, 2000 – September 15, 2004**
Screening Centers: 63 centers in the United States, 12 in Argentina, 4 in Chile, and 6 in Venezuela
Sponsor's medical expert:
CRO:

4.1.2. Objective/Rationale

The primary objective of this study was to determine if ciclesonide MDI 50 µg/day or 200 µg/day (ex-valve) (40 µg/day or 160 µg/day [ex-actuator]) administered once daily in the morning is non-inferior to placebo with respect to growth velocity in children with mild persistent asthma following a 12-month treatment period.

Secondary objectives were to investigate changes in growth in terms of bone age (wrist X-ray), and to investigate maintenance of asthma control and safety, after administration of ciclesonide MDI 40 µg/day or 160 µg/day, compared to placebo.

4.1.3. Study Design

This was a multinational, multi-center, randomized, double-blind, placebo-controlled, parallel group study in prepurbertal patients with mild persistent asthma treated previously with ICS. Eligible subjects were enrolled into a 6-month run in period at which time they were observed and baseline stadiometer measurements were collected. All corticosteroid medications were discontinued at the screening visit. During the last 2 weeks of the run-in the subjects received a placebo inhaler to use at home and baseline laboratory, X-ray, and PFT data were obtained. At the end of the run-in subjects were randomized (1:1:1) to receive placebo, ciclesonide 40 mcg QD (C40) or ciclesonide 160 mcg QD (C160) for 12 months.

The subjects were seen in the clinic at screening, 3 months and at randomization (6 months after screening visit). After randomization they were seen at 2 weeks and 1, 2, 3, 4, 6, 8, and 12 months after randomization. A final follow-up visit occurred 2 months after stopping study medication. Spirometry was performed at all visits. The AM-FEV₁ (after 6 hours without albuterol and prior to study drug) was performed 6, 3, and 0.5 months prior to randomization; at randomization and at 2 weeks, and 2, 4, 6, 8, 10, 12, and 14 months. Diaries were maintained throughout the treatment period to record adverse events, study medication doses and concomitant medications.

Protocol Amendments

Amendment 1 (March 28, 2001) stipulated that the dose of study medications was to be given between 8:00 and 8:30 AM instead of in the early evening. This was to facilitate obtaining PFTs prior to the dose.

Amendment 2 (January 29, 2002) changed the dosing time from 8:00 to 8:30 to 6:00 to 11:00 AM. In addition the normal ranges for urinary cortisol were amended by the central laboratory.

4.1.4. Study Population

Inclusion Criteria

- Females aged 5 to 7.5 years and males aged 5 to 8.5 years at screening
- History of mild persistent asthma for ≥ 3 months prior to screening
- Forced expiratory volume in one second (FEV₁) $\geq 80\%$ of predicted at screening, following at least a 4-hour albuterol withhold
- FEV₁ $\geq 80\%$ of predicted at Visit 3 and at Visit 4, following at least a 4-hour albuterol withhold
- Current asthma therapy with non-corticosteroid asthma medications on an as-needed (i.e., albuterol) or daily (i.e., cromones, leukotriene receptor antagonists, long-acting β_2 -agonists, theophylline, etc.) basis, or low doses of ICS
- Tanner Classification of Sexual Maturity no greater than Stage 1
- Height within normal limits (5th to 95th percentile inclusive) at screening
- Growth velocity ≥ 3 rd percentile during the 6-month run-in period
- Ability to demonstrate the effective use of the MDI devices and perform reproducible PFTs
- Willingness and ability to comply with the study procedures, and appropriate written informed consent for the subject obtained from parent or guardian.

Exclusion Criteria

- Asthma severity:
 - History of life-threatening asthma, including any history of significant hypercarbia (pCO₂ >45 mm Hg), prior intubation, respiratory arrest, or seizures as a result of an exacerbation of asthma

- Severe respiratory impairment (≥ 2 inpatient hospitalizations within 1 year prior to Visit 1, or any emergency room visit for asthma within 6 months prior to Visit 1)
- Other medical conditions:
 - History or evidence of abnormal growth
 - Any disease or condition that might substantially affect growth
 - Any clinically relevant deviation from normal in either the general physical examination or laboratory parameters, as evaluated by the principal investigator, that might interfere with the study, that might require treatment, or might interfere with the ability to obtain height measurements
 - History of substance abuse, mental illness or retardation
 - History or presence of glaucoma or posterior subcapsular cataracts
 - Known hypersensitivity to any ingredients in the study medications
 - Abnormal oropharyngeal examination at Visit 3. Any physical findings suggestive of oral candidiasis were to be verified with a culture analyzed by the central laboratory. A positive culture for oral candidiasis disqualified the subject from the study
- Preceding and concomitant medication:
 - Previous daily or alternate-day OCS treatment for a total of ≥ 60 days within the 2 years prior to Visit 3 and/or any use of OCS within 30 days prior to Visit 1 or during the run-in period. Subjects requiring OCS during the run-in period were not to be included in the study;
 - Treatment with ICS for more than one 14-day course during the run-in period or during the 30 days prior to Visit 1 with more than the following doses of ICS:
 - Beclomethasone: 168 $\mu\text{g}/\text{day}$
 - Triamcinolone: 400 $\mu\text{g}/\text{day}$
 - Flunisolide: 500 $\mu\text{g}/\text{day}$
 - Fluticasone: 100 $\mu\text{g}/\text{day}$
 - Budesonide Turbuhaler: 200 $\mu\text{g}/\text{day}$
 - Treatment with intranasal corticosteroids during the baseline period for more than two 14-day courses at least 3 months apart. Subjects were not allowed to use any intranasal corticosteroids during the double-blind treatment period
- Inability or unwillingness to use all study medication devices as instructed.

Withdrawal Criteria

- Any subject who progressed to Tanner Stage 2
- Any female who developed menses
- If a subject required a prohibited medication
- If the urine cortisol corrected for creatinine was abnormal at the randomization visit
- The following conditions could be an indication for withdrawal:
 - Use of a non-study ICS
 - A respiratory illness
 - Less than 75% compliance with the study medication

4.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Placebo MDI BID (1 puff QD)
- Ciclesonide MDI 160 mcg QD (1 puff QD)
- Ciclesonide 40 mcg BID (1 puff QD)

HFA albuterol (100 µg per actuation [90 µg ex-actuator] was supplied for acute symptoms.

The following concomitant medications were permitted throughout the study as long as they were started prior to screening and the dose was kept constant:

- Topical corticosteroids: Low-potency topical corticosteroid creams or ointments equivalent to ≤1% hydrocortisone were permitted for occasional dermatologic use
- Non-steroidal asthma medications:
 - Inhaled short-acting β₂ agonists (albuterol),
 - Leukotriene receptor antagonists (montelukast sodium, zafirlukast),
 - Cromones (cromolyn sodium, nebulized cromolyn, nedocromil),
 - Xanthine derivatives (theophylline, aminophylline);

The following medications were to be withheld prior to PFTs conducted at Visits 3 to 14:

- Inhaled or nebulized albuterol or other short-acting β₂-agonists for at least 4 hours
- Oral β₂-agonists (albuterol tablets) for at least 12 hours
- Atrovent® (ipratropium bromide) or immediate-release theophylline for at least 12 hours
- Serevent®(salmeterol xinofoate) for at least 24 hours
- Sustained-release theophylline for at least 48 hours

The following concomitant medications were prohibited from screening onward:

- Any ICS or ICS/LABA combination other than the study medication
- Any intranasal corticosteroid
- Any investigational drug other than randomized study medication

Compliance was assessed by the patient's notation in the diary that the medication was taken and by weighing the returned canisters. Non-compliance was a possible indication for exclusion if there was more than 2 periods with 5 consecutive days of non-compliance.

Efficacy Evaluation

Height was measured using standard stadiometry techniques. The stadiometer was calibrated within 4 hours prior to each measurement. Four acceptable measurements were taken at each visit and the median value was used in the analysis. Measurements were made with the subject in bare feet and care was taken that they stood tall.

Wrist X-rays were obtained to assess bone age. The films were graded according to the Greulich and Pyle radiographic atlas [4].

Spirometry was performed according to the 1995 ATS standards, and the FEV₁ in liters and as a percent of predicted was recorded. Measurements were obtained in triplicate within 1 hour of **the previous day's dose of study medication**, and 4 hours after the last albuterol dose. Peak flow meters were distributed at the discretion of the investigator. The readings were not included in the case report forms.

Safety Evaluation

The primary safety analysis was based on collection and recording of adverse events in the standard manner. In addition, 24-hour urines for cortisol were collected at 39 sites and 10-hour urine cortisol measurement were obtained at 36 sites (5 sites collected both) at randomization and at the end of the study. Oropharyngeal examination was performed 2 weeks prior to randomization, and at 2, 4, 6, 8, 10, 12 and 14 months of follow-up.

A summary of the study procedures is shown in Table 64.

Table 64. Schedule of Study Events

Activity	Run-in period (Screening/baseline/ Qualifying Phases)			Randomiza- tion	Double-blind period									Final/ Early D/C ^b	Follow- up period
	1 ^a	2 ^a	3 ^a		4	5	6	7	8	9	10	11	12		
Visit															
Month or week	-6 mon	-3 mon	-2 wk	0	2 wk	1 mon	2 mon	3 mon	4 mon	6 mon	8 mon	10	12 mon	14 mon	
Study day	-180±7	-90±7	-14±5	1	14±3	30±5	60±5	90±5	120±5	182±5	240±5	300±5	365±5		
Informed consent/assent	X														
Medical history	X														
Physical exam (w/Tanner evaluation)	X		X						X		X		X		
Oropharyngeal examination ^c			X				X		X	X	X	X	X	X	
Pulmonary function test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory sample			X							X			X		
Urine cortisol test			X ^d										X	X	
Dispense urine collection container			X									X	X		
Hand-wrist X-ray			X										X		
Inclusion/exclusion criteria review	X		X	X											
Height measurement by stadiometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Issue diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense peak flow meter	X								X	X	X	X	X		
Collect and review diary		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense single-blind study drug			X												

Activity	Run-in period (Screening/Baseline/ Qualifying Phases)			Randomiza- tion	Double-blind period									Final/ Early D/C ^b	Follow- up period
	1 ^a	2 ^a	3 ^a		4	5	6	7	8	9	10	11	12		
Visit															
Month or week	-6 mon	-3 mon	-2 wk	0	2 wk	1 mon	2 mon	3 mon	4 mon	6 mon	8 mon	10	12 mon	14 mon	
Study day	-180±7	-90±7	-14±5	1	14±3	30±5	60±5	90±5	120±5	182±5	240±5	300±5	365±5		
Collect single-blind study drug				X											
Dispense double-blind study drug				X	X	X	X		X	X	X	X			
Collect double-blind study drug					X	X	X	X	X	X	X	X	X		
Weigh study drug canister			X	X	X	X	X	X	X	X	X	X	X		
Dispense rescue medication and update study medication log	X	X	X	X	X	X	X	X	X	X	X	X			
Instruct subject on emergency treatment	X	X		X	X		X		X	X	X	X			
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Schedule next visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Note: For double-blind treatment months not listed for a scheduled visit (months 5, 7, 9, and 11), phone calls for compliance were to be made.

^a Subject (and parent or guardian) was to be contacted twice between Visit 1 and Visit 2 and twice between Visit 2 and Visit 3.

^b For subjects who discontinue (D/C) double-blind study treatment early (before 50 weeks).

^c If a fungal infection of the mouth or throat was suspected, a culture was to be obtained to confirm the diagnosis.

^d The results from the urine sample had to be reviewed prior to randomization.

4.1.6. Statistical Analysis Plan

Analysis Variables

The primary growth endpoint was the growth velocity during the double-blind treatment period. The primary estimate of growth velocity was the linear regression estimate of growth velocity which was determined from the slope of the linear regression using all of the available measurements (at least 3). A supportive estimate was based on the difference in height measurement at the last available visit compared to the baseline value. An additional supportive analysis was performed using only subjects who completed at least 50 weeks of treatment.

Secondary growth endpoints were a shift analysis of change in growth velocity, change from baseline in height, growth velocity during the follow-up period, and shift analysis of bone age vs chronologic age, and a completer analysis. Analyses were further performed on a subgroup of subjects who had not reached sexual maturity during the study, and a subgroup including subjects who were never treated with non-study corticosteroids during the trial.

Pulmonary function was analyzed as the change from baseline at each visit.

Withdrawal was analyzed as the time to and rate of withdrawal from double-blind treatment due to lack of efficacy, time to and rate of withdrawal from double-blind treatment due to lack of efficacy or asthma adverse event, and time to and rate of withdrawal for any reason.

Adverse events and laboratory values were analyzed in the standard manner. For the laboratory values a Predefined change abnormal (PCA) is a change from baseline to an abnormal level and is an increase from baseline of at least a predefined amount. Values for the PCA were defined for each analate. The Clinically noteworthy abnormal laboratory value (CNALV) was a value that was considered medically important by the sponsor. They were predetermined for glucose levels (> 2 times ULN) and absolute eosinophil counts ($> 1.0 * 10^3$ cells/mm³).

A total of 39 study sites were assigned to collect 24-hour urine samples for cortisol and 36 sites were assigned to collect 10-hour urine samples. Samples were obtained at baseline, end of active treatment and at the end of 2 months off of treatment. The free cortisol and cortisol corrected for **creatinine were reported. An additional analysis of the "valid" samples, based on the quality of the urine sample, were planned.** However, only 13% of the samples qualified so the sub-set analysis was not performed. The number of invalid samples was assumed to be related to the fact that the quality criteria were based on adult values.

Sample Size

Sample size was calculated assuming a common SE of 1.4 cm/year, a non-inferiority delta of 0.5 cm/year, and 90% power to conclude non-inferiority. Non-inferiority of each ciclesonide dose vs placebo was assessed using a 95% one-sided confidence interval. Using these specifications a sampled size of 135 subjects per treatment arm was required. Assuming a 10% drop-out rate 150 subjects per arm (total 450) were planned for recruitment. To be absolutely sure of enough subjects, 661 were randomized.

Study Populations

The safety population included all subjects who received at least one dose of double-blind study medication.

The modified intent to treat mITT population included all randomized subjects who received at least 4 months of study medication and who had at least one stadiometer reading at baseline and 4 months.

The per-protocol (PP) population consisted of all the subjects in the ITT population who did not have an important protocol deviation. The determination about the presence of an important protocol deviation was made for each subject prior to breaking the blind. The list of major protocol violation includes the following events:

- The subjects was > Tanner stage 1 at baseline
- Study medication for < 4 months
- Diary recorded compliance <70% during double-blind treatment
- Use of prohibited medications as described in exclusion criteria
- Height at screening M 5th percentile
- Growth velocity during the run-in < 3rd percentile
- Beyond age specification

In addition, individual measurements were not included if they had been made directly after a short course of corticosteroids.

Primary Analysis

The primary objective of the study was to demonstrate the non-inferiority of ciclesonide on growth compared to placebo. The analysis used an ANCOVA of the linear regression estimate of growth velocity with baseline growth velocity, height, age and age², gender, gender-by-age interaction, race, previous corticosteroid use and age of asthma diagnosis as co-variates. The non-inferiority of ciclesonide treatment was assessed by comparing the 2 ciclesonide dose regimens against placebo using a 2-sided 95% confidence interval. A stepwise procedure was used to control the Type I error rate. The initial 2-sided 95% confidence interval was for the difference between ciclesonide 40 µg/day and placebo. If non-inferiority of ciclesonide 40 µg/day compared to placebo could be concluded (lower limit of ciclesonide 40 µg to placebo difference was greater than -0.5 cm/yr), then the non-inferiority of ciclesonide 160 µg/day as defined by the 2-sided 95% confidence interval for ciclesonide 160 µg/day minus placebo was formally assessed. The non-inferiority bound of -0.5 cm/year was derived from the results of previous studies comparing growth in pre-pubertal children treated with fluticasone and placebo.

4.2. Results

4.2.1. Study Population

Disposition

A total of 1127 subjects were screened and 661 were randomized and treated; 221 to placebo, 221 to C40, and 219 to C160. Of the screening failures, 35 were not enrolled due to abnormal growth at baseline. The mean height of the screen failures at baseline was 118.78 cm compared to 119.59 cm for the subject enrolled.

Of the randomized subjects, 369 (83.9%) completed the course of treatment. Withdrawal was the same in the placebo and C40 groups (18.1%) and slightly less (14.2%) in the C160 group (Table 65). Adverse reactions were the most common indication for withdrawal and the distribution was similar to the distribution of overall withdrawals (6.3, 6.3, and 3.7% in the placebo, C40, and C160 subjects, respectively). Lack of efficacy was reported as a reason for withdrawal in only 2 (0.9%) of the placebo subjects and 1 C160 subject, although protocol violations were reported in 4.5% of the placebo subjects compared with 1.8 and 2.3% of the C40 and C160 subjects. There were no deaths. A total of 169 (76.5%), 164 (74.2%), and 164 (74.9%) of the placebo, C40, and C160 subjects, respectively, completed the treatment and follow-up phase of the study. The completer population consisted of 183 placebo, 184 C40, and 187 C160 subjects. The discrepancy between these numbers and the number discontinued early is due to a few subjects who were treated for more than 350 days, but who stopped study medication prior to the last visit, which was scheduled for up to a few days later than 350 days after starting the medication.

Table 65. Disposition of Subjects in Study 343

	Placebo	Dose of Ciclesonide		
		40 QD	160 QD	Overall
Randomized & treated	221	221	219	440
Discontinued	40 (18.1)	40 (18.1)	31 (14.2)	71 (16.1)
Reason for discontinuation:				
Adverse event	14 (6.3)	14 (6.3)	8 (3.7)	22 (5.0)
Did not wish to continue	7 (3.2)	5 (2.3)	6 (2.7)	11 (2.5)
Lost to follow-up	6 (2.7)	4 (1.8)	5 (2.3)	9 (2.0)
Poor compliance	3 (1.4)	5 (2.3)	4 (1.8)	9 (2.0)
Protocol violation	10 (4.5)	4 (1.8)	5 (2.3)	9 (2.0)
Lack of efficacy	2 (0.9)	0	1 (0.5)	1 (0.2)
Death	0	0	0	0
Other	5 (2.3)	10 (4.5)	7 (3.2)	17 (3.9)
Entered follow-up period	179 (81.0)	177 (80.1)	184 (84.0)	361 (82.0)
Completed 55 days of follow-up	169 (76.5)	164 (74.2)	164 (74.9)	328 (74.5)

There were only 19 reported protocol violations that resulted in withdrawal. Of the 10 placebo subjects withdrawn due to protocol violations, 6 were due to use of prohibited asthma medications. These 6 subjects remained in the mITT population. Four subjects were excluded

from the mITT due to procedural errors: incorrectly measured growth, accidentally breaking the blind, incorrect timing of visit and low growth at baseline. Four subjects in the C40 group were withdrawn due to protocol violation: three due to use of prohibited medication and 1 due to an abnormal urinary cortisol at baseline. The latter subject was excluded from the mITT. In the C160 group there were 5 subjects withdrawn due to protocol violations: 2 for prohibited medications, 1 low FEV₁, 1 was excluded at the investigator's discretion and one for poor compliance.

Compliance with study medication was high: >90% compliance in >85% of the subjects in each treatment group by diary record. Compliance assessed by canister weight was slightly lower: 79.6, 81.9, and 80.4% in the placebo, C40, and C160 groups, respectively. This was attributed to errors in canister weighing procedures.

A total of 52 (7.9%) of the randomized subjects were excluded from the ITT population. The exclusion was based on a failure to receive medication and/or to have a stadiometer height after 115 days of treatment. The mITT population included 609 subjects: 210, 206, and 202 placebo, C40 and C160 subjects, respectively.

There were 126 (19.1%) subjects excluded from the PP population: 45 in the placebo group, 41 in the C40 group, and 40 in the C160 group. Most of the exclusions were due to the same exclusions that resulted in exclusion from the mITT or due to ingestion of prohibited medication.

Demographics

Of the 661 subjects randomized 67.2% were male, and the mean age (Range) was 6.7 (5.0 – 8.6) years. The girls were < 7.5 and all but one of the boys was <8.5 years of age. The one boy who was 8.6 years of age did not progress beyond Tanner Stage I during the trial. The predominant racial group was white (71.0% compared with 4.2% black and 24.8% other). All of the characteristics were approximately equal across the treatment groups (Table 66). Approximately 60% of the subjects in each group was Hispanic which is due in part to the large enrollment in South America. Seventy-three percent of the subjects were enrolled in Argentina, Chile, or Venezuela, compared with 27% in the US despite the larger number of centers located in the USA. On average 7 plus subjects were enrolled at each US site compared to 30 plus at each site in South America.

Table 66. Demographic Characteristics of the Enrolled Population

	Dose of Ciclesonide			
	Placebo	40 QD	160 QD	Overall
Total ITT Population	221	221	219	440
Gender, % M	(66.5)	(67.9)	(67.1)	(67.5)
Age, mean (SD)	6.7 (0.95)	6.6 (0.97)	6.7 (0.93)	6.7 (0.95)
Race, %				
White	69.7	68.8	74.4	71.6
Black	4.5	4.1	4.1	4.1
Other	25.8	27.1	21.5	24.3

Hispanic, %	57.5	60.2	62.6	61.4
Geographic region, %				
USA	30.3	29.0	25.1	27.0
South America	69.7	71.0	74.9	73.0
Stadiometer height, mean cm (SD)	120.1 (7.5)	119.3 (7.2)	119.7 (6.9)	119.5 (7.0)
Weight, mean kg (SD)	24.9 (5.7)	24.6 (5.2)	24.8 (5.6)	24.7 (5.4)

The mean height (SD) of the entire group was 119.7 (7.2) cm and the mean weight (SD) was 24.8 (5.5) kg. The means were similar across the treatment groups.

Because the run-in lasted for 6 months, the mean age, height, and weight of the children had increased by the time of randomization as shown in Table 67. Approximately 48% of the children had a chronologic age that was older than the radiographic bone age, suggesting bone mineralization delay in a substantial number of the children. The percentage of children with delayed bone mineralization did not differ across the treatment groups or geographic regions.

Reviewer: The delayed bone mineralization was attributed to the underlying disease despite the fact that the asthma was mild by PFT criteria (mean FEV1 = 94% predicted, see below) and only 20% of the children had taken corticosteroids prior to enrollment. Findings by region...

Table 67. Demographic Variables at Randomization

	Dose of Ciclesonide			
	Placebo	40 QD	160 QD	Overall
Total ITT Population	221	221	219	440
Age, mean (SD)	7.2 (0.95)	7.1 (0.97)	7.2 (0.93)	7.2 (0.95)
Stadiometer height, mean cm (SD)	123.4 (7.6)	122.6 (7.1)	122.9 (6.9)	122.7 (7.0)
Weight, mean kg (SD)	26.4 (6.3)	26.1 (5.5)	26.3 (6.1)	26.2 (5.8)
Bone age relative to chronologic age, n (%)	219	221	219	440
High	36 (16.3)	44 (19.9)	41 (18.7)	85 (19.3)
Normal	75 (33.9)	70 (31.7)	75 (34.2)	145 (33.0)
Low	108 (48.9)	107 (48.4)	103 (47.0)	210 (47.7)

Reviewer: Fifteen to 20 subjects were not included in the mITT population. The demographic characteristics of mITT were similar to the characteristics of the randomized subjects.

Height was measured during the 6-month baseline period to obtain a baseline value for linear growth (Table 68). The baseline mean values (SD) for the subjects in the C160 treatment group were lower (6.20 [1.6]) than in the placebo (6.45 [1.5]) and C40 groups (6.59 [1.3]). This difference was seen in all of the subgroups, but was particularly prominent in the older children. In the girls older than 7, the mean baseline growth (SD) was 6.57 (1.7) and 5.90 (1.4) cm/yr in the children treated with placebo and C160, respectively. In the boys older than 8 the respective rates were 6.50 (1.1) and 5.58 (1.8). The relatively low growth rates in the C160 group were

reported in subjects enrolled in the USA and in South America. It is noted that relatively few US subjects (47) were treated with C160.

Table 68. Baseline growth of mITT population calculated using linear regression of all measured points

	Placebo	Dose of Ciclesonide		
		40 QD	160 QD	Overall
mITT population	201	206	202	408
Overall, mean (SD)	6.49 (1.5)	6.59 (1.3)	6.20 (1.6)	6.39 (1.5)
Females, n	67	67	71	138
All, cm/yr	6.54 (1.5)	6.64 (1.4)	6.18 (1.6)	6.40 (1.5)
≤ 7 years, cm/yr	6.52 (1.3)	6.95 (1.5)	6.32 (1.6)	6.62 (1.6)
> 7 years, cm/yr	6.57 (1.7)	6.09 (1.0)	5.90 (1.4)	5.99 (1.2)
Males, n	134	139	131	270
All, cm/yr	6.47 (1.5)	6.56 (1.3)	6.21 (1.6)	6.39 (1.4)
≤ 8 years, cm/yr	6.45 (1.6)	6.73 (1.3)	6.46 (1.4)	6.60 (1.3)
> 8 years, cm/yr	6.50 (1.1)	5.85 (1.5)	5.58 (1.8)	5.85 (1.5)
Region				
USA, n	56	60	47	107
Cm/yr	6.65 (1.9)	6.66 (1.3)	6.37 (1.5)	6.53 (1.4)
South America, n	145	146	155	301
Cm/yr	6.43 (1.3)	6.56 (1.3)	6.15 (1.5)	6.35 (1.5)

Reviewer: The difference in growth rates in the treatment groups could not be explained by differences in steroid use prior to enrollment because steroid use prior to enrollment was similar in all of the treatment groups (see below). In addition, when the baseline rate of growth was analyzed by prior steroid use, baseline growth was not slower in those who had previously taken steroids.

Asthma

Asthma was diagnosed 3.8, 3.8, and 4.0 years prior to enrollment in the placebo, C40, and C160 subjects respectively. The mean absolute FEV₁ was 1.4 L in each treatment group and this corresponded to a FEV₁ % predicted of 93.0 to 96.2% (Table 69).

Table 69. Characteristics of Asthma in the Randomized Population

	Placebo	Dose of Ciclesonide		
		40 QD	160 BID	Overall
Total	221	221	219	440
Duration				
Years, mean (SD)	3.8 (2.0)	3.8 (2.0)	4.0 (2.0)	3.9 (2.0)
Range	0 - 7.9	0 - 8.2	0.1 - 8.2	0.1 - 8.2
FEV ₁				
Mean Absolute, ml (SD)	1.4 (0.29)	1.4 (0.28)	1.4 (0.26)	2.65 (0.65)
Mean % predicted, % (SD)	93.0 (9.7)	96.2 (12.0)	94.4 (11.0)	79.2 (8.3)

At least 93% of the subjects in each treatment group took a β-adrenergic agonist in the 30 days prior to enrollment. The next most common medication was a leukotriene receptor antagonist

which was taken by 52.0, 52.0, and 47.9% of the placebo, C40, and C160 subjects, respectively. Some form of inhaled corticosteroid was taken by 19.0, 19.5, and 21.0% of the placebo, C40, and C160 subjects, respectively. The mean values and distributions for these variables were not different in the mITT population. During the run-in period, medication usage was similar to that seen prior to enrollment except that inhaled corticosteroid use decreased to 10.0, 10.9, and 12.8% of the placebo, C40, and C160 subjects.

4.2.2. Efficacy Results

Primary Efficacy Outcome

The primary analysis was performed on the growth rates during the run-in and randomized treatment period using a linear regression method of all the measurements. However the growth rate during follow-up (after study medication was discontinued) was obtained at only two time points and the analysis was based on the difference between the two points. As a supportive analysis and to aid in the comparison between the randomized treatment period and the follow-up period, growth was also analyzed by the two-point method during randomized treatment.

Using the linear regression method of analysis, the mean growth rate was less during randomized treatment than during the run-in in all of the treatment groups. The baseline growth rates (6.49 and 6.59 cm/yr in the placebo and C40 groups, respectively) and changes that occurred during randomized treatment (decrease of 0.73 and 0.84 cm/yr in the placebo and C40 group respectively) were similar in the placebo and C40 groups. The children in the C160 group had a slightly lower baseline growth rate (6.2 cm/yr), and the unadjusted change during treatment was a decrease of 0.60 cm/yr (Table 70).

Comparing growth during the follow-up period to that observed during the randomized treatment period (using the 2-point analysis for both time periods) there was a less than 0.1 cm/year difference in the placebo and C160 group, while growth in the C40 group was 0.21 cm/year higher during the follow-up than during randomized treatment. If the 2-point analysis of the follow-up period is compared to the linear regression results for the randomized treatment period for the placebo and C160 subjects, there again appears to very little effect of treatment. In the C40 group growth during the follow-up period was 0.31 cm/yr greater than during randomized treatment. There was no apparent explanation for the lower baseline growth rate in the C160 group as the baseline age, height, and pre-enrollment steroid use were similar across the treatment groups. Concomitant ICS use was less in the C160 group (6.4%) than in the other treatment groups (10.0 and 10.4% in the placebo and C40 groups, respectively).

Table 70 . Growth Velocity (cm/year) During Baseline Period, Randomized Treatment, and Follow-up

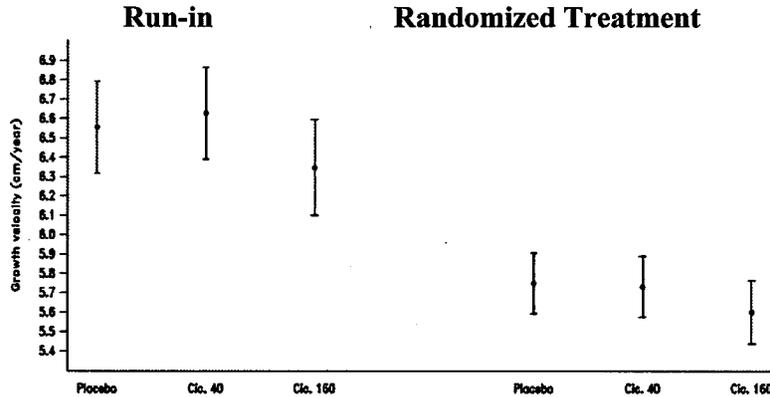
	Placebo	Dose of Ciclesonide		Overall
		40 QD	160 BID	
Total	201	206	202	408
Run-in, mean (SD) (Linear Regression)	6.49 (1.5)	6.59 (1.3)	6.20 (1.6)	6.36 (1.5)

Median (Range)	6.32 (3.5-15.5)	6.46 (3.2-10.6)	6.15 (1.5-12.6)	6.36 (1.5-12.6)
Randomized Treatment (Linear Regression)				
Mean (SD)	5.76 (1.0)	5.75 (1.0)	5.60 (0.9)	5.67 (1.0)
Median (Range)	5.74 (2.3-10.1)	5.66 (3.3-8.8)	5.58 (2.2-9.5)	5.64 (2.2-9.5)
Randomized Treatment (2-point assessment)				
Mean (SD)	5.84 (0.08)	5.85 (0.09)	5.66 (0.09)	
Follow-up (2-point assessment)				
Mean (SD)	5.75 (3.2)	6.06 (4.1)	5.64 (3.4)	5.85 (3.8)

Reviewer: The Applicant used the linear regression method for the randomized treatment period because there were multiple measurements and the estimate of growth was thought to be more precise. However, if growth was not linear throughout the period, and it probably was not, then the two point estimate may actually be more accurate. The FDA statistical reviewer performed an analysis of growth in 6-month periods using the 2-point comparisons. The growth during follow-up covered only a 2 month period. The baseline mean (SD) growth was 6.47 (1.47), 6.55 (1.28), and 6.22 (1.57) in the placebo, C40, and C160 groups respectively. The baseline growth was significantly less in the C160 subjects than in the other two groups. The growth rate in the first 6 months of randomized treatment was lower than the growth rate during the run-in period in all of the treatment groups (5.61 [1.51], 5.67 [1.53], and 5.59 [1.45] in the placebo C40, and C160 groups, respectively). In the second six months of randomized treatment growth increased slightly in the placebo and C40 groups (5.87 [1.44] and 5.88 [1.47], respectively) and fell further in the C160 group (5.55 [1.32]). During the follow-up period, after randomized treatment had been discontinued, the growth rate in the placebo group decreased slightly and it increased in the C40 and C160 groups (5.75 [3.17], 6.06 [4.11], and 5.64 [3.37] in the placebo C40, and C160 groups, respectively). The most dramatic change in growth rate occurred between the run-in period and the first 6 months of randomized treatment, and the growth rate decreased in all of the treatment groups. It is unlikely that this was due to the increased age of the subjects as the rates increased subsequently despite the increased age of the subjects and no change in randomized treatment.

The mean growth results are shown graphically in Figure 10.

Figure 10. Growth Velocity During Run-in and Randomized Treatment



The statistical analysis of the difference between treatment groups showed no difference (Table 71) comparing ciclesonide to placebo treatment. The values in the table were obtained using the linear regression method. The results of the statistical analysis using the two point method were essentially identical.

Table 71. Growth Velocity Comparing Active Treatment to Placebo.

Treatment	N	LS mean (SE) Cm/yr	Difference from placebo		
			LS mean (SE)	95% CI	Inferiority p-value
Placebo	201	5.75 (0.08)			
C40	206	5.73 (0.08)	-0.02 (0.09)	-0.19, 0.16	0.0001
C160	202	5.60 (0.08)	-0.15 (0.09)	-0.33, 0.03	0.0001

The results of the per-protocol analysis were also supportive of the conclusion of non-inferiority. The results of other supportive analyses were also almost identical. This included an analysis restricted to subjects who completed the study, and an analysis performed on all subjects who had measurements at 12 months of follow-up even if they had discontinued the study medication at some time in the past. For this analysis the mean (SE) growth was 5.78 (0.09) cm/yr in the placebo (n=191), 5.78 (0.08) cm/yr in the C40 (n=193) and 5.65 (0.09) cm/yr in the C160 (n=194) subjects.

Secondary Efficacy Outcomes

Few subjects had extremely high or low growth rates during the double-blind treatment period. Most of the values lay between 25 to 75%: 64.2, 55.8, and 64.9% of the subjects in the placebo, C40, and C160 groups, respectively. Less than 2% of the subjects in any of the treatment groups had growth curves that were <3% or >97% of the predicted normal values.

Reviewer: It is not stated explicitly, but I believe the percentiles refer to the Baumgartner Growth Velocities percentiles (3)

Compared to placebo, there were no systematic differences in the shift in growth category (high, normal, low growth rates) in the subjects treated with ciclesonide (Table 72).

Table 72. Percentage of Subjects Within each Treatment Group with Shifts in Growth Category During Double-Blind Treatment

Study	Height Compared to Normal Standards*			
	Low	Normal	High	Total
EndBaseline				
Placebo				
Low	5.0	8.5	3.4	19.4
Normal	9.0	30.8	7.5	41.8
High	5.0	24.9	6.0	38.9
Ciclesonide, 40 mcg				
Low	3.9	10.7	2.9	20.4
Normal	12.6	23.8	6.8	38.0
High	7.8	21.3	10.3	41.7
Ciclesonide, 160 mcg				
Low	5.9	16.4	5.5	23.9
Normal	9.4	28.2	2.0	39.1
High	7.5	20.3	5.0	37.2

* Low, normal, and high is defined in terms of normal growth curves. For this table, Low = lower 25th percentile, Normal = 25 to 75th percentile, and High = higher than the 75th percentile.

The distribution of bone age as related to chronological age was also examined at the beginning and end of the trial. A high chronological age compared to bone age suggests a slowing of bone maturation. The percentage of subjects who went from a normal ratio to a high ratio (delayed bone maturation) was 9.0, 8.6, and 9.1% in the placebo, C40, and C160 groups, respectively (Table 73).

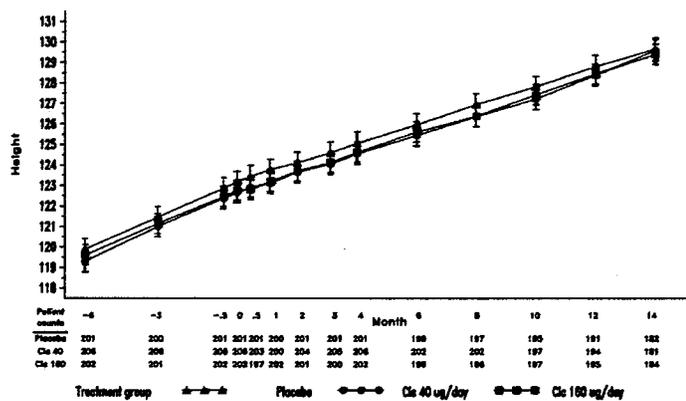
Table 73. Changes in Chronological/Bone Age during Treatment

Treatment Baseline status	Number (%) of subjects at end of double-blind treatment period			
	Low	Normal	High	Total
Placebo				
Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal	11 (6.2%)	122 (68.9%)	7 (4.0%)	140 (79.1%)
High	0 (0.0%)	16 (9.0%)	21 (11.9%)	37 (20.9%)
Ciclesonide 40 µg/day				
Low	6 (3.2%)	3 (1.6%)	0 (0.0%)	9 (4.9%)
Normal	15 (8.1%)	115 (62.2%)	8 (4.3%)	138 (74.6%)
High	0 (0.0%)	16 (8.6%)	22 (11.9%)	38 (20.5%)
Ciclesonide 160 µg/day				
Low	3 (1.7%)	1 (0.6%)	0 (0.0%)	4 (2.3%)
Normal	11 (6.3%)	119 (68.0%)	2 (1.1%)	132 (75.4%)
High	0 (0.0%)	16 (9.1%)	23 (13.1%)	39 (22.3%)

mITT = modified intention-to-treat.

The measured stadiometer heights are plotted by visit in Figure 11 .

Figure 11. Stadiometer Height



Sub-group Analysis

In the placebo group, the mean growth rate was slightly higher for girls (mean [SE] 5.85 [0.12 cm/yr]) compared to the boys (mean [SE] 5.67 [0.084] cm/yr). However the differences between placebo and ciclesonide treatment were similar. When divided into age-gender strata, the older girls (>7 years) who were treated with C160 may have had a greater slowing of growth (mean [SE] -0.59 [0.27] cm/yr) that either the girls < 7 years of age (mean [SE] -0.03 [0.21] cm/yr) or either of the male groups (mean [SE] -0.11 [0.14] and -0.19 [0.21] cm/yr in those ≤8 and >8 years, respectively).

Only one third of the subject population was enrolled in the US. However, in this sample (N=163) there was no apparent effect of ciclesonide on growth (Table 74). The mean [SE] difference between growth during ciclesonide treatment compared to placebo was 0.03 (0.17) and 0.01(0.18) cm/yr in the C40 and C160 groups, respectively. This is in comparison to the growth rates (mean [SE]) observed in South America of (mean [SE] -0.05 [0.11] cm/yr and [SE] -0.17 [0.11] cm/yr comparing C40 and C160 to placebo, respectively).

Table 74. Differences in Growth Rates by Region

Region Treatment	N	LS mean ± SE (cm/year)	Difference vs. placebo	
			LS mean ± SE	2-sided 95% CI
USA				
Placebo	56	5.91 ± 0.127	-	-
Ciclesonide 40 µg/day	60	5.94 ± 0.124	0.03 ± 0.172	(-0.31, 0.37)
Ciclesonide 160 µg/day	47	5.92 ± 0.140	0.01 ± 0.182	(-0.35, 0.36)
South America				
Placebo	145	5.73 ± 0.087	-	-
Ciclesonide 40 µg/day	146	5.68 ± 0.087	-0.05 ± 0.108	(-0.26, 0.16)
Ciclesonide 160 µg/day	155	5.56 ± 0.086	-0.17 ± 0.106	(-0.38, 0.04)

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.
 Differences vs. placebo are calculated as ciclesonide minus placebo.

Source: Table T - 53, pg. 382.

A small difference was also seen in growth rates in subjects treated with C160 who were concomitantly taking leukotriene receptor antagonists (Table 75). However, this

Table 75 . Growth in Subjects Treated Concomitantly with Leukotriene Inhibitors.

Leukotriene receptor antagonist use Treatment	N	LS mean ± SE (cm/year)	Difference vs. placebo	
			LS mean ± SE	2-sided 95% CI
Without leukotriene receptor antagonist use				
Placebo	88	5.60 ± 0.110	-	-
Ciclesonide 40 µg/day	90	5.68 ± 0.112	0.08 ± 0.135	(-0.19, 0.34)
Ciclesonide 160 µg/day	92	5.65 ± 0.111	0.04 ± 0.135	(-0.22, 0.31)
With leukotriene receptor antagonist use				
Placebo	113	5.87 ± 0.104	-	-
Ciclesonide 40 µg/day	116	5.77 ± 0.102	-0.10 ± 0.121	(-0.33, 0.14)
Ciclesonide 160 µg/day	110	5.57 ± 0.108	-0.30 ± 0.122	(-0.54, -0.06)

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.
 Differences vs. placebo are calculated as ciclesonide minus placebo.

Source: Table T - 59, pg. 392.

may be affected by the relative high rate of growth in the placebo subjects who were also taking leukotriene receptor antagonists.

Excluding subjects who did not receive rescue treatment with corticosteroids during the randomized treatment period resulted in a smaller difference between treatment groups (Table 76). The mean (SE) maximum difference comparing placebo to ciclesonide treatment was -0.09 (0.090) cm/yr for the subjects treated with 160 mcg.

Table 76. Change in Growth in Subjects not Treated with Prohibited ICS

Treatment	N	LS mean ± SE (cm/year)	Difference vs. placebo	
			LS mean ± SE	2-sided 95% CI
Placebo	190	5.70 ± 0.081	-	-
Ciclesonide 40 µg/day	190	5.71 ± 0.080	0.02 ± 0.090	(-0.16, 0.19)
Ciclesonide 160 µg/day	193	5.60 ± 0.083	-0.09 ± 0.090	(-0.27, 0.08)

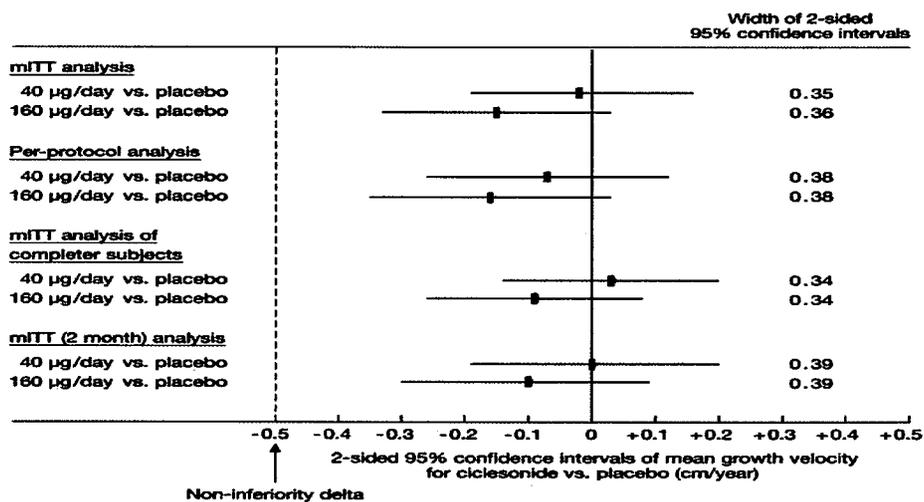
CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.
 Differences vs. placebo are calculated as ciclesonide minus placebo.

Source: *Table T - 60, pg. 394.*

Growth Summary

As can be seen in Figure 12, the changes in linear growth during ciclesonide treatment were very small. At 40 mcg per day there was no change in growth rate, and at 160 mcg daily, the mean effect size was -0.15 cm/year with the 95% confidence limits overlapping zero. In only two small subgroups did the difference in rate of growth approach statistical significance: in girls older than 7 years and in subjects treated with leukotriene receptor antagonists

Figure 12. Summary Effects of Ciclesonide on Growth



In both cases the differences were small (0.29 and 0.30 cm/yr for the gender and leukotriene analysis respectively), and of questionable clinical significance. In all of the treatment groups, including placebo, the rate of growth decreased during the randomized treatment period. This change was attributed to the subjects being older during the randomized treatment period. However, growth was slightly higher during the second six months of randomized treatment which can not be explained on the basis of a change in subject age, or a change in therapy.

One problem with the study is the failure to document drug use. Blood levels of ciclesonide (or the active metabolite) were not determined and the pulmonary function results of the (see below) are not helpful because the subjects had mild asthma and many would not have needed corticosteroids. A dramatic deterioration in pulmonary function would not have been expected even if the subjects had not received an inhaled corticosteroid.

Maintenance of Asthma Control

The safety population was used for the assessment of changes in pulmonary function. The FEV₁% fell by a small amount over the course of the study in all of the treatment groups (Table 77). The absolute FEV₁ increased by 9.6, 8.9, and 10.3% in the placebo, C40, and C160 groups, respectively. However, the growth in lung size did not keep up with the growth in height because the FEV₁ % predicted decreased by 3.7, 3.6, and 2.5% in the placebo, C40 and C160 groups.

Table 77. Change in FEV₁ and FEV₁% During 12 Months of Treatment with Ciclesonide

Parameter Treatment	N	Baseline mean	Change from baseline LS mean ± SE	Difference vs. placebo		
				LS mean ± SE	2-sided 95% CI	p-value
FEV₁ percent predicted						
Placebo	201	92.97	-3.74 ± 0.817	-	-	-
Ciclesonide 40 µg/day	206	96.26	-3.62 ± 0.801	0.11 ± 1.104	(-2.06, 2.28)	0.9193
Ciclesonide 160 µg/day	202	94.87	-2.45 ± 0.808	1.28 ± 1.103	(-0.88, 3.45)	0.2458
Percent change in FEV₁ ^a						
Placebo	201	1.407	9.56 ± 1.001	-	-	-
Ciclesonide 40 µg/day	206	1.435	8.89 ± 0.988	-0.67 ± 1.355	(-3.33, 1.99)	0.6213
Ciclesonide 160 µg/day	202	1.419	10.32 ± 0.997	0.77 ± 1.356	(-1.90, 3.43)	0.5719

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.

^a FEV₁ at baseline measured in liters.

Differences vs. placebo are calculated as ciclesonide minus placebo.

In the mITT population 16 subjects (4 [2%], 8 [3.9], and 4 [2.0] in the placebo, C40 and C160 groups, respectively) discontinued study medication due to lack of efficacy or an asthma attack.

Reviewer: In the safety population 27 patients were withdrawn from study medication because of an asthma attack (9, 12, and 6 in the placebo, C40, and C160 groups, respectively). See safety discussion, below.

4.2.3. Safety

4.2.3.1 Exposure

The safety population consisted of 661 subjects who were treated with double-blind medication (221, 221, and 119 were treated with placebo, C40, and C160, respectively). The mean exposure to study drug (325.3, 329.5, and 332.6 days in the placebo, C40, and C160 groups) was 7 days longer in the C160 subjects than in those treated with placebo.

4.2.3.2 Adverse Events

Overall Assessment of Adverse Events

Almost all subject reported at least on AE during the year of treatment (89.6, 94.6, 90.0% in the placebo, C40, and C160 groups, respectively). The incidence of serious AEs was low, and the highest rate was seen in the C40 group (5.0%) compared to 2.7 and 3.2% in the placebo and C160 subjects, respectively (Table 78). AEs leading to withdrawal were equally common in the placebo and C40 group (6.3%) and less common in the C160 subjects (3.2%). There were no deaths.

Table 78. Overall Summary of Adverse Events.

	Dose of Ciclesonide			
	Placebo	40 QD	160 QD	Total
N	221	221	219	440
All AEs	198 (89.6)	209 (94.6)	197 (90.0)	406 (92.3)
Serious AEs	6 (2.7)	11 (5.0)	7 (3.2)	18 (4.1)
AEs leading to withdrawal	14 (6.3)	14 (6.3)	7 (3.2)	21 (4.8)
Deaths	0	0	0	0

The most common adverse events were in the Infections and infestations SOC of the MedDRA classification system. Infectious disorders and most of the other SOC and preferred terms were more common in the C40 group (Table 79). Infections were reported in 81.9% of the C40 subjects compared to 75.1 and 79.9% in the placebo and C160 subjects, respectively.

Nasopharyngitis was the most common infectious manifestation, followed by pharyngitis, upper respiratory tract infection, influenza, bronchitis, and rhinitis, ear infection, and sinusitis. All of these were more common in the C40 group than either the placebo or C160 subjects.

Respiratory complaints were recorded for 48.4, 54.8, and 41.6% of the placebo, C40, and C160 subjects, respectively. The most common of these preferred terms was asthma, which was reported in 33.9, 33.5, and 29.7% of the subjects, respectively.

Table 79. AEs Occurring in 3% or More Subjects in Any Treatment Group, by System Organ Class and Selected Preferred Terms

SOC and Preferred Term	Placebo	Dose of Ciclesonide		
		40 QD	160 QD	Overall

N	221	221	219	440
All AEs	84 (55.3)	88 (57.9)	79 (52.0)	167 (54.9)
Infections and infestations	75.1	81.9	79.9	80.9
Nasopharyngitis	26.2	31.7	31.1	31.4
Pharyngitis	15.4	16.3	12.8	14.5
Upper Respiratory Tract Infection	11.8	14.0	12.8	13.4
Influenza	9.0	13.1	10.0	11.6
Bronchitis	10.0	10.4	10.0	10.2
Rhinitis	9.5	10.0	5.9	8.0
Ear infection	6.3	8.6	5.9	7.3
Sinusitis	4.5	7.2	5.5	6.4
Tonsillitis	3.6	5.9	6.8	6.4
Respiratory tract infection	3.2	4.1	7.3	5.7
Gastroenteritis	3.6	5.9	4.6	5.2
Varicella	3.2	4.5	5.9	5.2
Bronchitis, acute	5.4	5.0	5.0	5.0
Otitis media	3.6	5.4	4.1	4.8
Enterobiasis	1.8	1.8	4.1	3.0
Viral infection	1.8	1.8	4.1	3.0
Respiratory tract infection, viral	3.6	2.3	3.2	2.7
Viral upper respiratory tract infection	2.7	3.2	1.8	2.5
Viral pharyngitis	3.2	3.2	1.4	2.3
laryngitis	3.6	0.5	1.4	0.9
Respiratory, thoracic, and mediastinal	48.4	54.8	41.6	48.2
Asthma	33.9	33.5	29.7	31.6
Cough	5.4	9.5	7.8	8.6
Rhinitis allergic	5.9	8.1	4.1	6.1
Pharyngolaryngeal pain	3.6	3.6	4.1	3.9
Bronchial obstruction	2.3	4.5	2.7	3.6
Nasal congestion	1.8	3.2	2.7	3.0
Epistaxis	2.7	4.1	1.4	2.7
Rhinorrhea	1.8	1.4	3.2	2.3
General disorders	22.2	29.0	21.0	25.0
Pyrexia	19.9	28.1	20.1	24.1
Nervous system disorders	19.5	19.5	21.0	20.2
Headache	18.1	18.6	19.6	19.1
Gastrointestinal disorders	16.7	19.0	13.2	16.1
Vomiting	5.9	5.9	4.6	5.2
Toothache	1.4	4.1	2.3	3.2
Diarrhea	2.7	2.3	3.2	2.7
Abdominal pain	4.1	2.7	2.3	2.5
Injury, poisonings and procedures	9.5	14.0	10.5	12.3
Arthropod bite	3.2	0.5	1.4	0.9
Skin and Subcutaneous tissue	9.5	10.4	7.8	9.1
Impetigo	1.8	3.6	1.4	2.5
Eye disorders	2.7	5.4	2.0	5.2
Musculoskeletal disorders	5.4	4.5	5.5	5.0
Immune system	1.4	4.1	4.6	4.3
Hypersensitivity	0.9	4.1	1.8	3.0
Ear and labyrinth disorders	5.0	3.6	3.7	3.6
Ear pain	3.6	3.6	3.7	3.6
Blood and Lymphatic system	2.3	3.2	1.8	2.5

Most of the events were regarded as mild (81.0, 87.8, and 83.6% in the placebo, C40, and C160 groups, respectively), and less than 5% were severe (3.6, 4.5, and 2.3% in the placebo, C40, C160 groups, respectively).

Since oropharyngeal adverse events are known to be common during therapy with ICS, a grouping of pharyngolaryngeal pain, pharyngitis, and oral candidiasis was produced. There was only 1 case of oral candidiasis in a placebo subject, 25 of pharyngolaryngeal pain and 94 of pharyngitis. Pharyngitis was least frequent in the C160 subjects (12.8%) compared to 15.4 and 16.3% of the placebo and C40 subjects, respectively.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths in this study. Serious adverse events were reported for 6 placebo, 11 C40, and 7 C160 subjects. The most common serious event was asthma, which was reported in 4, 6, and 1 subject in the placebo, C40, and C160 groups, respectively. All other events were reported in 1 subject or less. There were 2 pneumonia events (lobar pneumonia and pneumonia), both reported in C40 subjects.

Withdrawal due to an adverse event occurred in 35 (5.3%) of the subjects overall. The most common event requiring withdrawal was asthma which occurred in 9 (4.1%), 12 (5.4%), and 6 (2.7%) of the placebo, C40, and C160 subjects, respectively. Two placebo subjects were withdrawn due to upper respiratory tract infections, and all other events occurred in one or less subjects. One subject was withdrawn from the placebo group due to precocious puberty.

Other Events on Note

There were 2 cases of significant overdose, defined as three or more times the morning or afternoon dose (6 puffs from either AM or PM inhaler). Neither case was associated with an adverse event. One 5 year-old male took 4 puffs daily of C160 for 24 days. A 7 year-old girl received three puffs of C40 without event.

During the follow-up period 158 subjects experienced adverse events (56 [25.3%], 61 [27.6%], and 41 [18.7%] in the placebo, C40, and C160 subjects, respectively). Asthma, Nasopharyngitis, and headache were reported by $\geq 3\%$ of the subjects. As in the active treatment period, all of the events were slightly more frequent in the C40 group (Table 80).

Table 80. Adverse Events Reported in the Follow-up Period

	Dose of Ciclesonide			
	Placebo	40 QD	160 QD	Total
N	221	221	219	440
All AEs	56 (25.3)	61 (27.6)	41 (18.7)	102 (23.2)
Asthma	7.2	9.0	6.8	8.0
Nasopharyngitis	1.8	4.5	2.7	3.6
Headache	2.3	3.2	0.5	1.8

Ophthalmologic examinations were performed at 2 sites in response to concerns of the local IRB. In 35 subjects examined, 2 cataracts were identified more than 14 days after termination of

treatment. One of the subjects was a 5 year-old both who had been treated with placebo, and the other was a girl who had been treated with C40. Neither had been treated with corticosteroids prior to enrollment in the study. No baseline examinations were performed and follow-up is pending.

4.2.3.6 Laboratory Results

The mean baseline and Week 12 values for all hematology and routine safety chemistry analyses were within the normal range.

For both the hematology and chemistry examinations there were few individuals with shifts out of the normal range over the course of the study, and the distribution of these subjects was similar across the treatment groups.

Laboratory values that reached the Predefined Change Abnormal (PCA) range were uncommon. Table 81 lists the number of subjects in each treatment group in which more abnormalities were seen in the actively treated subjects than placebo, and where at least 3% of the subjects showed the abnormality. In no case was there a dramatic difference between the placebo and actively treated subjects. An increase in the eosinophil count was the most common abnormality, and it was seen most often in the placebo subjects (11.4% compared to 7.7 and 7.8% in the C40 and C160 subjects).

Table 81. Laboratory Values with PCA Changes During Treatment

	PCA Amount / direction	Placebo	C40	C160
N				
Alkaline phosphatase	28 U/L ↑	15/201	17/209	14/206
Albumin	6 GI/L ↑	5/201	7/209	8/206
Leukocytes	1 GG/L ↓	4/202	7/208	7/206
Neutrophils	3.18 GG/L ↑	9/202	10/208	11/206

Clinically noteworthy abnormalities were defined for glucose (> 2 time ULN) and the absolute eosinophil counts (> 1 *10³/mm³). At the end of the treatment period abnormalities were only seen in the eosinophil counts. Eleven placebo, 9 C40, and 5 C160 subjects had high eosinophil counts at the end of treatment.

Abnormal laboratory values were reported as adverse events for 1 placebo and 3 C40, and 3 C160 subjects. No single event was reported in more than one subject, and none resulted in discontinuing study medication. One C40 subject developed idiopathic thrombocytopenic purpura. The Applicant has been unable to obtain the relevant laboratory data from the local medical facility.

HPA-axis Evaluation

Urine was collected for 24-hour cortisol measurement at 39 study sites. Originally a second analysis of “valid” samples defined by the quality of the urine collection was planned. However

only 13% of the samples met the criteria, so only the overall summaries were calculated. It was hypothesized that the number of samples that did not meet the criteria was high because the criteria were derived from adults. The changes in the mean values were small over the course of treatment and the difference from the change during placebo treatment was very small (Table 82).

Table 82. Urinary Cortisol

	N	Baseline Mean	Change from Baseline LS mean (SE)	Difference from placebo	95% CI
Placebo	102	11.37	-0.24 (0.94)		
C40	109	10.56	0.31 (0.96)	0.54 (1.07)	-1.57, 2.66
C160	97	10.08	-0.70 (0.97)	-0.46 (1.12)	-2.65, 1.72

Reviewer: Without quality control it is very difficult to accept the above data as definitive.

4.2.3.7 Physical Examination including Vital Signs.

No clinically significant changes were seen during the treatment period. All subjects were Tanner Stage 1 during the run-in. One subject in each treatment groups progressed to > Stage 1 during the trial. The placebo and C160 subject did so at month 12 and the C40 subject progressed at Month 4.

4.3 Summary and Discussion

This study was designed to assess the effect of ciclesonide on growth in prepubertal children. Approximately 200 subjects in each treatment group were treated with placebo, 40 mcg or 160 mcg ciclesonide once daily for 12 months. Various assessments of growth were made and none showed a significant effect of either dose of ciclesonide compared to placebo. On the other hand, a decrease in growth of 0.6 to 0.7 cm/year is in keeping with the changes seen after treatment with other inhaled corticosteroids, and it is only because there was a similar decrease in the placebo group that there is no drug effect. This unexplained decrease in growth in the placebo group makes it difficult to accept the results of this study as a definitive growth assessment. The failure to collect adequate urine samples for the cortisol measurements also does not increase confidence in the results.

5 Study # XRP1526B/3028

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**

5.1 Protocol

5.1.1 Administrative

Enrollment Dates: **November 18, 2005 – March 3, 2006**
Screening Centers: 15 centers in the United States
Sponsor's medical expert:
CRO:

5.1.2. Objective/Rationale

The primary objective of the study was 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 MDI fitted with an integrated Trudell dose indicator.

The Secondary objective was to assess the safety of ciclesonide administered using the MDI fitted with the Trudell dose indicator

5.1.3. Study Design

This was a multi-center, randomized, open-label, parallel group study in mild-moderate asthmatics 4 years of age or older. Subjects were randomly assigned to either a 15-day or 30 day treatment group (1:4). The subjects in both groups were issue a 120-shot canister that delivered 40 mcg ciclesonide per puff. The center staff primed the canisters with 3 actuations and then instructed the subjects to take four puffs each morning. In the 30-day group the dose indicator should have registered zero and the dose indicator should have ceased making a clicking sound if actuated further. The subjects were seen at randomization, day 8 and 15 for the 15-day group and additionally at day 22 and 30 in the 30-day group. The functionality of the dose counter was assessed by comparing the reading on the counter to daily diary entries made by the subjects at home.

Protocol Amendments

Two protocol amendments were introduced prior to subject enrollment. The amendments were primarily administrative and for clarifying purposes.

5.1.4. Study Population

Inclusion Criteria

- Males or females 4 years of age and older
- History of mild-to-moderate persistent asthma, as defined by NAEPP Guidelines
- Forced expiratory volume in 1 second (FEV₁) \geq 60% of predicted at Visit 1
- Reversibility of FEV₁ of at least 12% (relative to the pre-bronchodilator value in L) and \geq 0.2 L after inhalation of 180 μ g albuterol (ex-actuator), or documented history of reversibility of FEV₁ by at least 12% (relative to the pre-bronchodilator value in L) and \geq 0.2 L within 1 year before screening
- Able to demonstrate acceptable oral inhaler technique
- Written informed consent at enrollment into the study

Exclusion Criteria

- Inability of the patient (or the guardian for younger patients) to read the dose indicator scale or to hear the clicking sound when the dose indicator was actuated
- Pregnancy
- Breast-feeding
- Female patients of childbearing potential unless practicing an adequate method of birth control, or unless sexual abstinence was confirmed at informed consent, or unless premenarchal and prepared to accept counseling on reproductive issues in case of becoming menarchal
- History of hypersensitivity to the investigational product or to similar drugs
- Previous randomization in this study
- Treatment with any investigational product in the last 30 days before study entry
- Clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult
- History of drug or alcohol abuse
- Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study
- Patient unlikely to comply with protocol, eg, uncooperative attitude, inability to return for follow-up visits, and unlikelihood of completing the study
- Patient was the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

Withdrawal Criteria

- At their own request or at the request of their legally authorized representative
- **If, in the Investigator's opinion, continuation** in the study would have been detrimental to **the patient's well-being**
- At the specific request of the Sponsor
- Pregnancy: If a patient became pregnant during the trial, she had to be followed up until the outcome of the pregnancy was known. If pregnancy occurred, the Investigator had to contact the Sponsor immediately for further instruction
- Loss of study medication.

5.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Ciclesonide MDI 160 mcg QD (4 puffs QD of a 40 mcg/puff solution) for 30 days
- Ciclesonide MDI 160 mcg QD (4 puffs QD of a 40 mcg/puff solution) for 15 days

HFA albuterol (100 µg per actuation [90 µg ex-actuator]) was supplied for acute symptoms.

The following concomitant medications were permitted throughout the study as long as they were started prior to screening and the dose was kept constant:

- Topical corticosteroids: Low-potency topical corticosteroid creams or ointments equivalent to $\leq 1\%$ hydrocortisone were permitted for occasional dermatologic use
- Non-steroidal asthma medications:
 - Inhaled short-acting β_2 agonists (albuterol),
 - Leukotriene receptor antagonists (montelukast sodium, zafirlukast),
 - Cromones (cromolyn sodium, nebulized cromolyn, nedocromil),
 - Xanthine derivatives (theophylline, aminophylline);

The following concomitant medications were prohibited from screening onward:

- Any ICS or ICS/LABA combination other than the study medication
- Oral or injectable corticosteroid

Compliance was assessed by the patient's notation in the diary that the medication was taken and by weighing the returned canisters. Poor compliance was defined as $<70\%$ of the expected actuations.

Efficacy Evaluation

The dose counter is labeled in increments of 20 actuations, but the indicator advances after 10 actuations. A red zone appears when there are only 20 actuations remaining. The subjects

brought the MDI with them to all center visits and the counter display was recorded by the center staff. The subjects kept a diary of medication use. They entered the dose counter reading before and after dosing, and separately indicated the number of puffs they had inhaled. Finally the subjects entered the reading when the counter ceased to click.

The canisters without the actuator were weighed after priming and before distribution to the subjects. The canisters were weighed at each visit. A patient satisfaction survey was also performed.

Safety Evaluation

The primary safety analysis was based on collection and recording of adverse events in the standard manner. No laboratory data was collected.

5.1.6. Statistical Analysis Plan

Analysis Variables

The primary efficacy outcome was the comparison of the Trudell dose counter and the diary count. The two counts were considered to be in agreement when they were within 20% of one another. Primary variables 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 (ie, $\pm 20\%$ of 10 puffs)
- Number and percentage of devices with actuation consistency at the end of the study, where actuation consistency was defined as a Trudell count within $\pm 20\%$ 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 variables included the following:

- Number and percentage of devices with actuation consistency between the Trudell count and the canister weight count (ie, the number of puffs calculated from change in canister weight between baseline and end of study), where actuation consistency was defined as a Trudell count within $\pm 20\%$ of the canister weight count
- Functionality of the dose indicators that reached zero, as assessed by 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.

Sample Size

Sample size was chosen to assure an adequate number of subjects less than 12 and greater than 65 years of age. Approximately 125 were planned to be randomized with 100 in the 30-day group and 25 in the 15-day group. Ten percent of the patients were planned to be <12 and 10% > 65 years of age.

Study Populations

The safety population included all subjects who received at least one dose of double-blind study medication.

The intent to treat ITT population included all randomized subjects who used at least 10 actuations of study medication as recorded in the diary.

Primary Analysis

Ratio of correct advances: The number of actuations between any 2 advances of the dose indicator was summarized. If the number was between 8 and 12 the two counts were determined to be in agreement. Because each canister contained 120 actuations and the counter advanced with each 10 actuations, the expected number of advances was 12 for subjects who continued in the study for 30 days. Including the acceptable 20% error rate, the acceptable number was 11.8 to 12.2.

Ratio of correct advances (%) = $100 \times (\text{correct advances}/\text{expected advances})$.

Actuation consistency: The actuation consistency between the Trudell dose indicator count and the diary count as compared to the daily dosing diary record was also assessed for each MDI for the entire study period. The 2 counts were considered to be in agreement when the Trudell count was within $\pm 20\%$ of the diary count. The number and percentage of devices with agreement between the 2 counts was calculated for each treatment group and overall.

Percentage of devices with major discrepancies: A major discrepancy was defined as a Trudell count that differed from the diary count by >20 counts.

Analysis of Secondary Efficacy Variables

The Trudell count was compared to the canister weight for the entire treatment period. In a preliminary set of in vitro experiments, the Applicant verified that weighing the canister at the beginning of use (after priming) and at the end of use and knowing the average weight of an actuation, to assess the number of actuations actually performed. The average per-puff weight was 59.3 mg ($\pm 10\%$), so the number of actuations was calculated as follows:

$$W_{\text{begin}} - W_{\text{end}}/59.3$$

The dose indicator functionality was assessed as the number and percentage of dose indicators that ceased to make a clicking sound upon actuation after the canister was empty.

5.2. Results

5.2.1. Study Population

Disposition

A total of 179 subjects were screened and 125 were randomized; 100 in the 30-day group and 25 in the 15-day group. None was discontinued from the 15-day group and 7 discontinued from the 30-day group. Three of the subjects in the 30-day group withdrew due to adverse events and the others were lost to follow-up. All of the subjects received at least 10 actuations of study medication and were included in the ITT population.

Demographics

Of the 125 subjects randomized 36% were male, the mean (Range) of age was 39.6 (6 – 76) years (Table). The predominant racial group was white (80.0% compared with 7.2% black and 12.8% other). The age distribution showed 13 subjects less than 12 and 11 subjects > 65 years of age.

Table 83. Demographic Characteristics of the Enrolled Population

	Statistic	Dose of Ciclesonide		
		15-day	30-day	Overall
Total ITT Population	n	25	100	125
Gender, % M	%	(52.0)	(32.0)	(36.0)
Age (yrs)	mean (range)	32.8 (8-72)	41.3 (6-76)	39.6 (6-76)
<12	n	2	11	13
12- < 65	n	22	79	101
≥ 65	n	1	10	11
Race				
White	%	80.0	80.0	80.0
Black	%	8.0	7.0	7.2
Other	%	12.0	13.0	12.8
Height (cm)				
Overall	Mean (range)	161 (123-183)	163 (117-191)	163 (117-191)
< 12 years of age		126 (123-128)	137 (117-147)	135 (117-147)
≥ 12 years of age		165 (150-183)	166 (145-191)	166 (145-191)
Duration of Asthma (yrs)				
Overall	Mean (range)	18.8 (0.2-58.4)	23.4 (0.2-72.1)	22.5 (0.2-72.1)
< 12 years of age		6.4 (5.3-7.4)	5.3 (0.3-11.2)	5.4 (0.3-11.2)
≥ 12 years of age		19.9 (0.2-58.4)	25.6 (0.2-72.1)	24.6 (0.2-72.1)
Previous participation in a ciclesonide study	n(%)	7 (28)	29 (29)	36 (29)

The subjects in the 30-day group were older (41.3 years as compared to 32.8 years in the 15-day group). The children less than 12 years of age were on average 11 cm taller than the children in the 15-day group and the adolescents and adults in the 30-day group had had asthma approximately 6 years longer than the adults in the 15-day group.

Pulmonary Function

While the absolute spirometric volumes were smaller in the children, the FEV₁% was 77% predicted across the treatment groups and age groups (Table 84).

Table 84. Baseline Pulmonary Function

	Mean (range)		
	15-day	30-day	Overall
Total ITT Population	25	100	125
FEV1 (L)			
Overall	2.5 (1.1-4.8)	2.3 (0.7-4.9)	2.4 (0.7-4.9)
<12 years	1.2 (1.1-1.4)	1.5 (0.7 – 1.9)	1.4 (0.7-1.9)
≥ 12 years	2.6 (1.6-4.8)	2.4 (1.3 – 4.9)	2.4 (1.3-4.9)
FEV1 (%)			
Overall	77.4 (61-100)	77.0 (60-109)	77.1 (60-109)
<12 years	77.0 (75-79)	73.3 (60-86)	74.0 (60-86)
≥ 12 years	77.5 (61-100)	77.4 (60-109)	77.4 (60-109)
FVC (L)			
Overall	3.4 (1.4-5.9)	3.2 (0.8-6.2)	3.2 (0.8-6.2)
<12 years	1.6 (1.4-1.8)	1.8 (0.8-2.4)	1.8 (0.8-2.4)
≥ 12 years	3.5 (2.3-5.9)	3.3 (1.6-6.2)	3.4 (1.6-6.2)

Compliance was 100% in 96% of the 15-day subjects and in 87% of the 30-day subjects. All the remainder had 90 to 100% compliance.

5.2.2. Efficacy Results

Primary Efficacy Outcome

For the primary outcome, the Trudell advances were compared to the diary recordings. If the **counter advanced after 8 – 12 puffs** ($\pm 20\%$) the advance was classified as correct. According to this criterion 83.5% of the advances were correct (Table 85). However, because some advances were premature and some late, at the end of the canister the overall count showed major discrepancy in only 4% (120/125 [96%] of the counters were accurate).

Table 85 . Comparison of Trudell Dose Counter and Diary Measurements

	Mean (range)		
	15-day	30-day	Overall
Total ITT Population	25	100	125
Ratio of correct advances			
Mean (SD)	79.9 (26.3)	84.4 (20.1)	83.5 (21.5)
range	16.7 - 100	8.3 – 109.1	8.3 – 109.1
Agreement between counter and diary, n (%)	24 (96.0)	96 (96.0)	120 (96.0)
Major discrepancies, n (%)	1 (4.0)	4 (4.0)	5 (4.0)

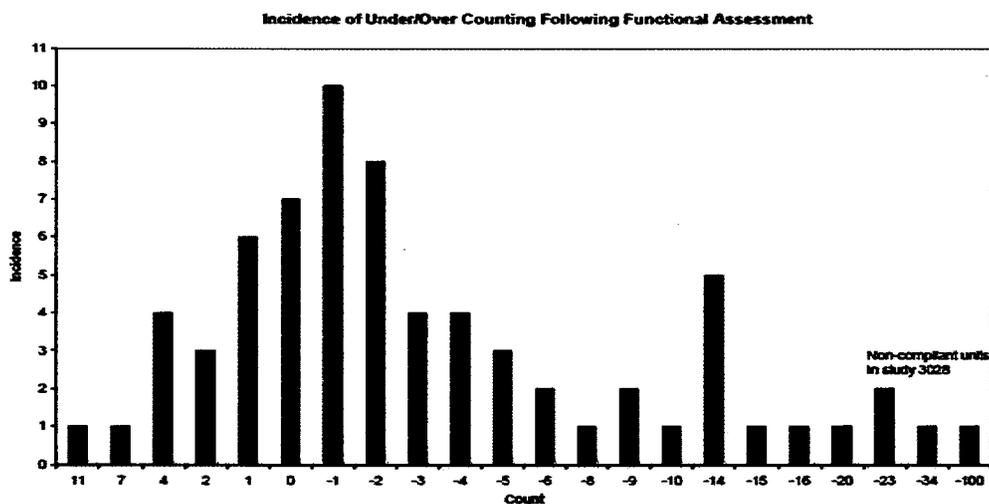
Four of the 5 devices were those identified as having major discrepancies, above. The fifth canister was only slightly out of range at +20.7%. In 4 of the 5 devices with major discrepancies

the problem was thought to be in the manufacturing process. The counters were substantially lower than either the diary entries or the canister weights, and the clinic-monitored Trudell counts agreed with the patient's diary entries. The devices were returned to the manufacturer for further examination. In one patient the counter did not agree with the diary recordings, but it did agree with the canister weights and it was thought that the subject (8 years old) may have made inaccurate entries into the diary.

Secondary Efficacy Outcomes

Fifty-two of the canisters performed as predicted, but 73 had some type of error and were subjected to further investigation. Of the total 125 canisters, 5 (4.0%) undercounted by 20 or more (Figure 13).

Figure 13. Trudell dose counter reading compared to canister weights



The sponsor attributed the undercounting to a manufacturing error, though the manufacturer examined the returned canisters and determined that there was no defect. In the CMC section of the application it is noted that the counter is known to undercount if the actuator is not depressed in the center and if the actuations are repeated too close to one another. [redacted]

Reviewer: According to the CMC submission in the original NDA the minimum fill weight was [redacted] for the 60 or 120 actuation canisters. The minimum fill weight included the desired actuations [redacted] respectively) for priming for the 60 and 120 actuation canisters, respectively, [redacted] for leakage over a 2 year half-life, and [redacted] for overfill. If the minimum desired overfill is [redacted] actuations then the minimum acceptable fill weight would be [redacted], respectively. (These calculations are based on an average actuation weight of [redacted]) Actual measured fill weights were also presented in the original NDA (CMC Table P.2.3.4-1 and P.2.3.4-2). The means were 6.1 and 9.6 g for the 60 and 120-actuation canisters, respectively. Both

distributions had a standard deviation of 0.28 g. Given the distribution of actual weights, the probability of a canister with a fill weight of [] of the normal distribution.) Assuming fill weight and counter function are independent, the probability of a drug product with a fill weight [] and a counter that undercounted by [] is the product of the two probabilities []

Sixty-eight patients (68.0%) in the 30-day group recorded a total of ≥ 120 puffs in their diary at the end of the study, and 42 of these 68 (61.8%) also recorded that their devices reached zero (Table 86). Eleven of the 42 devices recorded as having reached zero (26.2%) were also recorded as continuing to make a clicking sound upon further actuation. Thirty-two patients (32.0%) in the 30-day group recorded a total of < 120 puffs in their diary at the end of the study, and 9 of these 32 patients (28.1%) also recorded that their devices reached zero. Three of the 9 devices recorded as having reached zero (33.3%) were also recorded as continuing to make a clicking sound upon further actuation

Table 86. Counter Functionality

Total ITT Population	100
Number with > 120 puffs actuations	68/100 (68%)
Number of dose counters that reached zero	42/68 (61%)
Number of dose counters that clicked after reaching zero	11/42 (26.2%)

At the end of the study 122/125 (97.6%) of the diary counts were within 20% of the canister weights. One of the three was one of the canisters with a major discrepancy discussed above.

According to the patient satisfaction questionnaire, the subjects generally thought that the counter was accurate and helped them assess the amount of medication left.

Sub-group Analysis

The results did not differ by age.

5.2.3. Safety

5.2.3.1 Exposure

The safety population consisted of 125 subjects. Of the 25 subjects in the 15-day group, 24 were treated for at least 9 days. Of the 100 in the 30-day group, 87 were treated for the full 30 days.

5.2.3.2 Adverse Events

Overall Assessment of Adverse Events

Four subjects in the 15-Day group and 25 in the 30-Day group reported an adverse event. None was classified as serious and none resulted in death. 3 subjects in the 30-Day group were withdrawn due to an adverse event (Table 87).

Table 87. Overall Summary of Adverse Events.

	Dose of Ciclesonide		
	15 Day	30 Day	Total
N	25	100	125
All AEs	4 (16.0)	25 (25.0)	29 (22.5)
Serious AEs	0	0	0
AEs leading to withdrawal	0	3 (3.0)	3 (2.4)
Deaths	0	0	0

The most common adverse events were in the Infections and infestations SOC of the MedDRA classification system: 2 (8%) of the 15-Day and 13 (13%) of the 30-Day subjects. As in the other studies in this submission, nasopharyngitis was the most common infectious manifestation, followed by, upper respiratory tract infections and influenza (Table 88). Asthma was the most common respiratory complaint and occurred in 2 subjects in each group. Oropharyngeal candidiasis was not reported in any subject.

Table 88 . AEs Occurring in 3% or More Subjects in Any Treatment Group, by System Organ Class and Selected Preferred Terms

SOC and Preferred Term	Dose of Ciclesonide		
	40 QD	160 QD	Overall
N	25	125	129
All AEs	4 (16.0)	25 (25.0)	29 (22.5)
Infections and infestations	2 (8.0)	13 (13.0)	15 (11.6)
Nasopharyngitis	2 (8.0)	3 (3.0)	5 (3.9)
Upper Respiratory Tract Infection	0	6 (6.0)	6 (4.7)
Influenza	0	2 (2.0)	2 (1.6)
Respiratory, thoracic, and mediastinal	3 (12.0)	7 (7.0)	10 (7.7)
Asthma	2 (8.0)	2 (2.0)	4 (3.1)
Pharyngolaryngeal pain	0	2 (2.0)	2 (1.5)

Only one event (pain in an extremity) in a 30-Day subject was considered severe and this was unlikely to be related to drug treatment.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths or serious adverse events.

Withdrawal due to an adverse event occurred in 3 (3.0%) of the 30-Day subjects. There was one case, each, of increased heart rate in an 11 year old girl, respiratory infection, and chest pain.

Other Events

There were no overdoses. One subject reported blurred vision accompanying a headache. No cataract was seen on examination. No laboratory analysis was performed and there were no clinically important changes in vital signs.

5.3 Summary and Discussion

In this study, made up of 15- and 30-Day cohorts, the pre-specified level of accuracy was demonstrated. The counter did not appear to affect the delivered dose or the particle size distribution, and only 5/125 (4%) of the canisters tested were deficient as defined by the **Applicant's criteria of an, undercounted of [] or greater** when compared to the diary recordings. In data submitted with the original NDA, a mean fill weight for the 120-actuation canisters was demonstrated to be 9.6 g with a standard deviation of 0.28 g. These data show substantial overfill and a probability that any canister would have less than [] extra doses (beyond the prescribed 120) of []. This, combined with the finding that only [] of the counters undercounted by more than [] counts suggests that there is less than a 0.1% probability that a counter would register a positive number when it was actually empty. Functionality will be further improved by additional warnings in the patient instructions on the correct use of the delivery device.

10.2 LINE-BY-LINE LABELING REVIEW

REFERENCES

1. Dann RS. Review and Evaluation of Methods for Computing Confidence Intervals for the Ratio of Two Proportions and Implications to Non-Inferiority Clinical Trials. Univ of North Carolina at Chapel Hill, Masters Thesis, 2003.
2. AREDS Report No. 9. A Randomized, Placebo-Controlled Clinical Trial of High-Dose Supplementation with Vitamins C and E and Beta Carotene for Age-Related Cataract and Vision Loss; Arch Ophthalmol 2001;1439-52.
3. Baumgartner R. Incremental growth tables: supplementary to previously published charts. Am J Clin Nutr 1986; 43:711-722.
4. **Ballinger PW, MS. Merrill's Atlas of Radiographic Positions and Radiologic Procedures.** 7th edition, Mosby-Year Book, Inc, 1991.

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this page is the manifestation of the electronic signature.**

/s/

Carol Bosken
12/18/2007 01:34:49 PM
MEDICAL OFFICER

Lydia McClain
12/19/2007 05:43:58 PM
MEDICAL OFFICER
I concur with the recommendation for approval

**Medical Officer's Review NDA 21-658
Ophthalmology Consult**

Application Number: NDA 21-658
Review Date: December 2, 2007
Name: Alvesco (ciclesonide)
Therapeutic Class: Inhaled corticosteroid
Applicant: Sanofi-Aventis Pharmaceuticals
Proposed Indication: Asthma
Submitted: Study Report for Study 3027

Requested:

Given the results of Study 3027, can we accept the Applicant's conclusion that the risk of developing corneal opacities during treatment with ciclesonide 320 mcg BID is equivalent to the risk when patients are treated with beclomethasone 320 mcg BID?

Reviewer's Comments: *Corneal opacities are not in question with this application; the question above is assumed to mean lens opacities, and the question has been corrected in other sections of this review.*

I. Background

The DPAP is currently evaluating a complete response to NDA 21-658 submitted to support the approval of ciclesonide (Alvesco) a corticosteroid formulated as an HFA-inhalation solution for the treatment of asthma. In the original submission (December 22, 2004) a 12-week study in adults and adolescents with moderate to severe asthma who had previously been treated with inhaled corticosteroids showed an unexpected and substantial increase in new cataracts when treated with ciclesonide 320 mcg BID compared to subjects treated with fluticasone. The other studies in the submission either did not include an ophthalmologic examination or showed only a slight/equivocal increase in cortical events in the ciclesonide-treated subjects.

b(4)

NDA 21-658 _____
_____ The Applicant was advised to perform studies to compare once and twice daily dosing, and in addition, they agree to perform a detailed long term study to evaluate the potential for ciclesonide to increase the incidence of cataracts. Study 3027 was a 12-month trial conducted in 1500 adults previously treated with ICS who received slit lamp examinations at the beginning of treatment and at 4, 8 and 12 months after treatment with ciclesonide 320 mcg BID or beclomethasone 320 mcg BID. The study used a noninferiority design, and no placebo was administered. The protocols were reviewed by the Division of Pulmonary and Allergic Products after consultation with the Division of Ophthalmologic Products. During the course of the study a blinded review of the results was

performed, and a higher incidence of events was found than expected. On this basis, the Applicant requested a change in the non-inferiority boundary for the comparison between ciclesonide and beclomethasone to 1.33. In a second consultation, the Ophthalmology Division rejected the new non-inferiority boundary (NIB) and stated that it should not be higher than 1.1. This opinion was transmitted to the Applicant.

A complete response to the approvable action on NDA 21-658 has been submitted and the full study report for Study 3027 was included. Of note, the Applicant retained the revised NIB despite our recommendation. At first reading of the study report, the statistical analysis of the NIB did not appear to be important because the number of subjects with Class I, Class II, and Class III events were all less during ciclesonide treatment than during treatment with beclomethasone. However, on closer examination, there were some findings that are of concern.

1) When the LOC III classifications were broken down into their component parts, the superiority of ciclesonide was restricted to nuclear and cortical opacities. For the more pathognomonic posterior subcapsular (PSC) opacities, ciclesonide was uniformly inferior (More subjects in all Class groups and a greater mean increase in the score). The differences were small, but given the opposite findings for nuclear and cortical opacities are of concern.

2) When the total treatment group was divided by age, the subjects over 60 years of age actually had a higher incidence of all events (Class I, II, and III) as well as PSC events. Unfortunately there were not many subjects over 60 years of age (130). However, given the increased risk for developing cataracts in the older age group, the findings could be important. The Applicant divided the group into those over and under 40 years of age and found no differences.

Study Design

This was a multinational, multi-center, randomized, double-blind, active-controlled, parallel group study of the effects of ciclesonide-HFA 640 mcg daily and beclomethasone 640 mcg daily on lens opacification in adults with moderate to severe persistent asthma. Eligible subjects were enrolled into a 1 to 14-day screening period after which they were randomized (1:1) to receive either ciclesonide or beclomethasone by inhalation. They were treated for 12 months and seen in follow-up at 4, 8, and 12 months after initiation of treatment. At each visit a slit-lamp examination was performed to grade lens opacities. Visual acuity, intraocular pressure and pulmonary function was also assessed at each visit. Throughout the treatment period the subjects maintained a diary indication how much study medication they took every day. A protocol amendment was submitted to change the non-inferiority bound (NIB) from 1.1 to 1.33. This change was not accepted by the Agency.

Ophthalmologic examinations were performed at baseline, and month 4, 8, and 12. The same ophthalmologist was to perform the examinations on each subject; if this was impossible, a trained and certified examiner was to be substituted. The examination consisted of the following procedures performed in the order listed:

- Manifest refraction
- Visual acuity of each eye
- Intraocular pressure measured by tonometry.
- Slit lamp examination for Lens grading: LOC III

- Nuclear opalescence
- Nuclear color
- Cortical lens opacity
- Posterior subcapsular lens opacity

The primary efficacy evaluation was based on the ophthalmologic examination. Lens opacification was assessed by slit lamp examinations using the LOCS III classification. The primary endpoint was the occurrence of a Class I lens event within 12 months. A Class I lens event was defined as any of the following events in either eye:

- Increase from baseline in LOCS III grade of ≥ 0.5 (nuclear opalescence), or ≥ 0.8 (cortical) or ≥ 0.5 (posterior subcapsular)
- Cataract surgery since baseline

Baseline

Treatment	C320b (N=743)		BDP (N=742)	
	R	L	R	L
Nuclear opalescence*	1.4 (0.9) 0.1 - 3.8	1.4 (0.9) 0.1 - 3.8	1.4 (0.9) 0.1 - 3.7	1.4 (0.9) 0.1 - 3.7
Cortical opacity*	0.4 (0.6) 0.1 - 3.2	0.4 (0.5) 0.1 - 3.1	0.4 (0.6) 0.1 - 2.9	0.4 (0.5) 0.1 - 2.9
Posterior subcapsular opacity*	0.2 (0.2) 0.1 - 1.8	0.2 (0.2) 0.1 - 2.0	0.2 (0.2) 0.1 - 1.9	0.2 (0.2) 0.1 - 2.0
Visual Acuity	87.0 (4.7) 58 - 100	86.9 (4.9) 65 - 99	87.0 (4.8) 66 - 99	87.0 (4.9) 64 - 99
Intraocular pressure	14.8 (3.0) 6.0 - 30.0	14.6 (3.0) 6.5 - 28.0	14.8 (2.8) 8.0 - 22.5	14.7 (2.8) 8.0 - 24.0

Class I Lens events

	N	% of Subjects with Class I event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320b	743	36.1 (1.82)	0.94	0.82, 1.08	1.33	<0.0001
BDP	742	38.4 (1.83)				

Reviewer's Comments: *There is no difference in rates of cataract development based on the original planned analysis. The planned analysis was designed based on information known at the start of the trial. If the study had been planned today, the Ophthalmology Group would have asked that the primary analysis be based on posterior subcapsular changes of 0.3 or more instead of total lens changes based on the threshold scale described in this study.*

Type of lens event	Observed proportions: Number (%) of subjects		Life table estimates: Percent of subjects \pm SE	
	CIC-HFA (N = 743)	BDP-HFA (N = 742)	CIC-HFA (N = 743)	BDP-HFA (N = 742)
Class I	255 (34.3%)	273 (36.8%)	36.1 \pm 1.8	38.4 \pm 1.8
Nuclear opalescence	210 (28.3%)	227 (30.6%)	29.7 \pm 1.7	32.0 \pm 1.8
Cortical opacity	60 (8.1%)	66 (8.9%)	8.5 \pm 1.1	9.3 \pm 1.1
Posterior subcapsular opacity	20 (2.7%)	17 (2.3%)	2.8 \pm 0.6	2.4 \pm 0.6
Class II	99 (13.3%)	117 (15.8%)	14.0 \pm 1.3	16.4 \pm 1.4
Nuclear opalescence	82 (11.0%)	103 (13.9%)	11.7 \pm 1.2	14.5 \pm 1.3
Cortical opacity	14 (1.9%)	13 (1.8%)	2.0 \pm 0.5	1.8 \pm 0.5
Posterior subcapsular opacity	10 (1.3%)	6 (0.8%)	1.4 \pm 0.4	0.8 \pm 0.3
Sustained Class II	66 (8.9%)	81 (10.9%)	9.4 \pm 1.1	11.5 \pm 1.2
Nuclear opalescence	55 (7.4%)	71 (9.6%)	7.9 \pm 1.0	10.1 \pm 1.1
Cortical opacity ^a	6 (0.8%)	9 (1.2%)	0.8 \pm 0.3	1.2 \pm 0.4
Posterior subcapsular opacity ^a	5 (0.7%)	1 (0.1%)	0.7 \pm 0.3	0.1 \pm 0.1
Class III	57 (7.7%)	65 (8.8%)	8.1 \pm 1.0	9.2 \pm 1.1
Nuclear opalescence	44 (5.9%)	54 (7.3%)	6.3 \pm 0.9	7.6 \pm 1.0
Cortical opacity	12 (1.6%)	11 (1.5%)	1.7 \pm 0.5	1.6 \pm 0.5
Posterior subcapsular opacity ^a	7 (0.9%)	4 (0.5%)	0.9 \pm 0.4	0.5 \pm 0.3

BDP = beclomethasone; CIC = ciclesonide.
 NC = estimates not calculated because at least one treatment group had less than 10 events.
^a Life table estimates were obtained using the standard life table method if there were fewer than 10 events in each treatment group because the modified method requires 10 or more events in at least one treatment group to provide robust estimates.

Reviewer's Comments: *The distributions demonstrate higher proportions of posterior subcapsular opacities in the ciclesonide group, particularly with the more severe changes in posterior subcapsular opacities; however, the number of patients in each group is small.*

Treatment	N	Baseline mean	Change from baseline	Ciclesonide-HFA vs. beclomethasone-HFA	
			LS mean \pm SE (LOCS III grade)	LS mean \pm SE	2-sided 95% CI
Nuclear opalescence					
Ciclesonide-HFA	743	1.33	0.22 \pm 0.019	-0.016 \pm 0.020	-0.056, 0.024
Beclomethasone-HFA	742	1.36	0.23 \pm 0.018		
Cortical					
Ciclesonide-HFA	743	0.36	0.14 \pm 0.018	-0.018 \pm 0.020	-0.057, 0.021
Beclomethasone-HFA	742	0.35	0.16 \pm 0.017		
Posterior subcapsular					
Ciclesonide-HFA	743	0.14	0.06 \pm 0.009	0.018 \pm 0.010	-0.001, 0.037
Beclomethasone-HFA	742	0.15	0.05 \pm 0.009		

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; N = mITT population; SE = standard error.
Ciclesonide-HFA vs. beclomethasone-HFA is calculated as ciclesonide-HFA minus beclomethasone-HFA.

Reviewer's Comments: *The change from baseline demonstrates a higher mean change of posterior subcapsular opacities in the ciclesonide group compared to the beclomethasone group, but the difference is not statistically significant.*

Variable	Number (%) of subjects	
	Ciclesonide-HFA (N = 743)	Beclomethasone-HFA (N=742)
Nuclear opalescence		
Decrease	121 (16.3%)	145 (19.5%)
No change	151 (20.3%)	123 (16.6%)
Increase by 0.1 to 0.4	261 (35.1%)	247 (33.3%)
Increase by 0.5 to 0.8	128 (17.2%)	124 (16.7%)
Increase by ≥ 0.9	82 (11.0%)	103 (13.9%)
Cortical		
Decrease	48 (6.5%)	49 (6.6%)
No change	343 (46.2%)	320 (43.1%)
Increase by 0.1 to 0.7	292 (39.3%)	307 (41.4%)
Increase by 0.8 to 1.4	46 (6.2%)	53 (7.1%)
Increase by ≥ 1.5	14 (1.9%)	13 (1.8%)
Posterior subcapsular		
Decrease	16 (2.2%)	26 (3.5%)
No change	542 (72.9%)	550 (74.1%)
Increase by 0.1 to 0.4	165 (22.2%)	149 (20.1%)
Increase by 0.5 to 0.8	10 (1.3%)	11 (1.5%)
Increase by ≥ 0.9	10 (1.3%)	6 (0.8%)

The 2 highest categories of increase for each type of opacity together correspond to the Class I lens event criteria, and the highest categories correspond to the Class II lens event criteria.

Reviewer's Comments: *The distributions demonstrate higher proportions of posterior subcapsular opacities in the ciclesonide group, particularly with the more severe changes in posterior subcapsular opacities; however, the number of patients in each group is small.*

Question

Given the results of Study 3027 can we accept the Applicant's conclusion that the risk of developing lens opacities during treatment with ciclesonide 320 mcg BID is equivalent to the risk when patients are treated with beclomethasone 320 mcg BID?

Response:

Based on the results presented, it appears that the use of both ciclesonide and beclomethasone present a significant risk in the development of cataracts, but the risk does not appear to be significantly greater in ciclesonide than in beclomethasone. It is not possible to evaluate the effect on intraocular pressure based on the analyses conducted to date. There are additional analyses which may be informative and would be worth having carried out.

1. A comparison between groups (ciclesonide and beclomethasone) of the percentage of left eye and of right eyes that have a higher posterior subcapsular change of 0.3 or greater at eight month and at twelve months.
2. A comparison between groups (ciclesonide and beclomethasone) of the distribution of left eye and of right eyes that have a higher posterior subcapsular change of <-0.1, -0.1, 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1 or greater at eight months, and at twelve months.
3. A comparison between groups (ciclesonide and beclomethasone) of the percentage of left eye and of right eyes that have a higher intraocular pressure change of 7mmHg or greater at four months, at eight months and at twelve months.
4. A comparison between groups (ciclesonide and beclomethasone) of the distribution of left eye and of right eyes that have a higher intraocular pressure change of 7 mmHg or greater, 10 mmHg or greater and 15 mmHg or greater at four months, at eight months and at twelve months.

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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this page is the manifestation of the electronic signature.**

/s/

Wiley Chambers
12/3/2007 10:43:37 AM
MEDICAL OFFICER

Wiley Chambers
12/3/2007 10:44:55 AM
MEDICAL OFFICER

REQUEST FOR CONSULTATION

TO (Division/Office):
Division of Anti-Infective and Ophthalmology Products
FD-520

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products, HFD-570

DATE
October 3, 2007

IND NO

NDA NO.
21-658

TYPE OF DOCUMENT
N

DATE OF DOCUMENT
July 10, 2007

NAME OF DRUG
Alvesco (ciclesonide)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Inhaled Corticosteroid

DESIRED COMPLETION DATE
November 5, 2007

NAME OF FIRM: Sanofi-Aventis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for an ophthalmologic review of study findings of concern with NDA 21-658 Alvesco (ciclesonide).

Question: Given the results of Study 3027 can we accept the Applicant's conclusion that the risk of developing corneal opacities during treatment with ciclesonide 320 mcg BID is equivalent to the risk when patients are treated with beclomethasone 320 mcg BID?

Included with this consult are previous consults from your Division and the Medical Officer's draft review of Study 3027. The submission is in the EDR Dated July 10, 2007.

CC:

Dr. Wiley Chambers
Archival NDA 21-658
HFD-570/Division File
570/Jackson

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

I. Background

The DPAP is currently evaluating a complete response to NDA 21-658 submitted to support the approval of ciclesonide (Alvesco) a corticosteroid formulated as an HFA-inhalation solution for the treatment of asthma. In original submission (December 22, 2004) a 12-week study in adults and adolescents with moderate to severe asthma who had previously been treated with inhaled corticosteroids showed an unexpected and substantial increase in new cataracts when treated with ciclesonide 320 mcg BID compared to subjects treated with fluticasone. The other studies in the submission either did not include an ophthalmologic examination or showed only a slight/equivocal increase in cortical events in the ciclesonide-treated subjects.

(b)(4)

NDA 21-658 was not approved (

_____). The Applicant was advised to perform studies to compare once and twice daily dosing, and in addition, they agree to perform a detailed long term study to evaluate the potential for ciclesonide to increase the incidence of cataracts. Study 3027 was a 12-month trial conducted in 1500 adults previously treated with ICS who received slit lamp examinations at the beginning of treatment and at 4, 8 and 12 months after treatment with ciclesonide 320 mcg BID or beclomethasone 320 mcg BID. The study used a non-inferiority design, and no placebo was administered. The protocols were reviewed by the Division of Pulmonary and Allergic Products after consultation with the Division of Ophthalmologic Products. During the course of the study a blinded review of the results was performed, and a higher incidence of events was found than expected. On this basis, the Applicant requested a change in the non-inferiority boundary for the comparison between ciclesonide and beclomethasone to 1.33. In a second consultation, the Ophthalmology Division rejected the new non-inferiority boundary (NIB) and stated that it should not be higher than 1.1. This opinion was transmitted to the Applicant.

A complete response to the approvable action on NDA 21-658 has been submitted and the full study report for Study 3027 was included. Of note, the Applicant retained the revised NIB despite our recommendation. At first reading of the study report, the statistical analysis of the NIB did not appear to be important because the number of subjects Class I, Class II, and Class III events were all less during ciclesonide treatment than during treatment with beclomethasone. However, on closer examination, there were some findings that are of concern. 1) When the LOC III classifications were broken down into their component parts, the superiority of ciclesonide was restricted to nuclear and cortical opacities. For the more pathognomonic posterior subcapsular (PSC) opacities, ciclesonide was uniformly inferior (More subjects in all Class groups and a greater mean increase in the score). The differences were small, but given the opposite findings for nuclear and cortical opacities are of concern. 2) When the total treatment group was divided by age, the subjects over 60 years of age actually had a higher incidence of all events (Class I, II, and III) as well as PSC events. Unfortunately there were not many subjects over 60 years of age (130). However, given the increased risk for developing cataracts in the older age group, the findings could be important. The Applicant divided the group into those over and under 40 years of age and found no differences.

II. Question

Given the results of Study 3027 can we accept the Applicant's conclusion that the risk of developing corneal opacities during treatment with ciclesonide 320 mcg BID is equivalent to the risk when patients are treated with beclomethasone 320 mcg BID?

III. Enclosures

A. MO draft review of Study 3027 (The complete study report is available in EDR (...n21658\N_000\207-07-10\clinstat\3027... The written report is contained in ...3027\3027.pdf. Files 3027\3027a-d contain the appendices)

B. Ophthalmology Consults # 1 and 2

3 Study # XRP1526B/3027

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

(Note: this is a draft protocol. Additional information may be requested of the Applicant. In the review, ciclesonide 320 mcg BID is abbreviated as C320B and beclomethasone 320 mcg BID is abbreviated as BDP. Tables copied from the application abbreviated ciclesonide as CIC-HFA and beclomethasone as BDP-HFA)

3.1 Protocol

3.1.1 Administrative

Enrollment Dates: January 19, 2004 – June 21, 2005
Screening Centers: 102 centers in the USA, 7 in Poland and 10 in S. Africa
Sponsor's medical expert: _____
CRO: _____

b(4)

3.1.2. Objective/Rationale

The primary objective of the study was to demonstrate the non-inferiority of ciclesonide compared to beclomethasone-HFA in the occurrence of a Class I lens event for nuclear opalescence, cortical, and posterior subcapsular lens opacification within 12 months. Lens event outcomes were determined by the occurrence of a protocol-specified change in lens opacification using the LOCS III method for grading lens opacities, or the occurrence of cataract.

The secondary objective of the study was to compare ciclesonide to beclomethasone for changes in various sub-scores of the LOCS III.

3.1.3. Study Design

This was a multinational, multi-center, randomized, double-blind, active-controlled, parallel group study of the effects of ciclesonide-HFA 640 mcg daily and beclomethasone 640 mcg daily on lens opacification in adults with moderate to severe persistent asthma. Eligible subjects were enrolled into a 1 to 14-day screening period after which they were randomized (1:1) to receive either ciclesonide or beclomethasone by inhalation. They were treated for 12 months and seen in follow-up at 4, 8, and 12 months after initiation of treatment. At each visit a slit-lamp examination was performed to grade lens opacities. Visual acuity, intraocular pressure and pulmonary function was also assessed at each visit. Throughout the treatment period the subjects maintained a diary indicating how much study medication they took every day.

3.1.3.2 Protocol Amendments

Protocol Amendment 1 (May 19, 2004) stipulated that the number of clinical centers would be reduced from 200 to 125. It also increased the sample size from 1200 to 1500.

Protocol Amendment 2 (November 20, 2004) stated that all subjects in the modified intent-to-treat (ITT) population were to be analyzed according to the treatment randomized to unless there was a drug dispensing error. If the subject received the incorrect drug under the study staff's direction, they were to be returned to the correct arm as soon as possible. The order of the ophthalmology examinations was specified and the ophthalmologist was instructed not to review the previous LOCS III assessments.

Protocol Amendment 3 (June 28, 2005) was implemented due to an unexpectedly high incidence of Class I events. The non-inferiority bound (NIB) was originally chosen to detect infrequent events. Therefore, the sponsor adjusted the original NIB for event rates $\geq 30\%$ to a constant value of 1.333. This bound allowed the conclusion of non-inferiority if the number of Class I lens events with test treatment was not more than a third larger than that of the control treatment.

Reviewer: Protocol Amendment was submitted to the Agency for review. The Agency did not accept the logic for the change in NIB and reported to the Applicant that the NIB should be no higher than 1.11 (See FDA Statistics Review for details).

3.1.4. Study Population

Inclusion Criteria

- Males and females 18 years or older
- Moderate to severe persistent asthma of at least 2 months prior to Screening
- At Screening, forced expiratory volume in one second (FEV₁) $\geq 40\%$ and $\leq 85\%$ of predicted
- Documented use of ICS therapy at any dose for at least one month prior to Screening
- Ability to demonstrate acceptable oral inhaler technique
- Non-smoker for at least the past year and less than a 10 pack-year total smoking history
- Written informed consent agreement.

Exclusion Criteria

- History of prior cataract surgery in either eye;
- Evidence of congenital cortical cataract;
- Inability to grade opacities in either eye with LOCS III at the baseline
- Inability to dilate pupils to at least 6.0 mm
- Nuclear opalescence with a LOCS III grade ≥ 4 in either eye at the baseline
- Cortical lens opacities with a LOCS III grade ≥ 3 in either eye at the baseline
- Posterior subcapsular lens opacities with a LOCS III grade ≥ 2 in either eye at the baseline
- Elevated intraocular pressure requiring treatment
- BCVA less than 74 letters (equivalent to vision worse than 20/30) in either eye at baseline
- Females who were pregnant, lactating or had a positive pregnancy test at screening
- More than one in-patient hospitalization in the past year for asthma exacerbation
- More than 2 bursts of oral steroids per year for each of the past 2 years prior to Screening
- Chronic use of oral, injectable, or topical steroids except for ICSs for any condition. Topical corticosteroids designated as having a mild potency by the Stoughton-Cornell Scale or the European Guideline for levels of corticosteroid activity were allowed
- Any chronic condition likely to require treatment with oral or systemic corticosteroids other than asthma
- Topical ocular steroid treatment within 3 months prior to Screening
- Chronic or recurrent inflammatory disease in either eye likely to result in visual abnormalities or require treatment with ocular steroids
- History of drug or alcohol abuse
- Any clinically significant medical condition that would interfere with the subject's ability to participate in and comply with the study protocol
- Subject unlikely to comply with protocol
- Subject was the investigator or any sub-investigator, research assistant, pharmacist, study
- Staff or relative thereof directly involved in the conduct of the study
- Hypersensitivity to the investigational products
- Treated with any investigational drug/product within 30 days prior to Visit 1 (Screening).

Withdrawal Criteria

Subjects could be withdrawn if any of the following occurred:

- At their own request
- In the investigator's opinion continued participation in the study would be detrimental to the subject
- In the event of a protocol deviation at the discretion of the Investigator or the Sponsor

Subjects had to be withdrawn if any of the following occurred:

- Poor compliance defined as failure to take medication or to come to clinic visits
- Exacerbation of asthma requiring >2 courses of systemic corticosteroids
- Pregnancy
- Cataract surgery

3.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Ciclesonide MDI-HFA 320 mcg BID (4 puffs 80 mcg BID)
- Beclomethasone-HFA MDI 320 mcg BID (4 puffs 80 mcg BID)

Compliance was assessed by the patient's notation in the diary that the medication was taken. The number of inhalers returned was also compared to the number dispensed. At 35 selected sites blood was collected for ciclesonide and des-ciclesonide levels as an exploratory way of measuring compliance. The intent was to collect serum samples on at least 375 randomized subjects.

Concomitant medications were supposed to have been kept to a minimum during randomized treatment. The following concomitant medications were permitted throughout the study:

- Intranasal corticosteroids: up to 1 month if absolutely necessary for severe allergic rhinosinusitis
- Systemic corticosteroids: up to 2 bursts for the treatment of acute asthma. If a third course was required the subject had to be withdrawn
 - Recommended dose of prednisone was 60 mg as a single dose for 3 days followed by a 10 mg/day taper over the next 5 days
 - The decision to initiate or continue the course for >8 days was left to the investigator, but should be discussed with sponsor
 - Systemic corticosteroids for other conditions were allowed if absolutely necessary
- Mild-potency topical corticosteroids
- β_2 -agonists, long and short-acting
- Leukotriene receptor antagonists
- Xanthine derivatives
- Cromolyn
- Anticholinergic agents

The following concomitant medications were prohibited from screening onward:

- Non-study ICS
- Chronic use of otic or ophthalmic preparations containing corticosteroids

Ophthalmologic Examination

Ophthalmologic examinations were performed at baseline, and month 4, 8, and 12. The same ophthalmologist was to perform the examinations on each subject; if this was impossible, a trained and certified examiner was to be substituted. The examination consisted of the following procedures performed in the order listed:

- Manifest refraction
- Visual acuity of each eye
- Intraocular pressure measured by tonometry.
- Slit lamp examination for Lens grading: LOC III
 - Nuclear opalescence
 - Nuclear color
 - Cortical lens opacity
 - Posterior subcapsular lens opacity

To assure consistency, the examiners were trained at baseline and recertified twice during the trial. Recertification required 70% correct answers on a certification examination.

Other Safety Variables

Adverse events, routine hematology and chemistry blood tests, and urinalysis for glucose and protein were performed at baseline and at month 4 and 12. Serum for ciclesonide and des-ciclesonide was collected at selected centers at baseline and month 4 and 12. Physical examinations and vital signs completed the safety evaluation.

Efficacy Evaluation

Efficacy was not the primary objective of the study but pulmonary function was monitored with spirometry. The forced vital capacity was obtained following the 1994 ATS standards at baseline and at all follow-up visits.

Schedule of Events

The timing of the various examinations is summarized in Table .

Table Summary of Events

Study Day	Screen	Random	Treatment Period				
	-1 to -14	0	1	60	120	180-300	365
Visit number	1		2	3	4	5,6,7	8
Informed consent	X						
Randomization		X					
Medical history	X						
Physical examination	X				X		X
Review medication	X		X	X	X	X	X
Spirometry	X		X	X	X	X	X
Ophthalmology exam*	X				X	X**	X
Laboratory tests	X				X		X
Issue & Review Diary	X		X	X	X	X	X
Adverse event review			X	X	X	X	X
Dispense appropriate medications			X	X	X	X	X

*Ophthalmologic exam consists of refraction, visual acuity, IOP, and slit lamp examination

**Only performed at visit 6 (month 8)

3.1.5 Analysis

Primary Variable

The primary efficacy evaluation was based on the ophthalmologic examination. Lens opacification was assessed by slit lamp examinations using the LOCS III classification. The primary endpoint was the occurrence of a Class I lens event within 12 months. A Class I lens event was defined as any of the following events in either eye:

- Increase from baseline in LOCS III grade of ≥ 0.5 (nuclear opalescence), or ≥ 0.8 (cortical) or ≥ 0.5 (posterior subcapsular)
- Cataract surgery since baseline

If a subject had any of the events listed above during the 12 months of treatment they were classified as having the event for analysis purposes. This was true even if the event was not observed at a later date.

Key secondary variables

LOCS III lens events

- Occurrence of a Class II lens event. A Class II lens event is defined as any of the following events in either eye:
 - Increase from baseline in LOCS III grade of ≥ 0.9 (nuclear opalescence), ≥ 1.5 (cortical), or ≥ 0.9 (posterior subcapsular),
 - Cataract surgery
- A sustained Class II lens event is defined as a Class II lens event observed at any time point with presence of a Class I lens event in the same eye at the next time point. If the Class II lens event was observed only at the last examination, then there should also be a Class I lens event in the same eye at the time point immediately preceding the last one.
- Occurrence within 12 months in either eye of a Class III lens event. A Class III lens event is defined as any of the following events in either eye
 - 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),
 - Cataract surgery.

Change in LOCS III grade from baseline

- Maximum increase in LOCS III grade during the study for (a) nuclear opalescence, (b) cortical opacity, and (c) posterior subcapsular opacity by eye and in either eye
- Change from baseline to each timepoint in LOCS III grade for (a) nuclear opalescence, (b) cortical opacity, and (c) posterior subcapsular opacity. The change from baseline was derived by eye and for the highest value in either eye for each subject.

Other secondary variables

- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.5 (nuclear opalescence) in either eye
- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.8 (cortical) in either eye
- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.5 (posterior subcapsular) in either eye

BCVA-corrected visual acuity score

The BCVA score was calculated as the sum of the number of letters read correctly at the 4-meter distance plus 30 added if 20 or more letters were read correctly. If fewer than 20 letters were read, the score was the sum of the number of letters read correctly at the 4-meter distance plus the number of letters read at the 1-meter distance.

The following endpoints were reported:

- Change from baseline to each time-point in BCVA, derived by eye and for the lowest value in either eye for each subject;
- Change from baseline to the lowest on-study visual acuity by eye and in either eye.

Intraocular pressure

Two measurements were made and a third measurement was to be done if the first 2 measures differed by more than 2 mmHg. The median of the 2 or 3 measurements became the intraocular pressure determination. The median was calculated as the mean (midpoint) of the 2 measurements or was the middle value when the 3 measurements are arranged in ascending or descending order.

The following endpoints were reported:

- Change from baseline to each time-point in median intraocular pressure (mmHg), derived by eye and for the highest value in either eye for each subject;
- Change from baseline to the highest median intraocular pressure (mmHg) on-study by eye and in either eye.

Other events

Negative lens events were recorded when the LOS III readings decreased non-reversing event was one that was present at two visits

Pulmonary Function Variables

The following endpoints were reported:

- Change in post-bronchodilator FEV₁ (L) from baseline to Month 4, Month 8, Month 12 and end of study, where the end of study timepoint was the last available timepoint under treatment derived using the last observation carried forward (LOCF) principle
- Percent change in post-bronchodilator FEV₁ from baseline to Month 4, Month 8, Month 12 and end of study
- Change in post-bronchodilator FEV₁ percent predicted from baseline to Month 4, Month 8, Month 12 and end of study
- Change in post-bronchodilator FVC (L) from baseline to Month 4, Month 8, Month 12 and end of study.

3.1.6.1 Statistical Analysis Plan

Sample Size

This study was an assessment of non-inferiority of ciclesonide-HFA compared with beclomethasone-HFA for the primary endpoint of Class I lens event. Non-inferiority was demonstrated if the upper bound of the one-sided 97.5% confidence interval of the risk ratio was less than the NIB. Sample size was computed using the following expression based on the Taylor series expansion of the variance of the logarithm of the risk ratio (1).

$$\text{var}(\log_e(p_T/p_C)) \approx (1/n) \left[\frac{1}{R} + 1 \right] - 2/n$$

A LOCS III-based Class I lens event rate of approximately 8% was anticipated in the control group. No data were available in the intended study population. The event rate was extrapolated from the finding of a 3% lens event rate (defined using a larger change in lens opacity) in subjects of 40 to 49 years of age in the Age-Related Eye Disease Study (AREDS)(2). Using the criteria described above in subjects whose mean age was approximately 65 years was anticipated to increase the rate to approximately 8% within 12 months. As specified in the protocol, approximately 503 subjects were required per treatment group to achieve 90% power for non-inferiority based on a one-sided 97.5% confidence interval of the risk ratio. The anticipated drop out rate was increased based on observations from an e long-term study [XRP1526B-323/324LT] completed after the original protocol for the cataract study had been written. Therefore Protocol Amendment 1 was required to increase the sample size. It was therefore planned to randomize 1500 subjects into 2 treatment groups (750 subjects per group), assuming a discontinuation rate of 30%.

Study Populations

The modified intention to treat (mITT) population included all randomized subjects who received medication and who had at least 1 valid post treatment LOC III measurement.

A LOCS III measurement was deemed valid (each eye evaluated separately) if:

- The diameter of the pupil was at least equal to 6 mm (with or without eye dilatation)
- The LOCS III grade was within the valid range for nuclear opalescence (0.1 to 6.9) and for cortical or posterior subcapsular opacities (0.1 to 5.9)
- The examination was done by a certified ophthalmologist according to the list of valid certification numbers for that site
- The post-baseline LOCS III measurements were done at least after one month following exposure to the study drug and within 14 days from the end of study treatment period

The per-protocol (PP) population consisted of all the subjects in the mITT population who did not have an important protocol deviation. The determination about the presence of an important protocol deviation was made for each subject prior to breaking the blind.

The list of major protocol violation includes the following events prior to treatment:

Prior to Screening

- No documented use of ICS therapy for asthma at any dose for at least 21 days during the month prior to Screening;

- History of prior cataract surgery in either eye
- Nuclear opalescence with a LOCS III grade ≥ 4 in either eye at the screening slit-lamp examination
- Cortical lens opacities with a LOCS III grade ≥ 3 in either eye at the screening slit-lamp examination
- Posterior subcapsular lens opacities with a LOCS III grade ≥ 2 in either eye at the screening slit-lamp examination
- Elevated intraocular pressure (> 25 mmHg) requiring treatment for glaucoma (ATC S01E) at Screening
- BCVA score of less than 72 letters in either eye at Screening
- Treatment with more than 2 bursts of oral (prednisolone 60 mg/day for 3 days) or injectable (one shot of injectable equivalent to one burst of oral) steroids per year for each of the past 2 years prior to Screening
- Topical ocular steroid treatment within 3 months prior to Screening unless agreed with the sponsor
- Chronic use of oral steroids except ICSs for any condition.

During Treatment

- Use of non-study medication ICSs for more than 14 days prior to an eye examination (i.e., between 2 consecutive visits);
- Use of any ocular steroid at any time during the treatment period for more than 14 days;
- Use of intranasal corticosteroids continuously for more than one month;
- Subject received more than 2 bursts of oral (prednisolone 60 mg/day for 3 days) or injectable (one shot of injectable equivalent to one burst of oral) steroids during the 12-month treatment period;
- Overall compliance to study medication was less than 70%;
- Less than 4 months on study medication.

Statistical Analysis

Analysis of the primary endpoint was determined by the life-table estimate of the event at Month 12 using the mITT population. Since the number of subjects who completed the study with no event was expected to be high, the cumulative probability of failure in the standard life-table estimate would have been an overestimate. Therefore an alternative method, which managed withdrawals with their actual fractions of completion for the interval of withdrawal was used. Three time intervals were defined as 0 to 120, 121 to 240, and 241 to 360 days. Non-inferiority of ciclesonide-HFA versus the control (beclomethasone-HFA) was demonstrated if the upper bound of the one-sided 97.5% confidence interval was less than the NIB (see section below). If non-inferiority was demonstrated, then superiority of ciclesonide-HFA over control was to be subsequently tested by comparing the upper bound of the one-sided 97.5% confidence interval to one.

If non-inferiority of ciclesonide-HFA versus the control was demonstrated for the primary endpoint of Class I lens events, then non-inferiority of ciclesonide-HFA based on Class II, sustained Class II, and Class III lens events was also assessed using a one-sided 97.5% confidence interval for each type of event.

Subjects who withdrew prior to study completion without a Class I lens event were considered censored for this analysis. Since the withdrawal of subjects before the occurrence of a Class I lens event was expected to be unrelated to lens opacification, it was assumed that the censoring for the primary endpoint of Class I lens events was non-informative. Any event occurring after 390 days was censored for the analysis. Subjects with an early termination visit within the first 30 days after first intake of study medication were censored regardless of the outcome of the LOCS III examination.

Non-inferiority bound

The NIB was defined as a function of the control event rate for pc ranging from 2% to 12%:

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

This function insured 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 study protocol was extended to a higher range, maintaining a decreasing functional form, with a minimum of 1.333. The NIB was then the maximum of 1.333 and the value obtained by the function. The NIB could not be less than 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.

Reviewer: The change in NIB to 1.333 was not agreed upon by the Agency (See FDA Statistical Review for details.)

Pooling of Centers

For statistical analysis, centers with less than 3 subjects per treatment group were pooled. Centers were ordered within country (USA, Poland, and S Africa) by number of subjects. Starting with the smallest enrollers, centers were added sequentially until the pooled group contained at least 3 subjects per treatment group. For statistical purposes the pooled groups were considered single centers.

2.2. Results

2.2.1. Study Population

Disposition

A total of 2032 subjects were screened and 464 failed, resulting in randomization of 1568 subjects (785 treated with ciclesonide 320 mcg BID (C320B) and 783 treated with budesonide (BDP). Of those enrolled, 1552 subjects received treatment and were included in the safety population (Table). Of those who were randomized and treated, 743 C320B and 742 BDP subjects had valid ophthalmologic examinations and were included in the mITT population. This represented 94.7% of the randomized population. The per-protocol (PP) population (those without major protocol violations) consisted of 673 C320B and 676 BDP subjects (86% of those randomized).

Of the 1552 subjects who were randomized and treated, 1354 (86.4% of those randomized) completed the course of treatment (Table 1). Withdrawal was equivalent in the two treatment groups (14.4% in the C320B group and 12.9% in the BDP subjects). Differing from the short term efficacy trials, but similar to other long-term follow-up studies, the most common cause of withdrawal was patient request (4.2 and 4.1% of the C320B and BDP subjects, respectively). Adverse reactions were the second most common indication for withdrawal (3.7, and 2.8% in the C320B and BDP subjects, respectively). Loss to follow-up accounted for 1.7% of those randomized and lack of efficacy was reported as a reason for withdrawal in only 0.5% if those randomized,

Table 1. Disposition of Subjects in Study 3027

	C320B	BDP	Overall
Randomized	785	783	1568
Treated	776 (98.9)	776 (99.1)	1552 (99.0)
Discontinued	113 (14.4)	101 (12.9)	214 (13.64)
Reason for discontinuation:			
Did not wish to continue	33 (4.2)	32 (4.1)	65 (4.1)
Adverse event	29 (3.7)	22 (2.8)	51 (3.3)
Lost to follow-up	16 (2.0)	10 (1.3)	26 (1.7)
Protocol violation	15 (1.9)	21 (2.7)	36 (2.3)
Lack of efficacy	5 (0.6)	3 (0.4)	8 (0.5)
Death	1 (0.1)	1 (0.1)	2 (0.1)
Other	14 (1.8)	12 (1.5)	26 (1.7)

Of the 1568 subjects randomized, 36 subjects were withdrawn for major protocol violations. The number withdrawn for protocol violations was greater in the BDP group (2.7% compared with 1.9% of the C320B subjects). In addition, the number withdrawn due to ingestion of prohibited medication for asthma was twice as high in the BDP group (7) than in the C320B group (3). On the other hand, the number of subjects in the mITT who took some form of prohibited corticosteroid was greater in the C320B group (49) than in the BDP group (33) and fewer of the C320B subjects (17) than the BDP subjects (23) failed to take study medication as prescribed. Overall, the subjects in the mITT who were treated with ciclesonide had a higher exposure to corticosteroids than did the BDP subjects. All subjects with concomitant steroid exposure or with failure to take study medication as prescribed were excluded from the PP population.

Reviewer: Text Table 11 (pg 113 of the study report) lists the protocol violations that were present in the mITT

population, not protocol violations that led to exclusion. This is concluded from an analysis of datasheet ASV.xpt. Most of the subjects excluded from the mITT were excluded because of lack of a valid post-treatment ophthalmology examination.

Demographics

1485 subjects in the mITT population 39.9% were male and the mean age (Range) was 43.1 (18 - 80) years (Table 2). More than 60% were over 40 years of age, and 130 (63 in the C320B group and 67 in the BDP group) were over 60 years of age. The predominant racial group was White (83.5% compared with 8.8% Black and 7.7% Other). Most of the subjects (76.8%) were never smokers and the US was the site of enrollment of 84.6% of the subjects.

Table 2. Demographic characteristics of the ITT population

	C320b	BDP	Overall
Total ITT Population	743	742	1485
Gender, % M	(40.0)	(39.8)	(39.9)
Age, mean (SD)	42.9 (12.9)	43.3 (12.6)	43.1 (12.8)
≥40 years, N (%)	460 (61.9)	466 (62.8)	926 (62.4)
Race, %			
White	83.0	84.0	83.5
Black	9.2	8.5	8.8
Other	7.8	7.5	7.7
Smoking History			
Never	76.6	77.0	76.8
Region, %			
USA	84.7	84.6	84.6
Poland	6.5	6.2	6.3
South Africa	8.9	9.2	9.0

The baseline ophthalmologic values (Table 3) were almost identical in the two treatment groups. The range of values for intraocular pressure were somewhat smaller for the BDP subjects (8.0 – 24.0) than for the C320B subjects (6.0 – 30.0) but the means were very close (14.8 and 14.6 for the right and left eyes in the C320B subjects and 14.8 and 14.7 for the right and left eyes of the BDP subjects).

Table 3. Baseline values for ophthalmologic examinations

Treatment	C320b (N=743)		BDP (N=742)	
	R	L	R	L
Nuclear opalescence*	1.4 (0.9) 0.1 - 3.8	1.4 (0.9) 0.1 - 3.8	1.4 (0.9) 0.1 - 3.7	1.4 (0.9) 0.1 - 3.7
Cortical opacity*	0.4 (0.6) 0.1 - 3.2	0.4 (0.5) 0.1 - 3.1	0.4 (0.6) 0.1 - 2.9	0.4 (0.5) 0.1 - 2.9
Posterior subcapsular opacity*	0.2 (0.2) 0.1 - 1.8	0.2 (0.2) 0.1 - 2.0	0.2 (0.2) 0.1 - 1.9	0.2 (0.2) 0.1 - 2.0
Visual Acuity	87.0 (4.7) 58 - 100	86.9 (4.9) 65 - 99	87.0 (4.8) 66 - 99	87.0 (4.9) 64 - 99
Intraocular pressure	14.8 (3.0) 6.0 - 30.0	14.6 (3.0) 6.5 - 28.0	14.8 (2.8) 8.0 - 22.5	14.7 (2.8) 8.0 - 24.0

* Part of LOC III examination

The mean duration of asthma (SD) was 21.7 (13.8) years (Table 4), and all of the subjects had used an inhaled corticosteroid within 90 days of enrollment. Short acting selective β -adrenergic agonists were the second most frequently used medication (88.4 and 90.2% of the C320B and BDP subjects, respectively). The mean FEV₁ (SD) was 2.4 (0.6) L and the mean (SD) FEV₁ percent predicted was 71.7 (10.6) percent.

Table 4. Characteristics of Asthma – ITT Population

	C320b	BDP	Overall
Total	743	742	1485
Duration			
Years, mean (SD)	21.9 (15.5)	22.3 (14.7)	22.1 (15.1)
Range	0.3 - 63.8	0.2 - 64.0	0.2 - 64.0
FEV ₁			

Mean Absolute, ml (SD)	2.4 (0.6)	2.4 (0.6)	2.4 (0.6)
Range	0.5 - 4.3	0.8 - 4.3	0.5 - 4.3
FEV ₁			
Mean % predicted, % (SD)	71.7 (10.7)	71.6 (10.6)	71.7 (10.6)
Range	41.0 - 90.2	40.3 - 87.1	40.3 - 90.2

Compliance with Treatment

As assessed by diary recordings, more than 88% of the subjects had a compliance of at least 90%. In a subset of 255 subjects treated with ciclesonide, blood levels of ciclesonide and des-ciclesonide were measured to further assess compliance. As can be seen in Table 5, none of the subjects had the parent compound (ciclesonide) or the metabolite (des-ciclesonide) in their blood at screening. At month 4 and 12, 88 to 89% of the subjects had measurable levels of des-ciclesonide and 26 to 29% had measurable levels of ciclesonide. Subjects who terminated early had a lower incidence of positive blood levels for both ciclesonide (0%) and the metabolite (57.1%).

Table 5. Blood Levels of Ciclesonide and its active metabolite

Visit / Status	n/N (%) of subjects	
	Ciclesonide (pg/mL) (N = 255)	des-ciclesonide (pg/mL) (N = 255)
Screening		
Absence	242/242 (100%)	242/242 (100%)
Presence	0/242 (0%)	0/242 (0%)
Month 4		
Absence	168/236 (71.2%)	25/236 (10.6%)
Presence	68/236 (28.8%)	211/236 (89.4%)
Month 12		
Absence	173/235 (73.6%)	28/235 (11.9%)
Presence	62/235 (26.4%)	207/235 (88.1%)
Early termination		
Absence	7/7 (100%)	3/7 (42.9%)
Presence	0/7 (0%)	4/7 (57.1%)
Overall		
Absence	348/478 (72.8%)	56/478 (11.7%)
Presence	130/478 (27.2%)	422/478 (88.3%)

Note: 11 subjects among the 255 subjects to be sampled had no serum concentration measurement at any visit.

The actual values of the blood levels varied widely. For instance, the endpoint value for the metabolite ranged from 10.4 to 1200 pcg/mL and the value for ciclesonide ranged from 25.4 to 1180 pcg/mL.

2.2.2. Efficacy Results

Primary Efficacy Outcome

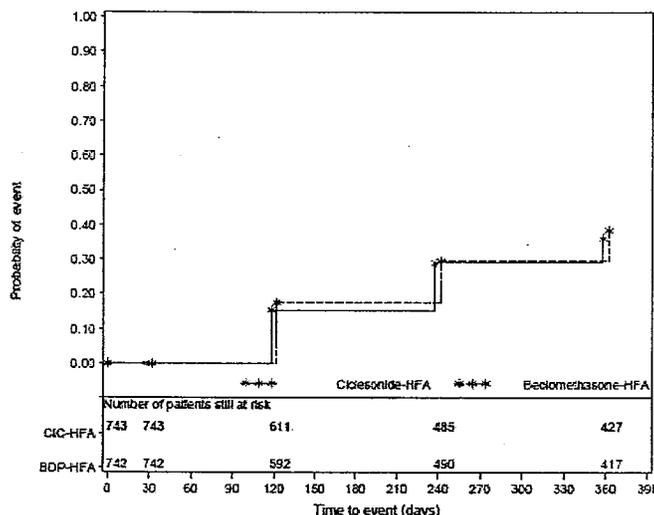
By the life-table analysis (Table 6), the incidence of Class I ophthalmology events was slightly lower (36.1%) in the ciclesonide-treated subjects than in the BDP-treated subjects (35.4%). The risk ratio (95% CI) comparing ciclesonide to BDP was 0.94 (0.82, 1.08) and the p-value for non-inferiority was <0.0001. The results of the per-protocol analysis were supportive. If subjects with major protocol violations were excluded, the risk ratio (95% CI) was 0.926 (0.807, 1.068). As part of a further sensitivity analysis, the risk was also calculated assuming that all drop-outs as had the event. In this instance the risk ratio (95% CI) was 0.971 (0.864, 1.091).

Table 6. Analysis of Class I lens events in the mITT population by life-table estimate

	N	% of Subjects with Class I event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320b	743	36.1 (1.82)	0.94	0.82, 1.08	1.33	<0.0001
BDP	742	38.4 (1.83)				

The development of Class I changes in the mITT population are shown graphically in Figure 1 .

Figure 1. Development of Class I events



No important subgroup interactions were noted.

Secondary efficacy outcome measures

Class II events were more severe and less common. Of the subjects treated with ciclesonide, 14.0% showed Class II changes compared with 16.4% of the subjects treated with BPD. Similarly, sustained (observed on more than one visit) Class II events were reported in 9.4% of the ciclesonide and 11.5% of the BDP-treated subjects.

Table 7. Change in Class II lens events

	N	% of Subjects with Class II event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320B	743	14.0 (1.31)	0.86	0.67, 1.10	1.62	<0.0001
BDP	742	16.4 (1.39)				
	N	% of Subjects with sustained Class II event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320B	743	9.4 (1.11)	0.821	0.60, 1.12	1.796	<0.0001
BDP	742	11.5 (1.20)				

Class III events were reported for 57 (7.7%) of the C320B subjects and 65 (8.8%) of the BDP-treated subjects. Only 1 subject had cataract surgery during the course of the trial.

The LOCS III classification is made up of a combination of three evaluations: nuclear opalescence, cortical opacity, and posterior subcapsular opacity (PSC). While all may affect vision, the PSC changes are most characteristic of the changes induced with corticosteroid treatment. As shown in Table 8, while the overall scores were consistently lower in the C320B-treated subjects compared to the BDP subjects, the sub-score for PSC opacity was consistently higher

for the C320B subjects. The differences were small, but over years of treatment, could become clinically meaningful.

Table 8. LOCS III Classification by Treatment group

Type of lens event	Observed proportions:		Life table estimates:	
	Number (%) of subjects		Percent of subjects ± SE	
	CIC-HFA (N = 743)	BDP-HFA (N = 742)	CIC-HFA (N = 743)	BDP-HFA (N = 742)
Class I	255 (34.3%)	273 (36.8%)	36.1 ± 1.8	38.4 ± 1.8
Nuclear opalescence	210 (28.3%)	227 (30.6%)	29.7 ± 1.7	32.0 ± 1.8
Cortical opacity	60 (8.1%)	66 (8.9%)	8.5 ± 1.1	9.3 ± 1.1
Posterior subcapsular opacity	20 (2.7%)	17 (2.3%)	2.8 ± 0.6	2.4 ± 0.6
Class II	99 (13.3%)	117 (15.8%)	14.0 ± 1.3	16.4 ± 1.4
Nuclear opalescence	82 (11.0%)	103 (13.9%)	11.7 ± 1.2	14.5 ± 1.3
Cortical opacity	14 (1.9%)	13 (1.8%)	2.0 ± 0.5	1.8 ± 0.5
Posterior subcapsular opacity	10 (1.3%)	6 (0.8%)	1.4 ± 0.4	0.8 ± 0.3
Sustained Class II	66 (8.9%)	81 (10.9%)	9.4 ± 1.1	11.5 ± 1.2
Nuclear opalescence	55 (7.4%)	71 (9.6%)	7.9 ± 1.0	10.1 ± 1.1
Cortical opacity ^a	6 (0.8%)	9 (1.2%)	0.8 ± 0.3	1.2 ± 0.4
Posterior subcapsular opacity ^a	5 (0.7%)	1 (0.1%)	0.7 ± 0.3	0.1 ± 0.1
Class III	57 (7.7%)	65 (8.8%)	8.1 ± 1.0	9.2 ± 1.1
Nuclear opalescence	44 (5.9%)	54 (7.3%)	6.3 ± 0.9	7.6 ± 1.0
Cortical opacity	12 (1.6%)	11 (1.5%)	1.7 ± 0.5	1.6 ± 0.5
Posterior subcapsular opacity ^a	7 (0.9%)	4 (0.5%)	0.9 ± 0.4	0.5 ± 0.3

BDP = beclomethasone; CIC = ciclesonide.

NC = estimates not calculated because at least one treatment group had less than 10 events.

^a Life table estimates were obtained using the standard life table method if there were fewer than 10 events in each treatment group because the modified method requires 10 or more events in at least one treatment group to provide robust estimates.

The mean changes in cataract scores are small. However, the pattern of smaller increases in the nuclear and cortical opacities and larger increases in PSC for the C320B-treated subjects remains (Table 9).

Table 9. Mean changes in LOCS III Scores

Treatment	N	Baseline mean	Change from baseline	Ciclesonide-HFA vs. beclomethasone-HFA	
			LS mean ± SE (LOCS III grade)	LS mean ± SE	2-sided 95% CI
Nuclear opalescence					
Ciclesonide-HFA	743	1.33	0.22 ± 0.019	-0.016 ± 0.020	-0.056, 0.024
Beclomethasone-HFA	742	1.36	0.23 ± 0.018		
Cortical					
Ciclesonide-HFA	743	0.36	0.14 ± 0.018	-0.018 ± 0.020	-0.057, 0.021
Beclomethasone-HFA	742	0.35	0.16 ± 0.017		
Posterior subcapsular					
Ciclesonide-HFA	743	0.14	0.06 ± 0.009	0.018 ± 0.010	-0.001, 0.037
Beclomethasone-HFA	742	0.15	0.05 ± 0.009		

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; N = mITT population; SE = standard error. Ciclesonide-HFA vs. beclomethasone-HFA is calculated as ciclesonide-HFA minus beclomethasone-HFA.

The argument is further made that the distribution of size change was similar in the two treatment groups. In Table 10, the changes are grouped into decrease, no change, and three degrees of increase, and the point is made that most of the subjects had no change or a decrease.

Table 10. Distribution of change in LOCS III Scores

Variable	Number (%) of subjects	
	Ciclesonide-HFA (N = 743)	Beclo-methasone-HFA (N=742)
Nuclear opalescence		
Decrease	121 (16.3%)	145 (19.5%)
No change	151 (20.3%)	123 (16.6%)
Increase by 0.1 to 0.4	261 (35.1%)	247 (33.3%)
Increase by 0.5 to 0.8	128 (17.2%)	124 (16.7%)
Increase by ≥ 0.9	82 (11.0%)	103 (13.9%)
Cortical		
Decrease	48 (6.5%)	49 (6.6%)
No change	343 (46.2%)	320 (43.1%)
Increase by 0.1 to 0.7	292 (39.3%)	307 (41.4%)
Increase by 0.8 to 1.4	46 (6.2%)	53 (7.1%)
Increase by ≥ 1.5	14 (1.9%)	13 (1.8%)
Posterior subcapsular		
Decrease	16 (2.2%)	26 (3.5%)
No change	542 (72.9%)	550 (74.1%)
Increase by 0.1 to 0.4	165 (22.2%)	149 (20.1%)
Increase by 0.5 to 0.8	10 (1.3%)	11 (1.5%)
Increase by ≥ 0.9	10 (1.3%)	6 (0.8%)

The 2 highest categories of increase for each type of opacity together correspond to the Class I lens event criteria, and the highest categories correspond to the Class II lens event criteria.

Reviewer: The distributions in Table actually show that there were a higher proportion of subjects with large increases in PSC in the C320b group (10 [1.3%]) compared to the subjects treated with BDP (6 [0.8%]). The absolute numbers are small, but the proportion suggests that almost twice as many subjects treated with C320 developed these changes compared to the BDP group. Confirming the trend is the increased number of subjects in the BDP group whose opacities decreased (26 [3.5%]) compared to the subjects treated with ciclesonide (16 [2.2%]). The results of the primary and supportive secondary analysis are quite consistent. While the overall LOCS III grade was lower in the subjects treated with C320b, the scores for the change in PSC were slightly higher in the C320b-treated subjects.

In a sub-set analysis, it is stated that the changes in LOCS III were equivalent in all of the age groups. The supporting table, reproduced here as table 11, shows the proportion of subjects with Class I, II, III, and sustained Class II events divided by age 40 years or less. The proportion with events is slightly higher in the older age groups for all of the categories other than Class III events. The incidence in the BDP group was higher than that in the subjects treated with C320b in both age groups.

Table 11. LOCS III Scores by Age-group

Type of lens event	Percent of subjects ± SE			
	< 40 years		≥ 40 years	
	CIC-HFA (N= 283)	BDP-HFA (N= 276)	CIC-HFA (N= 460)	BDP-HFA (N=466)
Class I lens event	31.1 ± 2.9	31.7 ± 2.9	39.1 ± 2.3	42.3 ± 2.3
Class II lens event	12.2 ± 2.0	14.8 ± 2.2	15.2 ± 1.7	17.3 ± 1.8
Sustained Class II lens event	8.7 ± 1.7	11.5 ± 2.0	9.9 ± 1.4	11.5 ± 1.5
Class III lens event	3.1 ± 1.1	4.2 ± 1.2	1.1 ± 1.5	1.2 ± 1.5

CIC = ciclesonide; BDP = beclomethasone. SE = standard error.

Reviewer: Age 40 may be too young a cutoff to distinguish between subjects at an average or elevated risk of developing cataracts. If the age groups are <40, 40 to 60, and >60 years, it appears that subjects over 60 years of age developed all classes of cataracts at a higher rate when treated with ciclesonide than during treatment with beclomethasone (Table 12). The difference in treatment was most marked for Class II and III events where 25 and 22% of the ciclesonide-treated subjects, respectively, reported events compared with 17.5% of the BDP-treated subjects for both classes of events.

Table 12. LOCS III Scores by Age-group

	Ciclesonide		BDP	
	N	N (%) Positive	N	N (%) Positive
Class I				
Overall	743	255 (34.3)	742	273 (36.8)
<40 years	308	89 (28.9)	298	93 (31.2)
40 – 60 years	368	130 (35.3)	381	147 (38.6)
> 60 years	67	36 (53.7)	63	33 (52.4)
Class II				
Overall	743	99 (13.3)	742	117 (15.7)
<40 years	308	36 (11.7)	298	43 (14.4)
40 – 60 years	368	46 (12.5)	381	63 (16.5)
> 60 years	67	17 (25.4)	63	11 (17.5)
Class III				
Overall	743	57 (7.7)	742	65 (8.8)
<40 years	308	8 (2.6)	298	13 (4.4)
40 – 60 years	368	34 (9.2)	381	41 (10.8)
> 60 years	67	15 (22.4)	63	11 (17.5)

If the incidence of PSC is examined separately, the differences are even more dramatic (Table 13). In the 60 and older group, 4 times as many ciclesonide-treated subjects reported Class III events compared with the BDP-treated group. Unfortunately, the over 60 age-group was not well represented in the sample. There were only 130 subjects (63 and 67 in the C320B and BDP groups respectively) over 60 years of age compared with over 300 in each treatment group who were 40 to 60 years of age and almost 300 in each treatment group less than 40 years of age. Despite the small number of subjects over 60 this finding is of concern since this is the age group most predisposed to develop cataracts.

Table 13. Change in PSC grade by age*

Age in years	N	Ciclesonide	BDP
< 40	606	0.040	0.024
40 – 60	749	0.049	0.043
> 60	130	0.184	0.111

* Taken from datasets AEF01.xpt through AEF010.xpt

The differences between men and women were small and not clinically meaningful. There was some variability when comparing geographic region (Table 14) but for the most part, the incidence in the C320B group was lower than in the BDP treated subjects. There was a relatively low incidence of Class I events in South Africa for both treatment groups

and of Class III events in Poland. In South Africa, sustained Class II and Class III events were more common in the Ciclesonide-treated subjects.

Table 14. LOCS III Scores by Geographic Region

Type of lens event	Percent of subjects ± SE					
	United States		Poland		South Africa	
	CIC-HFA (N= 629)	BDP-HFA (N= 628)	CIC-HFA (N= 48)	BDP-HFA (N= 46)	CIC-HFA (N= 66)	BDP-HFA (N= 68)
Class I lens event	37.4 ± 2.0	39.5 ± 2.0	32.6 ± 7.0	41.8 ± 7.6	26.5 ± 5.6	25.8 ± 5.5
Class II lens event	15.0 ± 1.5	17.2 ± 1.5	6.3 ± 3.6	9.3 ± 4.5	10.8 ± 3.9	13.9 ± 4.3
Sustained Class II lens event	9.5 ± 1.2	11.7 ± 1.3	6.3 ± 3.6	9.3 ± 4.5	10.8 ± 3.9	10.7 ± 3.9
Class III lens event	8.4 ± 1.1	9.6 ± 1.2	2.1 ± 2.1	4.7 ± 3.3	9.4 ± 3.7	7.6 ± 3.3

CIC = ciclesonide; BDP = beclomethasone. SE = standard error.

Source: Table T - 62, pg. 484, Table T - 72, pg. 496, Table T - 82, pg. 507, Table T - 92, pg. 518

An analysis performed on subgroups defined by baseline category of opacities showed similar changes in the two treatment groups when the absolute increase in mean area of opacities was compared. However, this analysis also showed a larger increase in PSC for most categories compared to BDP.

Other Ophthalmologic Variables

The LS mean (SE) decrease in visual acuity was 2.65 (0.15) for ciclesonide-treated subjects and 2.96 (0.15) for subjects treated with beclomethasone. The mean (SD) increase in intraocular pressure was 1.48 (2.25) and 1.64 (2.18) mm Hg in the ciclesonide and BDP-treated subjects, respectively. The median change was 1.5 mm Hg in both groups with a range of -6.0 to 16.0 mm Hg in the ciclesonide group and -5.5 to 9.0 mm Hg in the BDP group.

Asthma Control

Post-bronchodilator pulmonary function was obtained at baseline and at each follow-up visit. The analyses were performed on the subjects who were in the study at the time of measurement. Improvement in function was seen in both treatment groups, but it was very small and the difference between C320 and BDP was inconsequential (Table 15).

Table 15. Pulmonary Function After 12 months of Treatment with C320B and BDP

Parameter Treatment	N	Baseline mean	Change from baseline LS mean ± SE	Difference vs. beclomethasone-HFA	
				LS mean ± SE	2-sided 95% CI
FEV₁ (L)					
Ciclesonide-HFA	739	2.68	0.06 ± 0.014	-0.013 ± 0.015	-0.043, 0.017
Beclomethasone-HFA	740	2.71	0.08 ± 0.013		
FEV₁ percent predicted					
Ciclesonide-HFA	739	79.4	1.14 ± 0.401	-0.624 ± 0.445	-1.497, 0.249
Beclomethasone-HFA	740	80.5	1.76 ± 0.396		
Percent change in FEV₁^a					
Ciclesonide-HFA	739	2.68	3.14 ± 0.572	-0.862 ± 0.642	-2.121, 0.396
Beclomethasone-HFA	740	2.71	4.00 ± 0.569		

95% confidence interval; LS = least squares; mITT = modified intent-to-treat; N = mITT population; SE = standard error.

^aFEV₁ at baseline measured in liters.

Differences vs. beclomethasone-HFA are calculated as ciclesonide-HFA minus beclomethasone-HFA.

Source: Table T - 142, pg. 595; Table T - 148, pg. 607; Table T - 145, pg. 600

3.2.3. Safety

3.2.3.1 Exposure

The total safety population included 1552 individuals, 776 in each treatment group. Exposure to study medication was comparable in the two treatment groups. The mean (SD) exposure was 337.7 (68.7) and 339.4 (68.1) days in the C320B and BDP-treated subjects, respectively. The respective ranges were 10 to 380 and 18 to 386 days.

3.2.3.2 Adverse Events

Overall Assessment of Adverse Events

The overall incidence of AEs was slightly lower in the C320B group than in those treated with BDP (Table 16). The incidence of serious AEs and AEs leading to withdrawal was low, however serious AEs were more common in the BDP group (5.9% compared to 4.0% in the C320B group) whereas AEs leading to withdrawal were more common in the C320B group (3.6% compared to 2.6% in the BDP group). There was one death in each treatment group. Neither was considered by the investigator to be treatment related (See below for details).

Table 16. Overall summary of adverse events.

	C320B	BDP	Total
N	776	776	1552
All AEs	648 (83.5)	664 (85.6)	1312 (84.5)
Serious AEs	31 (4.0)	46 (5.9)	77 (5.0)
AEs leading to withdrawal	23 (3.6)	20 (2.6)	43 (2.8)
Deaths	1 (0.1)	1 (0.1)	2 (0.1)

Grouped by MedDRA SOC, the most common adverse events were in the Infections and infestations category (65.2 and 66.6% in the C320B and BDP groups, respectively) followed by Respiratory, Thoracic and Mediastinal disorders (31.3 and 27.3%, respectively) and Musculoskeletal and Connective Tissue Disorders (21.3 and 18.0%, respectively). Gastrointestinal Disorders, Nervous System Disorders, Injury, Poisoning, and Procedural Complications affected 15 to 17% of the subjects in both treatment groups. Eye Disorders were reported in 11% of both treatment groups and Skin, General, Psychiatric, Investigations were reported in 4 to 8%.

Listed by MedDRA preferred term, the most common events were Nasopharyngitis, Upper respiratory tract infection, Sinusitis, Asthma, and Headache (Table 17). Nasopharyngitis was reported in 3.4% more subjects treated with C320B than in subjects treated with BDP while Lower Respiratory Tract Infection and Candidiasis were reported more frequently in the BDP group (2.5 and 4.9% difference, respectively). Most of the other events occurred with similar frequency in the two groups (difference <2%), although Pain in extremity and Arthralgia were almost twice as frequent in the C320 group as in the BDP subjects. This corresponds to the elevated level of Connective Tissue Disorders seen in the listing of AEs by SOC.

Table 17. AEs Occurring in 3% or more subjects in any treatment group, by system organ class and Selected preferred terms

SOC and Preferred Term	C320B	BDP
N	776	776
All AEs	648 (83.5)	664 (85.6)
Nasopharyngitis	162 (20.9)	136 (17.5)
Upper Respiratory Tract Infection	151 (19.5)	148 (19.1)
Sinusitis	114 (14.7)	108 (13.9)
Asthma	96 (12.4)	100 (12.9)
Headache	81 (10.4)	81 (10.4)
Influenza	60 (7.7)	63 (8.1)
Bronchitis	51 (6.6)	62 (8.0)
Pharyngolaryngeal pain	42 (5.4)	51 (6.6)
Cough	44 (5.7)	43 (5.5)
Back pain	41 (5.3)	53 (6.8)
Diarrhea	35 (4.5)	24 (3.1)
Arthralgia	32 (4.1)	17 (2.2)

Urinary Tract Infection	30 (3.9)	16 (2.1)
Viral upper respiratory tract infection	30 (3.9)	24 (3.1)
Pain in extremity	27 (3.5)	15 (1.9)
Gastroenteritis viral	25 (3.2)	19 (2.4)
Sinus headache	18 (2.3)	25 (3.2)
Nausea	16 (2.1)	25 (3.2)
Lower Respiratory Tract infection	12 (1.5)	31 (4.0)
Oral candidiasis	11 (1.4)	49 (6.3)

Tabulating oropharyngeal adverse events separately, resulted in a balance of events in the two treatment groups (Table 18). Oral candidiasis, oropharyngeal candidiasis and Pharyngolaryngeal pain were more common during BDP treatment while Pharyngitis and Dysphonia were more common during C320 treatment.

Table 18. Oropharyngeal Adverse Events

SOC and Preferred Term	C320B	BDP
N	776	776
Oral candidiasis	1.4	6.3
Oropharyngeal candidiasis	0.1	0.4
Pharyngitis	2.6	1.8
Pharyngolaryngeal pain	5.4	6.6
Dysphonia	2.2	1.5

The incidence of AEs classified as Mild and Moderate was approximately equal with > 10% classified as severe. There were 105 (13.5%) events classified as severe in the C320 group and 116 (14.9%) were classified as severe in the BDP group.

Alert Terms

The following description occurs on page 151 of the study report:

“Ophthalmologic findings considered by the ophthalmologist to be clinically relevant were defined in the clinical study protocol as alert terms. These alert term events were subject to expedited reporting to the sponsor’s Pharmacovigilance department for blinded review while the study was still being conducted. The alert term events recorded in the Pharmacovigilance database consisted of diagnoses and symptoms, and therefore do not correspond directly with the TEAE reporting in the clinical database. The alert term events were not recorded in the CRF and were therefore not entered into the clinical database.”

The section further states that while there were more of these events in the C320B treatment group, some of the events were increased in the BPD group. Conjunctivitis, eye pain, migraine, conjunctivitis allergic, and eye infection more common in the C320 group and vitreous floaters, chalazion, blepharitis, and pinguecula more common in the BPD group. Referring to the reference tables (*Listing C.3.2 – 19 and C.3.2 – 20*) the total tally of events appears to be 216 for ciclesonide and 172 for Other (?BDP).

Reviewer: This is an extremely confusing section of the report. The description above does not tally with the protocol which states in section 8.1.3 the following: “No special events are subject to reporting as alert terms in this study”. The tables that are referenced for the data (Listing C.3.2 – 19 and C.3.2 – 20) contain three lists, one for Fexofenadine, one for Ciclesonide and one for other. There is no explanation for the inclusion of Fexofenadine and no indication that “Other” refers to beclomethasone, although the numbers in the table fit into the text description in the study report. Finally, the lists of events include spinal osteoarthritis and pain in extremity, although this was supposed to be a list of ophthalmologic events. A query will be submitted to the Applicant.

Serious Adverse Events and Events Leading to Withdrawal

C subject died in each of the treatment groups. A 54 year old obese female who was randomized to ciclesonide and who had a strong family history of myocardial infarction but no personal history of chest pain, hypertension or diabetes was admitted to the hospital unresponsive and cyanotic. She died later in the day and the autopsy attributed death to “acute coronary insufficiency due to marked atherosclerotic cardiovascular disease, resulting in fatal myocardial infarction.” One 31 year old male completed treatment with BDP and 19 days later committed suicide.

Serious adverse events were reported for 31 (4.0%) of the C320B subjects and for 46 (5.9%) of the BPD subjects. The most common events were asthma (5 [0.6%] and 4 [0.5%] in the C320B and BPD subjects, respectively), lobar pneumonia (3 [0.4%] and 1 [.1%], respectively) and nephrolithiasis (2 [0.2%] and 0, respectively). All of the other events occurred in 1 or fewer individuals. If all forms of pneumonia are combined (lobar pneumonia, bronchopneumonia, pneumonia, and pneumonia primary atypical) then there were 6 (0.8%) cases of pneumonia in the C320B group compared to 2 (0.3%) in the BPD group.

Four subjects (1 C320B and 3 BPD) were assessed by the treating-physician as sustaining a severe AE that was possibly related to treatment. The C320B subject was a 47 year-old male who had a retinal hemorrhage diagnosed on day 263 of treatment during a routine follow-up ophthalmologic examination. On day 271 the study medication was discontinued due to the onset of the third asthma exacerbation. Of the subjects treated with BDP, one developed significant hypertension and extrasystoles during treatment, one had an elevation in transaminases and one developed a cataract that was treated with surgery. The subject with the elevated transaminases was also taking arthrotec, simvastatin, and zafirlukast. The transaminases remained elevated a week after stopping BPD, but decreased after stopping the other medication.

Withdrawal from treatment due to an adverse event occurred infrequently (28 [3.6%] and 20 [2.6%] of the C320 and BPD subjects, respectively). The excess withdrawals in the C320B group were classified as asthma (11 [1.4%] and 1 [0.1%] in the C320B and BPD groups respectively), dysphonia (2 [0.3%] and 0, respectively) and hypertension (2 [0.3%] and 0 respectively). One subject in each treatment group was withdrawn due to pneumonia/bronchopneumonia but 5 subjects were withdrawn from the BDP group due to an eye complaint compared to 2 in the C320B group. A total of 47 subjects (26 [3.4%] and 21 [2.7%] of the C320B and BPD groups, respectively) had study treatment withheld temporarily due to an adverse event.

Overdosage

A 58 year-old female took 16 puffs bid of C320B on one day and 12 puffs bid on another day. No adverse effects were reported.

2.2.3.6 Laboratory Results

The mean baseline, 4-month and 12-month values for all hematology and routine safety chemistry analyses were within the normal range.

Individual shifts in laboratory values and highly abnormal values were unusual. The eosinophil counts tended to increase over the year of treatment and this trend was more prominent in the C320 group. Of the subjects who were normal at baseline, none was low at the end of the study and 15 (1.9%) of the C320B and 5 (0.6%) of the BPD subjects had values at the end of the study that were over the laboratory normal value. Similarly, 13/750 (1.7%) of the C320B and 7/748 (0.9%) of the BPD subjects had absolute eosinophil counts that increased more than the predefined abnormal amount (PCA) of 0.37 GG/L. The clinically important level for an increase in absolute eosinophil count was $> 1.0 \times 10^3 \text{ mm}^3$ and this occurred in three C320B subject and no BPD subjects. A clinically important increase in glucose was taken as $>12.8 \text{ mmol/L}$ and this occurred in one C320B subject and 3 BPD subjects. An increase of $> 5.5 \text{ mmol/L}$ was taken as the PCA for serum potassium and this occurred in 4 BPD subjects. The greatest increase was 5.7 mmol/L.

Abnormal laboratory values were reported as adverse events for 26 (3.4%) of the C320 and 30 (3.9%) of the BPD subjects (Table 19). Other than the subject with elevated transaminase (described above) the events were all considered mild to moderate and none resulted in termination of therapy.

Table 19. Laboratory values reported as adverse events

SOC and Preferred Term	C320	BDP
N	776	776
All Laboratory results reported as AEs	26 (3.4)	30 (3.9)
Blood uric acid increased	4 (0.5)	1 (0.1)

Blood glucose increased	3 (0.4)	1 (0.1)
Alanine amiontransferase increased	2 (0.3)	3 (0.4)
Aspartate aminotransferase increased	2 (0.3)	3 (0.4)
Blood alkaline phosphatase increased	2 (0.3)	0
Hypokalemia	2 (0.3)	1 (0.1)
Blood cholesterol increased	1 (0.1)	2 (0.3)
Hypercholesterolemia	1 (0.1)	2 (0.3)
Oral candidiasis	0	3 (0.4)
Diabetes mellitus	0	1 (0.1)
Hematuria	0	2 (0.3)
White blood cell increased	0	3 (0.4)

Visual Acuity

During the conduct of the study, the DSMB requested heightened follow-up of subjects with changes in visual acuity (VA). Reports were submitted to the board for any subject with a 10-letter change in visual acuity along with the investigators assessment of cause. Of the 7 subjects with a fall in VA, three in the C320 and 2 in the BPD group had associated lens opacities.

2.2.3.7 Physical Examination including Vital Signs.

The mean values for vital signs were within the normal range in both treatment groups. Physical examinations included abnormalities in 30% of the subjects at 4 and 12 months in both treatment groups. However, in only 8% of the subjects had a normal exam at baseline and an abnormal exam at the end of the study.

Mean values for baseline and Week 12 vital signs were comparable across the treatment groups. Changes during treatment were uncommon and clinically insignificant.

3.2.3.3 Pregnancy

Five pregnancies were reported during the course of the study. Of these 5 were females taking C320 and 5 were females taking BPD. In addition 3 female partners of male subjects in the C320 group and 2 female partners of males in the BPD group became pregnant. None of the subjects in the C320 group had a negative outcome. One BPD subject had a cesarean section at 40 weeks of gestation and at an unknown time after that reported that the baby's left kidney was larger than the right kidney. The baby was jaundiced at birth. No medical confirmation of this event was reported. There was, in addition, one spontaneous abortion at 20 weeks in the BPD group.

3.3 Summary and Discussion

This study was designed to compare the development of cataracts in adults treated with ciclesonide 320 mcg BID with adults treated with beclomethasone 320 mcg BID. Treatment lasted for 12 months and the outcomes were careful measurements of lens opacities using the LOCS III scoring system. The primary outcome, the difference in the proportions of subjects developing Class I (the smallest) changes, was consistently slightly smaller in the ciclesonide-treated subjects when compared to subjects treated with BDP. On the other hand the LOCS III scoring system is made up of three components. It assesses opacities in the nucleus, the cortical, and the posterior subcapsular region. Opacification of the PSC region is more typical of the reaction to corticosteroid treatment than in opacification of the other two regions. While the differences in treatment were quantitatively small, the mean increase in PSC score was larger in the C320B-treated subjects compared to the BDP subjects. Also, the differences were greatest in the subjects over 60 years of age, the group most susceptible to the development of cataracts.

References

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