

fluticasone subjects took $\geq 90\%$ of the medication. One subject in the fluticasone group never received study medication and this patient was excluded from the safety population.

Table 116. Disposition of Subjects in Study 342LT

| | Number (%) Subjects | | |
|-----------------------------------|----------------------|---------------------|------------------|
| | Ciclesonide n=128 | Fluticasone n=62 | Total n = 190 |
| Completed Study | 96 (75.0) | 45 (72.6) | 141 (74.2) |
| Reason for Discontinuation | | | |
| Consent withdrawn | 9 (7.0) | 10 (16.1) | 19 (10.0) |
| Adverse Event | 11 (8.6) | 1 (1.6) | 12 (6.3) |
| Lost to follow-up | 5 (3.9) | 3 (4.8) | 8 (4.2) |
| Lack of Efficacy | 5 (3.9) | 0 | 5 (2.6) |
| Other | 3 (2.3) | 2 (3.2) | 5 (2.6) |
| Protocol violation | 0 | 2 (3.2) | 2 (1.1) |
| Compliance | 4 (3.1) | 2 (3.2) | 6 (3.2) |
| Death | 0 | 0 | 0 |

As can be seen in Table 117, the demographic and clinical variables were evenly distributed between the two treatment groups. Similar to the pivotal trial, 62% were male and the mean age was 8.6 years. About 10% of the subjects were less than 6 years old (13 [10.2%] on ciclesonide and 7 [11.5%] on fluticasone). African-Americans made up 16.4% of the ciclesonide group and 18.0% of those treated with fluticasone. The pulmonary function variables were closely matched with a mean FEV₁ of 1.5 L which was approximately 79 % of predicted. The pulmonary function at the beginning of the long-term follow-up was higher than that measured at the beginning of the pivotal trial (Mean FEV₁ in study 342 at baseline = 1.35 L).

Table 117. Demographic and Clinical Characteristics of Subjects Enrolled in Study 342LT

| | | Ciclesonide n=128 | Fluticasone n=61 | Total n=189 |
|---------------------|-----------|----------------------|---------------------|----------------|
| Gender, n(%) | Male | 81 (63.3) | 37 (60.7) | 118 (62.4) |
| | Female | 47 (36.7) | 24 (39.3) | 71 (37.6) |
| Age, years | Mean (SD) | 8.5 (2.1) | 8.6 (2.2) | 8.6 (2.1) |
| | Range | 4-11 | 4-12 | 4-12 |
| Race, n(%) | White | 89 (69.5) | 44 (72.1) | 133 (70.4) |
| | Black | 21 (16.4) | 11 (18.0) | 32 (16.9) |
| | Asian | 4 (3.1) | 1 (1.6) | 5 (2.6) |
| | Other | 14 (11.0) | 5 (8.2) | 19 (10.1) |

| | | Ciclesonide | Fluticasone | Total |
|------------------------------------|-----------|--------------------|--------------------|--------------|
| Hispanic, n(%) | | 23 (18.04) | 15 (24.6) | 38 (20.1) |
| Duration of Asthma (years) | Mean (SD) | - 5.5 (2.8) | 5.6 (2.7) | 5.5 (2.8) |
| | Range | 0.6-11.7 | 0.8 – 10.5 | 0.6-11.7 |
| FEV₁, Liters | Mean (SD) | 1.54 (0.48) | 1.54 (0.60) | 1.54 (0.49) |
| | Range | 0.571-2.84 | 0.51-2.89 | 0.42-3.02 |
| FEV₁ % predicted | Mean (SD) | 79.5 (15.1) | 79.4 (17.3) | 79.5 (15.8) |
| | Range | 30.2-120.5 | 31.5-127.0 | 30.2-127.0 |

1.12.2.2. Safety results

After enrollment in study 342LT, The ciclesonide subjects were treated for a mean of 310.6 days (median 363, range 1-386) and the fluticasone subjects were treated for a mean of 296.0 days (median 363., range 1-385). The average daily dose of ciclesonide was 132.3 ± 36.0 mcg (range 47-162 mcg) and the average daily dose of fluticasone was 159.0 ± 41.8 mcg/day (range 104-200). The highest dose of study drug was prescribed for 63 (49.2%) of the ciclesonide subjects and 28 (45.9%) of the fluticasone subjects throughout the study.

The adverse event experience of the population is summarized in Table 118. Of the 3 serious AEs (all ciclesonide), there was 1 periorbital cellulitis and 2 cases of status asthmaticus (*see adverse events*). There were fewer overall AEs and AEs denoted as “other significant adverse events” in the fluticasone group (73.8 and 70.5% respectively) than in those treated with ciclesonide (85.9 and 81.3% respectively).

Table 118. Summary of Adverse Events in Study 342LT

| | Ciclesonide n=129 | Fluticasone n=64 | Total n=193 |
|---|------------------------------|-----------------------------|------------------------|
| All adverse events, n (%) | 110 (85.9) | 45 (73.8) | 155 (80.3) |
| Serious adverse events, n (%) | 3 (2.3) | 0 | 3 (1.5) |
| Deaths, n | 0 | 0 | 0 |
| Other significant adverse events (n [%]) resulting in : | 105 (82.0) | 43 (70.5) | 148 (76.7) |
| Discontinue medication | 11 (8.6) | 1 (1.6) | 12 (6.2) |
| Interrupt therapy | 3 (2.3) | 4 (6.6) | 7 (3.6) |
| Interrupt therapy | 4 (3.1) | 3 (4.9) | 7 (3.6) |
| Increase dose | 17 (13.3) | 6 (9.8) | 23 (11.9) |
| Other intervention | 17 (13.3) | 6 (9.8) | 23 (11.9) |
| Treated with medication | 104 (81.3) | 43 (70.5) | 147 (76.2) |
| Important laboratory abnormalities, n (%) | 1 (0.8) | 0 | 1 (0.5) |

1.12.2.3. Adverse Events

At the end of the year follow-up 155, (80.3%) of the subjects had reported at least 1 adverse event: 110 (85.9%) of the ciclesonide and 45 (73.8%) of the fluticasone subjects. The most

common treatment-emergent adverse events by system were infections/infestations with 63.3% of the ciclesonide and 57.41% of the fluticasone subjects reporting events. The incidence of upper respiratory infection, NOS and upper respiratory infection, viral NOS, as well as nasopharyngitis and streptococcal pharyngitis was higher in the ciclesonide-treated subjects (Table 119). On the other hand, sinusitis and influenza were slightly more frequent in the fluticasone group. There were 2 cases of oropharyngeal candidiasis in each group, but this resulted in an incidence of 1.6 % in the ciclesonide group compared with 3.3% in the fluticasone group because of the 2:1 randomization.

Table 119. Adverse Events Reported in Study 342LT

| | Number (%) Subjects | |
|------------------------------------|----------------------|----------------------|
| | Ciclesonide n=128 | Fluticasone n= 61 |
| All adverse events | 110 (85.9) | 45 (73.8) |
| Infections and infestations | 81 (63.3) | 35 (57.4) |
| Nasopharyngitis | 32 (25.0) | 10 (16.4) |
| Sinusitis, NOS | 13 (10.2) | 11 (18.0) |
| Upper respiratory tract | 34 (26.6) | 10 (16.4) |
| Influenza | 5 (3.9) | 5 (8.2) |
| Upper respiratory tract, viral | 3 (2.3) | 2 (3.3) |
| Pharyngitis, streptococcal | 8 (6.3) | 1 (1.6) |
| Viral infection, NOS | 6 (4.7) | 2 (3.3) |
| Otitis media | 13 (10.0) | 2 (3.3) |
| Oral candidiasis | 2 (1.6) | 2 (3.3) |
| Gastroenteritis | 12 (9.4) | 3 (4.9) |
| Respiratory manifestations | 72 (56.2) | 20 (32.8) |
| Asthma exacerbation | 42 (32.8) | 10 (16.4) |
| Cough | 5 (3.9) | 5 (8.2) |
| Nasal oedema | 5 (3.9) | 1 (1.6) |
| Pharyngolaryngeal pain | 12 (9.4) | 5 (8.2) |
| Bronchitis | 4 (3.1) | 1 (1.6) |
| Rhinitis, allergic | 4 (3.1) | 3 (4.9) |
| Epistaxis | 5 (3.9) | 1 (1.6) |
| Rhinitis, perennial | 5 (3.9) | 0 |
| General Disorders | 21 (16.4) | 11 (18.0) |
| Pyrexia | 20 (15.6) | 7 (11.5) |
| Influenza-like illness | 3 (2.3) | 5 (8.2) |
| Nervous system | 22 (17.2) | 11 (18.0) |
| Headache | 18 (14.1) | 9 (14.8) |
| Migraine | 1 (0.8) | 2 (3.3) |

| | Number (%) Subjects | |
|---|---------------------|------------------|
| | Ciclesonide | Fluticasone |
| Musculoskeletal | 7 (5.5) | 4 (6.6) |
| Back Pain | 2 (1.6) | 2 (3.3) |
| Gastrointestinal | 26 (20.3) | 14 (23.0) |
| Upper abdominal pain | 6 (4.7) | 3 (4.9) |
| Vomiting | 7 (5.5) | 5 (8.2) |
| Aphthous stomatitis | 5 (3.9) | 2 (3.3) |
| Darrheoa, NOS | 5 (3.9) | 1 (1.6) |
| Dyspepsia | 4 (3.1) | 3 (4.9) |
| Nausea | 0 | 3 (4.9) |
| Ear Disorders | 5 (3.9) | 5 (8.2) |
| Ear pain | 2 (1.6) | 5 (8.2) |
| Skin | 10 (7.8) | 11 (18.0) |
| Urticaria, NOS | 4 (3.1) | 1 (1.6) |
| Eczema | 2 (1.6) | 3 (4.9) |
| Dermatitis, atopic | 0 | 3 (4.9) |
| Injury, poisoning, procedural complication | 14 (10.9) | 8 (13.1) |
| Joint sprain | 2 (1.6) | 2 (3.3) |
| Immune System Disorders | 3 (2.3) | 3 (4.9) |
| Allergy to arthropod bite | 0 | 2 (3.3) |

Respiratory tract AEs were the next most frequent with 56.3% of the ciclesonide subjects and 32.8% of the fluticasone subjects reporting AEs. A large percentage of the respiratory AEs seen in the ciclesonide subjects were due to asthma exacerbations (32.8% in ciclesonide, and 16.4% in fluticasone subjects). The other organ systems showed a predominance of adverse events in the fluticasone group, but the differences between the two treatment groups was small.

Eye Involvement

There were 171 subjects with a slit lamp examination at baseline and at the end of the study. All slit lamp examinations were normal at baseline (119 ciclesonide subjects and 52 fluticasone subjects). One fluticasone-treated subject who was described as normal at baseline, had bilateral congenital cataracts noted at 6 months and again at 1 year.

One ciclesonide -treated subject, an 11 year-old girl developed low tension glaucoma diagnosed on study day 224 (July 1, 2002) with positive Heidelberg retinal tomography and optical coherence tomography. No intraocular pressures (IOP) were recorded at that time. Six weeks after the diagnosis, the IOPs were 14 and 12 mm Hg. Glaucoma had not been noted on the six month examination on study day 190. The study medication was discontinued and the adverse event was described as ongoing at the last visit.

Serious Adverse Events

There were no deaths in this study. There were 4 treatment-emergent serious adverse events in 3 of the ciclesonide-treated subjects. One 7 year-old female, randomized to ciclesonide-160, presented to the hospital ER with periorbital cellulitis of the left eye on study day 167. Seven days later she was hospitalized, and treated with antibiotics, and had her ciclesonide held for 4 days. The cellulitis lasted 130 days but was described as resolved without sequelae at the end of the study. Two additional ciclesonide subjects sustained episodes of status asthmaticus which precipitated withdrawal from the study.

Laboratory Values

The alkaline phosphatase reached the PCA level (above normal and increasing >28 U/L over the course of the study) in 8% of the subjects in both treatment groups. Despite the similar proportion of abnormal values, the maxima were greater in the fluticasone group. There were 3 subjects having levels > 500 U/L (range 555, to 747 U/L) compared with none in the ciclesonide group (maximum 456 U/L). On the other hand the transaminases and bilirubin values were unremarkable.

The eosinophil count was clinically noteworthy ($>1.0 \times 10^3$ cells/mm³) in 2 subjects in each treatment group (1.11 & 1.19×10^3 cells/mm³ in the ciclesonide group and 1.08 & 1.25×10^3 in the fluticasone group). The PCA values for eosinophil count were reached in 7/106 (6.6%) of the ciclesonide and 3/48 (6.3%) of the fluticasone-treated subjects.

Neutrophil counts and total white cell counts were recorded as having fallen to below the PCA level (1×10^3 cells/ mL in 4/106 (3.8%) of the ciclesonide subjects, but in none of the fluticasone subjects. The range of abnormal values was 0.77 – 1.27 for the neutrophil count and 3.98-4.31 for the total white count. Eight values were below the normal value ($4.0 - 4.35 \times 10^3$ cells/mm³ depending on age) but none was extremely low. Five were between 3.48 and 4.00×10^3 cells/mm³, and 3 were 4.11 – 4.15×10^3 cells/mm³.

HPA-axis Function

Samples were collected for HPA-axis evaluation at 3 sites. However, results were available at both baseline and follow-up for the cosyntropin tests in only three subjects in each treatment group. Defining normal HPA-axis function as a baseline serum cortisol of ≥ 5 mcg/dL and a post-stimulation value of ≥ 18 mcg/dL the 3 ciclesonide subjects were normal at baseline and follow-up. The 3 fluticasone subjects were normal at baseline, but abnormal after treatment. Two had a peak post-stimulation serum cortisol of 17 mcg/dL and 1 had a basal level of 3 μ g/dL. This last subject had a post cosyntropin stimulation level of 19 mcg/dL.

1.12.2.4. Pulmonary function

Results from spirometry were available for 183 (125 ciclesonide, and 58 fluticasone) subjects at baseline and follow-up. The baseline FEV₁ was 1.53 in both treatment groups. The change in baseline was 250 and 290 ml in the ciclesonide and fluticasone subjects respectively.

1.12.3. Discussion and Conclusions

The design and results of this 12-month follow-up closely resemble the results of study 341lt. There was a higher incidence of candidiasis (3.3% vs. 1.6%) in the fluticasone group compared to the ciclesonide group. A much higher percentage of subjects in the ciclesonide group (32.8%) reported experiencing an asthma exacerbation compared with 16.4% of the fluticasone-treated subjects. Eye involvement was uncommon, but 1 ciclesonide subject developed glaucoma. Serious adverse events were rare and there were no deaths.

1.13. Study #344LT

A multicenter, randomized, open-label, one year long-term safety study of ciclesonide metered dose inhaler 50 µg/day to 200 µg/day (ex-valve) (40 – 160 µg/day ex-actuator) administered once daily or fluticasone dry powder inhaler (Flovent®Rotadisk®) 50 µg or 100 µg administered twice daily for the treatment of children with persistent asthma.

1.13.1. Protocol

1.13.1.1. Administrative

Enrollment: March 20, 2002 – October 15, 2003

Clinical Director: _____

Sites: 29 clinics in the United States

1.13.1.2. Objective

To establish the long-term (1-year) safety of ciclesonide metered-dose inhaler (MDI) at doses of 50 mcg to 200 mcg/day ex-valve (40 mcg to 160 mcg/day ex-actuator) as compared to twice daily dosing with fluticasone dry powder inhaler (DPI) (Flovent®Rotadisk®) 50 mcg to 100 mcg/day in children with mild to severe persistent asthma.

1.13.1.3. Overall Design

This open-label one year safety study was of similar design to study 341LT and 432LT with the exception that there was not a 3-month pivotal trial preceding enrollment into the long term study and randomization was in a 4:1 ratio between once daily ciclesonide and twice daily fluticasone at the following doses:

Ciclesonide 160 mcg (160 mcg/puff x 1 puff) QD

Fluticasone 100 mcg (50 mcg/puff x 2 puffs) BID.

1.13.2. Results

1.13.2.1. Subjects

Of the 356 subjects screened, 232 were randomized (186 to ciclesonide and 46 to fluticasone). Of the randomized subjects, 137 (73.7%) and 40 (87.0%) of the ciclesonide and fluticasone subjects completed the 1 year follow-up respectively (Table 120). More subjects in the ciclesonide group withdrew due to withdrawal of consent, adverse events, and lack of efficacy (34 [17.8%] ciclesonide vs 1 [2.2%] fluticasone), while more subjects in the

fluticasone group withdrew due to protocol violations (8.7%) vs 5.9% in the ciclesonide group. If the adverse events due to asthma exacerbations are added to the lack of efficacy withdrawals, 16 (11.7%) subjects in the ciclesonide group withdrew due to poor asthma control compared to none in the fluticasone group.

Table 120. Disposition of Subjects in Study 344LT

| | Number (%) Subjects | | |
|-----------------------------------|----------------------|---------------------|------------------|
| | Ciclesonide n=186 | Fluticasone n=46 | Total n = 232 |
| Completed Study | 137 (73.7) | 40 (87.0) | 177 (76.3) |
| Reason for Discontinuation | | | |
| Consent withdrawn | 12 (6.5) | 1 (2.2) | 13 (5.6) |
| Adverse Event | 12 (6.5) | 0 | 12 (5.2) |
| Lost to follow-up | 9 (4.8) | 0 | 9 (3.9) |
| Lack of Efficacy | 10 (5.4) | 0 | 10 (4.3) |
| Other | 10 (5.4) | 1 (2.2) | 11 (4.7) |
| Protocol violation | 11 (5.9) | 4 (8.7) | 15 (6.5) |
| Compliance | 3 (1.6) | 0 | 3 (1.3) |
| Death | 0 | 0 | 0 |

Compared to the other trials there were a large number of protocol violations. However, many of these were for taking other steroids to treat asthma exacerbations. If these are excluded then there were 6 (4.4%) and 3 (6.5%) administrative protocol violations in the ciclesonide and fluticasone groups respectively.

As can be seen in Table 121, the demographic and clinical variables were evenly distributed between the two treatment groups. Approximately two-thirds of the subjects were male and the mean age was 8.2 years. African-Americans made up 22.4.2% of the population and Hispanics 14.7%. A higher proportion of the subjects in the ciclesonide group described themselves as Hispanic (16.1% vs 8.7% for the fluticasone subjects) whereas more of the fluticasone subjects described themselves as Black (28.3% vs 21.0% for ciclesonide). The pulmonary function variables were closely matched with a mean FEV₁ of 1.53 L which was approximately 80% of predicted.

Table 121. Demographic and Clinical Characteristics of Subjects Enrolled in Study 344LT

| | | Ciclesonide n=186 | Fluticasone n=46 | Total n=232 |
|-----------------------------------|-----------|------------------------------|-----------------------------|------------------------|
| Gender, n(%) | Male | 120 (64.5) | 31 (67.4) | 151 (65.1) |
| | Female | 66 (35.5) | 15 (32.6) | 81 (34.9) |
| Age, years | Mean (SD) | 8.2 (2.0) | 8.3 (2.0) | 8.2 (2.0) |
| | Range | 4-11 | 4-11 | 4-11 |
| Race, n(%) | White | 121 (65.1) | 29 (63.0) | 150 (64.7) |
| | Black | 39 (21.0) | 13 (28.3) | 52 (22.4) |
| | Asian | 3 (1.6) | 0 | 3 (1.3) |
| | Other | 23 (12.3) | 4 (8.7) | 27 (11.6) |
| Hispanic, n(%) | | 30 (16.1) | 4 (8.7) | 34 (14.7) |
| Duration of Asthma (years) | Mean (SD) | 4.85 (2.95) | 4.47 (2.65) | 4.77 (2.87) |
| | Range | 0.4 – 11.1 | 0.7 – 8.7 | 0.4 – 11.1 |
| FEV1, Liters | Mean (SD) | 1.54 (0.45) | 1.48 (0.45) | 1.53 (0.45) |
| | Range | 0.50 – 2.60 | 0.63 – 2.50 | 0.50 – 2.60 |
| Ciclesonide (n = 185) | | | | |
| Fluticasone (n =46) | | | | |
| FEV1 % predicted | Mean (SD) | 80.8 (13.45) | 76.7 (12.63) | 80.0 (13.4) |
| | Range | 27.5 – 109.8 | 53.5 – 103.7 | 27.5 – 109.8 |

Prior to enrollment, 91.8% of the subjects were taking a short-acting β -agonist, 60.7% were taking an inhaled corticosteroid, 27.1% a long-acting β -agonist, and 41.8% a leukotriene inhibitor. The distribution of prior medication was similar between the treatment groups except that only 82.6% of the fluticasone subjects took a short acting β -agonist compared with 94.1% of the ciclesonide subjects, and 50.0% of the fluticasone subjects took an inhaled corticosteroid compared with 63.4% of the ciclesonide subjects.

1.13.2.2. Safety results

After enrollment in study 344LT, the ciclesonide subjects were treated for a mean of 300.4 days (median 364, range 1-392) and the fluticasone subjects were treated for a mean of 323.5 days (median 363.5, range 14-374). The average daily dose of ciclesonide was 149.6 ± 24.2 mcg (range 55-160 mcg) and the average daily dose of fluticasone was 174.8 ± 38.8 mcg/day (range 91-200). In the ciclesonide group, 140 (75.3%) were treated with the maximum dose throughout the study while 31 (67.4%) of the fluticasone subjects were treated with the maximum dose. Diary-recorded compliance was high with 90.3% of the ciclesonide subjects and 91.3% of the fluticasone subjects receiving >90% of the study medication.

The adverse event experience of the population is summarized in Table 122. The overall incidence was similar in the two treatment groups. However, the ciclesonide-treated subjects suffered more serious events (5.4% compared with 2.2% for fluticasone) and more events

required discontinuation of the study medication (6.5%) compared with none for fluticasone. In the ciclesonide group 8/10 of the serious adverse events were for an asthma exacerbation whereas this did not occur in the fluticasone group (*See Severe Adverse events below*).

Table 122. Summary of Adverse Events in Study 344LT

| | Number (%) Subjects | | |
|---|----------------------|---------------------|----------------|
| | Ciclesonide n=186 | fluticasone n=46 | Total n=232 |
| All adverse events | 167 (89.8) | 42 (91.3) | 209 (90.0) |
| Serious Adverse Events | 10 (5.4) | 1 (2.2) | 11 (4.7) |
| Deaths | 0 | 0 | 0 |
| Other Significant adverse events | 163 (87.6) | 41 (89.1) | 204 (87.9) |
| Discontinue medication | 12 (6.5) | 0 | 12 (5.2) |
| Interrupt therapy | 9 (4.8) | 3 (6.5) | 12 (5.2) |
| Reduce dose | 0 | 1 (2.2) | 1 (0.4) |
| Increase dose | 5 (2.7) | 1 (2.2) | 6 (2.6) |
| Other intervention | 30 (16.1) | 9 (19.6) | 39 (16.8) |
| Treated with medication | 162 (87.6) | 41 (89.1) | 203 (87.5) |
| Medically important laboratory abnormalities | 6 (3.2) | 1 (2.2) | 7 (3.0) |

1.13.2.3. Adverse Events

At the end of the year follow-up, 209 (90.0%) of the subjects had reported at least 1 adverse event: 167 (89.8%) of the ciclesonide and 42 (91.3%) of the fluticasone subjects. The most common treatment-emergent adverse events by system were infections/infestations with 66.1% of the ciclesonide and 80.4% of the fluticasone subjects registering these complaints (Table 123). The excess of events in the fluticasone group was not localized to any one diagnostic category. There was instead, a small increase in incidence in upper respiratory tract infection, viral NOS, gastroenteritis, viral infection, pneumonia oral candidiasis and urinary tract infection. Even so, the incidence of upper respiratory infection NOS, nasopharyngitis, sinusitis, and otitis media was higher in the ciclesonide group. There were 2 cases of oropharyngeal candidiasis in each group, but this resulted in an incidence of 1.1 % in the ciclesonide group compared with 4.3% in the fluticasone group because of the 4:1 randomization.

Table 123. Adverse Events Reported in ≥ 3% of the Subjects in Study 344lt

| | Number (%) Subjects | |
|------------------------------------|----------------------|----------------------|
| | Ciclesonide n=128 | Fluticasone n= 46 |
| All adverse events | 167 (89.8) | 42 (91.3) |
| Infections and infestations | 123 (66.1) | 37 (80.4) |
| Nasopharyngitis | 43 (23.1) | 10 (21.7) |
| Sinusitis, NOS | 38 (20.4) | 7 (15.2) |
| Upper respiratory tract , NOS | 49 (26.3) | 11 (23.9) |
| Influenza | 9 (3.9) | 2 (4.3) |
| Upper respiratory tract, viral | | |
| Pharyngitis, streptococcal | 10 (5.4) | 4 (8.7) |
| Viral infection, NOS | 11 (5.9) | 6 (13.0) |
| Ear infection, NOS | 10 (5.4) | 4 (8.7) |
| Pharyngitis | 10 (5.4) | 2 (4.3) |
| Otitis media | 10 (5.4) | 1 (2.2) |
| Oral candidiasis | 23 (12.4) | 3 (6.5) |
| Gastroenteritis | 2 (11) | 2 (4.3) |
| Pneumonia, NOS | 12 (9.4) | 4 (8.7) |
| Urinary tract infection | 2 (1.1) | 2 (4.3) |
| | 1 (0.5) | 2 (4.3) |
| Respiratory manifestations | 113 (60.8) | 30 (65.2) |
| Asthma exacerbation | 72 (38.7) | 16 (34.8) |
| Cough | 18 (9.7) | 8 (17.4) |
| Nasal congestion | 18 (9.7) | 2 (4.3) |
| Pharyngolaryngeal pain | 32 (17.2) | 10 (21.7) |
| Bronchitis | 5 (2.7) | 4 (8.7) |
| Rhinitis, allergic | 9 (4.8) | 2 (4.3) |
| Epistaxis | 9 (4.8) | 3 (6.5) |
| General Disorders | 40 (21.5) | 6 (13.0) |
| Pyrexia | 31 (16.7) | 6 (13.0) |
| Nervous system | 54 (29.0) | 17 (37.0) |
| Headache | 53 (28.5) | 16 (34.8) |
| Sinus headache | 1 (0.5) | 2 (4.3) |
| Musculoskeletal | 20 (10.8) | 4 (8.7) |
| Pain in extremity | 6 (3.2) | 0 |
| Myalgia | 2 (1.1) | 2 (4.3) |

| | Number (%) Subjects | |
|---|---------------------|------------------|
| | Ciclesonide | Fluticasone |
| Gastrointestinal | 59 (31.7) | 20 (43.5) |
| Upper abdominal pain | 27 (14.5) | 5 (10.9) |
| Vomiting | 22 (11.8) | 7 (15.2) |
| Nausea | 12 (6.5) | 2 (4.3) |
| Darrheoa, NOS | 8 (4.3) | 4 (8.7) |
| Toothache | 5 (2.7) | 4 (8.7) |
| Dyspepsia | 4 (2.2) | 2 (4.3) |
| Constipation | 0 | 2 (4.3) |
| Ear Disorders | 12 (6.5) | 3 (6.5) |
| Ear pain | 11 (5.9) | 2 (4.3) |
| Skin | 25 (13.4) | 9 (19.6) |
| Rash | 10 (5.4) | 7 (15.2) |
| Injury, poisoning, procedural complication | 40 (21.5) | 6 (13.0) |
| Limb injury | 8 (4.3) | 2 (4.3) |
| Skin laceration | 7 (3.8) | 0 |
| Immune System Disorders | 15 (8.1) | 3 (6.5) |
| Hypersensitivity, NOS | 10 (5.4) | 1 (2.2) |
| Investigations | 4 (2.2) | 3 (6.5) |
| Weight increased | 0 | 2 (4.3) |

Adverse events in the respiratory system were the second most frequent with 60.8% of the ciclesonide subjects and 65.2% of the fluticasone subjects reporting AEs. There were a few more asthma exacerbations in the ciclesonide subjects (38.7% ciclesonide, 34.8% fluticasone). However, the fluticasone subjects had more pharyngolarygeal pain and cough.

There were more gastrointestinal and nervous system AEs in the fluticasone subjects with 34.8 % of the fluticasone subjects reporting headache compared with 25.8% of the ciclesonide subjects.

Serious Adverse Events

No deaths were reported. There were 10 (7.8%) serious adverse events in the ciclesonide group compared with 1(2.2%) in the fluticasone group. In the ciclesonide-treated subjects 80% of the serious AEs were due to an asthma exacerbation. In addition there was one subject each with multiple traumatic injuries, suicidal ideation, and appendicitis. There was one fecal impaction in the fluticasone group. Twelve of the ciclesonide subjects were withdrawn from the study due to adverse events. All of these were due to asthma exacerbations except for 2 subjects with upper respiratory tract infections and one subject with multiple injuries.

Eye Involvement

There were 212 subjects with a slit lamp examination at baseline and at the end of the study. Lenticular opacities were detected in 1 ciclesonide treated-subject at baseline. Of the 211 subjects with a normal slit lamp examination at the beginning of the study, 4 in the ciclesonide group developed bilateral trace cataracts all of which were posterior subcapsular in location. One subject developed a unilateral posterior subcapsular cataract and one subject developed a unilateral anterior sutural opacity. One fluticasone-treated subject developed bilateral trace posterior subcapsular cataracts. In all, 6 (3.2%) of the ciclesonide subjects and 1 (2.2%) of the fluticasone subjects developed cataracts. The 7 subjects who developed cataracts were re-examined by a second ophthalmologist after the study evaluation was completed, and none of the findings was confirmed. There was no case of glaucoma reported.

Laboratory Values

The alkaline phosphatase reached the PCA level (above normal and increasing >28 U/L over the course of the study) in 8.7% of the ciclesonide subjects and 11.6% of the fluticasone subjects. In general the changes in transaminases were unremarkable. However, one ciclesonide subject had an SGOT of 55 that was reported as an adverse event.

The eosinophil count was clinically noteworthy ($>1.0 \times 10^3$ cells/mm³) in 2 ciclesonide subjects (1.04 & 2.42×10^3 cells/mm³) and in 1 fluticasone subject (1.2×10^3 cells/mm³). The PCA values for eosinophil count were reached in 2/162 (1.2%) of the ciclesonide and 2/43 (4.7%) of the fluticasone-treated subjects.

Other laboratory values that were reported as adverse events included hematuria, Gilbert's syndrome (bilirubin 4.1), cholesterol of 262 mg/dL, potassium of 3.3 mmol/L, neutrophils of 0.7×10^3 cells/mcL in the ciclesonide subjects and a total white count of 15.2×10^3 cells/mcL in the fluticasone group.

HPA-axis Function

Samples were collected for HPA-axis evaluation in 2 sites. However, results were available at both baseline and follow-up in only 9 ciclesonide and 5 fluticasone subjects. Defining normal HPA-axis function as a baseline serum cortisol of ≥ 5 $\mu\text{g/dL}$ and a post-stimulation value of ≥ 18 $\mu\text{g/dL}$, one fluticasone subject was normal at baseline, but abnormal after treatment due to a peak post stimulation cortisol of 17 $\mu\text{g/dL}$.

1.13.2.4. Pulmonary function

Results from spirometry were available for 229 (183 ciclesonide, 46 fluticasone) subjects at baseline and follow-up. The baseline FEV₁ was 1.54 in the ciclesonide group and 1.48 in the fluticasone group. The change from baseline was 160 and 300 ml in the ciclesonide and fluticasone subjects respectively.

1.13.3. Discussion and Conclusions

In this 12-month safety study, the baseline spirometry was similar to the baseline function of the subjects enrolled into the other 1-year long term studies 341lt and 342lt. In this study, there was a higher percentage of infectious and respiratory adverse events in the fluticasone

CLINICAL REVIEW

NDA # 21-658, Ciclesonide (Alvesco™)

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group than in the ciclesonide group. The percentage of asthma exacerbations as an adverse event was only slightly higher in the ciclesonide group than the fluticasone group. At the same time, withdrawals due to asthma exacerbations and asthma listed as a severe adverse event occurred in approximately 10% of the ciclesonide subjects but in none of the fluticasone subjects. The percentage of cataracts was slightly higher in the ciclesonide group (3.2%) as compared with 2.2% of the fluticasone subjects. The applicant again had the cases reviewed and could confirm none of the original findings. The objections to this methodology are the same as described in the review of study 341. To be valid the exams would have to be repeated in the entire population. HPA-axis evaluation was conducted in a limited number of subjects. A single fluticasone subject with a peak post-stimulation cortisol of 17 mcg/dL at the end of treatment was the only abnormality reported.

**APPEARS THIS WAY
ON ORIGINAL**

2. DETAILED LABELING CHANGES OR REVISED DRUG LABEL

Detailed labeling changes had not been completed at the time of this review.

CITATIONS

Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Aual Life Res* 1996; 5:35-46

Kharitonov S, Alving K, Barnes PJ (1997): Exhaled and nasal nitric oxide measurements recommendations. *Eur Respir J* 10:1683-1693

Silkoff PE, McClean PA, Slutsky AS, Furlott HG, Hoffstein E, Wakita S, Chapman KR, Szalai JP, Zamel N (1997): Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. *Am J Respir Crit Care Med*. 155: 260-267

Thompson WL, Brunelle RL, Emas GG, Simpson PJ, Walker RL. Routine laboratory tests in clinical trials. Indianapolis: Lilly Research Laboratories, Eli Lilly and Company; 1986.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Carol Bosken
9/23/04 09:07:40 AM
MEDICAL OFFICER

Lydia McClain
9/23/04 09:18:36 AM
MEDICAL OFFICER

I disagree with the recommendation that ciclesonide — mcg
— and 160 mcg BID be approved. See
Team Leader Memo

MEDICAL OFFICER 45-DAY Filing REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

| | |
|---|---------------------------------|
| APPLICATION: NDA # 21-658 | TRADE NAME: Alvesco™ |
| APPLICANT/SPONSOR: Aventis | USAN NAME: Ciclesonide |
| MEDICAL OFFICER: Carol H. Bosken, MD | |
| TEAM LEADER: Lydia Gilbert-McClain, MD | CATEGORY: Corticosteroid |
| DUE DATE: October 24, 2004 | ROUTE: Oral Inhalation |

SUBMISSIONS REVIEWED IN THIS DOCUMENT

| <u>Document Date</u> | <u>CDER Stamp Date</u> | <u>Submission</u> | <u>Comments</u> |
|----------------------|------------------------|-------------------|-------------------------------------|
| Dec 22, 2003 | Electronic | N (000) | Original NDA |
| Feb 5, 2004 | Electronic | N (000) BZ | NDA with electronic links corrected |

RELATED APPLICATIONS

| <u>Stamp Date</u> | <u>Application #</u> | <u>Application Type</u> | <u>Approval Date</u> |
|-------------------|----------------------|-------------------------|----------------------|
| April 10, 1998 | IND 53,391 | Original IND | |

REVIEW SUMMARY: Ciclesonide (Alvesco) is a synthetic pro-steroid that is metabolized to an active form in the lung. This application is submitted to support its use for the maintenance treatment of asthma in patients years of age and older. The recommended dose is

 Four 12-week, randomized, double-blind pivotal trials (#321, 322, 323/324, and 325) are submitted to support the recommended doses in adults. Studies 326 and 323/324LT are one year continuations of 321, 322, and 323/324 designed to assess long-term safety. Study 325 is a steroid-lowering potential of high doses of ciclesonide. The is supported by 2, 12-week trials (341, 342) each of which have 1-year continuations (341LT, 342LT). An additional study (344) was conducted for one year. Both the adult and pediatric 1-year extensions are still in progress. However more 205 patients have been treated for at least one year.

In all but study 325, FEV1 is the primary outcome measure with asthma symptoms, albuterol use, and QOL measurements as secondary outcomes. The safety assessment included HPA axis evaluation as well as enumeration of adverse events. In addition, selected centers obtained samples for PK measurements. In study 325 oral corticosteroid use was the primary outcome. Of the numerous PK studies submitted, one (102) is a 12-week randomized, double blind trial and will be included in the review of safety outcomes.

Preliminary analysis of the safety results of study 323/324 showed an excess incidence of cataracts in the patients treated with ciclesonide. A proposed 1-year study to further evaluate ocular changes after treatment with ciclesonide will not be completed prior to the PDUFA date for the application.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

| | | |
|-------------------------|--|---|
| IND/NEW STUDIES: | <input type="checkbox"/> SAFE TO PROCEED | <input type="checkbox"/> CLINICAL HOLD |
| NDA/SUPPLEMENTS: | <input checked="" type="checkbox"/> FILEABLE | <input type="checkbox"/> NOT FILEABLE |
| | <input type="checkbox"/> APPROVAL | <input type="checkbox"/> APPROVABLE <input type="checkbox"/> NOT APPROVABLE |
| OTHER ACTION: | | |

b(4)

I. General Information

Ciclesonide (Alvesco™) is a poorly absorbed, non-halogenated corticosteroid that has a low affinity for the glucocorticoid receptor. It is delivered as an aerosol via a metered-dose inhaler propelled by HFA-134 with a fine particle distribution that results in 50% of the inhalation being deposited in the lung. In the lung and other tissues, it is rapidly metabolized to des-ciclesonide, whose glucocorticoid receptor affinity is 12 times that of dexamethasone. The sponsor purports that any ciclesonide that is swallowed is metabolized to inactive metabolites in the first pass through the liver, resulting in low plasma levels of ciclesonide and des-ciclesonide. The sponsor contends that this pharmacokinetic profile gives ciclesonide a high anti-inflammatory potency with low systemic exposure. The current NDA is submitted to support the use of ciclesonide as a maintenance treatment of asthma in patients —years of age and older. b(4)

II. Regulatory and Foreign Marketing History

A. Regulatory History

Ciclesonide is a new molecular entity. An IND (53,391) was submitted in 1997 and then inactivated because the Agency felt the preclinical and clinical data were inadequate to support the proposed dose. After making changes to their protocols and obtaining phase I clinical data in Europe, the IND was reactivated in January 1998 by Byk Gulden (US Representative – Altana).

The applicant, came in for an EOP2 Meeting on October 22,1999. They stated that they wanted to submit studies supporting the use of ciclesonide in both the adult : _____ population in one NDA and the Division agreed. The Division advised the applicant that they would need to treat 100 subjects exposed for 1 year and 300 subjects 6 months as per ICH guidelines. However, in response to the question” Does the FDA accept the submission in the pediatric indication based on 6-months long term study?” The meeting minutes read as follows: “The Division stated that 6 months long term safety data may be adequate if the adult database supports safety of the higher doses.” b(4)

Ownership of the IND was transferred to Aventis Pharmaceuticals in May 2001. However, data from the original toxicology studies, submitted by Byk Gulden in 1997, were reviewed in May 2002. At that time the results of testicular pathology on individual dogs was submitted and showed “spermiogenic disturbance” in all of the treated dogs and none of the controls. In response to the Division’s concerns about this issue, Aventis convened a Pathology Working Group (PWG) to review the slides. The reviewers read selected slides and concluded that all of the previously described abnormalities were actually artifacts. After extensive discussion within the Agency, the following comment was appended to the Divisional meeting notes before they were sent to the sponsor:

“this finding (the abnormal pathology) represents a very low level of concern regarding possible risk to human subjects. This conclusion is based on several factors, including the absence of evidence of cellular injury, and the findings of the external expert pane. The Division feels that it is reasonable to remove reference to this finding from the Informed Consent. Please note that, while we are comfortable

removing the informed consent language, we cannot at this time, state that we are entirely dismissing the finding. This will be an issue to address during the review of the application when the NDA is submitted."

On several occasions during the development program the Division expressed a concern that the sponsor was censoring the safety data by reporting only those events which they considered to be attributable to the drug. This was particularly an issue with some of the early studies submitted by Byk Gulden. In two letters to the Division dated February 7 and 21, 2003 Aventis said they had reviewed their data and that all events were recorded.

Reviewer: The current study reports appear to provide all of the safety data. The overall AE rate is 50 – 60%, and separate listings are provided for total and drug-related events

Subsequently (5/16/03) the applicant requested another meeting with the Agency to discuss the results of the safety analysis of clinical study 323/324. An excess of new cataracts was seen in adults treated with ciclesonide (11) compared to placebo (1) and fluticasone (1) after 12 weeks of treatment. The applicant suggested that this was not of concern because there was no prospective protocol for cataract detection and therefore, the enumeration of this event was biased. The Agency, with input from the Division of Anti-inflammatory and Ophthalmic Drugs, disagreed stating that a well conducted trial, at least one year long and preferably 3 years long, would have to be performed to resolve this issue. The medical reviewer for the pulmonary division stated that the lack of the follow-up ophthalmologic evaluation would not be a filing issue, but that it would be a serious review issue that would result in label warnings if no new data were submitted. The protocol for the ophthalmology study has been reviewed by the Division. However, patient enrollment will not be complete until June 2004, and the results will not be available for review prior to the PDUFA date for this NDA.

B. Foreign Marketing History

None

III. Items Required for Filing and Reviewer Comments

A. Reviewer Comments

1. This is an electronic NDA submission that contained many inactive electronic links in the original submission. After a T-con with the applicant on February 3, 2004, an updated application with the appropriate links was submitted on February 5. The electronic addresses in the remainder of this review are for the updated submission.

2. Financial disclosure

investigators reported receiving \$26,000 to \$40,000 each from the applicant in addition to grant-related payments. of the investigators worked in . However, they worked at different sites and on different studies. One of the investigators screened patients and enrolled . The other screened and enrolled .

One investigator in , screened patients and enrolled , and one investigator in , screened patients and enrolled .

b(6)

3. Indexes and references

References are listed at the end of Module 5. Copies of selected articles are listed as hpbio\pubs\authornamedate.pdf.

B. Necessary Elements (21 CFR 314.50)

Table 1. Necessary Elements

| Item | Type | Status | Location (<i>electronic</i>) \\CDSESUB1\N21658\N_000\2004-02-05 |
|------|---|--|--|
| | Application Form (FDA 356h) | Present | 356h.pdf |
| | Formatting for Electronic Filing Format Table of Contents / Indexes Labeling | Present | |
| 1 | Index / Table of Contents | Present | ndatoc.pdf |
| 2 | Samples and Labeling Proposed Package Insert Proposed Label Proposed Medication Guide | No Present No | Labeling\summary.pdf Labeling\proposed.pdf |
| 3 | Summary Labeling Marketing History Chemistry, Manufacturing, & Controls (CMC) Drug Product Drug Substance Nonclinical Pharmacology and Toxicology Human Pharmacokinetics and Bioavailability Clinical Adult efficacy Pediatric efficacy Adult safety Pediatric safety Altana studies: safety Phase I study: safety Benefits vs Risks | Present n/a 1 page 185 pgs 7 pgs 2 pgs 48 166 103 75 228 173 160 51 Pg 58-60 | \summary\summarytoc.pdf \labeling\summary.pdf \summary\2.3qosintroduction.pdf ... \2.3p drugproduct.pdf ... \2.3s drugsubstance.pdf \summary\2.6.1introduction.pdf ... \2.6.2,3,4,5,6,7 \summary\2.7.1biopharmaceuticalstudies.pdf \summary\2.7.2clinicalpharmaceuticalstudies.pdf \summary\2.7.3aclinicalefficacy.pdf \summary\2.7.3bclinicalefficacy.pdf \summary\2.7.4aclinicalsafety.pdf \summary\2.7.4bclinicalsafety.pdf \summary\2.7.4cclinicalsafety.pdf \summary\2.7.4dclinicalsafety.pdf \summary\2.5clinicaloverview.pdf |
| 4 | CMC | Present | \Cmc\cmctoc.pdf |

| Item | Type | Status | Location (<i>electronic</i>) \\CDSESUB1\N21658\N_000\2004-02-05 |
|------|---|---------|---|
| | Environmental Impact statement: Request categorical exclusion | | \\Other\environ.pdf |
| 5 | Nonclinical Pharmacology and Toxicology | Present | \\Pharmtox\pharmtox.pdf |
| 6 | Human Pharmacokinetics and Bioavailability | Present | \\Hpbio\hpbiotoc.pdf |
| 8 | Clinical | | No separate toc |
| 8.5 | Controlled studies | Present | \clinstat\321\study321.pdf \clinstat\321\study321a.pdf \clinstat\322\study322.pdf \clinstat\322\study322a.pdf \clinstat\study323_324\study323_324.pdf \clinstat\study323_324\study323_324a.pdf \clinstat\study323_324\study323_324b.pdf \clinstat\study325.pdf \clinstat\325\study325a.pdf \clinstat\325\study325b.pdf \clinstat\341\study341.pdf \clinstat\341\study341a.pdf \clinstat\342\study342.pdf \clinstat\342\study342a.pdf \clinstat\342\study342b.pdf \clinstat\323h_324h\study323h_324h.pdf \clinstat\323h_324h\study323h_324ha.pdf \clinstat\323h_324h\study323h_324hb.pdf \clinstat\study341h.pdf \clinstat\study342h.pdf \clinstat\study344h.pdf \clinstat\study273_2000.pdf \clinstat\study81_2001.pdf \clinstat\study130_2001.pdf \clinstat\study58_99.pdf \clinstat\study49_2000.pdf \clinstat\study185_99.pdf \clinstat\study217_99.pdf \clinstat\study193_2000.pdf \clinstat\study185_2001.pdf \clinstat\study225_2001.pdf \clinstat\study116_2000.pdf \clinstat\study126_99.pdf \clinstat\study119_2002.pdf \clinstat\study196_2002.pdf \clinstat\study13_2000.pdf \clinstat\study246_99.pdf \clinstat\study134_97.pdf \clinstat\study236_97.pdf \clinstat\study143_2000.pdf \clinstat\study188_98k1.pdf |
| 8.7 | Uncontrolled studies | Present | \clinstat\study326h.pdf \clinstat\study138_2001.pdf \clinstat\study277_2000.pdf |
| 8.8 | Integrated Summary of Effectiveness Adult Children 4 – 11 years old | Present | Summary\2.7.4aclinicalefficacy.pdf Summary\2.7.4bclinicalefficacy.pdf |
| 8.9 | Integrated Summary of Safety | Present | |

| Item | Type | Status | Location (electronic) \\CDSESUB1\N21658\N_000\2004-02-05 |
|------|--|---|--|
| 8.11 | Adult Children 4 – 11 years old Altana Phase I studies Potential for Abuse Benefits vs Risks | Pg 57 Pg 58 | Summary\2.7.4aclinicalsafty.pdf Summary\2.7.4bclinicalsafty.pdf Summary\2.7.4cclinicalsafty.pdf Summary\2.7.4dclinicalsafty.pdf Summary\2.5clinicoverview.pdf Summary\2.5clinicaloverview |
| 8.12 | Statements of Good Clinical Practice: 6 Adult trials 5 Pediatric trials Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures Auditing information | Pg 14 Pg 11 Pg 39 pg 40 pg 35 pg 49 pg 50 pg 31 pg 29 | summary\2.7.3aclinical efficacy.pdf summary\2.7.3bclinical efficacy.pdf Clinstat\321\study321.pdf ...\322\study322.pdf ...\study323_324\study323_324.pdf ...\341\study341/pdf ...\342\study342.pdf ...\study 344lt.pdf ...\study326.lt.pdf |
| 9 | Safety Updates | No | |
| 10 | Statistics | | |
| 11 | Case Report Tabulations | Present | Crf\crtoc.pdf |
| 12 | Case Report Forms (for patients who died or did not complete studies) | Present | Crf\crtoc.pdf |
| 13 | Patent Information | Present | Other\patentinfo.pdf |
| 14 | Patent Certification | Present | Other\patcert.pdf |
| 16 | Investigator Debarment Certification | Present | Other\debar.pdf |
| 17 | Field copy certification (if applicable) | Present | Other\fieldcert.pdf |
| 18 | User Fee Cover Sheet | Present | Other\userfee.pdf |
| 19 | Financial Disclosure | Present | Other\financial.pdf |
| 20 | Other Claimed Marketing Exclusivity Pediatric Use | Present Present | Other\exclusiv.pdf Pediatric Studies 341, 342, 344. See Module 5, Clinical studies |

IV. Clinical Studies

The applicant is proposing the following indications:

b(4)

“ALVESCO is indicated for the maintenance treatment of asthma as prophylactic therapy in adult : ~~12 years of age~~ years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma management. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time”

The suggested doses of ciclesonide are 80 – 320 mcg [redacted] for patients on bronchodilators only, and those with mild-moderate asthma on ICS. For patients with severe asthma on ICS the recommended dose is [redacted] mcg BID. For patients on maintenance OC the recommended dose is [redacted] mcg BID. Thus the range of daily doses being proposed is [redacted], mcg OD. The drug product is a canister containing ciclesonide in concentrations of [redacted], 80, and 160 mcg/puff. The highest dose ([redacted] mcg/day) will require four puffs BID from a high-concentration canister.

b(4)

The applicant has submitted four pivotal trials to support the above doses in adults (321, 322, 323/324, and 325). There are 2, one-year continuations of the primary 12-week studies (323/324LT and 326). In addition, study 325 is a stand-alone trial in severe asthmatics on maintenance oral corticosteroids (OC) and the primary outcome is reduction in OC dose. A 12-week PK study (102) was combined with the primary clinical trials in the ISS. It was a randomized, blinded treatment trial and is appropriate for an analysis of adverse events. Of note, in the two adult pivotal 12-week trials the analysis is stratified by prior treatment. One stratum enrolled patients treated with steroids and/or leukotriene inhibitors and/or cromones and the other stratum enrolled patients treated who had taken long and/or short acting bronchodilators. The pulmonary function entry criteria were different in the two strata. In stratum 1 the patients were required to have a FEV1 of 65-100% predicted whereas the subjects in stratum 2 were required to have a FEV1 of 60 – 85% predicted.

Reviewer: Although there are not many subjects treated with either salmeterol or anti-leukotriene inhibitors alone, it might be useful to reanalyze the data looking at a more homogenous group of patients, .ie., a group treated with steroids and a group treated with only short-acting β -agonists.

Two pivotal trials were submitted to [redacted] in the [redacted] year old population (341 and 342), and each of these had one-year continuations (341LT and 342LT). Study 344LT was a separate trial that was carried out for one year in the pediatric population. The maximum number of patients treated is listed in the Table 2 below. Only 81 patients under 12 years of age were treated for a year, but the total (adult and pediatric) treated for a year is 205. There is also a growth study (343) in progress, but no results are submitted with the application. Similarly, there is a 1-year study in progress to look for cataracts (study 197) which will not complete enrollment until June 2004. It is projected that the study reports for study 343 and study 197 will be completed in January 2005.

b(4)

Table 2 Extent of Exposure

| Type of Study | # Trials | # Subjects |
|---|-----------|-----------------------------|
| Phase I | | |
| Inhaled formulations (MDI & DPI) | 25 | 445 |
| Oral, intravenous, % nasal | 11 | 122 |
| Adult Phase II/III | | |
| Aventis 12-week studies | 4 | 1102 |
| Aventis OCS* reducing study | 1 | 96 |
| Aventis 1-year safety | 2 | 423 {125 ≥ 12 m, 333 ≥ 6 m} |
| Aventis 4-week pharmacodynamic safety study | 1 | 24 |
| Altana supportive studies (integrated) | 14 | 2225 |
| Altana supportive studies (not integrated) | 2 | 601 |
| Children Phase II/III | | |
| Aventis 12-week studies | 2 | 768 |
| Aventis 1-year safety | 3 | 443 (80 ≥ 12 m, 306 ≥ 6 m) |
| Altana short-term growth | 1 | 24 |
| All studies | 30 | 5302 |

* Oral corticosteroids

Twenty randomized studies, most of them performed by Altana early in development, are submitted to support the efficacy of ciclesonide in the adult population. Eight of these contained a placebo arm. Of the eight with a placebo arm, 4 were less than 12 weeks in duration and were performed with a prototype dry-powder inhaler. Two were less than 12 weeks, but were performed with the to-be-marketed HFA inhaler and three were 12-week studies. Of the supporting studies, all but five were conducted in subjects who were 18 years or above. The other five were conducted in subjects 12 and above.

Additional safety studies include an evaluation of the HPA axis after 29 days of treatment with 320 and 640 mcg ciclesonide BID (study 103) compared with fluticasone 440 and 880 mcg BID

The applicant has submitted three separate safety summaries: one for the pivotal adult trials, one for the pivotal trials in 4-11 year-olds, and one that combines all of the Aventis and Altana trials. The adult safety summary includes study 102 which is a 12 week PK study.

All of the adults were treated in clinics in the United States. A minority of the children (18.6%) were treated in Mexico or Poland.

V. Pediatric Rule

NDA #, Enter drug,

9

Studies have been submitted to support the use of ciclesonide in _____ years of age.
The Division has agreed to defer studies on children less than 4 years of age until 2007.

b(4)

**APPEARS THIS WAY
ON ORIGINAL**

Table 3. Summary of Pivotal Studies

| Study # | Design | Asthma | Age | Dosage (mcg) Ciclesonide | Freq | Comparator | Time | N* exposed to Ciclesonide | Outcome |
|-----------|------------|-------------------------------|------------|--------------------------|------------|------------------------|------|-------------------------------|--------------------------------|
| 321 | R, DB, PC | Mild-mod (Stratified) | ≥12 years | 80 160 320 | OD HFA | Placebo | 12 w | 133/112 128/105 131/112 | FEV1 QOL Cortisol/PK |
| 322 | R, DB, PC | Mild-mod (Stratified) | ≥12 years | 80 160 320 | OD HFA | Placebo | 12 w | 124/109 123/110 124/102 | FEV1 QOL Cortisol/PK |
| 326 | Open-label | Mild-mod (flu study 321, 322) | ≥12 years | 80 160 320 | OD HFA | --- | 12m | 226/185/33 | Interim Analysis AE & cortisol |
| 323/324 | R, DB, PC | Severe On ICS | ≥12 years | 160 320 | BID HFA | Placebo Fluticasone | 12 w | 127/101 130/104 | FEV1 |
| 325 | R, DB, PC | On ICS & OC FEV1 40-80% | ≥12 years | 320 640 | BID HFA | Placebo | 12w | 47/47 49/48 | OC reduction |
| 323/324LT | R, DB | Severe | ≥12 years | 160 320 | BID | Beclomethasone | 12 m | 198/148/95 | Interim Analysis |
| 102 | R, DB, PC | Mild-Severe BD only | | 320 320 | OD BID | fluticasone | 12 w | 40 42 | Cosyntropin stim |
| 341 | R, DB, PC | Mild-Severe | 4-11 years | 40 80 160 | OD HFA | Placebo | 12 w | 126/103 135/117 122/104 | FEV1 |
| 342 | R, DB, PC | Mild-Severe | 4-11 years | 40 80 160 | OD HFA | Placebo | 12 w | 130/109 126/109 134/121 | FEV1 |
| 341LT | Open | Mild-Severe | 4-11 years | 160 | OD | Fluticasone | 12 m | 129/89/36 | Interim |
| 342LT | Open | Mild-Severe | 4-11 years | 160 | OD | Fluticasone | 12 m | 128/95/44 | Interim |
| 344LT | Open | Mild-Severe | 4-11 years | 160 | OD HFA | Fluticasone | 12 m | 186/122/1 | Interim |

* # randomized to receive ciclesonide/ completed the study or randomized to receive ciclesonide/ completed 6 months/completed the study

Table 4. Summary of Supporting Studies

| Study | Design | Asthma | Age | Dose | Freq | Comparator | Time | n | Outcome |
|--------|--|-----------------------|-------|-------------------|---------------------|---------------------------|-----------------------------|------------|--|
| 273 | R, DB, PC | Steroid depend | ≥ 18 | 80 320 | OD HFA | Placebo | 12 w | 120 115 | AM PEF |
| 81 | R, DB, PC Open follow | Steroid depend | ≥ 18 | 160 640 | OD HFA | Placebo | 12 w + 40 w open f/u | 107 112 | AM PEF |
| 130 | R, DB, PC | FEV1 55-85% | ≥ 12 | 160 | BID HFA | Beclomethasone Placebo | 12 w | 192 | FEV1 |
| 58 | R, DB, PC | FEV1 60-90% | ≥ 18 | 640 | OD HFA | Placebo | 4w | 25 | FEV1 |
| 49 | R, DB, PC 6-Way crossover | FEV1 >60% | ≥ 18 | 320 640 640 | Evening " BID | Placebo Fluticasone | 9 d 3-12 week washout | 27 | FEV1 Cortisol AUC Blood and urine |
| 185/99 | R, DB | Symptomatic on ICS | 18-75 | 320 640 | BID HFA | --- | 12 w | 177 188 | PEF |
| 217 | R, DB | FEV1 50-90% | 18-75 | 160 160 | Morning Evening | --- | 8w | 110 99 | FEV1, PEF 24-hr urine cortisol |
| 193 | R, DB | FEV1 50-90% | 12-75 | 80 320 | OD | Budesonide BID | 12 w | 182 195 | FEV1, PEF 24-hr urine cortisol |
| 185/01 | R, DB | Symptomatic on ICS | 18-75 | 640 1280 | OD | Budesonide | 12 w | 177 188 | FEV1, PEF 24-hr urine cortisol |
| 225 | R, DB | FEV1 50-90% | 12-75 | 320 | Evening | Budesonide OD | 12 w | 198 | FEV1, PEF |
| 116 | R, DB ciclesonide dose, but open for budesonide | FEV1 50-80% | 18-70 | 160 320 | OD | Budesonide OD | 6 w | 28 32 | FEV1, PEF |
| 126 | R, Crossover | FEV1 >60% | 18-45 | 320 | OD | Budesonide OD | 2 w 3-8 week | 15 | AMP challenge, exhale NO, |

C. Decision

This application is Fileable.

V. DSI Review/ Audit Decision

Study Center 28 (Medford, Oregon) enrolled 54 subjects (39 adults in studies 321 and 323, and 15 children in study 341) which was the fourth largest enrollment of all the study centers. In addition, there was one death in a 12 year-old while on the treatment protocol.

Study Center 58 (Dartmouth, Massachusetts) enrolled 51 adults in study 321 and 323, which was the maximum adult enrollment. They also enrolled 16 children in study 342.

Study Center 83 (Cincinnati, Ohio) enrolled 43 adults in Studies 322 and 323 and 20 children into study 342.

VI. Timeline for Review

Table 5. Timeline for Review

| Milestone | Target Date for Completion |
|-----------------------------|----------------------------|
| Stamp Date | December 22, 2004 |
| 321/322/326 | March 15, 2004 |
| 323/325/102 | April 1, 2004 |
| 341/342/341/2Lt | April 15, 2004 |
| 344 | May 1, 2004 |
| Integrated Efficacy Summary | May 15, 2004 |
| Integrated Safety Summary | June 1, 2004 |
| Draft Review | July 1, 2004 |
| Advisory Committee Meeting | Late August |
| Label Review | Early September |
| Wrap-up Meeting | Mid September |
| Due Date | September 24, 2004 |
| PDUFA Date | October 24, 2004 |

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Carol Bosken
2/11/04 02:53:48 PM
MEDICAL OFFICER

Lydia McClain
2/11/04 04:41:06 PM
MEDICAL OFFICER

**Addendum to Medical Officer Team Leader Memorandum
Memorandum to File:**

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NDA 21-658

Drug Products: Alvesco™ (ciclesonide) HFA Inhalation Aerosol → mcg, 80 mcg, 160 mcg

Sponsor: Aventis Pharmaceuticals Inc.

Memo Date: October 13, 2004

From: Lydia I. Gilbert-McClain, MD, FCCP, Medical Team Leader

RE: Comments to the Applicant

The Data submitted with the application demonstrated efficacy of ciclesonide in the higher dosage strengths in adults and adolescents with moderate to severe asthma previously maintained on inhaled or oral corticosteroid therapy but not in patients with mild to moderate asthma maintained on bronchodilator therapy alone.

The initial recommendation in the Team Leader memo was for an approval of the higher dosage strengths [administered twice daily] in patients with moderate to severe asthma on inhaled corticosteroids or taking oral corticosteroids. This recommendation necessitated major changes to the label with essentially a rewrite of the CLINICAL TRIALS section, ADVERSE REACTIONS, and DOSAGE and ADMINISTRATION sections to write a Package Insert (PI) for an indication for asthma in a subset of the asthma population.

The Package Insert as revised to limit the indication of ciclesonide for the treatment of asthma to a subset of the asthma population makes for a package insert that is not comprehensible to healthcare providers. Ciclesonide is a corticosteroid and corticosteroids are used in the maintenance treatment of asthma. A package Insert that states that a corticosteroid works for asthma but only in patients with a certain degree of asthma severity would not be comprehensible to healthcare practitioners. The Package Insert should guide physicians about the safe and effective use of the product in the clinical setting. From the data submitted, it was demonstrated that patients with severe asthma on oral corticosteroids (prednisone) treated with high doses (640 mg twice daily) of ciclesonide could significantly reduce the dose of oral prednisone taken for control of asthma. From this study, it is clear that ciclesonide works as a corticosteroid, however the effective dose and dosing interval for patients with mild to moderate asthma has not been clearly demonstrated in the clinical trials. Lack of this information frustrates efforts to write a comprehensible label. Therefore, this application should be given an approvable action with comments to the sponsor to conduct further studies to fully define the effective and safe dose and dosing frequency for the full range of asthma severity. The following comments should be conveyed to the Applicant in the Approvable letter.

COMMENTS TO THE APPLICANT

1. The submitted clinical data do not support efficacy of ciclesonide for the proposed indication of maintenance treatment of asthma as prophylactic therapy in adult _____ of age and older. Specifically, the clinical data do not support the efficacy of ciclesonide for the maintenance treatment of asthma in patients with mild to moderate asthma. This deficiency may be addressed by the following:

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- Provide data from adequate and well controlled studies that demonstrate efficacy of ciclesonide for the maintenance treatment of asthma that covers the full range of asthma severity. These studies should be designed primarily to assess the efficacy of ciclesonide in patients with mild to moderate asthma and should cover a range of doses.
- 2. The submitted clinical data do not support once daily dosing of ciclesonide. The once daily dosing frequency should be evaluated in clinical studies against the same total daily dose administered at different dosing frequencies to determine the efficacy and safety of ciclesonide administered once daily compared to administration at more frequent intervals (e.g. twice daily).
- 3. Cataracts were seen in the 12-week treatment period in study 323/324. Conduct a cataract study of at least 12 months treatment duration to address this safety signal.
- 4. The following general comment pertain to the Package Insert. Labeling comments will be forwarded upon review of the response to the deficiencies listed above.
- The pharmacodynamic data submitted _____
_____ with ciclesonide compared to the active comparator because the studies did not use equally efficacious doses of ciclesonide and the active comparator.

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

/s/

Lydia McClain
10/13/04 04:26:55 PM
MEDICAL OFFICER

Medical Team Leader Review Memorandum

Memorandum to File:

NDA 21-658

Drug Products: ALVESCO™ (ciclesonide) HFA Inhalation Aerosol
—mcg, 80 mcg, 160 mcg

Sponsor: Aventis Pharmaceuticals Inc.

Memo Date: September 22nd, 2004

Memo From: Lydia I. Gilbert-McClain, MD, FCCP, Medical Team Leader

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This memorandum provides a summary of the results of the clinical program, pertinent interdisciplinary findings, and my recommendations on approvability for NDA 21-658. For full details of the clinical development program and results please refer to Dr. Carol Bosken's medical officer review.

Background/Administrative History

A new drug application for Alvesco™ was submitted to the Agency on December 22, 2003. The PDUFA due date on this application is October 23, 2004. The application was submitted under 505(b)1 of the Food Drug and Cosmetic Act. The proposed indication is for the maintenance treatment of asthma in adult _____ years of age and older. The proposed dose is dependent on asthma severity and prior asthma therapy. In adults and adolescents (≥ 12 years) with mild to moderate asthma previously on bronchodilators alone, or inhaled corticosteroids, the proposed dose is 80 mcg _____ daily up to a maximum dose of _____ mcg once daily. For patients with

_____ For patients on oral corticosteroids, the proposed dose is 320 mcg twice daily up to a maximum dose of _____ mcg twice daily. _____

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The drug development program for Alvesco™ was carried out under IND 53, 391 which was first opened in 1997. The IND was initially owned by Byk Gulden with Altana as the US representative. The initial phase 1 and phase 2 studies were conducted by Byk Gulden/Altana and the EOP2 meeting for the development program (Oct 22, 1999) was held with Byk Gulden/Altana. A letter from Byk Gulden/Altana transferring ownership of the IND to Aventis Pharmaceuticals was received by the Division in May 2001. Aventis Pharmaceuticals Inc. conducted the entire phase 3 program to support this NDA. During the phase 3 program, Aventis requested permission from the Division to combine two of their studies #323 and # 324 into one because of difficulty with enrollment and the Division agreed with this request (Tcon March 7, 2002). The combined study became study 323/324. An increased number of cataracts in the ciclesonide arm compared to placebo and fluticasone propionate MDI was seen in this study, and a meeting was held with Aventis on June 2, 2003 to discuss this finding. The Division informed Aventis that

this safety finding was a concern and that a safety study specifically designed to evaluate cataracts would need to be conducted. Aventis was also informed that if the results of this study were not available at the time of the NDA submission and the drug were to be approved, that the finding of cataracts in the clinical study would be included in the label.

Chemistry Manufacturing and Controls and Establishment Evaluation

Ciclesonide is a non-halogenated glucocorticoid with a molecular weight of 540.7. The molecular formula is $C_{32}H_{44}O_7$. Ciclesonide inhalation aerosol is developed in — strengths as pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a solution of ciclesonide in propellant HFA 134a and ethanol. Each inhalation unit delivers — mcg ex-actuator (— mcg ex-valve), 80 mcg ex-actuator (100 mcg ex-valve), or 160 mcg ex-actuator (200 mcg ex-valve). The device contains a standard valve and canister with a simple press and breath actuator. There have been no issues with clogging of the valve orifices. There are no major issues with the drug product or the drug substance. There is dose proportionality across strengths, and no particle size distribution issues. The drug product does not contain a dose counter however a CMC post-approval agreement would be able to address this. At the time of this writing, the field inspection had not yet been conducted.

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OVERVIEW OF CLINICAL PROGRAM

The clinical development program for ciclesonide was conducted under IND 53, 391 and was designed to evaluate the efficacy and safety of the drug for the maintenance treatment of asthma in — adult patients — years of age and older. At the time of the NDA submission, a total of 60 studies had been completed with ciclesonide. Of these studies, 32 phase 1 studies were conducted by Byk Gulden/Altana Pharma (including 2 studies conducted by Teijin, their Japanese partner for the development of intranasal and inhaled ciclesonide formulations. There were also 15 phase 2/3 clinical studies conducted by Byk Gulden/Altana Pharma in subjects with asthma that evaluated doses between 80 mcg and 1280 mcg administered once or twice daily. A separate clinical program was initiated in December 2000 by Aventis Pharmaceuticals Inc. The Aventis asthma clinical program consists of 13 clinical studies. Of these, 6 are placebo-controlled 12-week treatment efficacy and safety studies (the pivotal studies), 4 are one-year safety extension studies of the pivotal studies, 1 is a separate long-term safety study in the pediatric population, 1 is a 4-week physiology (bronchial hyperresponsiveness) study, and 2 are pharmacodynamic studies. Approximately 3,700 patients participated in the Aventis clinical program. Of these, about 2,400 patients were exposed to treatment with ciclesonide including about 1,878 patients in the placebo-controlled pivotal studies.

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The 4-week physiology study in mild asthmatics showed that ciclesonide 320 mcg once daily attenuated bronchial hyperresponsiveness after adenosine monophosphate (AMP) challenge. Separate dose ranging studies were not conducted, however, the 12-week pivotal efficacy and safety studies were designed to evaluate the effectiveness of a range of once daily doses from 80 mcg to 320 mcg daily and twice daily doses from 160 mcg to 640 mcg twice daily in separate studies. There were no clinical studies designed to evaluate the efficacy of once daily dosing compared to twice daily dosing although the Division indicated at the EOP2 meeting that this should be incorporated in the clinical

trials. The Applicant purports that the pharmacological properties of the drug make it ideal for daily administration. This is based on the concept that ciclesonide is believed to undergo lipid conjugation in the lung creating a reservoir in the target tissue resulting in slow release over time and thus a potentially longer duration of activity. Ciclesonide itself is a pro-drug that is hydrolyzed by airway esterases to the active metabolite RM1. A brief summary of the efficacy and safety data is given below. For more details please refer to the medical officer review completed by Dr. Carol Bosken.

EFFICACY

Aventis conducted 6 pivotal efficacy and safety studies. Four of these were conducted in adolescents and adults ≥ 12 years of age (studies 321, 322, 323/324, and 325) and 2 were conducted in children 4 – 11 years of age (studies 341 and 342). All 6 studies were double-blind, randomized, placebo-controlled, parallel-group studies with a 12-week treatment period that compared ciclesonide in doses ranging from 80 mcg once daily to 640 mcg twice daily to placebo.

Once daily dosing studies

Aventis conducted 4 placebo-controlled studies with ciclesonide administered once daily in the morning. In the adult [≥ 12 years of age] program (studies 321 and 322), the doses evaluated were:

80 mcg [40 mcg x 2 puffs]
160 mcg [80 mcg x 2 puffs]
360 mcg [160 mcg x 2 puffs]

In the pediatric [4 – 11 years of age] program (studies 341 and 342), the doses studied were:

40 mcg [40 mcg x 1 puff]
80 mcg [80 mcg x 1 puff]
160 mcg [160 mcg x 1 puff]

These 4 studies were of similar design and the patients enrolled had a history of asthma for at least 6 months and demonstrated FEV₁ reversibility of $\geq 12\%$ following inhalation of albuterol. The mean FEV₁ was ~ 2.44 L (70% predicted) in the adult studies and 1.3 L (68% predicted) in the pediatric studies. Patients enrolled were either previously maintained on bronchodilators alone or maintained on inhaled corticosteroids (ICS). Patients were randomized into 2 strata depending on prior asthma therapy with patients previously maintained on ICS randomized to stratum 1 and patients previously maintained on bronchodilators alone randomized to stratum 2. Randomization to 12 weeks treatment with ciclesonide or placebo was preceded by a 5 to 28-day placebo run-in period.

The primary efficacy endpoint in these 4 studies was the change from baseline in the AM pre-dose FEV₁ (in L for the adult studies, or % predicted for the pediatric studies) at end-of-study (Week 12[LOCF]). Secondary endpoints assessed in these studies included asthma symptom scores, albuterol use, nighttime awakenings, and the Asthma Quality of Life Questionnaire (AQLQ). To address the issue of multiplicity with the different doses of ciclesonide, a hierarchical step-down approach was used in the analysis of the primary

endpoint. Secondary endpoints were considered supportive and were not adjusted for multiplicity.

A total of 1,015 patients ≥ 12 years of age and older were randomized to 12 weeks of treatment with ciclesonide 80, 160, or 320 mcg or placebo once daily in the morning. Only the ciclesonide 320 mcg once daily dose had a significant improvement in AM pre-dose FEV₁ that was replicated. The LS mean improvement in FEV₁ with ciclesonide 320 mcg once daily compared to placebo was 0.15 L and 0.12 L in study 321 and 322 respectively. In study 321, ciclesonide 160 mcg once daily did not have a significant improvement in AM pre-dose FEV₁ compared to placebo (0.07 L; $p = 0.16$) however in study 322, a significant improvement in pre-dose FEV₁ (L) was seen with ciclesonide 80 mcg and 160 mcg once daily. When the efficacy data are analyzed by strata, only patients previously maintained on ICS had a significant improvement in FEV₁ whereas, patients who were previously on bronchodilators alone did not show efficacy. This finding was seen in both studies and held true even when the data from both studies were pooled.

Secondary endpoints trended in the direction of efficacy and generally favored ciclesonide over placebo but the results were inconsistent in the two studies and lacked dose ordering. For example, in study 321, The AM PEF (L/min) decreased by 2.8 L in the placebo group and increased with ciclesonide treatment [range 13.4 to 22.35 L/min] with the greatest improvement (22.35 L/min) seen in the ciclesonide 320 mcg once daily group. However, in study 322, the greatest improvement in AM PEF was seen with ciclesonide 160 mcg once daily (25.7 L/min) compared to 11.8 L/min with the ciclesonide 320 mcg once daily group. Daily albuterol use (puffs/day) decreased by approximately 1 puff/day across both studies (-1.52 to -1.88 puffs/day in study 321 and -1.01 to -1.24 puffs/day in study 322). In study 322, ciclesonide 160 mcg once daily outperformed ciclesonide 320 mcg once daily in the secondary endpoints. Similarly, in the AQLQ, although there was a clinically meaningful improvement in the Overall Score with ciclesonide 320 mcg once daily in study 321, in study 322 a clinically meaningful improvement was seen only with ciclesonide 160 mcg once daily. More subjects in the placebo group than in the ciclesonide groups withdrew from the studies due to lack of efficacy but the results were disparate in the two studies. Compared to placebo (30% withdrawal due to lack of efficacy), the percentage of withdrawals due to lack of efficacy in study 321 was 13.55%, 9.4% and 6.1% in the ciclesonide 80, 160, and 320 mcg treatment groups respectively, whereas, in study 322, the withdrawal rate was essentially the same across the ciclesonide treatment groups (range 5.6% - 7.3%) compared to 19% in the placebo group. Of note is the fact that the studies were not designed to provide specific criteria *a priori* for "lack of efficacy" but this was left up to the discretion of the investigators and this flaw in the study design must be taken into account when interpreting these results.

In the two pediatric studies (341 and 342), 1,031 patients aged 4 – 11 years were randomized to treatment with ciclesonide 40, 80, or 160 mcg or placebo once daily for 12 weeks. Efficacy of ciclesonide once daily was not established in these studies. In one of the studies (342), ciclesonide 160 mcg once daily had a significant improvement in AM

pre-dose FEV₁% predicted compared to placebo (3.48% improvement corresponding to an improvement of ~ 0.07 L [p=0.02]). Secondary efficacy endpoints showed inconsistent results in the two studies. For example, the greatest improvement in AM PEF compared to placebo was seen with ciclesonide 80 mcg (16.3 L/min) in study 341 while ciclesonide 40 mcg and 160 mcg once daily only showed modest improvement (4.3 L/min and 9.7 L/min respectively). However, in study 342 the improvement in AM PEF was essentially the same for the 3 doses (6.2 L/min to 8.7 L/min). The decrease in albuterol use was trivial (< 1 puff/day) across the studies. Withdrawals due to lack of efficacy was slightly higher in the placebo group (11% to 14%) and was lower in all the ciclesonide treatment groups but did not show consistent dose ordering. None of the ciclesonide treatment arms in the pediatric studies had a clinically meaningful improvement in the Overall Score in the AQLQ.

Table 1 below summarizes the primary efficacy results of the once daily dosing studies.

Table 1: Once Daily Dosing Studies (Adult and Pediatric Population)

| Study # | Ciclesonide 40 | Ciclesonide 80 | Ciclesonide 160 | Ciclesonide 320 |
|--|----------------|----------------|-----------------|-----------------|
| 321 (Adults) | - | x | x | ✓ |
| 322 (Adults) | - | ✓ | ✓ | ✓ |
| 341 (Peds) | x | x | x | |
| 342 (Peds) | x | x | ✓ | |
| ✓ = Significant improvement compared to placebo in primary efficacy endpoint | | | | |
| x = Not significant | | | | |

Twice Daily dosing studies

Aventis conducted 2 studies in the adult population with ciclesonide using a twice daily dosing regimen. Study 323/324 (n=531) was conducted in patients with moderate to severe asthma previously maintained on ICS to evaluate the efficacy of ciclesonide 160 mcg and 320 mcg twice daily. This study also included a fluticasone propionate MDI 440 mcg twice daily treatment arm. Study 325 (n=140) was conducted in patients with severe asthma on oral corticosteroids (OCS) to evaluate the efficacy of ciclesonide 320 mg and 640 mcg twice daily in reducing oral prednisone use. Patients in both studies had characteristics of severe persistent asthma [mean FEV₁ 1.79L (53% predicted) in study 323/324, and 1.64L (55% predicted) in study 325]. The mean daily prednisone use for patients in study 325 at randomization was 12.4 mg/day. The primary efficacy endpoint for study 323/324 was the change in FEV₁(L) from baseline compared to placebo at Week 12 (LOCF). For study 325, the primary efficacy endpoint was the percent reduction in oral corticosteroid use from baseline compared to placebo at Week 12. In both studies, ciclesonide had a significant improvement compared to placebo for the primary efficacy endpoint. The results for the primary and some of the secondary endpoints are displayed in the table. Unlike the efficacy findings in the once daily dosing studies, the primary efficacy results tended to show dose ordering and the secondary efficacy results were more consistent. These results are shown in Table 2.

Table 2: Efficacy Results Twice Daily Dosing Studies
(Change from Baseline to Endpoint: Difference from Placebo [LS means])

| Efficacy Endpoints | Study 323/324 | | | Study 325 | |
|---|------------------------|------------------------|-------------------|------------------------|------------------------|
| | Ciclesonide 160 BID | Ciclesonide 320 BID | FP MDI 440 BID | Ciclesonide 320 BID | Ciclesonide 640 BID |
| FEV ₁ (L) | 0.11 | 0.18 | 0.24 | - | - |
| % Reduction OCS | - | - | - | 51.59 | 66.75 |
| AM PEF (L/min) | 18 | 20 | 31 | 4.32 | 15.97 |
| ↓ in albuterol use (puffs/day) | 0.62 | 0.49 | 1.12 | 0.07 | 0.08 |
| **Withdrawals (%) | 15.7 | 10.8 | 7.4 | 12.8 | 6.3 |
| ** Withdrawals [due to lack of efficacy] in placebo was 39% in 323/324 and 29% in 325 | | | | | |

As can be seen in the table, the twice daily doses in these 2 studies were significantly superior to placebo for the primary efficacy endpoints and the secondary efficacy results tended to support the primary efficacy findings. It is important to note that the studies were not designed to allow replication of the 160 mcg twice daily dose. The only twice daily dose with replicate efficacy results is the 320 mcg BID dose. The efficacy of the 640 BID dose was not replicated however, given that the 320 mcg BID dose is efficacious, replication of the 640 BID dose is not necessary.

SAFETY

Safety data are derived from the 13 clinical studies. Approximately 1,196 patients were exposed to ciclesonide in the 12-week adult studies in doses ranging from 80 mcg QD to 640 mcg BID. Of note, the highest ciclesonide doses (320 mcg BID and 640 mcg BID) had the lowest number of subjects exposed in the 12-week studies [n = 177 exposed to 320 mcg BID; n=48 exposed to 640 BID]. However, the overall number of subjects exposed to ciclesonide 320 mcg BID in the long-term one-year studies met the minimum requirement by ICH standards. A total of 342 subjects were exposed to ciclesonide in doses up to 320 mcg BID for at least 6 months. Of these, 132 subjects in study 323/324LT completed the one-year safety follow up and the mean daily dose of ciclesonide was 576.7 ± 113.2 mcg/day. In study 326 (the 1-year safety extension of studies 321 and 322), 175 subjects were exposed to ciclesonide for 1 year with 90 subjects received 320 mcg QD. The design of the long-term studies was such that the dose of ciclesonide could be varied throughout the year. The highest proposed dose of 640 mcg BID was not studied in any of the long term studies.

The most frequently reported adverse events in the controlled studies were headache and AEs of the upper respiratory system (sinusitis, rhinitis, upper respiratory tract infection NOS). The frequency of these events was similar in the placebo and the ciclesonide-treatment groups. Oral candidiasis was reported in 11 (1%) of ciclesonide-treated subjects [vs. 4(0.9%) in placebo] in the controlled studies with doses up to 320 mcg BID. In the oral corticosteroid sparing study, 9(9.4%) of the ciclesonide-treated subjects [vs. 0 in

placebo] had oral candidiasis. Laboratory abnormalities did not reveal any particular trend.

Of clinical concern is the finding of lenticular opacities in one of the 12-week controlled (323/324) and the corresponding one-year safety follow up clinical study (323/324 Lt). A total of 13 (5.1%) cataracts were reported in the ciclesonide-treated subjects in the 12-week treatment period compared to 1(0.7%) and 2(1.4%) in the placebo and fluticasone propionate treatment groups respectively. In the 1-year follow up, 14(3.5%) cataracts were reported in the ciclesonide-treated group compared to 7(3.6%) in the beclomethasone dipropionate HFA (QVAR) 320 mcg BID group. Although these percentages are similar, more careful analysis of these cases revealed some notable differences. There were 3 cases of subcapsular cataracts found exclusively in the ciclesonide-treated group. Additionally, 3 cases of glaucoma were reported in the ciclesonide-treated subjects and 1 of these cases prompted withdrawal from the study due to severity. There were no reports of glaucoma in the QVAR group. These data are not conclusive but indicate the need for a study to further evaluate whether treatment with ciclesonide is associated with an increase incidence of cataracts. While it has been reported that long-term use of ICS may cause cataract formation (particularly in elderly patients)¹, it is unusual to observe this in 12-week treatment studies and this finding warrants a more definitive study. There was only one death reported in the adult studies and it was unrelated to the study drug and there were no serious drug-related adverse events.

The adverse event profile in the pediatric population 4 to 11 years of age was similar to the adult population including the finding of posterior subcapsular cataracts. Three subjects in the 12-week studies (one each in ciclesonide 40, 80, and 160 mcg treatment arms) who had normal eye exams at baseline had posterior subcapsular cataracts at end-of-study. There was one death in one of the long-term studies of a 12-year old female who had a sudden cardiorespiratory event at school. The cause of death was not fully determined at autopsy but was deemed unrelated to treatment with ciclesonide.

Clinical Pharmacology and Biopharmaceutics

Extensive pharmacokinetic characterization of ciclesonide was conducted through a large number of studies including 3 dose-response studies in adults and 2 in pediatric subjects conducted by both Byk Gulden/Altana and Aventis Pharmaceuticals Inc. These studies are reviewed in detail in Dr. Suarez-Sharp's Clinical Pharmacology and biopharmaceutics review. The systemic exposure of ciclesonide and RM1 (the major metabolite) in asthmatics receiving a single dose of ciclesonide 1600 mcg (ex-valve) was similar to that observed in healthy subjects. The mean C_{max} and $AUC_{0-\infty}$ of RM1 following multiple dose administration of ciclesonide 320 mcg QD increased up to 26% compared to single dose. Time to reach steady-state was not addressed, however it is expected to be achieved within 2 to 3 days of repeated once daily dosing. Metabolism of RM1 appears to be predominantly catalyzed (83%) by CYP3A4.

¹ Cumming RG, et.al. Use of inhaled corticosteroids and the risk of cataracts. N Eng J Med 1997;337:8-14

Of note, no dose response (measured as change from baseline in FEV₁ or cortisol suppression) was observed in adult or pediatric studies. The potential for cortisol suppression with ciclesonide evaluated by measurement of the serum cortisol AUC₀₋₂₄ [the 4-week PD study # 103] and by assessment of the effect on the HPA axis [the 12-week PD study #102] was compared to fluticasone propionate MDI. Both studies showed that the degree of cortisol suppression with ciclesonide in the range of doses studied (320 BID x 12 weeks and 640 BID x 4 weeks) was not higher than that observed for fluticasone propionate (440 BID x 12 weeks, and 880 BID x 4 weeks). The major flaw in these PD comparative studies is that the studies were not designed to compare equally efficacious doses of ciclesonide and fluticasone and therefore, these results must be viewed with caution since the finding of "less" cortisol suppression with ciclesonide compared to fluticasone cannot be adequately determined by comparing doses of these drugs that have vastly disparate efficacy. From the clinical data submitted, fluticasone propionate had numerically higher improvement in FEV₁ compared to ciclesonide in study 323/324 where a comparative arm of fluticasone propionate MDI 440 mcg BID was incorporated. (see Table 2). Also, it should be pointed out that the lowest effective dose of fluticasone propionate is only 44 mcg BID compared to what appears to be at least 320 mcg/day for ciclesonide.

Preclinical pharmacology/toxicology

During drug development, there was a concern regarding the potential for testicular toxicity. Upon further assessment of this concern no direct evidence of cellular damage was found. The other pre-clinical findings seen during development were consistent with glucocorticoid effects.

Data Quality, Integrity, and Financial Disclosure

DSI audited six sites that participated in the phase 3 clinical studies in adults and pediatric patients. Four of these sites were selected primarily due to high enrollment and the death of a 12 year old child reported from one study site. Two additional sites were selected by DSI in response to previous complaints received (for-cause inspections). Four of the sites inspected had no findings of irregularities and the final recommendation was "voluntary action indicated" (VAI). Two sites had minor violations (inadequate recordkeeping, follow up examinations not conducted) resulting in the issuance of a 483 by DSI and the inspection being classified as "voluntary action indicate -response received" (VAI-RR). At these two sites, there were no significant discrepancies with the data listings and each investigator provided a response to the items listed on the 483 and provided corrective actions to prevent similar violations from recurring in the future. Overall, DSI concluded that the data submitted in support of the NDA were acceptable.

There were no ethical issues/irregularities discovered during the review of the studies submitted to the NDA. Four investigators reported receiving \geq \$26,000 in addition to grant-related payments from the Applicant. These investigators enrolled very few patients in the clinical studies and these small numbers are not expected to impact the conclusions from the data.

Pediatric Considerations

The Applicant conducted studies in children 4 to 11 years of age as part of the pediatric program and children 12 years of age and older were included in the adult program. Studies with twice daily dosing were not conducted in subjects 4 to 11 years of age and the once daily dosing studies _____ Should the Applicant wish to _____

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_____ . In the acknowledgement letter to the NDA, the Division informed the Applicant that studies in pediatric patients under 4 years of age were being deferred until October 23, 2007. The sponsor subsequently submitted a request for a waiver of pediatric studies in subjects less than 6 months of age. The request for a waiver seems appropriate and could be granted at the appropriate time. A growth study has not been conducted by Aventis Pharmaceuticals and at this time it does not seem appropriate to request a growth study given that the drug has not demonstrated efficacy in the pediatric population in whom the growth study would need to be conducted. Of note however, Byk Gulden/Altana has an ongoing one-year growth study in pediatric patients 5 – 7.5 years of age (females) and 5 to 8.5 years of age (males) with doses of 40 mcg and 160 mcg once daily (study 343). A negative finding in this study would not obviate the need for a growth study in the future should an efficacious dose of ciclesonide in pediatric patients be found that would support approval.

Product Name

The Applicant has proposed the name Alvesco™. The name has been reviewed by the Office of Drug Safety and they have no objections to the name proposed.

Labeling

The label has been reviewed extensively throughout the review cycle to streamline the primary review however, at this time the label has not been edited. Should this application be headed toward an approval action, extensive changes would need to be made to the label. Major revisions would include (among other things) the removal of the sections comparing the cortisol effect of ciclesonide to fluticasone propionate, rewriting of the clinical trials section, and revision of the indication, and the dosing & Administration sections. Also the claims of onset of action within 24 hours, and improvement in quality of life would need to be deleted.

Discussion/Conclusions

The efficacy of ciclesonide in the maintenance treatment of asthma was studied using a once daily dosing and a twice daily dosing regimen in doses ranging from 40 mcg once daily to 640 mcg twice daily. The lowest total daily dose to achieve statistical significance was the 320 mcg dose. I disagree with the recommendation in the primary medical officer and the statistical review that ciclesonide _____ daily be approved. According to the Code of Federal Regulations 21CFR 314.25 an application can be deemed not approvable if *“there is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.26, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.”* [21CFR 314.25 (b)(5)]

b(4)

The studies using the once daily dosing regimen were not adequately designed to evaluate the efficacy of the once daily dosing regimen. At the EOP2 meeting (Oct 22, 1999) the Division indicated that once daily dosing vs. twice daily dosing should be compared in the clinical program. This study design was never incorporated in the phase 3 pivotal studies. This comparison is critical in evaluating the efficacy of once daily dosing administration of ICS since data from other ICS indicate that once daily administration of ICS may be less efficacious than twice daily dosing. To date, the Agency has only approved one ICS (Pulmicort Turbuhaler) with a once daily dosing regimen but this is for use only in patients who have been previously controlled on inhaled corticosteroids² as an "add on" to the approved twice daily dosing regimen. The data supporting the approval of a once daily regimen came from a study that evaluated Pulmicort Turbuhaler 200 or 400 mcg QD compared to placebo in patients with mild to moderate asthma. Patients were stratified for prior ICS use and entered a 6-week treatment period followed by a 12-week maintenance treatment period. The results showed that once-daily dosing was most clearly effective for those patients previously maintained on orally inhaled corticosteroids. In the case of fluticasone propionate (FP)³ although there was statistically significant improvement with once daily administration of FP Diskus 500 mcg (6.47% improvement in FEV₁ vs. placebo), this dosing regimen was less efficacious than FP Diskus 250 mcg BID (18.47% improvement in FEV₁ vs. placebo) and !

b(4)

The ciclesonide development program has not incorporated a study design that evaluated once daily vs. twice daily dosing and the only once daily dose that showed efficacy was the 320 mcg dose. Even without a direct comparison of once daily vs. twice daily dosing in the ciclesonide development program, the overall findings of the once daily dosing studies strongly suggest that the once daily dosing regimen is an inferior dosing regimen. In the adult program, patients who were previously on bronchodilators alone did not have a significant response to treatment, and efficacy of the once daily doses was not demonstrated in the pediatric (4 to 11 years) population. There was no clear dose response or trend towards a dose response for the primary efficacy endpoint with the once daily dosing regimen, whereas, in the studies with a twice daily dosing regimen there was more of a dose response.

Looking at the results of the once daily dosing studies from a purely statistical viewpoint, it can be argued that the 320 mcg QD dose was replicated and therefore meet the criteria for "substantial" evidence. However, this argument must take into account the fact that the 320 mcg QD dose showed significance only in a subset of the study population (i.e. those who had previously been on ICS). Given that ICS dosing for the maintenance treatment of asthma is based on prior asthma therapy, the finding that ciclesonide 320 mcg once daily was not efficacious in patients previously maintained on bronchodilators alone is critical since asthma patients previously on bronchodilators alone without adequate asthma control would be the very patients who would warrant treatment with an

² Physicians' Desk Reference: Pulmicort Turbuhaler

³ Inhaled Fluticasone Propionate by Diskus in the Treatment of Asthma – A Comparison of the Efficacy of the Same Nominal Dose Given Either Once or Twice a Day. Mary E. Purucker et.al CHEST 2003; 124:1584-1593

ICS. The Applicant proposes _____, however the data do not support this claim. Approval of ciclesonide 320 mcg _____ daily for only patients with mild to moderate asthma previously maintained on ICS, invokes the notion that patients with mild to moderate asthma who are candidates for treatment with ICS but currently are on bronchodilators alone, would first have to receive therapy with another ICS, and then subsequently switch to treatment with ciclesonide. Under these circumstances, it would be difficult to write a label that would be comprehensible to practicing physicians.

b(4)

Secondly, the 160 mcg twice daily dose was not replicated and I disagree with the recommendation in the primary medical officer review that this dose should be approved. It can be argued that the 160 mcg BID dose does not need to be replicated since the 320 mcg QD dose was statistically superior to placebo. The findings of the 320 mcg QD dose may have supported the 160 BID dose if the two doses were evaluated concomitantly in at least one of the studies, but this was not done. Finally, although the 640 mcg BID dose does not need to be replicated, the exposure data with this dose is very limited and recommendations on approvability should take this into account.

In conclusion, from an efficacy standpoint there is really only support for the 320 BID and the _____ BID dose of ciclesonide in patients with moderate to severe asthma on ICS or taking oral corticosteroids. Of note, the NDA is for _____ strengths of ciclesonide _____ mcg, 80 mcg, and 160 mcg. If only the highest doses of ciclesonide are approved, the lower strengths (____ mcg and 80 mcg) would need to be withdrawn from the application.

b(4)

Recommendations on Approvability

- From a clinical standpoint, the data submitted support the approval of Alvesco™ HFA Inhalation Aerosol _____ mcg for a limited indication for the maintenance treatment of asthma in patients 12 years of age and older with moderate to severe asthma previously maintained on inhaled corticosteroids or requiring oral corticosteroid therapy.
- The recommended dose in patients with moderate to severe asthma on ICS is _____ mcg BID. For patients on oral corticosteroid therapy, the recommended starting dose is 320 mcg BID with _____ mcg BID the highest recommended dose.
- From a clinical standpoint, the data do not support approval of Alvesco™ for the maintenance treatment of asthma in _____ years of age.
- From a clinical standpoint, the data do not support the approval of Alvesco™ for the maintenance treatment of asthma in patients previously maintained on bronchodilators alone.
- From a clinical standpoint, the data do not support approval of Alvesco™ in a _____ daily dosing regimen.

b(4)

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/s/

Lydia McClain
9/23/04 10:09:03 AM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

FROM: Division of Pulmonary and Allergy Drug Products, HFD-570
Medical Reviewer: Carol H. Bosken, M. D.
Medical Team Leader: Lydia I Gilbert-McClain, MD

SUBJECT: NDA 21-658 Ciclesonide HFA Aerosol 80, 160, and 320 mcg

TO: DSI

DATE: February 27, 2004

APPEARS THIS WAY ON ORIGINAL

any unusual symptomatology, concurrent medications, and protocol violations, in addition to the routine auditing.

Site 58 is added because it both enrolled a large number of patients and it participated in the cortisol studies. In addition, none of the other sites enrolled patients into study 342. Study 342 is the only pivotal pediatric trial that showed efficacy and therefore, at least one site from that study should be audited.

APPEARS THIS WAY ON ORIGINAL

Site 28 (Continued)
Study 323

| Patient ID | Visit Date | Fev1 | Visit Date | Adverse Event | Visit Date | Glucose |
|------------------|------------|------|------------|-----------------------------|------------|---------|
| 028/32403 | 05/08/02 | 1.2 | 04/18/02 | Low back strain | 03/19/02 | 86 |
| 028/32404 | 04/10/02 | 1.35 | 05/30/02 | | | |
| 028/32406 | 05/14/02 | 1.66 | 03/30/02 | Increased allergic rhinitis | 03/21/02 | 86 |
| 028/32407 | 08/09/02 | 3.65 | 04/25/02 | Asthma exacerbation | 05/07/02 | 91 |
| | | | 05/23/02 | | | |
| | | | 05/30/02 | | | |
| | | | 06/14/02 | Oral candidiasis | 08/09/02 | 136 |
| | | | -6/16/02 | | | |
| Study 341 | | | | | | |
| 028/34106 | 09/14/01 | 1.63 | 11/26/01 | Sore throat | 11/29/01 | 91 |
| 028/34109 | 10/23/01 | 1.9 | None | | 12/18/01 | 90 |
| 028/34112 | 01/10/02 | 1.77 | 10/14/01 | Cold | 01/10/02 | 116 |
| | | | 10/27/01 | | | |
| 028/34113 | 11/26/01 | 1.33 | 10/06/01 | Increased allergic rhinitis | 01/21/02 | 98 |
| 028/34118 | 05/07/02 | 2.63 | 10/22/01 | Nausea & Vomiting | 06/04/02 | 86 |
| | | | 03/03/02 | | | |
| 028/34120 | 05/16/02 | 1.13 | None | | 07/11/02 | 79 |
| 028/34121 | 05/28/02 | 1.88 | 04/25/02 | Fever | 09/20/02 | 55 |

| | | | | | | |
|-----------|----------|----|----|----|----|----|
| 058/32414 | 12/17/01 | 19 | 21 | 19 | 13 | 21 |
| 058/32419 | 03/16/02 | 15 | 22 | 21 | 15 | 22 |

Site 58 (Continued)

| | Visit Date | Fev1 | Visit Date | Cteyele | Ctgdri | Visit Date | Glucose |
|------------------|------------|------|------------|---------|--------|------------|---------|
| Study 321 | | | | | | | |
| 058/32107 | 11/10/01 | 2.84 | | | | 11/10/01 | 87 |
| 058/32116 | 01/07/02 | 2.79 | | | | 01/07/02 | 96 |
| 058/32131 | 03/18/02 | 2.11 | | | | 03/01/02 | 90 |
| 058/32139 | 08/30/02 | 4.09 | | | | 08/30/02 | 88 |
| 058/32144 | 07/06/02 | 1.78 | | | | 01/29/02 | 86 |
| Study 342 | | | | | | | |
| 058/34202 | 10/22/01 | 1.71 | | | | 10/22/01 | 93 |
| 058/34206 | 01/16/02 | 1.68 | | | | 01/16/02 | 89 |
| 058/32409 | 08/18/01 | 2.02 | | | | | |
| 058/34213 | 05/08/02 | 1.52 | | | | 05/08/02 | 91 |
| 058/34215 | 02/28/02 | 1.17 | | | | 05/15/02 | 90 |
| 058/34217 | 11/27/01 | 1.53 | | | | 06/15/02 | 117 |
| 058/34219 | 07/12/02 | 2.28 | | | | 07/12/02 | 94 |
| 058/34224 | 03/09/02 | 2.34 | | | | | |
| Study 323 | | | | | | | |
| 058/32405 | 09/22/01 | 2.63 | 09/22/01 | N | --- | 09/22/01 | 104 |
| 058/32411 | 08/25/01 | 1.38 | 11/10/10 | Y | 1 | 11/10/01 | 91 |
| 058/32412 | 11/14/01 | 1.26 | 11/14/01 | Y | 2 | 11/14/01 | 99 |
| 058/32414 | 12/17/01 | 2.56 | 12/17/01 | N | --- | 12/17/01 | 88 |

| | | | | | | | |
|-----------|----------|------|----------|---|-----|----------|----|
| 058/32419 | 03/16/02 | 2.27 | 03/16/02 | N | --- | 03/16/02 | 96 |
| 058/32420 | 12/31/01 | 1.1 | 12/31/02 | Y | 1 | 02/11/02 | 75 |
| 058/32423 | 03/16/02 | 1.0 | 03/16/02 | Y | 2 | 03/16/02 | 90 |

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/s/

Lydia McClain
3/1/04 09:34:25 AM