Demographics

There were 53 males and 70 females. The mean age was 4.2 years, and 57 (43.9%) were less than 4 years old. The majority were Caucasian (69.1%) and 10.6% were Black (Table 27).

Table 27. Demographics of Children 2 to 5 Years of Age in the ITT population

	Placebo N=42	C200 N=81	Total N=123
Age, n (%)			
2 years	7 (16.1)	14 (17.3)	21 (17.1)
3 years	12 (28.6)	21 (25.9)	33 (26.8)
4 years	9 (21.4)	24 (29.6)	33 (26.8)
5 years	14 (33.3)	22 (27.2)	36 (29.3)
Mean years (SD)	4.3 (1.2)	4.1 (1.1)	4.2 (1.1)
Gender (% Male)	50.0	39.5	43.1
Race (%)			
Caucasian	73.8	66.7	69.1
Black	11.9	9.9	10.6
Other	14.3	23.4	20.3
Hispanic (%)	40.5	48.1	45.5
Type of skin test (%)			
Current	47.6	59.3	55.3
Antigen Challenge (mm)			
Mean (SD)	5.5 (2.4)	5.1 (1.9)	5.2 (2.1)
Range	3 - 14	3 - 16	3 - 16
Control Challenge (mm)			
Mean (SD)	0	0	0

The mean (SD) response to antigen challenge was 6.3 (1.5) mm and the mean (SD) response to diluent control was 0.0 (0.0mm). The means did not vary among the treatment groups.

Mean compliance by diary or bottle weight was >90% in both treatment groups.

Reviewer: Prior medication ingestion was relatively uncommon (post-text Table 14.1.4.1 pg100/3861) in this young population. Eleven subjects (7 [8.4%] and 4 [9.5%] of the placebo and C200 subjects, respectively) had taken a nasal steroid prior to enrollment. A single C200 subject took pulmocort.

2.2.3 Efficacy Results

Efficacy Outcome

Efficacy was assessed using the 24 hour AM r-TNSS comparing baseline to the values obtained throughout the 12-week treatment period. The baseline values were 7.4 in the placebo group and 6.7 in the C200 group. The mean scores fell more with C200 treatment than placebo (Table 28). The differences in scores for the individual symptoms were most marked for nasal congestion and runny nose.

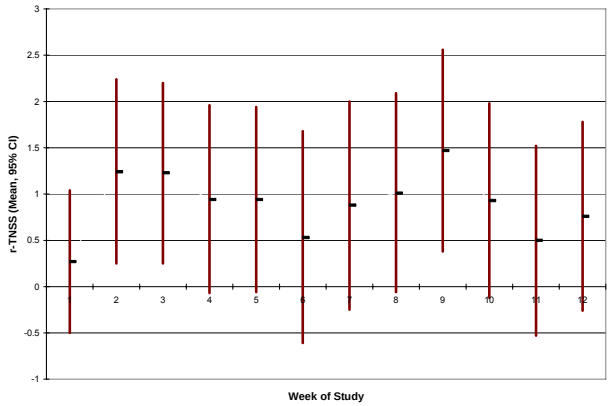
Table 28. Change in Symptom Scores After 12 Weeks of Treatment of 2-5 Year-Olds

24-hr r-TNSS	Placebo N=42	C200 N=81
Baseline, mean(SD)	7.4 (2.4)	6.7 (2.7)
Change from Baseline, LS mean (SE)	-1.5 (0.3)	-2.3 (0.2)
Treatment difference 95% CI		0.86 0.13, 1.60
PNSS	N=41	N=81
Baseline	7. (2.4)	7.2 (2.9)
Change from Baseline	-3.6 (0.5)	-3.3 (0.3)
Treatment difference 95% CI		-0.32 (-1.5, 0.81)

The PNSS also fell in both treatment groups, but the decrease was greater in the placebo than the C200 group. Rescue medication use was infrequent and similar in the two treatment groups. The C220 subjects took rescue medication on 6.1% of the treatment days and the placebo subjects on 5.2% of the days.

The weekly averages and 95% confidence intervals for the r-TNSS are shown in Figure 5. The lower border of the confidence interval cleared zero on 3 of the 12 weeks in which it was measured.

Figure 5. Weekly Summary of 24-hour r-TNSS



2.2.3 Safety

Extent of exposure

The mean duration of exposure was 82 days in both treatment groups. On the other hand, only 88.1% of the placebo subjects received >80 days of treatment compared with 92.8% of the C200 subjects.

Adverse Events

Overall, 73 (58.4%) of the subjects reported adverse events (Table 29). The incidence was slightly higher in the C200 group (60.2%) compared with the placebo subjects (54.8%), but most of the events were reported in only 1 or 2 subjects. Pyrexia was the most common event and it was reported in 16.7 and 15.7% of the placebo and C200 subjects, respectively. The next most frequent events, in order, were upper respiratory tract infection, cough, otitis media, sinusitis, and influenza. Upper respiratory tract infection, otitis media, sinusitis, and influenza were more frequent in the C200 subjects while pyrexia and cough were more frequent in the placebo group. The vast majority of the events were mild and only 4.8 and 3.6% of the events were described as severe in the placebo and C200 groups respectively. Other than "Platelet count increased" the events are those commonly reported in this patient population.

Table 29. Adverse Events Experienced by >3% Subjects of either treatment group during 12 Weeks of Treatment

	Placebo N=42	C200 N=81	Total N=123
Subjects with one event, n (%)	23 (58.4)	50 (60.2)	73 (58.4)
Pyrexia	7 (16.7)	13 (15.7)	20
Upper respiratory tract infection	4 (9.5)	11 (13.3)	15
Cough	4 (9.5)	7 (8.4)	11
Otitis media	2 (4.8)	6 (7.2)	8
Sinusitis	1 (2.4)	6 (7.2)	7
Influenza	1 (2.4)	4 (4.8)	5
Platelet count increased	1 (2.4)	4 (4.8)	5
Increased systolic BP	0	3 (3.6)	3
Headache	0	3 (3.6)	3
Nasopharyngitis	1 (2.4)	3 (3.6)	4
Vomiting	2 (4.8)	3 (3.6)	5 (4.0)
Gastroenteritis	2 (4.8)	2 (2.4)	4
Alanine aminotransferase increased	2 (4.8)	1 (1.2)	3
Epistaxis	2 (4.8)	1 (1.2)	3
Pharyngolaryngeal pain	2 (4.8)	1 (1.2)	3
Rash	2 (4.8)	0	1

The elevated platelet counts were all reported from one center, however, the laboratory examinations, themselves, were performed at a single laboratory. See the section on Laboratory results, below, for more details.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths or serious adverse events. Three subjects withdrew due to adverse events, two in the C200 group and one placebo subject. In one of the C200 subjects, a severe headache and dizziness were reported after taking the first dose and in the other subject, the report was of burning of the nose and eyes after taking the medication. In both cases the subject refused to continue the medication. The placebo subject was discontinued by the investigator due to a combination of worsening asthma and the development of a rash.

Laboratory Results

There were no notable changes in mean values for hematology or chemistry blood tests comparing baseline to the end of study values. Five out of the 40 abnormal platelet counts (>440 * 10^3 cells/mm^3) were reported as adverse events (see above) and one value of 601 * 10^3 cells/mm^3 was reported as an alert range laboratory abnormality in a placebo subject (see below).

Reviewer: There was an extraordinarily high incidence of abnormal laboratory values at baseline in this study. Of 19 chemistry variables, more than 5% of the subjects were abnormal at baseline for 8 anylates in the C200 subjects and for 5 in the placebo subjects. Abnormal baseline values were particularly prominent for the determination of BUN (13.4% of subjects abnormal), CK (13.4% abnormal), Calcium (22.7% abnormal), and phosphorous (15.9%).

Table 30 ***Abnormal Blood Tests at Baseline***

Test	*Normal Value*	*Placebo N=40*	*C200 N=79*	*Total % Abnormal N=119*
BUN, % Hi		*7.5 %*	*16.5 %*	*13.4 %*
Range (mmol/L)	*1.4 – 5.7*	*6.1*	*(6.1 -7.5)*	
CK, % Hi		*7.5 %*	*16.5 %*	*13.4 %*
Range (U/L)	*2 - 167*	*(182 – 406)*	*(173 -361)*	
Calcium, % Hi		*17.5 %*	*22.8*	*22.7 %*
Range (mmol/L)	*2.14 – 2.62*	*(2.67 – 2.79)*	*(2.64 – 2.77)*	
Glucose, % Hi		*---*	*1.3%*	*2.1 %*
% Lo	*3.9 – 7.8*	*7.5%*	*10.1%*	*9.2 %*
Range (mmol/L)		*(3.3 – 3.8)*	*(3.1 – 3.8)*	
Lipase, % Hi		*5.0%*	*8.9%*	*7.6 %*
Range (U/L)	*3 – 32*	*(37 – 42)*	*(34 -45)*	
Phosphorous, % Hi		*17.5%*	*15.2%*	*15.9 %*
Range (mmol/L)	*1 – 1.78*	*(1.81 – 2.2)*	*(1.81 – 2.07)*	
		N=40	*N=76*	*N=116*
Eosinophils, % Hi		*12.5*	*18.4*	*16.4 %*
Range (%)	*0 – 4*	*(0 - 11)*	*(0 - 15)*	
Hemoglobin, % Hi		*10.0*	*14.5*	*12.9%*
Range (g/dL)	*105 – 151*	*(112 – 151)*	*(119 – 153)*	
Lymphocytes, % Hi		*27.5*	*18.4*	*20.7%*
% Lo	*13 – 53*	*2.5*	*1.3*	*1.7%*
Range		*(12 – 64)*	*(12 – 76)*	
Neutrophils, % Lo		*7.5*	*7.9*	*7.8%*
	31 – 78	*(24 – 74)*	*(16 – 79)*	
Platelets, % Hi		*10.0*	*18.4*	*15.5%*
Range (k/mm3)	*200 - 440*	*(203 – 571)*	*(220 – 619)*	

The percentage abnormal for the hematology anylates ranged from a low of 5.2% for the white count to a high of 20.7% for an elevation of the percentage of lymphocytes in the differential. In most cases the elevations were not extreme and a visual inspection of the distribution of values suggested that the laboratory normal values had been incorrectly determined (A smooth single peak that is shifted relative to normal range). On the other hand, some of the distributions show

a cutoff at the upper limit of normal. Finally, the mean changes over the six weeks of treatment were trivial, although between 12 and 25% of the C200 subjects had an increase from normal in the values for Calcium, CK, Phosphate, and Urea. In the placebo group 12% (4/32) of those who started out normal had an abnormal Calcium at the end of the study, and 8.3% (3/36) had abnormal BUNs. However, all other values increased in less than 3%.

Laboratory values that exceeded predetermined upper limits for alert values were reported for 4 Placebo (one each, Platelets>444 * 10^3 cells/mm^3, Potassium > 5.3 mEQ/L, and 2 ALT > 30 U/L) and 5 C200 subjects (Potassium > 5.3 mEQ/L in 2 subjects, and one each, WBC count > 12.0 * 10^3 cells/mm^3, ALT > 30 U/L, and Eosinophils >4%). There were no sequelae from these events and no subject was withdrawn as a consequence.

HPA-Axis Evaluation

Blood samples for cortisol were obtained from 40 and 79 of the placebo and C200 subjects, respectively. The samples were all obtained before 9:30 AM and only three were obtained between 9:00 and 9:30. The LS mean plasma cortisol increased in both treatment groups over the course of the study (Table 31). The increase was greater in the placebo-treated subjects, but the difference did not reach statistical significance.

Table 31. HPA-axis Evaluation in subjects 2 to 5 years of age

Serum cortisol (mcg/dL) comparing baseline to 1-12 week average	Placebo N=40	C200 N=79
Baseline, mean(SD)	9.85 (3.8)	9.83 (3.9)
Change from Baseline, LS mean (SE)	1.94 (0.7)	0.99 (0.5)
Treatment Difference 95% CI	0.95 -0.72, 2.63	

Reviewer: The cortisol data suffers from the same deficiency as the other laboratory data. All of the distributions are shifted rightward resulting in many values above the normal limit at baseline as well as at the endpoint in both groups. As with the CK, phosphate, and Calcium determinations the baseline levels started out relatively high and increased further during the trial.

In response to the FDA query about the laboratory normal values [redacted] the Applicant noted that the reported cortisol normal values were incorrect. Instead of a normal range of 2.5 to 12.2 mcg/dL the correct range was 5.0 to 25.0 mcg/dL. When the baseline values were assessed after this correction, 3 subjects (2 C200 and 1 placebo) had a low baseline value and one C200 subject had a baseline value of 26.3 mcg/dL. The Applicant comment about the other laboratory values was that they were not far from the normal range and that possibly some of the children were dehydrated.

Physical Examination including ENT

The general physical examinations and vital signs were normal throughout the study for most subjects. The nasal examination was recorded as abnormal in 88 and 90% of the placebo and

C200 subjects, respectively. At the end of the study the percentages were unchanged. There were no reported perforations.

2.3 Summary and Discussion

This 12-week, randomized comparison of ciclesonide nasal spray 200 mcg once daily to placebo was designed to demonstrate the safety of ciclesonide nasal spray in the treatment of 2 to 5 year-olds with PAR. Demonstrating efficacy was a secondary objective, although, the 24 hour-reflective TNSS improved more in the C200 group than in placebo. The physician's assessment of nasal symptoms actually suggested that the placebo subjects fared better during the trial. These two outcomes can be reconciled if it is remembered that the r-TNSS was analyzed with a repeated measures ANOVA that includes all of the 12-weekly averages in the analysis, while the physician's assessment compared baseline to end of study score only. If an analysis had been performed on the baseline TNSS compared to the endpoint, the results would have been similar to those of the PNSS because the difference between placebo and C200 was not statistically different on the last three weeks of the trial. Finally, it should be noted that the 100 mcg dose of ciclesonide was not administered in this study, so the study provides no support for the proposed recommended dose of 100 mcg once daily.

The safety analysis showed a spectrum of adverse events that was similar to that seen in other studies in the subject group. Events were uncommon and mild. The ENT examination failed to show any evidence of septal ulceration or perforation. The mild abnormalities in the routine safety blood tests are probably artifacts. However, as in previous studies submitted to support approval of this product, the results suggest a general laxity in supervision of the laboratories. After the new normal values were used to assess the changes in plasma cortisol there were no apparent abnormalities induced by ciclesonide treatment. However, a single AM plasma measurement is not adequate to assess HPA-axis function.

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/s/

Carol Bosken
10/11/2007 04:43:57 PM
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Lydia McClain
10/12/2007 10:02:35 AM
MEDICAL OFFICER
I concur with the recommendation for approval of Omnaris 200 mcg once daily for treatment of SAR symptoms in children 6 to 11 years