

**05-3006** A DOUBLE-BLIND COMPARISON OF RHINOCORT® (BUDESONIDE) AQUA, MDI AND PLACEBO IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS

**SUMMARY**

This was a double-blind, randomized, parallel-group, multi center, Canadian trial that enrolled over 300 patients  $\geq 12$  years of age with ragweed-induced seasonal allergic rhinitis (SAR) in a three-week treatment protocol. It compared two different doses, 256  $\mu\text{g}$  and 400  $\mu\text{g}$ , of aqueous budesonide administered once daily, 200  $\mu\text{g}$  of budesonide from a pressurized nasal metered dose inhaler (pMDI) given twice daily and placebo. Multiple ordinal scale endpoints were defined without primacy among them, correction for multiple endpoints or correction for an interim analysis that was performed. All active treatments were superior to placebo, by these various indices. Although none of the active treatments was statistically differentiable from another, the pMDI consistently produced greater reductions in combined and individual morning and evening nasal symptoms and in the overall assessment of treatment efficacy endpoint. No consistent dose proportionality was found between the two aqueous budesonide formulations. The mean change from baseline of the 24-hour urine cortisol showed an increase in the placebo group and a decline in two of the three budesonide groups over the three-week, double-blind period. The 24-hour urine cortisol adjusted for creatinine excretion showed little difference between the active treatments and placebo. No separate safety or efficacy analyses were undertaken in pediatric patients.

**OBJECTIVE**

The primary purpose of this protocol was to compare the relative effects of placebo and intranasal budesonide, as two aqueous suspensions and as one pMDI aerosol, in the treatment of SAR. A secondary objective was to determine the systemic effects of the budesonide formulations in relation to placebo, measured as change in the 24-hour urinary cortisol excretion in a subset of patients over the three treatment weeks [39:1, 10].

**PROTOCOL**

This was a double-blind, randomized, parallel-group design undertaken at seven Canadian centers. A 1-week baseline period was followed by a 3-week treatment period, during which the patients received two different doses of aqueous budesonide (256  $\mu\text{g}$  or 400  $\mu\text{g}$  once daily), budesonide from a pressurized nasal pMDI (200  $\mu\text{g}$  BID) or placebo. The patient visited the clinic on three occasions; at the study entry, after the baseline period and after the treatment period. All patients started treatment at the early part of the ragweed pollination period, as evidenced by daily ragweed pollen counts [39:8, 11].

**TREATMENT**

Budesonide was provided as an aqueous suspension at a concentration of 2 mg/mL or 1.28 mg/mL in 10 mL glass vials with a mechanical pump. Each actuation delivered 100  $\mu\text{g}$  or 64  $\mu\text{g}$  of budesonide and each bottle contained 200 doses. The pMDI delivered 50  $\mu\text{g}$  per actuation of budesonide and each pressurized canister contained 200 doses. The placebo

was said to be identical in appearance to the aqueous budesonide formulation. The dosage of the aqueous formulations was two sprays in each nostril once daily in the morning, producing total daily doses of 256 µg and 400 µg. The dosage for the budesonide pMDI was two actuations in each nostril twice daily, producing a total daily dose of 400 µg (200 µg BID). Patients were given terfenadine 60 mg tablets as rescue medication. Other antihistamines of the investigator's choice were allowed, with the exception of [redacted]. Allergic conjunctivitis was treated with cromolyn sodium drops or a naphazoline-antazoline combination (Vasocon A®) [39:13, 15-6].

## PATIENTS

A total of 324 patients were randomized at the seven centers. The four groups had approximately equal numbers of patients after randomization: 82 to aqueous budesonide 400 µg daily, 81 to aqueous budesonide 256 µg daily, 79 to the budesonide pMDI and 82 to placebo. Three hundred and eighteen patients entered the treatment period. Patients had to be ≥ 12 years of age and had ≥ 1-year history of ragweed-induced SAR. This diagnosis had to be verified by a positive skin prick test to ragweed extract before the study. Patients using topical nasal steroids and systemic corticosteroids within 1-2 months prior to the study were excluded. Ongoing immunotherapy for ragweed sensitivity was permitted if the maintenance dose was kept constant during the study. Use of proscribed antihistamines, cromones, topical or oral decongestants and vasoconstrictors were also prohibited within several days before enrollment. Baseline demographic measures (age, height, weight, race, gender distribution, disease duration) were similar between the four treatment groups [39:12-3, 24, 42-8].

## PARAMETERS

Symptom evaluation was accomplished through the use of twice daily diary entries made by each patient for the preceding 12-hour period. Symptoms evaluated were blocked nose, runny nose, sneezing and eye symptoms, each on a four-point scale from '0' (no symptoms) to '3' (severe symptoms). Patients also recorded the number of doses of their nasal spray in the diary and any use of rescue medication. At the last visit, patients filled out an overall assessment of treatment efficacy on 5-point scale ranging from '0' (symptoms were aggravated by treatment) to '4' (total symptom control) with '1' indicating 'no control'. Adverse events were elicited by a standard question during the two double-blind study visits, or by spontaneous reporting. In a subset of about half of the patients, urinary cortisol were collected at visits 2 and 3. There was no single, prospectively defined efficacy variable, but rather several had equal primacy. These included combined symptom scores, individual nasal symptom scores (blocked nose, runny nose, sneezing), the patient overall assessment of efficacy and weekly use of terfenadine. Baseline and treatment scores, of various sorts, were determined by an average of the scores at those visits. Along with the multiplicity of primary endpoints, without statistical correction for them, these data were subject to an interim analysis, also without statistical correction for this additional analysis [39:16-9, 22-3]. Therefore, any Type I Error probabilities associated with inferential tests will be artificially

smaller than they would have been had the appropriate corrections been made; i.e., a bias toward finding statistical significance.

## EFFICACY

### Overall Assessment of Treatment Efficacy:

Of the patients in the aqueous budesonide 400 µg daily group, 28.8% rated symptom control as 'total' after three weeks of treatment. The corresponding percentages for the aqueous budesonide 256 µg daily group was 25.0%, for the budesonide pMDI 200 µg BID group was 34.6% and for the placebo group was 2.6%. Each active treatment was statistically significantly different from placebo, but not from one another, although the pMDI produced the most favorable score in this end point, relative to the two other active treatments [39:30-2].

### Combined Nasal Symptoms:

The mean change from baseline showed that each active treatment achieved statistical significance and this change was significantly different from placebo, at both morning and evening rating times. However, no dose proportionality was seen within the two doses of aqueous budesonide. That is, the lower of the two once-daily doses produced the greater decline in the combined nasal symptom score at both morning and evening. There was no significant difference in the magnitude of symptom score change between any of the active treatments, although the budesonide pMDI produced the greatest mean symptom reduction of the three active treatments at both morning and evening [39:32, 48-53]. Evening symptom scores at baseline and changes in them with treatment, were very similar. The evening scores are presented below as representative of both.

DESCRIPTIVE STATISTICS OF EVENING NASAL AND EYE SYMPTOMS DURING RUN-IN AND TREATMENT [39:49-51]							
All Patients Treated (A = Aqua, p = pressurized MDI)		Run-In		Treatment		Difference	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Blocked Nose	Placebo	1.36	0.80	1.34	0.81	0.00	0.56
	Budesonide A 400 µg	1.32	0.72	0.79	0.71	-0.52	0.65
	Budesonide A 256 µg	1.23	0.78	0.57	0.52	-0.66	0.66
	Budesonide p 400 µg	1.24	0.76	0.57	0.56	-0.68	0.73
Runny Nose	Placebo	1.13	0.72	1.20	0.75	0.09	0.58
	Budesonide A 400 µg	1.06	0.77	0.52	0.62	-0.54	0.67
	Budesonide A 256 µg	1.14	0.71	0.51	0.53	-0.63	0.65
	Budesonide p 400 µg	1.13	0.75	0.44	0.48	-0.69	0.69

DESCRIPTIVE STATISTICS OF EVENING NASAL AND EYE SYMPTOMS DURING RUN-IN AND TREATMENT [39:49-51]							
All Patients Treated (A = Aqua, p = pressurized MDI)		Run-In		Treatment		Difference	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Sneezing	Placebo	1.15	0.65	1.04	0.68	-0.10	0.45
	Budesonide A 400 µg	1.14	0.68	0.52	0.56	-0.62	0.56
	Budesonide A 256 µg	1.04	0.73	0.45	0.52	-0.59	0.63
	Budesonide p 400 µg	1.14	0.68	0.45	0.47	-0.69	0.56
Combined Nasal Symptoms	Placebo	3.62	1.84	3.58	1.99	0.00	1.31
	Budesonide A 400 µg	3.52	1.80	1.83	1.58	-1.68	1.64
	Budesonide A 256 µg	3.35	1.97	1.52	1.36	-1.82	1.68
	Budesonide p 400 µg	3.51	1.80	1.46	1.34	-2.05	1.64
Eye Symptoms	Placebo	1.25	0.70	0.96	0.67	-0.28	0.53
	Budesonide A 400 µg	1.14	0.69	0.79	0.68	-0.35	0.53
	Budesonide A 256 µg	1.15	0.78	0.74	0.65	-0.42	0.62
	Budesonide p 400 µg	1.14	0.76	0.76	0.65	-0.38	0.68

**Individual Nasal Symptoms:**

For each of the individual symptoms (blocked nose, runny nose, sneezing), change from baseline was statistically significant and was significantly greater for each of the three active treatments than for placebo; at both morning and evening. As was true for the combined nasal symptom score, there was no evidence for dose proportionality between the two doses of aqueous budesonide. The budesonide pMDI produced consistently greater reductions in each of the three nasal symptoms than did either of the aqueous formulations [39:32-3, 48-53].

**Eye Symptoms:**

The mean change from baseline showed that each treatment achieved statistical significance at both morning and evening, including the placebo group. This change from baseline was significantly greater for each of the three active treatments compared to placebo, at both morning and evening rating times. Though there was no statistical difference between the active treatment groups with regard to this twice-daily measured variable, the aqueous budesonide 256 µg formulation provided the greatest reduction in eye symptoms both in the morning and evening [39:32-4, 48-53].

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**Adverse Events:**

Three hundred and sixteen patients were evaluable for AE's and reported a total of 338 AE's during both baseline and treatment periods. The percentage of patients reporting AE's was greater during treatment than during baseline for all groups including placebo, possibly consistent with the longer duration of the treatment period. All three active budesonide treatment groups had a greater percentage of patients reporting AE's during treatment compared with placebo. The AE's listed below are those that occurred in > 1% of a treatment group and occurred more frequently in at least one of the active treatment groups than in the placebo group: respiratory infection; pharyngitis; coughing; fatigue; pain; and, epistaxis [39:63-6].

**Serious Adverse Events:**

One AE was classified as serious and was a traumatic wrist fracture in a 15-year old male after three weeks of treatment [39:35-6]

**Discontinuation Due to Adverse Events:**

This category includes four patients, two from the aqueous budesonide 400 µg daily group (nausea, facial rash) , one from the aqueous budesonide 256 µg daily group (sore throat) and one from the placebo arm (facial rash) [39:36-7].

**Nasal Examination:**

Rhinoscopic examinations at visits 1 and 3 showed no findings of candida infections. Of five clinical abnormalities and structural defects, only 'hypertrophy of the conchae' showed shifts to greater degrees of abnormality between visits 1 and 3 with the active treatments, compared to placebo. [39:34, 54-8]

**Urine Cortisols:**

Twenty-four hour urine cortisols were obtained from about half of the patients in the protocol. They were analyzed as raw values and as adjusted ratios with 24-hour urine creatinines. The mean change from baseline of the 24-hour urine cortisol showed an increase in the placebo group and a decline in two of the three budesonide groups between the second and third visit (over the three-week, double-blind period). The 24-hour urine cortisol adjusted for creatinine excretion showed little difference between the active treatments and placebo. These are shown in the table below [39:35, 59-61].

24-HOUR URINE CORTISOL & CREATINE ADJUSTMENT OF THEM OVER THE THREE-WEEK TREATMENT PERIOD [39:60-1]							
All Patients Treated		Run-In		Treatment		Difference	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Urine Cortisol (nmol/24h)	Aqua 400 µg QAM	122.7	52.0	124.4	100.3	1.6	84.8

24-HOUR URINE CORTISOL & CREATINE ADJUSTMENT OF THEM OVER THE THREE-WEEK TREATMENT PERIOD [39:60-1]							
All Patients Treated		Run-In		Treatment		Difference	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
	Aqua 256 µg QAM	144.3	72.7	134.0	69.8	-16.6	68.3
	pMDI 200 µg BID	161.9	157.9	123.8	64.9	-41.6	135.6
	Placebo	138.8	78.8	146.4	68.9	8.0	63.5
Urine Creatinine (mmol/24h)	Aqua 400 µg QAM	10.9	4.4	11.7	4.5	0.8	3.2
	Aqua 256 µg QAM	12.3	5.3	14.2	6.1	1.3	4.8
	pMDI 200 µg BID	11.2	4.0	11.5	3.6	0.3	3.3
	Placebo	10.4	4.2	12.0	3.6	1.6	3.9
Adjusted Urine Cortisol (nmol Cortisol per mmol Creatinine)	Aqua 400 µg QAM	12.0	4.6	10.8	6.9	-1.3	6.8
	Aqua 256 µg QAM	12.8	8.5	9.6	3.8	-3.2	8.4
	pMDI 200 µg BID	13.6	7.5	10.9	5.4	-2.9	8.6
	Placebo	15.5	16.3	12.2	4.6	-3.5	17.4

The 'mean difference' is taken from differences in two measures in each individual, and averaged over all individuals. It is normally identical to the 'difference between means' unless drop outs occur, which was the case in the table above and explains why 'run-in mean' minus 'treatment mean' does not equal 'difference mean' in most of the rows.

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**05-3011 A DOUBLE BLIND COMPARISON OF RHINOCORT® AQUA (BUDESONIDE), BECOTIDE® NASAL (BECLOMETHASONE DIPROPIONATE) AND PLACEBO IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS**

**SUMMARY**

This was a blinded, randomized, parallel-group, placebo-controlled trial carried out at five centers in Norway that enrolled 236 patients  $\geq 18$  years of age with birch pollen seasonal allergic rhinitis (SAR) over a three-week treatment period. It compared 256  $\mu\text{g}$  of budesonide nasal spray, given once daily in the morning, with an identical-appearing placebo and a single-blinded positive control, 400  $\mu\text{g}/\text{day}$  of beclomethasone nasal spray administered twice daily. The beclomethasone formulation was unapproved for the U.S. market. Several co-primary efficacy variables were analyzed without correction for multiple endpoints. Nasal symptom scores, individual and combined, and the overall assessment of treatment efficacy all showed changes from baseline that were significantly different from placebo for both active treatments. Comparisons between active treatments did not approach significance for any endpoint. Twenty-four hour urine cortisol, adjusted for creatinine excretion, showed a decline over the treatment period for both active treatments and an increase for placebo. The greatest decline between run-in and treatment periods in urine cortisol concentration, 24-hour urine cortisol and 24-hour urine cortisol/creatinine ratio was in the budesonide group.

**OBJECTIVE**

The purpose of this study was a comparison of the relative effects of budesonide aqueous nasal spray (256  $\mu\text{g}$  once daily), beclomethasone dipropionate aqueous nasal spray (200  $\mu\text{g}$  twice daily = 400  $\mu\text{g}$  daily) and placebo in patients with birch pollen induced SAR. A secondary objective was to determine the systemic effects of the steroid formulations in relation to placebo, measured as 24-hour urinary cortisol excretion in a subset of patients [43:1, 144].

**PROTOCOL**

This was a randomized, parallel-group, placebo-controlled trial carried out at five centers in Norway. It was double-blind with respect to budesonide and placebo and single-blind for beclomethasone and budesonide or placebo. Patients with birch pollen induced allergic rhinitis were randomized to into three groups of equal size to be treated with budesonide, beclomethasone or placebo. There was a 1-2 week baseline period and all patients began the blinded portion of the study within the first week (3 days  $\pm$  4 days) of the birch pollen season. During the 3-week treatment period, subjects recorded nasal and ocular symptom severity daily. Twenty-four hour urinary cortisol and creatinine were measured before and after the treatment period in half of the patients [43:1, 134-5].

SAR STUDY 3011 – PROCEDURE FLOW DIAGRAM [43:135]			
Procedure	Visit (End of Week)		
	1 (0)	2 (1)	3 (4)
History & Randomization	X		
Rhinoscropy	X	X	X
Patient Diary	X	X	X
Adverse Events		X	X
Patient Assessment			X
Urine Sampling		X	X

### TREATMENT

The investigational drugs were aqueous suspensions in glass bottles fitted with mechanical spray pumps and each bottle contained approximately 200 doses. Active and placebo budesonide were in 10 mL bottles of identical appearance. Active drug bottles contained 1.28 mg budesonide/mL and each actuation delivered 50  $\mu$ L or 64  $\mu$ g of budesonide. This was administered as two sprays in each nostril once daily in the morning. Beclomethasone was in a container that was different in appearance from the budesonide and placebo. Each actuation of the spray delivered 50  $\mu$ g of beclomethasone and this was given as two sprays in each nostril twice daily in the morning and evening. Terfenadine [redacted] was supplied as 60 mg tablets with instructions to take 1-2 tablets daily if nasal symptoms became intolerable. [redacted] eye drops were supplied as single dose pipettes and instructions were to use 1-2 drops in each eye four times daily for intolerable symptoms. These rescue medications, terfenadine and cromolyn, were also offered during the baseline period [43:32, 138, 140].

### PATIENTS

Two hundred thirty-six patients were treated at five centers. Three patients discontinued prematurely during the baseline run-in period (urticaria, whiplash injury, GI discomfort), leaving 233 approximately evenly divided into the three groups; budesonide (78), beclomethasone (77) and placebo (78). The treatment groups were all comparable in terms of gender, age, height, weight and duration of allergic rhinitis. All patients were Caucasians. All patients were older than 17 years of age and had a history of birch pollen induced allergic rhinitis, verified by skin test. Exclusion criteria were: hypersensitivity to the treatment or rescue medications; pregnant or lactating women; patients with untreated mycobacterial, fungal, viral or bacterial infection; asthma requiring treatment with inhaled steroids unless banned from cortisol testing portion of the protocol; systemic steroids within two months; topical nasal steroids within one month; current immunotherapy unless constant throughout the study; antihistamines (except for rescue terfenadine); intranasal cromoglycate; topical/oral decongestants or vasoconstrictors within three days; or, abnormalities or diseases of the nose that might hinder this comparative study [43:25, 38, 137].

## PARAMETERS

Efficacy was assessed by the daily, morning, subjective scoring of nasal symptoms (blocked nose, runny nose, sneezing) over the prior 24 hours which was kept in a diary. Each of these symptoms was rated on a four-point scale ranging from 'no symptoms' (= 0) to 'severe symptoms that interfered with normal sleep or daily activities' (= 3). This study was estimated to have an 80% power to detect a treatment difference of 0.33 in individual symptom scores with a standard deviation of 0.7; two-tailed  $\alpha = 0.05$  as analyzed by ANOVA on ranks. The number of antihistamine tablets used in the same 24-hour period was also recorded in the diary. At the last clinic visit, the patient was asked to evaluate the ability of the test medication to control nasal symptoms according to a five-point scale ranging from 'symptoms aggravated' (= 0) and 'no control over symptoms' (= 1) to 'total control over symptoms' (= 4). Safety was assessed by: rhinoscopy at each visit; analysis of 24-hour urine cortisol at visits 2 & 3; and, adverse events reported in response to a standard question asked at each visit [43:32-6].

## EFFICACY

Pollen counts, expressed as pollen densities, in the city of Oslo were reported between 21 April and 26 May 1992 and showed that these were mostly zero during the run-in period and present during the treatment interval. A simultaneous plot of combined nasal symptom scores showed only the most general of relationships to daily pollen counts. That is, the placebo group reported more symptoms during the treatment period than during the run-in, but there was no immediate and daily association with pollen counts [43:52]. All three treatment groups consumed more terfenadine tablets during the treatment period than during the run-in but the increase was greatest for the placebo group, so antihistamine use did not account for a finding of efficacy of active treatments compared with placebo [43:41]. There were several co-primary efficacy-variables in this protocol and no mention of any multiple endpoint correction of inferential testing. Identified as co-primary were the three nasal symptom scores and the patient's assessments of the study drug's ability to control symptoms [43:150]. The study report subsequently identified an additional variable as co-primary, the combined nasal symptom score, but this appears to have been retrospectively defined [43:36].

### Individual Symptoms:

The mean patient scores of the symptom severity were calculated over the 1-2-week baseline and the 3-week treatment periods. The following table presents the means and standard deviations for the individual nasal symptoms, combined nasal symptoms and eye symptoms. It is recognized that describing ordinal scale data with arithmetic means and standard deviations assumes an information content that the data demonstrably do not possess and it is with this caveat that the following information is presented [43:46, 50].

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DESCRIPTIVE STATISTICS OF MORNING NASAL AND EYE SYMPTOMS DURING RUN-IN AND TREATMENT [43:46, 50]							
All Patients Treated		Run-In		Treatment		Difference	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Blocked Nose	Placebo	0.90	0.74	1.34	0.70	0.44	0.58
	Budesonide	0.80	0.75	0.73	0.71	-0.07	0.53
	Beclomethasone	0.79	0.60	0.75	0.62	-0.05	0.59
Sneezing	Placebo	0.52	0.56	0.97	0.61	0.44	0.56
	Budesonide	0.42	0.45	0.40	0.43	-0.02	0.44
	Beclomethasone	0.45	0.51	0.45	0.49	-0.01	0.47
Runny Nose	Placebo	0.61	0.60	0.88	0.68	0.26	0.61
	Budesonide	0.42	0.59	0.45	0.54	0.03	0.46
	Beclomethasone	0.47	0.59	0.45	0.53	-0.03	0.51
Combined Nasal Symptoms	Placebo	2.03	1.60	3.19	1.77	1.14	1.52
	Budesonide	1.64	1.56	1.58	1.41	-0.07	1.22
	Beclomethasone	1.72	1.43	1.64	1.37	-0.09	1.27
Eye Symptoms	Placebo	0.51	0.59	1.03	0.70	0.51	0.53
	Budesonide	0.36	0.41	0.75	0.61	0.39	0.51
	Beclomethasone	0.40	0.58	0.72	0.64	0.32	0.59

A comparison of changes from baseline scores showed statistically significant differences between the each active treatment group and placebo for all individual nasal symptoms, without correction for multiple tests. The retrospectively defined endpoint, combined nasal symptoms, also showed significant differences between both active treatments and placebo. The endpoint eye symptoms, increased from baseline in all groups, showing the least beneficial effect of either active treatment over placebo for this symptom score measure. Eye symptoms also showed a significant difference from placebo for beclomethasone, but not for budesonide. Comparisons between the active groups did not approach statistical significance for any endpoint.[43:50-1].

**Overall Assessment of Treatment Efficacy:**

This was the result of a single, five-point ordinal scale score contributed by each patient at visit 3, the end of the study. As was the case with the individual nasal symptoms, statistical significance was shown for each active treatment compared to placebo but not between active treatments [43:45]

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## SAFETY

### Adverse Events:

Of the 233 patients who entered the blinded treatment period, 61 patients reported a total of 73 AE's. The break down by group of both patients and reported numbers of AE's was similar for all groups: budesonide (23 patients, 25 AE's); beclomethasone (18 patients, 25 AE's); and, placebo (20 patients, 23 AE's) [43:63].

### Serious Adverse Events:

Two AE's were categorized as serious. A 29 year old male suffered head trauma during a football game resulting in nausea and headaches for the following 24 hours. This occurred during the run-in period. A 45 year old female had a chronic tongue ulcer before entry into the trial that was later diagnosed as cancer with local symptoms of mild to moderate intensity [43:61].

### Discontinuation Due to Adverse Events:

A 57 year old female discontinued the study after 16 days of treatment because of nasal soreness which normalized completely 9 days after termination. She had received budesonide [43:62].

### Nasal Examination:

Nasal examination with rhinoscopy were done at all clinic visits, one through three. Ten different examination elements were rated on a four-point scale (0-3) of 'none,' 'mild,' 'moderate' and 'severe.' Inspection of these tables of results fails to show any element that is worse in either active treatment group than placebo, or worsens over the course of the double-blind treatment more than placebo. No findings consistent with Candida infection were reported at any of the three visits [43:53-8].

### Urine Cortisols:

Twenty-four hour urine samples were collected at visits 2 and 3 and analyzed for cortisol and creatinine. The 24-hour total urine cortisol declined over the course of the double-blind treatment for all three groups, but beclomethasone and placebo groups exhibited about the same degree of decrease, which was half of the decrease in the budesonide group. When the total 24-hour urine cortisol was adjusted for muscle mass, by the total 24-hour urine cortisol/creatinine ratio, both active treatments showed a decline over the treatment period, while the placebo group showed an increase. The largest decline over the treatment period for every measure of urine cortisol (concentration, total amount/24-hours and cortisol/creatinine total amount per 24-hours ratio) was seen in the budesonide group. Inferential tests were applied to these measures and only the urine cortisol concentration was found to exhibit a statistically significant decline after treatment with both active drugs compared to an increase with placebo. As has been noted before, analyses of these safety endpoints were not prospectively defined nor was the study powered to find a difference between them, so the meaning of statistical significance, or its absence, is not really applicable [43:59-61].

24-HOUR URINE CORTISOL & CREATINE VALUES OVER THE TREATMENT PERIOD [43:59, 61]							
All Patients Treated		Run-In		Treatment		Difference	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Urine Cortisol Concentration (nmol/L)	Placebo	55.5	44.9	71.4	55.5	15.82	55.13
	Budesonide	53.8	42.8	44.8	27.2	-8.95	30.56
	Beclomethasone	56.8	36.6	53.3	28.6	-3.51	29.53
Urine Cortisol (nmol/24h)	Placebo	65.1	59.3	61.8	31.9	-3.34	61.70
	Budesonide	53.9	35.6	42.9	25.8	-10.93	25.07
	Beclomethasone	59.8	26.6	55.1	29.0	-4.66	24.98
Urine Creatinine (mmol/24h)	Placebo	11.9	3.3	12.1	4.6	0.18	4.20
	Budesonide	12.1	4.4	11.1	3.7	-0.92	3.84
	Beclomethasone	11.9	4.4	11.7	3.4	-0.20	3.90
Adjusted Urine Cortisol (nmol Cortisol per mmol Creatinine)	Placebo	5.3	3.6	5.7	3.9	0.34	3.05
	Budesonide	4.5	2.8	3.8	1.8	-0.76	2.07
	Beclomethasone	5.4	2.8	4.9	2.8	-0.53	2.76

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**05-3030** A PLACEBO-CONTROLLED STUDY COMPARING RHINOCORT®  
AQUA (BUDESONIDE) WITH FLIXONASE® (FLUTICASONE  
PROPIONATE) IN PATIENTS WITH SEASONAL ALLERGIC RHINITIS

**SUMMARY**

This was a two-center, European, randomized, parallel-group study that compared two once-daily doses of budesonide to placebo given in a 4-week double-blind design. Both doses provided greater reduction in nasal symptom scores than did placebo, but there was no evidence of dose proportionality. Once-daily nasal fluticasone was given to another treatment group in a single-blind fashion and it too resulted in a greater reduction in nasal symptoms than did placebo, and of about the same magnitude as provided by either dose of budesonide. This effect was not attributable to increased use of rescue medication in the active treatment arms, which used less rescue antihistamine than did the placebo group. A post-hoc analysis of onset of action on nasal symptoms was attempted and showed virtually no effect on combined nasal symptom scores until an evaluation at 26-36 hours. At this time point, the combined nasal symptom score change from baseline was only about 40% of the mean change for the entire treatment period. Both doses of budesonide were associated with more adverse events than placebo or fluticasone and these adverse events consisted mostly of respiratory symptoms, most commonly 'asthma aggravated.'

**OBJECTIVE**

The purpose was to compare the safety and efficacy of two doses of an aqueous suspension of budesonide (128 or 256 µg daily) with that of fluticasone propionate nasal spray (200 µg daily) and placebo given once daily for the treatment of Seasonal Allergic Rhinitis (SAR) [46:1, 14].

**PROTOCOL**

This was a randomized, parallel-group, four-week study carried out in two centers, one in the U.K. and one in Denmark. The study was double-blind with respect to budesonide and placebo, but only single-blind, with respect to fluticasone. A one-week baseline period was followed by a four-week treatment period, which could be extended to six weeks if the daily-measured pollen peak occurred later than usual. The study consisted of five visits; screening, baseline, randomization (0th week), after 2 weeks of treatment and after 4-6 weeks of treatment [46:14-5].

**TREATMENT**

Each bottle of budesonide nasal spray delivered 64 µg per actuation, contained 200 actuations and delivered a daily dose of either 128 µg or 256 µg once daily, divided between the two nostrils. Each bottle of fluticasone propionate nasal spray delivered 50 µg per actuation, contained 120 actuations and delivered a daily dose of 200 µg once daily, divided between the two nostrils. Each morning, patients were to administer one spray in each nostril from bottle 'A' and one spray in each nostril from bottle 'B'. Rescue medication consisted

of terfenadine (60 mg) and cromolyn sodium eye drops (20 mg/mL) which were taken, as needed, during the baseline and treatment periods [46:19].

## PATIENTS

A total of 635 patients were randomized: 64 to placebo; 190 to budesonide 128 µg; 191 to budesonide 256 µg; and, 190 to fluticasone 200 µg. Patients had to be ≥ 18 years of age and had ≥ 1-year history of grass-pollen induced SAR. This diagnosis had to be verified by a skin prick test or RAST < 2 years before the study. Patients using topical nasal steroids, systemic corticosteroids and immunotherapy within 1-2 months prior to the study were excluded. Baseline demographic measures (age, gender distribution, disease duration) were similar between the four treatment groups [46:16, 29].

## PARAMETERS

Symptom evaluation was accomplished through the use of a daily diary kept by each patient. Every evening, patients scored individual symptoms experienced in the preceding 24-hour period. Symptoms evaluated were blocked nose, runny nose, sneezing and eye symptoms, each on a four-point scale from '0' (no symptoms) to '3' (severe symptoms). Patients also recorded the number of doses of their nasal spray in the diary and any use of rescue medication. At the last visit, patients filled out an overall assessment of treatment efficacy on 5-point scale ranging from '0' (symptoms were aggravated by treatment) to '4' (total symptom control) with '1' indicating 'no control'. Adverse events were elicited by a standard question during the two double-blind study visits, or by spontaneous reporting. There was no single, prospectively defined efficacy variable, but rather several had equal primacy. These included combined symptom scores, individual nasal symptom scores (blocked nose, runny nose, sneezing) and the patient overall assessment of efficacy. Comparisons were based on patients who had received at least one dose of the treatment medication. Baseline and treatment scores, of various sorts, were determined by an average of all such scores in that period provided by each patient [46:21-3, 26].

## EFFICACY

### Combined Nasal Symptoms:

The mean change from baseline showed that each active treatment was statistically significantly different from placebo, in terms of symptom reduction from baseline, but no correction for multiple tests of significance was made. No dose proportionality was seen between the two doses of budesonide, nor was there any significant difference in the magnitude of symptom score change from baseline between any of the active treatments [46:32, 52-4].

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DESCRIPTIVE STATISTICS OF EVENING NASAL AND EYE SYMPTOMS DURING RUN-IN AND TREATMENT [46:52-3]							
All Patients Treated		Run-in		Treatment		Difference	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Blocked Nose	Placebo	0.80	0.83	1.06	0.71	0.26	0.64
	Budesonide 128 µg	0.85	0.69	0.49	0.48	-0.35	0.62
	Budesonide 256 µg	0.77	0.67	0.45	0.52	-0.33	0.51
	Fluticasone 200 µg	0.80	0.71	0.51	0.52	-0.28	0.63
Runny Nose	Placebo	1.02	0.86	1.48	0.67	0.46	0.74
	Budesonide 128 µg	1.05	0.70	0.58	0.46	-0.47	0.68
	Budesonide 256 µg	0.92	0.66	0.46	0.49	-0.46	0.59
	Fluticasone 200 µg	1.01	0.76	0.58	0.53	-0.44	0.74
Sneezing	Placebo	1.03	0.66	1.33	0.61	0.31	0.67
	Budesonide 128 µg	1.09	0.67	0.61	0.46	-0.48	0.63
	Budesonide 256 µg	1.04	0.62	0.51	0.47	-0.54	0.57
	Fluticasone 200 µg	1.05	0.68	0.60	0.48	-0.45	0.63
Combined Nasal Symptoms	Placebo	2.84	2.09	3.87	1.77	1.02	1.82
	Budesonide 128 µg	2.97	1.70	1.68	1.20	-1.29	1.68
	Budesonide 256 µg	2.73	1.64	1.42	1.31	-1.31	1.44
	Fluticasone 200 µg	2.86	1.82	1.68	1.37	-1.18	1.76
Eye Symptoms	Placebo	0.84	0.72	1.10	0.56	0.25	0.63
	Budesonide 128 µg	0.94	0.69	0.92	0.60	-0.02	0.60
	Budesonide 256 µg	0.90	0.65	0.83	0.60	-0.06	0.55
	Fluticasone 200 µg	0.88	0.64	0.87	0.58	0.00	0.63

A post-hoc analysis was performed to determine the onset of action of the two active doses of budesonide compared with placebo. The onset of action was assessed from the diary data reporting the first three time points after the first dose. These three corresponded roughly to 2-12 hours, 26-36 hours and 50-60 hours after the first dose and were analyzed separately. No diary data were available in between these three time intervals. There was no difference in symptom score change from baseline between placebo and either of the budesonide groups at the earliest evaluation interval, 2-12 hours after treatment. Statistical significance was found in the symptom score change for both budesonide doses at the latest two time intervals [46:5-7]. However, probabilities derived from a prospective inferential ANOVA model have no known applicability to post-hoc analyses, so the meaning of this finding of 'statistical significance' is not defined. Perhaps a more representative reference is

that the point estimate of the combined symptom score change for the 26-36 hour interval was less than half of the mean change from baseline for the treatment period as a whole. Even at the latest post-hoc interval, 50-60 hours after treatment, the combined symptom score change was only about 70% of the point estimate for the entire treatment period, indicating that the maximum symptom score change had not been achieved [46:7, 52].

#### Individual Nasal Symptoms:

The findings for individual nasal symptoms paralleled those of the combined nasal symptom endpoint. Each treatment was statistically significantly superior to placebo for each of the three nasal symptoms in the change-from-baseline endpoint. In addition, budesonide 256 µg daily was statistically superior to fluticasone 200 µg daily for the symptom, 'sneezing,' although there was no correction for the multiple comparisons that were made [46:33, 53-4].

#### Overall Assessment of Treatment Efficacy:

As was true of the last two efficacy endpoints, there were statistically significant differences between the active treatment groups and the placebo group, but no significant differences between the active groups [46:33, 55].

#### Other Therapy:

The weekly use of eye drops increased from baseline in all groups, but exhaustive two-group comparisons showed no significant differences in change from baseline between any two treatments. The weekly consumption of antihistamines showed a reduction of about 50% in the three active treatment groups, while the placebo patients nearly doubled their consumption. With respect to change from baseline, there was a statistically significant difference between placebo the active groups but no difference between active treatment groups. There was also no evidence of dose proportionality between the two budesonide doses [46:30, 50-1].

## SAFETY

#### Adverse Events:

Of the 601 evaluable patients, 201 (33%) reported 268 AE's during the study, including the baseline period. Fifty-eight patients (32%) treated with budesonide 128 µg daily reported 77 AE's and 62 patients (34%) treated with budesonide 256 µg daily reported 82 AE's. The proportion of patients reporting AE's and the total number of AE's that they reported were very similar for the two budesonide doses and higher than either number of patients reporting AE's or the total number of AE's reported for either fluticasone or placebo groups. Forty-three (24%) of patients receiving fluticasone reported 58 AE's. In the placebo group, 15 patients (25%) reported 20 AE's. Both doses of budesonide were associated with more adverse events than placebo or fluticasone and these adverse events consisted mostly of respiratory symptoms, the most common of which was 'asthma aggravated.' No ready explanation for this finding is apparent [46:39-41, 65-74].

**Serious Adverse Events:**

Three of these were reported: 1) 37-year old male was found to have a basal cell skin carcinoma on screening prior to taking any study medication; 2) 25-year old female 13 days into the double-blind period reported nausea and abdominal pain extending to the kidney area which resolved four days after beginning antibiotic treatment for pyelonephritis; and, 3) 42-year old male was found to have a carcinoma of the tongue during screening and prior to taking any study medication [46:37-8].

**Discontinuation Due to Adverse Events:**

Six patients discontinued the study during the treatment period because of adverse events. There was one in each of the budesonide groups, three in the fluticasone group and one in the placebo group. There were no AE's that were common to any group or to each other. The AE's included pyelonephritis, toothache, epistaxis, sinusitis, asthma and headache. [46:38-9].

**Nasal Examination:**

No patient showed any evidence of a candida infection. There were only a few cases of clinically relevant abnormal findings and no differences between groups [46:37, 57-64].

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**05-3012 A PLACEBO CONTROLLED DOSE COMPARATIVE STUDY OF  
RHINOCORT® AQUA IN PATIENTS WITH PERENNIAL RHINITIS --  
A MULTICENTER STUDY**

**SUMMARY**

The intent was to demonstrate equal efficacy in perennial allergic rhinitis (PAR) for two doses of aqueous budesonide that have been studied in pivotal trials and are well up on the asymptote of the dose response curve. The sponsor did not demonstrate any difference in efficacy for doses from 32 µg to 256 µg once daily in the pivotal trials, rendering this comparison of the highest of these doses with an even higher dose as uninteresting. This was also a study of adults without any testing of hypothalamic-pituitary-adrenal axis function that offered no new safety information. Beyond a description of the trial, no formal efficacy review of it was performed.

**OBJECTIVE**

This protocol was designed to compare the relative efficacy of an intranasal aqueous suspension of budesonide administered twice daily at two doses (256 µg/day and 400 µg/day) with placebo in the treatment of PAR, as evaluated by various symptom scores. Previous trials in seasonal allergic rhinitis showed no statistical difference between the total daily administration of 256 µg or 400 µg of aqueous budesonide. This study was designed to test a twice daily regimen in adults with a related condition, PAR, at these two doses [74:9].

**PROTOCOL**

This was a seven-center, Canadian, randomized, double-blind, placebo-controlled, parallel-group study. It began with a two-week baseline period and was followed by a six-week treatment period. Patients returned for clinic visits after three and six weeks of treatment [74:10].

**TREATMENT**

The lower dose budesonide group self-administered 256 µg/day as one spray (64 µg in each spray) in each nostril in the morning and evening. The higher dose budesonide group self-administered 400 µg/day as one spray (100 µg in each spray) in each nostril in the morning and evening. Rescue medication for nasal symptoms was loratadine 10 mg and the maximal dose was two tablets daily. [redacted] and Vasocon® A (naphazoline hydrochloride + antazoline phosphate) were supplied as rescue eye drops [74:13, 15].

**PATIENTS**

Adults, 18 years of age or older, with at least a one-year history of PAR and with at least minimal nasal symptoms were recruited. Two hundred thirty-nine patients were enrolled and 26 discontinued the study during the treatment period. The 213 patients completing the trial were fairly evenly distributed among the treatment groups: 66 in the budesonide 256 µg/day group; 73 in the budesonide 400 µg/day group; and, 74 in the placebo arm [74:24, 28].

## PARAMETERS

Several co-primary efficacy variables were studied: change in the mean individual symptoms as well as the combined nasal symptom score and the overall assessment of treatment efficacy. These were examined over the 2-week baseline and the two 3-week treatment periods, covering the first and last 3 weeks of the 6-week treatment period. Individual nasal symptoms consisted of blocked nose, runny nose and sneezing. No apparent statistical correction was made for the multiple endpoints that were analyzed. Comparison of groups was based on change from baseline of these various measures. Weekly use of rescue antihistamines and eye drops were also analyzed. Safety assessment was primarily by AE's elicited by a standard question at the study visits [74:19, 22].

APPEARS THIS WAY  
ON ORIGINAL

**05-3024** A PLACEBO CONTROLLED COMPARATIVE STUDY OF  
BUDESONIDE (RHINOCORT® AQUA) AND AZELASTINE  
(RHINOLAST®) IN THE TREATMENT OF PERENNIAL ALLERGIC  
RHINITIS

**SUMMARY**

Azelastine (Astelin®) was FDA-approved in November '96 for symptomatic use in seasonal allergic rhinitis [REDACTED] [COMIS data base]. It is a 0.1% aqueous solution and each spray delivers 137 µg of the hydrochloride, equivalent to 125 µg of the base. The single recommended dose is two sprays in each nostril twice daily, which is the same as that of the unapproved active control [REDACTED] used in this study. The comparison of azelastine intranasal to budesonide is not particularly germane to any approval or promotional purposes in the U.S. An unapproved formulation [REDACTED] was used to treat an unapproved indication (perennial allergic rhinitis = PAR). No special populations, safety or efficacy end points were investigated in this trial. Beyond a description of the trial, no formal efficacy review of it was performed.

**OBJECTIVE**

This study was designed to investigate the efficacy of budesonide 256 µg intranasal given once daily and azelastine 280 µg intranasal given twice daily, compared to placebo in the treatment of perennial allergic rhinitis [80:13].

**PROTOCOL**

This was a four-center, United Kingdom, randomized, blinded, parallel-group placebo-controlled study. It was double-blind with respect to budesonide and the identically packaged placebo. It was single (investigator) blind with respect to the dissimilar appearing azelastine. Patients entered the study before the start of the actual treatment in order to record their nasal symptoms during a two-week run-in period. Treatment began after the run-in period and lasted for six weeks. Patients returned at weeks three and six for clinic visits [80:14].

**TREATMENT**

The budesonide (Rhinocort Aqua) group, self-administered 256 µg/day as two sprays (64 µg each spray) in each nostril in the morning. The azelastine [REDACTED] group received 560 µg/day, given as one spray (140 µg in each spray) in each nostril in the morning and in the evening. During the run-in and treatment periods, terfenadine [REDACTED] mg was used. The maximum daily dose was two tablets, as required to manage rhinitis symptoms [80:19].

**PATIENTS**

Adults, 18 years of age or older, with at least a two-year history of PAR and with at least minimal nasal symptoms were recruited. A total of 145 patients finished the study: 46 in the azelastine group, 50 in the budesonide group and 49 in the placebo group [80:1, 15-17].

## PARAMETERS

Several co-primary efficacy variables were studied: change in the mean individual symptoms as well as the combined nasal symptom score and the global assessment of efficacy at weeks three and six were all tested for, without apparent correction for multiple end points. Individual symptoms consisted of three nasal symptoms (blocked nose, runny nose and sneezing) and eye symptoms. Each separate symptom was rated on a scale of '0-3', from no symptoms to severe symptoms, sufficient to interfere with normal daily activity or sleep. The global assessment of treatment efficacy was a five-point scale rating obtained only at weeks three and six; without a baseline measure. A secondary efficacy variable was the weekly rescue medication use. Safety assessment was primarily AE's elicited by a standard question at the study visits [80:21, 23, 26].

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## INTEGRATED SAFETY SUMMARY

### SUMMARY

Rhinocort was associated with only slightly more adverse events (AE's) than controls and the more frequent AE's were related to local respiratory tract symptoms. Local irritation and epistaxis were prominent early and nasal septum perforation first appeared in post-marketing surveillance. Epistaxis report frequency increased with patient age. Slowing of growth was shown in pre-pubertal children both relative to healthy normals and to perennial allergic rhinitis patients treated with cromolyn. Systemic corticosteroid effects were suggested by reductions in peripheral eosinophil counts and in 24-hour urine cortisol from baseline. Both of these effects persisted for at least two years. Neither morning cortisol nor Cortrosyn-stimulation testing revealed any evidence of adrenal suppression.

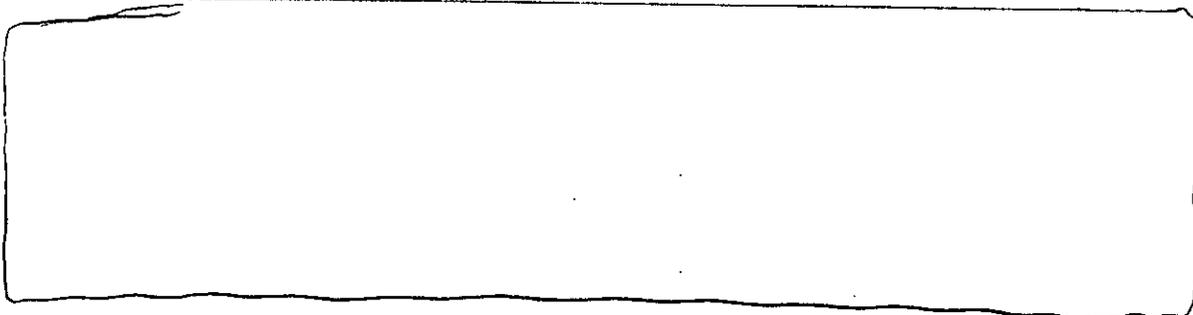
The AE data base consisted of over 8000 patients internationally, the youngest of which was two years of age. Of these, about 3300 received Rhinocort formulations in doses of 32 to 800  $\mu\text{g}$  per day. The exposure ranged in duration from a single dose to 60 months of treatment, but the majority of patients were treated from 3 to 6 weeks.

Seven trials provided safety data on over 2400 patients for comparison of Rhinocort Aqua with placebo, and about one fifth of these were treated with placebo. Overall, AE's were only very slightly more common with Rhinocort Aqua than placebo. AE's in which the frequency was greater in Rhinocort Aqua than placebo arms, were uniquely manifestations of upper or lower airway symptoms. The frequency of 'nasal irritation' was stable or increased with increasing Rhinocort Aqua doses. 'Epistaxis' was more frequent with all doses of Rhinocort Aqua than placebo, and the frequency increased with categorical patient age. 'Epistaxis' also showed dose proportionality, when measured by the frequency of early terminations due to AE's.

Over 5900 patients were enrolled in supportive studies of four formulations of budesonide; the pressurized metered dose inhaler, dry powder inhaler, aqueous spray or Tween-stabilized aqueous solution. Two deaths were encountered, but neither was reasonably attributable to use of an intranasal steroid. Early terminations due to AE's reflecting local nasal symptoms were more common with budesonide formulations than with placebo or positive controls.

Single-dose trials in healthy volunteers had shown a large suppression of urinary cortisol excretion by various intranasal steroids. The same formulations when given for one week caused relatively less urinary cortisol suppression, leaving open the question of hypothalamic-pituitary-adrenal axis effects with long-term use of these products. A related question was the effect on growth, especially in pre-pubertal children. These topics were addressed in two studies.

A Swedish study of children five to fifteen years of age with perennial allergic rhinitis provided follow up for one, two and five years. They were treated with the pressurized metered dose inhaler or the Aqua spray at various doses at various times in the trial. Small but consistent decreases in the mean eosinophil count from study entry over two years of follow-up suggested the possibility of a corticosteroid effect. No control group was available for comparison so heights were compared to predicted heights for age and sex. These showed relative slowing of growth, over one, two and five years. The trial design did not permit attribution of this effect to the disease or to the treatment. Twenty-four hour urine cortisol showed mean reductions from baseline at all but the longest exposure duration, but neither basal morning serum cortisol nor Cortrosyn-stimulated serum cortisol showed any systematic changes during any follow-up period.



Post-marketing surveillance again reported the localization of AE's to the respiratory tract. Nasal irritation and epistaxis were prominently reported. Somewhat unexpected was the relatively large number of reports of nasal septum perforation, perhaps a consequence of more prolonged follow up of the nasal irritation reported in earlier trials.

#### EXPOSURE

The overall exposure to Rhinocort was taken from an analysis of AE data from approximately 8000 patients from 66 completed and [redacted] The primary focus of these studies was on the aqueous suspension and dry powder formulations of intranasal budesonide. Detailed analyses of AE rates in the active treatment group compared with placebo were performed on data compiled from seven primary studies of Rhinocort Aqua in patients with seasonal or perennial allergic rhinitis. Two of these seven were carried out in the US and five were non-US studies. Supportive safety analyses were also done on 59 completed and [redacted] supportive clinical trials. Data from the 76 clinical trials are presented in the following table.

SAFETY DATA, STUDIES AND PATIENTS BY TYPE OF STUDY: ALL TREATMENT GROUPS [111:11, 16]						
Study Type		Number Studies	Number Subjects	Deaths	Serious AE's	D/C due to AE
Primary		7	2471	0	4	65
Completed Supportive	U.S.	2	127	1	18	93
	non-U.S.	57	4040			



The duration of exposure in these seven studies was from one to six weeks and the median duration for each treatment was about 22 days [111:25].

**Adverse Events:**

AE's with a frequency of  $\geq 1\%$  in the Rhinocort Aqua group are listed in the following table by preferred term and body system with the frequency in the placebo group listed for comparison. The denominators for the percentages were 538 placebo patients and 1526 Rhinocort Aqua patients [111:28, 112:98-110].

AE FREQUENCY $\geq 1\%$ IN RHINOCORT OR PLACEBO GROUPS, BY SYSTEM AND PREFERRED TERM [111:28, 112:98-110]			
Body System	Preferred Term	Placebo n (%)	Rhinocort Aqua n (%)
All Systems	Any AE	208 (39)	629 (41)
Respiratory	Respiratory Infection	52 (10)	123 (8)
	Pharyngitis	16 (3)	62 (4)
	Coughing	5 (<1)	29 (2)
	Sinusitis	10 (2)	28 (2)
	Asthma Aggravated	3 (<1)	27 (2)
	Nasal Irritation	6 (<1)	26 (2)
	Bronchospasm	7 (1)	25 (2)
	Rhinitis	7 (1)	16 (1)
Bleeding/Clotting	Epistaxis	25 (5)	117 (8)
CNS/PNS	Headache	42 (8)	113 (7)
Whole Body	Flu-Like Disorder	12 (2)	17 (1)

The shaded cells emphasize those AE preferred terms that were more frequently associated with Rhinocort Aqua than with placebo. Overall, AE's were very slightly more frequent in patients who received Rhinocort compared with placebo and these were almost uniformly manifest in the upper or lower respiratory tract.

When the frequencies of AE's for each daily dose were displayed for each preferred term, the only AE to show stable or monotonically increasing frequency with increasing dose was 'Nasal Irritation.' The frequency of AE's by preferred term was very similar for males and females. When the AE preferred term frequencies were used to compare all Rhinocort Aqua groups with placebo for time of onset of the AE, there were no systematic trends. The frequencies of AE's by preferred term was also similar at both extremes of age; i.e., age  $\geq 60$  years compared to age  $<18$  years, with the single exception of 'epistaxis' [111:30-3, 36, 112:117-165, 221-248].

FREQUENCY OF 'EPISTAXIS' BY AGE RANGE AND TREATMENT GROUP [111:32-3, 112:140, 143, 150, 153, 156, 163]			
Treatment Group	Age Range n (%)		
	age < 18	18 < age < 60	age > 60
Placebo	3 (3)	20 (5)	2 (8)
Total Rhinocort Aqua	19 (5)	86 (8)	12 (17)

'Epistaxis' was more frequently reported over all doses of Rhinocort Aqua than placebo and the frequency increased with increasing categorical age in both groups, as is shown in the table above. The point estimates of frequency for the Total Rhinocort Aqua group contains enough patients to be reliable at each age category. At issue is the accuracy and reliability of the point estimates of epistaxis for the placebo group, which rely on smaller numbers of patients, especially in the highest age category (number of patients of age  $\geq 60$  years = 25).

#### Deaths:

No deaths were reported in the seven primary trials [111:37].

#### Serious Adverse Events:

Four serious AE's were reported and patients reporting three of them had received placebo. The single patient reporting a serious AE who had been treated with Rhinocort Aqua was a 15-year old male who suffered a traumatic fracture of the left wrist during a soccer game after 21 days of treatment with 400  $\mu\text{g}/\text{day}$  [111:37-8].

#### Discontinuations Due To Adverse Events:

Sixty-five patients were discontinued due to AE's in these seven primary protocols. The frequency of discontinuation because of AE's in the placebo group and in the various corticosteroid topical nasal formulation groups was 2-3%. When the 41 patients treated with Rhinocort Aqua were examined for frequency in treatment groups at different doses, the same 2-3% frequency was seen at all dose levels.

'Epistaxis' stands out among other AE's because it exhibited dose proportionality as measured by early terminations due to AE's. It was not the cause of any discontinuations in the placebo, 32  $\mu\text{g}/\text{day}$  or 64  $\mu\text{g}/\text{day}$  Rhinocort Aqua groups. However, an increasing frequency was noted with increasingly larger doses of Rhinocort Aqua. Based on the number of patients in the dose group discontinuing because of any AE, 'epistaxis' was the reason for patients terminating early because of an AE in increasing frequency with increasing dose (128  $\mu\text{g}/\text{day}$  = 1/8 (12.5%); 256  $\mu\text{g}/\text{day}$  = 7/19 (36.8%); 400  $\mu\text{g}/\text{day}$  = 3/5 (60%). Similar calculations based on a denominator of the number of patients in the treatment group showed a similar trend (128  $\mu\text{g}/\text{day}$  = 1/357 (0.28%); 256  $\mu\text{g}/\text{day}$  = 7/662 (1.06%); 400  $\mu\text{g}/\text{day}$  = 3/160 (1.88%) [111:38-41].

## SUPPORTIVE TRIALS

Over 5900 patients were, or are, enrolled in supportive studies of aqueous or dry powder formulations of intranasal budesonide. Data were presented from patients exposed to four formulations: the pMDI; the aqueous suspension (Rhinocort Aqua); an experimental aqueous solution in Tween (solution); and, the DPI. Of [ ] supportive studies, 59 were completed by 12/31/95 and [ ] were ongoing. These data will be separately analyzed within the 'completed' and 'ongoing' groups. Because of the large number of combined patients and differences in the designs of the supportive studies, only AE's which were 'serious,' including deaths, or resulted in patient discontinuation from the study were reported in the ISS. A total of 2 deaths, 29 serious AE's and 100 discontinuation due to AE's were reported from these 69 trials as of 12/31/95 [111:63].

## COMPLETED SUPPORTIVE STUDIES

Data from approximately 4167 patients were included with the following diagnoses: seasonal allergic rhinitis or SAR (25 studies), perennial allergic rhinitis or PAR (13 studies), nasal polyposis (6 studies), healthy volunteers (11 studies), PAR & SAR (1 study), asthma (1 study), pigeon-breeder's disease (1 study) and otitis media (1 study). Formulations of budesonide studied included Aqua (33 studies), pMDI (12 studies), DPI (21 studies) and solution (7 studies). The number of studies per formulation sum to more than the total number of completed studies because more than one formulation may have been used in any study [111:63].

### Deaths:

One death was reported from these completed clinical studies. A 64-year old male died in a boating accident after five weeks of treatment with 200 µg BID of Aqua. High winds were reported to have caused the boat to capsize. Death was attributed to drowning when the submerged body was retrieved from the water on the following day, though no autopsy was performed [111:65, 189:328-31].

### Serious Adverse Events:

A total of 18 serious AE's, including the single death, were reported by 17 patients in the completed clinical studies. Fourteen of the AE's were seen in 13 patients who received a budesonide formulation. The AE's attributed to different formulations were: Aqua = 6; pMDI = 1, and DPI = 7 (in 6 patients). These serious AE's had little commonality in symptomatology or organ system involvement and most occurred within days of beginning treatment [111:64-9].

### Discontinuations Due To Adverse Events:

There were 93 patients who terminated participation in the study early because of an intercurrent AE. Thirty of the 69 patients terminating prematurely and treated with budesonide, quit partially or completely because of local nasal symptoms. This is in contrast with the 2 of 18 placebo patients and 1 of 6 active comparator patients who also terminated early because of AE's attributable to nasal symptoms. Five cases of sinusitis were reported

to have caused early termination among patients treated with budesonide, but there were three cases among the placebo treated patients. This fails to implicate budesonide in facilitating local infections, specifically sinusitis [111:69-73].

#### ONGOING SUPPORTIVE STUDIES

#### BACKGROUND SAFETY INFORMATION

##### Hypothalamic-Pituitary-Adrenal (HPA) Axis:

Single-dose trials in healthy volunteers revealed relatively large suppression of urinary free cortisol excretion by Aqua compared to equivalent doses of DPI and beclomethasone. It was noted that the delivered dose of the Aqua formulation was larger than from the pMDI formulation. Comparable delivered doses of Aqua, pMDI and DPI were administered to healthy volunteers in another study. First-dose and seven-day multiple-dose urinary cortisol showed similar degrees of suppression for all formulations and all affected less suppression after one week of multiple dose administration. After the first dose, all formulations produced about 40% urinary cortisol decrease from baseline. This dramatic reduction was ameliorated after seven days of treatment, when urinary cortisol showed only a 15-20% reduction from baseline for all three formulations [111:105-6].

#### Growth:

The use of systemic corticosteroids has been associated with growth suppression in infants and children. Both Rhinocort pMDI (256 µg/day, nominally 400 µg/day) and methylprednisolone IM (60 mg/day) produced short-term growth reductions over six weeks of treatment, as measured by lower leg growth (knemometry) and compared to terfenadine. Another study of knemometry after four weeks of treatment with the Rhinocort DPI was interpreted as not supporting short-term growth suppression in children [111:117-8].

#### OPEN-LABEL, LONG-TERM SAFETY STUDIES

Though HPA axis and growth suppression over one to several weeks are of interest, the more clinically relevant time frame is months to years. Three studies were designed to assess long-term safety. Two studies were in children (05-2071 and 05-3046) and one was in adults with PAR (05-3047). One study, 05-2071, was completed and the other two were ongoing as of the 12/31/95 date of the ISS. The two studies in children assessed the effect of Rhinocort Aqua on long-term statural growth and adrenal function [111:98].

#### COMPLETED STUDY

05-2071 AN OPEN LONG-TERM STUDY OF BUDESONIDE (RHINOCORT®) IN CHILDREN WITH PERENNIAL RHINITIS: A MULTI CENTER STUDY

This was an uncontrolled, multi center, open-label, long-term study of the systemic effects of intranasal budesonide in children 5-15 years of age with perennial rhinitis, allergic (skin test positive) or non-allergic, of at least one year duration. No topical nasal treatment was permitted; e.g., steroids or cromolyn. Oral, systemic or inhaled steroids were prohibited. Rescue medication for nasal symptoms was a combination product, [redacted] which contained [redacted] mg brompheniramine and [redacted] mg phenylpropanolamine in one tablet, and was maximally taken twice daily. Eye symptom rescue medication was [redacted] eye drops, which contained [redacted] mg antazoline and [redacted] mg naphazoline. There were 3 phases in the study and the first 2 phases were conducted at 6 centers in Sweden. Seventy-eight children entered and 73 completed the first 12 month phase. Forty-seven entered and 39 completed the second year of the trial. Sixteen patients from a single center entered the third through fifth years of the study, and 14 of them completed the entire 5 years.

During the first year, all of the children were treated with Rhinocort pMDI. During months 13-18 all patients were treated with Rhinocort Aqua Nasal Spray. After 18 months, the patients were free to choose between the two formulations. During the last 6 months of the trial (months 55-60), all of the patients again switched to Rhinocort Aqua Nasal Spray. All patients started using the pMDI and taking a total daily dose of 256 µg (nominal dose 400 µg) which could be adjusted for each patient to control symptoms. Safety variables included ophthalmological examination, height, weight, plasma cortisol, urine cortisol, white blood cell count, differential cell count and spontaneous AE reports. Height and weight were determined at entry, 1, 3, 6, 9, 12, 18 and 24 months. Wrist radiographs, for bone age

determination, were taken at entry and 12 months. Blood and urine cortisol measures were made at entry and every six months [111:100, 98:6, 14, 17].

**Laboratory Results:**

Compared with mean values at entry, the largest differences over 12 months of treatment were found in total white blood cell count (increased), percent neutrophils (increased), percent eosinophils (decreased), percent basophils (decreased) and serum creatinine (increased). When these data were followed for a total of 24-months, percent eosinophils and percent basophils continued to show a decrease from study entry [98:27, 54-7, 65, 70, 71]. These laboratory findings represented small but consistent changes in the mean values at each visit. It should be noted that elevated circulating white blood cell counts and reduced eosinophil counts are normal metabolic accompaniments of systemic corticosteroid treatment.

**Adverse Events:**

AE's were separated into the first and second year reporting periods. During each year of treatment, the most frequent number of patients reporting AE's, by preferred term, are listed in the table below.

MOST FREQUENT NUMBER OF PATIENTS REPORTING ADVERSE EXPERIENCES BY PREFERRED TERM [98:29, 81-2]		
Preferred Term	First Year patients (% of N = 77)	Second Year patients (% of N = 46)
Respiratory Infection	46 (59.7)	14 (30.4)
Rhinitis (mostly nasal dryness)	23 (29.9)	12 (26.1)
Bronchospasm	11 (14.3)	3 (6.5)
Epistaxis	16 (20.8)	3 (6.5)
Headache	10 (13.0)	4 (8.7)

**Deaths:**

No deaths were reported.

**Serious Adverse Events:**

After one month treatment with budesonide, a 9-year old female suffered a grand mal seizure. The seizure was represented as the benign epilepsy of children. After anti-epileptic therapy had been instituted, budesonide treatment was resumed [98:29].

**Discontinuations Due To Adverse Events:**

Two other patients discontinued budesonide treatment due to AE's. One patient experienced nasal irritation and one stopped because of an unsatisfactory effect [98:29].

**Growth:**

The difference between observed and predicted mean values of height and weight of children were compared between visits. Predicted values for each was taken from Swedish standard growth charts. The table below shows the heights and weights of those patients who were enrolled in the study for 1 year, 2 years and 5 years [111:121, 98:75-6, 99:23]. The most obvious finding is that the children in the study were larger than predicted by Swedish standards, for their sex and age [98:28]. There was a reduction in the observed-predicted height difference between baseline and the various follow up time points. These data were reassessed, at my request, in units of mean observed height as percent of predicted height, without adding any new insight. That is, the data showed greater than 100 % of predicted mean observed height at each visit and in each group and a downward trend in this measure after the baseline visit [6/13/97 FAX:3-4].

05-2071 – EFFECT OF INTRANASAL BUDESONIDE ON GROWTH IN CHILDREN [111:121, 98:75-6, 99:23]					
Study Point	N	Drug	Dose Delivered in µg Mean (Range)	Mean Difference of Observed Minus Expected	
				Height in cm mean (SD)	Weight in kg mean (SD)
Patients who completed the first 12-month study period					
Baseline	68	N/A	N/A	3.62 (6.98)	3.92 (7.27)
12 months	68	pMDI	241 (64-256)	3.42 (7.37)	4.03 (7.62)
Patients who completed the 24 month study period					
Baseline	31	N/A	N/A	2.87 (6.98)	3.96 (7.26)
12 months	31	pMDI	241 (64-256)	2.66 (7.00)	3.61 (7.09)
24 months	31	Aqua	331 (200-600)	2.85 (7.31)	4.33 (8.05)
Patients who completed the 60 month study period					
Baseline	13	N/A	N/A	4.44 (5.76)	5.79 (6.17)
12 months	13	13 pMDI	209 (64-256)	4.29 (6.25)	5.00 (5.55)
24 months	13	7 Aqua 6 pMDI	314 (200-400) 235 (128-256)	3.54 (7.23)	4.98 (5.87)
36 months	13	8 Aqua 5 pMDI	325 (0-400) 256 (256-256)	3.97 (6.72)	5.50 (5.82)
48 months	13	7 Aqua 6 pMDI	345 (0-400) 213 (128-256)	3.46 (6.30)	4.58 (7.75)
60 months	13	13 Aqua	354 (200-500)	3.43 (8.14)	3.85 (8.64)

By this measure, similar to a historical control-group of healthy children, growth slowed in budesonide-treated perennial rhinitis patients over both one and five years of continuous treatment. The lack of statistical significance, cited by the sponsor, is not germane

because the sample size was not chosen to provide sufficient power (1-β) to show significance.

Another measure of growth, bone maturation, was determined by radiologic examination of the left wrists and hands of participants, at entry and after 12 months. These were subjected to two different methodological analyses for bone age and the change in radiologic bone age was compared to the change in chronological age of the same children to detect growth suppression. Both radiologic measures of bone age provided point estimates of bone maturation that were comparable to, but exceeded slightly actual chronological maturation. The implication was that these measures did not detect a mean suppressive effect of budesonide on radiologic bone growth over one year of follow up [98:19, 77-8, 103-8]. The same criticisms directed at the height measurement endpoint also apply to radiological bone growth; i.e. historical controls and haphazard sample size selection.

**HPA Axis:**

The table below summarizes patients who were followed for 1, 2 and 5 years, and displays 8:00-9:00 am serum and, where appropriate, 24-hour urine cortisol longitudinally. No sequential diminution from baseline was seen in plasma cortisol for the one- and two-year completers. Urine cortisol did show a reduction from baseline at six and twelve months in all three groups. The small number of five-year completers showed a reduction in plasma cortisol that returned to baseline by the 48th month. By the 60th month, both plasma and urine cortisol had returned to above baseline.

05-2071 – EFFECT OF INTRANASAL BUDESONIDE ON PLASMA AND URINE CORTISOL IN CHILDREN [111:115-6, 98:66-7, 99:24, 26, 5/30/97 Telecon, 6/2/97 FAX]						
Study Point	N	Drug	Delivered Dose in µg Mean (Range)	Plasma Cortisol (nmol/L) mean (SD)	N	Urine Cortisol (nmol/24 hours) mean (SD)
Patients who completed the first 12-month study period						
Baseline	73	N/A	N/A	335 (125.5)	64	48 (28.9)
6 months	73	pMDI	241 (64-256)	346 (122.1)	64	40 (19.0)
12 months	73	pMDI	252 (64-256)	359 (113.5)	64	44 (25.3)
Patients who completed the 24 month study period						
Baseline	30	N/A	N/A	365 (132.5)	N/A	54 (37.4)
6 months	30	pMDI	241 (64-256)	390 (121.2)	N/A	39 (17.3)
12 months	30	pMDI	252 (64-256)	395 (110.9)	N/A	47 (30.8)
18 months	30	Aqua	341 (64-256)	377 (129.1)	N/A	N/A
24 months	30	Aqua/pMDI	331 (148-400)	391 (149.2)	N/A	N/A
Patients who completed the 60 month study period						
Baseline	13	N/A	N/A	428 (130.9)	16	62.2 (45.8)

05-2071 – EFFECT OF INTRANASAL BUDESONIDE ON PLASMA AND URINE CORTISOL IN CHILDREN [111:115-6, 98:66-7, 99:24, 26, 5/30/97 Telecon, 6/2/97 FAX]						
Study Point	N	Drug	Delivered Dose in µg Mean (Range)	Plasma Cortisol (nmol/L) mean (SD)	N	Urine Cortisol (nmol/24 hours) mean (SD)
6 months	13	13 pMDI	202 (64-256)	404 (125.1)	16	38.9 (15.2)
12 months	13	13 pMDI	212 (64-256)	389 (85.7)	15	50.0 (31.4)
18 months	13	13 Aqua	354 (200-400)	340 (78.2)	N/A	N/A
24 months	13	7 Aqua 6 pMDI	314 (200-400) 235 (128-256)	397 (120.9)	N/A	N/A
36 months	13	8 Aqua 5 pMDI	314 (0-400) 256 (256-256)	385 (101.1)	N/A	N/A
48 months	13	7 Aqua 6 pMDI	345 (15-400) 213 (128-256)	449 (146.8)	N/A	N/A
60 months	13	13 Aqua	354 (200-500)	519 (214.2)	14	75.4 (54.5)

A few individuals among the 13 patients completing five years of treatment had plasma cortisol values below the normal reference range (200-700 µg) and all but one returned to the normal range before completion of the trial. One patient who used no concomitant medications in the last three years of the study, #3436, showed low values for plasma cortisol for the 48th, 54th and 60th months (last three consecutive visits), which returned to normal four months after study termination. Concomitant urine cortisols for this patient were not available [111:114, 99:24, 32]. Taken together, some suppression of 24-hour urine cortisols was apparent for the first twelve months following initiating chronic treatment with budesonide. This was not reproducibly found with spot morning plasma cortisols.

#### ONGOING STUDIES – INTERIM REPORTS

05-3046 A RANDOMIZED OPEN LABEL COMPARISON OF RHINOCORT® (BUDESONIDE) AQUA PUMP SPRAY VERSUS NASALCROM® (CROMOLYN SODIUM) IN THE TREATMENT OF CHILDREN WITH PERENNIAL ALLERGIC RHINITIS

The primary purpose of this study was to determine the influence of long-term treatment for 12 months with budesonide, administered once daily as an aqueous suspension from a spray pump, on HPA-axis, growth and bone mineral density in children with PAR and compare it to nasal cromolyn. The purpose of this interim report was to provide 6-month safety data. This is an ongoing, open-label comparison between two positive control drugs, without a placebo group. Patients of both genders ranged in age from 6 to 17 years. Male or female pediatric patients completing the short-term pivotal trial, 05-3039, were allowed to enroll in this study after completing a 4-week washout period. Additional prepubertal patients who had not completed the short-term trial but who had a diagnosis of PAR for at least the two prior years were also enrolled. The trial consists of a one-week baseline run-in period, followed by 52 weeks of active treatment with either 256 µg of budesonide (64

µg/spray) once daily or 10.4 mg of the cromolyn (5.2 mg/spray) four times daily. Budesonide and cromolyn patients were randomized in a 2:1 ratio. After three months, budesonide could be titrated down to a dose no lower than 128 µg once daily. A preparation of chlorpheniramine maleate and pseudoephedrine was available in capsules (4 mg/60 mg), or half-strength syrup (2 mg/30 mg), as rescue medication. Proscribed medications included: 1) systemic corticosteroids; 2) topical nasal or inhaled steroids, except for the study medication and two (up to) 4-week treatments with topical nasal beclomethasone for the cromolyn group for intolerable symptoms; 3) any other antihistamines; and 4) oral or nasal decongestants except for the rescue medication. Visits occurred at enrollment, randomization and five times during the active treatment period, after 4, 12, 26, 39 and 52 weeks. So far 171 patients, of the anticipated 300 patients (190 pre-pubertal), from 20 U.S. centers have been enrolled [89:4-5, 12, 17, 19, 24-5].

**Laboratory Results:**

None were summarized in this interim report.

**Adverse Events:**

Sixty-one patients reported one, or more AE's. Forty-two patients (37%) were in the budesonide group and 19 (33%) were in the cromolyn arm. The following table shows AE's which occurred with a frequency  $\geq 1\%$  in the budesonide group and were more frequent in the budesonide, than in the cromolyn arm.

05-3046 AE FREQUENCY $\geq 1\%$ IN THE RHINOCORT GROUP AND MORE FREQUENT IN RHINOCORT THAN CROMOLYN GROUP, BY SYSTEM AND PREFERRED TERM [89:42-3, 75-6]			
Body System	Preferred Term	Nasalcrom n (%)	Rhinocort Aqua n (%)
All Systems	Any AE	19 (33)	42 (37)
Respiratory	Pharyngitis	1 (2)	8 (7)
	Coughing	1 (2)	3 (3)
	Sinusitis	2 (3)	4 (4)
Resistance Mechanisms	External Otitis	0 (0)	2 (2)
GI	Gastroenteritis	0 (0)	2 (2)
Bleeding/Clotting	Epistaxis	0 (0)	3 (3)

The relatively large number of AE's that indicate some involvement of the upper or lower respiratory tract was also found in the placebo-controlled trials.

**Deaths:**

No deaths were reported during the course of this study [89:43].

**Serious Adverse Events:**

Two serious AE's were reported by the time of the 30 November 1996 cut-off date. A 10-year old male patient (#0106), who had been in the cromolyn group, was hospitalized with a severe exacerbation of his recently diagnosed asthma. An 8-year old female (#0542), who had been in the budesonide group and in the treatment phase of the protocol for 3 months, was admitted to the hospital for tonsillectomy and adenoidectomy and discharged the same day [89:43-4].

**Discontinuations Due To Adverse Events:**

Three patients terminated early because of an AE, two from the budesonide group and one from the cromolyn arm. An 11-year old female (#0144), who had received budesonide for 6 months, reported severe dyspnea, but recovered the same day. A 12-year old female (#0350), who had received budesonide for 6 months, reported taste perversion which remitted when the drug was withdrawn. A 17-year old male (#0372), who had received cromolyn for 18 days, was diagnosed with a sinus infection and treated with a prednisone burst following a 10-day trial of an antibiotic, and recovered completely [89:44-5].

**Growth:**

As originally designed, the various growth measures were planned to compare baseline values against those at one year. The results of this interim safety report are, therefore, a bit sparse. Comparison of skeletal and chronological age at baseline for all patients completing 6 months of treatment, showed that both treatment groups were well matched by this measure [89:50, 89]. A summary of height at each study visit, for all patients completing 6 months of treatment, showed approximately a 2.5 cm height advantage at baseline for the Nasalcrom group, which progressively widened at all follow up visits, as demonstrated in the table below.

SUMMARY OF HEIGHT AT EACH STUDY VISIT FOR ALL PATIENTS WHO COMPLETED SIX MONTHS OF TREATMENT [89:90]						
Study Visit	Study Week	Rhinocort Aqua (RA), in cm		Nasalcrom (Nc), in cm		Nc - RA, in cm (% mean RA)
		n	Mean (S.D.)	n	Mean (S.D.)	
1	-1	56	142.46 (18.15)	21	144.95 (13.35)	2.49 (1.75)
2	0	56	142.63 (18.13)	21	145.14 (13.43)	2.51 (1.76)
3	4	56	142.97 (18.27)	21	145.53 (13.16)	2.56 (1.79)
4	12	56	143.92 (18.31)	21	146.49 (13.08)	2.57 (1.79)
5	26	56	144.85 (18.18)	21	147.81 (13.11)	2.96 (2.04)

This suggests a some progressive slowing of growth in the budesonide group or, less likely, a progressive stimulation of growth in the Nasalcrom group. This effect was limited to the pre-pubertal subgroup of children and was reflected in the calculated growth velocity (cm/month) at each visit [89:53, 90].

**HPA Axis:**

In this interim safety summary, morning and Cortrosyn-stimulated plasma cortisol levels collected at baseline (Visit 2) and after 12 weeks (Visit 4). The following table shows these variables and the mean percent change in them. The mean percent change was calculated for individuals and averaged. It need not correspond to the 'percent change in means,' and does not in the table below [89:45-7].

BASAL (PreStim) AND CORTROSYN-STIMULATED (Stim) CORTISOL LEVELS FOR ALL PATIENTS AT BASELINE (Visit 2), AFTER 12 WEEKS OF TREATMENT (Visit 4) AND THE CHANGE IN BASAL CORTISOL OVER THE TWO VISITS (Visit 4-2) [3/6/97 P-25, Table 4]							
Treatment (n)	Visit 2 (Baseline)			Visit 4			Visit 4-2
	PreStim.	Stim.	Stim-PreStim (mn % chng)	PreStim.	Stim.	Stim-PreStim (mn % chng)	PreStim Dif (mn % chng)
Budesonide (95)	273	580	141	307	569	105	25
Nasal crom (47)	304	584	126	304	559	104	14

The morning (PreStim) mean cortisol was lower in the budesonide group than in the Nasal crom group at baseline (Visit 2). After 12 weeks (Visit 4), the morning (PreStim) cortisol was virtually identical in both groups, though having increased more in the budesonide group, from a slightly low mean value at Visit 2. Cortrosyn-stimulated plasma cortisol rose more in the budesonide group, at Visit 2, than in the Nasal crom arm. After 12 weeks, mean percent change in stimulated cortisol were the same in both arms of the trial. A similar table for the subset of pre-pubertal patients was not very different, as is seen below

BASAL (PreStim) AND CORTROSYN-STIMULATED (Stim) CORTISOL LEVELS FOR PRE-PUBERTAL PATIENTS AT BASELINE (Visit 2), AFTER 12 WEEKS OF TREATMENT (Visit 4) AND THE CHANGE IN BASAL CORTISOL OVER THE TWO VISITS (Visit 4-2) [3/6/97 Table 5]							
Treatment (n)	Visit 2 (Baseline)			Visit 4			Visit 4-2
	PreStim.	Stim.	Stim-PreStim (mn % chng)	PreStim.	Stim.	Stim-PreStim (mn % chng)	PreStim Dif (mn % chng)
Budesonide (59)	274	581	143	317	575	99	31
Nasal crom (30)	312	605	132	319	587	105	21

In short, the basal morning plasma cortisol and the Cortrosyn-stimulated plasma cortisol data from the interim analysis of this trial did not show evidence of HPA axis suppression.

05-3047

A RANDOMIZED, OPEN-LABEL COMPARISON OF RHINOCORT® (BUDESONIDE) AQUA PUMP SPRAY, VERSUS BECONASE AQ® (BECLOMETHASONE DIPROPIONATE) IN THE TREATMENT OF ADULTS WITH PERENNIAL ALLERGIC RHINITIS

This study was directed toward determining the long-term (one-year) effect of intranasal budesonide (256 µg/day), administered once daily as an aqueous suspension from a spray pump, compared with aqueous beclomethasone dipropionate (336 µg/day), administered twice daily, in adults with PAR. Patients of both genders, who were > 17 years of age and had successfully completed 05-3039 were eligible. Rescue medication for nasal symptoms was [redacted] (chlorpheniramine maleate 4 mg, pseudoephedrine 60 mg). Proscribed drugs included systemic corticosteroids, topical intranasal steroids (other than the study medication), antihistamines (other than the rescue medication) and nasal or oral decongestants. This is an interim report from an ongoing U.S. trial providing 6-month safety data on the first 164 patients randomized into the protocol by 30 November 1996. Following a four-week washout period and a one-week baseline, patients were randomized on a 2:1 basis; 110 (67%) placed in the budesonide arm, and 54 (33%) in the beclomethasone arm. They ranged in age from 18-79 years (mean = 38) and had a history of PAR for at least two years. Routine laboratory studies were only planned at screening and after one year of treatment so the only evaluable safety parameters, at six months, were AE's and drop-outs [93:2, 5, 11, 22, 23, 35, 37, 39].

**Laboratory Results:**

None were summarized in this interim report.

**Adverse Events:**

A total of 66 (40%) of patients reported one or more AE's, 46 (42%) in the budesonide arm and 20 (37%) in the beclomethasone group. The AE's are listed in the table below by body system and by preferred term for the two active treatment arms, where the total number of patients reporting an AE under any preferred term was greater than one..

AE FREQUENCY > 1 PATIENT IN COMBINED RHINOCORT AND PLACEBO GROUPS, BY SYSTEM AND PREFERRED TERM [93:54-5]			
Body System	WHO Preferred Term	Rhinocort Aqua (N = 110) number of patients (%)	Beconase AQ (N = 54) number of patients (%)
All Systems	Any AE	46 (42)	20 (37)
Respiratory	Respiratory Infection	12 (11)	4 (7)
	Sinusitis	6 (5)	1 (2)
	Pharyngitis	3 (3)	3 (6)
	Rhinitis	4 (4)	0 (0)
	Bronchitis	2 (2)	0 (0)
Body as a Whole	Accident or Injury	5 (5)	4 (7)
	Back Pain	3 (3)	2 (4)
	Pain	1 (1)	2 (4)
	Allergic Reaction	1 (1)	1 (2)

AE FREQUENCY > 1 PATIENT IN COMBINED RHINOCORT AND PLACEBO GROUPS, BY SYSTEM AND PREFERRED TERM [93:54-5]			
Body System	WHO Preferred Term	Rhinocort Aqua (N = 110) number of patients (%)	Beconase AQ (N = 54) number of patients (%)
	Fever	1 (1)	1 (2)
	Flu-like Disorder	2 (2)	0 (0)
Gastro-Intestinal	Tooth Disorder	3 (3)	0 (0)
	Abdominal Pain	1 (1)	1 (2)
	Gastroenteritis	1 (1)	1 (2)
	Nausea	1 (1)	1 (2)
Platelet, Bleeding & Clotting	Epistaxis	4 (4)	2 (4)
Musculoskeletal	Cramps	1 (1)	1 (2)
Urinary	UTI	0 (0)	3 (6)
Skin & Appendages	Photosensitivity Reaction	2 (2)	0 (0)

The body system under which most preferred terms fell was respiratory, which is in accord with previous trials. With the small number of patients reporting and uneven group sizes, it is difficult to conclude that any difference between the two intranasal steroids exists [93:37, 54-5].

**Deaths:**

No deaths have been reported [93:38].

**Serious Adverse Events:**

Five serious AE's were reported by the November '96 cut off date, one of which is incompletely reported at the time of the compilation of the integrated safety summary.

- a. A 62-year old male (01-0101) had a ten-year old lesion removed from his forearm which was histologically diagnosed as a basal cell carcinoma. At the time of surgery he had been treated with budesonide for six months.
- b. A 52-year old female (05-0185) was found to have localized colon cancer while undergoing evaluation for anemia and required a partial colectomy. At the time of her surgery she had received 51 days of budesonide treatment.
- c. A 69-year old male (05-0190) with a history of depression over the preceding three years, was diagnosed as having severe depression requiring hospitalization six months after beginning treatment with budesonide.
- d. A 69-year old female (16-0425), was hospitalized after 46 days of beclomethasone treatment for surgical repair of a torn rotator cuff that was injured before she entered the clinical trial.
- e. A 21-year old female (10-0299) with asthma at study entry developed an exacerbation of bronchospasm requiring hospitalization 57 days after beginning treatment with budesonide.

With the possible exception of the last patient, these cases are unlikely to represent a complication of intranasal steroid therapy for PAR [93:39-40].

**Discontinuations Due To Adverse Events:**

Three patients terminated prematurely, two because of AE's and both had received budesonide. One patient (05-0190), a 69-year old male with a history of depression over the preceding three years, was diagnosed as having severe depression requiring hospitalization six months after beginning treatment. The other (16-0420), a 22-year old male, developed Candidiasis of the left nasal septum 1-2 months after starting treatment [93:41-2].

**POST-MARKETING EXPERIENCE**

Three intranasal formulations of budesonide have been approved for marketing in 52 countries worldwide: Rhinocort Nasal Inhaler (pMDI), Rhinocort Aqua Nasal Spray and an intranasal budesonide dry powder inhaler (DPI). It has been estimated that from 1983, when the product was first marketed, to January 1996, there have been over 10.5 million patient years of treatment with some form of intranasal budesonide. A total of 460 post-marketing AE reports from all sources for the three formulations were reported by the sponsor. Spontaneous reports accounted for the majority (348) of these, which represent safety data received by Astra and its licensees as well as cases reported in the scientific literature. Some of the more common of these are listed below in descending order of reported frequency. The shaded cells represent common local respiratory tract symptoms and facilitate comparison with a post-marketing spontaneous-report table in the safety update portion of this review [111:18, 124, 147-9].

348 SPONTANEOUS REPORTS OF 515 ADVERSE EVENTS, ALL RHINOCORT FORMULATIONS, FROM 1983 THROUGH JANUARY 1996 [111:147-9]	
Adverse Event	Number of Reports
Accident and/or Injury	49
Rhinitis	35
Rash	29
Nasal Septum Perforation	28
Contact Dermatitis	25
Urticaria	20
Nasal Irritation	19
Face Edema	17
Decreased Therapeutic Response	17
Epistaxis	15
Allergic Reaction	13
Anosmia	11

348 SPONTANEOUS REPORTS OF 515 ADVERSE EVENTS, ALL RHINOCORT FORMULATIONS, FROM 1983 THROUGH JANUARY 1996 [111:147-9]	
Adverse Event	Number of Reports
Headache	10
Angioedema	9
Dizziness	9
Dyspnea	8
Sinusitis	8
Pharynx Disorder	7
Pruritus	6

Eight of the 348 spontaneous reports were serious AE's and included: two reports of allergic reactions, two reports of convulsions, and one report each of nasal septum perforation, facial edema, paresis and neuritis. One additional report of adrenal cortical suppression was seen in a 7-year old girl, who showed growth retardation after long-term use of both orally inhaled and intranasal budesonide. The total daily doses were 400 µg/day of the orally inhaled product and 200 µg/day of the intranasal formulation. The patient developed Cushingoid symptoms after the dose of the orally inhaled budesonide was raised to 1000 µg/day.

The remainder of the 460 reports came from National Adverse Drug Reaction Advisory Committee (ADRAC) Reports which were sent to Astra as data list printouts from national health authorities of suspected AE's [111:124-5]. Some of the more common of these are listed below in descending order of reported frequency [111:124-6, 198-9].

112 ADRAC REPORTS OF 140 ADVERSE EVENTS, ALL RHINOCORT FORMULATIONS, FROM 1983 THROUGH 1 JANUARY 1996 [111:198-9]	
Adverse Event	Number of Reports
Nasal Septum Perforation	32
Angioedema	11
Urticaria	9
Rhinitis	8
Rash	7
Epistaxis	5
Face Edema	3
Palpitation	3
Pruritus	3
Rash, Erythematous	3

Cases of nasal septum perforation from both spontaneous reports and ADRAC listings were not previously noted. This unusual AE may be a more severe manifestation of the locally irritating AE's that dominated earlier reports.

**THREE MONTH SAFETY UPDATE (12/3/96 SUBMISSION)**

The Rhinocort Aqua NDA was submitted 7/29/96 and included information that was current through 12/31/95. This first safety update provides information that became apparent between 12/31/95 and 7/31/96, including post-marketing U.S. and foreign safety information. Safety data from 1 completed and [ ] ongoing [ ] and 4 completed and [ ] ongoing [ ] studies of intranasal budesonide were included. Only studies of Rhinocort Aqua Nasal Spray and budesonide administered as a DPI were included in this report. Studies limited to the Rhinocort Nasal Inhaler pMDI were not included in this safety update [12/3/96 1:7-9].

SAFETY DATA, STUDIES AND PATIENTS BY TYPE OF STUDY: ALL TREATMENT GROUPS [12/3/96 1:9, 11-15]						
Study Type		Number Studies	Number Subjects	Deaths	Serious AE's	D/C due to AE
Completed Supportive	U.S.	1	148	0	1	2
	non-U.S.	4	126	0	0	1
Ongoing Supportive						
TOTAL						

**Deaths:**

No new death reports have been received during this reporting period [12/3/96 1:16].

**Serious Adverse Events (SAE's):**

Only seven serious AE's were reported from the 19 trials and over 2400 anticipated patients. One such was reported from a completed U.S. study, [ ] were reported from [ ] ongoing [ ] and [ ] serious AE's were reported from the [ ] ongoing trials treatment [12/3/96 1:15, 20-1, 23-4, 28-9, 37-8].

**Completed U.S. Trials**

05-3002

Patient #140 reported a severe sinusitis and was hospitalized for treatment.

**Ongoing U.S. Trials**

05-3046

Patient #0116 was hospitalized for an asthma exacerbation after having taken Nasalcrom for over one month.

Patient #0419 was hospitalized for burns received from a hot cooking oil accident after over one year on treatment with Nasalcrom.

05-3047

Patient #0233 had an exacerbation of asthma, for which [ ] had prior history, after 8 months of treatment with Rhinocort Aqua.

Patient #0169 suffered a cerebral embolism after 6 months of treatment with Beconase AQ.

Ongoing [ ] Trials

Discontinuations Due To Adverse Events:

Twelve early termination due to AE's were reported. Two of these came from a completed U.S. study, 9 from ongoing U.S. trials and 1 from a completed non-U.S study [12/3/96 1:15, 20-3, 26-8, 35].

Completed U.S. Trial

05-3002

Patient #140 was summarized under SAE's, above.

Patient #211 suffered from a 21-year history of seasonal headaches, a 15-year history of SAR and developed nasal and ear congestion and a cough with yellow sputum. The placebo study medication was discontinued and treatment with antibiotics and nasal steroids was followed by recovery after 4 weeks.

Ongoing U.S. Trials

05-3046

Patient #0109 developed nasal crusting and soreness after 198 days of treatment with Rhinocort Aqua.

Patient #0226, in the Nasalcrom arm, experienced an exacerbation of SAR and was left with a serous otitis following 131 days of treatment.

Patient #0286 discontinued Rhinocort Aqua because of nasal bleeding and crusting after 28 days of treatment.

Patient #0818 first experienced a bad taste and upset stomach on the first day of Nasalcrom treatment and finally discontinued because of taste perversion on the 77th day.

05-3047

Patient #0168 developed a dry, runny nose followed by epistaxis after 14 days of treatment with Rhinocort Aqua.

Patient #0169 was reviewed under SAE's, above.

Patient 0192 developed fibromyalgia and depression after 4 months of treatment with Rhinocort Aqua and finally terminated after 300 days of treatment with this study medication.

Patient #0464 began sneezing the first day [redacted] received Beconase AQ, reporting that the medication smelled like flowers, and finally terminated on the 83rd day.

Patient #0233 discontinued Rhinocort Aqua after 240 days of treatment because of an exacerbation of asthma, for which [redacted] had a 27-year history.

#### Completed non-U.S. Trials

05-9219

Patient #5 was withdrawn because of mild erythema around the eyes and a swollen face after 11 days of placebo treatment.

#### OTHER SAFETY CONSIDERATIONS

In one of the ongoing U.S. clinical trials (05-3046) both growth and HPA axis are being studied in children of ages 6 to 17 years. The updated interim report to this NDA is scheduled for January 1997. No non-U.S. studies of the effect of budesonide on growth or HPA axis in children are under way [12/3/96 1:32, 38].

#### POST-MARKETING EXPERIENCE

During the seven month period, from 1 January through 31 July 1996, the sponsor estimates that there have been approximately 0.5 million patient years of exposure to intranasally inhaled budesonide worldwide. This safety update presents data for all formulations of Rhinocort budesonide, including the pMDI, DPI and Aqua nasal spray.

Spontaneous reports of AE's associated with budesonide use numbered 118 and about half of the reports were from the U.S. No deaths were reported in conjunction with any budesonide product. No SAE's were reported for the Aqua nasal spray formulation. There were three SAE's reported for the pMDI: one each nasal septum perforation, hypokalemia and amnesia. The more common spontaneous reports of AE's and SAE's for all formulations are listed in the table below [12/3/96 1:39, 42, 57].

106 SPONTANEOUS REPORTS OF 162 ADVERSE EVENTS, ALL RHINOCORT FORMULATIONS, FROM 1/1/96 THROUGH 7/31/96 [12/3/96 1:57]	
Adverse Event	Number of Reports
Accident and/or Injury	18
Nasal Septum Perforation	15
Epistaxis	11
Rhinitis	11
Contact Dermatitis	7
Nasal Irritation	7
Decreased Therapeutic Response	7
Face Edema	5
Rash	4
Headache	4
Nausea	4

The local respiratory tract symptoms are shaded in the cells of the table above to facilitate comparison with a post-marketing spontaneous-report table presented earlier in this review.

ADRAC reports did not identify any deaths or SAE's associated with any Astra budesonide formulation. They did contribute 12 reports of 24 AE's. The two most commonly reported AE's were somnolence(4/24) and nasal septum perforation (2/24) [12/3/96 1:79].

#### ADDENDUM TO THE THREE MONTH SAFETY UPDATE (1/22/97 SUBMISSION)

This submission covered the latest information on growth, HPA axis evaluation and bone-age available from the ongoing trial 05-3046.

Demographic data for 313 randomized pediatric patients were summarized in this update. Of these, 241 (77%) were pre-pubertal and 71 (23%) were pubertal at the screening visit. A total of 110 patients completed one year of treatment and remained pre-pubertal throughout. Seventy-seven were in the Rhinocort group and 33 were in the Nasalcrom arm [1/22/97 Pp 8-9].

#### Growth:

Stadiometric measurements of shoeless height were obtained at clinic visits over the year of follow up and converted to growth velocity by least squares linear regression analysis over each interval. Six-month estimates were provided in the original study report, were converted to units of cm/year and are presented here for comparison with the one-year findings.

GROWTH VELOCITY OVER 6- & 12-MONTH PERIODS FOR PATIENTS WHO REMAINED PRE-PUBERTAL THROUGHOUT THE MEASUREMENT PERIOD [89:53, 1/22/97 P 42]			
Treatment Group		Growth Velocity (cm/year) Over Each Treatment Period	
		6 Months	12 Months
Rhinocort Aqua	Mean (Range)	4.68 ( )	5.18 ( )
	number	34	77
Nasalcrom	Mean (Range)	5.88 ( )	6.13 ( )
	number	12	33

The sponsor notes that the growth velocity discrepancy between the two treatment groups is most notable in males, when exploratory analyses were applied to the one-year data [80:53, 1/22/97 Pp 41-2]. These data confirm the earlier finding of slowed growth velocity associated with Rhinocort or, conversely, accelerated growth associated with Nasalcrom.

**HPA Axis:**

The 12-month data presented in the table below looks superficially like the six-month data presented in an earlier table, however there is a difference. The data below are presented as the percent change in means rather than the mean percent change over all individuals. This was an exigency forced by available analyses and is for the purpose of preliminary data evaluation, not final inference testing.

BASAL (PreStim) AND CORTROSYN-STIMULATED (Stim) CORTISOL LEVELS FOR ALL PATIENTS AT BASELINE (Visit 2), AFTER 52 WEEKS OF TREATMENT (Visit 7) AND THE CHANGE IN BASAL CORTISOL OVER THE TWO VISITS (Visit 7-2) [1/22/97 P-51, Table H.2]							
Treatment (n)	Visit 2 (Baseline)			Visit 7			Visit 7-2
	PreStim.	Stim.	Stim-PreStim (% mn chng)	PreStim.	Stim.	Stim-PreStim (% mn chng)	PreStim Dif (% mn chng)
Budesonide (131)	275	578	110	273	585	114	-0.7
Nasalcrom (70)	296	593	100	292	586	100	-1.35

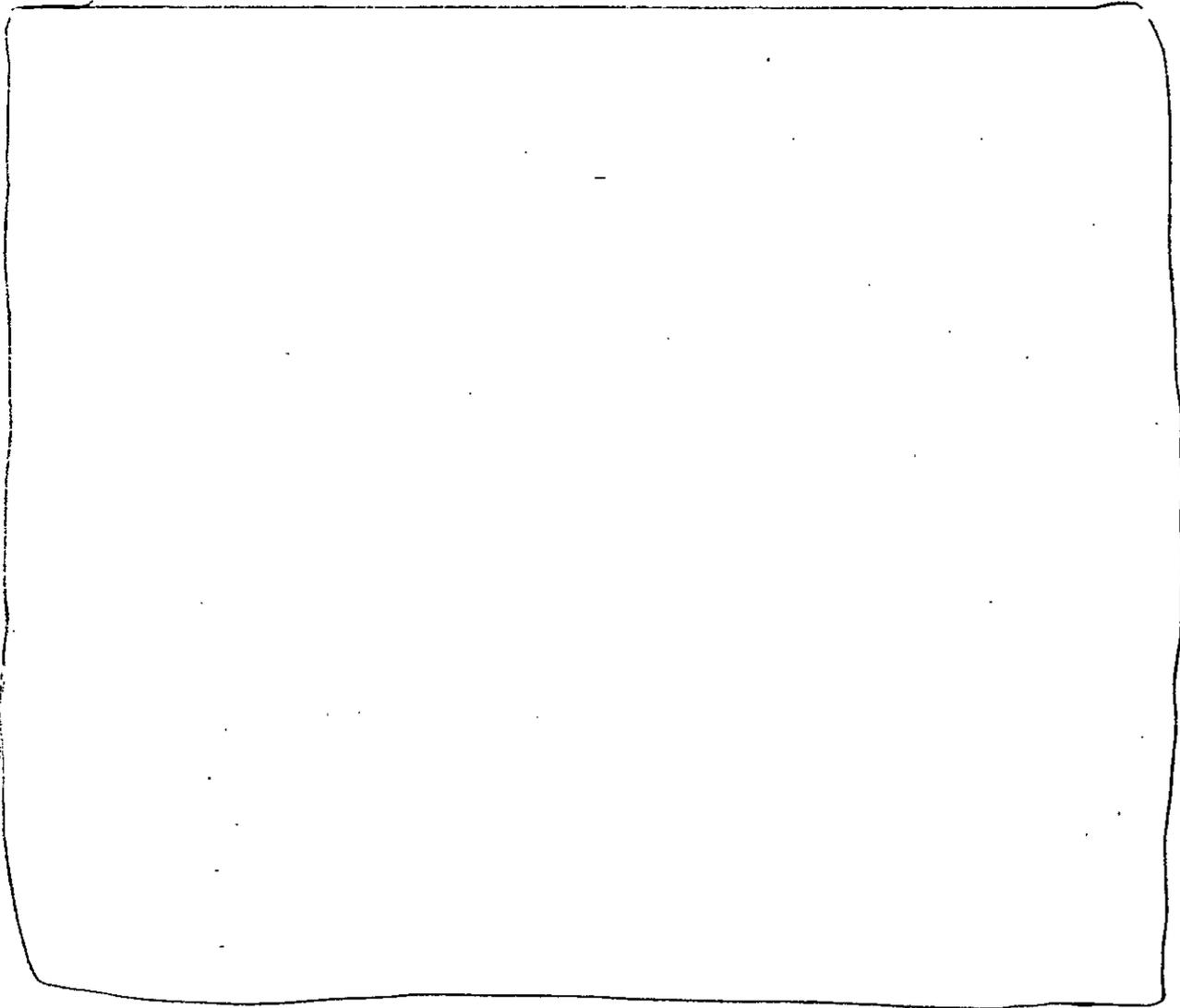
These data do not suggest HPA axis suppression by budesonide, as evaluated by these measures.

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## **LABELING**

The most recent labeling proposals are included below. A full labeling review will be prepared when the labeling proposals have been finalized and this drug has been approved. Selected labeling proposals have been extracted and are presented for ready reference and comparison with the efficacy and safety findings in this review.

Indications: "Rhinocort Aqua Nasal Spray is indicated for the management of symptoms of seasonal or perennial allergic rhinitis in adults and children, 6 years and older" [1:10, 6/13/97:12].



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