CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

MEDICAL REVIEW(S)

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MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-746	**APPLICATION TYPE:**	NDA Safety Update 2
SPONSOR:	Astra USA	**PROPRIETARY NAME:**	Rhinocort Aqua
CATEGORY:	corticosteroid	**USAN NAME:**	budesonide
		ROUTE:	intranasal
MEDICAL OFFICER:	R. F. Anthracite	**REVIEW DATE:**	31 August 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
27 February 1998	2 March 1998	safety update	

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY:

This one-year safety update spanned the dates, 31 July 1996 through 31 July 1997, since the last data submitted in the 120-day safety updated. It included data from two completed U.S. trials, 05-3046 and 05-3047, two completed non-U.S. trials, 05-3021 and 05-3031 as well as a smattering of reports from [redacted] trials that are ongoing]. Local respiratory tract AE's predominated, as has been previously reported. Uniquely in this submission, 'sinusitis' was about twice as frequently associated with Rhinocort Aqua than with either of the active controls, Beconase or Nasalcrom. Statistically significant growth suppression in prepubertal children was found in a large randomized, open-label, parallel-group trial during a one-year treatment period. A lesser increase in bone mineral density was also seen in these prepubertal children treated with Rhinocort Aqua than with Nasalcrom, further suggestion of a systemic corticosteroid effect.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION

New Clinical Studies:	_____	**HOLD**	XXX	**MAY PROCEED**
NDA/Efficacy/Label Supplements:	_____	**APPROVABLE**	_____	**NOT APPROVABLE**

SIGNATURES

Reviewer: /S/ _____ **Date:** 31 August 1998

Team Leader: /S/ _____ **Date:** 8/31/98

SUMMARY

This one-year safety update spanned the dates, 31 July 1996 through 31 July 1997, since the last data submitted in the 120-day safety updated. It included data from two completed U.S. trials, 05-3046 and 05-3047, two completed non-U.S. trials, 05-3021 and 05-3031 as well as a smattering of reports from [redacted] trials that are ongoing [5:8-10].

Local respiratory tract AE's predominated, as has been previously reported. Uniquely in this submission, 'sinusitis' was about twice as frequently associated with Rhinocort Aqua than with either of the active controls, Beconase or Nasalcrom. Statistically significant growth suppression in prepubertal children was found in a large randomized, open-label, parallel-group trial during a one-year treatment period. A lesser increase in bone mineral density was also seen in these prepubertal children treated with Rhinocort Aqua than with Nasalcrom, further suggestion of a systemic corticosteroid effect.

REPORT COMPOSITION

The breakdown of the four major study protocols that were included in this report are found in the following summary table. The table does not include [redacted] ongoing [redacted] studies which will eventually enroll [redacted] patients, but which contributed little real information to the current report. Two completed U.S. studies contributed 514 patients to the data base, 339 of which took Rhinocort Aqua and 175 took placebo. Two completed non-U.S. studies included 452 patients of which 170 took Rhinocort Aqua, 45 took Rhinocort Turbuhaler, 125 took an active comparator and 112 took placebo [5:11, 17].

DESIGN FEATURES OF THE MAJOR STUDIES IN THIS SAFETY UPDATE [5:14]

Study Number	Control	Budesonide Dose	Design (Duration)	Patients
COMPLETED U.S. STUDIES (n=514)				
05-3046	Nasalcrom 10.4 mg QID	Rhinocort Aqua 256 µg QD	open-label, randomized, parallel-group (12 months)	313 children with PAR*
05-3047	Beconase AQ 168 µg BID	Rhinocort Aqua 256 µg QD	open-label, randomized, parallel-group (12 months)	201 adults with PAR*
COMPLETED NON-U.S. STUDIES (n=452)				
05-3021	Placebo	Rhinocort Aqua 128 µg BID, Rhinocort DPI** 100 µg BID	double-blind, placebo-controlled (6 weeks)	138 adults with nasal polyposis
05-3031	Placebo, Fluticasone propionate 200 µg QD	Rhinocort Aqua 128 µg BID	double-blind, placebo-controlled, randomized, parallel-group (6 weeks)	314 adults with PAR*

*PAR = Perennial Allergic Rhinitis
**DPI = Dry Powder Inhaler

AE's were reported by 78% of the patients in the two long-term U.S. trials and the most frequent were respiratory infection (41%), sinusitis (15%), headache (14%) and flu-like syndrome (8%). Sinusitis was more frequently associated with Rhinocort Aqua (19%) than with patients receiving either Beconase (9%) or Nasalcrom (8%). Analyses of AE's by gender, age (ages: 6-12, 13-17, 18-59 and >59 years), ethnic group, intensity, and time to onset were unrevealing. However analysis of putative causality showed that epistaxis and rhinitis were most commonly attributed to Rhinocort Aqua treatment (60% and 29%, respectively) [5:48, 51, 54, 63, 70, 77, 84].

EFFECT ON GROWTH IN CHILDREN

Study 05-3046 was a randomized, active-contolled, open-label study comparing the effects of Rhinocort Aqua (256 µg per day) to Nasalcrom (41.6 mg per day) on growth in children ages 6-17 years treated for 52 weeks. Summaries and analyses were performed separately for prepubertal (Tanner Stage I at screening) and for pubertal patients [5:89]. A total of 313 patients were randomized and received study drug; 206 received Rhinocort Aqua and 107 received Nasalcrom. The study population was primarily prepubertal (77%) and male (66%) with a mean age of 9.3 years. Mean total growth in prepubertal patients over the 52-week treatment period was 5.23 and 6.02 cm in the Rhinocort Aqua and Nasalcrom treatment groups, respectively, which achieved statistical significance. Mean prepubertal growth velocity over the same one-year span was 5.20 and 5.98 cm/year in the Rhinocort and Nasalcrom groups, respectively, and was also significant [3:8]. Normalized bone mineral density in prepubertal children increased less in the Rhinocort-treated group than in the group treated with Nasalcrom, barely missing statistical significance [3:271, 5:91].

[redacted]

SERIOUS ADVERSE EVENTS (SAE's)

A total of 21 SAE's were reported, 11 from the two completed U.S. studies and 10 from the [redacted] protocols. None derived from the two completed non-U.S. studies [5:19]. Narrative summaries of patients suffering SAE's who were exposed to Rhinocort Aqua in the completed trials were reviewed and include diverse diagnoses [5:30, 37].

Study 05-3046 (n=1 patient)
pharyngitis (tonsillectomy)
Study 05-3047 (n=5 patients)
basal cell skin carcinoma, colon carcinoma, depression, bronchospasm (2)

[redacted]

DISCONTINUATIONS DUE TO ADVERSE EVENTS

A total of 24 patients discontinued prematurely due to AE's in this report; 18 from the two completed U.S. protocols and 6 from the two completed non-U.S. studies. None were reported from the [redacted] protocols [5:19, 107]. Narrative summaries of patients who discontinued prematurely because of AE's and who were exposed to Rhinocort Aqua in the completed trials were reviewed and once again did not reveal any common elements not previously discovered [5:32, 100].

Study 05-3046 (n=6 patients)

nasal irritation, dyspnea, bronchospasm, taste perversion, rhinitis/infection (2)

Study 05-3047 (n=5 patients)

rhinitis, depression, fibromyalgia, moniliasis, nasal septal perforation

Study 05-3031 (n=2 patients)

chondrosarcoma, accident/injury

POST-MARKETING EXPERIENCE

Reports were from 21 countries for all intranasal formulations of Rhinocort including pressurized metered dose inhaler (pMDI), dry powder inhaler (Turbuhaler) and Rhinocort Aqua. The current submission included the 118 spontaneous reports that were previously reviewed and reported in the 120-day safety update and gave a total of 329 spontaneous reports of AE's associated with a Rhinocort intranasal formulation. These were broken down by formulation as follows: 57 (12.7%) in conjunction with Rhinocort Aqua, 224 (68%) associated with Rhinocort pMDI, 36 (11%) with Rhinocort Turbuhaler and in 13 cases the formulation was unidentified. No deaths were reported and SAE's have been of diverse etiologies: alopecia, nasal septal perforation, anosmia, hypokalemia, amnesia, implant infection, missed abortion, Paget's disease of bone, retinal disorder and psychosis. Nasal septal perforation again emerged as a frequently reported SAE and as a non-serious AE [5:108-9,111-5].

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

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ON ORIGINAL

JUL 14 1997

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: 20-746	APPLICATION TYPE: NDA
SPONSOR: Astra USA	PRODUCT/PROPRIETARY NAME: Rhinocort Aqua
	USAN / Established Name: budesonide
CATEGORY OF DRUG: corticosteroid	ROUTE OF ADMINISTRATION: intranasal
MEDICAL REVIEWER: R. F. Anthracite	REVIEW DATE: 7/9/97

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
7/29/96	7/30/96	NDA	
11/4/96	11/5/96	Query Responses	legacy from departing MO
11/8/96	11/12/96	Query Responses	legacy from departing MO
11/13/96	11/14/96	Computer Transfer	
11/15/96	11/19/96	Query Responses	legacy from departing MO
11/20/96	11/21/96	Query Responses	legacy from departing MO
11/27/96	11/29/96	Query Responses	legacy from departing MO
12/3/96	12/4/96	Safety Update(SU)	120-day information
12/6/96	12/6/96	Computer Transfer	CANDA Acrobat files on CD
1/22/97	1/23/97	SU Addendum	
3/6/97	3/7/97	Query Responses	3038, 3046 cortisols; 3039 dose-response linear regression
6/3/97	6/4/97	Cortisol Tables	2071 table corrections
6/13/97	6/16/97	Query Response	2071 heights & cortisols

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review:

Four doses of intranasal budesonide 32, 64, 128 & 256 µg/day were all equally and significantly more efficacious than placebo in reducing a ten-point combined nasal symptom score for seasonal and perennial allergic rhinitis patients who were ≥ 6 years of age. Reduction in 24-hour urine cortisols was seen most convincingly in children over months to years of follow up without any concomitant reduction in basal (morning) or Cortrosyn-stimulated serum cortisols. Evidence of growth retardation in prepubertal children was reported at doses ≥ 128 µg/day.

Outstanding Issues:	
Recommended Regulatory Action:	N drive location:
New Clinical Studies: _____ Clinical Hold	_____ Study May Proceed
NDAs:	
Efficacy / Label Supp.: ✓ Approvable	_____ Not Approvable
Signed: Medical Reviewer: /S/ /S/	Date: 7/9/97
Medical Team Leader: /S/	Date: 7/14/97

T.L.: See T.L. memo. Agree that Rhone-Poulenc is approvable. Labeling review to follow.

/S/ 7/14/97

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EXECUTIVE SUMMARY OF EFFICACY AND SAFETY

The two pivotal trials, 3038 and 3039, and five supplementary studies, 3006, 3011, 3012, 3024 and 3030, evaluated the efficacy of intranasal aqueous budesonide (Rhinocort Aqua), given once daily for treatment of perennial and seasonal allergic rhinitis (PAR, SAR). The primary efficacy variable in the pivotal trials was the nasal index score (NIS), a ten-point (0-9) symptom scale comprised by the addition of three component nasal symptoms, sneezing, rhinorrhea and obstruction, each rated on a four-point scale (0-3).

Two placebo-controlled pivotal trials of over 800 pediatric and adult patients demonstrated that virtually all doses of the aqueous budesonide nasal spray (32, 64, 128 and 256 µg/day) produced average daily NIS changes from baseline that were significantly better than placebo. Analysis of individual symptom score components of the NIS showed similar results for each. No dose proportionality was evident for combined or individual symptoms scores in either pivotal study. Exploratory analyses of pediatric (5 years < age < 18 years) and adult subsets showed less impressive treatment effects in the pediatric group. A retrospective analysis of onset-of-action in 3039, the PAR study, demonstrated some separation of the NIS change-from-baseline group mean, over all active treatments, from placebo as early as 24 hours after initiating treatment. This difference from placebo increased from 24 to 72 hours, the end of the exploratory onset-of-action analysis. At 72 hours, the NIS score difference between active treatments and placebo was about 2/3 of that found over the entire treatment period. Another retrospective onset-of-action analysis was submitted with 3030, a four-week European SAR study of over 600 adult patients comparing two doses of Rhinocort Aqua with intranasal fluticasone and placebo. At 50-60 hours after starting Rhinocort Aqua treatments, the difference from baseline in the NIS was about 70% of the point estimate for the entire treatment period. This was quantitatively very similar to the findings in 3039.

Five supplementary trials were all conducted outside of the United States. Rhinocort Aqua doses ranged from 128 to 400 µg, and were usually administered once daily, except for 3012, in which total daily doses of 256 and 400 µg were divided for twice daily administration. The supplementary studies were exclusively in adult patients (age > 17 years) except for 3006, which included patients as young as 12 years of age. Most of these supplementary studies included positive controls: e.g., the budesonide pressurized metered dose nasal inhaler (3006); beclomethasone nasal spray (3011); fluticasone nasal spray (3030); and, azelastine nasal spray (3024). Budesonide efficacy in all supplementary studies supported the findings in the pivotal trials: all tested Rhinocort Aqua doses were statistically significantly better than placebo in terms of single and/or combined nasal symptom scores; no dose proportionality was evident between different daily doses of aqueous budesonide; and, no differences between budesonide and other intranasal corticosteroid positive controls were found.

Other symptom score efficacy endpoints were secondary in the pivotal trials and sometimes co-primary in supplementary studies. The supplementary trials were replete with

multiple primary endpoints, none of which were statistically corrected for attendant Type I errors. The Overall Evaluation of Treatment Efficacy deserves special note because its name implies a global evaluation. In the SAR trial 3038, this secondary endpoint was measured for each individual nasal symptom, somewhat at odds with the implication of its name. In other trials, it was a global measure. In all cases, it added no new information above that supplied by the combined and individual symptom scores. Quality of Life was determined by two published instruments in 3039. One test was validated in adolescents and showed no overall difference between placebo and any treatment. An instrument validated and applied to adult patients found significant differences of treatment from placebo in the highest and lowest dose groups (32 and 256 μg/day) in overall score. Ocular symptom scores did not reveal any consistent treatment effects.

Various antihistamine rescue medications in several studies showed significant reductions in treatment groups compared with placebo. The magnitude of this difference in pill consumption from placebo was usually between 0.5 to 2 pills per week, though one study (3030) found a difference of 3.5 pills per week. The PAR trial 3039 showed a qualitative decrease in nasal eosinophils from baseline in active treatment groups that was significantly different from placebo. This was most apparent in the pediatric age group, which also showed a concomitant and dose proportional increase in nasal bacteria. Small declines in circulating platelet counts were associated with treatment in both pivotal trials, but the significance of this is unknown.

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 μg 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. 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 cortisols from baseline. Both of these effects persisted for at least two years. Neither morning serum cortisols nor Cortrosyn-stimulation testing revealed any evidence of adrenal suppression.

REVIEWER RECOMMENDATION

Rhinocort Aqua is unquestionably efficacious in the treatment of adults with both seasonal and perennial allergic rhinitis at all doses tested, from 32 to 256 μg given once daily in the morning, without any dose proportionality in any outcome variable. Therefore, it is difficult to recommend criteria by which dose titration might be accomplished. As currently formulated, the lowest dose that the to-be-marketed formulation delivers is 32 μg/spray, or 64 μg given once daily. There is a potential for growth retardation in prepubertal children

treated with ≥ 128 µg/day of Rhinocort Aqua, as well as less dramatic efficacy in the pediatric age group at all doses. A once daily dose of 64 µg (32 µg/spray) should be the recommended starting dose for adults. It is likely that this medication is also efficacious in children, from a host of other public domain material available. However, the choice of dose will be complicated by the possibility of growth retardation in this younger age group that was indicated in two open-label studies.

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NOTE TO READERS

Square brackets are used throughout this review to include references to the original NDA volumes and pages. FAX communications and teleconferences are distinguished by the words, 'FAX' or 'Telecon' preceeding a date and optional volume and page reference. A leading date indicates a separate submission and is followed by an optional volume number and a page reference. Several volumes/pages, submissions and events may all be referenced in one set of brackets, [VOL:PAGE, PAGE-Page, VOL:PAGE-Page, DATE VOL:PAGE, 'TELECON' DATE].

CONDUCT OF THE REVIEW

The safety profile of intranasal steroids was reasonably well typified, so the initial evaluation of this NDA was directed at the efficacy findings of the two pivotal trials, 3038 and 3039, with secondary emphasis on safety. The five supplementary efficacy protocols were reviewed next, 3006, 3011, 3012, 3024 and 3030.

DESIGN FEATURES OF SEVEN PRIMARY, RANDOMIZED, PLACEBO-CONTROLLED EFFICACY STUDIES [1:159-60]

Study/Country (# randomized)	Controls	Rhinocort Aqua Dose	Design	Patients	Treatment Duration
Seasonal Allergic Rhinitis					
3038/US (406)	placebo	256, 128, 64 & 32 µg QD	DB	adults & children (≥ 6 years)	4 weeks
3006/Canada (318)	Aqua placebo & Rhinocort pMDI 200 µg BID	400 & 256 µg QD	DB Aqua, SB pMDI	adults & children (≥ 12 years)	3 weeks
3011/Norway (233)	Aqua placebo & BDP 200 µg BID	256 µg QD	DB Aqua, SB BDP	adults	3 weeks
3030/UK & Denmark (602)	Aqua placebo & FP 200 µg QD	256 & 128 µg QD	DB Aqua, SB FP	adults	4-6 weeks
Perennial Allergic Rhinitis					
3039/US (478)	placebo	256, 128, 64 & 32 µg QD	DB	adults & children (≥ 6 years)	6 weeks
3012/Canada (239)	placebo	200 & 128 µg BID	DB	adults	6 weeks
3024/UK (195)	Aqua placebo & AZE 280 µg BID	256 µg QD	DB Aqua, SB AZE	adults	6 weeks

BDP = beclomethasone dipropionate nasal spray
FP = fluticasone propionate nasal spray
AZE = azelastine nasal spray

A general safety review was based on the Integrated Safety Summary, and included separate review of two growth studies in pre-pubertal children, 2071 and 3046, as well as a separate review of a long-term, open-label extension to the pivotal study 3039, 3047.

All case report forms (CRF's) on each patient who terminated prematurely because of an adverse event (AE) in the two pivotal trials were reviewed. No discrepancies between these CRF-data and line listings were found. The two deaths identified in supportive trials underwent similar scrutiny [186: all pages, 187: all pages, 189:296-352, 192:287-405, 193:all pages, 194:1-60]. The only discrepancy from summary reports identified was the absence of CRF's for the mother of an aborted anencephalic fetus. A 26-year old female on birth control pills found she was pregnant 15 days after completion of the study. An ultrasound was obtained because a fetal heart beat was not detected and it showed spina bifida and anencephaly. The patient aborted a fetus estimated to be at 8 weeks gestation. The double-blind treatment code was not broken at the time of the only report, in the ISS. The aborted fetus was considered to be a 'death' and an AE, but the study participant wasn't involved and her CRF's were not made available [111:90, Telecon 6/30/97 with Dave Pizzi of Astra].

CHEMISTRY, MANUFACTURING AND CONTROL

Rhinocort Aqua Nasal Spray (budesonide) is designated chemically as [(RS)-11-Beta, 16-Alpha, 17, 21-Tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde]. Budesonide is a mixture of two epimers (22R and 22S) both of which have a high glucocorticosteroid activity. Its empirical formula is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Budesonide is a white to off-white, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol and freely soluble in chloroform.

It is an intranasal spray inhaler containing micronized budesonide in a suspension of microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, hydrochloric acid for adjustment to pH 4.5 and purified water. Rhinocort Aqua Nasal Spray is available in two dose strengths 32 or 64 μg. These doses represent the dose delivered to the nose following each actuation. Each bottle contains at least 120 metered sprays and this formulation is free of propellants [1:2-3, 86].

CLINICAL PHARMACOLOGY

Budesonide is a glucocorticosteroid having a potent glucocorticoid activity and weak mineralocorticoid activity. Glucocorticosteroids are thought to have a wide range of inhibitory activities against multiple cell types and mediators involved in allergic and non-allergic mediated inflammation. They seem to have a greater effect on the delayed (6-hour) response to antigen challenge than on the immediate response (20 minutes), though the clinical significance of this is unknown [1:3-4].

Budesonide is rapidly and extensively biotransformed by the liver to metabolites found to be much less potent than the parent compound. In vitro studies with human liver homogenates have shown budesonide to be rapidly metabolized to two major metabolites, 16α-hydroxy-prednisolone and 6β-hydroxybudesonide, catalyzed by cytochrome P450 3A isoenzymes. The glucocorticoid activities of these two metabolites are < 1% of that of the

parent compound. Low systemic effects were hoped for on the basis of extensive first-pass hepatic degradation and low potency of the metabolites. Fatty acid conjugation of budesonide is a novel metabolic pathway that takes place in the airway tissue. The fatty acid conjugates can be hydrolyzed, enzymatically, regaining budesonide. The potential for an intranasal steroid to cause systemic adverse events, is dependent on the rate and extent of metabolic inactivation and on the extent of absorption. Following nasal application of the aqueous suspension, the systemic availability of budesonide was 13-14% of the dose [1:24-5, 94]. This is comparable to the 20% systemic availability of the U.S. approved pressurized metered dose nasal inhaler which delivers a starting dose of 256 µg daily [1997 Physicians' Desk Reference:552].

Particle deposition studies showed that the aqueous spray was concentrated mostly in the anterior part of the nose and that no particles reached the lung. Thirty minutes after administration, 56% of the particles were retained at the initial site of deposition. Another study of different combinations of metered volume and spray-cone angles showed deposition similar to the first study, regardless of volume and angle [1:90].

Theoretically, it might be expected that the metabolism of budesonide would be affected in patients taking other drugs that inhibit or are metabolized by CYP3A; e.g, ketoconazole, troleandomycin, erythromycin and cyclosporin. In healthy subjects, coadministration of budesonide and ketoconazole increased budesonide plasma concentrations and increased relative systemic availability by a factor of 8. Small, or no effects on budesonide kinetics were found when it and omeprazole or cimetidine were administered together [1:95].

Patients with biopsy-proven hepatic cirrhosis have been given oral and intravenous budesonide and the systemic availability and plasma concentrations of budesonide approximately doubled. Studies in patients with kidney dysfunction have not been performed. Intact budesonide is not excreted by the kidneys, but the metabolites are and might reach higher levels in patients with renal impairment. However, the metabolites have negligible corticosteroid activity. No PK studies in the elderly have been formerly undertaken. Differential gender analysis was done in two Pulmicort studies and no differences in PK parameters were found. Intranasal budesonide, administered to 7-14 year-old children, produced plasma concentrations that were about twice as high as in adults. Intravenous infusion in children resulted in systemic clearance per kilogram body weight that was higher, and a plasma half-life that was shorter, than in adults from cross-study comparisons [1:96-7].

FOREIGN MARKETING HISTORY

Rhinocort Aqua, the aqueous suspension spray, has been approved for treatment of seasonal or perennial allergic rhinitis in a number of countries. In addition, there are two other marketed formulations of Rhinocort (budesonide), the pressurized metered dose nasal inhaler and the dry powder Turbuhaler. The earliest of these international approvals was 1982 when Denmark approved the pressurized metered dose nasal inhaler. In 1986,

Denmark, Finland, Sweden and New Zealand approved the aqueous suspension formulation. Since, and including these beginnings, the aqueous formulation has been approved in 34 countries, the pressurized metered dose inhaler formulation in 43 and the dry powder inhaler in 24. Another 4-8 countries have one or another of the three formulations under evaluation.

In July 1989, aerosol-based drug delivery systems were withdrawn from the Swedish market following the ban on the use of chlorofluorocarbons (CFC's) in Sweden. The nasal inhaler was subsequently withdrawn from the markets in several countries due to the Montreal Protocol and its Copenhagen Amendments regarding production and use of CFC's [1:27-31].

In 1984, the results of the first pre-clinical carcinogenicity study was released to various countries. This showed an increased frequency of gliomas in male rats. A second study was carried out in male rats and failed to confirm the increased frequency of gliomas, but did find an increased frequency of hepatocellular tumors. Hepatocarcinoma was found in concurrent reference treatments, prednisolone and triamcinolone. A third male rat study did not demonstrate an increased frequency of either gliomas or hepatocellular tumors. In 1985, the U.K. decided that the license to market should not be revoked. Earlier this year, Rhinocort Aqua passed review by the CDER Carcinogenicity Assessment Committee [5/30/97 Review & Evaluation of Pharmacology & Toxicology Data, Luqi Pei, Ph.D.].

05-3038 A DOUBLE-BLIND COMPARISON OF FOUR DOSES OF RHINOCORT® AQUA PUMP SPRAY (BUDESONIDE) AND PLACEBO IN THE TREATMENT OF ADULTS AND CHILDREN WITH SEASONAL ALLERGIC RHINITIS

SUMMARY

This was a U.S., two-region, fourteen-center, four-double-blind-week, placebo-controlled, parallel-group trial of over 400 seasonal allergic rhinitis (SAR) patients with ages ≥ 6 years who had demonstrated ragweed allergy. Three concentrations of budesonide were administered as one or two active-drug intranasal sprays administered to each nostril once daily. The total daily treatment doses were 32, 64, 128 and 256 μg and the rescue medication was chlorpheniramine. The primary efficacy variable was the change from baseline in average nasal index score (NIS) which ranged from 0-9. This score was a composite of nasal obstruction or congestion, runny nose and sneezing each of which was rated as a score ranging from 0-3. All doses were significantly different from placebo, but no convincing dose proportionality was shown by the NIS. That is the lowest daily dose (32 μg) was as efficacious as the highest (256 μg). The three symptom components of the NIS were separately and significantly different from placebo at virtually all doses. Among the secondary efficacy variables, nasal itching also showed significantly decreased symptoms compared with placebo, but ocular symptoms (itching, tearing and redness) were unaffected. Adverse events (AE's) were very slightly more common in the budesonide group than the placebo group, but there was no dose proportionality. Basal cortisols and Cortrosyn-stimulated serum cortisols, taken at one point in time, were evaluated before and after four weeks of treatment. No changes in these measures of adrenocortical function differentiated any of the treatment groups. Small dose-proportional decreases in platelet count were noted, but shift tables did not reveal major changes in individuals and no episode of non-local bleeding diathesis was reported.

OBJECTIVE

The purpose was to determine the therapeutic efficacy and safety of four dosages of budesonide administered once daily by an intranasal aqueous suspension pump spray versus placebo in adults and children with ragweed-induced allergic rhinitis [31:42].

PROTOCOL

This was a randomized, placebo-controlled, double-blind, multicenter (14), multi-dose (4), six-week study of adult (age ≥ 18 years) and pediatric (age 6-17 years) patients in two geographic regions that was carried out between August and October 1994 [31:21, 43]. The study consisted of four clinic visits (Visits 1 through 4). There was a one-week, single-blind, placebo, baseline period followed by a four-week, double-blind treatment period. The baseline period was seven days, extended to 14 days if nasal symptoms were insufficient, or if rescheduling of the visit was necessary. After randomization at Visit 2, patients returned to the clinic every two weeks for Visits 3 and 4. A deviation of ± 3 days was permitted for

scheduling these visits. At the end of the study, patients were treated according to the routines at the clinic [31:51-2].

SAR STUDY 3038 – PROCEDURE FLOW DIAGRAM [31:55]				
Procedure	Visit (Week)			
	1 (-1)	2 (0)	3 (2)	4 (4)
History, Physical Exam & Skin Test	X			
Nasal Exam	X	X	X	X
Lab Assessment (1) & Serum Pregnancy Test (1)	X			X
Urine Pregnancy Test (1)		X	X	
Basal (a.m.) Cortisol Test (1,2)	X			X
ACTH - Stimulation Test (2)	X			X
Overall Evaluation of Efficacy			X	X
Adverse Events		X	X	X
(1) Repeat, if necessary, (once only) prior to Visit 2 (2) At 10 selected sites				

TREATMENT

The test drug was budesonide, administered as an aqueous suspension at concentrations of 0.32 mg/mL, 0.64 mg/mL and 1.28 mg/mL provided in 10 mL glass bottles fitted with a mechanical pump spray. Each actuation delivered 50 µl, i.e., 16 µg, 32 µg and 64 µg of budesonide, respectively, and each bottle contained at least 100 doses. At the conclusion of Visit 1, patients received two identical bottles of budesonide placebo, labeled A and B, and were instructed to take one dose (actuation) in each nostril, from each bottle, daily in the morning. Patients were instructed to administer the first dose using bottle A followed by bottle B. At Visits 2 and 3, patients received two new identical bottles and the same instructions. Patients on active treatment received either 32 µg, 64 µg, 128 µg or 256 µg daily according to the following scheme.

INTRANASAL DOSING REGIMEN			
Daily Dose	Treatment Bottle		Total Number of Bottles
	A	B	
Placebo	Placebo	Placebo	2
32 µg	16 µg per actuation	Placebo	2
64 µg	32 µg per actuation	Placebo	2
128 µg	64 µg per actuation	Placebo	2
256 µg	64 µg per actuation	64 µg per actuation	2

The placebo was said to be identical to the active drug. Test drugs and placebo were manufactured by Astra in Södertälje, Sweden. The batch numbers of the test drug used in this study were:

0.32 mg/mL (16 µg/dose) = UE 12
0.64 mg/mL (32 µg/dose) = UE 13
1.28 mg/mL (64 µg/dose) = TI 21

Commercially available 4 mg Chlor-Trimeton tablets or 2 mg/5 mL Chlor-Trimeton syrup, manufactured by [redacted] was used as rescue medication with the following dosing instructions [31:49-51, 54]:

Age 6-12 years	0.5 tablet (2 mg) p.r.n. up to a maximum of 3 tablets in 24 hours (12 mg).
	or
	One teaspoonful p.r.n. up to a maximum of 6 teaspoonfuls in 24 hours (12 mg).
Age > 12 years:	One tablet p.r.n. up to a maximum of 4 tablets in 24 hours (16 mg).

PATIENTS

Five hundred and sixty-four patients were screened for entry into the study, of which 406 were randomized to participate in the double-blind portion. Approximately 20% of these were randomized to each of the treatment groups (range 19.2% to 20.4%) [31:80]. The distribution of a host of demographic variables among the treatment groups at baseline is demonstrated in the following table.

PATIENT BASELINE DEMOGRAPHIC CHARACTERISTICS OF TREATMENT GROUPS [31:81]

Statistic	Characteristic	Placebo (n=83)	32 µg (n=78)	64 µg (n=79)	128 µg (n=83)	256 µg (n=83)	Total (n=406)
COUNTS	Male	49	38	47	47	43	224
	Female	34	40	32	36	40	182
	Caucasian	72	73	64	70	73	352
	Black	7	3	11	8	7	36
	Oriental	0	0	2	0	1	3
	"Other" Race	4	2	2	5	2	15
MEANS	Rhinitis Duration (yrs)	14.9	15.1	13.7	14.4	15.2	14.7
	Age (yrs)	25.6	25.2	24.9	25.6	25.7	25.4
	Height (inches)	64.2	64.9	64.5	64.7	64.3	64.5
	Weight (lbs)	144.3	148 1	141.7	147.9	136.9	143.7

Patients reported taking medications prior to enrollment and these were categorized as: 1)systemic antihistamines; 2)nasal preparations; 3)analgesics; 4)allergens; 5)cough and cold preparations; and, 6)unspecified. All treatment groups had very similar numbers of patients and percent of patients that reported using medications in each of these categories [31:139].

Inclusion Criteria [31:45-6]:

1. Age ≥ 6 years of either gender.
2. Clinical diagnosis of ragweed-induced allergic rhinitis for ≥ 2 years. The previous years symptoms should have been at least "moderate" (≥ 2+) and required treatment with at least antihistamines. Ragweed sensitivity was verified by a positive skin test, 2+ or greater, within the previous 12 months.
3. At least 2/3 of the following symptoms: 1)blocked nose, 2)runny nose, or 3)sneezing during ≥ 4/7 days during the 7-14 day baseline period. At least 1/3 nasal symptoms should have had a score ≥ 2 ("moderate") during the four days.

Exclusion Criteria [31:46-49]:

1. Significant current medical diseases.
2. History of carcinoma, excluding basal cell carcinoma, within the past five years. A history of psychosis or poor motivation that might invalidate the consent.
3. Planned inpatient hospitalization during the study.
4. Clinically significant baseline laboratory test which may have either put the patient at risk because of participation, may have influenced the results or the influenced the patient's ability to participate.
5. Female patients of childbearing potential unless surgically sterile or using medically accepted contraceptive measures. All female patients of childbearing potential must have had a negative serum pregnancy test at Visit 1.
6. Patients recently exposed, or at risk of being exposed, to chicken pox or measles.
7. Patients with known hypersensitivity to budesonide or Chlor Trimeton.
8. Structural abnormalities of the of the symptomatic enough to cause nasal obstruction, as judged by the investigator.
9. Nasal conditions, including infectious rhinitis, sinusitis, rhinitis medicamentosa, atrophic rhinitis and perennial rhinitis. Patients with coexisting perennial rhinitis may have been included if seasonal allergic rhinitis showed clear exacerbations.
10. Upper respiratory tract infection ≤ 2 weeks prior to Visit 1.
11. Treatment with any of the following medications:
    A. Topical nasal glucocorticosteroid ≤ 1 month of Visit 1.
    B. Immunotherapy for ragweed pollen for < 6 months, or not on a stable maintenance dose.
    C. Short-acting antihistamines, topical or oral decongestants, vasoconstrictors, or other medications which could mask the symptoms of rhinitis; e.g., tricyclic anti-depressants, major tranquilizers or anti-epileptic agents, within three days of enrollment (Visit 1).
    D. Long-acting antihistamine use: terfenadine < 2 days, loratadine < 4 days or astemizole < 12 weeks before Visit 1.
    E. Nasal cromolyn sodium or nedocromil < 2 weeks prior to Visit 1.
    F. Systemic glucocorticosteroid therapy < 2 months prior to Visit 1.
    G. Inhaled or systemic glucocorticosteroids for asthma.
12. A history of drug or alcohol abuse within < 5 years.

13. Patients planning to travel outside of the geographical region for > 3 consecutive days during the study.
14. Treatment with an investigational drug in the previous 30 days.
15. Previous randomization into the study.

PARAMETERS

The primary efficacy variable was change in nasal index score (NIS), calculated as the sum of three nasal symptoms: 1)runny nose; 2)congestion or blocked nose; and, 3)sneezing. Each was rated on a 0-3 scale, assessed each morning and recorded in the patient diary [31:42, 57].

0 = no symptoms
1 = mild symptoms -- present but not troublesome
2 = moderate symptoms -- frequently troublesome, but not sufficient to interfere with normal daily activity or night-time sleep
3 = severe symptoms -- sufficiently troublesome to interfere with normal daily activity or night-time sleep

The NIS was used to determine the sample size for inferential statistical analysis and was calculated as the baseline average, over the seven days before treatment, compared with the average over the four-week treatment period. Patients were included in the analysis if they had baseline and at least one double-blind observation. The average NIS for the treatment period was calculated as the average over those days for which data were available in patients who withdrew prematurely [31:67-8].

Secondary efficacy analysis was performed on the NIS for days which were considered part of the peak rhinitis season based on daily pollen counts [31:61]. Other secondary variables included individual nasal symptom scores (congestion, runny nose, sneezing and nasal itching), ocular complex symptoms (itching, redness and tearing) and amount of rescue medication taken [31:69, 73-4]. The Overall Evaluation of Efficacy by the patient was a scaled estimate of the treatment effect on nasal symptoms [31:58].

0 = symptoms were aggravated
1 = no control over symptoms
2 = minor control over symptoms
3 = substantial control over symptoms
4 = total control over symptoms

Safety analyses of AE's, clinical laboratory measurements, vital signs and physical examinations were performed on all randomized patients. AE's were elicited only at clinic visits by posing the following question, "Have you experienced any health problems or other symptoms not usually related to your hay fever since the last visit?" Responses to this query, as well as spontaneous patient reports of symptoms, were recorded as AE's. Both basal and Cortrosyn Stimulation Test cortisol levels were collected at ten centers at Visits 1 and 4 [31:60-1, 74]. Laboratory safety variables drawn at each visit consisted of venous blood samples for:

RBC count, hemoglobin, hematocrit, WBC count, differential count, platelet count, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase and HCG

Urine samples were analyzed for:

glucose, protein and HCG

All analyses, except urine pregnancy tests, were performed by a central laboratory, the [redacted] [31:59].

EFFICACY RESULTS

Patient participation lasted from August 18, 1994, when the first patient was enrolled, through October 31, 1994, when the last patient completed the study. The fourteen investigative sites were divided evenly between the Midwest and Northeast regions of the United States.

Primary Variable:

The primary efficacy variable, change in NIS from baseline (mean daily NIS over seven pre-treatment days) to treatment (mean daily NIS over four treatment weeks), was analyzed by ANCOVA. The model included terms for treatment, center, treatment-by-center interaction and baseline NIS. Treatment-by-center interaction was not significant and was removed from the model. Center effect and baseline NIS were adjusted for in the model. In the overall analysis of the two combined regions, all active treatment groups had significantly greater decreases from baseline, compared to placebo. In terms of the dependent variable, adjusted mean change in NIS, no dose proportional effect was in evidence. The lowest dose, 32 µg produced the same effect as doses up to eight times as large [31:87]. The following table demonstrates that every budesonide dose reduced the baseline average symptom score by about one point more than placebo (maximum NIS is nine).

MEAN CHANGE IN AVERAGE "NIS" FOR ALL PATIENTS [31:88, 151]				
Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (83)	4.9	4.2	-0.77	-1.13, -0.40
32 µg (78)	5.0	3.4	-1.64 (2)	-2.02, -1.26
64 µg (79)	5.0	3.5	-1.54 (2)	-1.92, -1.17
128 µg (83)	5.1	3.5	-1.57 (2)	-1.93, -1.20
256 µg (82)	5.1	3.2	-1.82 (2)	-2.19, -1.45
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

The magnitude of these changes in the NIS for all treatment groups was not associated with greater rescue medication use. In fact, the placebo group, with the smallest reduction in NIS also had the greatest number of patients taking rescue medication [31:85, 144-5].

The daily mean NIS, for each treatment group relative to placebo, was plotted overlaying the daily pollen count. Each of the active doses showed a similar pattern. At the beginning of double-blind treatment, when pollen counts were highest, the NIS showed little separation of placebo from active treatments for the first 1-2 weeks. The NIS fell slightly in both groups throughout the double-blind period. Following the initial two weeks, each active treatment group showed a mean daily NIS that was consistently below that of the placebo group until the last 1-2 weeks of the trial, when the pollen counts were lowest. At this end of the treatment period, the mean daily NIS of all active treatment groups matched (128 µg group) or exceeded that of placebo (other three active treatments) [31:88, 239-42]. This may indicate irritation caused by the treatment unbalanced by any treatment benefit, due to falling pollen counts.

Assessment of a dose-response effect was approached by linear regression of the NIS on the lowest and highest active treatments [31:93, 154, 253]. This analysis was considered to be inadequate because it failed to use half of the data points and the more complete linear regression analysis of all four active concentrations was requested. The slope of the regression line was not statistically different from zero for all patients taken together [3/6/97 1:56-7].

Primary Variable By Region:

In addition to the combined analysis, the study protocol required the same type of analyses be carried out on each of the two regions, separately [31:68]. The Midwest region showed results that were qualitatively similar to the combined analysis. Due to the lesser number of patients, confidence intervals were about one third wider than for the combined analysis and statistically significant difference from placebo was achieved only for the highest three doses [31:89].

MEAN CHANGE IN AVERAGE "NIS" FOR MIDWEST REGION PATIENTS [31:89, 151]				
Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (41)	4.9	4.4	-0.69	-1.21, -0.17
32 µg (42)	5.3	4.2	-1.09	-1.60, -0.57
64 µg (39)	4.9	3.4	-1.69 (2)	-2.23, -1.15
128 µg (42)	5.3	3.6	-1.65 (2)	-2.16, -1.13
256 µg (41)	5.4	3.4	-1.95 (2)	-2.48, -1.43
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

The Northeast region also produced results that were qualitatively similar to the combined analysis but with much greater variability in the adjusted mean change, among the budesonide doses. Statistical differences from placebo were found for the 32 and 256 µg doses, but not for the 64 µg dose. The 128 µg dose barely missed statistical significance

($p<0.070$) [31:90]. As was true with the Midwest region, the confidence intervals were about one third wider than for the combined analysis, due to the smaller sample size.

MEAN CHANGE IN AVERAGE "NIS" FOR NORTHEAST REGION PATIENTS [31:90, 151]				
Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (42)	4.9	4.1	-0.82	-1.34, -0.30
32 µg (36)	4.7	2.5	-2.33 (2)	-2.90, -1.76
64 µg (40)	5.1	3.6	-1.36	-1.90, -0.83
128 µg (41)	5.0	3.4	-1.49	-2.02, -0.96
256 µg (41)	4.8	3.1	-1.72 (2)	-2.25, -1.19
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

The apparently strong efficacy showing of the 32 µg dose and inconsistent dose-proportionality in the Northeast region prompted the sponsor to examine daily pollen counts at all centers in the two regions. Although not explicated in the NDA, "pollen count" and "ragweed pollen count" are used interchangeably in this document and refer to the count/m^3 of morphologically identified ragweed pollen [1/14/97 Teleconference with Dave Pizzi at Astra USA].

Daily pollen counts were collected at each site by a [redacted] device, expressed as the number of ragweed pollen grains per cubic meter and averaged within each of the two regions [31:25, 61]. Graphic displays of daily ragweed pollen counts for each study center were overlaid with time lines for treatment of each participant identified as to placebo or budesonide group. This visual display of ragweed pollen exposure for subjects during the study permitted an assessment of this across treatment groups, study centers and regions. Except for Northeast region study center #9, patients of both treatment groups over all centers seemed to have a reasonable degree of exposure to maximum available ragweed pollen counts for most of their participation in the trial [31:148-9, 234-7; 3/6/97 1:16-9]. Counts in the Northeast region were lower than counts recorded in the Midwest, though the duration of the elevated daily pollen counts was comparable in the two regions [31:78-9, 233]. The lower pollen count was advanced as an explanation for the lack of strict dose proportional changes in the NIS, in the Northeast region. It is interesting and revealing to note that both the Midwest and Northeast regions had the same average adjusted mean change over all budesonide doses, in excess of placebo (0.905 NIS) despite putative differences in ambient ragweed pollen counts.

Primary Variable By Age:

Ages 6 through 17 years defined the pediatric group and did not show a strictly dose proportional effect. All four treatments groups performed better than placebo. However, only the highest dose achieved statistical significance.[31:90-1, 313-5].

MEAN CHANGE IN AVERAGE "NIS" FOR PEDIATRIC PATIENTS [31:91, 151]				
Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (35)	4.8	4.2	-0.66	-1.25, -0.06
32 µg (33)	4.8	3.8	-1.09	-1.71, -0.47
64 µg (32)	4.8	3.9	-0.95	-1.59, -0.32
128 µg (38)	4.8	3.4	-1.41	-1.98, -0.83
256 µg (37)	4.6	3.0	-1.75 (2)	-2.34, -1.17
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

For the adult age group (age ≥ 18 years), the active treatment groups were all significantly better than placebo at reducing the NIS from baseline. All four active treatments were equally effective and no dose proportionality was seen [31:91, 313-5].

MEAN CHANGE IN AVERAGE "NIS" FOR ADULT PATIENTS [31:91, 151]				
Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (48)	5.0	4.2	-0.81	-1.29, -0.34
32 µg (45)	5.1	3.1	-2.07 (2)	-2.55, -1.58
64 µg (47)	5.1	3.2	-1.96 (2)	-2.44, -1.48
128 µg (45)	5.4	3.6	-1.69 (2)	-2.18, -1.20
256 µg (45)	5.5	3.4	-1.93 (2)	-2.42, -1.43
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

This analysis by age was retrospectively defined, so prospective inferential statistics and Type I Errors are not really applicable terms and are included here to reference the presentation of these data in the NDA document.

Secondary Variables:
NIS Components

Breakdown of the NIS into its three components, showed that each component had an adjusted mean change from baseline that was significantly different from placebo for virtually all doses. Only the 64 µg dose narrowly failed to achieve statistical significance from placebo for the nasal congestion score ($p<0.058$) [31:159-61].

MEAN CHANGE IN AVERAGE NASAL CONGESTION SCORE FOR ALL PATIENTS [31:159]				
Treatment (n)	Mean Baseline NCS	Mean Treatment NCS	Adjusted(1) Mean Change	95% CI
Placebo (83)	1.9	1.6	-0.25	-0.38, -0.11

MEAN CHANGE IN AVERAGE NASAL CONGESTION SCORE FOR ALL PATIENTS [31:159]				
Treatment (n)	Mean Baseline NCS	Mean Treatment NCS	Adjusted(1) Mean Change	95% CI
32 µg (78)	1.7	1.3	-0.47 (2)	-0.61, -0.33
64 µg (79)	1.8	1.4	-0.43	-0.57, -0.29
128 µg (83)	1.8	1.3	-0.50 (2)	-0.63, -0.36
256 µg (82)	1.8	1.3	-0.57 (2)	-0.71, -0.44
(1) adjusted for center effect and baseline NCS		(2) statistically significant change, difference from placebo		

MEAN CHANGE IN AVERAGE RUNNY NOSE SCORE FOR ALL PATIENTS [31:160]				
Treatment (n)	Mean Baseline RNS	Mean Treatment RNS	Adjusted(1) Mean Change	95% CI
Placebo (83)	1.5	1.3	-0.27	-0.40, -0.14
32 µg (78)	1.7	1.1	-0.56 (2)	-0.70, -0.42
64 µg (79)	1.6	1.1	-0.52 (2)	-0.66, -0.39
128 µg (83)	1.7	1.1	-0.54 (2)	-0.67, -0.40
256 µg (82)	1.7	1.1	-0.58 (2)	-0.71, -0.45
(1) adjusted for center effect and baseline RNS		(2) statistically significant change, difference from placebo		

MEAN CHANGE IN AVERAGE SNEEZING SCORE FOR ALL PATIENTS [31:161]				
Treatment (n)	Mean Baseline SS	Mean Treatment SS	Adjusted(1) Mean Change	95% CI
Placebo (83)	1.5	1.3	-0.26	-0.39, -0.12
32 µg (78)	1.6	1.0	-0.59 (2)	-0.73, -0.45
64 µg (79)	1.6	1.0	-0.59 (2)	-0.72, -0.45
128 µg (83)	1.6	1.1	-0.54 (2)	-0.67, -0.40
256 µg (82)	1.5	0.9	-0.66 (2)	-0.80, -0.53
(1) adjusted for center effect and baseline SS		(2) statistically significant change, difference from placebo		

Over all centers in both regions, each of the three components of the NIS demonstrated the efficacy of virtually all doses of budesonide over placebo treatment. However, none of these three NIS component scores provided evidence of increased efficacy with daily doses in excess of 32 µg.

Secondary Symptom Scores

These consisted of nasal itching, eye itching, eye redness and tearing. Nasal itching scores decreased significantly for the 32, 128 and 256 µg treatment groups in comparison with placebo. Ocular symptom scores showed no treatment group differences, although eye tearing scores decreased significantly from baseline for the 32 µg treatment group, compared with placebo [31:95, 162-5].

Patient Overall Evaluation Of Efficacy

Despite the name of this index, it was was a five-point scale (0-4) used to rate each of the four nasal symptoms individually. It was administered at weeks two and four and was used to compare each of the four doses of budesonide against placebo for each symptom. No baseline was established for any of the treatment groups. When the average score for weeks two and four was adjusted for center effect and the change from placebo was subjected to analysis, statistically significant difference from placebo was achieved for all doses over all symptoms. The only one of the four symptoms that showed a monotonically decreasing mean symptom score with increasing daily dose was 'sneezing'. 'Nasal obstruction', 'nasal itch' and 'rhinorrhea' all failed to show dose proportional efficacy by this measure [31:95, 166].

Per Protocol Analysis

Of the 406 patients there were 23 with major protocol violations, leaving 383 patients for this secondary efficacy analysis. The violations included: 1)lack of rhinitis symptoms for at least 4/7 days prior to randomization (15 patients); 2)< 2 weeks of double blind diary data available (7 patients); and, 3)non-compliance with the study medication (1 patient). Analysis of the average NIS over both regions showed that every dose of budesonide achieved statistical significance from placebo. Analysis by region and patient age, parallel the findings of the modified intent-to-treat analysis [31:96, 169].

SAFETY

Adverse Events:

A total of 113 patients reported one or more AE's, 94 (29%) in the budesonide treatment groups and 19 (23%) in the placebo group. The table below shows AE's reported by a greater proportion of patients receiving budesonide than placebo and with a frequency of >1%.

NUMBER OF PATIENTS (%) REPORTING AE's BY BODY SYSTEM WHERE TREATMENT AE's > PLACEBO AE's AND FREQUENCY > 1% [31:170-2]

Body System	WHO-Preferred Term	Placebo (n = 83)	All Budesonide Doses (n = 323)
Respiratory	Pharyngitis	1 (1)	9 (3)
	Coughing	1 (1)	5 (2)
	Sinusitis	0 (0)	5 (2)
Nervous (Central & Peripheral)	Headache	4 (5)	22 (7)

NUMBER OF PATIENTS (%) REPORTING AE's BY BODY SYSTEM WHERE TREATMENT AE's > PLACEBO AE's AND FREQUENCY > 1% [31:170-2]			
Body System	**WHO-Preferred Term**	**Placebo (n = 83)**	**All Budesonide Doses (n = 323)**
Urinary	Infection	0 (0)	5 (2)
ALL SYSTEMS	ANY AE	19 (23)	94 (29)

No evidence for dose proportionality of any AE was found, mirroring a similar negative finding in the efficacy analysis. Fewer AE's were reported in the pediatric group (24% budesonide, 17% placebo) compared to the adult group (33% budesonide, 27% placebo). In most analyses, AE's were slightly more common with budesonide than with placebo.

Serious Adverse Events:

One serious AE occurred in a placebo patient. A 43 year old Caucasian male fell, breaking his jaw. Alcohol was involved [31:101].

Discontinuation Due to Adverse Events:

Eight (2%) of the 406 randomized patients were discontinued due to the AE's, none of which met the definition of 'serious'. Seven of these patients had been exposed to budesonide and one to placebo. The eight AE's consisted of lymphadenopathy, sinusitis (2), dyspepsia, edema, bronchitis/URI, allergic reaction and asthma aggravation [31:96-7, 170-2, 175-9, 183].

Surveillance Examinations and Studies:

The results of physical examinations, vital signs, weights, nasal examinations and laboratory tests did not provide any changes unique to either placebo or to any of the active treatment groups that appeared to have any clinical relevance. Platelet counts did decline in a dose dependent manner from -0.6 to -4.5 thousands/microliter for placebo through 256 µg groups, but shift tables from visits 1 and 4 did not reveal major platelet count changes and no episode of a bleeding diathesis was reported. A very slight decrease in peripheral eosinophils was seen in each group, including placebo, but this was not proportional to active drug dose [31:210, 213, 223].

Plasma Cortisol Levels:

Both basal and Cortrosyn-stimulated cortisol levels were collected at ten centers at both baseline (visit 1) and visit 4. This subset involved 62 placebo patients and 237 budesonide patients, the latter about evenly divided among the four dose level groups. The differences between baseline and visit 4, basal and post-Cortrosyn-stimulated cortisol levels were examined in shift tables and by tabular means for all treatment groups. The data in the following tables were configured to compare the basal cortisol at visit 1 with the basal cortisol at visit 4 to detect any suppression over the duration of treatment. In addition, the percent increase in the Cortrosyn stimulated cortisol level at the visits 1 and 4 were compared to

determine if response to this stimulation had been suppressed over the four weeks. [31:103, 227-31 and amended 3/6/97 1:79-81].

BASAL (PreStim) AND CORTROSYN-STIMULATED (Stim) CORTISOL LEVELS FOR ALL PATIENTS AT BASELINE (Visit 1), AFTER FOUR WEEKS OF TREATMENT (Visit 4) AND THE CHANGE IN BASAL CORTISOL OVER THE TWO VISITS (Visit 4-1) [3/6/97 Table 1]							
Treatment	Visit 1 (Baseline)			Visit 4			Visit 4-1
	PreStim.	Stim.	Stim-PreStim (mn % chng)	PreStim.	Stim.	Stim-PreStim (mn % chng)	PreStim Dif (mn % chng)
Placebo (n = 62)	350	709	134	384	705	108	29
All Rx (n = 237)	374	715	122	409	713	100	21
32 µg (n = 56)	419	735	107	443	734	91	13
64 µg (n = 58)	368	733	131	414	726	99	27
128 µg (n = 62)	339	678	124	377	685	109	21
256 µg (n = 61)	373	717	125	405	710	99	20

At both visits, the mean pre-stimulated and Cortrosyn stimulated cortisols were mostly higher in the budesonide patients than in the placebo group. Comparing placebo with budesonide, the percent change after Cortrosyn stimulation was slightly less for the latter at visits 1 and 4. Over the four weeks of the study the mean pre-stimulated cortisol rose slightly in all groups and by about the same percent. Further breakdown of the entire group by age is found in the following two tables.

BASAL (PreStim) AND CORTROSYN-STIMULATED (Stim) CORTISOL LEVELS FOR PEDIATRIC PATIENTS AT BASELINE (Visit 1), AFTER FOUR WEEKS OF TREATMENT (Visit 4) AND THE CHANGE IN BASAL CORTISOL OVER THE TWO VISITS (Visit 4-1) [3/6/97 Table 2]							
Treatment	Visit 1 (Baseline)			Visit 4			Visit 4-1
	PreStim.	Stim.	Stim-PreStim (%)	PreStim.	Stim.	Stim-PreStim (%)	PreStim Dif (%)
Placebo (n = 27)	309	655	155	350	688	128	38
All Rx (n = 108)	316	660	138	363	653	106	27
32 µg (n = 26)	296	635	144	345	631	111	22
64 µg (n = 23)	319	660	126	369	655	99	20
128 µg (n = 31)	315	655	132	358	664	120	27
256 µg (n = 28)	333	689	147	383	658	92	35

BASAL (PreStim) AND CORTROSYN-STIMULATED (Stim) CORTISOL LEVELS FOR ADULT PATIENTS AT BASELINE (Visit 1), AFTER FOUR WEEKS OF TREATMENT (Visit 4) AND THE CHANGE IN BASAL CORTISOL OVER THE TWO VISITS (Visit 4-1) [3/6/97 Table 3]

Treatment	Visit 1 (Baseline)			Visit 4			Visit 4-1
	PreStim.	Stim.	Stim-PreStim (%)	PreStim.	Stim.	Stim-PreStim (%)	PreStim Dif (%)
Placebo (n = 35)	381	750	118	410	719	93	21
All Rx (n = 129)	422	761	109	447	764	94	16
32 µg (n = 30)	525	821	75	529	824	73	6
64 µg (n = 35)	401	781	135	444	773	99	31
128 µg (n = 31)	363	701	116	395	706	98	15
256 µg (n = 33)	407	740	105	424	753	104	8

These data provide no evidence of adrenal suppression, as measured by change in basal (pre-stimulated) cortisol or change, at one point in time in response to Cortrosyn stimulation, over the four weeks of the trial in either age group or over all ages.

05-3039 A DOUBLE-BLIND COMPARISON OF FOUR DOSES OF RHINOCORT® (BUDESONIDE) AQUA PUMP SPRAY AND PLACEBO IN THE TREATMENT OF ADULTS AND CHILDREN WITH PERENNIAL ALLERGIC RHINITIS

SUMMARY

This was a randomized, placebo-controlled, double-blind, multicenter (20), multi-dose (4), parallel-group, six-week study of over 470 pediatric and adult perennial allergic rhinitis (PAR) patients with ages ≥ 6 years. Three concentrations of budesonide were administered as one or two active-drug intranasal sprays administered to each nostril once daily in the morning. The total daily treatment doses were 32, 64, 128 and 256 μg and rescue medication was not permitted. The primary efficacy variable was the change from baseline in average nasal index score (NIS) which ranged from 0-9. This score was a composite of nasal obstruction or congestion, runny nose and sneezing each of which was rated as a score ranging from 0-3. Over all patients, three of the four active treatment groups showed significantly greater NIS decreases from baseline than placebo and the fourth dose (128 μg) barely failed to achieve statistical significance. No dose proportional effect was in evidence. Breakdown of the NIS into its three components, showed that each component provided an adjusted mean change from baseline that was significantly different from placebo for at least half of the active doses, and dose proportionality was absent. A retrospective analysis of NIS by patient age, dichotomized at 18 years, "demonstrated" no efficacy for any active treatment for patients < 18 years old and efficacy of all active treatments for patients ≥ 18 year of age. Another retrospective analysis of onset-of-action "showed" efficacy of the highest and lowest doses at 24 hours. Among the secondary symptom scores (nasal itching and ocular symptoms), only eye redness scores decreased significantly from baseline and only in the lowest dose group. Nasal eosinophils decreased and nasal bacteria counts increased in all treatment groups and this was most prominent in the pediatric age group. Platelet counts declined slightly over the course of the study, but this was not a dose-proportional effect.

OBJECTIVE

The purpose was to determine the therapeutic efficacy and safety of four dosages of budesonide administered once daily by an intranasal aqueous suspension pump spray versus placebo in adults and children with perennial allergic rhinitis [62:22].

PROTOCOL

This was a randomized, placebo-controlled, double-blind, multicenter (20), multi-dose (4), six-week study of adult (age ≥ 18 years) and pediatric (age 6-17 years) patients that was carried out between December 1994 and April 1995 [62:16, 23]. The study consisted of five clinic visits (Visits 1 through 5). There was a one-week, single-blind, placebo, baseline period followed by a six-week, double-blind treatment period. The baseline period was seven days,. After randomization at Visit 2, patients returned to the clinic every two weeks for Visits 3, 4 and 5. A deviation of ± 3 days was permitted for scheduling these visits [62:31].

PAR STUDY 3039 – PROCEDURE FLOW DIAGRAM [62:34]					
Procedure	Visit (Week)				
	1 (-1)	2 (0)	3 (2)	4 (4)	5 (6)
Medical History & Skin Test	X				
Physical Exam	X				X
Nasal Exam	X	X	X	X	X
Rhinoprobe™ Sampling (nasal cytology)		X			X
Lab Assessment (1) & Serum Pregnancy Test (1)	X				X
Urine Pregnancy Test (1)		X	X	X	
Quality of Life Questionnaire		X			X
Overall Evaluation of Treatment Efficacy			X	X	X
Adverse Events		X	X	X	X
(1) Repeat, if necessary, (once only) prior to Visit 2					

TREATMENT

The test drug was budesonide, administered as an aqueous suspension at concentrations of 0.32 mg/mL, 0.64 mg/mL and 1.28 mg/mL provided in 10 mL glass bottles fitted with a mechanical pump spray. Each actuation delivered 50 μl, i.e., 16 μg, 32 μg and 64 μg of budesonide, respectively, and each bottle contained at least 100 doses. At the conclusion of Visit 1, patients received two identical bottles of budesonide placebo, labeled A and B, and were instructed to take one dose (actuation) in each nostril, from each bottle, daily in the morning. Patients were instructed to administer the first dose using bottle A followed by bottle B. At Visits 2 and 3, patients received two new identical bottles and the same instructions. Patients on active treatment received either 32 μg, 64 μg, 128 μg or 256 μg daily according to the following scheme.

INTRANASAL DOSING REGIMEN			
Daily Dose	Treatment Bottle		Total Number of Bottles
	A	B	
Placebo	Placebo	Placebo	2
32 μg	16 μg per actuation	Placebo	2
64 μg	32 μg per actuation	Placebo	2
128 μg	64 μg per actuation	Placebo	2
256 μg	64 μg per actuation	64 μg per actuation	2

The placebo was said to be "identical." The test drugs were to be gently shaken prior to each use. Test drugs and placebo were manufactured by Astra in Södertälje, Sweden. The batch numbers of the test drug used in this study were:

0.32 mg/mL (16 μg/dose) = UK 20
0.64 mg/mL (32 μg/dose) = UK 25

1.28 mg/mL (64 μg/dose) = UK 30

No rescue medication was permitted in this trial and the necessity for it resulted in premature termination of the patient from the study [3/19/97 Teleconference with Dave Pizzi at Astra USA, 62:29, 30, 33].

PATIENTS

Six hundred and forty-five patients were screened for entry into the study, of which 478 were randomized to participate in the double-blind portion. Two hundred and fifty-seven were ≥ 18 years of age (54%) and 221 were 6-17 years old (46%) [62:16]. Approximately, 20% of these were randomized to each of the treatment groups (range 19.2% to 20.5%) [62:56]. The distribution of many demographic variables among the treatment groups at baseline is shown in the following table.

PATIENT BASELINE DEMOGRAPHIC CHARACTERISTICS OF TREATMENT GROUPS [62:57]

Statistic	Characteristic	Placebo (n=97)	32 μg (n=98)	64 μg (n=92)	128 μg (n=93)	256 μg (n=98)	Total (n=478)
COUNTS	Male	45	50	52	50	48	245
	Female	52	48	40	43	50	233
	Caucasian	89	87	85	82	91	434
	Black	1	5	3	6	2	17
	Oriental	0	1	2	1	0	4
	"Other" Race	7	5	2	4	5	23
MEANS	Rhinitis Duration (yrs)	13.9	14.0	15.0	12.7	12.8	13.7
	Age (yrs)	24.4	24.1	25.4	24.3	25.2	24.7
	Height (inches)	62.4	63.5	63.6	63.1	62.8	63.1
	Weight (lbs)	129	132.6	139.3	130.7	138.7	134.0

Inclusion Criteria [62:25-6]

1. Age ≥ 6 years of either gender.
2. Clinical diagnosis of perennial rhinitis for ≥ 2 years. The previous years symptoms should have been at least moderately severe and required treatment. Patients who had only used decongestants were excluded.
3. Perennial allergen sensitivity was verified by a positive Multi-Test skin test (≥ 3 mm than negative control, diluent) at screening. "Positive" was defined by a reaction to at least one of 12 PAR antigens (7 molds, dog & cat epithelia, 2 dust mite and one cockroach antigen). Eighteen SAR antigens (4 grasses, 6 weeds and 8 trees/shrubs) were also administered, but a positive reaction did not exclude the patient from the study unless that seasonal antigen was in season [63:5; 62:26, 28,

246, 280]. If the intradermal skin test was used to confirm a response, positive was defined as $\geq$ 5 mm larger than the negative control.

4. At least 2/3 of the following symptoms: 1)blocked nose, 2)runny nose, or 3)sneezing during $\geq$ 4/7 days during the 7-14 day baseline period. A nasal symptom score $\geq$ 2 for any four days, out of the last seven in the baseline period.

Exclusion Criteria [62:26-9]

1. Significant current medical diseases.
2. History of carcinoma, excluding basal cell carcinoma, within the past five years. A history of psychosis or poor motivation that might invalidate the consent.
3. Planned inpatient hospitalization during the study.
4. Clinically significant baseline laboratory test which may have either put the patient at risk because of participation, may have influenced the results or the influenced the patient's ability to participate.
5. Female patients of childbearing potential unless surgically sterile or using medically accepted contraceptive measures. All female patients of childbearing potential must have had a negative serum pregnancy test at Visit 1.
6. Patients recently exposed, or at risk of being exposed, to chicken pox or measles.
7. Patients with known hypersensitivity to budesonide..
8. Structural abnormalities symptomatic enough to cause nasal obstruction, as judged by the investigator.
9. Nasal conditions, including infectious rhinitis, sinusitis, rhinitis medicamentosa, atrophic rhinitis and atrophic rhinitis. Patients with coexisting seasonal allergic rhinitis may have been included if the specific allergen was not in season.
10. Upper respiratory tract infection $\leq$ 3 weeks prior to Visit 1.
11. Treatment with any of the following medications:
    A. Topical nasal glucocorticosteroid $\leq$ 1 month of Visit 1.
    B. Immunotherapy for perennial rhinitis for < 6 months, or not on a stable maintenance dose.
    C. Short-acting antihistamines, topical or oral decongestants, vasoconstrictors, or other medications which could mask the symptoms of rhinitis; e.g., tricyclic anti-depressants, major tranquilizers or anti-epileptic agents, within three days of enrollment (Visit 1).
    D. Long-acting antihistamine use: terfenadine < 2 days, loratadine < 4 days or astemizole < 12 weeks before Visit 1.
    E. Nasal cromolyn sodium or nedocromil < 2 weeks prior to Visit 1.
    F. Systemic glucocorticosteroid therapy < 1 month prior to Visit 1.
    G. Inhaled or systemic glucocorticosteroids for asthma.

PARAMETERS

The primary efficacy variable was change in nasal index score (NIS), calculated as the sum of three nasal symptoms: 1)runny nose; 2)congestion or blocked nose; and, 3)sneezing.

Each was rated on a 0-3 scale, assessed each morning and recorded in the patient diary [62:37, 46].

0 = no symptoms
1 = mild symptoms -- present but not troublesome
2 = moderate symptoms -- frequently troublesome, but not sufficient to interfere with normal daily activity or night-time sleep
3 = severe symptoms -- sufficiently troublesome to interfere with normal daily activity or night-time sleep

The NIS was used to determine the sample size for inferential statistical analysis and was calculated as the baseline average, over the seven days before treatment, compared with the average over the six-week treatment period. Patients were included in the analysis if they had baseline and at least one double-blind observation. The average NIS for the treatment period was calculated as the average over those days for which data were available in patients who withdrew prematurely [62:46-7].

Secondary variables included individual nasal symptom scores (congestion, runny nose, sneezing and nasal itching), ocular complex symptoms (itching, redness and tearing), nasal cytology and amount of rescue medication taken. The Overall Evaluation of Efficacy by the patient was a five-point scaled estimate of the treatment effect on overall nasal symptoms at visits 3, 4 and 5 without a baseline determination.

0 = symptoms were aggravated
1 = no control over symptoms
2 = minor control over symptoms
3 = substantial control over symptoms
4 = total control over symptoms

Quality of life and health status were measured by two scales. One scale was designed for patients aged 12-17 years and the other for adults, aged 18 years and older. Both were designed for rhinoconjunctivitis by Juniper and Guyatt and have been published in refereed medical journals. The adolescent scale was used for children < 12 years of age, with full recognition that the scale had not been validated for this young age group [62:37-8, 81].

Safety analyses of AE's, clinical laboratory measurements, vital signs and physical examinations were performed on all randomized patients. AE's were elicited only at clinic visits by posing the following question, "Have you experienced any health problems or other symptoms not usually related to your nasal allergies since the last visit?" Responses to this query, as well as spontaneous patient reports of symptoms, were recorded as AE's [62:37]. Laboratory safety variables drawn at each visit consisted of venous blood samples for:

RBC count, hemoglobin, hematocrit, WBC count, differential count, platelet count, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase and HCG

Urine samples were analyzed for:

glucose, protein and HCG

All analyses, except urine pregnancy tests, were performed by the [redacted] Laboratories [62:39].

EFFICACY RESULTS

Primary Variable:

The primary efficacy variable, change in NIS from baseline (mean daily NIS over seven pre-treatment days) to treatment (mean daily NIS over six treatment weeks), was analyzed by ANOVA. The model included terms for treatment, center, treatment-by-center interaction and baseline NIS. The treatment-by-center interaction was not significant, and was removed from the model [62:62]. Three of the four active treatment groups showed significantly greater NIS decreases from baseline than placebo and the 128 µg dose barely failed to achieve statistical significance ($p < 0.051$). In terms of the dependent variable, adjusted mean change in NIS, no dose proportional effect was in evidence. The lowest dose, 32 µg produced the same effect as doses up to eight times as large [62:63]. The following table demonstrates that every budesonide dose reduced the baseline average symptom score by half-to-three-quarters more of a NIS score point than placebo (maximum NIS score was nine).

MEAN CHANGE IN AVERAGE "NIS" FOR ALL PATIENTS [62:63, 123]

Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (96)	6.3	4.7	-1.53	-1.87, -1.19
32 µg (97)	6.0	3.9	-2.25 (2)	-2.59, -1.91
64 µg (92)	6.3	4.2	-2.06 (2)	-2.41, -1.71
128 µg (92)	6.0	4.1	-2.01	-2.36, -1.66
256 µg (97)	6.1	3.9	-2.29 (2)	-2.63, -1.95

(1) adjusted for center effect and baseline NIS

(2) statistically significant change, difference from placebo

The magnitude of these changes in the NIS for all treatment groups was not associated with a greater numbers of drop-outs because of disease deterioration or failure to improve. In fact, the placebo group, with the smallest reduction in NIS, only had the number of drop-outs because of disease deterioration that was the average for all of the groups, 6% [62:60, 106-8].

Daily mean NIS scores were plotted as a function of study days and showed a consistent pattern for each treatment group relative to placebo. During the baseline period, all groups showed rising and overlapping mean NIS scores. Over the first week of the double-blind treatment period, the mean daily NIS score fell by one quarter to one third of its maximum baseline value in all groups, including placebo. Thereafter, the NIS scores stabilized in all groups. Throughout the treatment period, each of the active treatment groups showed a mean daily NIS that was below that of the placebo, though there was no visual difference among the curves of the four active treatments [62:213]. These curves show a

marked placebo effect, a consistent treatment effect without dose proportionality and no evidence of tachyphylaxis among any of the active treatments over the six-week double-blind period.

Assessment of a dose-response effect was approached by linear regression of the NIS on the lowest and highest active treatments [62:65, 124]. This analysis was considered to be inadequate because it failed to use half of the data points and the more complete linear regression analysis of all four active concentrations was requested. The slope of the regression line was not statistically different from zero for all patients taken together or separated into pediatric and adult age groups [3/6/97 1:66-9].

Primary Variable By Age:

Ages 6 through 17 years defined the pediatric group and did not show a dose proportional effect. All four treatments groups performed better than placebo. However, no dose achieved statistical significance from placebo [62:65].

MEAN CHANGE IN AVERAGE "NIS" FOR PEDIATRIC PATIENTS [62:64, 123]				
Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (44)	6.1	4.6	-1.62	-2.13, -1.10
32 µg (44)	6.0	4.1	-2.01	-2.52, -1.49
64 µg (43)	6.3	4.3	-1.95	-2.47, -1.43
128 µg (45)	6.0	4.6	-1.59	-2.10, -1.09
256 µg (43)	6.1	4.1	-2.14	-2.65, -1.62
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

For the adult age group (age $\geq$ 18 years), the active treatment groups were all statistically significantly better than placebo at reducing the NIS from baseline. All four active treatments were equally effective and no dose proportionality was seen [62:64-5].

MEAN CHANGE IN AVERAGE "NIS" FOR ADULT PATIENTS [62:64, 123]				
Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (52)	6.4	4.8	-1.45	-1.92, -0.98
32 µg (53)	6.1	3.7	-2.44 (2)	-2.90, -1.98
64 µg (49)	6.4	4.1	-2.15 (2)	-2.63, -1.66
128 µg (47)	6.1	3.7	-2.40 (2)	-2.90, -1.91
256 µg (54)	6.1	3.7	-2.42 (2)	-2.87, -1.96
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

This analysis by age was retrospectively defined, so prospective inferential statistics and Type I Errors are not really applicable terms and are included here to reference the presentation of these data in the NDA document.

Primary Variable Onset of Action:

A post-hoc analysis was performed on all treated patients to study the onset of action of budesonide, compared with placebo, and to determine the time course of efficacy. The NIS was analyzed separately at three time points after the first dose of medication, that is at 24, 48 and 72 hours. The results for all treatments are presented in the three tables below, each of which represents one of the three time points, and each summarizes the NIS scores for all prior time points [71:3-8; 4/4/97 & 4/18/97 Teleconferences with Dave Pizzi at Astra USA].

MEAN CHANGE IN AVERAGE "NIS" FOR ALL PATIENTS, CHANGE IN BASELINE TO 24 HOURS AFTER FIRST DOSE [71:6]

Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (96)	6.3	5.8	-0.44	-0.79, -0.09
32 µg (97)	6.0	5.1	-1.02 (2)	-1.37, -0.67
64 µg (92)	6.3	5.3	-0.94	-1.30, -0.58
128 µg (91)	6.0	5.2	-0.90	-1.27, -0.54
256 µg (97)	6.1	5.0	-1.16 (2)	-1.51, -0.81

(1) adjusted for center effect and baseline NIS (2) statistically significant change, difference from placebo

MEAN CHANGE IN AVERAGE "NIS" FOR ALL PATIENTS, CHANGE IN BASELINE TO 48 HOURS AFTER FIRST DOSE [71:7]

Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (96)	6.3	5.6	-0.65	-0.99, -0.31
32 µg (97)	6.0	5.0	-1.12	-1.46, -0.78
64 µg (92)	6.3	5.2	-1.07	-1.42, -0.72
128 µg (91)	6.0	5.0	-1.07	-1.42, -0.72
256 µg (97)	6.1	5.0	-1.13 (2)	-1.47, -0.80

(1) adjusted for center effect and baseline NIS (2) statistically significant change, difference from placebo

MEAN CHANGE IN AVERAGE "NIS" FOR ALL PATIENTS, CHANGE IN BASELINE TO 72 HOURS AFTER FIRST DOSE [71:8]

Treatment (n)	Mean Baseline NIS	Mean Treatment NIS	Adjusted(1) Mean Change	95% CI
Placebo (96)	6.3	5.5	-0.76	-1.08, -0.43

MEAN CHANGE IN AVERAGE "NIS" FOR ALL PATIENTS, CHANGE IN BASELINE TO 72 HOURS AFTER FIRST DOSE [71:8]				
Treatment (n)	**Mean Baseline NIS**	**Mean Treatment NIS**	**Adjusted(1) Mean Change**	**95% CI**
32 µg (97)	6.0	4.8	-1.33 (2)	-1.65, -1.00
64 µg (92)	6.3	5.0	-1.25 (2)	-1.59, -0.91
128 µg (91)	6.0	5.0	-1.17	-1.51, -0.83
256 µg (97)	6.1	4.9	-1.28 (2)	-1.61, -0.95
(1) adjusted for center effect and baseline NIS		(2) statistically significant change, difference from placebo		

An examination of the mean changes in NIS indicates a greater effect at 72 hours of all active treatments, compared with placebo, and a general absence of dose proportionality at any given time point. This analysis was retrospectively defined, so prospective inferential statistics and Type I Errors are not applicable terms and are included here only to reference the presentation of these data in the NDA document.

Secondary Variables:
NIS Components

Breakdown of the NIS into its three components, showed that each component showed an adjusted mean change from baseline that was significantly different from placebo for at least half of the active doses. Only the 64 and 128 µg concentrations failed to achieve statistical significance from placebo for the runny nose and sneezing scores [62:129-131].

MEAN CHANGE IN AVERAGE NASAL CONGESTION SCORE (NCS) FOR ALL PATIENTS [62:129]				
Treatment (n)	**Mean Baseline NCS**	**Mean Treatment NCS**	**Adjusted(1) Mean Change**	**95% CI**
Placebo (96)	2.3	1.9	-0.46	-0.58, -0.34
32 µg (97)	2.2	1.6	-0.71 (2)	-0.83, -0.59
64 µg (92)	2.3	1.6	-0.67 (2)	-0.80, -0.55
128 µg (92)	2.3	1.6	-0.65 (2)	-0.77, -0.52
256 µg (97)	2.2	1.6	-0.71 (2)	-0.83, -0.58
(1) adjusted for center effect and baseline NCS		(2) statistically significant change, difference from placebo		

MEAN CHANGE IN AVERAGE RUNNY NOSE SCORE (RNS) FOR ALL PATIENTS [62:130]				
Treatment (n)	**Mean Baseline RNS**	**Mean Treatment RNS**	**Adjusted(1) Mean Change**	**95% CI**
Placebo (96)	2.1	1.6	-0.55	-0.68, -0.43
32 µg (97)	2.0	1.3	-0.77 (2)	-0.90, -0.64
64 µg (92)	2.2	1.4	-0.71	-0.85, -0.58

MEAN CHANGE IN AVERAGE RUNNY NOSE SCORE (RNS) FOR ALL PATIENTS [62:130]				
Treatment (n)	Mean Baseline RNS	Mean Treatment RNS	Adjusted(1) Mean Change	95% CI
128 µg (92)	2.1	1.4	-0.69	-0.83, -0.56
256 µg (97)	2.0	1.3	-0.78 (2)	-0.90, -0.65
(1) adjusted for center effect and baseline RNS		(2) statistically significant change, difference from placebo		

MEAN CHANGE IN AVERAGE SNEEZING SCORE (SS) FOR ALL PATIENTS [62:131]				
Treatment (n)	Mean Baseline SS	Mean Treatment SS	Adjusted(1) Mean Change	95% CI
Placebo (96)	1.8	1.3	-0.52	-0.39, -0.12
32 µg (97)	1.8	1.0	-0.77 (2)	-0.73, -0.45
64 µg (92)	1.9	1.2	-0.66	-0.72, -0.45
128 µg (92)	1.6	1.1	-0.67	-0.67, -0.40
256 µg (97)	1.8	1.0	-0.80 (2)	-0.80, -0.53
(1) adjusted for center effect and baseline SS		(2) statistically significant change, difference from placebo		

Each of the three components of the NIS demonstrated the efficacy of the highest and lowest doses of budesonide over placebo treatment. However, none of these three NIS component scores provided evidence of dose proportional efficacy with daily doses in excess of 32 µg.

Secondary Symptom Scores

These consisted of nasal itching, eye itching, eye redness and tearing and were analyzed using ANCOVA, with the baseline score as a covariate. Neither nasal itching nor ocular symptom scores showed statistically significant treatment group differences from placebo, with the single exception of the eye redness scores, which decreased significantly from baseline for the 32 µg treatment group, compared with placebo [62:66, 132-5].

Patient Overall Evaluation Of Efficacy

This five-point scale (0-4) for nasal symptoms was determined at weeks two, four and six. The results were averaged over these visits and used to compare each of the four doses of budesonide against placebo. No baseline was established for any of the treatment groups. When the average score for all three weeks was adjusted for center effect and the change from placebo was subjected to analysis, statistically significant differences were achieved for all doses and all doses resulted in almost identical degrees of symptom score differences from placebo. That is, the 32 µg dose produced as much of a mean difference from placebo as did all of the other doses, including the highest, the 256 µg dose. The entire study group was retrospectively partitioned into adult (age $\geq$ 18 years) and pediatric (age 6-17 years) patients and reanalyzed. A slightly larger magnitude of change from placebo was seen in the pediatric

age group than in the adults but the same lack of dose proportionality was evident in both groups [62:37, 67, 136].

Rhinoprobe™ Nasal Cytology

Changes in scores from baseline to visit 5 for all patients were recorded for bacteria, basophils, eosinophils, goblet cells and neutrophils. The overall analysis of all age groups showed that eosinophils and basophils decreased in all treatment groups compared with placebo, but the decreases were not dose-proportional. Decreases were more apparent in the pediatric group than in the adults. Circulating eosinophils and basophils were not similarly affected. A monotonic increase in bacteria with dose was seen in all patients treated and was most apparent in the pediatric age subset. This last is a rare example of dose proportionality with the concentrations chosen for this drug [62:67-8, 137-40, 196].

Quality of Life (QOL)

Two rhinoconjunctivitis test were employed. Two published instruments were applied to patients ≥ 12 years of age, one for patients of ages 12-17 years and a second for patients of ages > 17 years. The QOL scale designed for adolescents was also used for patients < 12 years of age but was not validated for this age range and results are not included here. Results for the two published instruments applied to patients of the appropriate ages showed no significant differences in overall score from placebo for any active dose in the adolescent age group. The adults did show significant differences from placebo in overall score for the lowest and highest active doses (32 μg and 256 μg groups) but no dose proportionality was evident by this measure [62:68, 143-8; 3/26/97 & 4/18/97 Teleconferences with Davy Pizzi of Astra USA].

Per Protocol Analysis

Of the 451 patients there were 26 with major protocol violations, leaving 451 patients for this secondary efficacy analysis. The violations included: 1)lack of rhinitis symptoms for at least 4/7 days prior to randomization (17 patients); 2)use of prohibited medications (5); 3)no double blind diary data available (3 patients); and, 4)incorrect dosing or eight doses taken daily for 15 consecutive days (1 patient). The results of the "Per Protocol" analysis of change in NIS from baseline were similar to the results of the "All Patients" analysis. In the overall analysis, each concentration of budesonide was statistically significantly superior to placebo, this significance was apparent only in the adult age group and dose proportionality was again absent in the overall analysis and in each age group [62:69, 151]

SAFETY

Adverse Events:

A total of 236 patients reported one or more AE's, 186 (49%) in the budesonide treatment groups and 50 (52%) in the placebo group. The table below shows AE's reported by a greater proportion of patients receiving budesonide than placebo and with a frequency of >1%.

NUMBER OF PATIENTS (%) REPORTING AE's BY BODY SYSTEM WHERE TREATMENT AE's > PLACEBO AE's AND FREQUENCY > 1% [62:152-4]			
Body System	**WHO-Preferred Term**	**Placebo (n =97)**	**All Budesonide Doses (n =381)**
Respiratory	Pharyngitis	4 (4)	28 (7)
	Bronchospasm	1 (1)	7 (2)
Platelet, Bleeding & Clotting	Epistaxis	2 (2)	29 (8)
Gastrointestinal	Gastroenteritis	0 (0)	6 (2)
Resistance Mechanisms	Otitis Media	0 (0)	6 (2)
ALL SYSTEMS	ANY AE	50 (52)	186 (49)

Evidence of dose proportionality was not found for any of these AE's. The proportion of budesonide-to-placebo patients reporting AE's in the pediatric group was 1.24 (52% budesonide, 42% placebo) and was higher than 0.77 for the adult group (46% budesonide, 60% placebo) [62:69-71, 152-62].

Serious Adverse Events:

No serious AE's were reported during the course of this study [62:76].

Discontinuation Due to Adverse Events:

Of the 478 patients randomized into this study, eleven (budesonide = 10 (3%), placebo = 1 (1%)) were discontinued due to AE's none of which were classified as 'serious.' The eleven AE's were bronchospasm (2), urticaria, contact dermatitis, headache, respiratory infection, flu-like disorder (2), epistaxis, hypoaesthesia and viral infection [62:72-6].

Surveillance Examinations and Studies:

The results of physical examinations, vital signs, weights, nasal examinations and laboratory tests did not provide any changes unique to either placebo or to any of the active treatment groups that appeared to have any clinical relevance. Platelet counts showed a decline from visit 1 to visit 5 in the budesonide group, but evidence for dose proportionality was absent [62:76-7, 170-201].