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CLINICAL STUDY REPORT

DRUG SUBSTANCE	Budesonide aqueous nasal spray
DOCUMENT NO.	SD-005-CR-0170
VERSION NO.	01
STUDY CODE	SD-005-0170
DATE	07 November, 2000

FINAL

An Investigation of the use of the Rhinocort® Aqua in the Treatment of Chronic Rhinosinusitis

STUDY PERIOD:	03 December 1997 - 16 August1999
PHASE OF DEVELOPMENT:	IIIB
STUDY DESIGN:	Double-blind, placebo controlled, randomized, parallel group design.
DIAGNOSIS:	Adult Chronic Rhinosinusitis.
TEST DRUG AND DOSAGE:	Budesonide aqueous nasal spray (Rhinocort ® Aqua)
COMPARATOR DRUG AND DOSAGE:	Placebo
DURATION OF TREATMENT:	20 weeks

The study was conducted in accordance with the principles of Good Clinical Practice.

INVESTIGATOR SIGNATORY:

SPONSOR'S SIGNATORY:

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AstraZeneca

DRUG PRODUCT	Rhinocort® Aqua	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide aqueous nasal spray	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SD-005-CR-0170		
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FINAL

An Investigation of the use of the Rhinocort® Aqua in the Treatment of Chronic Rhinosinusitis

INVESTIGATOR

V. Lund, Royal Nat Throat, Nose & Ear Hospital, LONDON, UK

STUDY CENTRE(S)

Multi-centre, multi-national study: 7 centres in UK, 6 centres in Hungary and 6 centres in South Africa.

PUBLICATION (REFERENCE)

No publications.

Table 1.

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT ENROLLED	3 December 1997	IIIB
- DATE OF LAST PATIENT COMPLETED	16 August 1999	

OBJECTIVES

The primary objective was to determine the efficacy of Rhinocort® Aqua/budesonide aqueous nasal spray (BANS) 128 μg twice daily, compared with placebo in patients with symptoms of chronic rhinosinusitis (CRS).

The secondary objective was to evaluate the tolerability of BANS in patients with symptoms of chronic rhinosinusitis (CRS).

STUDY DESIGN

The study was of a double-blind, placebo-controlled, randomized, parallel group design.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

The diagnosis was adult CRS with symptoms for more than 12 weeks.

The main inclusion criterion at **visit 1** was: A clinical diagnosis of adult CRS as indicated by the following criteria: The presence of two or more of the following four major factors, with each one having been present for more than 12 weeks.

Major factors:

facial pain/facial pressure/facial headache
facial congestion/nasal blockage/nasal obstruction
purulence/discoloured discharge
impairment of sense of smell

The main inclusion criterion for randomization at **visit 2** was: Patients demonstrating CRS symptoms (as defined in main inclusion criteria above), over the last seven days of the run-in. On four out of the last seven days, the patient should have at least one symptom, either morning or evening, with a score of ≥ 2.

The main exclusion criteria were:

Structural (also due to previous surgery) abnormalities in the nose (e.g. severe septal deviation or nasal polyps (of grade 2, i.e. polyps beyond the middle meatus) symptomatic enough to cause significant nasal obstruction as judged by the investigator.
Previous nasal surgery within the last 21 months.
Previous radical sinus surgery or repeated sinus operations.
Use of systemic steroid therapy for any reason within eight weeks prior to visit 1.
Use of topical nasal steroid treatment within four weeks prior to visit 1.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

The test product was BANS, administered intranasally twice daily (morning and evening) with 1 actuation in each nostril, with a strength of 1.28 mg/mL. Each bottle contained 120 doses of 64 μg budesonide. The Batch numbers of BANS were: YH 53, ZM 68

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

The comparator product was placebo aqueous spray identical in appearance to the test product, administered intranasally twice daily in the morning and evening with 1 actuation in each nostril. The batch number of placebo aqueous spray were ZL 25, YG 22.

DURATION OF TREATMENT

The treatment was given twice daily (morning and evening) for 20 weeks.

MAIN VARIABLE(S):

- **EFFICACY**

Primary efficacy variable was the combined major symptom scores (the sum of the individual symptom scores) of CRS.

The secondary efficacy variables were the:

Individual symptom scores.
Time to first exacerbation.
Number of exacerbations.
Chronic Sinusitis Survey (CSS).
Health related quality of life (HRQL) questionnaire (SF-36).
Patient's overall evaluation of treatment efficacy (POE).

The Explorative variables were:

Nasal Cytology-Rhinoprobe™.
Peak Nasal Inspiratory Flow (PNIF) measurements at clinic visits.
(CT-scan at visit 2 for baseline information. Results presented in Patient Characteristics, Section 9.5.1)

- **SAFETY**

Tolerability was evaluated by means of nasal examination, haematology analyses and standard adverse event questioning.

STATISTICAL METHODS

The primary efficacy variable was a combined symptom score of CRS, i.e. sum of symptom scores for facial pain/facial pressure/facial headache, facial congestion/nasal blockage/nasal obstruction and nasal discharge, and impairment in sense of smell. For this variable the mean values for morning and evening over the antibiotic-free period during run-in (baseline) and the 20-week treatment period were calculated for each patient. The Endpoint, defined as the patient mean change from baseline to the treatment period was subject to an ANOVA model (with treatment and country as factors). The baseline mean score was included in this model. The individual CRS symptom scores were analysed in a similar way. For the secondary and explorative variables the endpoint was the change from visit 2 (randomisation) to the last visit using an ANOVA model with factors as described above.

The intention to treat (ITT) analyses was used.

PATIENTS

The planned number of patients as well as the number of randomized and treated are included in Table 2.

Table 2. Patients

	BANS 128 µg b.i.d.	Placebo	Total
No. planned	75	75	150
No. randomized and treated	81	86	167
- Males/Females	35/46	41/45	76/91
- Mean age, years (range)	38(19-65)	43(18-78)	41(18-78)
No. analysed for efficacy	75	80	155
No. analysed for safety	75	80	155
No. completed	67	67	134

SUMMARY - CONCLUSION(S)

- EFFICACY RESULTS

A total of 167 patients were evaluated for efficacy (ITT).

Primary variable:

BANS improved the combined symptom scores statistically significant more than placebo. The reduction of the overall treatment including 20 weeks of the combined symptom score in the morning was 1.85 in the BANS group and 0.82 in the placebo group (p=0.005) and in the evening 1.78 in the BANS group and 1.02 in the placebo group (p=0.012).

Secondary variables:

The efficacy results from the individual symptom scores are presented in Table 3 (data expressed as adjusted mean change from from baseline over the 20-week treatment period, last value carried forward):

Table 3. Individual symptom scores

VARIABLES	BANS 128 μg b.i.d.	Placebo	
	Baseline mean/Change	Baseline mean/Change	p-value (BANS vs Placebo)
Facial pain/facial pressure/facial headache - Morning	1.38 / -0.38	1.33 / -0.25	0.139
Facial pain/facial pressure/facial headache - Evening	1.40 / -0.39	1.33 / -0.29	0.287
Facial congestion/ nasal blockage/obstruction - Morning	1.88 / -0.67	1.85 / -0.34	**<0.001**
Facial congestion/ nasal blockage/obstruction - Evening	1.75 / -0.60	1.78 / -0.33	**0.004**
Nasal discharge - Morning	1.48 / -0.50	1.47 / -0.29	**0.016**
Nasal discharge - Evening	1.43 / -0.51	1.41 / -0.25	**0.003**
Impairment in sense of smell - Morning	1.43 / -0.32	1.27 / -0.27	**0.047**
Impairment in sense of smell - Evening	1.38 / -0.30	1.25 / -0.26	0.066

Time to first Exacerbation and number of exacerbations:

No analyses was performed due to the low frequency of exacerbations (BANS=1.3, Placebo=1.1).

CSS:

Data were available from patients in UK and South Africa. There was no significant difference between the treatment groups in the domain “Sinusitis symptom scores” (p=0.716) or “Medication usage score” (p=0.851), where the latter was invalidated by the Exclusion criteria in the protocol.

HRQL (SF-36):

Except for the “General health” - domain (p=0.035), there were no significant difference between the treatment groups.

POE:

Patients receiving BANS rated treatment efficacy higher than did patients receiving placebo (p=0.015).

Explorative variables:

Nasal cytology:

It was initially planned that the clinics in UK should do the cytology sampling (88 patients), but only samples from 43 patients were evaluable.

No cytologicial statistically significant difference between the BANS and placebo treated groups was found. A difference in the occurrance of Bacteria was observed.

PNIF:

For PNIF the BANS group improved their measurements from a baseline mean of 141.6 L/ Min with additional 49.1, compared with the placebo group who had a baseline mean of 131.6 L/Min and improved additional 10.4 ($p < 0.001$).

- **SAFETY RESULTS**

The treatment with BANS was well tolerated in patients with CRS and no clinically important new drug-safety related findings were identified in this study.

DATE OF THE REPORT

November 07, 2000