AstraZeneca

Drug product:	Rhinocort Aqua®	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Budesonide		
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Bioequivalence study in healthy volunteers comparing the pharmacokinetic profiles of budesonide delivered from the Rhinocort Aqua® winged applicator (current and pH-modified formulation) and from the Rhinocort Aqua® new nasal device (pH-modified formulation)

PRINCIPAL INVESTIGATOR

STUDY CENTRE

There was one centre in Uppsala, Sweden.

PUBLICATIONS

Not at the time of writing this report.

STUDY DATES

Phase of development	Clinical Pharmacology (I)
First subjects enrolled	2 May 2002
Last subject completed	6 July 2002

OBJECTIVES

The primary objective of the study was to investigate whether the winged applicator (WA) of Rhinocort Aqua (pH modified formulation) gave bioequivalent plasma concentrations of budesonide to that of the approved WA of Rhinocort Aqua (current formulation).

The secondary objective was to investigate whether the new nasal device (NND) of Rhinocort Aqua (pH modified) gave bioequivalent plasma concentrations of budesonide to that of the approved WA of Rhinocort Aqua (current).

The primary variable for both objectives was the area under the plasma concentration curve of budesonide extrapolated to infinity ($AUC_{0-\infty}$).

The secondary variables for both objectives were the maximum plasma concentration (C_{max}) and AUC_{0-t}, where t is the last measurable time point.

STUDY DESIGN

This was an open, randomized, 3-way cross-over, bioequivalence study comparing the systemic availability of 256 µg budesonide in healthy volunteers when delivered via Rhinocort Aqua WA (current vs. the pH modified) and the Rhinocort Aqua NND (pH modified) vs. the Rhinocort Aqua WA (current). The resulting plasma concentrations of budesonide were monitored for 12 hours after drug administration.

TARGET SUBJECT POPULATION AND SAMPLE SIZE

Healthy men and women between 18 and 65 years took part in this study. None had allergic rhinitis, polyposis or major septum deviation, no women were pregnant or breast-feeding, none smoked.

The sample size was chosen in order to have 90% power to show bioequivalence both for WA (pH modified) vs. WA (current) **and** for Rhinocort Aqua NND (pH modified) vs. WA (current), i.e. the primary **and** secondary objectives. A study with 117 completed subjects was calculated to provide approximately 95% power to show average bioequivalence between two formulations for each of $AUC_{0-\infty}$, AUC_{0-t} and C_{max}, given that the true $AUC_{0-\infty}$, AUC_{0-t} and C_{max} for the two formulations did not differ more than 5%. The power to show bioequivalence for both comparisons, given the same assumptions, was therefore approximately 0.95^2 i.e. approximately 90%. 239 subjects were enrolled, 125 were randomized, and 120 completed the study

INVESTIGATIONAL PRODUCTS: DOSAGE, MODE OF ADMINISTRATION AND BATCH NUMBERS

Reference product

Rhinocort Aqua (budesonide) nasal spray 32 µg/dose, 120 doses, WA (current), pH 4.5. Four sprays per nostril (8 sprays x 32 µg = Total dose 256 µg). Batch No. 1070112026.

Investigational products

Rhinocort Aqua (budesonide) nasal spray 32 µg/dose, 120 doses, WA (pH modified), pH 4.0. Four sprays per nostril (8 sprays x 32 µg = Total dose 256 µg). Batch No. DB 109-02/4.

Rhinocort Aqua (budesonide) nasal spray 32 µg/dose, 120 doses, NND (pH modified), pH 4.0. Four sprays per nostril (8 sprays x 32 µg = Total dose 256 µg) Batch No. DC 109-02/3.

DURATION OF TREATMENT

Single doses were given on three separate occasions, with a wash-out period of at least 4 days but within 14 days.

CRITERIA FOR EVALUATION (MAIN VARIABLES)

Pharmacokinetics

- Primary variable was the $AUC_{0-\infty}$
- Secondary variables were C_{max} and AUC_{0-t}. Other pharmacokinetic parameters were described (T_{max}, MRT and $T_{1/2}$)

Safety

Adverse events were collected by means of standard questions put to the subjects at visits 2-5. At visit 4, a pregnancy test (if applicable) was performed.

STATISTICAL METHODS

$AUC_{0-\infty}$ was compared between the treatments using a multiplicative analysis of variance model (ANOVA).

Bioequivalence between the Rhinocort Aqua WA (pH modified) and Rhinocort Aqua WA (current) was to be concluded if the 90% confidence interval for the $AUC_{0-\infty}$ ratio for the two treatments fell entirely within 80-125%. Bioequivalence between the Rhinocort Aqua NND (pH modified) and Rhinocort Aqua WA (current) could only be concluded if the Rhinocort Aqua WA (pH modified) was bioequivalent with the Rhinocort Aqua WA (current).

AUC_{0-t} and C_{max} were analyzed and tested for bioequivalence in the same way as $AUC_{0-\infty}$.

Safety variables were analyzed using descriptive statistics.

SUBJECT POPULATION

A total of 239 subjects were enrolled, 125 subjects were randomized. There were 73 men and 52 women, with a mean age of 25.7 years. All except four were Caucasian, the other subjects were black. 120 subjects completed the study. Five subjects discontinued the study.

- Subject No. 8 was withdrawn due to concomitant medication and positive drug screening (opiates) during the second treatment period (visit 3, after receiving the treatment).
- Subject No. 29 withdrew due to personal reasons after completing two treatment periods (visits 2 and 3).
- Subject No. 69 was withdrawn due to an SAE (abdominal pain) in the first treatment period (visit 2, after receiving the treatment).
- Subject No. 109 was withdrawn due to intake of Ipren (ibuprofen) at several timepoints in the second treatment period (after receiving the treatment at visit 3).
- Subject No. 119 withdrew due to personal reasons in the first treatment period (after receiving the treatment at visit 2).

The subject flow is shown in Table S1

Table S1. Subject flow

Enrolled Subjects	239
Not randomized	114
- Eligibility criteria not fulfilled	32
- Other reason	82
Randomized	125
Discontinued	5
- Eligibility criteria not fulfilled	2
- Adverse Event	1
- Other reason	2
Completers	120

PHARMACOKINETIC RESULTS

The mean plasma concentration curves of budesonide were similar for all three versions of Rhinocort Aqua. The mean concentrations of budesonide are plotted on a logarithmic scale in Figure S1.

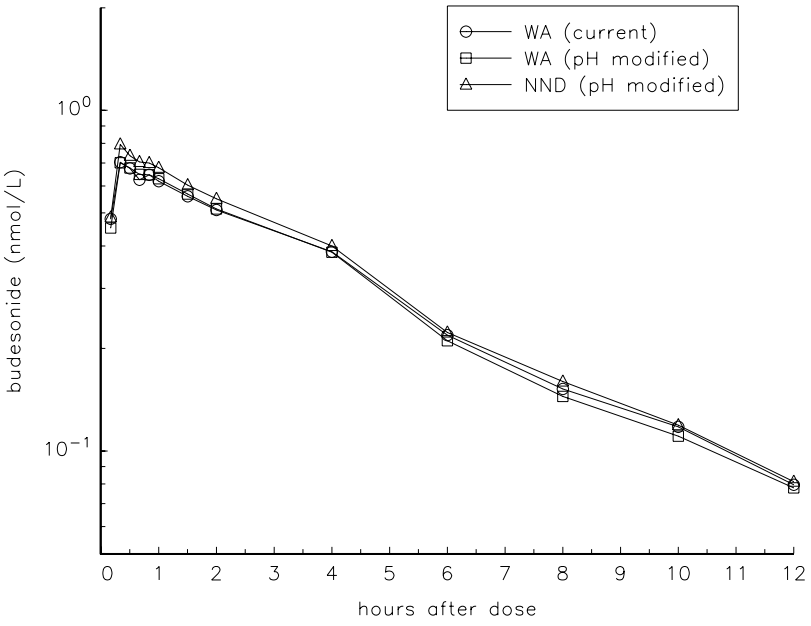

Figure S1. Mean plasma concentrations of budesonide (logarithmic scale)

The similarities in plasma concentration curves are also reflected in the pharmacokinetic variables, as summarized in Table S2.

Table S2. Pharmacokinetic parameters for budesonide

	Rhinocort Aqua WA (current)		Rhinocort Aqua WA (pH modified)		Rhinocort Aqua NND (pH modified)	
parameter	mean	95% conf.lim.	mean	95% conf.lim.	mean	95% conf.lim.
$AUC_{0-\infty}$ (nmol/L ·h)	3.78	3.66 - 3.91	3.70	3.58 - 3.83	4.04	3.91 - 4.18
AUC_{0-t} (nmol/L ·h)	3.32	3.21 - 3.43	3.26	3.15 - 3.37	3.55	3.43 - 3.67
MRT (h)	5.69	5.41 - 5.97	5.59	5.31 - 5.86	5.75	5.47 - 6.02
$T_{1/2}$ (h)	3.97	3.81 - 4.15	3.91	3.74 - 4.08	3.95	3.78 - 4.12
T_{max} (min)[1]	30	10 - 120	30	10 - 240	30	10 - 120
C_{max} (nmol/L)	0.77	0.74 - 0.81	0.76	0.72 - 0.80	0.87	0.82 - 0.91

1. Median and range

The bioequivalence tests are summarized in Table S3.

Table S3. Pharmacokinetic parameters for budesonide, bioequivalence tests

	Rhinocort Aqua WA (pH modified) vs. WA (current)[1]		Rhinocort Aqua NND (pH modified) vs. WA (current)[1]	
parameter	mean	90% conf.lim.	mean	90% conf.lim.
$AUC_{0-\infty}$ (nmol/L ·h)	0.98	0.94 - 1.02	1.07	1.03 - 1.11
AUC_{0-t} (nmol/L ·h)	0.98	0.94 - 1.02	1.07	1.03 - 1.11
MRT (h)	-0.10	-0.43 - 0.23	0.06	-0.27 - 0.39
$T_{1/2}$ (h)	0.98	0.93 - 1.04	0.99	0.94 - 1.05
C_{max} (nmol/L)	0.98	0.93 - 1.04	1.12	1.06 - 1.19

1. Ratios (%) for $AUC_{0-\infty}$, AUC_{0-t}, C_{max} and $T_{1/2}$, difference for MRT

The first bioequivalence test was between Rhinocort Aqua WA (current) and Rhinocort Aqua WA (pH modified). The mean $AUC_{0-\infty}$ ratio was estimated to be 0.98 with 90% confidence interval 0.94-1.02. Since the confidence interval was entirely contained within the bioequivalence limits 0.80-1.25, the two formulations were bioequivalent with respect to $AUC_{0-\infty}$. The mean ratios for AUC_{0-t} and C_{max} were also 0.98 and the bioequivalence criterion was fulfilled also for these parameters. Therefore Rhinocort Aqua WA (pH modified) can be concluded to be bioequivalent with Rhinocort Aqua WA (current).

The second bioequivalence comparison was between Rhinocort Aqua NND (pH modified) and Rhinocort Aqua WA (current). The mean $AUC_{0-\infty}$ ratio was estimated to be 1.07 with 90% confidence interval 1.03-1.11. Since the confidence interval was entirely contained within the bioequivalence limits 0.80-1.25, the two formulations were bioequivalent with respect to $AUC_{0-\infty}$. The mean ratios for AUC_{0-t} and C_{max} were 1.07 and 1.12, respectively, and the bioequivalence criterion was fulfilled also for these parameters. Since the bioequivalence criterion was fulfilled for all three parameters, and since Rhinocort Aqua WA

(pH modified) was bioequivalent to the Rhinocort Aqua WA (current), it can be concluded that Rhinocort Aqua NND (pH modified) is bioequivalent with Rhinocort Aqua WA (current).

SAFETY RESULTS

Overall, all treatments were well tolerated. The overall frequency and nature of AEs as well as the number of subjects reporting AEs was similar between all treatments with approximately 20% of the subjects reported at least one AE for each treatment. The most commonly reported AE was headache. This was reported for 10 subjects (8%) using Rhinocort Aqua WA (current), for 7 subjects (6%) using Rhinocort Aqua WA (pH modified) and for 8 subjects (7%) using Rhinocort Aqua NND (pH modified). The second and third most commonly reported AEs were nasopharyngitis and pharyngitis, respectively. The most frequently reported AEs were consistent with AEs commonly reported in studies with nasal corticosteroids (headache, nasopharyngitis, pharyngitis and epistaxis). One serious AE (abdominal pain) was reported after first treatment day with Rhinocort Aqua NND (pH modified), the subject was withdrawn from the study. The SAE was not considered treatment related. No other serious AEs, death or other discontinuations due to AEs occurred.

Date of the report

11 February 2003