CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

STRANGE

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,746 **Submission Date:** July 29, 1996

Drug Name, Dose and Formulation: Rhinocort Aqua (Budesonide) nasal spray, 32 and 64 µg budesonide per spray

Sponsor: Astra USA Inc., West Borough, MA-01581

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: New Drug Application, 3S

ISSUE: 21-day Filing

BACKGROUND

Rhinocort Aqua nasal spray contains budesonide which is a non-halogenated, synthetic glucocorticosteroid with potent local anti-inflammatory properties and low systemic activity. The proposed indication for this product is for the management of symptoms of seasonal or perennial allergic rhinitis in adults and children (6 years and older). The proposed starting dose for adults and children is ___ µg once daily. Rhinocort nasal inhaler is the currently approved product, in U.S., containing budesonide (which is a CFC containing product). Another dosage form containing budesonide, Pulmicort turbuhaler (a dry powder inhaler), is currently under development/review.

The nasal spray, Rhinocort Aqua, the subject of this application, is an intranasal spray inhaler containing micronized budesonide in a suspension of microcrystalline cellulose and carboxymethyl cellulose sodium, in purified water. The sponsor has proposed to market two strengths, 32 and 64 µg per spray.

II. OBJECTIVES

This submission is an NDA to request approval for Rhinocort Aqua nasal spray, at 2 dosage strengths 32 and 64 µg per spray, for the management of symptoms of seasonal or perennial allergic rhinitis in patients 6 years of age and older.

III. PHARMACOKINETIC / BIOAVAILABILITY STUDIES

The pharmacokinetics of budesonide have been studied following several different routes of administration, including intranasal, oral inhalation as well as oral, rectal, and intravenous administration. The sponsor has submitted 33 clinical studies as part of human pharmacokinetics and bioavailability section. Studies related to analytical methodology, drug deposition, single and multiple dose pharmacokinetics, systemic bioavailability, metabolism and disposition of budesonide have been submitted. Drug interaction studies with cimetidine, ketoconazole and omeprazole have been provided. A study in patients with compromised hepatic function has also been submitted. Two studies in children were submitted. No specific pharmacokinetic study in elderly subjects was provided.

IV. COMMENTS

1. Studies to investigate the single dose pharmacokinetics of budesonide following intranasal administration via Rhinocort Aqua nasal spray have been conducted.
2. There are several PK studies submitted that were conducted using different dosage forms (CFC nasal spray, turbuhaler, oral, IV products etc.). Pertinent to the NDA under consideration (Rhinocort Aqua), there are 2 PK studies and 2 deposition studies. Also, there are 2 drug interaction studies of interest. The first PK study is an absolute bioavailability study in adults which includes an IV arm, Rhinocort Aqua nasal spray and Rhinocort CFC nasal spray (which is the currently approved product). The second study is a PK study in children. Since it is only a reformulation, the studies submitted are adequate for filing. There are several clinical studies with this product as well.
3. The formulation used in the pivotal clinical trials (for the 32 and 64 µg strengths) is same as the to-be marketed formulation. The pump used for this product is same throughout the development process for this product.

V. RECOMMENDATION

This submission has been reviewed for fileability by the Office of Clinical Pharmacology and Biopharmaceutics. This section of the NDA is organized, indexed, and paginated in a manner to initiate a substantial review. Hence, the submission is fileable.

/S/ 09/09/96

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation II

FT Initialed by Dale Conner, Pharm.D. /S/ 9/9/96

CC list:
HFD-570: NDA 20,746; HFD-570: Division file; HFD-570: CSO\Gretchen Strange;
HFD-570: Medical Reviewer; HFD-570: Chemist; HFD-570: Pharmacologist;
HFD-870: Dale Conner; HFD-870: John Hunt; HFD-870: ChenMe; HFD-850: Biopharm\Lesko;
HFD-870: Chron; HFD-870: Drug; HFD-870: Venkata Ramana S. Uppoor; HFD-340: Viswanathan;
HFD-205: FOI.

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-746
Budesonide
32 and 64 µg/actuation

SUBMISSION DATE:
09/08/97

BRAND NAME:
Rhinocort Aqua Nasal Spray

SPONSOR: Astra USA, Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Responses To The Agency's Comments Code: 3S

TITLE: "Review of The Sponsor's Responses"

SYNOPSIS:

Budesonide is a glucocorticoid which has potent anti-inflammatory but weak mineralocorticoid activity. NDA 20-746 (Rhinocort Aqua Nasal Spray; budesonide 32 and 64 µg/actuation) and its amendments were submitted to the Agency between 07/29/96 and 06/16/97 by Astra USA. They had been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) on 05/20/97 and 06/26/97. They were found overall acceptable, however, several comments on assay methods used were conveyed to the sponsor for future submission of assay reports.

Submitted to 09/08/97 amendment were **1)** a new assay validation report for the analysis of [redacted] (Report Nos. 850-RD-0388) and **2)** responses to the Agency's comments including new quality assurance (QA) data which were missing in Study No. 05-0254.

Since **1)** the validation report No. 850-RD-0388 is for a new assay method and **2)** no additional human pharmacokinetic (PK) studies are submitted under NDA 20-746 for review which use the above new method, the above new assay validation report will not be reviewed at this time and it will be reviewed once new PK studies are submitted in the future.

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Additional QA data were submitted for Study No. 05-0254 and they are reviewed and summarized below:

Quality Control (QA):
Intraday (CV%): 4 -17% at 0.1 nmol/L
Interday (CV%): 28% at 0.1 nmol/L (n=10), 5.5% at 0.3 nmol/L (n=5), and 5.5% at ≈1.83 nmol/L (n=5)

The sponsor's other responses were also reviewed and found overall acceptable.

RECOMMENDATION:

The amendment that was submitted to NDA 20-746 for Rhinocort (budesonide) Aqua Nasal Spray on 09/08/97 by Astra has been reviewed by OCPB/DE II. OCPB/DPE II is of the opinion that the sponsor's responses are found overall acceptable and the validation report No. 850-RD-0388 for a new assay method will be reviewed in the future once new PK studies which use the new assay method are submitted.

APPEARS THIS WAY
ON ORIGINAL

/S/

10/02/97
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT initialed by Dale P. Conner, Pharm.D. /S/ 10/2/97

cc: NDA 20-746, HFD-570 (Anthracite, Trout), HFD-870 (M.L. Chen, D. Conner, T.M. Chen), CDR (B. Murphy).

JUN 26 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-746
Budesonide
32 and 64 μg/actuation

SUBMISSION DATE:
05/22/97 (Serial No. NBB)
06/16/97

BRAND NAME:
Rhinocort Aqua Nasal Spray

SPONSOR: Astra USA, Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Responses To The Agency's Requests Code: 3S

TITLE: "Review of Revised Package Insert and The Sponsor's Responses"

SYNOPSIS:

Budesonide is a glucocorticoid which has potent anti-inflammatory but weak mineralocorticoid activity. On 07/29/96, the sponsor, Astra USA, submitted NDA 20-746 (Rhinocort Aqua Nasal Spray; budesonide 32 and 64 μg/actuation) to the Agency. The human pharmacokinetics/bioavailability (PK/Bio) section has been reviewed by the Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation II (OCPB/DPE II) on 05/20/97. It was found acceptable, however, the revised package Insert (PI) and several responses to the Agency's requests that were submitted on 05/22/97 have not been reviewed by OCPB/DPE II. Therefore, they are reviewed at this time.

Submitted to supplement 05/22/97 were revised PI (Appendix 1), assay validation reports for the analysis of plasma and urinary cortisol levels (Report Nos. 850-RD-0297 and 90-11809, respectively), etc. Further revised PI (June 13, 97 version) was submitted on 06/16/97. The above assay methodologies have never been submitted to the Agency for review previously. The results of assay validations are summarized below:

Report No. 850-RD-0297, modified from a previously reported method for plasma cortisol levels using [redacted]

Standard curves: 27.6, 138, 414, and 828 nmol/L (linear with $r^2 = 0.9999$ and graph presentation only; no data on recovery, accuracy, precision, etc, is available)

Quality Control (QA): (n = 10)

Intraday (CV%): 138 ± 2.9 nmol/L (2.1%), 279 ± 2.1 nmol/L (0.8%), and 621 ± 5.0 nmol/L (0.8%)

Interday (CV%): 142 ± 4.6 nmol/L (3.3%), 277 ± 11 nmol/L (4.1%), and 605 ± 13.3 nmol/L (2.2%)

Report No. 90-11809, a previously developed [redacted] method for urinary unconjugated cortisol levels.

Standard curves:	5-200 nmol/L (reported to be linear)
Recovery:	>80%
Limit of Quantitation (LOQ):	[redacted]
Quality Control (QA): (n=?)	
Intraday (CV%):	12% at 5 nmol/L, 7% at 10 nmol/L, and 4% at 150 nmol/L
Interday (CV%):	18% at 5 nmol/L, 18% at 10 nmol/L, and 15% at 150 nmol/L

RECOMMENDATION:

The sponsor's responses that were submitted to supplements dated 05/22/97 and 06/16/97 for Rhinocort Aqua Nasal Spray (budesonide 32 and 64 μg/actuation) have been reviewed by OCPB/DPE II. OCPB is of the opinion that 1) the assay validation reports are less than satisfactory, 2) minor revision for the sponsor's proposed PI (May 22, 97 version) is needed, and 3) other responses are found acceptable. The comment on the assay validation reports had been sent previously to the sponsor (bioreview dated 05/20/97). The Agency's version of PK subsection of the PI provided as shown below under Labeling Comment needs to be conveyed to the sponsor ASAP.

APPEARS THIS WAY
ON ORIGINAL

/S/

06/18/97

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT initialed by Dale P. Conner, Pharm.D. /S/ 6/26/97

cc: NDA 20-746, HFD-570 (Anthracite, Trout), HFD-870 (M.L. Chen, D. Conner, T.M. Chen), CDR (B. Murphy).

LABELING COMMENT: (The following Agency's version of PK subsection needs to be sent to the sponsor ASAP)

CLINICAL PHARMACOLOGY

Budesonide is a [redacted] having a potent glucocorticoid activity and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. [redacted] In glucocorticoid receptor affinity studies, the 22R form was twice as active as the 22S epimer.

[redacted]

The precise mechanism of [redacted] actions on inflammation in seasonal and perennial allergic rhinitis is not known. [redacted] have been shown to have a wide range of inhibitory activities against multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and [redacted] mediated inflammation.

[redacted] affect the delayed (6 hour) response to an allergen challenge more than the histamine-associated immediate response (20 minute). The clinical significance of these findings is unknown.

[redacted]

Pharmacokinetics

The pharmacokinetics of budesonide have been studied following nasal, oral, and intravenous administration. Budesonide is relatively well absorbed after both inhalation and oral administration, and is rapidly metabolized into metabolites with low [redacted] potency. The activity of Rhinocort Aqua is therefore believed to be due to the parent drug, budesonide.

[redacted]

Absorption: Following intranasal administration of Rhinocort Aqua, mean peak plasma concentration occurs at around 0.7 [redacted]. Compared to an intravenous dose, approximately 34 [redacted] of the delivered dose reaches the systemic circulation, most of which is absorbed through the nasal mucosa. While budesonide is well absorbed from the GI tract, the oral bioavailability of budesonide is low (~10%) primarily due to extensive first pass metabolism in the liver.

Distribution: Budesonide has a volume of distribution of approximately 2-3 L/kg and [redacted]. Budesonide shows no or marginal binding to glucocorticosteroid binding globulin. It rapidly equilibrates with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: Budesonide is rapidly and extensively metabolized in humans by the liver. Two major metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) are formed via cytochrome P450 3A isoenzyme-catalyzed biotransformation. In vitro studies on the binding of the two primary metabolites to the glucocorticoid receptor indicate that they have less than 1% of the affinity for the receptor as the parent compound budesonide. In vitro studies have evaluated sites of metabolism and showed negligible metabolism in skin, lung, and serum. No qualitative difference between the in vitro and in vivo metabolic patterns could be detected.

[redacted] Budesonide is excreted in the urine and feces in the form of metabolites. The 22R form was preferentially cleared [redacted] with a clearance value of 1.4 [redacted] L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was similar for both epimers and it appeared to be independent of dose.

After intranasal administration of a radiolabeled dose, 2/3 of the radioactivity was found in the urine and the remainder in the feces [redacted]. The [redacted] main metabolites of budesonide in the 0-24 hour urine sample following IV administration are 16α-hydroxyprednisolone (24%) and 6β-hydroxybudesonide (5%). An additional 34% of the radioactivity recovered in the urine was identified as conjugates.

Special Populations:

Geriatric: No specific pharmacokinetic study has been undertaken in subjects >65 year years of age.

Pediatric: After administration of Rhinocort Aqua Nasal Spray, the time to reach peak drug concentrations and plasma half-life were similar in children and in adults.

Gender:

Race: Budesonide pharmacokinetics have not been investigated with respect to different races.

Renal Insufficiency: The pharmacokinetics of budesonide have not been investigated in patients with renal insufficiency.

Hepatic Insufficiency: Reduced liver function may affect elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion.

Drug Interactions: The main route of metabolism of budesonide, as well as other is via cytochrome P450 (CYP3A). Concomitant administration of drugs which are known to inhibit the activity of CYP3A (e.g. and erythromycin), may inhibit the metabolism of budesonide.

Precautions:

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NDA 20-746 (Serial No. NBB) for Rhinocort Aqua Nasal Spray (Budesonide 32 and 64 μg/actuation)

Appendix 1:

Sponsor's Proposed Package Insert (May 22, 1997 version)

27 Page(s) Redacted

Draft

Labeling

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-746
Budesonide
32 and 64 μg/actuation

SUBMISSION DATE:
07/29/96
10/10/96 (Serial No. 000BB)
03/06/97 (Serial No. 000BB)

BRAND NAME:
Rhinocort Aqua Nasal Spray

SPONSOR: Astra USA, Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA (a new formulation for an approved drug) Code: 3S

TITLE: "Review of Human Pharmacokinetics and Bioavailability Studies of Rhinocort Aqua Nasal Spray"

SYNOPSIS:

On 07/29/96, the sponsor, Astra USA, submitted NDA 20-746 (Rhinocort Aqua Nasal Spray; budesonide) to the Agency for review. Budesonide is a glucocorticoid which has potent anti-inflammatory but weak mineralocorticoid activity. The sponsor is seeking approval for two strengths, 32 and 64 μg/actuation which used the same pump spray value, delivering 50 μl per actuation.

Rhinocort Aqua Nasal Spray is for the management of symptoms of seasonal or perennial rhinitis in adults and children. The recommended starting dose for adults and children ≥6 years old is [redacted] μg QD, delivered as two sprays of the 64 μg strength in each nostril once daily in the morning. The dose is to be individualized to establish the minimum effective dose. Please see the package insert (PI) in Appendix 2 for details.

Previously, filed under NDA 20-233 by the same sponsor was Rhinocort Nasal Inhaler, 50 μg/actuation (containing a mixture of CFC propellants) and it was reviewed and approved by the Agency on 02/14/94 for the same indication. Rhinocort Aqua Nasal Spray (NDA 20-746) is free of CFC propellants and as indicated by the sponsor, this is a stand-alone drug product, NOT a switch for Rhinocort 50 μg/actuation.

Submitted under Human Pharmacokinetics and Bioavailability section of this NDA were 33 pharmacokinetic/bioavailability (PK/Bio) studies. Twenty nine studies had been reviewed previously and were cross-referenced to NDA 20-233 and 20-441 (Pulmicort Turbuhaler; budesonide). Only 4 new PK/Bio studies were reviewed under NDA 20-746.

Some basic PK parameters obtained from this NDA are summarized here. Mean (±standard deviation; SD) total plasma clearance (CL) and terminal half-life ($T_{1/2}$) of

budesonide racemate (22R and 22S) in healthy adults after intravenous administration (IV) are 75.5 ± 13.2 l/hr and 2.65 ± 0.33 hr, respectively and they are consistent with those obtained previously. The absolute bioavailability (F_{abs}) for Rhinocort Aqua is estimated to be around 34.1 (±7.6) % of the delivered dose as compared to the IV dose and the delivered dose is around 97% of the metered dose.

In a single-dose PK study, the maximum nasal dose of Rhinocort Aqua, 256 μg, was given to child patients (≥6 years old). It has been shown that plasma peak level (C_{max}) for child patients is expected to be higher compared to that in adults when the same dose level was given. However, the mean time to C_{max} (T_{max}; 0.67-0.7 hr) is similar. In a multiple-dose PK study, the maximum nasal dose was given to healthy adults for 7 days, but only the cortisol suppression was monitored. Significant suppression (through HPA-axis) was observed when compared to baseline of plasma cortisol levels or urinary cortisol excretion. No differences, however, were found when compared to 7 days of 400 μg QD of Rhinocort or Pulmicort Turbuhaler given to the same adults. It is also found that seemingly the multiple dose showed less pronounced suppression as compared to the single dose.

The results of previous metabolism study using ^{3}H- and unlabeled budesonide (NDA 20-233) showed that **1)** budesonide is extensively metabolized and no unchanged drug was found in urine or feces, **2)** the mean recoveries of ^{3}H-radioactivity in urine and feces were around 90 % (up to 5 days) after IV or nasal administration, **3)** cytochrome P-450 3A4 is responsible for the metabolism of this drug, **4)** two major metabolites are 16α-hydroxyprednisolone (24%) and 6β-hydroxybudesonide (5%) plus an additional 34% of radioactivity recovered in the urine as conjugates (after IV administration), and **5)** both major metabolites had < 1% of affinity for the receptor in vitro as compared to the parent compound. Furthermore, it has been shown that **1)** budesonide is about 88% bound to plasma protein, **2)** 22R epimer is two times as active as the 22S epimer and it is preferentially cleared by the liver, and **3)** the two forms do not interconvert.

A PK study in subjects with hepatic impairment was conducted previously and it was concluded that dose adjustment for these patients is not needed. No PK study was conducted in subjects with renal impairment, since the drug is extensively metabolized. No major gender differences for budesonide were found in previous NDAs and also in this NDA. Drug-drug (D-D) interactions after co-administration with cimetidine or ketoconazole were investigated previously. Additional D-D interaction between budesonide and omeprazole was conducted in this NDA. The results of the D-D interaction studies showed that **1)** no significant changes in budesonide PK were noted after co-administration of cimetidine or omeprazole and **2)** several fold increase in area under the curve (AUC) of budesonide after co-administration of ketoconazole was found and it is presumably due to the inhibition of metabolic enzyme, cytochrome P-450 3A4, and as a result of an increase in oral bioavailability.

Only the to-be-marketed 64 μg strength was employed in the PK studies of this NDA. No study for dose proportionality (among the recommended dose range of 64 and 256 μg) nor equivalency study between the two to-be-marketed strengths was submitted under this NDA. However, the above two strengths were tested in the pivotal clinical trials which covered the above recommended dose range in the PI. Finally, the assay methods have been used and reviewed previously

RECOMMENDATION:

NDA 20-746 for Rhinocort Aqua (32 and 64 μg/actuation) that was submitted by Astra on 07/27/96 and the subsequent supplements have been reviewed by the Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the PK/Bio portion of this NDA is overall acceptable from a clinical pharmacology and biopharmaceutics perspective. Comments from OCPB/DPE II are provided in the General Comment and Labeling Comment sections of this bioreview. General Comment No. 3 as appropriate needs to be sent to the sponsor. Furthermore, the sponsor needs to revise the PK subsection of the PI and the revised PI will be reviewed separately once it is submitted to the Agency.

APPEARS THIS WAY
ON ORIGINAL

CPB Briefing on 05/09/97: Dr. M.L. Chen, Mr. J. Hunt, and Dr. D. Conner.

/S/

03/21/97

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Dale P. Conner, Pharm.D. DPC 03/28/97

FT initialed by Dale P. Conner, Pharm.D. /S/ 5/20/97

cc: NDA 20-746, HFD-570 (Anthracite, Trout), HFD-870 (M.L. Chen, D. Conner, T.M. Chen), CDR (B. Murphy).

TABLE OF CONTENTS:

Appendix 1:

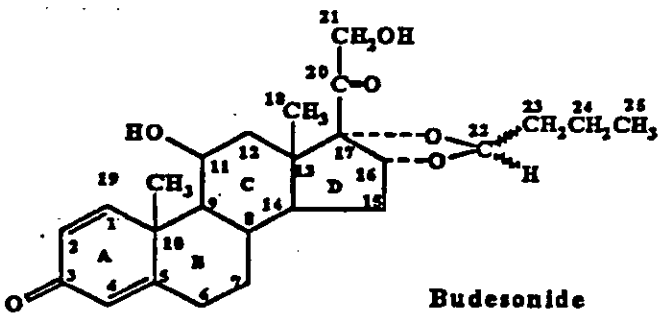
Appendix 1 contains the 4 individual studies reviewed under this NDA.

Appendix 2:

Appendix 2 contains additional detailed information such as PI, formulations used, etc. It is being retained in DPE II and can be obtained upon request.

I. BACKGROUND:

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. Its partition coefficient between n-octanol and water at pH 5.0 is 1.6×10^3. Budesonide has one chiral center and it is provided as the mixture of two epimers (22R and 22S). As reported by the sponsor, in standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol. Its chemical structure is shown below:



Budesonide

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II. SUMMARY OF PHARMACOKINETICS, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:

Four PK studies that have not been reviewed previously but relevant to the approval of Rhinocort Aqua Nasal Spray are reviewed and summarized below in **Table 1:**

Table 1

Study No.	Short Title	Study Design	Subj. (M/F)	Age (Range)	Dosing Regimen
05-0254	Single-Dose PK for Systemic Bioavailability	Open, Randomized Crossover 4x4	Healthy (7M/9F)	20-44	R. Aqua 400 μg, Aerosol 800 μg, Powder 800 μg, and 0.4 mg IV
05-3036	Single-Dose PK in Young Patients	Open	Rhinitic Children (10M/2F)	7-12	R. Aqua 256 μg*
05-3040	Multiple Dose for Effects on HPA-Axis	Open, Randomized Crossover 3x3	Healthy (10M)	19-27	R. Aqua 256 μg* QD x7 Powder 400 μg QD x7 Aerosol 400 μg QD x 7
08-3017	D-D Interaction With Omeprazole	Randomized, crossover 2x2, Placebo-Controlled	Healthy (6M/5F)	21-42	Budesonide CIR Capsule 9 mg x 1 + Omeprazole 20 mg QD x 6 vs. Budesonide CIR Capsule 9 mg x 1 + placebo 20 mg QD x 6

*. Rhinocort Aqua to-be-marketed formulation (64 μg/actuation).

1. PHARMACOKINETICS:

Chiral assay for 22R and 22S epimers was performed previously for some of the PK studies under NDA 20-233, but no such assay was used in this NDA. Mean (± SD) CL and $T_{1/2}$ values for budesonide racemate after IV administration to healthy adults are 75.5 ± 13.2 l/hr and 2.65 ± 0.33 hr, respectively, (Study No. 05-0254) and they are consistent with those obtained from the previously reviewed studies.

Mean (± SD) PK parameters obtained from healthy adults (Study No. 05-0254) and from rhinitic children (Study No. 05-3036) after single-dose nasal administration of budesonide are summarized below in **Table 2:**

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ON ORIGINAL

Table 2

Drug Product & Dose (No. of Subj.)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-t}[b] (ng-hr/ml)	F_{abs}[c] (%)
Rhinocort Aqua[a] 400 μg (n=15)	0.43 ± 0.18	0.67 ± 0.35	1.81 ± 0.51	33.1 ± 7.4[d] (34.1 ± 7.6)[e]
Rhinocort Aerosol MDI[a] 800 μg (n=15)	0.22 ± 0.13	2.04 ± 1.56	1.32 ± 0.59	13.8 ± 6.3 (22.6 ± 9.9)
Pulmicort TBH[a] 800 μg (n=16)	0.46 ± 0.25	0.39 ± 0.19	2.04 ± 1.01	21.5 ± 10.0 (40.2 ± 20.0)
Rhinocort Aqua[f] 256 μg (n=12)	0.71 ± 0.30	0.70 ± 0.64	2.37 ± 0.82	---------[g]

[a]. Adult dose was normalized to the same delivered dose of 385 μg (Study No. 05-0254).
[b]. AUC obtained from time zero to last detectable sampling point.
[c]. Compare to an IV dose.
[d]. Based on metered dose.
[e]. Based on delivered dose.
[f]. Child dose (256 μg) was not normalized (Study No. 05-3036).
[g]. No IV dose was given.

It should be noted that higher mean C_{max} and AUC_{0-t} values (1.07 ± 0.45 μg/ml and 3.56 ± 1.23 μg-hr/ml, respectively) are expected for children, if the child dose is normalized to the same adult (delivered) dose of 385 μg of Rhinocort Aqua. The mean T_{max} values in rhinitic children and in healthy adults, however, are comparable.

After administration of Rhinocort Aqua 400 μg (using the not-to-be-marketed [redacted], the F_{abs} of a delivered dose was calculated to be 34.1% and the delivered dose was estimated to be about 97% of the metered doses (Study No. 05-0254).

The maximum recommended dose of 256 μg QD was given to healthy adults for 7 days (Study No. 05-3040). However, only the plasma cortisol levels and urinary cortisol excretion were monitored and no budesonide PK data were obtained. For pharmacodynamic (PD) results, please see the PK/PD section of this review for details.

2. BIOEQUIVALENCE:

There are no bioequivalence (BE) issues between the clinically tested and the to-be-marketed formulations, since both strengths of the to-be-marketed formulation have been used in the pivotal clinical trials. No BE

study, however, was conducted between the not to-be-marketed Rhinocort Aqua formulation [redacted] actuation; [redacted] mg/ml) and the to-be-marketed formulation (64 μg/actuation; 1.28 mg/ml). For the compositions of formulations used in this NDA, please see Appendix 2 for details.

3. DOSE PROPORTIONALITY:

The recommended dose range (64 to 256 μg) was investigated in one clinical trial (with PD parameters measured only). No PK study was conducted to cover the above dose range nor was equivalency study between the two to-be-marketed strengths (32 and 64 μg/actuation).

4. METABOLISM AND IN VITRO:

The in vivo metabolism of budesonide had been studied and reviewed previously under NDA 20-233 using ^3H- and unlabeled budesonide. It has been shown that 1) budesonide is extensively metabolized and no unchanged drug was found in urine or feces, 2) the mean recoveries of ^3H radioactivity in urine and feces were 56.7% and 34% after IV and 56.1% and 33.4% after nasal administration, respectively, 3) cytochrome P-450 3A4 is responsible for the metabolism of this drug, 4) two major metabolites are 16α-hydroxyprednisolone (24%) and 6β-hydroxybudesonide (5%) plus an additional 34% of radioactivity recovered in the urine as conjugates (after IV administration), 5) their mean plasma $T_{1/2}$ values were reported to be 2.1 hr for 16α-hydroxyprednisolone and 5.6 hr for 6β-hydroxybudesonide, and 6) both major metabolites had < 1% of affinity for the receptor in vitro as compared to parent compound.

The results of previous in vitro studies showed that 1) budesonide is about 88% bound to plasma protein, 2) 22R epimer is two times as active as the 22S epimer and it is preferentially cleared by the liver, and 3) the two forms do not interconvert.

5. POPULATION:

The PK study of budesonide in cirrhotic subjects was conducted and reviewed previously under NDA 20-441. It was concluded that 1) the PK in healthy volunteers and cirrhotic patients were similar after IV administration of budesonide and 2) there was a 16% decrease in their mean CL and the mean AUC and C_{max} increased almost double after oral ingestion of budesonide. No inhalation study in cirrhotic patients was conducted for budesonide.

No PK study was conducted in renally impaired patients, since the drug is extensively metabolized with no parent drug found in the urine or feces.

6. GENDER:

There was no specific study conducted. However, a gender analysis on systemic exposure of budesonide was performed in two PK studies that were previously reviewed under NDA 20-441. The results showed that there were no significant gender effects on PK of budesonide. For this NDA, both male and female subjects were employed in 3 PK studies, however, the sponsor indicated that no major gender differences in most of the PK parameters of budesonide were found.

7. DRUG-DRUG INTERACTION:

D-D interaction between the orally administered ketoconazole and budesonide (Study No. 52-3002) was conducted previously and reviewed separately in a bioreview dated 11/19/96 under NDA 20-441. The results showed that 1) several fold increase in budesonide AUC value was observed, 2) no significant change in budesonide $T_{1/2}$ was found, and 3) the increase in the oral bioavailability of budesonide was presumably due to the inhibition of metabolic enzyme, cytochrome P-450 3A4, by co-administration of ketoconazole. Furthermore, the changes in budesonide PK due to the D-D interaction between cimetidine and budesonide were investigated and they were found to be mild (Study No. 850-CR-6007; NDA 20-233).

One additional D-D interaction study (No. 08-3017) was conducted under this NDA. Omeprazole 20 mg was given QD orally in the morning for 6 days. On Day 5, a dose of 3 x 3 mg CIR (controlled ileal release capsule) budesonide was given orally with omeprazole immediately with a standard breakfast. Plasma budesonide levels were monitored for 12 hr and the amount of cortisol excreted in urine was collected for 24 hr post dosing (Day 5). On Day 6, a second dose of 3 x 3 mg CIR budesonide (36 hr post first budesonide dose) was given immediately before dinner (the same recipe as the breakfast). Plasma budesonide levels were monitored between 0-3 hr and at 12th hr and the amount of cortisol excreted in urine was collected for 24 hr post dosing (Day 6).

The PK results of budesonide obtained from Study No. 08-3017 are summarized below in **Tables 3a and 3b:**

Table 3a (Morning Dose on Day 5):

Treatment (n = 11)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-12} (ng-hr/ml)
With Omeprazole	2.14 ± 1.20	3.2 ± 1.6	14.3 ± 7.2
With Placebo	2.06 ± 0.93	2.9 ± 1.3	14.1 ± 6.0

Table 3b (Evening Dose on Day 6):

Treatment (n = 11)	C_p^3 (ng/ml)[a]	T_{max} (hr)[b]	AUC_{0-3} (ng-hr/ml)
With Omeprazole	1.31 ± 0.78	2.6 ± 0.7	1.99 ± 1.52
With Placebo	0.87 ± 0.59	2.8 ± 0.4	1.29 ± 0.96

a. Monitored between 0-3 hr post dosing.
b. N = 10; (one female subject had zero plasma budesonide levels between 0 and 3 hr post evening dose on Day 6).

It was concluded that with or without omeprazole, 1) no differences in the mean AUC_{0-12} and C_{max} values for budesonide were found after the morning oral dose of budesonide (on Day 5) and 2) some but not significant differences in the mean AUC_{0-3} and C_p^3 (plasma level at 3 hr) values were found after the evening dose (on Day 6). Furthermore, plasma budesonide levels, however, seemed to be lower after the evening dose than in the morning dose and the reason is not clear.

Urinary cortisol levels were also monitored in this study and the results are summarized below in **Table 4**:

Table 4

0-24 hr Cortisol (nmole)	Baseline	Day 5	Day 6
With Omeprazole	98.1 ± 35.2	50.3 ± 21.4	44.6 ± 35.9
With Placebo	83.0 ± 30.3	41.9 ± 15.5	42.4 ± 22.0

The results of urinary excretion of (free) cortisol showed that with or without omeprazole, 1) no differences were found in baseline, in Day 5 after the morning dose and in Day 6 after the evening dose of budesonide and 2) neither omeprazole nor dosing regimen (morning or evening dose) affected the suppression of 24-hr urinary excretion of cortisol.

8. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

The cosyntropin-simulated cortisol suppression (through HPA-axis) was selected for PD measure for safety. It was reported that the cosyntropin-simulated cortisol suppression correlated with dose and corresponding

AUC (NDA 20-441). However, there were no PK/PD studies nor analysis of PK/PD relationship conducted for this drug product.

Study No. 05-3040 investigated the effect of a multiple dose of Rhinocort Aqua 256 μg QD (using the to-be-marketed formulation) on the HPA-axis. Only the plasma and urinary cortisol suppression through HPA-axis were monitored and no PK data were obtained. The results showed that after nasal administration of Rhinocort Aqua for 7 days, **1)** statistically significant ($p<0.05$) suppression (~10%) on plasma cortisol levels as compared to baseline was found, **2)** statistically significant suppression based on urinary cortisol excretion data was also found, **3)** no differences in effect on either plasma cortisol or urinary cortisol suppression were noted when compared to other formulations, doses, or routes of administration, and **4)** the multiple-dose treatment showed less pronounced suppression compared to the single dose (**Table 5**).

Table 5

Plasma Data	**Baseline**	**Rhinocort Aqua 256 μg x 7 days**	**Rhinocort Aerosol 400 μg x 7 days**	**Pulmicort Turbuhaler 400 μg x 7 days**
Cortisol $AUC_{0\text{-}24}$ (nmole-hr/l) on Day 7	4830 ±1006	4322 ± 1144*	4458 ± 1082*	4228 ± 1019*
Urine Data				
Cortisol $Ae_{0\text{-}24}$ (nmole) on Day 1	97.5 ± 61.2	65.2 ± 48.6**	54.6 ± 23.7**	54.6 ± 18.8**
Cortisol $Ae_{0\text{-}24}$ (nmole) on Day 7	———	81.5 ± 55.0**	72.1 ± 31.0**	79.5 ± 45.0**

*. Mild (~10%) but statistically significant suppression ($p<0.05$).
**. Statistically significant suppression ($p<0.05$).

9. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

Both 32 and 64 μg/actuation strengths of the to-be-marketed budesonide (Formulations B and D, respectively) were used clinically, however, only the 64 μg/actuation (Formulation D) was used in PK study Nos. 05-3036 and 05-3040 and Formulation C was used in Study 05-0254 (**Table 6**). For all the formulations used in the NDA, please see Appendix 2 for details.

Table 6

Formulation No.	B* (32 μg/ spray)	[redacted] spray)	D* (64 μg/ spray)
Ingredient (mg/1 ml)	[redacted]		
Budesonide Micronized (mg)			
Micronized Cellulose & Carboxyl-methyl Cellulose Sodium (mg)			
Glucose Anhydrous (mg)			
Polysorbate 80 (mg)			
Disodium Edetate (mg)			
Potassium Sorbate (mg)			
HCL adjust to pH			
Purified H_2O qs. to			

*. To-be-marketed formulations.

10. ASSAY METHODOLOGY:

The assay methods [redacted] Report No. 850-RD-0292 for plasma budesonide levels and [redacted] Report No. 90-11809 for cortisol level in urine) had been reviewed previously in NDAs 20-233 and 20-441. Minor modifications of the assay methods were made. The QA reports of the assay methods were found to be less satisfactory since as indicated in the previous reviews, 1) it is inappropriate to report the LOQ of [redacted] nmol/L (equivalent to [redacted] ng/ml), while the assay standard curves were prepared between 0.2 to 6.4 nmol/L and 2) two or three concentration points were used in daily quality control, however, they did not cover properly the standard curves constructed. In addition, the QA report for analyzing the plasma cortisol levels (Study No. 05-CR-3040) is not available (missing).

III. GENERAL COMMENTS: (No.3 needs to be sent to the sponsor)

1. There is no PK study conducted to assess the BE between the to-be-marketed 64 μg formulation D and the not to-be-marketed [redacted] formulation [redacted] The latter was used in a pivotal study (No. 05-0254) to obtain F_{abs} and other basic PK parameters. Since the two formulations have the same amounts of the same inactive ingredients except the active ingredient, budesonide, the BE is probably less of a concern. Therefore, no additional PK study is needed to address this issue.

2. There were no PK studies conducted to assess 1) the equivalence between the two to-be-marketed strengths, 32 and 64 μg/actuation, and 2) the dose proportionality for the recommended dose range in the PI, 64 to 256 μg.

As indicated by the sponsor in the NDA supplement dated 03/06/97, the above two issues had been discussed between the sponsor and the Agency. The Agency agreed that 1) the dose proportionality could be demonstrated using Pulmicort Turbuhaler (400 μg BID to 1600 μg BID) and using budesonide CIR capsules (3 mg to 15 mg QD) and 2) equivalency between the two to-be-marketed strengths, 32 and 64 μg/actuation has been demonstrated in vitro. Furthermore, due to the assay limitation, complete plasma profiles of budesonide could only be obtained for the highest dose (256 μg).

Finally, a discussion with the reviewing medical officer (Dr. Anthracite) was held on 03/17/97. It was indicated by him that for all the doses of 32, 64, 128, and 256 μg QD, the changes from baseline in average nasal index score (NIS) were significant, yet, no significant differences among doses were found and 2) no changes in the measurement of basal cortisols and cortrosyn-stimulated serum cortisols (taken at one point in time), differentiated the treatment groups.

Therefore, based on the above information, it is felt that no additional PK study(ies) is needed to fulfill the PK requirements regarding the equivalence and dose proportionality issues.

3. The analytical methods used for the PK studies submitted under this NDA are less satisfactory. The analytical methods had been submitted and reviewed previously under NDAs 20-233 and 20-441. Similar conclusions (the assay methods being less satisfactory) were drawn and the deficiencies have been sent to you previously. No improvement on the analytical methods was made ever since. Therefore, it is important to again summarize the deficiencies below for future improvement:

[redacted]

IV. LABELING COMMENT: (Already conveyed to the sponsor)

The Pharmacokinetics subsection under Clinical Pharmacology section of the package insert needs a revision. The template for the pharmacokinetic information to be presented in the package insert has been sent to the sponsor by fax through the CSO (Ms. G. Trout). Therefore, the sponsor's revised PI will be reviewed separately once it is submitted to the Agency.

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NDA 20-746 (Rhinocort Aqua Nasal Spray)

Appendix 1:

Individual Study Reports

Title: "Systemic Availability of Budesonide Administered As Three Different Nasal Formulations: Pressurized Aerosol, Aqueous Suspension, and Insufflated Powder"

Investigator and Study Site:

The study was conducted by M. Grind, MD at Department of Human Pharmacology, Astra Draco AB, Sweden

Objective:

To measure the F_{abs} values of the three nasal formulations of budesonide.

Study Design:

This was an open, randomized, 4x4 crossover study with a washout period of at least 6 wks.

Population:

Sixteen (7M + 9F) healthy subjects completed the study and their mean (± SD) age, BW, and height are 31.3 (± 8.3) years old, 66.8 (± 14.1) kg, and 172 (± 11) cm, respectively.

Formulation, Dosage, and Administration:

Not-to-be-marketed Rhinocort Aqua [redacted] formulations (C, C1, and C2; Treatment C), Rhinocort Aerosol (Treatment B), Pulmicort Turbuhaler (Treatment D) formulations, and budesonide IV solution (Treatment A) were used in this study. For the formulation, batch no./size and date/site of manufacture, please see Appendix 2 for details.

On the treatment day, the subjects arrived at the clinic after an overnight fasting. A normal breakfast was served at the clinic 0.5 hr before start of treatment and the subjects were abstained from food for 4 hr and from beverages for 2 hr post dosing.

A total (nominal) dose of 400 μg of budesonide was given 4 puffs in each nostril (Treatment C) and 800 μg from a pressurized nasal aerosol (Treatment B; 8 x 50 μg/puff for each nostril) were given. For nasal insufflation from a powder inhaler (Treatment D), a dose of 800 μg was given by 4 x 100 μg/insufflations in each nostril. An IV infusion of 400 μg in 16 ml (over 8 min) was given (Treatment A).

Sample Collection:

Venous blood (20 ml each) was withdrawn immediately before dosing and at 10, 20, 30, 45, 60 min and 2, 4, 6, 8, and 10 hr post dosing of nasal administration. For IV treatment phase, blood was taken immediately before dosing and at 8, 15, 30, 45, 60 min and 2, 4, 6, 8, and 10 hr post dosing. Blood samples were immediately centrifuged (1500 x g) for 10 min. Plasma was harvested and then divided into two tubes and stored frozen at -20°C until analysis.

Assays:

Budesonide in plasma was assayed at the Bioanalytical Labs, Astra Draco by a method of [redacted] Standard curves of 0.1 up to 6.4 nmol/L were prepared with an LOQ of [redacted] using 3 ml plasma. The above assay method (report No. 850-RD-0292) for racemic 22 RS-budesonide has been reviewed previously and found acceptable. Please see the bioreview of NDA 20-441 (Pulmicort Turbuhaler; budesonide) dated 05/07/96 in OCPB/DPE II drug review files for details. The QA data obtained from this study are summarized below:

Standard curves:	0.20-6.40 nmol/L (linear)
Precision (CV%):	10-18% at 0.1 nmol/L (reported only)
Accuracy:	85-95% at 0.1 nmol/L (reported only)
LOQ:	[redacted]

The QA data that were submitted on 10/10/96 upon Agency's request are summarized below:

Standard curves:	0.2-6.40 nmol/L
Intraday (CV%):	Not available
Interday (CV%):	7.1% at 0.3 nmol/L (n=24), 4.5% at ≈2.22 nmol/L (n=10), and 7.7% at ≈1.88 nmol/L (n=15).
Accuracy:	98% at 0.3 nmol/L (n=24)

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of budesonide and descriptive statistics were used.

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Results:

As indicated by the sponsor, the LOQ was [redacted] (equivalent to [redacted] and it has been verified down to this range previously. However, for this study, the standard curve was prepared down to 0.2 nmol/L only. Therefore, it is inappropriate to report the LOQ of [redacted] In addition, for QA data, there were three points used, but they did not cover properly the range of standard curve prepared. The assay results are, therefore, less satisfactory. Individual budesonide plasma levels were spot checked and they were found acceptable. For study results, please see PK summary of this bioreview for details.

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Study No. 05-3036 (Volume 1.11)

Title: "Plasma Concentrations of Budesonide in Rhinitic Children After Nasal Administration As An Aqueous Suspension"

Investigator and Study Site:

The study was conducted by [redacted] at [redacted]

Objective:

To determine the plasma concentration profile of budesonide in rhinitic children aged 6-12 years old.

Study Design:

This was an open, single-dose study.

Population:

A total of 12 (10M+2F) children with a diagnosis of seasonal or perennial rhinitis completed the study and their mean (± SD) age, BW, and height are 9.8 (± 1.5) years old, 37.9 (± 8.9) kg, and 142 (± 10.) cm, respectively.

Formulation, Dosage, and Administration:

The to-be-marketed formulation (D; 64 μg/puff) was used. For the batch no./size and date/site of manufacture, please see Appendix 2 for details.

On the treatment day, the subjects arrived at the clinic after an overnight fasting. A normal breakfast was served at the clinic 0.5 hr before start of treatment and the subjects were abstained from food for 4 hr and from beverages for 2 hr post dosing. A total (nominal) dose of 256 μg of budesonide was given 2 x 64 μg/puff in each nostril.

Sample Collection:

Venous blood (10 ml each) was withdrawn immediately before dosing and at 10, 20, 30, 45, 60 min and 2, 4, and 6 post dosing. Blood samples were immediately centrifuged (1500 x g) for 10 min. Plasma was harvested and then stored frozen at -20°C until analysis.

Assays:

Budesonide in plasma was assayed at the Department of Bioanalytical Chemistry, Astra Draco by a method of [redacted] Standard curves of 0.1 up to 6.4 nmol/L were prepared with an LOQ of [redacted] using 3 ml plasma. The above assay method (report No. 850-RD-0331) for racemic 22 RS-budesonide is similar to that has been reviewed previously except the precision and accuracy were obtained on [redacted] Instruments. The above assay validation was reviewed previously and found acceptable. Please see the previous individual study No. 05-0254 for details. For this study, however, the standard curves between 0.2 and 6.4 nmol/L were used. The QA data (using 0.1, ≈2, and 4 nmol/L) that were submitted on 10/10/96 upon Agency's request are summarized below:

Standard curves:	0.2-6.40 nmol/L
Intraday (CV%):	0-4.9% at 0.1 nmol/L (n=2).
Interday (CV%):	8.9% at 0.1 nmol/L (n=6), 3.7% at ≈2 nmol/L (n=3), and 2.6% at 4 nmol/L (n=3).
Accuracy:	96% at 0.1 nmol/L (n=6) and 98% at 4 nmol/L (n=3).

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of budesonide and descriptive statistics were used.

Results:

The assay results are less satisfactory due to assay deficiency. Please see the Results section of previous study No. 05-0254 for details. Individual budesonide plasma levels were spot checked and they were found acceptable. For study results, please see PK summary of this bioreview for details.

APPEARS THIS WAY
ON ORIGINAL

Study No. 05-3040 (Volume 1.19)

Title: "Comparison of Effects on the HPA-Axis of Budesonide Administered as Three Different Nasal Formulations: Pressurized Aerosol, Aqueous Suspension, and Powder"

Investigator and Study Site:

The study was conducted by [redacted]

Objective:

To 1) assess plasma cortisol suppression (AUC_{0-24}) after multiple dosing and 2) assess urine cortisol suppression (Ae_{0-24}) after single and multiple dosing of three different nasal formulations of budesonide

Study Design:

This was an open, randomized, multiple dose, 4-way crossover study with a washout period of at least 4 days.

Population:

Twenty (10M + 10 F) healthy subjects completed the study and their mean (± SD) age, BW, and height are 23 (± 3) years old, 70. (± 11) kg, and 175 (± 10.) cm, respectively.

Formulation, Dosage, and Administration:

The to-be-marketed Rhinocort Aqua formulation (D; 64 μg/puff) and Rhinocort Aerosol formulation (F; 50 μg/puff) and Pulmicort Turbuhaler formulation (H; 100 μg/dose) were used in this study. A placebo leg was employed in addition to the three active treatment groups. For the batch no./size and date/site of manufacture of the formulation used, please see Appendix 2 for details.

The study drug was administered QD in the morning for 7 days then treatment group rotated according the randomization list.

Sample Collection:

Venous blood (5 ml each) was withdrawn immediately before and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hr post dosing on Day 7 of each treatment phase. Blood

samples were immediately centrifuged (3000 x g) for 10 min. Plasma was harvested and then stored frozen at -20°C until analysis of cortisol levels.

Urine was collected for 24 hr on Days 1 and 7. Two of 10 ml of urine were transferred to test tubes and stored at -20°C until analysis of cortisol levels. For baseline assessment during the placebo leg, the subjects just reported to the clinic for similar 24-hr sampling.

Assays:

Cortisol in plasma was assayed at the [redacted] and an [redacted] method [redacted] was used. However, the sponsor indicated on 10/10/96 supplement that no QA report for plasma cortisol levels is available.

Cortisol in urine was assayed at [redacted] using a method based on [redacted] (No. 90-11809). Standard curves between 10 and 200 nmol/L were prepared. The above method has been reviewed previously and found acceptable. The QA data that were submitted on 10/10/96 upon Agency's request are summarized below:

Standard curves:	10-200 nmol/L
Intraday:	Not available.
Interday (CV%):	5.5% at 20 nmol/L (n=2), 9.4% at 100 nmol/L (n=2), and 6.7% at 132.8 nmol/L (n=2)
Accuracy:	96% at 20 nmol/L (n=2), 95% at 100 nmol/L (n=2), and 98% at 132.8 nmol/L (n=2).

Data Analyses:

Non-compartmental methods were used for calculating the AUC_{0-24} of plasma cortisol levels and descriptive statistics were used for plasma and urinary data.

Results:

The individual plasma and urinary cortisol levels were spot checked and they were found acceptable. For QA data, there were three points used, but they did not cover properly the range of standard curve prepared and intraday data were not available. The assay results are less satisfactory. For study results, please see PK summary of this bioreview for details.

Title: "Study of Possible Interaction between Budesonide and Omeprazole in Healthy Volunteers"

Investigator and Study Site:

The study was conducted by S. Lindgren, MD, Ph.D. at Clinical Research Lab. Astra Draco AB, Sweden.

Objective:

To investigate whether omeprazole dosed in the morning affects the PK and systemic effects of budesonide CIR capsules dosed in the morning or in the evening.

Study Design:

This was a double-blind concerning omeprazole, randomized, crossover and placebo-controlled study with a washout period of at least 12 weeks.

Population:

Eleven (6M + 5F) healthy subjects completed the study and their mean (± SD) age, BW, and height are 27.2 (± 6.2) years old, 74.2 (± 7.1) kg, and 175 (± 6) cm, respectively.

Formulation, Dosage, and Administration:

A CIR formulation of budesonide capsule that is approved outside the US (batch nos. DSK314 and DTF316) and [redacted] (omeprazole) 20 mg capsule (batch nos. H 431-13-5-3 and H 431-13-5-2) were used. A placebo (batch nos. H 459-6-3-2 and H 459-6-3-1) for Losec 20 mg was also used. Additional formation on the formulations/ compositions, batch size, and date/site of manufacture of the test drug products was provided in an NDA supplement dated 03/06/97.

In one treatment phase, subject was given either omeprazole or placebo daily in the morning for 6 days (according to randomization list). On Day 5, a dose of 3 x 3 mg CIR budesonide capsules was given with omeprazole (or placebo) and 200 ml water immediately before a standard breakfast, i.e., 3 slices of white bread (two with cheese and one with ham), 300 ml of coffee tea, or water and 100 ml of orange juice. No eating or drinking is allowed until a standard lunch (baked fish with mesh potatoes and one tomato, one slice of bread with cheese, and liquids) was served 4 hr post dosing. The same morning meal recipe was given for dinner 12 hr post dosing. On Day 6, a

second dose of 3 x 3 mg CIR budesonide capsules was given immediately before dinner (36 hr post first budesonide dose).

In the second treatment phase, subject who received omeprazole previously would receive placebo and vice versa. The budesonide dosing regimen remained the same.

Sample Collection:

For each treatment phase, venous blood (20 ml each) was withdrawn 1) on Day 5, immediately before and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hr post morning dosing of budesonide and 2) on Day 6, immediately before and at 0.5, 1, 1.5, 2, 3, and 12 hr post evening dosing of budesonide. Blood samples were immediately centrifuged (1500 x g) for 10 min. Plasma was harvested and stored frozen at -20°C (not more than one month) and then at -70°C until analysis for budesonide levels.

"Baseline" urine was collected for 24 hr on Day 4 and 24-hr urine was collected on Days 5 and 6. Two of 10 ml of urine were transferred to test tubes and stored at -20°C until analysis for cortisol levels.

Assays:

Budesonide in plasma was assayed at the Bioanalytical Chemistry, Astra Draco, AB by a method of combined [redacted]. Standard curves of 0.1 up to 6.4 nmol/L were prepared with an LOQ of [redacted] using 3 ml plasma. The above assay method (report Nos. 850-RD-0331) for racemic 22 RS-budesonide is similar to that has been reviewed previously except the precision and accuracy were obtained on [redacted] instruments. The above method was found acceptable. Please see the previous individual study No. 05-0254 for details. The QA results that were submitted on 10/10/96 upon Agency's request are summarized below:

Standard curve:	0.2-6.40 nmol/L
Intraday (CV%):	0-14% at 0.1 nmol/L (n=2).
Interday (CV%):	13% at 0.1 nmol/L (n=22), 4.0% at ≈2.0 nmol/L (n=11), and 3.4% at 4 nmol/L (n=11).
Accuracy:	102% at 0.1 nmol/L (n=22) and 104% at 4 nmol/L (n=11).

Cortisol in urine was assayed at [redacted] using a method based on [redacted] (No. 90-11809). The above method has been reviewed previously and found acceptable. The QA results that were submitted on 10/10/96 upon Agency's request are summarized below:

Standard curves	10-200 nmol/L
Intraday (CV%):	9.4% at 20 nmol/L (n = 2), 1.5% at 100 nmol/L (n = 2), and 0.3% at 132.8 nmol/L (n = 2).
Interday:	Not available.
Accuracy:	105% at 20 nmol/L (n = 2), 92% at 100 nmol/L (n = 2), and 94% at 132.8 nmol/L (n = 2).

Data Analyses:

Non-compartmental methods were used for calculating PK parameters of budesonide. Descriptive statistics were used for plasma and urinary data.

Results:

The individual plasma budesonide and urinary cortisol levels were spot checked and they were found acceptable. For QA data, there were three points used, but they did not cover properly the range of standard curve prepared and interday data were not available. The assay results are less satisfactory. For study results, please see PK summary of this bioreview for details.

NDA 20-746 (Rhinocort Aqua Nasal Spray)

Appendix 2:

1. Proposed Package Insert (07/23/96 version)

2. Formulations Used and Their Batch Nos./Sizes, Dates and Sites of Manufacturing

21 **Page(s) Redacted**

Draft

Labeling

3.B.11.c COMPOSITION OF INVESTIGATIONAL FORMULATIONS

A). Rhinocort Aqua µg/dose, corresponds to mg/ml

Name of ingredient	1 ml contains
Budesonide micronized	
Microcrystalline cellulose and Carboxymethylcellulose sodium	
anhydrous	
Polysorbate 80	
Disodium edetate	
Potassium sorbate	
Hydrochloric acid	
Purified water	

B). Rhinocort Aqua 32 µg/dose, corresponds to 0,64 mg/ml

Name of ingredient	1 ml contains
Budesonide micronized	
Microcrystalline cellulose and Carboxymethylcellulose sodium	
anhydrous	
Polysorbate 80	
Disodium edetate	
Potassium sorbate	
Hydrochloric acid	
Purified water	

C). Rhinocort Aqua µg/dose, corresponds to mg/ml

Name of ingredient	1 ml contains
Budesonide micronized	
Microcrystalline cellulose and Carboxymethylcellulose sodium	
anhydrous	
Polysorbate 80	
Disodium edetate	
Potassium sorbate	
Hydrochloric acid	
Purified water	

[1] About Hydrochloric acid

C1). Rhinocort Aqua µg/dose, corresponds to mg/ml

Name of ingredient	1 ml contains
Budesonide micronized	
Microcrystalline cellulose and Carboxymethylcellulose sodium anhydrous	
Polysorbate 80	
Disodium edetate	
Potassium sorbate	
Hydrochloric acid	
Purified water	

C2). Rhinocort Aqua µg/dose, corresponds to mg/ml

Name of ingredient	1 ml contains
Budesonide	
Microcrystalline cellulose and Carboxymethylcellulose sodium anhydrous	
Polysorbate 80	
Disodium edetate	
Potassium sorbate	
Hydrochloric acid	
Purified water	

D). Rhinocort Aqua 64 µg/dose, corresponds to 1,28 mg/ml

Name of ingredient	1 ml contains
Budesonide micronized	
Microcrystalline cellulose and Carboxymethylcellulose sodium anhydrous	
Polysorbate 80	
Disodium edetate	
Potassium sorbate	
Hydrochloric acid	
Purified water	

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3.B.11.b Investigational formulations summary

Study No. Report No.	Formulation	Pack size	Drug Product Batch No	Compo-sition	Batch size	Manufacturer	Date of manufacture	Budesonide micronized Batch No.	Budesonide Batch no	Manufacturer	Comments
05-0244 850-CR-2120	Rhinocort Turbuhaler 200 µg/dose	- [1]	-	-	-	-	-	219/ (12P)[2] 223/(114P) 223/(115)	182 187 187	APP APP APP	
05-0254 850-CR-2119	Rhinocort Aqua	10 ml	PE 61	C	[redacted]	APP	1989-05-29	205 209[3]	172 174	APP APP	
	"	10 ml	QE 120	C		APP	1990-04-23	229 231, 232[3]	193 195, 196	APP APP	
	"	10 ml	DQP 41	C1		Astra Draco[4]	1990-06-07	235	199	APP	
	"	10 ml	DQK 42	C2		Astra Draco	1990-10-11	-[5]	351-1	APP	
	Rhinocort Aerosol 50 µg/dose	200 doses	PC 160	P		[redacted]	1989-03-13	198 201	163 166	APP APP	
	"	200 doses	PL 168	P			1989-11-13	218	182	APP	
	Rhinocort Turbuhaler 100 µg/dose	200 doses	DQC 35	H		Astra Draco	1990-03-07	223/(114P)	187	APP	
	Budesonide Solution for inj. 25 µg/ml	20 ml	DQC 8	X		Astra Draco	1990-03-05	225	189	APP	
	"	20 ml	DRD 9	X		Astra Draco	1991-04-18	225	189	APP	
05-0255 850-CR-2137	Rhinocort Aqua	10 ml	QE 120	C		APP	1990-04-23	229 231, 232[3]	193 195, 196	APP APP	
	"	10 ml	PE 61	C		APP	1989-05-29	205 209[3]	172 174	APP APP	
	Rhinocort Turbuhaler 100 µg/dose	200 doses	DQC 37	H		Astra Draco	1991-03-16	227/ (116P)	191	APP	
	Pulmicort Turbuhaler 400 µg/dose	200 doses	PK 20	K3		APP	1989-11-02	218 / (28P)	182	APP	

[1] The substance was filled into the Turbuhaler at the clinic
[2] Batch No of Budesonide spheronized
[3] Not possible to decide witch of the batches that was actually used
[4] Astra Draco AB, Lund, Sweden
[5] No micronization was performed

[redacted]

30 June 1996

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Study No. Report No.	Formulation	Pack size	Drug Product Batch No	Compo-sition	Batch size	Manufacturer	Date of manufacture	Budesonide micronized Batch No.	Budesonide Batch no	Manufacturer	Comments
05-3036 05-CR-3036	Rhinocort Aqua 64 µg/dose	100 doses	VB 31A	D			1995-02-13	548-1	48080-02		
05-3038	Rhinocort Aqua 64 µg/dose	100 doses	TI 21	D			1993-09-28	397-1	28774-01		
05-CR-3038*	Rhinocort Aqua 32 µg/dose	100 doses	UE 13	B			1994-06-10	527-1	38756-01		
	Rhinocort Aqua 16 µg/dose	100 doses	UE 12	A			1994-06-08	527-1	38756-01		
05-3039	Rhinocort Aqua 64 µg/dose	100 doses	TI 21	D			1993-09-28	397-1	28774-01		
05-CR-3039*	"	100 doses	UK 30	D			1994-10-11	540-1	48079-01		
	Rhinocort Aqua 32 µg/dose	100 doses	UE 13	B			1994-06-10	527-1	38756-01		
	"	100 doses	UK 25	B			1994-10-10	540-1	48079-01		
	Rhinocort Aqua µg/dose	100 doses	UE 12	A			1994-06-08	527-1	38756-01		
	"	100 doses	UK 20	A			1994-10-10	540-1	48079-01		

* Pivotal study, for more information see separate table, Investigational formulations used in pivotal clinical trials

Study No. Report No.	Formulation	Pack size	Drug Product Batch No	Compo-sition	Batch size	Manufacturer	Date of manufacture	Budesonide micronized Batch No.	Budespnide Batch no	Manufacturer	Comments
05-3040	Rhinocort Aqua 64 µg/dose	200 doses	TB 15	D		APP	1993-02-08	377-1	28595-01		
05-CR-3040	Rhinocort Turbuhaler 100 µg/dose	200 doses	UP 79	H			1994-06-27	100/ (17)	17		
	Rhinocort Aerosol µg/dose	200 doses	TM 239	P			1993-12-07	407	38227-03		
05-9132 850-CR-2121	Rhinocort Aqua	10 ml	NC 13	C			1987-03	n.e.	n.e.		
05-9161	Rhinocort Aqua	10 ml	NL 19	C			1987-11	n.e.	n.e.		
850-CR-2125	"	10 ml	PE 61	C		APP	1989-05-29	205	172	APP	
	Rhinocort Aqua	10 ml	OC 201	E		APP	1988-03-11	209* 154	174 117	APP APP	
05-9163	Rhinocort Aqua	10 ml	PE 61	C		APP	1989-05-29	205	172	APP	
	Rhinocort Aerosol	200 doses	PC 160	P			1989-03-13	209* 198 201	174 169 166	APP APP APP	

[a] Astra Production Chemicals AB, Södertälje, Sweden (Subsidiaries of Astra Pharmaceutical Production AB, APP)
The Budesonide was synthesised according to the [redacted] method.

30 June 1996

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Investigational formulations summary

Supplementary details - pharmacokinetic studies

Study No. Report No.	Formulation	Drug Product Control	Composition	Batch size (capsules)	Manufacturer	Date of Manufacture	Budesonide micronized Batch No.	Budesonide Batch No.	Manufacturer
52-CR-3002	Budesonide capsule 2 mg	DTH 11	A		Astra Draco[1]	930805	354-01	360	APP[2]
08-CR-3017	Budesonide CIR capsule 3 mg	DSK 314 DTF 316	B B		Astra Draco	921012 930623	354-01 319-01	360 211	APP APP

2. Composition

A) Budesonide capsule 2 mg

Name of Ingredient	1 capsule contains
Budesonide micronized	

Budesonide CIR capsule 3 mg

Name of Ingredient	1 capsule contains
Budesonide micronized	
Polysorbate 80	

[1]Astra Draco AB, Lund, Sweden
[2]Astra Pharmaceutical Production AB, Södertälje, Sweden