CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-441/S009

Trade Name: Pulmicort Turbuhaler

Generic Name: budesonide inhalation powder, 200 mcg

Sponsor: Astra Pharmaceuticals

Approval Date: December 8, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-441/S009

CONTENTS

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Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-441/S009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-441/S-009

AstraZeneca LP
725 Chesterbrook Blvd.
Wayne PA 19087-5677

Attention: Eric Couture, Ph.D.
Director, Regulatory Affairs

Dear Dr. Couture:

Please refer to your supplemental new drug application dated October 29, 1999, received October 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler (budesonide inhalation powder).

We acknowledge receipt of your submissions dated March 15, June 12, and October 31, 2000. Your submission of June 12, 2000 constituted a complete response to our April 28, 2000 action letter.

This supplemental new drug application provides for changes to the spheronization process and modifications to the Turbuhaler device.

We have completed the review of this supplemental application, and it is approved.

Validation of the regulatory methods has not been completed. The methods validation information will be reviewed separately and comments will be forwarded. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Robert Meyer
12/8/00 04:40:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-441/S009

APPROVABLE LETTER

NDA 20-441/S-009

AstraZeneca
725 Chesterbrook Blvd
Wayne PA 19087-5677

Attention: Eric Couture, Ph.D.
Director, Regulatory Affairs

Dear Dr. Couture:

Please refer to your supplemental new drug application dated October 29, 1999, received October 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler (budesonide inhalation powder).

We acknowledge receipt of your submission dated March 15, 2000.

This supplement proposes changes to the spheronization process and modifications to the Turbuhaler device.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues.

1. Provide a commitment to propose acceptance criteria for [redacted] levels in the drug product by a specific date.

2. Institute a [redacted] for the drug product.

3. Provide a stage-by-stage comparison of [redacted] between the M0 and M0-ESP drug products at flow rates of [redacted] and [redacted] /min.

4. The following comments refer to the methods validation for the NDA.

   a. During Agency efforts to validate the delivered dose and aerodynamic fine particle size testing for the M0 drug product in our laboratories, it came to our attention that the manual methods submitted to the NDA had not been validated by AstraZeneca. Robotic methods had been validated instead of the manual methods. Clarify this situation, and indicate what methods/equipment have been used in methods validation of these tests for the M0-ESP drug product.

b. Clarify whether the AstraZeneca responses dated March 10, 1999, concerning the methods validation package for the M0 drug product have been appropriately incorporated into the methods validation package for the M0-ESP drug product.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-441
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Koble
HFD-570/Poochikian
HFD-570/Wakelekamp
HFD-570/Uppoor
HFD-570/Purucker
HFD-570/Meyer
DISTRICT OFFICE

Drafted by: GST/April 26, 2000
Initialed by: S. Barnes 4/26/00
B. Rogers for G. Poochikian 4/26/00
M. Wakelkamp 4/27/00
R. Uppoor 4/27/00
final: S.Barnes4/27/00
filename: n:\staff\troutg\20441ae

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-441/S009

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-441

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
AstraZeneca LP 725 Chesterbrook Blvd Wayne PA 19087-5677		009	29-OCT-99

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Pulmicort Turbuhaler	budesonide

8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC.
Pulmicort M0-ESP (200 mcg strength drug product) which includes changes in the spheronized powder and changes in the Turbuhaler device.	15-MAR-00. 12-JUN-00, 31-OCT-00 (subject of this review)

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
steroid anti-inflammatory	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
inhalation powder	200 ug: [redacted]

15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS
see USAN	CURRENT REVIEWED YES_ NO_ YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA # 20-441
HFD-570/div. File
HFD-570/Dkoble
HFD-570/Gpoochikian
HFD-570/Mpurucker
HFD-570/MwalkenkampBarnes
HFD-570/Gtrout
HFD-570/Sbarnes
R/D Init. By:_____
F/T by: B. Dkoble
doc # 9N20441.cr2

NOTE THAT REVIEW OF THE METHODS VALIDATION INFORMATION SUBMITTED IN S-009 HAS NOT BEEN COMPETED SINCE IT IS NOT RELATED TO THE SUBJECT OF S-009. THE INFORMATION WILL BE REVIEWED SEPARATELY

The MO-ESP drug product is the first step in a step-wise development approach to address the phase 4 commitment to improve the quality of the drug product.

18. CONCLUSIONS AND RECOMMENDATIONS:

From a chemistry, manufacturing, and controls perspective, it is recommended that the supplement be approved and an approval letter drafted by the project manager. The project manager should include a the standard comment concerning the firm's assistance in validating the method in the approval letter. The methods validation information provided in S-009 will be reviewed separately and comments forwarded to the NDA holder in a separate letter.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Dale L. Koble, Ph.D.		23-APR-00

32 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-44/ 5009

/s/

Dale Koble
12/8/00 04:36:39 PM
CHEMIST

Guiragos Poochikian
12/8/00 04:38:38 PM
CHEMIST

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-441

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
AstraZeneca LP 725 Chesterbrook Blvd Wayne PA 19087-5677		009	29-OCT-99

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Pulmicort Turbuhaler	budesonide

8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC.
Pulmicort M0-ESP (200 mcg strength drug product) which includes changes in the spheronized powder and changes in the Turbuhaler device. This is the first step in a step-wise development approach to address the phase 4 commitment to improve the quality of the drug product.	15-MAR-99

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
steroid anti-inflammatory	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
inhalation powder	200 ug; [redacted]

15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS
see USAN	CURRENT YES_ NO_ REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA # 20-441
HFD-570/div. File
HFD-570/Dkoble
HFD-570/Gpoochikian
HFD-570/Mpurucker
HFD-570/MwalkenkampBarnes
HFD-570/Gtrout

HFD-570/
R/D Init. By:_____
F/T by: B. Dkoble
doc # 9N20441.cr1

18. CONCLUSIONS AND RECOMMENDATIONS:
From a chemistry, manufacturing, and controls perspective, it is recommended that the supplement not be approved. The attached draft comments should be forwarded to the NDA holder by the project manager.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Dale L. Koble, Ph.D.		23-APR-00

50 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-441
S009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-441/S009

STATISTICAL REVIEW(S)

Statistical Review: NDA 20-441/S-009, Pulmicort Turbuhaler, AstraZeneca

Material reviewed: Study synopsis, pages 3-3 through 3-6 (document no. 004-CR-0708). Data for my analyses were provided on computer diskette.

This review concerns the sponsor's double-blind, randomized crossover study comparing the relative systemic availability of budesonide in healthy subjects after inhalations from the current U.S. version of Pulmicort Turbuhaler and from a modified U.S. version (ESP) of Pulmicort Turbuhaler.

Study Design

The study was a three-sequence, three-period replicated-crossover study, with replication of the reference product only. The three treatment administration periods occurred on visits 2, 3, and 4. The treatments studied were:

test product (T):	Pulmicort Turbuhaler (modified U.S. version, ESP) powder inhaler. Batch No. ZE 20, oral inhalation of four doses on treatment period.
reference product (R):	Pulmicort Turbuhaler (current U.S. version) powder inhaler. Batch No. ZI 441, oral inhalation of four doses on treatment period.

The study subjects were treated in six overlapping groups. The dates of treatment administration for each group were as follows:

	visit		
	2	3	4
group 1	03/15/99	03/22/99	03/29/99
group 2	03/16/99	03/23/99	03/30/99
group 3	03/17/99	03/24/99	03/31/99
group 4	03/18/99	03/25/99	04/01/99
group 5	03/19/99	03/26/99	04/02/99
group 6	03/20/99	03/27/99	04/03/99

For each group, the experimental design was as follows:

	visit		
	2	3	4
sequence 112	**R**	**R**	**T**
sequence 121	**R**	**T**	**R**
sequence 211	**T**	**R**	**R**

36 subjects participated in the study. 35 subjects completed all three periods of the study. One subject, number 31 in group 6, sequence 112, did not complete the study, providing data only for visits 2 and 3.

The subject numbers for each group and sequence were:

group	sequence	subject numbers
1	112	2 4
1	121	3 5
1	211	1 6
2	112	7 11
2	121	9 10
2	211	8 12
3	112	15 18
3	121	13 16
3	211	14 17
4	112	21 24
4	121	19 22
4	211	20 23
5	112	25 29
5	121	26 30
5	211	27 28
6	112	31 35
6	121	32 36
6	211	33 34

PK Responses Analyzed

The PK responses used in this review are

AUCs	AUC 0 to 12 hours, based on scheduled blood sampling times
AUCa	AUC 0 to 12 hours, based on actual blood sampling times
Cmax	maximum observed concentration
C12	12 hour concentration

In all cases, statistical analysis was carried out on log-transformed PK responses.

Comment on Sponsor's Analysis

The sponsor has designated one administration of the reference product R to a given subject as "replicate I" and the other administration as "replicate II". Since both replicates are the same lot of the same product, this distinction is artificial and serves no useful purpose for the assessment of bioequivalence between T and R. In my analyses, I did not use this "replicate" designation.

My Analyses

I used SAS PROC MIXED to analyze the results of the study. The SAS statements used were:

```
PROC MIXED;
CLASS SUBJ SEQ PER GRP TRT;
MODEL Y =
   GRP SEQ GRP*SEQ PER GRP*PER TRT/DDFM=SATTERTH;
RANDOM SUBJ(GRP*SEQ) SUBJ*TRT(GRP*SEQ);
ESTIMATE 'T VS. R' TRT -1 1/CL ALPHA=0.1;
RUN;
```

where Y is the PK response being analyzed (i.e. log(AUCs), log(AUCa), log(Cmax), or log(C12)). SUBJ, SEQ, PER, GRP, and TRT refer to subjects (1-36), sequences (112, 121, and 211), periods (visits 2, 3, and 4), groups (1-6), and treatments (T and R).

Results - ratio of geometric means

For the four PK responses analyzed, the point estimates and 90% confidence intervals for the ratio of geometric means (T over R) are:

PK response	point estimate	90% confidence interval
AUCs	99.60%	94.94% , 104.49%
AUCa	99.60%	94.95% , 104.49%
Cmax	101.41%	94.12% , 109.26%
C12	98.27%	90.93% , 106.20%

All of these 90% confidence intervals fall very comfortably within the usual bioequivalence limits of 80% to 125%.

Results - intrasubject variability of reference product

Replication of the reference product in each subject enables us to estimate the "pure" intrasubject variability of the reference product. These results, obtained from the PROC MIXED analysis, will be expressed in two related forms: the intrasubject standard deviation of the log transformed PK response, and the percent coefficient of variation of the untransformed PK response. These two quantities are related as follows:

$$\text{standard deviation of log- transformed response} = \sigma_{WR}$$

$$\%\ \text{CV of untransformed response} = 100\% \times \sqrt{e^{\sigma^2_{WR}} - 1}$$

The estimates for each of the PK parameters analyzed are:

	log scale std. dev.	original scale %CV
AUCs	0.13818	13.88%
AUCa	0.13803	13.87%
Cmax	0.19241	19.42%
C12	0.22400	22.68%

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods & Research staff

Concur: Stella Green Machado, Ph.D.
Director, Quantitative Methods & Research staff

cc:
Original NDA 20-441/S-009
HFD-870 Venkata R. Uppoor
HFD-870 Monique A. Wakelkamp-Barnes
HFD-870 Tien-Mien Chen
HFD-705 QMR Chron
HFD-705 Stella G. Machado
HFD-705 Donald J. Schuirmann

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-441/S009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-441/009

Generic name, dose and formulation:	budesonide dry powder filled metered dose inhaler, 200 µg strength
Trade name:	Pulmicort®Turbuhaler® M0-ESP
Sponsor:	AstraZeneca LP
Type of submission:	Supplemental NDA
Date of submission:	10/29/1999, 12/17/1999, 04/11/2000
Reviewer:	Monique Wakelkamp-Barnes, M.D., Ph.D.
Consultant:	Donald Schuirmann, mathematical statistician

I SYNOPSIS

The supplemental NDA 20-441/009 for Pulmicort Turbuhaler M0-ESP (budesonide inhalation powder) was submitted by AstraZeneca LP (725 Chesterbrook Blvd, Wayne, PA 19087) on 10/29/1999 for the indication of maintenance treatment of asthma.

Pulmicort Turbuhaler M0-ESP (Enhanced Spheronization Process) is an inhalation-driven, dry powder metered-dose inhaler, containing budesonide. The current submission is part of a phase IV commitment to improve batch-to-batch variability and within-batch dosing uniformity, as compared to the currently approved Pulmicort Turbuhaler M0. The enhanced spheronization process is aimed at generating smaller and more uniform spheres. The proposed M0-ESP product is to be [redacted]

The Human Pharmacokinetics and Bioavailability section of the NDA contained one study (study SD-004-0708), comparing the rate and extent of systemic availability between the Pulmicort Turbuhaler M0 currently approved in the U.S. and the new formulation, Pulmicort Turbuhaler M0-ESP, after inhalation in healthy subjects. It was shown that Pulmicort Turbuhaler M0 and Pulmicort Turbuhaler M0-ESP are bioequivalent.

No changes to the current labeling have been proposed.

Reviewer Comments (not to be sent to the sponsor)

1. During analysis of the bioequivalence study, the sponsor compared the mean value of the replicate administrations of the reference product to the single administration of the test product. Such an approach is expected to reduce the variance of the reference variables and does not take the treatment period effect into account. Donald Schuirmann, mathematical

statistician (Quantitative Methods Research Staff, Office of Biostatistics, CDER), was consulted to provide a statistical review of the data, using the individual datasets instead of mean values. A copy of the review is attached (Attachment 2). According to this analysis, 90% confidence intervals for the ratio of the geometric means of C_{max} (94.12% – 109.26%) and $AUC_{(0\text{-}12h)}$ (94.95% - 104.49%) were found to lie within the 80-125% bioequivalence limits.

2. The sponsor only calculated $AUC_{(0\text{-}12h)}$ values and did not provide $AUC_{(0\text{-}\infty)}$ estimates. However, in this case, the extrapolated part of the AUC constituted only a minor fraction of the total AUC (< 10%). This, combined with the finding that the 90% confidence interval for $AUC_{(0\text{-}12h)}$ generously passed the bioequivalence criteria, allows the acceptance of $AUC_{(0\text{-}12h)}$ data only, in addition to C_{max}.

II RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of this NDA supplement is acceptable to support the systemic exposure based bioequivalence of Pulmicort Turbuhaler M0-ESP to Pulmicort Turbuhaler M0.

Reviewer Date

_____ _____

Monique Wakelkamp-Barnes, M.D., Ph.D.

Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Ramana Uppoor, Ph.D., teamleader _____

cc NDA 20-441/S-009:
Division File
HFD-870: Shiew-Mei Huang
HFD-570: Ramana Uppoor
Monique Wakelkamp-Barnes
Dale Koble
Mary Purucker
Gretchen Trout
CDR: Barbara Murphy

III BACKGROUND / FORMULATION

Q.	***What is Pulmicort Turbuhaler M0-ESP? What differences are there between Pulmicort Turbuhaler M0-ESP and the currently approved Pulmicort Turbuhaler M0?***

Pulmicort Turbuhaler M0-ESP (Enhanced Spheronization Process) 200 µg/dose, 200 doses, is an inhalation-driven, dry powder metered-dose inhaler, containing budesonide. Each actuation provides 200 µg budesonide per metered dose, which delivers approximately 160 µg from the mouthpiece. During the manufacturing process of Pulmicort Turbuhaler, micronized budesonide is spheronized during a sequence of steps. The enhanced spheronization process aims at producing a reduced and more uniform aggregate size of the spheronized powder and an increase in size of spheronized subbatches, as compared to the currently approved product Pulmicort Turbuhaler M0. A summary of changes in Pulmicort Turbuhaler M0-ESP as compared to Pulmicort Turbuhaler M0 is shown in Attachment 1. The current submission is part of a phase IV commitment to improve batch-to-batch variability and within-batch dosing uniformity. According to the sponsor, [redacted]

Q.	***What studies have been submitted to the Human Pharmacokinetics and Bioavailability section of the NDA?***

The Human Pharmacokinetics and Bioavailability section of this NDA contains one study (study SD-004-0708), comparing the rate and extent of systemic availability between the Pulmicort Turbuhaler M0 currently approved in the U.S. and the new formulation, Pulmicort Turbuhaler M0-ESP, after inhalation in healthy subjects. The study has a cross-over replicate design, with replication of the M0 formulation only.

Reviewer note:
The sponsor originally requested to submit the supplemental NDA for M0-ESP without clinical data. However, the Agency required the sponsor to provide pharmacokinetic data linking the current and the new product and to show that they meet bioequivalence criteria. The need for future pharmacodynamic studies could not be excluded. Given the variability of the current product, it was also proposed that the sponsor investigate whether within-batch, within-subject bioequivalence for the current M0 formulation could be shown (correspondence dated 01/06/1999, 01/08/1999, 01/15/1999).

With regard to the proposed product, bioequivalence solemnly based on in vitro data and systemic exposure based PK would be considered sufficient, under the condition that bioequivalence to the current product based on systemic exposure can be demonstrated.

Q.	***Are there any differences between the Pulmicort Turbuhaler M0-ESP formulation used for the bioequivalence study SD-004-0708 and the to-be-marketed formulation?***

No.

The following batches were used in study SD-004-0708:
1) Pulmicort 200 Turbuhaler M0, batch ZI 441 (Reference)
2) Pulmicort 200 Turbuhaler M0-ESP, batch ZE20 (Test)

The M0 batch was a commercial batch manufactured in full scale using the approved process. The M0-ESP batch was manufactured in full scale using the proposed production process. The batch size contained [redacted] and was produced at the same site as the to-be-marketed formulation.

IV ASSAY METHODOLOGY AND VALIDATION

Q.	***What is the assay method for the determination of budesonide concentrations? How sensitive and specific is the assay?***

The sponsor submitted an assay validation report (Report No. 850-RD-0388, Jan 1997) for the determination of racemic (22RS) budesonide in plasma. Budesonide was isolated from [redacted] plasma samples by solid phase extraction and analyzed using [redacted] was used as the internal standard. The lower limit of quantitation was [redacted] fmol [redacted] nmol/L based on a [redacted] plasma sample volume) and the calibration curve was found to be linear over a [redacted] fmol range. Samples were found to be stable for several years when stored at [redacted] According to the sponsor, referring to an Astra Draco report from 1991, the assay method is specific for budesonide and any interference from metabolites is considered unlikely. The assay method has previously been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (NDA 20-929, OCPB review 03/20/1998) and was considered to perform satisfactorily.

Plasma samples from study SD-004-0708 were analyzed shortly after the study was completed (April 1999). A number of quality control samples were analyzed concomitantly with the study samples. Inter-assay precision at 0.036 nmol/L, 0.096 nmol/L and 4.00 nmol/L was 11.7%, 7.7% and 6.1%, respectively. Inter-assay accuracy was 106%, 106% and 105%, respectively. Intra-assay precision and accuracy values at 0.036 nmol/L, 0.096 nmol/L and 4.00 nmol/L for the different runs were satisfactory. Values below the LOQ (observed only in pre-dose samples) were treated as [redacted]

In summary, the submitted assay methodology and data appear to be adequate.

V CLINICAL PHARMACOLOGY

Q.	***Is there bioequivalence between the proposed Pulmicort Turbuhaler M0-ESP product and the approved product?***

Yes.

The aim of study SD-004-0708 was to compare the rate and extent of systemic availability between Pulmicort Turbuhaler M0 currently approved in the U.S. and the new formulation, Pulmicort Turbuhaler M0-ESP, after inhalation in healthy subjects. The study had a double-blind, randomized, three-sequence, three-period, replicated, cross-over design, with replication of the reference product only. Thirty-six healthy volunteers, age 18-39 yrs. were included, of which 21

were men and 15 were women. The study was conducted at AstraZeneca R&D Lund, Lund, Sweden.

The subjects were randomized into 6 groups of 6 subjects each. Each subject inhaled a single dose of 640 µg budesonide (4 actuations, 4x 160 µg delivery from the mouthpiece) on three occasions, **once** from the modified US version (Test Product) and **twice** from the current US version of Pulmicort Turbuhaler (Reference Product). Within each group, an equal number of subjects followed one of three possible treatment sequences, namely Ref-Ref-Test, Ref-Test-Ref or Test-Ref-Ref. Dose selection was based on the fact that 640 µg is the highest currently recommended single (delivered) dose for Pulmicort Turbuhaler. The replicated administration of the reference treatment aimed at obtaining a measure of within-subject variability. Study days were separated by a wash-out period of at least 3 days. Thirty-five subjects completed the study, one subject received 2 treatments with the reference product only. All subjects were served a standardized breakfast 30 min before drug administration. Lunch was served 4 h after dosing. Blood samples were taken pre-dose and at 10, 20, 40, 60 min and at 2, 4, 6, 9 and 12 hours after dosing.

Individual and mean budesonide concentrations as obtained for the different treatments are displayed in Figure 1. $AUC_{(0\text{-}12h)}$ and C_{max} values are shown in Table 1.

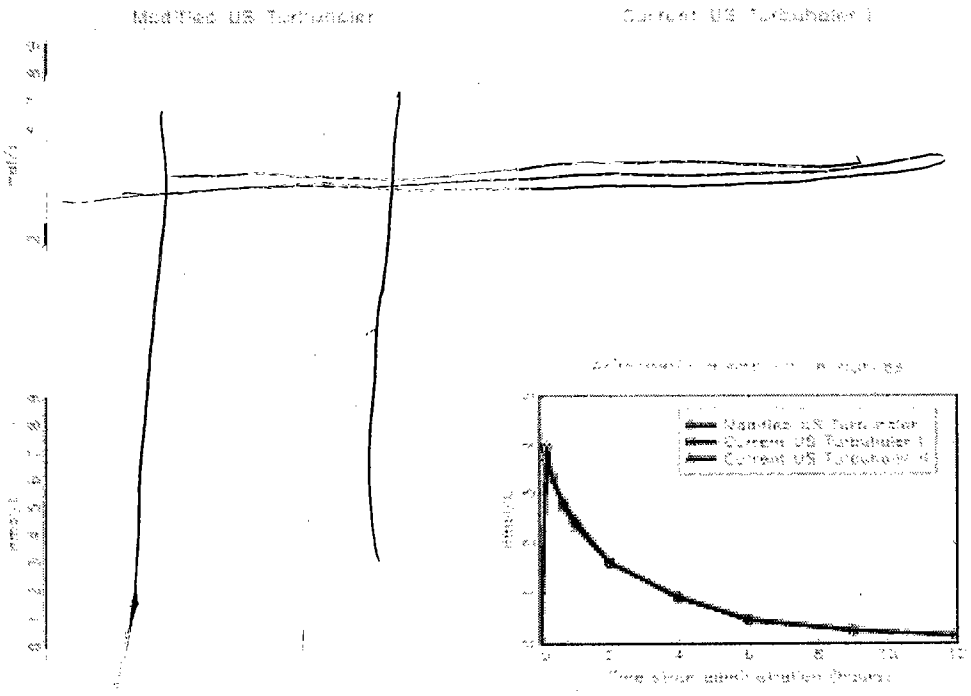


Figure 1. Individual and mean budesonide concentrations (nmol/L) after single administration of Pulmicort Turbuhaler M0-ESP and replicate administrations of Pulmicort Turbuhaler M0.

Table 1.

	Pulmicort Turbuhaler M0-ESP	Pulmicort Turbuhaler M0-I	Pulmicort Turbuhaler M0-II
$AUC_{(0\text{-}12h)}$ (nmol·min/L)			
Mean	625.5	625.0	634.2
SD	123.7	141.0	137.7
Range	377.3 – 852.3	389.2 – 1018.3	369.0 – 927.1
C_{max} (nmol/L)			
Mean	4.17	4.11	4.06
SD	1.27	1.20	1.25
Range	1.98 – 7.41	1.66 – 6.58	2.45 – 8.01

$AUC_{(0\text{-}12\,h)}$ and C_{max} after administration by inhalation of 640 µg budesonide using the test Pulmicort Turbuhaler M0-ESP formulation and replicate administration of the reference Pulmicort Turbuhaler M0 formulation (administration I and II), respectively.

$AUC_{(0\text{-}12h)}$ and C_{max} were selected as the primary variables to meet bioequivalence criteria. For both variables, the sponsor compared the mean value of the reference product to the (single) value of the test product. Pairwise comparisons between the three treatment regimens were made as well. The analysis provided by the sponsor indicated that Pulmicort Turbuhaler M0 and Pulmicort Turbuhaler M0-ESP are bioequivalent.

Comments:

1) The sponsor compared the mean value of the replicate administrations of the reference product to the single administration of the test product. Such an approach is expected to reduce the variance of the reference variables and does not take the treatment period effect into account. Donald Schuirmann, mathematical statistician (Quantitative Methods Research Staff, Office of Biostatistics, CDER), was consulted to provide a statistical review of the data, using the individual datasets instead of mean values. A copy of the review is attached (Attachment 2). According to this analysis, 90% confidence intervals for the ratio of the geometric means of C_{max} (94.12% – 109.26%) and $AUC_{(0\text{-}12h)}$ (94.95% - 104.49%) were found to lie within the 80-125% bioequivalence limits.

2) The replicated administration of the reference product allowed for an estimation of intra-subject variability. The coefficient of variation of C_{max} and $AUC_{(0\text{-}12h)}$ (original scale) was estimated at 19.42% and 13.87%, respectively (Attachment 2).

3) The sponsor only calculated $AUC_{(0\text{-}12h)}$ values and did not provide $AUC_{(0\text{-}\infty)}$ estimates. The Guidance on Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design, posted 10/5/1998, recommends the analysis of both $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$. $AUC_{(0\text{-}\infty)}$ is generally considered a better measure, since it is less dependent on the selection of a particular timepoint. However, in this case, the extrapolated part of the AUC constituted only a minor fraction of the total AUC (< 10%). This, combined with the finding that the 90% confidence interval for $AUC_{(0\text{-}12h)}$ generously passed the bioequivalence criteria, allows the acceptance of $AUC_{(0\text{-}12h)}$ data only.

4) Pairwise comparison of the two replicate treatments by the sponsor showed within-batch, within-subject bioequivalence between the M0 treatments (Tables 2 and 3).

Contrast	ratio (%)	90% C. I.	
Modified : mean of Current version replicates I and II	99.45	94.85	104.29
Modified : Current, replicate I			
Modified : Current, replicate II			
Current, replicate I : Current, replicate II			

Table 2. Sponsor-provided bioequivalence test of plasma budesonide $AUC_{(0\text{-}12h)}$ (nmol*min/L)

Contrast	ratio (%)	90% C. I.	
Modified : mean of Current version replicates I and II	101.14	94.29	108.47
Modified : Current, replicate I			
Modified : Current, replicate II			
Current, replicate I : Current, replicate II			

Table 3. Sponsor-provided bioequivalence test of plasma budesonide C_{max} (nmol/L)

VI LABELING

No changes to the current labeling have been proposed by the sponsor. There are no labeling recommendations from the Office of Clinical Pharmacology and Biopharmaceutics.

Summary of changes

AstraZeneca R&D Lund

ATTACHMENT 1

Introduction
Pulmicort Turbuhaler® (M0-ESP) powder inhaler, 200µg/dose, 200 doses
Document No. 1/99

Purpose	Item changed	*NDA product, MO*	*Enhanced product, MO-ESP*
Reduce sphere size	**Spheronization process**		
	Dosing unit		

22 October, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-441/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Memorandum of Telephone Facsimile Correspondence

Date: July 27, 2000

To: Eric Couture, Ph.D.
Director, Regulatory Affairs

Fax: 610-722-7784

From: Gretchen Trout
Project Manager

Subject: NDA 20-441/S-009
May 31, 2000 Meeting/teleconference

Reference is made to the meeting/teleconference held between representatives of your company and this Division on May 31, 2000. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1058.

Thank you.

IMTS #5887

INDUSTRY TELECONFERENCE MINUTES

DATE: May 31, 2000
NDA 20-441/S-009
PRODUCT: Pulmicort Turbuhaler
SPONSOR: AstraZeneca

FDA PARTICIPANTS:

Dale Koble, Chemistry Reviewer
Guirag Poochikian
Gretchen Trout, Project Manager

SPONSOR PARTICIPANTS:

Eric Couture, Director, Regulatory Affairs
Thomas Lööf, Project Manager, Pharmaceutical and Analytical R&D
Bo Olsson, Pharmaceutical and Analytical Development

BACKGROUND: AstraZeneca requested this teleconference to discuss the Division's comment 4.a. from the April 28, 2000, approvable letter for this supplement. The comment relates to validation of manual methods for testing delivered dose and aerodynamic particle size.

AstraZeneca stated that all of the data they have generated for the original Pulmicort MO device and the MO-ESP have been using the automated method. The test method does not specify automated or manual. They have validated the automated method and believe there would be increased variability with the manual method. AstraZeneca asked the Division for guidance. The Division explained that it is an Agency policy that we need a method we can verify in our laboratories. If AstraZeneca is using a robotic method we cannot duplicate this in the laboratory. AstraZeneca explained that they have [redacted] The Division explained that this is not practical because we need to be able to obtain samples and validate them [redacted] AstraZeneca can use their system for routine testing, but we also need a system we can validate.

AstraZeneca explained that they have concerns with the manual method having a variability of approximately 10% of the dose. The problem is handling of the equipment by the analyst, AstraZeneca has much more experience than the FDA analysts which could create variability. The Division stated AstraZeneca should provide written step-by-step instructions. The Division's bottom line is that we need a reliable method we can use to verify the claimed results and to test on a random basis without informing the sponsor. We can be flexible as to the timeline for AstraZeneca providing this, but they do need to provide it. The Division stated that if the results are very inconsistent with the automated method, this is a problem.

AstraZeneca questioned if they can [redacted] The Division replied that this is a policy issue and cannot be done. AstraZeneca

questioned [redacted] The Division replied that we would have to discuss this with our upper management.

AstraZeneca suggested submitting a comparison, not a complete validation of the manual method. The Division stated that they will have to provide ruggedness and robustness and analyst to analyst variability. AstraZeneca requested that they be able to provide this as a Phase 4 commitment. The Division agreed and requested a three month timeframe. AstraZeneca replied that they are thinking that there will be a significant development timeframe, depending on the scope of the validation, [redacted] The Division pointed out that the NDA has been approved for several years [redacted] The Division believes that 3-4 months is an adequate timeframe to have a reasonable method in place that can be used by other chemists. AstraZeneca stated that they need to discuss this with their team, then they will fax a plan to us and once agreement is reached they will include the commitment in their response to the Division's approvable letter. The Division and AstraZeneca agreed that this is only validation for the MO-ESP.

NOTE: On June 2, 2000, AstraZeneca sent a facsimile with a proposed timeline of the end of October 2000 (see attached facsimile). The Division notified AstraZeneca that this was acceptable, however they should specify the date; i.e., October 31, 2000.

Gretchen Trout
Project Manager

Cc: Orig. NDA 20-441
Div. File
HFD-570/Koble
HFD-570/Poochikian
HFD-570/Trout

Drafted: GST/June 27, 2000

Rd initial by: Poochikian/7-26-00
Koble/7-26-00

File name: 20441tel

MINUTES

AstraZeneca

Snc-009

Eric Couture, Ph.D.
Director, Regulatory Affairs

ORIGINAL

April 11, 2000

Robert Meyer, M.D., Director
Division of Pulmonary Drug Products
HFD-570 Room 10-B03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Meyer:

NDA 20-441/S-009
Pulmicort® Turbuhaler® (budesonide inhalation powder)
GENERAL CORRESPONDENCE:
RESPONSE TO FDA REQUEST FOR INFORMATION

Please refer to our approved NDA 20-441 for Pulmicort Turbuhaler, and our October 29, 1999 sNDA for Pulmicort Turbuhaler M0-ESP (S-009). Please also refer to a telephone conversation with Ms. Gretchen Trout, on April 5, 2000 where she requested a clarification regarding study report 004-CR-0708 submitted in the October 29, 1999 supplement. Specifically, Ms. Trout requested a description of how budesonide concentrations below the LOQ were handled for the calculation of AUC. Please see the attached response.

Please direct any questions or requests for additional information to me at 610-695-1263 (610-722-7784 fax), or, in my absence, to James Sullivan, Regulatory Project Manager at 610-695-1423.

Sincerely yours,

Eric Couture

Eric Couture, Ph.D.
Director, Regulatory Affairs

Sent via facsimile

cc: Gretchen Trout (CDER)
Federal Express No.: 819630311748

AstraZeneca

Question: How were the concentrations of budesonide, which were below the LOQ in Study Report 004-CR-0708, handled for the calculation of AUC?

Only the budesonide values measured prior to drug administration were below the LOQ. These values were treated as 0 nmol/L for the calculation of AUC.

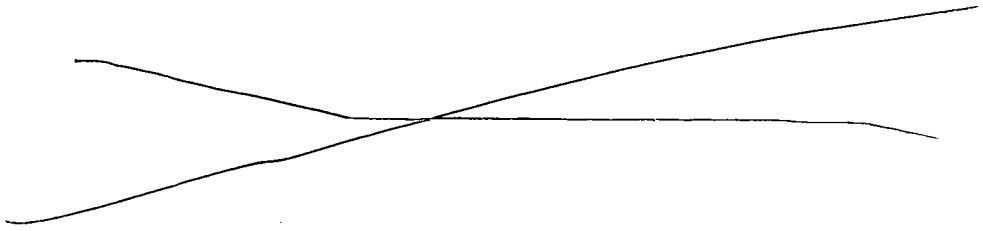
The before-dose samples are taken to show that there is no interference from concomitant medication and that there is no contamination of the samples. A review of all chromatograms from the before-dose samples (106 samples) showed 105 chromatograms with no integrated areas for budesonide and one chromatogram (subj. 20 at Visit 3, before-dose) with an integrated value below LOQ. It is not possible to determine if this value represents budesonide or is random noise since no validation has been done at this concentration level. None of the other chromatograms for the before-dose samples contained any peak at the budesonide retention time which could be integrated.

A calibration curve constructed by least square regression of the peak area ratios of budesonide over the internal standard is used for the quantification. Samples are only quantified within the range of the standard samples. Hence, values below this range are reported as nmol/L.

The tabulated areas of the calibration standard samples from the assay are given below and are followed by the area of the only before-dose sample for which an area was obtained.

Calibration samples

Data File	Sample Volume	Area Analyte	Area Int std	Sample Comment



Before-dose sample from subj. 20 at Visit 3, Before-dose

No other before-dose samples had any numerical value in Area Analyte

AstraZeneca

Explanations of Header
Data File = Internal Mass spectrometer filename
Sample Volume = mL
Area Analyte = The integrated area of budesonide in the sample
Area Int std = The integrated area of [redacted] in the sample
Sample Comment = Sample ID or the amount of added budesonide (STD) and Internal standard (IS) to the sample.

DEC 23 1999

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	20-441 (S-009)	**Sponsor:**	AstraZeneca
IND:			
Brand Name:	Budesonide	**Priority Classification:**	NDA Supplement (6-month review)
Generic Name:	Pulmicort Turbuhaler	**Indication(s):**	
Drug Class:	Corticosteroid	**Date of Submission:**	10/29/99
Dosage Form:	Dry powder inhaler	**Route of Admin.:**	Oral Inhalation
Dosing Regimen:		**Due Date of Review:**	04/29/2000
Division:	HFD-870	**Medical Division:**	HFD-570
Reviewer:	Tien-Mien Chen	**Team Leader:**	Ramana Uppoor

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling		X	
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies	X		
Mass Balance Study		X	
BA Studies		X	
Absolute BA		X	
Relative BA		X	
BE Studies	X		
Average BE	X		
Population BE		X	
Individual BE (*using replicate design but analysis not submitted)	X*		To be requested
Food-Drug Interaction		X	
Dissolution Tests (In Vitro-In Vivo Comparison Studies)		X	
Studies Using Human Biomaterials		X	
Plasma Protein Binding Studies		X	
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc		X	
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies	X		
PK, and Initial Safety and Tolerability in Healthy Volunteers	X		
Single Dose	X		
Multiple Dose		X	
PK, and Initial Safety and Tolerability in Patient Volunteers		X	

Single Dose		X	
Multiple Dose		X	
Dose Proportionality		X	
Single Dose		X	
Multiple Dose		X	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors		X	
Ethnicity		X	
Gender		X	
Pediatrics		X	
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors		X	
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies		X	
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers		X	
PK/PD studies in patients		X	
Individual Datasets for all PK and PK/PD studies in electronic format		X	To be requested
Other		X	
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	

Summary of the submission:

PulmicortTurbuhaler has been approved in 1997. After approval, a change was made in manufacturing process (Enhance Spheronization Process, ESP). The purpose of change is for obtaining uniform and smaller powder which packs better. This is intended to provide greater reproducibility of dose delivery allowing for the same metered dose delivered using a [redacted] device.

As previously agreed upon in a meeting with the Agency, the sponsor provided comparability data based on in vitro studies. To address the systemic exposure issue, the sponsor conducted a single-dose, replicate 3x3 crossover bioequivalence (BE) study (with a washout period of at least 48 hrs) in 36 healthy volunteers:

1. Current replicate I: 4x 160 μg/inh
2. Current replicate II: 4x 160 μg/inh
3. ESP (modified): 4x 160 μg/inh

This application is__X__is not___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)

1. Is the systemic exposure from product made using the modified ESP process greater than that made using the currently approved process?

2. Is individual BE also shown for the above comparison? (**Note**: Will be updated later after thorough review)

Requests/Comments are __X__ are not ___ to be sent to firm.

1. Individual datasets in electronic format (e.g., Excel spreadsheet or SAS transport file).

Signature Tien Mien Chen 12/23/99 R Uppoor 12/23/99

Primary Reviewer **Secondary Reviewer**

CC: NDA 20-441, HFD-850 (Electronic Entry or P. Lee), HFD-570 (Jani), HFD-870 (T. M. Chen, R, Uppoor, S. M. Huang), CDR (B. Murphy)