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*APPLICATION NUMBER:*  
**21-929**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# Clinical Pharmacology and Biopharmaceutics Review (FINAL)

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**NDA:** 21-929

**Date of Submission:** September 23, 2005

**Generic Name**

Budesonide/Formoterol  
(80 mcg/4.5 mcg and 160 mcg/4.5 mcg)

**Brand Name:**

SYMBICORT®

**Formulations:**

Pressurized Meter Dose Inhaler (pMDI)

**Route of Administration:**

Oral Inhalation

**Indication:**

Asthma

**Type of Submission:**

NDA

**Sponsor:**

AstraZeneca

**Reviewer:**

Sayed (Sam) Al Habet, R.Ph., Ph.D.

**Team Leader**

Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

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## **Recommendation:**

From the clinical pharmacology perspective, this NDA is acceptable.

## **Executive Summary:**

Symbicort is pressurized metered dose inhaler (pMDI) is a combination product consisting of budesonide and formoterol fumarate dehydrate. In terms of formulation, the clinical and to be marketed are the same. Therefore, there no bioequivalence study to establish a link between the clinical and to-be-marketed formulation was necessary in this NDA.

Budesonide is a corticosteroid and formoterol is a long-acting  $\beta$ 2-agonist. The product is proposed to be used in the long-term maintenance treatment of asthma in patients 12 years of age and older. The product is available in the following strengths:

- 80/4.5 mcg ((budesonide/formoterol) 120 actuation)
- 160/4.5 mcg (budesonide/formoterol) (120 actuation)

80/4.5 and 160/4.5, are to-be-marketed at this time, Therefore, from the clinical pharmacology perspective, the focus of the review will be on the to-be-marketed strengths. To better understand the content of this review and the entire clinical pharmacology program, it is important to introduce the following products/acronyms used throughout this NDA:

### **Combination Products:**

**Symbicort pMDI:** This was used in all clinical studies with a **standard** actuator

**Symbicort  $\sim$  pMDI:** This is the final-to-be marketed device with **shield** actuator

**Symbicort TBH:** This products contains dry-powder that is marketed outside the US

### **Budesonide (In the US, AstraZeneca)**

The following products are available in the US:

- Entocort EC capsule
- Pulmicort Respules
- Rhinocort Aqua Nasal Spray

### **Formoterol:**

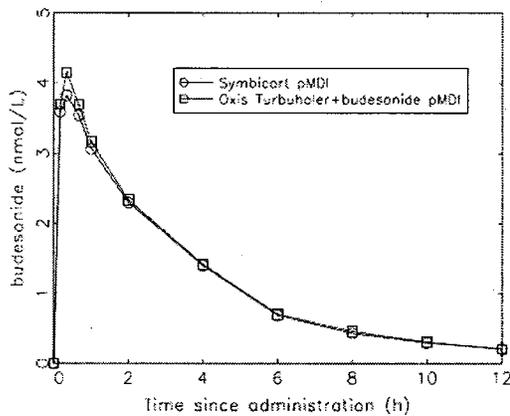
- Foradil Aerolizer (available in the US manufactured by Schering/Novartis)
- **OXIS TBH:** This is formoterol Turbuhaler (TBH) product available outside the US: It was used in some clinical pharmacology studies as comparator monoproduct.

Based on the data submitted to this NDA, the following conclusions can be made:

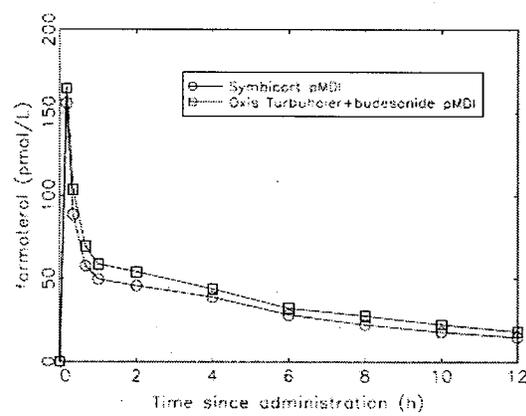
- The AUC ratio of budesonide from a combination product, Symbicort pMDI, is approximately 98% compared to that from budesonide pMDI alone (**Figure I and Table I**). However, the exposure of formoterol was approximately 84% from Symbicort pMDI relative to OXIS TBH (**Figure I and Table II**). Using the urine data, the systemic exposure to formoterol from Symbicort pMDI ranged from 82% to 135% relative to OXIS TBH.

**Figure I. Mean Plasma Concentration-Time Profiles of Budesonide and Formoterol (Study # 0721)**

**A) Budesonide**



**B) Formoterol**



**Table I. PK Parameters and 90% CI for Budesonide (Study # 0721)**

| Parameter                     | Symbicort pMDI vs.<br>Oxis Turbuhaler + budesonide pMDI |                |
|-------------------------------|---|----------------|
|                               | Ratio <sup>1</sup>                                      | 90% conf. lim. |
| AUC (nmol*h/L)                | 97.9  | (92.1, 104.1)  |
| AUC <sub>0-1</sub> (nmol*h/L) | 97.3  | (91.6, 103.4)  |
| C <sub>max</sub> (nmol/L)     | 97.2  | (89.0, 106.1)  |
| t <sub>1/2</sub> (h)          | 107.8   | (100.3, 115.8) |
| MRT (h)                       | 0.10  | (-0.07, 0.28)  |

<sup>1</sup> Difference for MRT, ratio in % for other parameters

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**Table II. PK Parameters, 90% CI , and Urine Excretion of Formoterol (Study # 0721)**

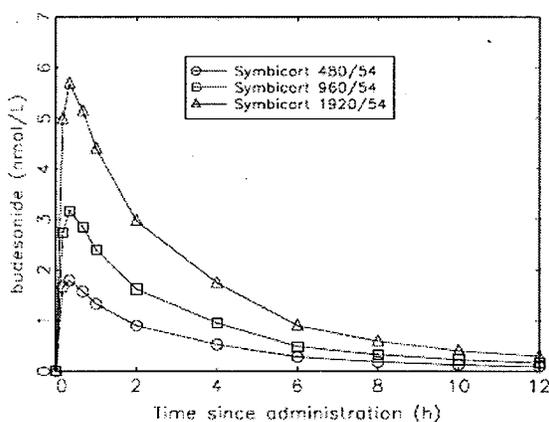
| Parameter                     | Symbicort pMDI vs.<br>Oxis Turbuhaler – budesonide pMDI |                |
|-------------------------------|---|----------------|
|                               | Ratio <sup>1</sup>                                      | 90% conf. lim. |
| AUC (pmol*h/L)                | 82.2  | (76.3, 88.6)   |
| AUC <sub>0-t</sub> (pmol*h/L) | 84.3  | (77.8, 91.5)   |
| C <sub>max</sub> (pmol/L)     | 92.9  | (82.5, 104.7)  |
| t <sub>1/2</sub> (h)          | 93.8  | (83.4, 105.4)  |
| MRT (h)                       | -0.47   | (-1.37, 0.43)  |
| A <sub>e</sub> (nmol)         | 81.5  | (75.2, 88.4)   |

<sup>1</sup> Difference for MRT, ratio in % for other parameters

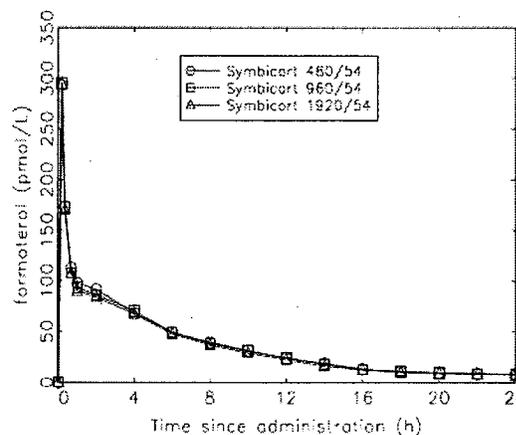
- A cross-study comparison reveals that, the systemic exposure (AUC) of budesonide from Symbicort pMDI ranged from 68% to 73% of Pulmicort TBH. Relative to Symbicort TBH, the AUC of budesonide from Symbicort pMDI was 90% and for formoterol was 116%.
- For dosage strengths equivalency, the systemic exposure to budesonide and formoterol appears to be comparable or lower for 160/4.5 compared to 80/4.5 (**Figures III**). The plasma concentration-time profiles for fomroterol were superimposed following the three dosage strengths. From this study it can also be concluded that there was apparent dose proportionality for budesonide. The dose proportionality for budesonide and also for formoterol was confirmed in other study (**Figures IV**).

**Figure III. Mean Plasma Concentration-Time Profiles for Budesonide and Formoterol Following Three Dosage Strength (Study # 723)**

**A) Budesonide**

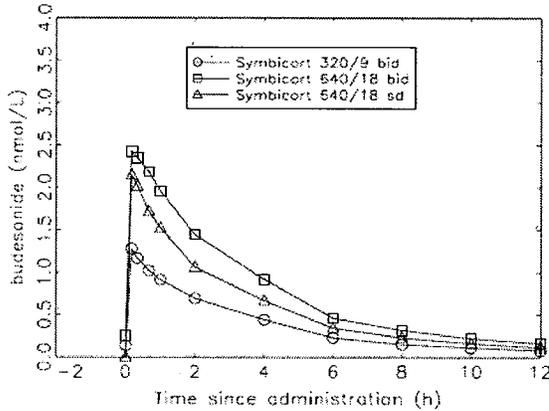


**B) Formoterol**

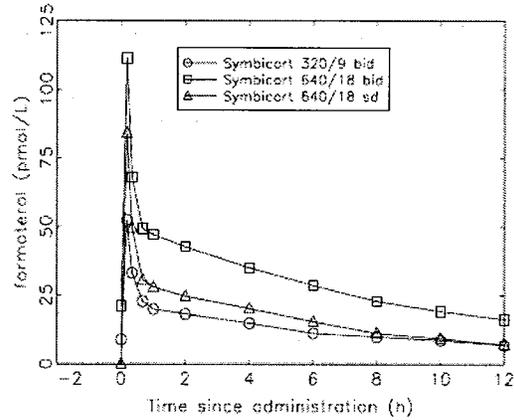


**Figure IV. Mean Plasma concentration-Time Profiles of Budesonide and Formoterol (Study # 724)**

**A) Budesonide**

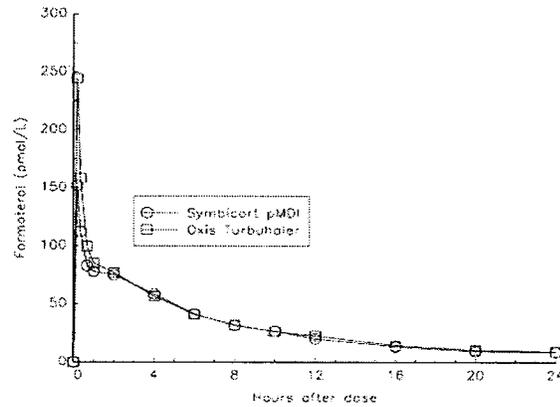
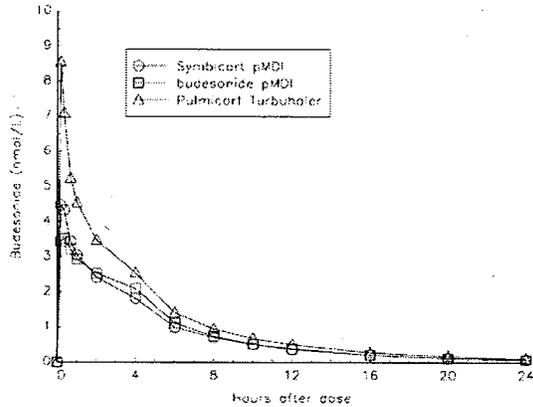


**B) Formoterol**



- It should be noted that the exposure to budesonide and formoterol was lower by approximately 30 to 50% after Symbicort pMDI compared to Pulmicort TBH or Oxis TBH (Figure V). The C<sub>max</sub> in particular was more affected for each component.

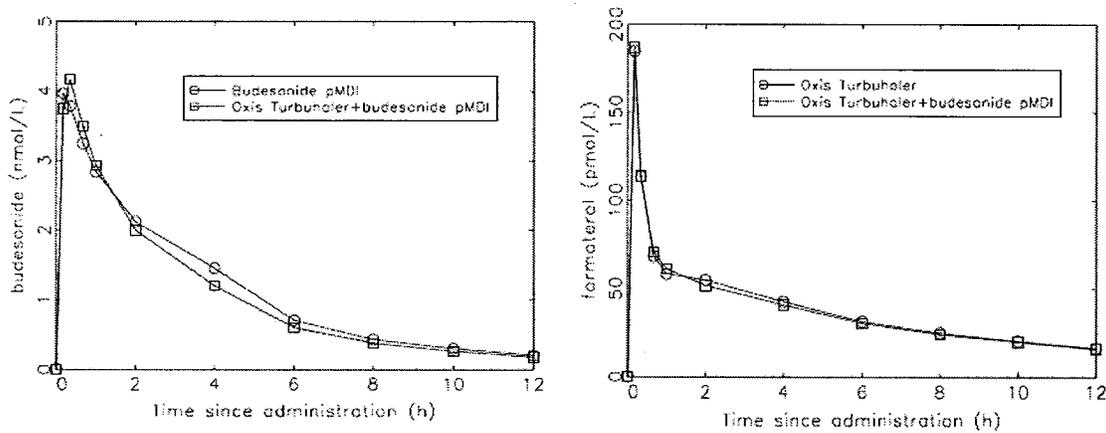
**Figure V. Mean Plasma Concentration-Time Profiles of Budesonide and Formoterol (Study # 10)**



- There was no evidence of interaction between budesonide and formoterol when each component was administered either alone (Budesonide pMDI vs Oxis TBH) or together Oxis TBH + Budesonide pMDI (Figure VI).

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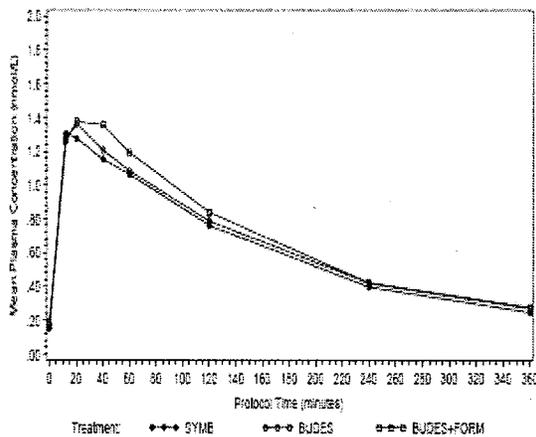
**Figure VI. Mean Budesonide and Formoterol Plasma Concentration-Time Profiles When Administered as Either Budesonide pMDI or Oxis TBH (Study # 722)**



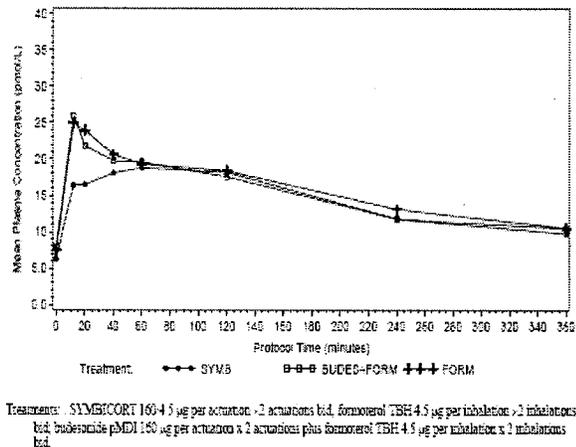
- Following two weeks of treatments, the steady-state plasma concentration-time profiles of budesonide and formoterol were almost superimposed following Symbicort PMDI and its mono-components in asthmatic patients 12 years or older (**Figure VII**).

**Figure VII. Mean Budesonide and Formoterol Plasma Concentration-Time Profiles (Clinical Study # 717)**

**A) Budesonide**



**B) Formoterol**



- Based on Pop PK analysis, there was no single covariate that raises any concern or may affect the PK characteristic of either budesonide or formoterol. Specifically, gender, weight, height and other demographic variants do not appear to affect the PK characteristic of either component. Therefore, based on Pop PK analysis none of the tested covariates may have a significant clinical impact on the performance of Symbicort.

**Conclusion:**

Overall, the systemic exposure to budesonide from Symbicort pMDI appears to be comparable to the exposure from the monoproducts. For formoterol, however, the systemic exposure appears to be comparable or slightly lower than the monoproduct. Therefore, no there is no systemic safety concern, at least from formoterol, when administered as combination product, Symbicort pMDI.

**Reviewer**

Sayed (Sam) Al Habet, R.Ph., Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
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Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader-----

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## Background:

Symbicort pressurized metered dose inhaler (pMDI) is a combination product consisting of budesonide and formoterol fumarate dehydrate available in the following strengths:

- 80/4.5 mcg (120 actuation)
- 160/4.5 mcg (120 actuation)

Budesonide is a corticosteroid and formoterol is a long-acting  $\beta$ 2-agonist. The product is proposed to be used in the long-term maintenance treatment of asthma in patients 12 years of age and older.

## What is the Formulation and Product/Device?

The clinical program for the development of Symbicort pMDI consisted of 14 Phase 1 clinical pharmacology/PK, 4 Phase 2 pharmacodynamic (PD) studies and 9 Phase 3 safety and efficacy studies. The focus of the review is on the PK studies comparing the bioavailability of Symbicort pMDI to mono-products (budesonide and formoterol).

No change was made between the clinical and the to-be-marketed formation. This formulation contains the active drugs, two excipients, and HFA 227 (Table 1).

**Table 1. Composition for the Clinical and the Commercial Formulation**

| Component   | Nominal concentration in canister |                         |
|---|-----------------------------------|-------------------------|
|   | 80/4.5 $\mu$ g product            | 160/4.5 $\mu$ g product |
| Budesonide micronized <sup>b</sup>                    |                                   |                         |
| Formoterol fumarate dihydrate micronized <sup>b</sup> |                                   |                         |
| PEG 1000  |                                   |                         |
| Povidone K25  |                                   |                         |
| HFA 227   |                                   |                         |

<sup>b</sup> Drug concentrations include formulation overages for both drug substances to compensate for drug losses on the can, valve, and actuator mouthpiece. Refer to P 2.2 Pharmaceutical Development – Drug Product for further details.

PEG Polyethylene glycol; HFA Hydrofluoroalkane

The device used in all clinical studies had a standard actuator. However, the to-be-marketed device will be attached to a shield actuator. The shield component is attached to the base of the canister. The rest of the assembly of the device such as the mouthpiece for the clinical and commercial device is identical. Based on *in vitro* testing, the performance of the two devices is virtually similar (see CMC review). Therefore, no bioequivalence study is necessary to establish the link between the two devices.

## **What Studies Submitted in this NDA?**

Since there was no change in the clinical and to-be-marketed formulation, no bioequivalence study was necessary. Therefore, the clinical pharmacology program was focused on the following issues:

- The PK characteristics following a single and multiple dose of Symbicort pMDI and mono-products.
- Potential interaction between budesonide and formoterol

Therefore, the sponsor conducted a series of studies in order to establish the relationship between the following products:

- Budesonide pMDI (used as active comparator in Phase 3 trial)
- OXIS TBH (used as active comparator in Phase 3 trial)
- Pulmicort TBH (for large safety data)

Some studies were conducted in healthy subjects and some in asthmatic adults or children. One important study was conducted to establish dosage strength equivalency and dose proportionality for the three formulation strengths. Furthermore, Pop PK and across studies analysis were performed to evaluate the entire PK data from different studies and to determine the effect of covariates on PK characteristics of budesonide and formoterol. To minimize confusion, the clinical pharmacology and biopharmaceutics studies will be summarized in this review under the following three main headings:

- A) Relative Bioavailability and Comparative Studies
- B) Multiple Dose/Steady State Studies
- C) Clinical/Phase 3 Studies with PK/PD subsets

The Pop PK and a cross-study PK analysis and conclusions will be summarized toward the end of the review.

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## Summary of Individual Studies:

### A) Relative Bioavailability and Comparative Studies

#### 1.0 Study # 0721 (Symbicort pMDI vs budesonide pMDI plus OXIS TBH):

##### Objective:

The objective of this study was to determine the systemic bioavailability of budesonide and formoterol when administered via Symbicort pMDI compared to individual components administered as budesonide pMDI Plus Oxis Turbuhaler (TBH).

##### Study Design:

- Two-way crossover, single dose
- n= 28 healthy adult subjects

##### Dose:

- Symbicort pMDI: 160/4.5 mcg x 8 actuation = **1280/36 mcg** (single dose)
- Oxis Turbuhaler (fermoterol): 4.5 mcg per inhalation x 8 = **36 mcg**
- Budesonide pMDI: 160 mcg per actuation x 8 = **1280 mcg**

##### Results:

- For budesonide, the ratio of AUC between Symbicort pMDI and OXI Turbuhaler **PLUS** budesonide was 98%. Also, the 90% CI for both C<sub>max</sub> and AUC was within 80-125% (**Table 1.1 and Figure 1.1**). The mean PK parameters are similar in both treatments (**Table 1.2**).
- For formoterol, however, the exposure was lower than that of budesonide (**Table 1.3 and Figure 1.2**). Based on the AUC ratio it was 82% when comparing Symbicort pMDI to mono-components given individually (Oxis Turbuhaler plus budesonide). The mean PK data is shown in **Table 1.4**. This was consistent with the urine excretion data which showed that the mean of 81.5% (**Table 1.3**). The fraction of administered dose excreted in urine were 8.8% and 10.9% for Symbicort pMDI and Oxis Turbuhaler + budesonide pMDI (**Table 1.5**).

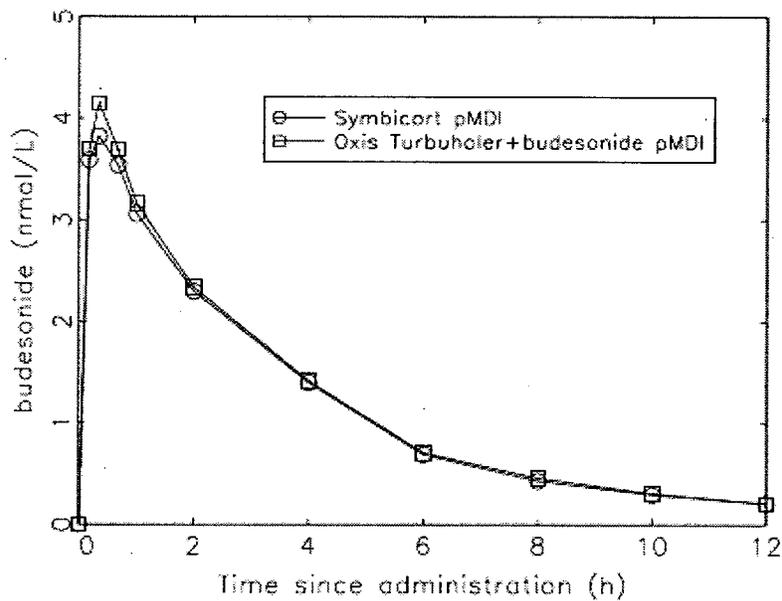
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**Table 1.1. PK Parameters and 90% CI for Budesonide (Study # 0721)**

| Parameter                     | Symbicort pMDI vs.<br>Oxis Turbuhaler + budesonide pMDI |                |
|-------------------------------|---|----------------|
|                               | Ratio <sup>1</sup>                                      | 90% conf. lim. |
| AUC (nmol*h/L)                | 97.9  | (92.1, 104.1)  |
| AUC <sub>0-t</sub> (nmol*h/L) | 97.3  | (91.6, 103.4)  |
| C <sub>max</sub> (nmol/L)     | 97.2  | (89.0, 106.1)  |
| t <sub>1/2</sub> (h)          | 107.8   | (100.3, 115.8) |
| MRT (h)                       | 0.10  | (-0.07, 0.28)  |

<sup>1</sup> Difference for MRT, ratio in % for other parameters

**Figure 1.1. Mean Plasma Concentration-Time Profiles of Budesonide (Study # 0721)**



**Table 1.2. Mean PK Parameters of Budesonide (Study 0721)**

| Parameter                     | Symbicort pMDI    |                | Oxis Turbuhaler +<br>budesonide pMDI |                |
|-------------------------------|-------------------|----------------|--------------------------------------|----------------|
|                               | Mean <sup>1</sup> | 90% conf. lim. | Mean <sup>1</sup>                    | 90% conf. lim. |
| AUC (nmol*h/L)                | 14.6              | (14.0, 15.3)   | 14.9                                 | (14.3, 15.6)   |
| AUC <sub>0-t</sub> (nmol*h/L) | 13.5              | (13.0, 14.1)   | 13.9                                 | (13.3, 14.5)   |
| C <sub>max</sub> (nmol/L)     | 3.9               | (3.7, 4.2)     | 4.0                                  | (3.8, 4.3)     |
| t <sub>1/2</sub> (h)          | 3.6               | (3.4, 3.8)     | 3.3                                  | (3.2, 3.5)     |
| MRT (h)                       | 4.3               | (4.1, 4.4)     | 4.1                                  | (4.0, 4.3)     |

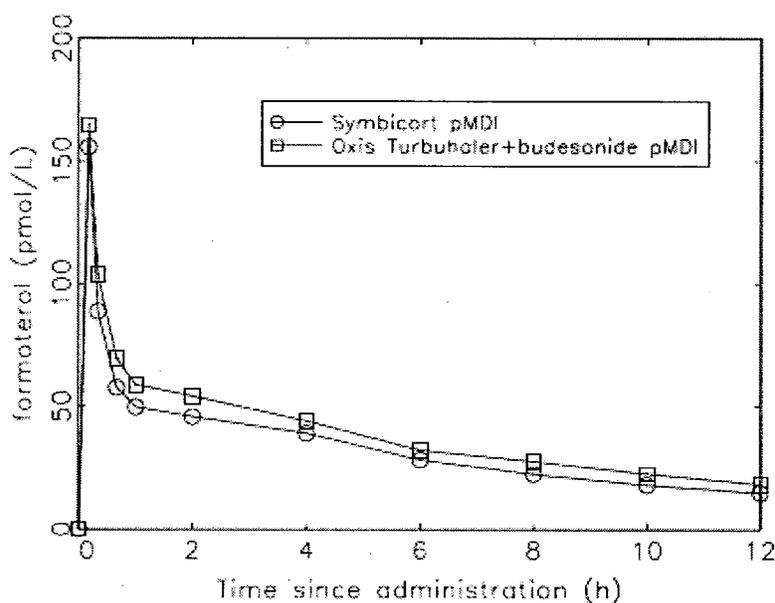
<sup>1</sup> Arithmetic mean for MRT, geometric means for other parameters

**Table 1.3. PK Parameters, 90% CI , and Urine Excretion of Formoterol (Study # 0721)**

| Parameter                     | Symbicort pMDI vs.<br>Oxis Turbuhaler + budesonide pMDI |                |
|-------------------------------|---|----------------|
|                               | Ratio <sup>1</sup>                                      | 90% conf. lim. |
| AUC (pmol*h/L)                | 82.2  | (76.3, 88.6)   |
| AUC <sub>0-1</sub> (pmol*h/L) | 84.3  | (77.8, 91.5)   |
| C <sub>max</sub> (pmol/L)     | 92.9  | (82.5, 104.7)  |
| t <sub>1/2</sub> (h)          | 93.8  | (83.4, 105.4)  |
| MRT (h)                       | -0.47   | (-1.37, 0.43)  |
| A <sub>e</sub> (nmol)         | 81.5  | (75.2, 88.4)   |

<sup>1</sup> Difference for MRT, ratio in % for other parameters

**Figure 1.2. Mean Plasma Concentration-Time Profiles of Formoterol (Study # 0721)**



**Table 1.4. Mean PK Parameters of Formoterol (Study 0721)**

| Parameter                     | Symbicort pMDI    |                | Oxis Turbuhaler +<br>budesonide pMDI |                |
|-------------------------------|-------------------|----------------|--------------------------------------|----------------|
|                               | Mean <sup>1</sup> | 90% conf. lim. | Mean <sup>1</sup>                    | 90% conf. lim. |
| AUC (pmol*h/L)                | 515.7             | (489.2, 543.7) | 627.1                                | (594.8, 661.2) |
| AUC <sub>0-1</sub> (pmol*h/L) | 384.9             | (363.5, 407.7) | 456.4                                | (431.0, 483.4) |
| C <sub>max</sub> (pmol/L)     | 147.0             | (135.1, 160.0) | 158.2                                | (145.4, 172.2) |
| t <sub>1/2</sub> (h)          | 6.0               | (5.5, 6.5)     | 6.4                                  | (5.9, 6.9)     |
| MRT (h)                       | 8.7               | (8.1, 9.4)     | 9.2                                  | (8.5, 9.8)     |
| A <sub>e</sub> (nmol)         | 7.6               | (7.2, 8.0)     | 9.3                                  | (8.8, 9.8)     |

<sup>1</sup> Arithmetic mean for MRT, geometric means for other parameters

**Table 1.5. Mean Amount of Formoterol Excreted in Urine (Study # 0721)**

| Parameter                    | Symbicort pMDI |              | Oxis Turbuhaler +<br>budesonide pMDI |              |
|------------------------------|----------------|--------------|--------------------------------------|--------------|
|                              | Mean           | Range        | Mean                                 | Range        |
| Ae <sub>0-24 h</sub> (nmol)  | 6.8            | (3.8 - 13.7) | 8.3                                  | (5.4 - 12.9) |
| Ae <sub>24-48 h</sub> (nmol) | 0.8            | (0.4 - 1.3)  | 0.9                                  | (0.5 - 1.5)  |
| A <sub>e</sub> (nmol)        | 7.6            | (4.3 - 15.0) | 9.3                                  | (6.2 - 14.2) |
| fe <sub>0-24 h</sub> (%)     | 8.0            | (4.4 - 16.0) | 9.7                                  | (6.3 - 15.0) |
| fe <sub>24-48 h</sub> (%)    | 0.9            | (0.4 - 1.5)  | 1.1                                  | (0.6 - 1.7)  |
| f <sub>e</sub> (%)           | 8.8            | (5.0 - 17.5) | 10.9                                 | (7.3 - 16.6) |

**Conclusion:**

Based on this data, it can be concluded that the relative bioavailability of budesonide after Symbicort pMDI relative to mono-products is close to 100% (98%). However, for formoterol is about 80%.

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## 2.0 Study 0713 (Symbicort pMDI vs Pulmicort TBH PLUS OXIS TBH)

### Objective:

The primary objective of this study was to determine the relative systemic bioavailability of budesonide and formoterol from Symbicort pMDI compared with Pulmicort Turbuhaler and Oxis Turbuhaler given at the same time.

### Design:

- Four-way crossover, replicate design, single dose
- n= 28 healthy adult subject

### Treatments:

- Symbicort pMDI: 160/4.5 mcg x 12 inhalation = **1920/54 mcg** (single dose).
- Pulmicort Turbuhaler (Budesonide, US Version) powder: 200 mcg equivalent to 160 mcg per dose x 6 = 1200 (equivalent to **960 mcg** delivered dose)
- OXIS Turbuhaler (formoterol, original version)): 4.5 mcg per inhalation x 6 = **27 mcg**

### Activated Charcoal Arms:

In order to block the fraction of the drug absorbed via the mouth and GI tract, two of the symbicort pMDI treatments and one of the two Pulmicort TBH plus Oxis TBH treatments were given together with activated charcoal.

### Results:

- The data in the absence and the presence of charcoal is summarized in **Tables 2.1-2.4** and **Figures 2.1 and 2.3**.
- Based on dose correction, the exposure for budesonide and formoterol was approximately 20% to 35% lower after Symbicort pMDI than monoproducts; Pulmicort Turbuhaler plus Oxis Turbuhaler (**Tables 2. 1-2.4** and **Figures 2.1-2.2**). The effect was more apparent for budesonide (30% to 35%).
- When administered with charcoal, the mean relative bioavailability for budesonide was 72% (95% CI: 63-82) and for formoterol was 82% (95% CI 71-95). The same trend was when administered without charcoal. In the absence of charcoal, the mean C<sub>max</sub> ratios were 65% (95% CI: 56-74) for budesonide and 95% (95% CI: 81-113) for formoterol. Therefore, the effect of charcoal appears to be less apparent for C<sub>max</sub> than for AUC. This may suggest that the initial peak is primarily a result of lung absorption rather than absorption from the GI tract.

**Table 2.1. Mean PK Parameters for Budesonide When Administered Without Charcoal**

| parameter                           | Symbicort pMDI |               | Pulmicort Turbuhaler + Oxis Turbuhaler |               | Symbicort vs. Pulmicort + Oxis <sup>1</sup> |               |
|-------------------------------------|----------------|---------------|--|---------------|---|---------------|
|                                     | mean           | 95% conf.lim. | mean                                   | 95% conf.lim. | mean  | 95% conf.lim. |
| AUC (nmol/L·h)                      | 19.0           | 17.3 - 20.9   | 13.1                                   | 11.9 - 14.5   | 72  | 63 - 82       |
| AUC <sub>0-4</sub> (nmol/L·h)       | 17.7           | 16.1 - 19.5   | 12.4                                   | 11.2 - 13.7   | 71  | 63 - 81       |
| C <sub>max</sub> (nmol/L)           | 6.05           | 5.47 - 6.69   | 4.68                                   | 4.22 - 5.19   | 65  | 56 - 74       |
| T <sub>1/2</sub> (h)                | 3.38           | 3.15 - 3.62   | 3.13                                   | 2.91 - 3.35   | 108   | 98 - 119      |
| MRT (h)                             | 4.02           | 3.88 - 4.16   | 3.75                                   | 3.61 - 3.90   | 0.27  | 0.07 - 0.47   |
| T <sub>max</sub> (min) <sup>2</sup> | 20             | 10 - 60       | 10                                     | 10 - 42       | 5   | 0 - 10        |

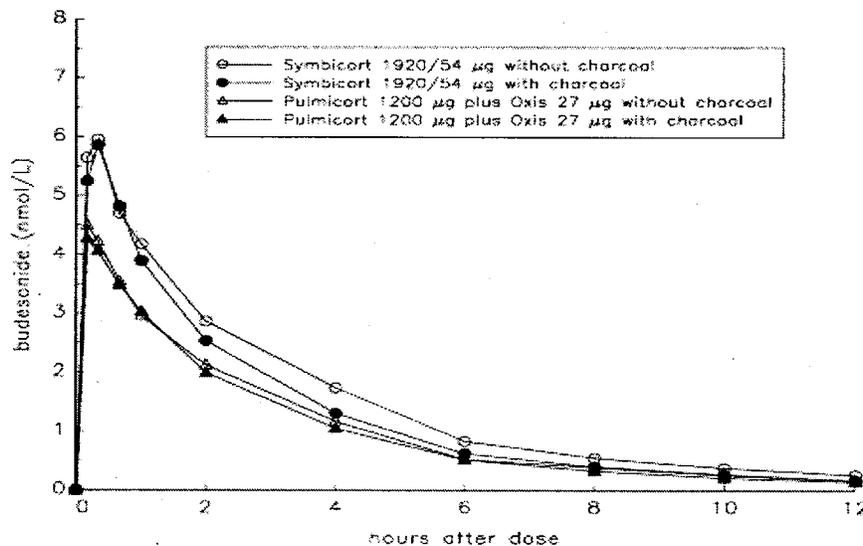
<sup>1</sup>Ratios (%) for T<sub>1/2</sub>, AUC<sub>0-4</sub>, AUC and C<sub>max</sub>, differences for MRT and T<sub>max</sub>. <sup>2</sup>Treatment median and range for T<sub>max</sub>. Hodge-Lehmann estimate for treatment comparison.

**Table 2.2. Mean PK Parameters for Budesonide When Administered With Charcoal**

| parameter                           | Symbicort pMDI |               | Pulmicort Turbuhaler + Oxis Turbuhaler |               | Symbicort vs. Pulmicort + Oxis <sup>1</sup> |               |
|-------------------------------------|----------------|---------------|--|---------------|---|---------------|
|                                     | mean           | 95% conf.lim. | mean                                   | 95% conf.lim. | mean  | 95% conf.lim. |
| AUC (nmol/L·h)                      | 15.9           | 14.5 - 17.4   | 12.2                                   | 11.2 - 13.4   | 65  | 57 - 74       |
| AUC <sub>0-4</sub> (nmol/L·h)       | 15.1           | 13.8 - 16.5   | 11.6                                   | 10.6 - 12.8   | 65  | 57 - 74       |
| C <sub>max</sub> (nmol/L)           | 6.09           | 5.53 - 6.71   | 4.45                                   | 4.04 - 4.91   | 68  | 60 - 78       |
| T <sub>1/2</sub> (h)                | 3.13           | 2.93 - 3.35   | 3.00                                   | 2.81 - 3.20   | 104   | 95 - 115      |
| MRT (h)                             | 3.47           | 3.33 - 3.61   | 3.52                                   | 3.38 - 3.66   | -0.05                                       | -0.25 - 0.15  |
| T <sub>max</sub> (min) <sup>2</sup> | 20             | 10 - 40       | 20                                     | 10 - 60       | 0   | -2 - 4        |

<sup>1</sup>Ratios (%) for T<sub>1/2</sub>, AUC<sub>0-4</sub>, AUC and C<sub>max</sub>, differences for MRT and T<sub>max</sub>. <sup>2</sup>Treatment median and range for T<sub>max</sub>. Hodge-Lehmann estimate for treatment comparison.

**Figure 2.1. Mean Plasma Concentration-Time Profiles of Budesonide With and Without Charcoal**



- Overall, treatment with charcoal significantly reduced the systemic exposure to formoterol but slightly affected budesonide. The effect was more pronounced after Symbicort pMDI than monoproducts. The mean relative bioavailability was 65% (95% CI: 57-74) for budesonide and 76% (95% CI 66-87) for formoterol. The C<sub>max</sub> ratios were 68% (95% CI: 60-78) for budesonide and 96% (95% CI: 82-114) for formoterol (Tables 2.3 and 2.4).

**Table 2.3. Mean PK Parameters for Formoterol when Administered Without Charcoal**

| parameter                           | Symbicort pMDI |               | Pulmicort Turbuhaler + OxisTurbuhaler |               | Symbicort vs. Pulmicort + Oxis <sup>1</sup> |               |
|-------------------------------------|----------------|---------------|---------------------------------------|---------------|---|---------------|
|                                     | mean           | 95% conf.lim. | mean                                  | 95% conf.lim. | mean  | 95% conf.lim. |
| AUC (pmol/L·h)                      | 751            | 677 - 833     | 456                                   | 412 - 506     | 82  | 71 - 95       |
| AUC <sub>0-t</sub> (pmol/L·h)       | 557            | 503 - 616     | 335                                   | 303 - 371     | 83  | 72 - 95       |
| C <sub>max</sub> (pmol/L)           | 227            | 201 - 256     | 119                                   | 105 - 134     | 95  | 81 - 113      |
| T <sub>1/2</sub> (h)                | 6.37           | 5.61 - 7.24   | 6.34                                  | 5.58 - 7.21   | 100   | 84 - 120      |
| MRT (h)                             | 9.56           | 8.28 - 10.85  | 9.40                                  | 8.11 - 10.68  | 0.17  | -1.58 - 1.92  |
| T <sub>max</sub> (min) <sup>2</sup> | 10             | 9 - 11        | 10                                    | 10 - 10       | 0   | 0 - 0         |

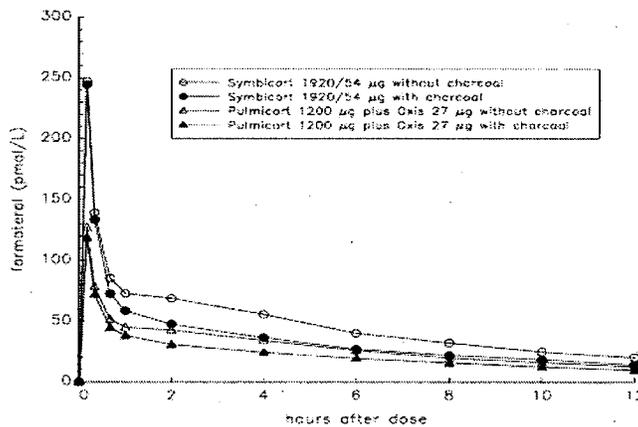
<sup>1</sup>Ratios (%) for T<sub>1/2</sub>, AUC<sub>0-t</sub>, AUC and C<sub>max</sub>, differences for MRT and T<sub>max</sub>.<sup>2</sup> Treatment median and range for T<sub>max</sub>. Hodge-Lehmann estimate for treatment comparison.

**Table 2.4. Mean PK Parameters for Formoterol When Administered With Charcoal**

| parameter                           | Symbicort pMDI |               | Pulmicort Turbuhaler + Oxis Turbuhaler |               | Symbicort vs. Pulmicort + Oxis <sup>1</sup> |               |
|-------------------------------------|----------------|---------------|--|---------------|---|---------------|
|                                     | mean           | 95% conf.lim. | mean                                   | 95% conf.lim. | mean  | 95% conf.lim. |
| AUC (pmol/L·h)                      | 538            | 487 - 594     | 356                                    | 322 - 393     | 76  | 66 - 87       |
| AUC <sub>0-t</sub> (pmol/L·h)       | 402            | 364 - 443     | 263                                    | 238 - 290     | 76  | 67 - 88       |
| C <sub>max</sub> (pmol/L)           | 219            | 195 - 246     | 114                                    | 101 - 128     | 96  | 82 - 114      |
| T <sub>1/2</sub> (h)                | 6.58           | 5.82 - 7.45   | 6.03                                   | 5.33 - 6.82   | 109   | 92 - 130      |
| MRT (h)                             | 9.08           | 7.84 - 10.31  | 9.32                                   | 8.08 - 10.55  | -0.24                                       | -1.99 - 1.50  |
| T <sub>max</sub> (min) <sup>2</sup> | 10             | 10 - 12       | 10                                     | 10 - 12       | 0   | 0 - 0         |

<sup>1</sup>Ratios (%) for T<sub>1/2</sub>, AUC<sub>0-t</sub>, AUC and C<sub>max</sub>, differences for MRT and T<sub>max</sub>.<sup>2</sup> Treatment median and range for T<sub>max</sub>. Hodge-Lehmann estimate for treatment comparison.

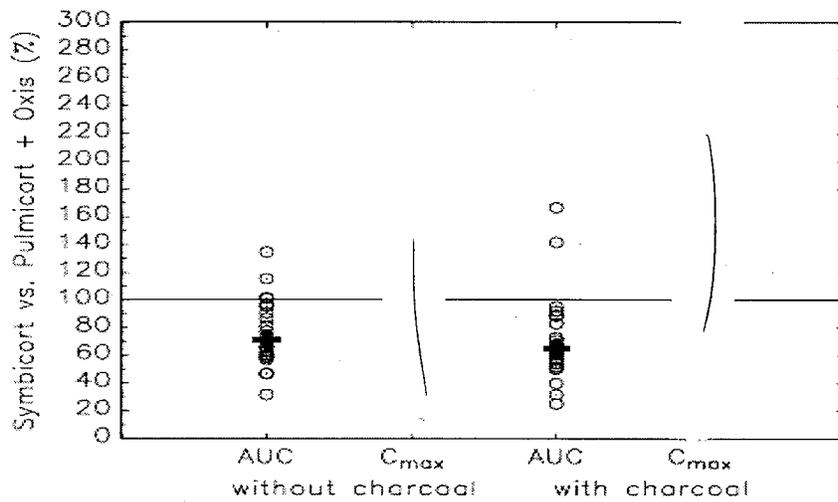
**Figure 2.2. Mean Plasma Concentration-Time Profiles of Formoterol With and Without Charcoal**



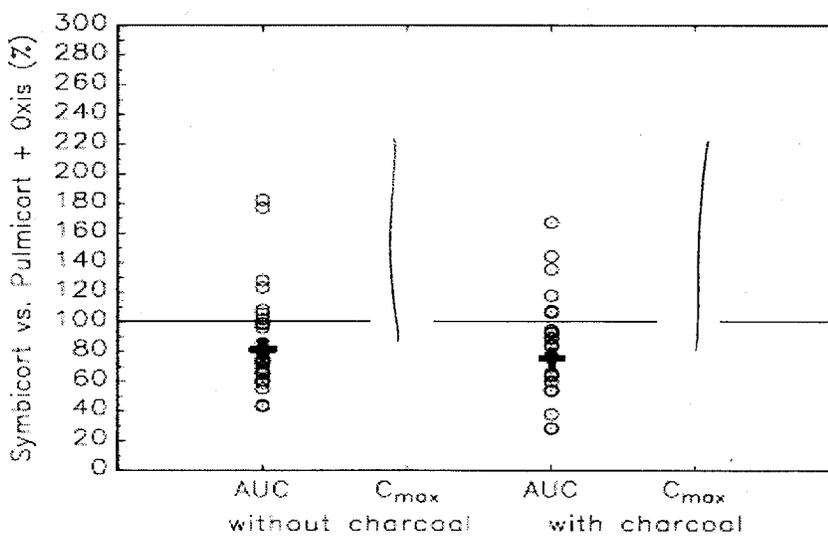
**Reviewer's Comments:**

The results from this study can be summarized in **Figures 2.3 and 2.4**. These figures show the relative bioavailability of budesonide and formoterol for dose corrected  $C_{max}$  and AUC with and without charcoal treatments. These figures show the trend at each treatment and the spread of the data with some outliers. It should be noted that the variability appears to be similar for the combination product and the mono-products. However, the data for formoterol is more spread and variable than that of budesonide (**Figures 2.3 and 2.4**). According to the sponsor, some of this variability could have been attributed to inadequacy in dosing.

**Figure 2.3. Individual and Mean Dose Corrected Budesonide AUC and  $C_{max}$  Ratios Between Symbicort pMDI and Pulmicort TBH Plus Oxis TBH (Study 713)**

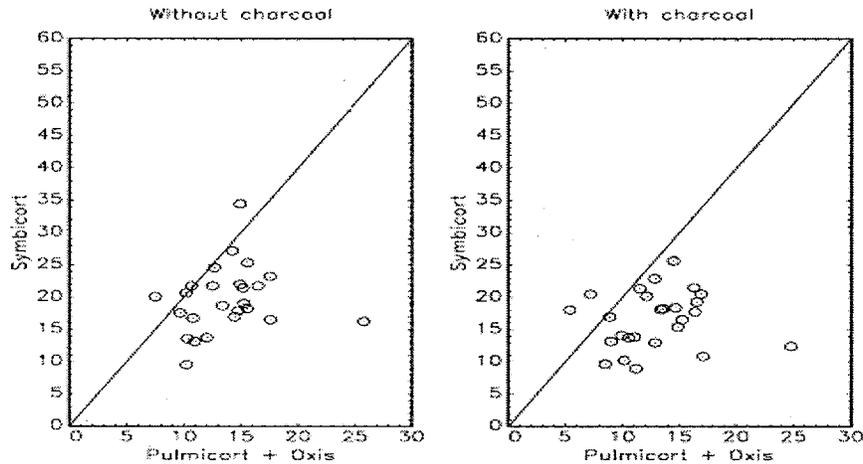


**Figure 2.4. Individual and Mean Dose Corrected Formoterol AUC and  $C_{max}$  Ratios Between Symbicort pMDI and Pulmicort TBH Plus Oxis TBH (Study 713)**

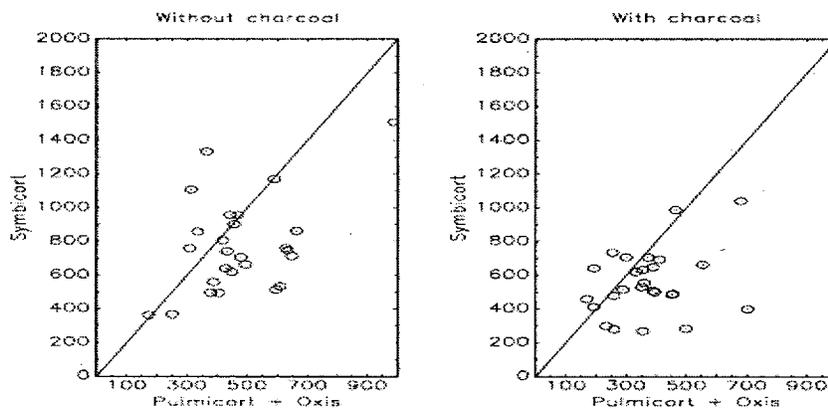


Considering all sources of variability in the data and all the possibility of dosing errors in some subjects, there appears to be some relationship between individual AUC for the combination product and mono-products for both budesonide (Figure 2.5) and formoterol (Figure 2.6). This relationship is not a perfect one, but it provides some idea of the trend at individual level and also further shows the lower trend of exposure for each component with Symbicort pMDI compared to monoproducts.

**Figure 2.5. Comparison of Individual Budesonide AUCs For Symbicort pMDI and Pulmicort TBH Plus Oxis TBH (Study 713)**



**Figure 2.5. Comparison of Individual Formoterol AUCs For Symbicort pMDI and Pulmicort TBH Plus Oxis TBH (Study 713)**



**Conclusions:**

The systemic bioavailability of budesonide and formoterol was 20% to 35% lower when administered from Symbicort pMDI than individual components from Pulmicort Turbuhaler plus Oxis Turbuhaler. The presence of charcoal significantly reduced the systemic exposure of formoterol. However, the effect of charcoal was less apparent for budesonide.

### 3.0 Study # D5896C00010 (Symbicort pMDI vs budesonide pMDI, Pulmicort TBH, and OXIS TBH)

#### Objectives:

The primary object of this study is to compare the PK of budesonide and formoterol after inhalation from Symbicort pMDI and after inhalation from Pulmicort TBH, budesonide pMDI, or Oxis TBH in adult asthma patients.

#### Design:

This is a single dose four-way crossover design in 29 **asthmatic adult** patients

#### Treatments:

- Symbicort pMDI: 160/4.5 mcg x 12 inhalation = **1920/54** mcg (single dose).
- Budesonide pMDI: 160 mcg x 12 = **1920 mcg**
- Pulmicort Turbuhaler (Budesonide, US version) powder: 200 mcg equivalent to 160 mcg per dose x 12 = 2400 (equivalent to **1920** mcg delivered dose)
- OXIS Turbuhaler (fermoterol, original version)): 4.5 mcg per inhalation x 12 = **54** mcg

In addition to blood collection, urine was collected over 48 hours for the determination of formoterol amount excreted.

#### Results:

- The exposure (C<sub>max</sub> and AUC) of budesonide was lower by approximately 30 to 50% after Symbicort pMDI and Budesonide pMDI compared to Pulmicort TBH (**Table 3.1 and 3.2 and Figures 3.1 and 3.2**).
- However, the budesonide exposure from Symbicort pMDI and Budesonide pMDI is similar with a ratio of 98%. Also, the AUC, but not the C<sub>max</sub>, was within 80 to 125% (**Table 3.2**). The C<sub>max</sub> was approximately 25% higher after Symicort pMDI compared to budesonide pMDI.

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**Table 3.1 Mean PK Parameters of Budesonide (Study # D5896C00010)**

| Parameter                     | Symbicort pMDI    |               | budesonide pMDI   |               | Pulmicort Turbuhaler |               |
|-------------------------------|-------------------|---------------|-------------------|---------------|----------------------|---------------|
|                               | Mean <sup>1</sup> | 90% conf.lim. | Mean <sup>1</sup> | 90% conf.lim. | Mean <sup>1</sup>    | 90% conf.lim. |
| AUC (nmol/L·h)                | 18.43             | 17.44 - 19.47 | 18.85             | 17.87 - 19.88 | 27.20                | 25.74 - 28.75 |
| AUC <sub>0-t</sub> (nmol/L·h) | 17.91             | 16.94 - 18.93 | 18.27             | 17.32 - 19.28 | 26.51                | 25.08 - 28.03 |
| MRT (h)                       | 5.70              | 5.56 - 5.85   | 5.98              | 5.84 - 6.12   | 5.49                 | 5.35 - 5.64   |
| t <sub>1/2</sub> (h)          | 4.67              | 4.41 - 4.95   | 5.07              | 4.79 - 5.36   | 4.99                 | 4.71 - 5.29   |
| t <sub>max</sub> (min)        | 20                | 10 - 120      | 20                | 10 - 240      | 10                   | 10 - 20       |
| C <sub>max</sub> (nmol/L)     | 4.48              | 4.07 - 4.94   | 3.60              | 3.28 - 3.95   | 8.21                 | 7.45 - 9.04   |

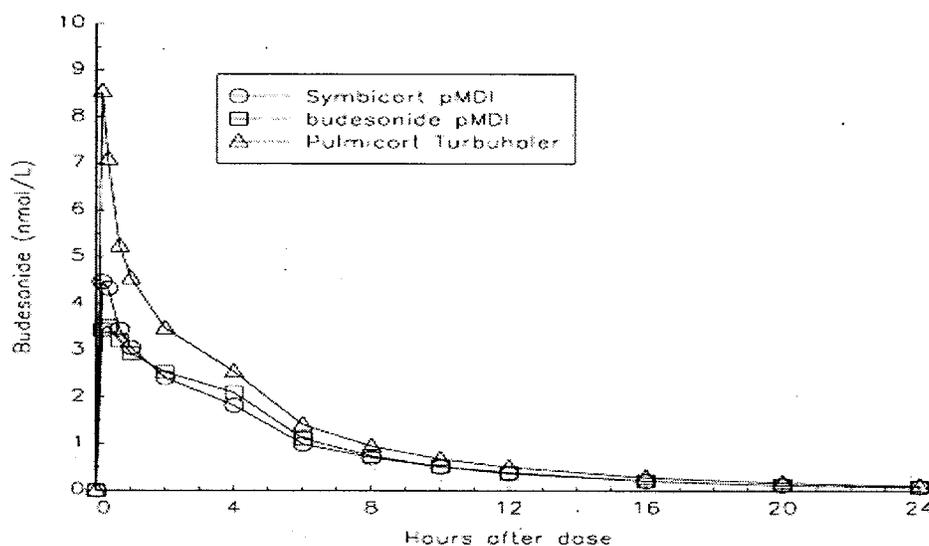
<sup>1</sup> Median and range for t<sub>max</sub>, arithmetic mean for MRT, and geometric means for the other parameters.

**Table 3.2 Statistical Analysis of PK Parameters for Budesonide (Study # D5896C00010)**

| Parameter              | Symbicort pMDI vs. budesonide pMDI <sup>1</sup> |               | Symbicort pMDI vs. Pulmicort Turbuhaler <sup>1</sup> |               | budesonide pMDI vs. Pulmicort Turbuhaler <sup>1</sup> |               |
|------------------------|---|---------------|--|---------------|---|---------------|
|                        | Mean  | 90% conf.lim. | Mean   | 90% conf.lim. | Mean  | 90% conf.lim. |
| AUC (%)                | 98  | 91 - 106      | 68   | 63 - 73       | 69  | 64 - 75       |
| AUC <sub>0-t</sub> (%) | 98  | 91 - 106      | 68   | 63 - 73       | 69  | 64 - 74       |
| MRT (h)                | -0.27   | -0.47 - -0.07 | 0.21   | 0.01 - 0.41   | 0.48  | 0.28 - 0.68   |
| t <sub>1/2</sub> (%)   | 92  | 85 - 100      | 94   | 86 - 101      | 102   | 94 - 110      |
| C <sub>max</sub> (%)   | 124   | 109 - 142     | 55   | 48 - 62       | 44  | 38 - 50       |

<sup>1</sup> Ratios for AUC, AUC<sub>0-t</sub>, C<sub>max</sub> and t<sub>1/2</sub>, difference for MRT

**Figure 3. 1 Mean Plasma Concentration-Time Profiles of Budesonide (Study # D5896C00010)**



- Similarly, the exposure to formoterol was lower after Symbicort pMDI compared to Oxis TBH (Tables 3.3 and 3.4 and Figure 3.2). The C<sub>max</sub> in particular was approximately 40% lower after Symbicort pMDI than after Oxis TBH. However, the AUC was marginally lower (13%) after Symbicort pMDI compared to Oxis TBH (Table 3.4). This low AUC is comparable to that seen for total amount excreted in urine over 48 hours. The systemic bioavailability of 13% based on AUC is not too far from the 18% based on amount of formoterol excreted in urine over 48 hours (Table 3.4).
- The percent of formoterol dose excreted unchanged in urine was approximately 8% ranging from approximately 7% to 10% (Table 3.3).

**Table 3.3 Mean PK Parameters of Formoterol (Study # D5896C00010)**

| Parameter <sup>2</sup>        | Symbicort pMDI    |               | Oxis Turbuhaler   |               |
|-------------------------------|-------------------|---------------|-------------------|---------------|
|                               | Mean <sup>1</sup> | 90% conf.lim. | Mean <sup>1</sup> | 90% conf.lim. |
| AUC (pmol/L·h)                | 747               | 671 - 832     | 861               | 776 - 954     |
| AUC <sub>0-t</sub> (pmol/L·h) | 640               | 578 - 709     | 733               | 665 - 808     |
| MRT (h)                       | 10.64             | 9.33 - 11.95  | 11.80             | 10.55 - 13.06 |
| t <sub>1/2</sub> (h)          | 7.88              | 6.87 - 9.05   | 8.75              | 7.67 - 9.99   |
| t <sub>max</sub> (min)        | 10                | 10 - 240      | 10                | 10 - 12       |
| C <sub>max</sub> (pmol/L)     | 136               | 119 - 156     | 222               | 194 - 253     |
| fe <sub>0-48h</sub> (%)       | 7.80              | 7.03 - 8.67   | 9.48              | 8.61 - 10.44  |

<sup>1</sup> Median and range for t<sub>max</sub>, arithmetic mean for MRT, and geometric means for the other parameters.

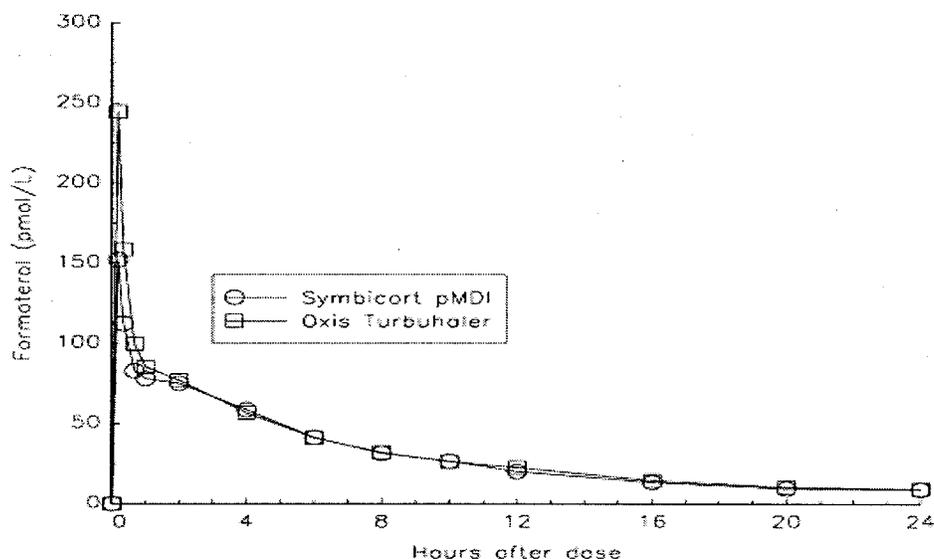
**Table 3.4 Statistical Analysis of PK Parameters for Formoterol (Study # D5896C00010)**

| Parameter <sup>2</sup>  | Symbicort pMDI<br>vs. Oxis Turbuhaler <sup>1</sup> |               |
|-------------------------|--|---------------|
|                         | Mean   | 90% conf.lim. |
| AUC (%)                 | 87   | 75 - 101      |
| AUC <sub>0-t</sub> (%)  | 87   | 76 - 101      |
| MRT (h)                 | -1.16  | -2.97 - 0.65  |
| t <sub>1/2</sub> (%)    | 90   | 74 - 109      |
| C <sub>max</sub> (%)    | 61   | 51 - 74       |
| fe <sub>0-48h</sub> (%) | 82   | 71 - 95       |

<sup>1</sup> Ratios for AUC, AUC<sub>0-t</sub>, C<sub>max</sub>, t<sub>1/2</sub>, and fe<sub>0-48h</sub>, difference for MRT

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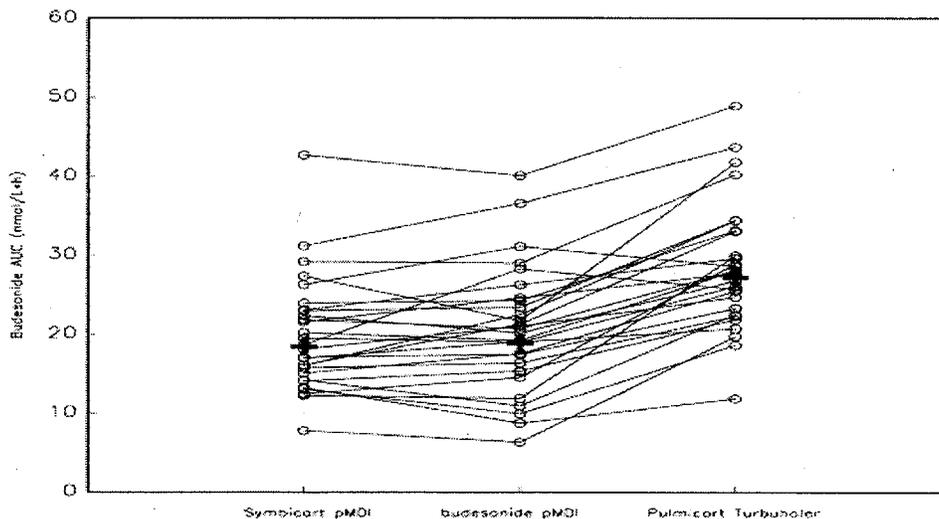
**Figure 3.2 Mean Plasma Concentration-Time Profiles of Formoterol (Study # D5896C00010)**



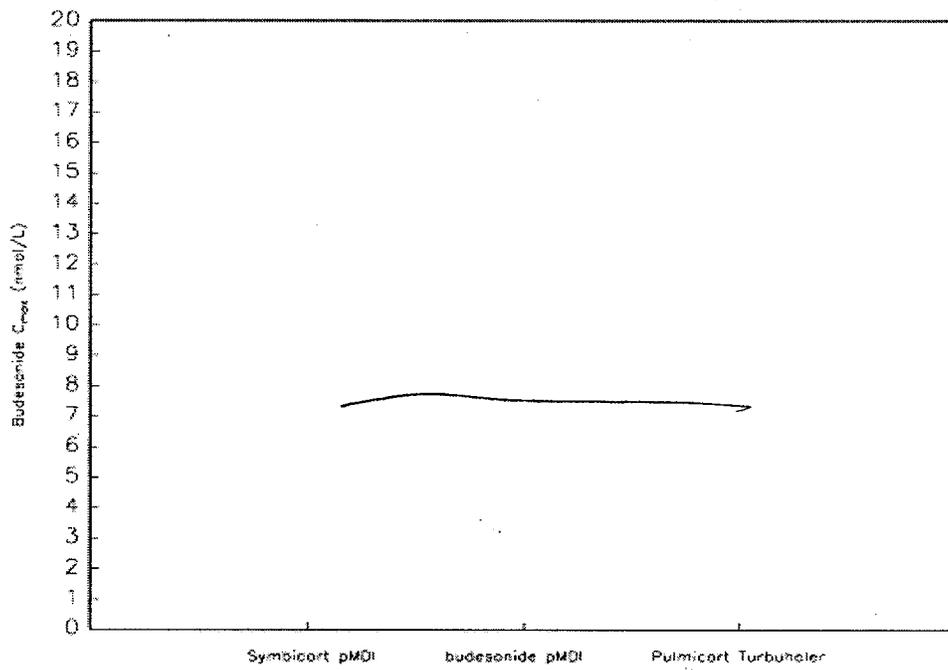
**Reviewer's Comments:**

- Examining the individual PK data (C<sub>max</sub> and AUC) for both budesonide and formoterol at all treatment shows relatively high inter-and intra-subject variability in the data, including in urinary excretion of formoterol (Figure 3.3-3.7).
- From the individual data it could be observed that the exposure to both budesonide and formoterol is lower after Symbicort pMDI compared to Pulmicort TBH or Oxis TBH. However, the exposure for budesonide after Symbicort pMDI and Budesonide pMDI is similar with a ratio of 98%.

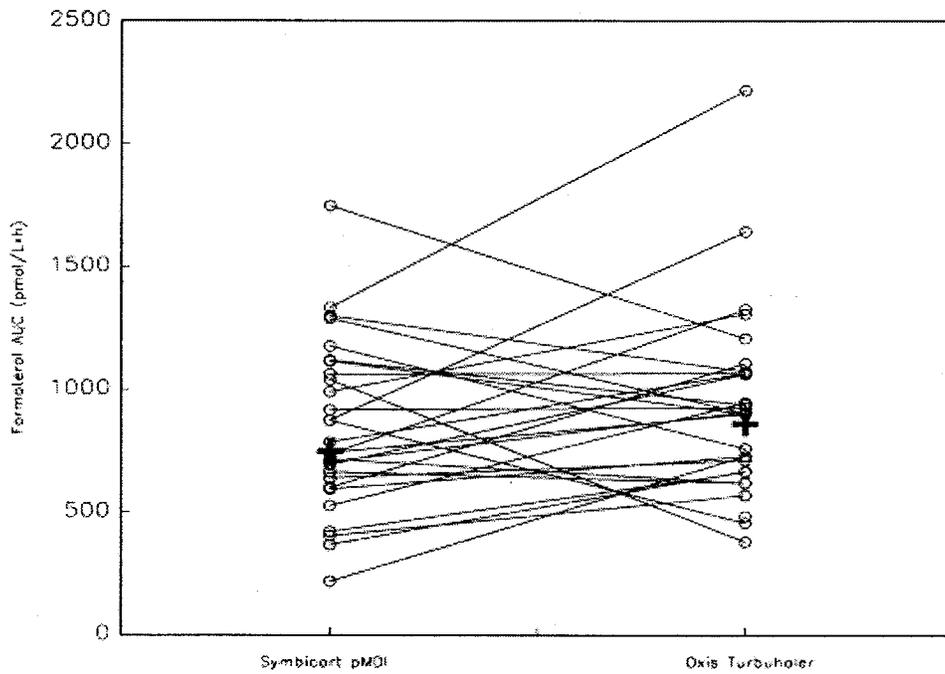
**Figure 3.3 Individual AUC Data for Budesonide (Study # D5896C00010)**



**Figure 3. 4 Individual Cmax Data for Budesonide (Study # 10)**



**Figure 3. 5 Individual AUC Data for Formoterol (Study # D5896C00010)**



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**Conclusions:**

- The systemic bioavailability of budesonide is approximately 30 to 50% lower after Symbicort pMDI and Budesonide pMDI compared to Pulmicort TBH. However, budesonide exposure from the former two products (Symbicort pMDI and Budesonide pMDI) is similar with a ratio of 98%.
- Similarly, the exposure to formoterol when administered as Symbicort pMDI is lower than Oxis TBH. The effect was more pronounced on the C<sub>max</sub> (39% low) than AUC (13% low). The bioavailability of formoterol from Symbicort pMDI relative to Oxis TBH based on AUC (13%) is comparable to that based on urine excretion data over 48 hours (18%).

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#### 4. Study # D5896C00013 (Symbicort pMDI vs Pulmicort TBH plus OXIS TBH)

##### Objectives:

The primary objective of this study was to compare the systemic availability of budesonide and formoterol after inhalation from Symbicort pMDI and Pulmicort TBH plus Oxis TBH in asthmatic children 6 to 11 years of age.

##### Design:

- Two-way crossover, single dose
- n= 24 **asthmatic children** (6 to 11 years) patients

##### Treatments:

- Symbicort pMDI: 160/4.5 mcg x 4 inhalation = **640/18** mcg (single dose).
- OXIS Turbuhaler (fermoterol, original version): 4.5 mcg per inhalation x 4 = **18** mcg
- Pulmicort Turbuhaler (Budesonide, US version) powder: 200 mcg equivalent to 160 mcg per dose x 4 = 800 (equivalent to **640 mcg** delivered dose)

Unlike the previous study #10, only 24 hours urine was collected for fomoterol measurement. Therefore, blood was collected only for budesonide plasma concentration measurement following all treatments.

##### Results:

- As observed in the previous studies, the exposure to budesonide after Symbicort pMDI was lower than Pulmicort TBH plus Oxis TBH (**Tables 4.1 and 4.2, and Figure 4.1**). The mean ratio for C<sub>max</sub> and AUC was approximately 60% and 75%, respectively (**Tables 4.1 and 4.2**).
- In this study 5 subjects had 16 missing plasma samples at various time points (10, 20, and 40 min). Therefore, the data was re-analyzed excluding these 5 subjects and presented in **Table 4.2**. This re-analysis did not make much difference to the data or conclusions.
- The amount of formoterol excreted in 24 hours urine collection was comparable between treatment, yet was about 10% higher after Symbicort than Pulmicort + Oxis TBH (**Table 4.3**). The mean percent of dose excreted unchanged in urine ranged from 3.1 to 3.5 %. It should be noted that this amount is approximately half of that amount excreted in the previous Study # 10 in adult asthmatic patients (~8%).

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**Table 4.1 Mean PK Parameters For Budesonide in ALL Subjects (Study # D5896C00013)**

| Parameter                           | Symbicort |               | Pulmicort + Oxis |               | Symbicort vs. Pulmicort + Oxis <sup>2</sup> |               |
|-------------------------------------|-----------|---------------|------------------|---------------|---|---------------|
|                                     | Mean      | 90% conf.lim. | Mean             | 90% conf.lim. | Mean  | 90% conf.lim. |
| AUC (nmol/L·h)                      | 4.22      | 3.32 - 5.37   | 5.75             | 4.52 - 7.32   | 73  | 52 - 103      |
| AUC <sub>0-t</sub><br>(nmol/L·h)    | 3.94      | 3.07 - 5.04   | 5.52             | 4.31 - 7.07   | 71  | 50 - 101      |
| MRT (h)                             | 3.78      | 3.44 - 4.12   | 2.90             | 2.55 - 3.24   | 0.88  | 0.39 - 1.37   |
| t <sub>1/2</sub> (h)                | 2.98      | 2.76 - 3.21   | 2.63             | 2.44 - 2.83   | 113   | 102 - 126     |
| t <sub>max</sub> (min) <sup>1</sup> | 20        | 10 - 240      | 20               | 10 - 62       |   |               |
| C <sub>max</sub> (nmol/L)           | 1.36      | 0.99 - 1.87   | 2.31             | 1.68 - 3.17   | 59  | 38 - 92       |

1 Median and range.

2 Ratios (%) for AUC, AUC<sub>0-t</sub>, C<sub>max</sub>, and t<sub>1/2</sub>, and difference for MRT.

**Table 4.2 Alternative Analysis of PK Parameters Excluding Five (5) Subjects with Missing Plasma Concentration Values (Study # D5896C00013)**

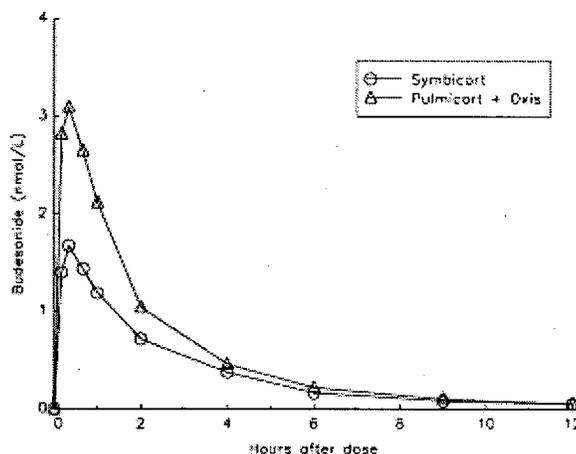
| Parameter                           | Symbicort |               | Pulmicort + Oxis |               | Symbicort vs. Pulmicort + Oxis <sup>2</sup> |               |
|-------------------------------------|-----------|---------------|------------------|---------------|---|---------------|
|                                     | Mean      | 90% conf.lim. | Mean             | 90% conf.lim. | Mean  | 90% conf.lim. |
| AUC<br>(nmol/L·h)                   | 4.19      | 3.10 - 5.67   | 5.35             | 3.95 - 7.24   | 78  | 51 - 120      |
| AUC <sub>0-t</sub><br>(nmol/L·h)    | 3.90      | 2.86 - 5.33   | 5.14             | 3.76 - 7.02   | 76  | 49 - 118      |
| MRT (h)                             | 3.78      | 3.34 - 4.22   | 2.85             | 2.41 - 3.29   | 0.93  | 0.30 - 1.55   |
| t <sub>1/2</sub> (h)                | 3.03      | 2.77 - 3.31   | 2.58             | 2.36 - 2.81   | 117   | 104 - 133     |
| t <sub>max</sub> (min) <sup>1</sup> | 20        | 10 - 240      | 20               | 10 - 62       |   |               |
| C <sub>max</sub> (nmol/L)           | 1.35      | 0.91 - 2.02   | 2.13             | 1.43 - 3.18   | 63  | 36 - 112      |

1 Median and range.

2 Ratios (%) for AUC, AUC<sub>0-t</sub>, C<sub>max</sub>, and t<sub>1/2</sub>, and difference for MRT.

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**Figure 4.1. Mean Plasma Concentration-Time Profile of Budesonide (Study # D5896C00013)**



**Table 4.3 Mean Urine Excretion Parameters For Formoterol (Study # D5896C00013)**

| Parameter               | Symbicort |               | Pulmicort + Oxis |               | Symbicort vs. Pulmicort + Oxis <sup>1</sup> |               |
|-------------------------|-----------|---------------|------------------|---------------|---|---------------|
|                         | Mean      | 90% conf.lim. | Mean             | 90% conf.lim. | Mean  | 90% conf.lim. |
| fe <sub>0-24h</sub> (%) | 3.48      | 2.73 - 4.43   | 3.09             | 2.43 - 3.93   | 113   | 80 - 158      |

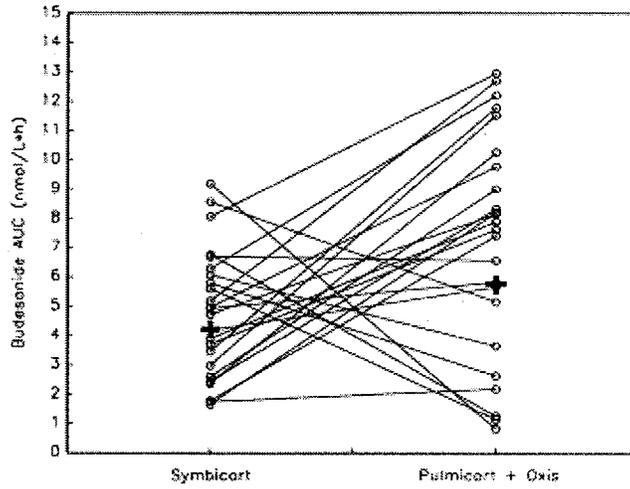
1 Ratio (%)

**Reviewer’s Comments:**

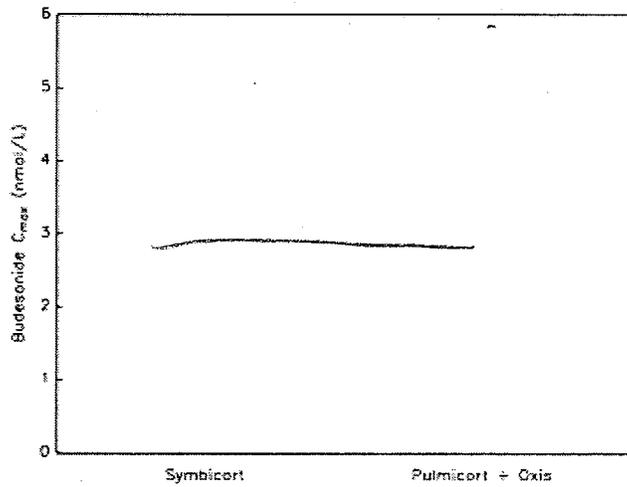
- As the previous studies, the data was variable, yet very consistent within each treatment. The %CV ranged from approximately 55% to 140% for C<sub>max</sub> and AUC in both treatment arms (Figures 4.2 and 4.3). In other words, there was clear trend in individual data that budesonide exposure was lower when administered as Symbicort pMDI than when administered as individual components of Pulmicort plus Oxis TBH (Figures 4.2 and 4.3).
- For formoterol, however, the spread of the urinary excretion data was consistent between the two treatments with the exception of one subject that appears to be an outlier in Symbicort pMDI arm (Figure 4.4). Therefore, considering the inter- and intra-subjects variability, the excretion of formoterol in urine appears to be comparable following both treatments.

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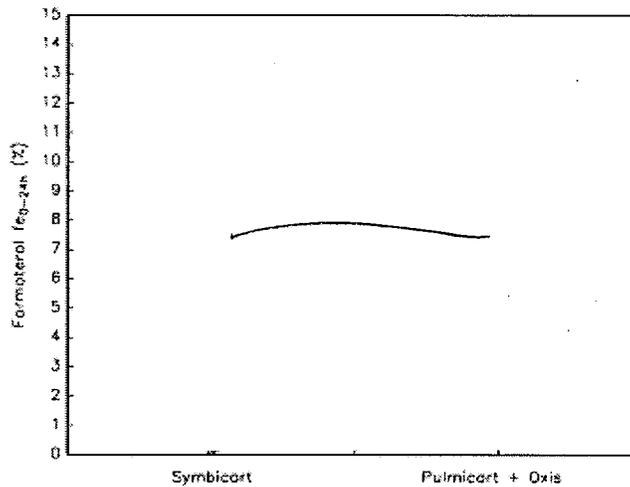
**Figure 4.2. Individual and Mean AUC for Budesonide (Study # D5896C00013)**



**Figure 4.3. Individual and Mean Cmax for Budesonide (Study # D5896C00013)**



**Figure 4.4. Individual Formoterol Amount Excreted in Urine (Study # D5896C00013)**



**Conclusions:**

The trend of lower exposure for budesonide and fomoterol following Symbicort pMDI relative to monoproducts is consistent with other studies. In this study the exposure to budesonide was 30 to 40% lower following Symbicort pMDI compared to monoproducts. No plasma samples were collected for formoterol in this study. However, urine data show a similar trend as that shown in the previous studies.

Variability was large in this studies with %CV ranging from approximately 50% to 140% following all treatments. Regardless of the variability, the trend at each treatment arm was consistent and producing a clear separation for overall mean.

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## 5.0 Study # 723 (Dosage Strength Equivalency/Dose Proportionality Study)

### Objective:

To investigate the PK dose proportionality of budesonide and the relative systemic bioavailability of formoterol when administered via three different formulation strengths of Symbicort pressurized metered dose inhaler (pMDI).

### Design:

- Three-way crossover, single dose
- n= 28 healthy subjects

### Treatments:

- Symbicort pMDI: 40/4.5 mcg x 12 inhalations = **480/54** mcg (single dose).
- Symbicort pMDI: 80/4.5 mcg x 12 inhalations = **960/54** mcg (single dose).
- Symbicort pMDI: 160/4.5 mcg x 12 inhalations = **1920/54** mcg (single dose).

### Results:

- There was clear dose/strength separation of budesonide for all treatments (**Table 5.1 and Figure 5.1**). However, normalizing the PK parameters (C<sub>max</sub> and AUC) for the given dose at each treatment the criteria for dose proportionality do not meet and deviate by approximately 10% to 15% for C<sub>max</sub> and AUC (**Tables 5.2 and 5.3**).
- In terms of dosage strengths equivalency, the data shows that the three dosage strengths are comparable with 90% CI limit within 80% to 125% for most of the PK parameters, but not all (**Table 5.2**).
- As expected, the plasma concentration time profiles for formoterol were superimposed for all treatments (**Figure 5.2**). Also, there was no change in PK parameters at all treatments (**Tables 5.4 and 5.5**). In addition, the normalized ratios for all treatments were within 80 to 125%.

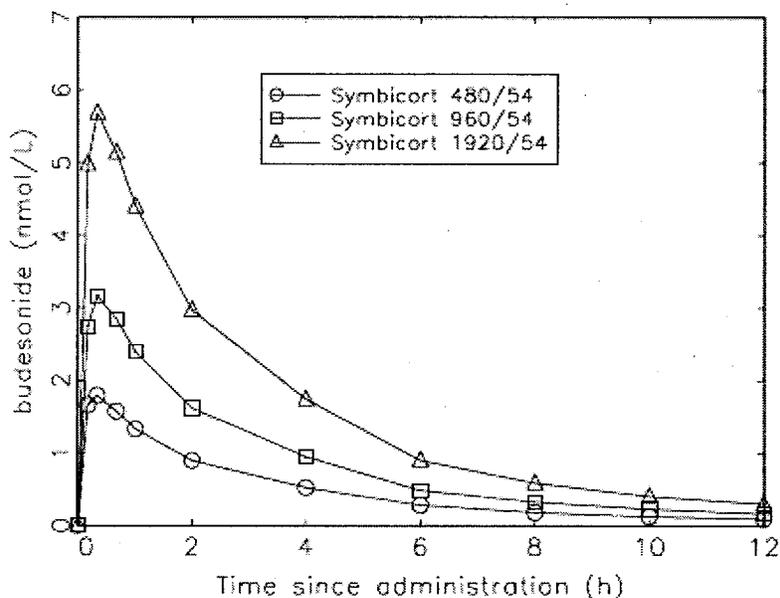
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**Table 5.1. Adjusted Means of PK Parameters of Budesonide AUC (Study # 723)**

| Parameter                     | Symbicort 480/54  |                | Symbicort 960/54  |                | Symbicort 1920/54 |                |
|-------------------------------|-------------------|----------------|-------------------|----------------|-------------------|----------------|
|                               | Mean <sup>1</sup> | 90% conf. lim. | Mean <sup>1</sup> | 90% conf. lim. | Mean <sup>1</sup> | 90% conf. lim. |
| AUC (nmol*h/L)                | 6.0               | (5.8, 6.3)     | 10.8              | (10.3, 11.3)   | 19.6              | (18.7, 20.5)   |
| AUC <sub>0-t</sub> (nmol*h/L) | 5.6               | (5.4, 5.8)     | 10.0              | (9.6, 10.4)    | 18.0              | (17.2, 18.8)   |
| C <sub>max</sub> (nmol/L)     | 1.8               | (1.7, 1.9)     | 3.2               | (3.0, 3.4)     | 5.4               | (5.0, 5.8)     |
| t <sub>1/2</sub> (h)          | 3.6               | (3.3, 3.8)     | 3.6               | (3.4, 3.8)     | 3.7               | (3.5, 4.0)     |
| MRT (h)                       | 4.2               | (4.0, 4.3)     | 4.2               | (4.1, 4.4)     | 4.3               | (4.2, 4.5)     |

<sup>1</sup> Arithmetic mean for MRT, geometric means for other parameters

**Figure 5.1. Mean Plasma Concentration-Time Profiles for Budesonide (Study # 723)**



**Table 5.2. Mean PK Parameters of Budesonide (Study # 723)**

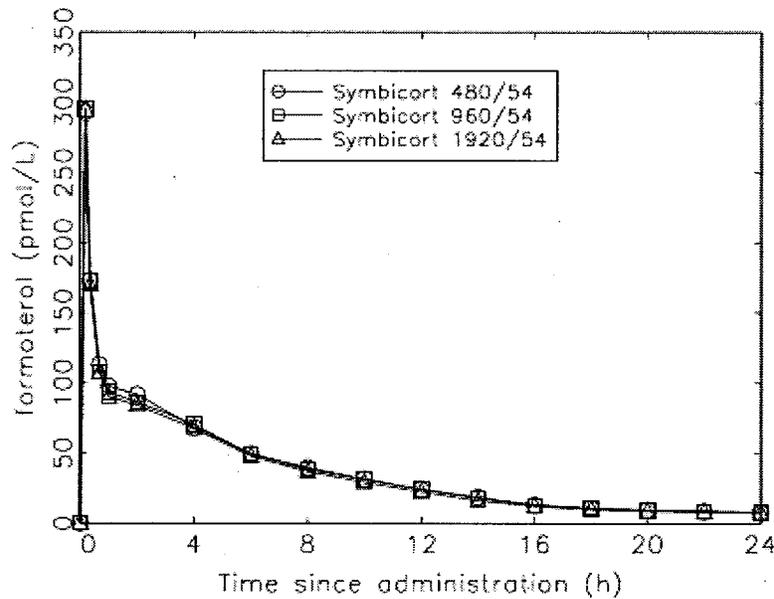
| Parameter                            | Symbicort 960/54 vs. Symbicort 480/54 |                | Symbicort 1920/54 vs. Symbicort 480/54 |                | Symbicort 1920/54 vs. Symbicort 960/54 |                |
|--------------------------------------|---------------------------------------|----------------|--|----------------|--|----------------|
|                                      | Ratio <sup>1</sup>                    | 90% conf. lim. | Ratio <sup>1</sup>                     | 90% conf. lim. | Ratio <sup>1</sup>                     | 90% conf. lim. |
| Dose-adjusted AUC (%)                | 89.6                                  | (84.2, 95.3)   | 81.2                                   | (76.3, 86.4)   | 90.7                                   | (85.2, 96.5)   |
| Dose-adjusted AUC <sub>0-t</sub> (%) | 89.2                                  | (83.9, 94.8)   | 80.5                                   | (75.6, 85.6)   | 90.2                                   | (84.8, 96.0)   |
| Dose-adjusted C <sub>max</sub> (%)   | 89.7                                  | (81.6, 98.6)   | 76.2                                   | (69.2, 83.9)   | 85.0                                   | (77.2, 93.5)   |
| t <sub>1/2</sub> (%)                 | 100.5                                 | (91.4, 110.4)  | 104.3                                  | (94.8, 114.8)  | 103.8                                  | (94.4, 114.3)  |
| MRT (h)                              | 0.08                                  | (-0.14, 0.30)  | 0.18                                   | (-0.04, 0.40)  | 0.10                                   | (-0.12, 0.32)  |

<sup>1</sup> Difference for MRT, ratio for AUC, AUC<sub>0-t</sub>, C<sub>max</sub>, and t<sub>1/2</sub>

**Table 5.3. Dose Proportionality Based on Budesonide AUC (Study # 723)**

| Parameter          | Mean | 95% conf. lim. |
|--------------------|------|----------------|
| Slope of covariate | 0.85 | (0.80, 0.90)   |

**Figure 5.2. Mean Plasma Concentration-Time Profiles for Formoterol (Study # 723)**



**Table 5.4. Mean PK Parameters of Formoterol (Study # 723)**

| Parameter              | Symbicort 960/54 vs. Symbicort 480/54 |                | Symbicort 1920/54 vs. Symbicort 480/54 |                | Symbicort 1920/54 vs. Symbicort 960/54 |                |
|------------------------|---------------------------------------|----------------|--|----------------|--|----------------|
|                        | Ratio <sup>1</sup>                    | 90% conf. lim. | Ratio <sup>1</sup>                     | 90% conf. lim. | Ratio <sup>1</sup>                     | 90% conf. lim. |
| AUC (%)                | 99.1                                  | (93.2, 105.3)  | 96.3                                   | (90.6, 102.4)  | 97.2                                   | (91.4, 103.4)  |
| AUC <sub>0-t</sub> (%) | 97.8                                  | (92.5, 103.3)  | 93.3                                   | (88.2, 98.6)   | 95.4                                   | (90.2, 100.9)  |
| C <sub>max</sub> (%)   | 100.0                                 | (91.3, 109.6)  | 98.7                                   | (89.9, 108.3)  | 98.6                                   | (89.9, 108.2)  |
| t <sub>1/2</sub> (%)   | 110.1                                 | (93.3, 129.9)  | 116.6                                  | (98.6, 137.9)  | 105.9                                  | (89.5, 125.2)  |
| MRT (h)                | 0.57                                  | (-1.02, 2.16)  | 1.81                                   | (0.20, 3.42)   | 1.24                                   | (-0.37, 2.85)  |

<sup>1</sup> Difference for MRT, ratio for AUC, AUC<sub>0-t</sub>, C<sub>max</sub>, and t<sub>1/2</sub>

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**Table 5.5. Adjusted Mean PK Parameters of Formoterol (Study # 723)**

| Parameter                     | Symbicort 480/54  |                | Symbicort 960/54  |                | Symbicort 1920/54 |                |
|-------------------------------|-------------------|----------------|-------------------|----------------|-------------------|----------------|
|                               | Mean <sup>1</sup> | 90% conf. lim. | Mean <sup>1</sup> | 90% conf. lim. | Mean <sup>1</sup> | 90% conf. lim. |
| AUC (pmol*h/L)                | 944.3             | (904.5, 985.8) | 935.3             | (896.0, 976.5) | 909.5             | (870.1, 950.6) |
| AUC <sub>0-t</sub> (pmol*h/L) | 860.7             | (827.8, 894.9) | 841.6             | (809.4, 875.1) | 802.9             | (771.4, 835.7) |
| C <sub>max</sub> (pmol/L)     | 274.8             | (257.5, 293.2) | 274.9             | (257.6, 293.2) | 271.1             | (253.6, 289.8) |
| t <sub>1/2</sub> (h)          | 7.1               | (6.3, 8.0)     | 7.8               | (7.0, 8.8)     | 8.3               | (7.4, 9.4)     |
| MRT (h)                       | 9.0               | (7.9, 10.1)    | 9.6               | (8.4, 10.7)    | 10.8              | (9.6, 11.9)    |

<sup>1</sup> Arithmetic mean for MRT, geometric means for the other parameters

**Conclusions:**

The three dosage strengths are comparable for budesonide. There is a good dose/exposure separation for budesonide as described by C<sub>max</sub> and AUC. However, the criteria for dose proportionality have not met in this study as they were deviated by approximately 10% to 15%. In other words, the AUC and C<sub>max</sub> of budesonide are expected to be lower by approximately 10% to 15% as the dose of budesonide increases from 480 mcg to 1920 mcg as tested in this study.

As expected, formoterol plasma concentration-time profiles following the three dosage strengths were well superimposed.

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## 6.0 Study # 724 (Dose Proportionality of Symbicort pMDI)

### Objectives:

The primary objective of this study was to investigate the PK dose proportionality of budesonide and formoterol when inhaled from Symbicort pMDI. The secondary objective was to investigate the relationship between single dose and repeated dose PK of budesonide and formoterol when inhaled from Symbicort pMDI.

### Study Design:

This was three-way crossover study in which 26 healthy subjects as follows:

**Treatment A (Multiple Dose):** Symbicort pMDI (160/4.5 mcg) x 2 actuations (320/9 mcg) BID x 5 days = **640/18 mcg** daily dose

**Treatment B (Multiple Dose):** Symbicort pMDI (160/4.5 mcg) x 4 actuations = 640/18 mcg per dose BID x 5 days = **1280/36 mcg** daily dose

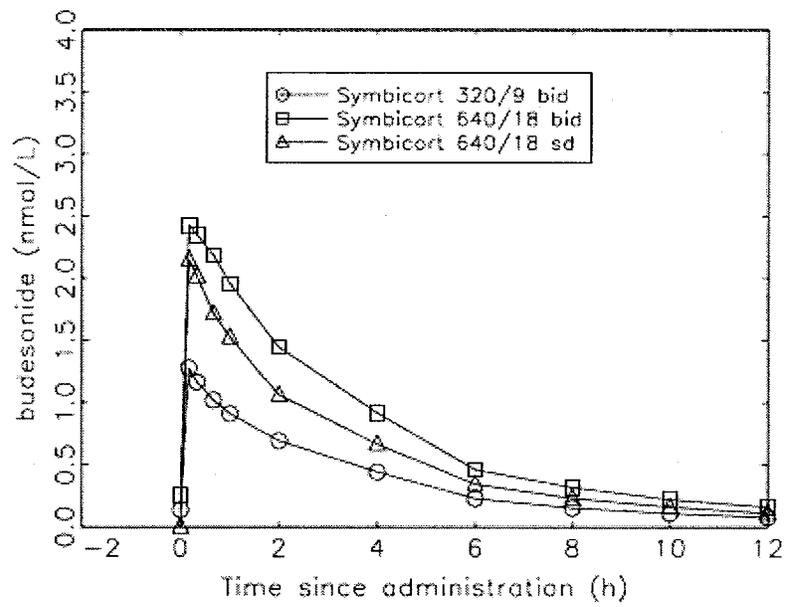
**Treatment C (Single Dose):** Symbicort pMDI (160/4.5 mcg) x 4 actuations = **640/18 mcg** as a single dose

### Results:

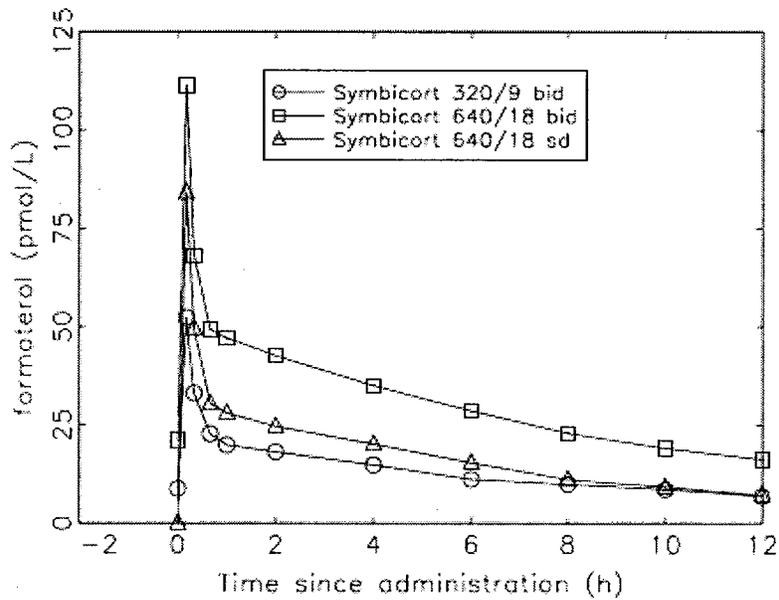
- The plasma concentration-time profiles show that the exposure to both budesonide and formoterol is doubled by doubling the dose, a characteristic of dose-proportionality (**Figures 6.1 and 6.2**).
- The dose normalized C<sub>max</sub> and AUC as well other derived statistical analysis such as the ratio and the 90% CI confirm that budesonide and formoterol exposure is dose proportional within the tested dose limits (**Tables 6.1-6**).
- The exposure to budesonide and formoterol was approximately 20% and 40% higher after 5 days BID administration than a single dose administration, respectively. The accumulation ratios were 132 % and 177% for budesonide and formoterol (**Table 6.6**).

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**Figure 6.1. Mean Budesonide Plasma concentration-Time Profiles (Study # 724)**



**Figure 6.2. Mean Formoterol Plasma concentration-Time Profiles (Study # 724)**



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**Table 6.1. Mean Budesonide PK Parameters (Study # 724)**

| Parameter                      | Symbicort 320/9 bid <sup>3</sup> |                | Symbicort 640/18 bid <sup>3</sup> |                | Symbicort 640/18 sd <sup>3</sup> |                |
|--------------------------------|----------------------------------|----------------|-----------------------------------|----------------|----------------------------------|----------------|
|                                | Mean <sup>1</sup>                | 90% conf. lim. | Mean <sup>1</sup>                 | 90% conf. lim. | Mean <sup>1</sup>                | 90% conf. lim. |
| AUC <sup>2</sup><br>(nmol*h/L) | 4.2                              | (4.0, 4.5)     | 8.8                               | (8.3, 9.3)     | 7.3                              | (6.9, 7.7)     |
| C <sub>max</sub> (nmol/L)      | 1.2                              | (1.1, 1.3)     | 2.4                               | (2.2, 2.6)     | 2.1                              | (1.9, 2.3)     |
| t <sub>1/2</sub> (h)           | 4.0                              | (3.8, 4.3)     | 3.8                               | (3.5, 4.0)     | 3.7                              | (3.5, 4.0)     |
| MRT (h)                        | 4.8                              | (4.6, 5.0)     | 4.6                               | (4.4, 4.8)     | 4.5                              | (4.3, 4.6)     |

<sup>1</sup> Arithmetic mean for MRT, geometric means for other parameters  
<sup>2</sup> 0-12 h for bid dosing, 0-∞ for single dose  
<sup>3</sup> bid - twice daily, sd - single dose

**Table 6.2. Statistical Analysis of Budesonide PK Parameters (Study # 724)**

| Parameter                          | Symbicort 640/18 bid vs.<br>Symbicort 320/9 bid** |                | Symbicort 640/18 bid vs.<br>Symbicort 640/18 sd** |                |
|------------------------------------|---|----------------|---|----------------|
|                                    | Ratio <sup>1</sup>                                | 90% conf. lim. | Ratio <sup>1</sup>                                | 90% conf. lim. |
| dose adjusted AUC* (%)             | 104.3   | (96.6, 112.6)  | 121.2   | (112.2, 130.8) |
| dose adjusted C <sub>max</sub> (%) | 100.4   | (90.0, 112.0)  | 115.6   | (103.6, 128.9) |
| t <sub>1/2</sub> (%)               | 93.6  | (85.5, 102.4)  | 100.9   | (92.2, 110.4)  |
| MRT (h)                            | -0.22   | (-0.46, 0.02)  | 0.14  | (-0.10, 0.38)  |

<sup>1</sup> Difference for MRT, ratio for AUC, C<sub>max</sub> and t<sub>1/2</sub>  
\* 0-12 h for bid dosing, 0-∞ for single dose  
\*\* bid - twice daily, sd - single dose

**Table 6.3. Mean Formoterol PK Parameters (Study # 724)**

| Parameter                      | Symbicort 320/9 bid <sup>3</sup> |                | Symbicort 640/18 bid <sup>3</sup> |                | Symbicort 640/18 sd <sup>3</sup> |                |
|--------------------------------|----------------------------------|----------------|-----------------------------------|----------------|----------------------------------|----------------|
|                                | Mean <sup>1</sup>                | 90% conf. lim. | Mean <sup>1</sup>                 | 90% conf. lim. | Mean <sup>1</sup>                | 90% conf. lim. |
| AUC <sup>2</sup><br>(pmol*h/L) | 151.7                            | (145.2, 158.4) | 356.7                             | (341.4, 372.6) | 256.4                            | (245.4, 267.8) |
| C <sub>max</sub> (pmol/L)      | 47.7                             | (44.5, 51.1)   | 104.6                             | (97.6, 112.1)  | 77.0                             | (71.8, 82.5)   |
| t <sub>1/2</sub> (h)           | 6.9                              | (6.3, 7.7)     | 7.0                               | (6.3, 7.7)     | 5.3                              | (4.8, 5.8)     |
| MRT (h)                        | 10.4                             | (9.5, 11.3)    | 10.3                              | (9.4, 11.3)    | 7.8                              | (6.9, 8.7)     |

<sup>1</sup> Arithmetic mean for MRT, geometric means for other parameters  
<sup>2</sup> 0-12 h for bid dosing, 0-∞ for single dose  
\*\* bid - twice daily, sd - single dose

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**Table 6.4. Statistical Analysis of Formoterol PK Parameters (Study # 724)**

| Parameter                          | Symbicort 640/18 bid vs.<br>Symbicort 320/9 bid** |                | Symbicort 640/18 bid vs.<br>Symbicort 640/18 sd** |                |
|------------------------------------|---|----------------|---|----------------|
|                                    | Ratio <sup>1</sup>                                | 90% conf. lim. | Ratio <sup>1</sup>                                | 90% conf. lim. |
| dose adjusted AUC* (%)             | 117.6   | (110.5, 125.1) | 139.1   | (130.8, 148.0) |
| dose adjusted C <sub>max</sub> (%) | 109.7   | (99.4, 121.0)  | 135.8   | (123.1, 149.8) |
| t <sub>1/2</sub> (%)               | 100.0   | (87.0, 115.0)  | 131.2   | (114.2, 150.8) |
| MRT (h)                            | -0.08   | (-1.38, 1.22)  | 2.55  | (1.25, 3.85)   |

<sup>1</sup> Difference for MRT, ratio for AUC, C<sub>max</sub> and t<sub>1/2</sub>  
\* 0-12 h for bid dosing, 0-∞ for single dose  
\*\* bid - twice daily, sd - single dose

**Table. 6.5 Dose Adjusted AUC**

| Drug component        | Symbicort 640/18 bid |                | Symbicort 640/18 sd |                |
|-----------------------|----------------------|----------------|---------------------|----------------|
|                       | Mean <sup>1</sup>    | 90% conf. lim. | Mean <sup>1</sup>   | 90% conf. lim. |
| Budesonide (nmol*h/L) | 8.8                  | (8.3, 9.3)     | 6.7                 | (6.3, 7.0)     |
| Formoterol (pmol*h/L) | 356.6                | (339.8, 374.2) | 201.0               | (191.5, 211.0) |

1. <sup>1</sup> Geometric means

**Table. 6.6. Accumulation Ratio (R<sub>ac</sub>) Based on AUC (Study # 724)**

| Drug component | Symbicort 640/18 bid vs.<br>Symbicort 640/18 sd |                |
|----------------|---|----------------|
|                | R <sub>ac</sub>                                 | 90% conf. lim. |
| Budesonide (%) | 132.3   | (122.7, 142.7) |
| Formoterol (%) | 177.4   | (165.7, 190.0) |

**Reviewer’s Comments**

This study demonstrates dose proportionality in exposure for budesonide and formoterol when administered as Symbicort pMDI. Like other studies, there was high variability in the data for both budesonide and formoterol. The doses tested in this study are within the proposed doses in the labeling.

**Conclusions:**

Based on this study it can be concluded that the exposure to budesonide and formoterol is proportional to dose.

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## 7.0 Study # 722 (PK interaction of Budesonide and Formoterol)

### Objective:

To investigate the pharmacokinetic interaction between budesonide and formoterol when administered simultaneously as budesonide pMDI and Oxis Turbuhaler compared with each product alone.

### Design:

This was a single dose three-way crossover study in 27 healthy subjects as follows:

**Treatment A** (Budesonide pMDI): Budesonide 160 mcg x 8 actuations= 1280 mcg

**Treatment B** (Oxis Turbuhaler): Formoterol 4.5 mcg x 8 inhalations = 36 mcg

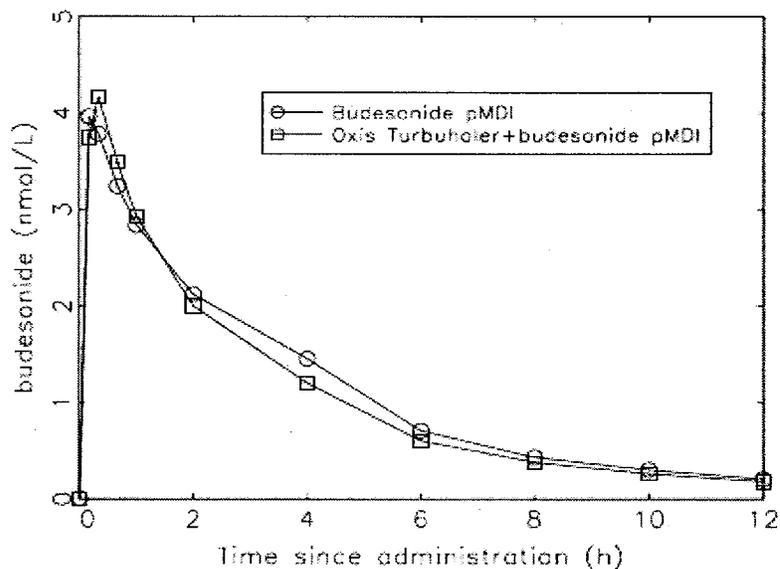
**Treatment C** (Combination):

- Oxis Turbuhaler): Formoterol 4.5 mcg x 8 inhalation = 1280 mcg single dose  
**PLUS**
- Budesonide pMDI: Budesonide 160 mcg x 8 actuation= 36 mcg single dose

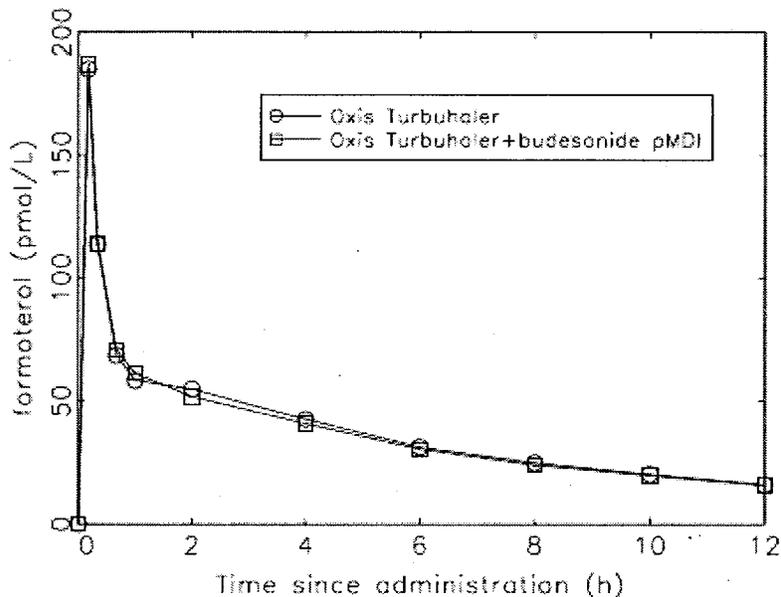
### Results:

- The plasma concentration-time profiles for both budesonide and formoterol are superimposed following corresponding treatments (**Figures 7.1 and 7.2**).
- There were no major noticeable changes in any of the PK parameter for either budesonide or formoterol in any of the treatments (**Tables 7.1-7.4**). The comparative ratios for the corresponding treatments for C<sub>max</sub> and AUC were close to unity (1.00) and the 90% CI was within 80 to 1025%.

7.1 Figure 1. Mean Budesonide Plasma Concentration-Time Profiles (Study # 722)



**7.2 Figure 1. Mean Formoterol Plasma Concentration-Time Profiles (Study # 722)**



**Table 7.1. Mean Budesonide PK Parameters (Study # 722)**

| Parameter                     | budesonide pMDI   |                      | Oxis Turbuhaler + budesonide pMDI |                      |
|-------------------------------|-------------------|----------------------|-----------------------------------|----------------------|
|                               | Mean <sup>1</sup> | 90% confidence limit | Mean <sup>1</sup>                 | 90% confidence limit |
| AUC (nmol*h/L)                | 13.9              | (13.2, 14.6)         | 13.0                              | (12.4, 13.7)         |
| AUC <sub>0-t</sub> (nmol*h/L) | 12.9              | (12.2, 13.5)         | 12.1                              | (11.5, 12.7)         |
| C <sub>max</sub> (nmol/L)     | 3.8               | (3.5, 4.1)           | 4.0                               | (3.6, 4.3)           |
| t <sub>1/2</sub> (h)          | 3.4               | (3.2, 3.7)           | 3.6                               | (3.3, 3.8)           |
| MRT (h)                       | 4.4               | (4.2, 4.5)           | 4.2                               | (4.0, 4.4)           |

<sup>1</sup> Arithmetic mean for MRT, geometric means for other parameters

**Table 7.2. Statistical Analysis of Budesonide PK Parameters (Study # 722)**

| Parameter                     | Oxis Turbuhaler + budesonide pMDI vs. budesonide pMDI |                      |
|-------------------------------|---|----------------------|
|                               | Ratio <sup>1</sup>                                    | 90% confidence limit |
| AUC (nmol*h/L)                | 93.8  | (87.5, 100.6)        |
| AUC <sub>0-t</sub> (nmol*h/L) | 93.9  | (87.5, 100.7)        |
| C <sub>max</sub> (nmol/L)     | 105.1   | (93.6, 117.9)        |
| t <sub>1/2</sub> (h)          | 104.3   | (95.1, 114.4)        |
| MRT (h)                       | -0.16   | (-0.42, 0.10)        |

<sup>1</sup> Difference for MRT, ratio in % for other parameters

**Table 7.3. Mean Formoterol PK Parameters (Study # 722)**

| Parameter                     | Oxis Turbuhaler   |                      | Oxis Turbuhaler + budesonide pMDI |                      |
|-------------------------------|-------------------|----------------------|-----------------------------------|----------------------|
|                               | Mean <sup>1</sup> | 90% confidence limit | Mean <sup>1</sup>                 | 90% confidence limit |
| AUC (pmol*h/L)                | 587.3             | (556.1, 620.3)       | 592.4                             | (561.0, 625.6)       |
| AUC <sub>0-1</sub> (pmol*h/L) | 447.4             | (430.8, 464.7)       | 432.1                             | (416.0, 448.7)       |
| C <sub>max</sub> (pmol/L)     | 180.5             | (170.7, 190.9)       | 178.9                             | (169.2, 189.1)       |
| t <sub>1/2</sub> (h)          | 5.9               | (5.2, 6.6)           | 6.5                               | (5.8, 7.2)           |
| MRT (h)                       | 8.3               | (6.6, 10.0)          | 9.9                               | (8.2, 11.6)          |

<sup>1</sup> Arithmetic mean for MRT, geometric means for other parameters

**Table 7.4. Statistical Analysis of Formoterol PK Parameters (Study # 722)**

| Parameter                     | Oxis Turbuhaler + budesonide pMDI vs. Oxis Turbuhaler |                      |
|-------------------------------|---|----------------------|
|                               | Ratio <sup>1</sup>                                    | 90% confidence limit |
| AUC (pmol*h/L)                | 100.9   | (93.4, 109.0)        |
| AUC <sub>0-1</sub> (pmol*h/L) | 96.6  | (91.5, 101.9)        |
| C <sub>max</sub> (pmol/L)     | 99.1  | (91.6, 107.2)        |
| t <sub>1/2</sub> (h)          | 109.6   | (93.0, 129.1)        |
| MRT (h)                       | 1.64  | (-0.76, 4.03)        |

<sup>1</sup> Difference for MRT, ratio in % for other parameters

**Conclusions:**

Based on this study it can be concluded that there was no evidence of PK interaction between budesonide and formoterol.

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## B) Multiple Dose/Steady State Studies

### 8.0 Study # D5896C00011 (Steady State PK of Symbicort pMDI)

#### Objectives:

The primary objective was to determine the steady-state (PK) of budesonide and formoterol after Symbicort pMDI in asthmatic and healthy subjects.

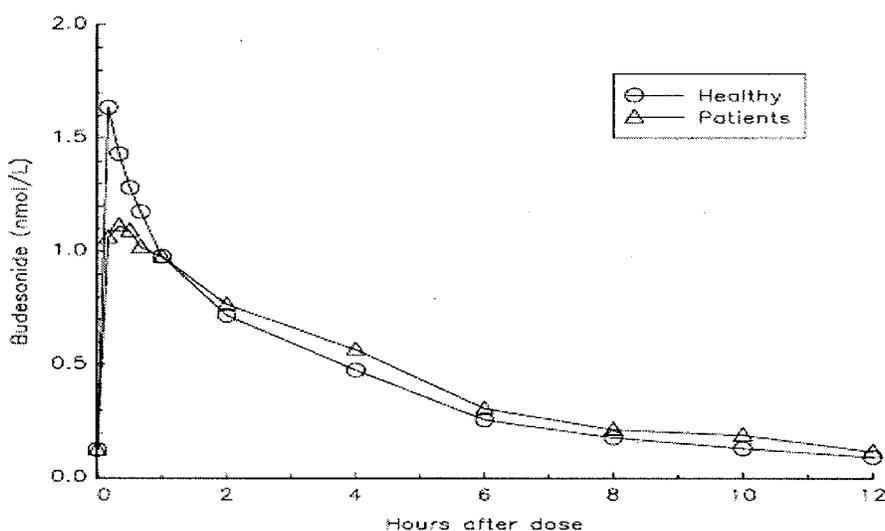
#### Study Design:

- Parallel-group and repeated dose study in adult asthmatic patients (n=26) and adult healthy subjects (n=26)
- Dose: 160/4.6 mcg x 2 actuations of Symbicort pMDI BID for 7 days
- Blood was collected for PK analysis over 12 hours on the 7th day

#### Results:

- Overall, the C<sub>max</sub> for budesonide and formoterol were approximately 30% to 50% lower in asthmatic patients than in healthy subjects (**Figures 8.1 and 2 and Tables 8.1 and 2**). However, the AUCs appear to be comparable in both groups. These observations are consistent with other studies.
- The relative bioavailability (patients vs healthy) for budesonide and formoterol was close to 100% (106% and 95%, **Table 8.1 and 8.2**). These observations are also consistent with other studies.

**Figure 8.1. Mean Budesonide Plasma Concentration-Time Profiles (Study # D5896C00011)**



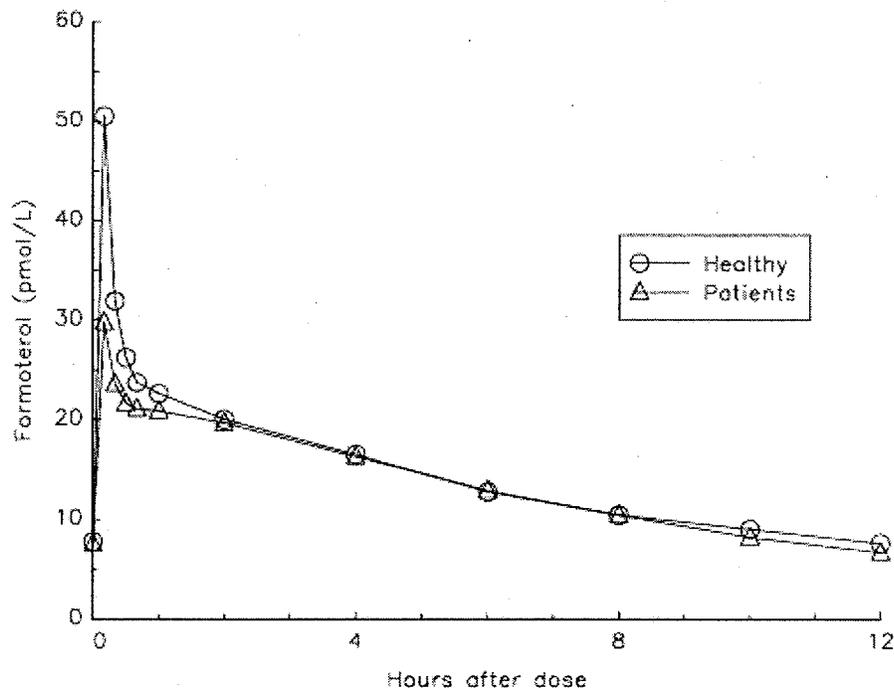
**Table 8.1. Mean Budesonide PK Parameters (Study # D5896C00011)**

| Parameter                           | Healthy |                  | Patients |                  | Patients vs. Healthy <sup>2</sup> |                  |
|-------------------------------------|---------|------------------|----------|------------------|-----------------------------------|------------------|
|                                     | Mean    | 90%<br>conf.lim. | Mean     | 90%<br>conf.lim. | Mean                              | 90%<br>conf.lim. |
| AUC <sub>0-12h</sub><br>(nmol/L·h)  | 4.63    | 4.09 - 5.25      | 4.91     | 4.33 - 5.56      | 106                               | 89 - 126         |
| MRT (h)                             | 4.76    | 4.35 - 5.17      | 5.48     | 5.07 - 5.89      | 0.72                              | 0.14 - 1.30      |
| t <sub>1/2</sub> (h)                | 3.86    | 3.49 - 4.27      | 3.73     | 3.38 - 4.13      | 97                                | 84 - 111         |
| t <sub>max</sub> (min) <sup>1</sup> | 10      | 10 - 60          | 21       | 10 - 60          |                                   |                  |
| C <sub>max</sub> (nmol/L)           | 1.58    | 1.37 - 1.82      | 1.15     | 1.00 - 1.32      | 73                                | 59 - 89          |
| AUC <sub>0-6h</sub><br>(nmol/L·h)   | 3.72    | 3.27 - 4.24      | 3.73     | 3.28 - 4.25      | 100                               | 83 - 121         |

1 Median and range.

2 Ratios (%) for AUC<sub>0-12h</sub>, C<sub>max</sub>, and t<sub>1/2</sub>, and difference for MRT.

**Figure 8.2. Mean Formeterol Plasma Concentration-Time Profiles (Study # D5896C00011)**



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**Table 8.2. Mean Formoterol PK Parameters (Study # D5896C00011)**

| Parameter                           | Healthy |                  | Patients |                  | Patients vs. Healthy <sup>2</sup> |                  |
|-------------------------------------|---------|------------------|----------|------------------|-----------------------------------|------------------|
|                                     | Mean    | 90%<br>conf.lim. | Mean     | 90%<br>conf.lim. | Mean                              | 90%<br>conf.lim. |
| AUC <sub>0-12h</sub><br>(pmol/L·h)  | 167     | 151 - 184        | 158      | 143 - 175        | 95                                | 82 - 110         |
| MRT (h)                             | 9.65    | 8.54 - 10.76     | 10.97    | 9.86 - 12.09     | 1.32                              | -0.25 - 2.90     |
| t <sub>1/2</sub> (h)                | 6.48    | 5.84 - 7.20      | 6.82     | 6.14 - 7.57      | 105                               | 91 - 122         |
| t <sub>max</sub> (min) <sup>1</sup> | 10      | 10 - 14          | 10       | 9 - 120          |                                   |                  |
| C <sub>max</sub> (pmol/L)           | 48      | 42 - 55          | 28       | 24 - 32          | 58                                | 48 - 70          |
| AUC <sub>0-6h</sub><br>(pmol/L·h)   | 111     | 100 - 123        | 102      | 92 - 113         | 92                                | 80 - 106         |

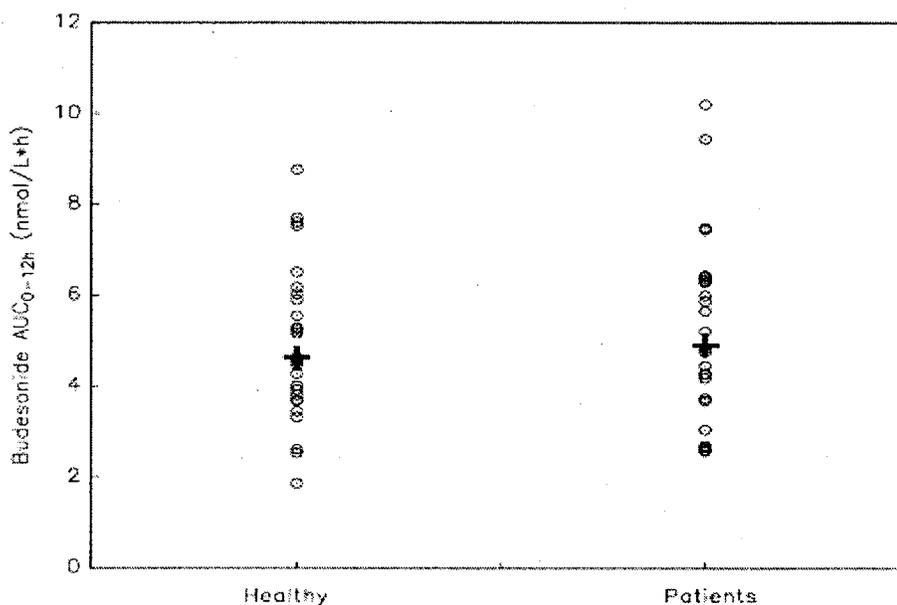
1 Median and range.

2 Ratios (%) for AUC<sub>0-12h</sub>, C<sub>max</sub>, and t<sub>1/2</sub>, and difference for MRT.

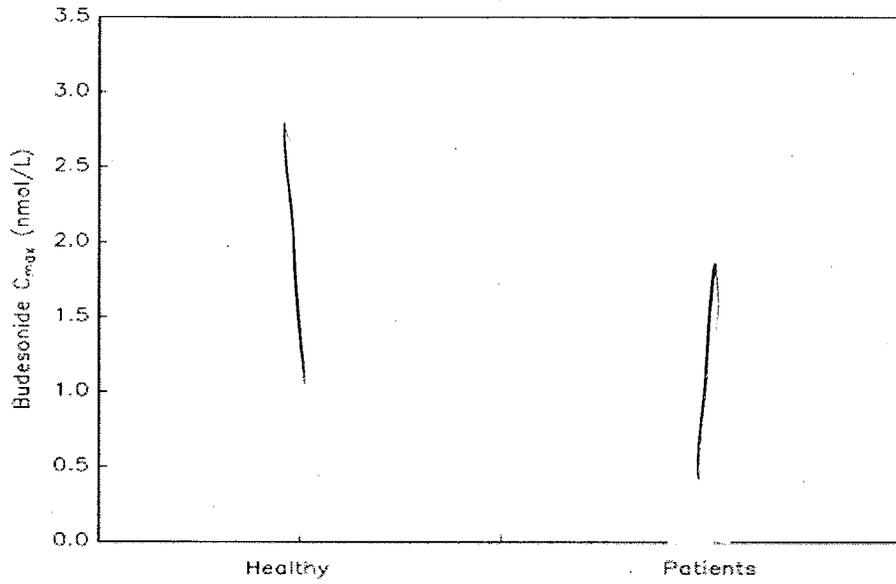
**Reviewer's Comments:**

The variability in the data was somewhat similar between asthmatic and healthy subjects for both budesonide and formoterol (Figures 8.3 to 8.6). Therefore, the observed low C<sub>max</sub> for both budesonide and formoterol in asthmatic patients compared to healthy subjects could be real. The reason (s) for this difference is unknown. These observations should be reflected in the label.

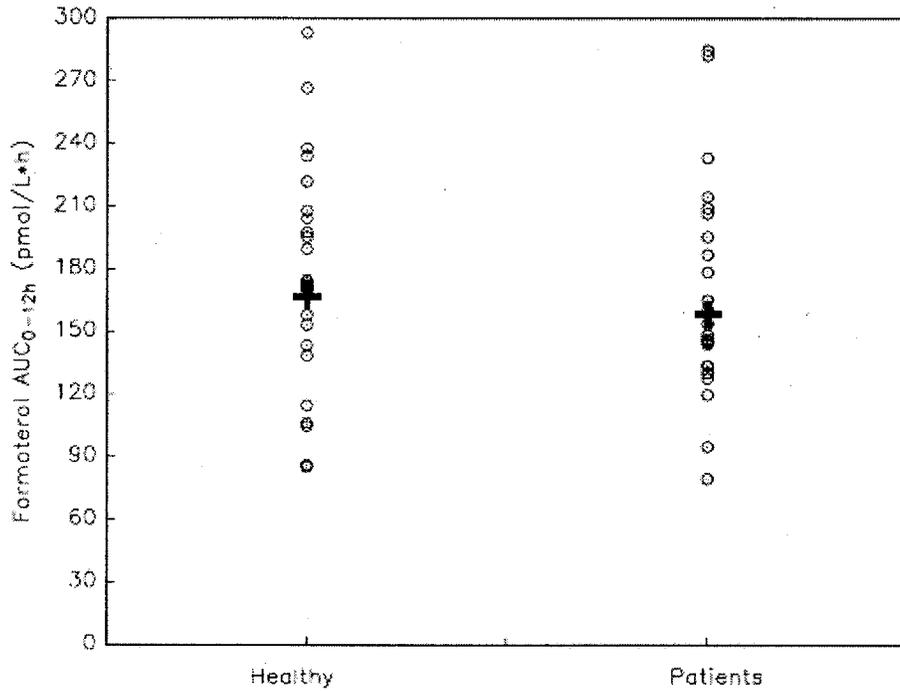
**Figure 8.3. Individual Budesonide AUC (Study # D5896C00011)**



**Figure 8.4. Individual Budesonide C<sub>max</sub> (Study # D5896C00011)**

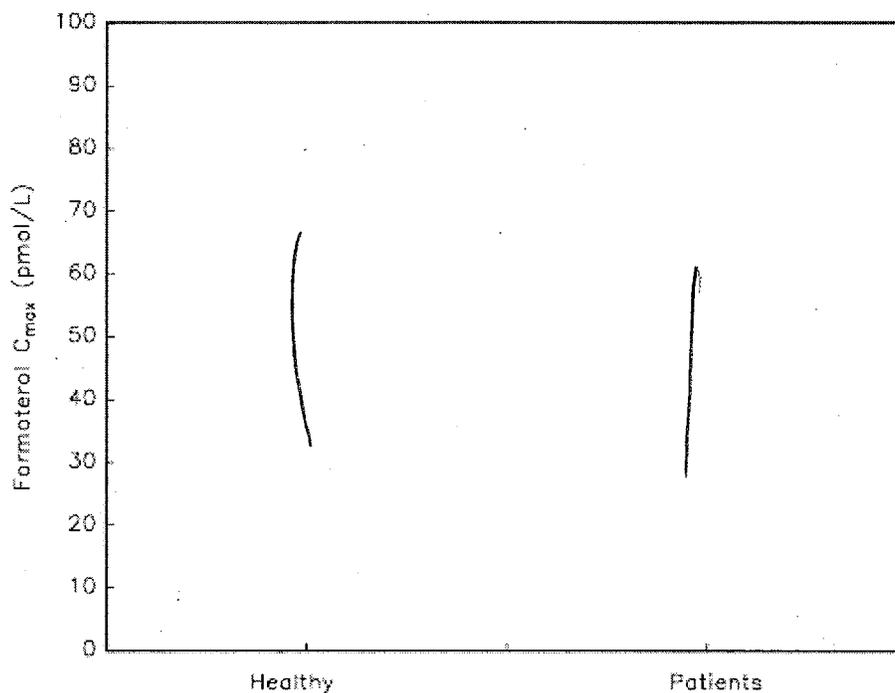


**Figure 8.5. Individual Formoterol AUC (Study # D5896C00011)**



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**Figure 8.6. Individual Formoterol C<sub>max</sub> (Study # D5896C00011)**



**Conclusions:**

The bioavailability of both budesonide and fomoterol in asthmatic patients relative to healthy subjects is comparable following Symbicort pMDI. However, the C<sub>max</sub> for both budesonide and formoterol is approximately 30% to 50% lower in asthmatic patients compared to healthy subjects. The data in reference to low C<sub>max</sub> should be reflected in the labeling.

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## 9.0 Study # 718 (Steady State in Pediatric and Adolescent Asthmatic Patients)

### Objective:

To compare efficacy and safety of Sybmicort pMDI with its monoproducts, budesonide and formoterol, in children aged 6 through 15 years with mild to moderate asthma.

### Design:

This was 12-week, double-blind, double-dummy, active-controlled trial in asthmatic patients 6 to 15 years of age.

### Treatments:

- Symbicort pMDI (40/4.5 mcg) x 2 actuations BID = 80/9 mcg per dose = 160/18 mcg daily dose
- Budesonide pMDI (40 mcg) x 2 actuations BID = 80/9 mcg per dose = 160/18 mcg daily dose
- Formoterol TBH (4.5 mcg) x 2 inhalations BID = 9 mcg per dose = 18 mcg daily dose

A limited number of blood samples for PK analysis were collected over 6 hours period after two weeks of treatment from a subset of approximately 16 patients in each treatment arm.

### Results:

- There was a considerable variability in the data as shown from the individual plasma concentration-time profiles for budesonide (**Figures 9.1 and 9.2**) and formoterol (**Figure 9.3 and 9.4**) following all treatments. Most of the variability occurs around the C<sub>max</sub> for either component.
- Overall, the systemic exposure to budesonide and formoterol was comparable following all treatments.

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**Table 9.1. Mean PK Parameters of Budesonide (Study # 718)**

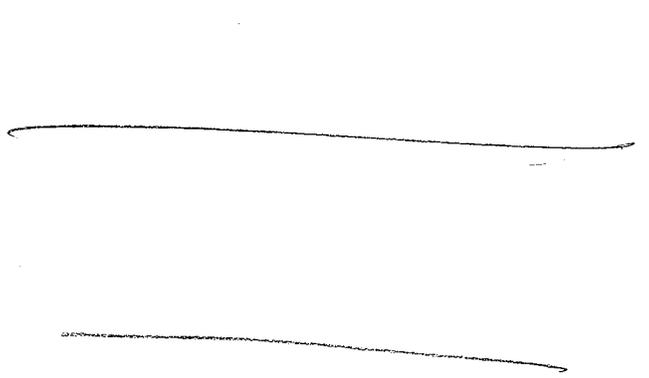
| Parameter                        | Treatment <sup>a</sup> |                      |       |                      | SYMB vs Budes |                |         |
|----------------------------------|------------------------|----------------------|-------|----------------------|---------------|----------------|---------|
|                                  | SYMB                   |                      | Budes |                      | Ratio         | 90% CI         | p-value |
|                                  | n                      | LS mean <sup>b</sup> | n     | LS mean <sup>b</sup> |               |                |         |
| AUC <sub>0-6</sub><br>(nmol·h/L) | 16                     | 0.968                | 14    | 1.096                | 0.883         | (0.680, 1.146) | 0.425   |
| C <sub>max</sub><br>(nmol/L)     | 16                     | 0.314                | 16    | 0.350                | 0.896         | (0.603, 1.332) | 0.642   |

<sup>a</sup> SYMB 40/4.5 µg per actuation ×2 actuations bid, Budes budesonide 40 µg per actuation ×2 actuations bid.

<sup>b</sup> Geometric least-squares mean.

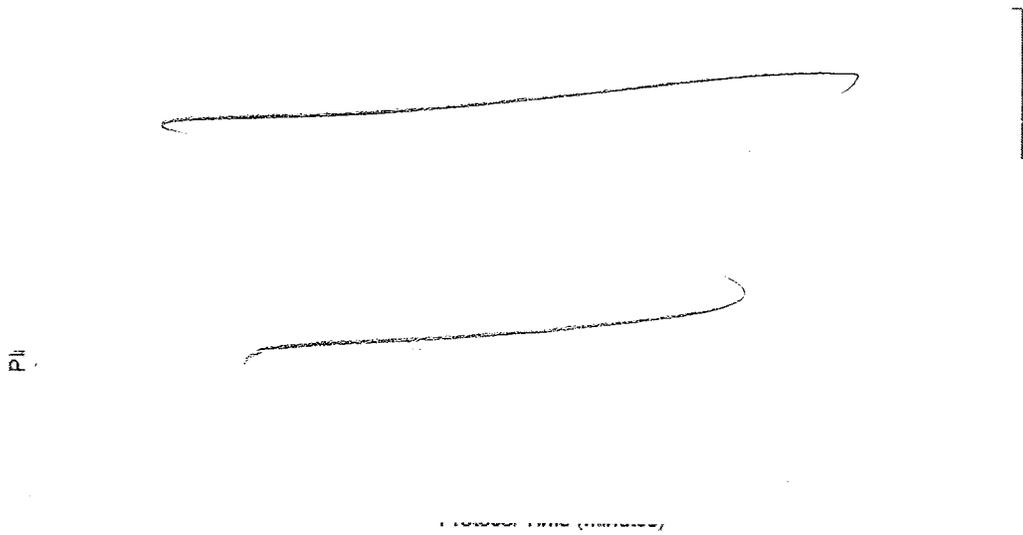
AUC<sub>0-6</sub> area under the curve from time 0 to 6 hours, C<sub>max</sub> maximum (peak) plasma drug concentration, PK-PP analysis set Pharmacokinetics per protocol analysis set.

**Figure 9.3. Individual Formetrol Plasma Concentrations-Time Profiles Following Symbicort pMDI (Study # 718)**



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**Figure 9.4. Individual Formetrol Plasma Concentrations-Time Profiles Following Formoterol (Study # 718)**



**Table 9.2. Mean PK Parameters of Formetrol (Study # 718)**

| Parameter                        | Treatment <sup>a</sup> |                      |    |                      | SYMB vs Form |                |         |
|----------------------------------|------------------------|----------------------|----|----------------------|--------------|----------------|---------|
|                                  | n                      | LS mean <sup>b</sup> | n  | LS mean <sup>b</sup> | Ratio        | 90% CI         | p-value |
| AUC <sub>0-6</sub><br>(pmol·h/L) | 16                     | 90.83                | 19 | 103.8                | 0.875        | (0.692, 1.107) | 0.344   |
| C <sub>max</sub><br>(pmol/L)     | 16                     | 21.14                | 20 | 34.59                | 0.611        | (0.466, 0.801) | 0.004   |

<sup>a</sup> SYMB 40/4.5 µg per actuation ×2 actuations bid, Form formoterol TBH 4.5 µg per actuation ×2 actuations bid.

<sup>b</sup> Geometric least-squares mean.

AUC<sub>0-6</sub> area under the curve from time 0 to 6 hours; C<sub>max</sub> maximum (peak) plasma drug concentration.  
PK-PP analysis set: Pharmacokinetics per protocol analysis set.

**Reviewer’s Comments:**

The data from this study is limited for two reasons. First there was a limited number of blood samples collected over 6 hours and second the Symbicort pMDI 40/4.5 mcg strength is not considered for marketing. No new information was provided in this study in relation to the PK characteristics than it is already known from other formal PK studies.

**Conclusions:**

In this group of children, the exposures to budesonide and formoterol appear to be comparable following the three treatment arms.

**10. Study # 719 (Symbicort pMDI 160/4.5 mcg vs Pulmicort TBH in 6 to 11 years old Asthmatics)**

**Design:**

This was a 26-week, open-label study with Symbicort pMDI and Pulmicort TBH in children 6 to <12 years of age with asthma.

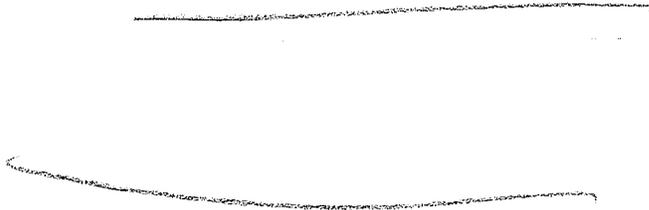
**Treatments:**

- Symbicort pMDI (160/4.5 mcg) x 2 actuations BID = 320/9 mcg per dose = 640/18 mcg daily dose
- Pulmicort TBH (200 mcg = 160 mcg budesonide per inhalation) x 2 inhalation BID = 320 mcg per dose = 640 mcg daily dose

**Results:**

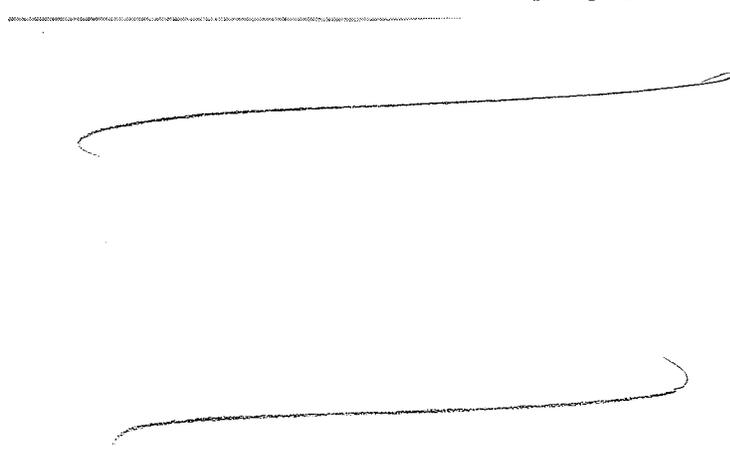
- Budesonide plasma concentration-time profiles following both treatments were comparable (**Figures 10.1 to 10.2**). The treatment ratios for budesonide for both C<sub>max</sub> and AUC were close to 1.00 (**Table 10.1**).
- The plasma concentration-time profiles for formoterol appears to be relatively flat/low in some subjects (**Figure 10.3**). The reason (s) for this low concentration is unknown.

**Figure 10.1. Individual Budesonide Plasma Concentrations-Time Profiles Following Symbicort pMDI (Study # 719)**



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**Figure 10.2. Individual Budesonide Plasma Concentrations-Time Profiles Following Pulmicort TBH (Study # 719)**



**Table 10.1. Mean PK Parameters of Budesonide (Study # 719)**

| Parameter                        | Treatment <sup>a</sup> |                      |      |                      | Ratio | SYMB vs PULM   |         |
|----------------------------------|------------------------|----------------------|------|----------------------|-------|----------------|---------|
|                                  | SYMB                   |                      | PULM |                      |       | 90% CI         | p-value |
|                                  | n                      | LS mean <sup>b</sup> | n    | LS mean <sup>b</sup> |       |                |         |
| AUC <sub>0-6</sub><br>(nmol·h/L) | 6                      | 4.632                | 5    | 4.289                | 1.080 | (0.442, 2.641) | 0.878   |
| C <sub>max</sub><br>(nmol/L)     | 6                      | 1.920                | 5    | 2.009                | 0.956 | (0.368, 2.481) | 0.933   |

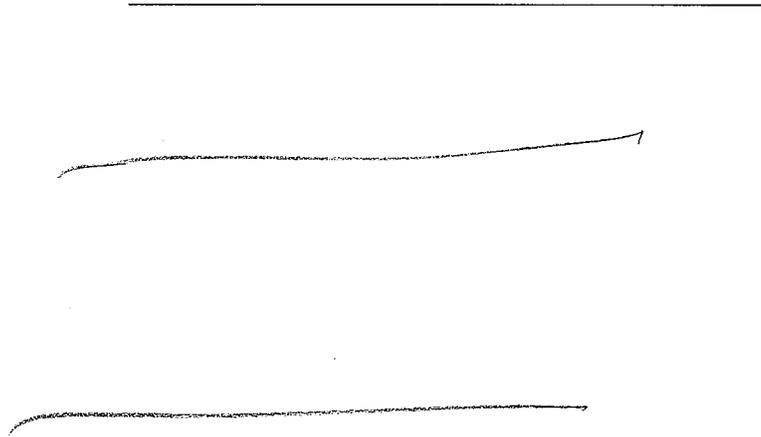
<sup>a</sup> SYMB SYMBICORT pMDI 160/4.5 µg per actuation ×2 actuations bid, PULM PULMICORT TBH 200 µg metered (approximately 160 µg delivered) per inhalation ×2 inhalations bid.

<sup>b</sup> Geometric least-squares mean.

AUC<sub>0-6</sub> area under the curve from time 0 to 6 hours, C<sub>max</sub> maximum (peak) plasma drug concentration.

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**Figure 10.3. Individual Formoterol Plasma Concentrations-Time Profiles Following Symbicort pMDI (Study # 719)**



**Conclusion:**

Although the data from this study is limited due to the small number of subjects (n=6) and blood samples, a conclusion can still be drawn to state that the exposure to budesonide is comparable between the two treatments.

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### C) Clinical/Phase 3 Studies Containing PK/PD Data:

#### 11.0 Study # 717 (12 Weeks Symbicort 160/4.5 mcg vs Mono-Products in >12 years of age and adults)

##### Objective:

The primary objective of this study is to compare the safety and efficacy of Symbicort pMDI.

##### Study Design:

- Double-blind, Placebo controlled in patients >12 years or older

##### Treatments:

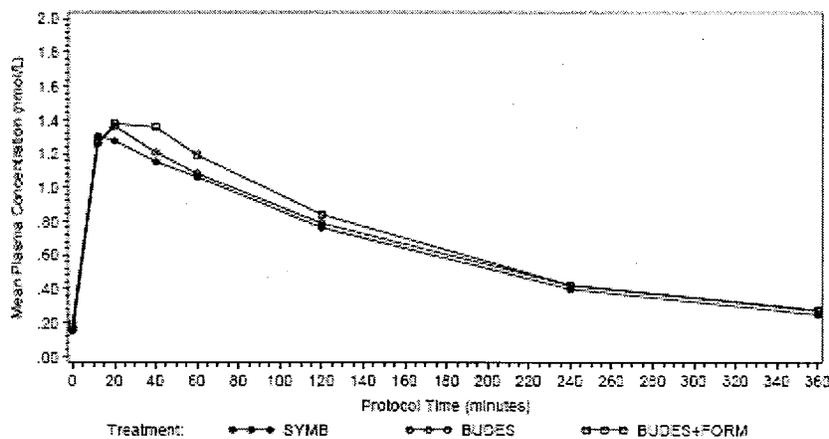
- Symbicort pMDI 160/4.5 mcg x 2 actuation BID
- Budesonide pMDI 160 mcg x 2 actuation BID
- Formoterol TBH 4.5 x 2 actuation BID
- Budesonide pMDI 160 mcg x 2 actuation BID + Formoterol TBH 4.5 x 2 actuation BID
- Placebo 2 actuation BID

In a small subset of patients (n=21-31) blood samples were collected over the first 6 hours on Week 2 (Visit 3). However, not all subjects have provided a complete sample set.

##### Results:

- The systemic exposure to budesonide and formoterol was comparable following Symbicort pMDI and mono-product, budesonide and formoterol (**Figure 11.1 and Tables 11.1 and 11.2**). The C<sub>max</sub> and AUC treatments ratio is close to 1 for each treatment (**Table 11.3**).

**Figure 11.1. Mean Budesonide Plasma Concentration-Time Profiles (Clinical Study # 717)**



**Table 11.1 Adjusted Mean Budesonide PK Parameters (Clinical Study # 717)**

| Parameter                     | SYMB <sup>a</sup> |                      | Budes <sup>a</sup> |         | Budes-form <sup>a</sup> |         |
|-------------------------------|-------------------|----------------------|--------------------|---------|-------------------------|---------|
|                               | n                 | LS mean <sup>b</sup> | n                  | LS mean | n                       | LS mean |
| AUC <sub>0-6</sub> (nmol·h/L) | 21                | 3.482                | 26                 | 3.645   | 31                      | 3.873   |
| C <sub>max</sub> (nmol/L)     | 21                | 1.311                | 26                 | 1.301   | 31                      | 1.369   |

<sup>a</sup> SYMB 160/4.5 µg per actuation x2 actuations bid; Budes budesonide 160 µg per actuation x2 actuations bid; Budes-Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

<sup>b</sup> Geometric least-squares mean.

AUC<sub>0-6</sub> area under the curve from time 0 to 6 hours, C<sub>max</sub> maximum (peak) plasma drug concentration.

**Table 11.2 Statistical Analysis of Formoterol PK Parameters (Clinical Study # 717)**

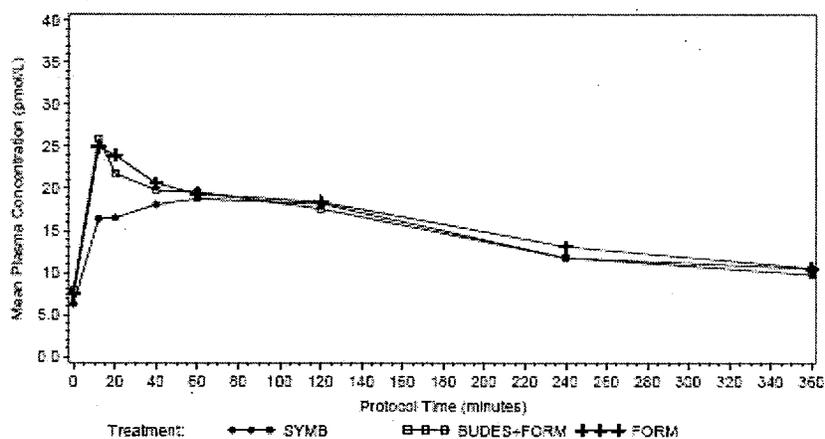
| Parameter                     | From ANCOVA                |              |         |                                 |              |         |
|-------------------------------|----------------------------|--------------|---------|---------------------------------|--------------|---------|
|                               | SYMB vs Budes <sup>a</sup> |              |         | SYMB vs Budes-form <sup>a</sup> |              |         |
|                               | Treatment ratio            | 90% CI       | p-value | Treatment ratio                 | 90% CI       | p-value |
| AUC <sub>0-6</sub> (nmol·h/L) | 0.955                      | 0.768, 1.187 | 0.725   | 0.899                           | 0.740, 1.092 | 0.364   |
| C <sub>max</sub> (nmol/L)     | 1.008                      | 0.773, 1.315 | 0.961   | 0.958                           | 0.774, 1.185 | 0.736   |

<sup>a</sup> SYMB 160/4.5 µg per actuation x2 actuations bid; Budes budesonide 160 µg per actuation x2 actuations bid; Budes-Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

AUC<sub>0-6</sub> area under the curve from time 0 to 6 hours, C<sub>max</sub> maximum (peak) plasma drug concentration.

- The systemic exposure to formoterol was slightly lower after Symbicort pMDI than mono product (Figure 6.3 and Tables 6.3 and 6.4). The treatment ratios for both C<sub>max</sub> and AUC appear to be close to 1 (Table 6.4).

**Figure 11.2. Mean Formoterol Plasma Concentration-Time Profiles (Clinical Study # 717)**



Treatments: SYMBICORT 160/4.5 µg per actuation x2 actuations bid; formoterol TBH 4.5 µg per inhalation x2 inhalations bid; budesonide pMDI 160 µg per actuation x 2 actuations plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

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**Table 11.3 Mean Formoterol PK Parameters (Clinical Study # 717)**

| Parameter                     | SYMB <sup>a</sup> |                      | Form <sup>a</sup> |         | Budes+form <sup>a</sup> |         |
|-------------------------------|-------------------|----------------------|-------------------|---------|-------------------------|---------|
|                               | n                 | LS mean <sup>b</sup> | n                 | LS mean | n                       | LS mean |
| AUC <sub>0-6</sub> (pmol·h/L) | 20                | 76.564               | 22                | 77.217  | 30                      | 80.919  |
| C <sub>max</sub> (pmol/L)     | 20                | 19.642               | 22                | 21.255  | 30                      | 24.681  |

<sup>a</sup> SYMB 160/4.5 µg per actuation x2 actuations bid, Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid, Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

<sup>b</sup> Geometric least-squares mean.

AUC<sub>0-6</sub> area under the curve from time 0 to 6 hours, C<sub>max</sub> maximum (peak) plasma drug concentration.

**Table 11.4 Statistical Analysis of Formoterol PK Parameters (Clinical Study # 717)**

| Parameter                     | From ANCOVA               |              |         |                                 |              |         |
|-------------------------------|---------------------------|--------------|---------|---------------------------------|--------------|---------|
|                               | SYMB vs Form <sup>a</sup> |              |         | SYMB vs Budes+form <sup>a</sup> |              |         |
|                               | Treatment ratio           | 90% CI       | p-value | Treatment ratio                 | 90% CI       | p-value |
| AUC <sub>0-6</sub> (pmol·h/L) | 0.992                     | 0.736, 1.337 | 0.962   | 0.946                           | 0.752, 1.190 | 0.683   |
| C <sub>max</sub> (pmol/L)     | 0.924                     | 0.671, 1.273 | 0.681   | 0.796                           | 0.633, 1.001 | 0.101   |

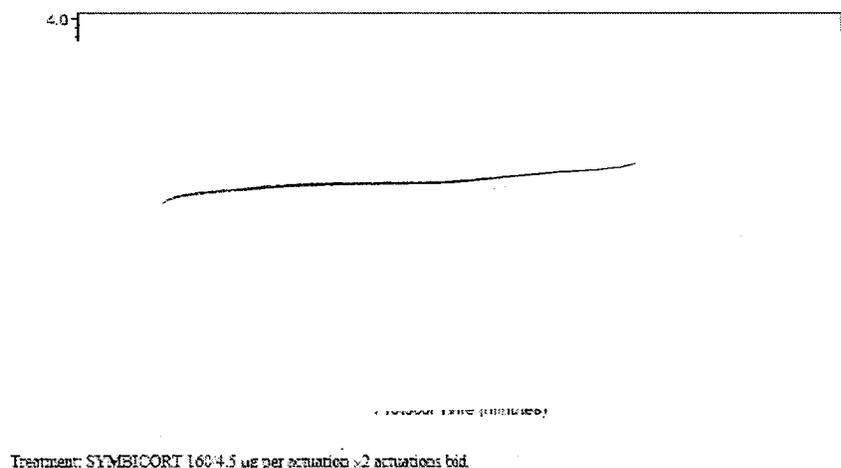
<sup>a</sup> SYMB 160/4.5 µg per actuation x2 actuations bid, Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid, Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

AUC<sub>0-6</sub> area under the curve from time 0 to 6 hours, C<sub>max</sub> maximum (peak) plasma drug concentration.

**Reviewer’s Comments:**

- There was a considerable variability in the plasma concentration-time profiles for both budesonide (**Figures 11.3-5**) and formoterol (**Figures 11.6-11.8**). The variability is more pronounced for formoterol since a few subjects did not show an early peak concentration in the plasma. There were several sources of variability in this study including but not limited to incomplete sampling and missing data.
- Overall, in terms of product performance and treatment comparison, the exposure from the three treatments appears comparable.

**Figure 11.3 Individual Budesonide Plasma Concentration-Time Profiles for Symbicort pMDI Treatment Group (Clinical Study # 717)**



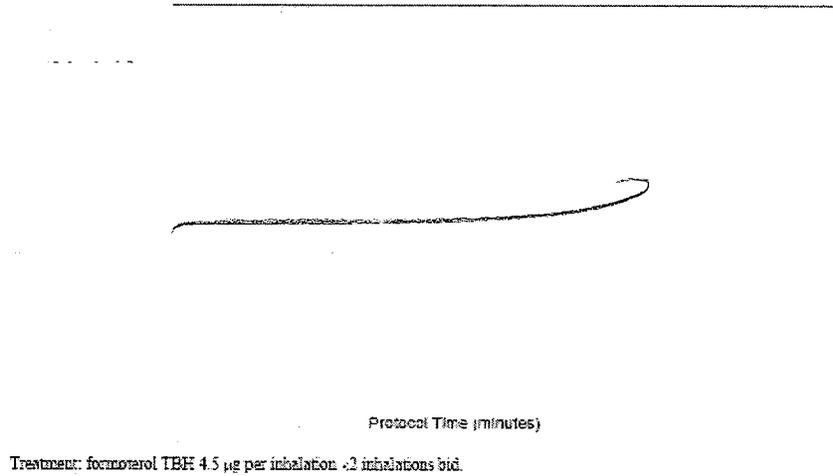
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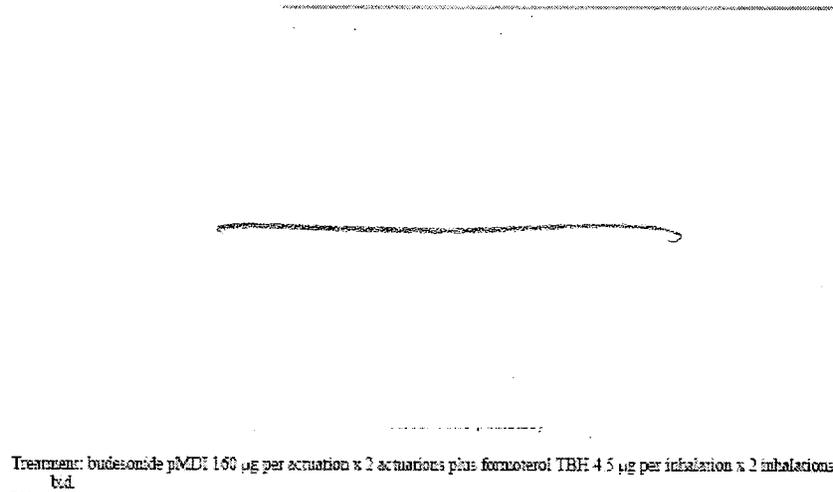
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**Figure 11.7 Individual Formoterol Plasma Concentration-Time Profiles for Budesonide treatment Group (Clinical Study # 717)**



**Figure 11.8 Individual Formoterol Plasma Concentration-Time Profiles for Budesonide + Formoterol Treatment Group (Clinical Study # 717)**



**Conclusions:**

Considering all sources of variability, the incomplete collection of blood samples and the limited number of samples (up to 6 hours), the exposure to budesonide and formoterol following the three treatments is comparable.

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## 12.0 Study # 729 (Bronchodilating Effects of Symbicort pMDI and Oxis TBH)

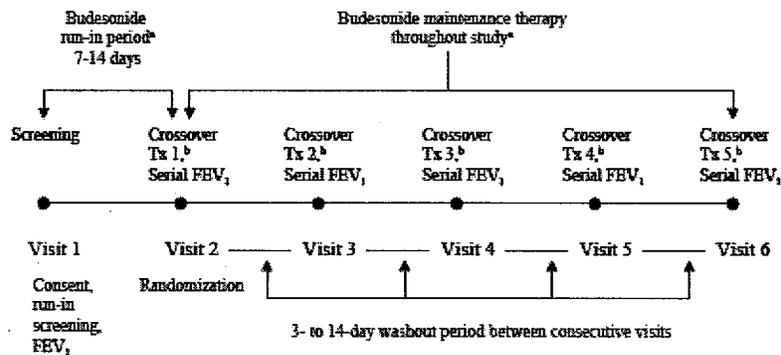
### Objectives:

The primary objective was to investigate the bronchodilating effect of formoterol when administered as Symbicort pMDI or Oxis TBH. The secondary object was to characterize the PK of formoterol following the administration of the two products.

### Study Design:

- Open label, active control, single dose, 5 period, and crossover in adult asthma.
- n= 175 to achieve 168 subjects

### Treatments/Design:



**Run in (7-14 days):** Budesonide (pMDI) 80 mcg x 2 actuations BID  
Total daily dose = 320

### Study Day:

- Budesonide pMDI x 4 actuations (B)
- SYMBICORT pMDI x 1 actuation plus budesonide pMDI x 3 actuations (S1)
- SYMBICORT pMDI x 2 actuations plus budesonide pMDI x 2 actuations (S2)
- SYMBICORT pMDI x 4 actuations (S4)
- OXIS TBH x 1 inhalation plus budesonide pMDI x 4 actuations (O1)
- OXIS TBH x 2 inhalations plus budesonide pMDI x 4 actuations (O2)
- OXIS TBH x 4 inhalations plus budesonide pMDI x 4 actuations (O4)

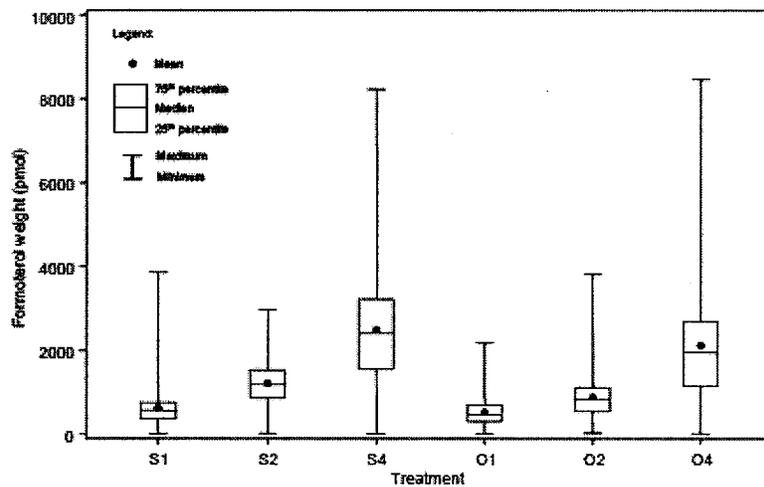
Only 12-hours urine sample was collected for formoterol measurement. No blood samples were collected for either budesonide or formoterol determination.

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**Results:**

- In this study 12-hours urine sample was collected for formoterol measurement. There was high variability in urine data as shown in **Figure 12.1**. There was some trend for increase in formoterol amount excreted in urine with dose.
- The systemic exposure to formoterol was 35% higher after Symbicort pMDI compared to Oxis TBH. This was consisted across all doses tested in this study (~30% to ~40%). **Table 7.1** shows the comparison for all treatments.

**Figure 12.1. Formoterol Urine Excretion Data**



O1, O2, and O4 OXIS TBH x1 actuation, x2 actuations, and x4 actuations, respectively.  
S1, S2, and S4 SYMBICORT pMDI x1 actuation, x2 actuations, and x4 actuations, respectively.  
pmol picomole.

**Reviewer’s Comments:**

The data from this study is in contrary to that seen in other studies were the exposure the exposure for formoterol is lower following Symbicort pMD than the corresponding mono product. The reason (s) for this discrepancy is unknown.

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**Table 12.1 Amount of Formoterol Excreted Urine (pmol)**

| Treatment comparison   | LSmeans | From ANOVA (ratios) |       | p-value |
|------------------------|---------|---------------------|-------|---------|
|                        |         | 95% CI              |       |         |
| S1 vs S2               | 0.52    | 0.431               | 0.632 | <0.001  |
| S1 vs S4               | 0.25    | 0.204               | 0.297 | <0.001  |
| S1 vs O1               | 1.34    | 1.112               | 1.626 | 0.002   |
| S1 vs O2               | 0.72    | 0.598               | 0.875 | 0.001   |
| S1 vs O4               | 0.32    | 0.266               | 0.390 | <0.001  |
| S2 vs S4               | 0.47    | 0.391               | 0.569 | <0.001  |
| S2 vs O1               | 2.58    | 2.130               | 3.116 | <0.001  |
| S2 vs O2               | 1.39    | 1.148               | 1.675 | 0.001   |
| S2 vs O4               | 0.62    | 0.511               | 0.747 | <0.001  |
| S4 vs O1               | 5.46    | 4.531               | 6.587 | <0.001  |
| S4 vs O2               | 2.94    | 2.435               | 3.550 | <0.001  |
| S4 vs O4               | 1.31    | 1.084               | 1.583 | 0.005   |
| O1 vs O2               | 0.54    | 0.445               | 0.651 | <0.001  |
| O1 vs O4               | 0.24    | 0.198               | 0.290 | <0.001  |
| O2 vs O4               | 0.45    | 0.368               | 0.539 | <0.001  |
| Overall S vs overall O | 1.35    | 1.207               | 1.502 | <0.001  |

ANOVA: Analysis of variance (multiplicative approach).  
 B: Budesonide only (no SYMBICORT pMDI or OXIS TBH).  
 CI: Confidence interval. LSmeans: Least squares means.  
 O: OXIS TBH treatment regardless of dose.  
 O1, O2, and O4: OXIS TBH x1 actuation; x2 actuations; and x4 actuations, respectively.  
 S: SYMBICORT pMDI regardless of dose.  
 S1, S2, and S4: SYMBICORT pMDI x1 actuation; x2 actuations; and x4 actuations, respectively.  
 SE: Standard error of the mean.

**Conclusion:**

The exposure to formoterol was approximately 35% higher following Symbicort pMDI than Oxis TBH. However, this is in contrast to what has been seen in other studies where the exposure for formoterol following Symbicort pMDI is lower than following individual component such as Oxis TBH. The reason (s) for these contradicting results is unknown.

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## Cross-Studies Analysis:

- A comparison of data from various studies shows that the dose corrected C<sub>max</sub> and AUC of budesonide are comparable in healthy and adult asthmatics (**Table 1**). However, it is lower in asthmatic children compared to adults.
- The same trend is also observed for formoterol data (**Table 2**). However, formoterol plasma concentration-time profiles were flat in a quite a few subjects in some studies. The reasons for this low formoterol concentrations is unknown.

**Table 1. Summary of Budesonide PK Parameters of Symbicort pMDI Across Studies**

| Parameters                       | Study                     | Sampling duration (h) | Dose (µg) | AUC (geometric mean: nmol·h/L) <sup>a</sup> | Dose-corrected AUC <sup>b</sup> | C <sub>max</sub> (geometric mean: nmol/L) <sup>a</sup> | Dose-corrected C <sub>max</sub> <sup>b</sup> | t <sub>max</sub> (median: min) | t <sub>1/2</sub> (geometric mean: h) <sup>c</sup> |
|----------------------------------|---------------------------|-----------------------|-----------|---|---------------------------------|--|--|--------------------------------|---|
| <b>Single dose</b>               |                           |                       |           |   |                                 |  |  |                                |   |
| Asthma                           | D58896C00010              | 24                    | 1920      | 18.4  | 9.6                             | 4.5  | 2.3  | 20                             | 4.7   |
|                                  | D58896C00006              | 36                    | 960       | 12.5  | 13.0                            | 3.7  | 3.9  | 15                             | 4.6   |
|                                  | D58896C00013 <sup>c</sup> | 12                    | 640       | 4.2   | 6.6                             | 1.4  | 2.2  | 20                             | 3.0   |
| Healthy                          | SD-039-0713               | 12                    | 1920      | 19.0  | 9.9                             | 6.1  | 3.2  | 20                             | 3.4   |
|                                  | SD-039-0721               | 12                    | 1280      | 14.6  | 11.4                            | 3.9  | 3.0  | 20                             | 3.6   |
|                                  | SD-039-0713               | 12                    | 480       | 6.0   | 12.5                            | 1.8  | 3.8  | 20                             | 3.6   |
|                                  |                           | 12                    | 960       | 10.8  | 11.3                            | 3.2  | 3.3  | 20                             | 3.6   |
|                                  |                           | 12                    | 1920      | 19.6  | 10.2                            | 5.4  | 2.8  | 20                             | 3.7   |
|                                  | SD-039-0724               | 12                    | 640       | 7.3   | 11.4                            | 2.1  | 3.3  | 10                             | 3.7   |
| <b>Repeated dose<sup>d</sup></b> |                           |                       |           |   |                                 |  |  |                                |   |
| Asthma                           | D58896C00011              | 12                    | 320       | 4.9   | 15.3                            | 1.2  | 3.8  | 21                             | 3.7   |
|                                  | SD-039-0717               | 6                     | 320       | 3.5   | 10.9                            | 1.3  | 4.1  | 18                             | --  |
|                                  | SD-039-0718 <sup>e</sup>  | 6                     | 80        | 1.0   | 12.5                            | 0.3  | 3.8  | 40                             | --  |
|                                  | SD-039-0719 <sup>e</sup>  | 6                     | 320       | 4.6   | 14.4                            | 1.9  | 5.9  | 12                             | --  |
| Healthy                          | D58896C00011              | 12                    | 320       | 4.6   | 14.4                            | 1.6  | 5.0  | 10                             | 3.9   |
|                                  | SD-039-0724               | 12                    | 320       | 4.2   | 13.1                            | 1.2  | 3.8  | 10                             | 4.0   |
|                                  |                           | 12                    | 640       | 8.8   | 13.8                            | 2.4  | 3.8  | 15                             | 3.8   |

<sup>a</sup> Values have been rounded to the nearest one-tenth. In the repeated-dose studies, AUC was calculated over the sampling duration.

<sup>b</sup> Dose-corrected values are calculated by dividing AUC or C<sub>max</sub> by the delivered dose in mg.

<sup>c</sup> Pediatric and adolescent study.

<sup>d</sup> In each of the repeated-dose studies, the dosage shown is the dosage administered immediately before the start of PK testing. Subjects in each of these studies were maintained on the dosage shown, administered bid.

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**Table 2. Summary of Formoterol PK Parameters of Symbicort pMDI Across Studies**

| Parameters                       | Study                    | Sampling duration (h) | Dose (µg)       | AUC (pmol·h/L) <sup>a</sup> | Dose corrected AUC <sup>b</sup> | C <sub>max</sub> (pmol) <sup>c</sup> | Dose corrected C <sub>max</sub> <sup>b</sup> | t <sub>max</sub> (min) | t <sub>1/2</sub> (h) <sup>d</sup> |
|----------------------------------|--------------------------|-----------------------|-----------------|-----------------------------|---------------------------------|--------------------------------------|--|------------------------|-----------------------------------|
| <b>Single dose</b>               |                          |                       |                 |                             |                                 |                                      |  |                        |                                   |
| <b>Asthma</b>                    | D5896C00010              | 24                    | 54              | 747                         | 13.8                            | 136                                  | 2.5  | 10                     | 7.9                               |
|                                  | D5899C00006              | 36                    | 54              | 819                         | 15.2                            | 149                                  | 2.8  | 15                     | 8.7                               |
| <b>Healthy</b>                   | SD-039-0713              | 12                    | 54              | 751                         | 13.9                            | 227                                  | 4.2  | 10                     | 6.4                               |
|                                  | SD-039-0721              | 12                    | 36              | 516                         | 14.3                            | 147                                  | 4.1  | 10                     | 6.0                               |
|                                  | SD-039-0723              | 24                    | 54 <sup>e</sup> | 944                         | 17.5                            | 275                                  | 5.1  | 10                     | 7.1                               |
|                                  |                          | 24                    | 54 <sup>f</sup> | 935                         | 17.3                            | 275                                  | 5.1  | 10                     | 7.8                               |
|                                  | 24                       | 54 <sup>g</sup>       | 910             | 16.9                        | 271                             | 5.0                                  | 10   | 8.3                    |                                   |
|                                  | SD-039-0724              | 12                    | 18              | 256                         | 14.2                            | 77                                   | 4.3  | 10                     | 5.3                               |
| <b>Repeated dose<sup>h</sup></b> |                          |                       |                 |                             |                                 |                                      |  |                        |                                   |
| <b>Asthma</b>                    | D5896C00011              | 12                    | 9               | 158                         | 17.6                            | 28                                   | 3.1  | 10                     | 6.8                               |
|                                  | SD-039-0717              | 6                     | 9               | 77                          | 8.6                             | 20                                   | 2.2  | 67                     | --                                |
|                                  | SD-039-0718 <sup>i</sup> | 6                     | 9               | 91                          | 10.1                            | 21                                   | 2.3  | 80                     | --                                |
|                                  | SD-039-0719 <sup>i</sup> | 6                     | 9               | 110                         | 12.2                            | 27                                   | 3.0  | 42                     | --                                |
| <b>Healthy</b>                   | D5896C00011              | 12                    | 9               | 167                         | 18.6                            | 48                                   | 5.3  | 10                     | 6.5                               |
|                                  | SD-039-0724              | 12                    | 9               | 152                         | 16.9                            | 48                                   | 5.3  | 9                      | 6.9                               |
|                                  |                          | 12                    | 18              | 357                         | 19.8                            | 105                                  | 5.8  | 10                     | 7.0                               |

<sup>a</sup> Values have been rounded to the nearest one-tenth. In the repeated-dose studies, AUC was calculated over the sampling duration.

<sup>b</sup> Dose-corrected values are calculated by dividing AUC or C<sub>max</sub> by the delivered dose in µg.

<sup>c</sup> The budesonide component of the SYMBICORT pMDI dose was 480 µg.

<sup>d</sup> The budesonide component of the SYMBICORT pMDI dose was 960 µg.

<sup>e</sup> The budesonide component of the SYMBICORT pMDI dose was 1920 µg.

<sup>f</sup> In each of the repeated dose studies, the dosage shown is the dosage administered immediately before the start of PK testing. In addition, subjects in each of these studies were maintained on the dosage shown, administered bid.

<sup>h</sup> Pediatric and adolescent study.

**Conclusions:**

Considering all the sources of variability among different studies including but not limited to subjects demographics, incomplete blood sampling, assays, study sites, and doses, the dose corrected exposure (C<sub>max</sub> and AUC) is reasonably similar between healthy and asthmatic subjects, including children. However, dosage titration and individualization is recommended for this product.

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## Population PK Analysis:

### Objectives:

The primary objective was to evaluate the impact of subject demographic characteristics on the PK of budesonide or formoterol from Symbicort pMDI.

### Method:

Several covariates were tested in the model including but not limited to: age, body weight, body surface area, lean body mass, ideal body weight, CLCR, dose, gender, and subject/patient status. Since the majority of subjects included in the PK analysis were Caucasian race was not included in the analysis as a covariate.

### Results:

- No covariate was identified to significantly impact the PK parameters of either budesonide or formoterol. Specifically, age, gender, or CLcr had no significant effect on the PK of either budesonide or formoterol.
- It should be noted however that the analysis shows that subjects with lower body weight may exhibit higher bioavailability of budesonide.
- Based on this analysis, the relative bioavailability of budesonide between pulmicort TBH and Symbicort pMDI is 115 % (**Table 1**). For formoterol, the relative bioavailability to Oxis TBH to Symbicort pMDI is 104% (**Table 2**). Considering all the variability among studies, these values are within those found in other individual studies within this review.

**Table 1. Pop PK Analysis for Budesonide**

| Parameter                              | Description   | Mean (standard deviation)<br>N=447 |
|--|---|------------------------------------|
| CLF (L/hr)                             | Apparent extravascular clearance                                    | 199 (10.4)                         |
| V <sub>z</sub> F (L)                   | Apparent volume of central compartment                              | 687 (175)                          |
| QF (L)                                 | Apparent intercompartmental distribution clearance                  | 50.3 (17.6)                        |
| V <sub>z</sub> F (L)                   | Apparent volume of peripheral compartment                           | 307 (88.3)                         |
| K <sub>a, 10</sub> (hr <sup>-1</sup> ) | First-order absorption rate constant of SYMBICORT pMDI              | 14.0 (7.89) <sup>a</sup>           |
| K <sub>a, 11</sub> (hr <sup>-1</sup> ) | First-order absorption rate constant of PULMICORT TBH               | 17.3 (9.67) <sup>b</sup>           |
| K <sub>a, 12</sub> (hr <sup>-1</sup> ) | First-order absorption rate constant of Budesonide pMDI             | 9.59 (5.62) <sup>c</sup>           |
| F <sub>1, 10</sub>                     | Bioavailability for SYMBICORT pMDI                                  | 1.10 (0.40) <sup>a</sup>           |
| F <sub>1, 11</sub>                     | Relative bioavailability between PULMICORT TBH and SYMBICORT pMDI   | 1.24 (0.61) <sup>b</sup>           |
| F <sub>1, 12</sub>                     | Relative bioavailability between Budesonide pMDI and SYMBICORT pMDI | 1.15 (0.40) <sup>c</sup>           |

<sup>a</sup> N=336.

<sup>b</sup> N=83.

<sup>c</sup> N=161.

**Table 2. Pop PK Analysis for Formoterol**

| Parameter <sup>a</sup> | Explanation   | Model-predicted value | Standard Error of Estimate (%) <sup>b</sup> |
|------------------------|---|-----------------------|---|
| $\theta_5, Q_4$        | Apparent intercompartmental distribution clearance between central compartment and peripheral compartment "4", $Q_4/F$ (L/hr) | 54.4                  | 5.85  |
| $\theta_6, V_4$        | Apparent volume of peripheral compartment "4", $v_4/F$ (L)  | 1660                  | 11.9  |
| $\theta_7, K_{a,1}$    | First-order absorption rate constant ( $\text{hr}^{-1}$ ) for SYMBICORT pMDI  | 61.0                  | 7.25  |
| $\theta_8, K_{a,2}$    | First-order absorption rate constant ( $\text{hr}^{-1}$ ) for OXIS TBH  | 36.3                  | 6.47  |
| $\theta_9, F_1$        | Relative bioavailability of OXIS TBH to SYMBICORT pMDI  | 1.04                  | 3.07  |
| $\omega_1^2, CL$       | Variance of apparent extravascular clearance  | 0.0151                | 46.6  |
| $\omega_2^2, V_1$      | Variance of apparent volume of central compartment  | $8.6 \times 10^{-11}$ | Too large                                   |
| $\omega_3^2, Q_3$      | Variance of apparent intercompartmental distribution clearance between central compartment and peripheral compartment "3"     | 0.109                 | 55.8  |
| $\omega_4^2, V_3$      | Variance of apparent volume of peripheral compartment "3"   | 0.0442                | 20.5  |
| $\omega_5^2, Q_4$      | Variance of apparent intercompartmental distribution clearance between central compartment and peripheral compartment "4"     | 0.211                 | 31.8  |
| $\omega_6^2, V_4$      | Variance of apparent volume of peripheral compartment "4"   | $6.73 \times 10^{-8}$ | Too large                                   |
| $\omega_7^2, K_{a,1}$  | Variance of the first-order absorption rate constant for SYMBICORT pMDI   | 55.1                  | 26.9  |
| $\omega_8^2, K_{a,2}$  | Variance of the first-order absorption rate constant for OXIS TBH   | 11.2                  | 27.2  |
| $\omega_9^2, F_0$      | Variance of bioavailability of SYMBICORT pMDI   | 0.0928                | 10.8  |
| $\omega_{10}^2, F_1$   | Variance of relative bioavailability of OXIS TBH to SYMBICORT pMDI  | 0.116                 | 15.9  |
| $\sigma^2$             | Residual variance   | 0.0224                | 5.09  |

<sup>a</sup> Pharmacokinetic parameters are referenced as theta ( $\theta$ ) subscripted with the parenthetical index number in the NONMEM subroutine, i.e. apparent extravascular clearance is  $\theta_1$ . Variances are referenced as omega-squared ( $\omega^2$ ) in the NONMEM subroutine.

**Conclusion:**

Based on this analysis, there was no single covariate that raises any concern or may affect the PK characteristic of either budesonide or formoterol.

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**Labelling Comments:**

The labeling comments will be incorporated directly into the sponsor's proposed label after the discussion with the review team

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30 Page(s) Withheld

           Trade Secret / Confidential

  8   Draft Labeling

           Deliberative Process

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/s/

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Sayed Al-Habet  
5/23/2006 02:52:58 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
5/23/2006 03:48:35 PM  
BIOPHARMACEUTICS  
I concur

11/02/05

**Office of Clinical Pharmacology and Biopharmaceutics**  
*New Drug Application Filing and Review Form*

| General Information About the Submission |                                       |   |                                      |
|--|---------------------------------------|---|--------------------------------------|
|  | Information                           |   | Information                          |
| NDA Number                               | 21-929                                | Brand Name                              | SYMBICORT®                           |
| OCPB Division I                          | HFD-870                               | Generic Name                            | Budesonide/Formoterol Fumarate MDI   |
| Medical Division                         | HFD-570                               | Drug Class                              | Anti-asthmatic (combination Product) |
| OCPB Reviewer                            | Sayed (Sam) Al Habet, R.Ph., Ph.D.    | Indication(s)                           | Asthma                               |
| OCPB Team Leader                         | Emmanuel (Tayo) Fadiran, R.Ph., Ph.D. | Dosage Form: MDI (Metered Dose Inhaler) | Inhalation                           |
|  |                                       | Dosing Regimen                          | As Needed (BID-TID)                  |
| Date of Submission                       | September 23, 2005                    | Route of Administration                 | Oral Inhalation                      |
| Estimated Due Date of OCPB Review        | May 23, 2006                          | Sponsor                                 | AstraZeneca                          |
| PDUFA Due Date                           | July 23, 2006                         | Priority Classification                 | S                                    |
| Division Due Date                        | June 23, 2006                         |   |                                      |

| Clin. Pharm. and Biopharm. Information   |                           |                             |                            |                          |
|--|---------------------------|-----------------------------|----------------------------|--------------------------|
|  | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
| <b>STUDY TYPE</b>  |                           |                             |                            |                          |
| 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                         |                             |                            |                          |
| <b>I. Clinical Pharmacology</b>  |                           |                             |                            |                          |
| Mass balance:  |                           |                             |                            |                          |
| Isozyme characterization:  |                           |                             |                            |                          |
| Blood/plasma ratio:  |                           |                             |                            |                          |
| Plasma protein binding:  |                           |                             |                            |                          |
| Pharmacokinetics (e.g., Phase I) -   |                           |                             |                            |                          |
| Healthy Volunteers-  |                           |                             |                            |                          |
| single dose:   | X                         | 4                           |                            |                          |
| multiple dose:   | X                         | 1                           |                            |                          |
| Patients-  |                           |                             |                            |                          |
| single dose:   |                           | 2                           |                            |                          |
| multiple dose:   |                           | 1                           |                            |                          |
| Dose proportionality -   |                           |                             |                            |                          |
| fasting / non-fasting single dose:   |                           | 1                           |                            |                          |
| fasting / non-fasting multiple dose:   |                           |                             |                            |                          |
| Drug-drug interaction studies -  |                           |                             |                            |                          |
| In-vivo effects on primary drug:   |                           |                             |                            |                          |
| In-vivo effects of primary drug:   |                           |                             |                            |                          |
| In-vitro:  |                           |                             |                            |                          |
| Subpopulation studies -  |                           |                             |                            |                          |
| ethnicity:   |                           |                             |                            |                          |
| gender:  |                           |                             |                            |                          |
| pediatrics:  |                           |                             |                            |                          |
| geriatrics:  |                           |                             |                            |                          |
| renal impairment:  |                           |                             |                            |                          |
| hepatic impairment:  |                           |                             |                            |                          |
| PD:  |                           |                             |                            |                          |
| Phase 2:   |                           |                             |                            |                          |
| Phase 3:   |                           |                             |                            |                          |
| PK/PD:   |                           |                             |                            |                          |

|   |                                       |   |  |  |
|---|---------------------------------------|---|--|--|
| Phase 1 and/or 2, proof of concept:                     |                                       |   |  |  |
| Phase 3 clinical trial:                                 |                                       |   |  |  |
| <b>Population Analyses -</b>                            |                                       |   |  |  |
| Data rich:  |                                       |   |  |  |
| Data sparse:  |                                       |   |  |  |
| <b>II. Biopharmaceutics</b>                             |                                       |   |  |  |
| <b>Absolute bioavailability:</b>                        |                                       |   |  |  |
| <b>Relative bioavailability -</b>                       |                                       |   |  |  |
| solution as reference:                                  |                                       |   |  |  |
| alternate formulation as reference:                     |                                       | 4   |  |  |
| <b>Bioequivalence studies -</b>                         |                                       |   |  |  |
| traditional design; single / multi dose:                | X                                     | 4   |  |  |
| replicate design; single / multi dose:                  |                                       |   |  |  |
| <b>Food-drug interaction studies:</b>                   |                                       |   |  |  |
| <b>Dissolution:</b>                                     |                                       |   |  |  |
| <b>(IVIVC):</b>   |                                       |   |  |  |
| <b>Bio-wavier request based on BCS</b>                  |                                       |   |  |  |
| <b>BCS class</b>  |                                       |   |  |  |
| <b>III. Other CPB Studies</b>                           |                                       |   |  |  |
| <b>Genotype/phenotype studies:</b>                      |                                       |   |  |  |
| <b>Chronopharmacokinetics</b>                           |                                       |   |  |  |
| <b>Pediatric development plan</b>                       |                                       |   |  |  |
| <b>Literature References</b>                            |                                       |   |  |  |
| <b>Total Number of Studies</b>                          | 6                                     |   |  |  |
| <b>Filability and QBR comments</b>                      |                                       |   |  |  |
|   | "X" if yes                            | Comments  |  |  |
| <b>Application filable ?</b>                            | <b>Yes</b>                            | Reasons if the application <u>is not</u> filable (or an attachment if applicable)<br>For example, is clinical formulation the same as the to-be-marketed one? |  |  |
| <b>Comments sent to firm ?</b>                          |                                       | Comments have been sent to firm (or attachment included). FDA letter date if applicable.  |  |  |
| <b>QBR questions (key issues to be considered)</b>      |                                       |   |  |  |
| <b>Other comments or information not included above</b> |                                       |   |  |  |
| <b>Primary reviewer Signature and Date</b>              | Sayed (Sam) Al Habet, R.Ph., Ph.D.    |   |  |  |
| <b>Secondary reviewer Signature and Date</b>            | Emmanuel (Tayo) Fadiran, R.Ph., Ph.D. |   |  |  |

CC: NDA HFD-570, HFD-870 (AI Habet, Fadiran, Malinowski), CDR (B. Murphy, biopharm file)

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/s/

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Sayed Al-Habet  
11/3/2005 02:50:04 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
11/4/2005 02:47:03 PM  
BIOPHARMACEUTICS  
i concur