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"Investigation of the pharmacokinetic interactions between inhaled formoterol and inhaled ciclesonide"

Clinical Study Report no.: 56E/99  
Protocol No.: BY9010/CP-029  
Development Phase of Study: Phase I  
Study Initiation Date: Sep 28, 2001  
Study Completion Date: Jan 20, 2002  
Chief Investigator: Manueal Koch, MD.  
ALTANA Pharma, Germany

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### Objectives

- to investigate of possible pharmacokinetic interactions of inhaled formoterol and inhaled ciclesonide.
- to assess safety and tolerability of the substances when given separately or in combination.

### Study Design

This was an open, randomized, 3-period-cross-over study in 24 healthy volunteers. The study consisted of a screening examination and three treatment periods where the single dose treatments:

- Treatment A (Reference 1): Ciclesonide in metered dose inhalers, each puff containing 200 µg (ex-valve)  
Dose: 800 µg ciclesonide (Four puffs of 200 µg each)  
This corresponds to an ex-actuator dose of 640 µg (4 puffs of 160 µg each)
- Treatment B (Reference 2): Formoterol as capsules in dry powder inhalers (Foradil PTM), each puff containing 12 µg  
dose: 24 µg formoterol (two puffs of 12 µg each)
- Treatment C (Test): Ciclesonide in metered dose inhalers (MDI), each puff containing 200 µg (ex-valve)  
Dose: 800 µg ciclesonide (Four puffs of 200 µg each). This corresponds to a ex-actuator dose of 640 µg (Four puffs of 160 µg each) immediately followed by formoterol as capsules in dry powder inhalers (Foradil PTM), each puff containing 12 µg;  
dose: 24 µg formoterol (two puffs of 12 µg each)

These treatments were administered in the morning of Study Day 1 of the respective treatment period. The wash-out between the treatments had to be in the range of seven to fourteen days.

### Study Subjects

The study population consisted of 24 Caucasian healthy subjects, 18 males and six females. Their mean age was 35 years (age range 23- 45 years), their mean height 175 cm (range 154 cm – 194 cm) and their mean weight 73 kg (range 53 – 99 kg). None of the subjects suffered from a clinical relevant active disease or medical condition.

### PK Measurements

Blood samples for pharmacokinetic purposes was to be taken at predose, 0.25 h (15min), 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h and 14 h after inhalation. Note that blood for pharmacokinetic purposes were only required on the study periods where ciclesonide was administered.

All urine of a subject of the following periods had to be sampled: predose, 0 h – 2 h, 2 h – 4 h, 4 h – 8 h, 8 h – 12 h, 12 h – 24 h, 24 h – 36 h, 36 h – 48 h. The sample volume of each period had to be recorded in the CRF. Note that urine for pharmacokinetic purposes was only be required in the study periods where formoterol was administered.

### **Analytical Method**

Determination of ciclesonide and its metabolite B9207-021 in serum was performed using a validated LC-MS/MS assay. The lower limit of quantitation were 25 and 10 pg/mL for B9207-015 and B9207-021, respectively. The analytical evaluation of formoterol in urine (if possible including its glucuronide conjugate) was performed by using a validated LC-MS/MS assay.

### **Data Analysis**

#### **PK Analysis**

Relevant PK parameters were calculated using non-compartmental methods.

### **Statistical Analysis**

For each primary variable, i.e. separately for each corresponding chemical entity, point estimate and 90%-confidence limits were given for the ratio of the population medians for Test and the respective Reference using a multiplicative model and a parametric analysis.

Equivalence between Test and the respective Reference, i.e. lack of interaction for the respective chemical entity, were concluded if the 90%-confidence interval was entirely within the equivalence range of 0.67 to 1.50. According to the sponsor, the extended equivalence range of 0.67 to 1.50 for the pharmacokinetic characteristics of metabolite B9207-021 was chosen recognizing that inhalation technique plays a major part in determining lung deposition. By the same token, the extended equivalence range of 0.67 to 1.50 was stipulated for the cumulative urinary excretion of formoterol.

## **RESULTS**

### **Analytical Method**

#### **In-Study Validation**

The calibration curves for B9207-015 and B9207-021 were linear with a coefficient of correlation equal or better than 0.9988 for B9207-015 and equal or better than 0.9991 for B9207-021.

The within-study (total study) accuracy as from the analysis of QC samples spiked in human serum for B9207-015 was in the range from \_\_\_\_\_; the corresponding within study accuracy for B9207-021 was between \_\_\_\_\_ and \_\_\_\_\_. The total precision for B9207-015 and B9207-021 was from \_\_\_\_\_ and from \_\_\_\_\_ respectively. Lower limits of quantification were 25 and 10 pg/ml for B9207-015 and B9207-021, respectively.

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Formoterol was quantitated by HPLC with UV spectrometric detection using the internal standard method. The limit of quantitation was set at 0.2 µg/l using 1.0 ml human urine. Calibration data, quality control data and chromatograms indicated that the method performed acceptably during the sample analyses. The accuracy of back-calculated concentrations ranged from -6.0 % to 6.6% and the CV% were less than or equal to 4.4%. The CV% of QC calculated values was between 5.8 and 7.5 and the accuracy ranged from -2.7 to 0.7. The mean coefficient of correlation was 0.9979. During the validation of the method the stability of formoterol in urine for three freeze/thaw cycles and for 24 h at room temperature was demonstrated. However, no long-term stability data in frozen samples were available yet.

### Pharmacokinetic Results

Figure 1 shows the concentration-time profile of ciclesonide following single inhalative dose of 800 µg with and without formoterol. Likewise Figure 2 shows the same for the metabolite. Mean (SEM) cumulative excretion of formoterol in healthy subjects following a single oral administration of formoterol at a dose level of 24 mcg with and without ciclesonide 800 µg are shown in Figure 3. Table 1 summarizes the PK characteristics of B9207-015 and its metabolite in the presence and absence of formoterol and the urinary excretion of formoterol with and without ciclesonide following single administration of the treatments. Figures 4 and 5 show the individual C<sub>max</sub> and AUC<sub>inf</sub> of RM1 following administration of the treatments. Table 2 summarizes the point estimates and 90% CI of the ratios of PK parameters of B9207-021 following single administration of 800 mcg B9207-015 with and without formoterol. Table 3 summarizes the point estimates and 90% CI of the ratios of PK parameters of formoterol following single administration of 24 mcg with and without ciclesonide.

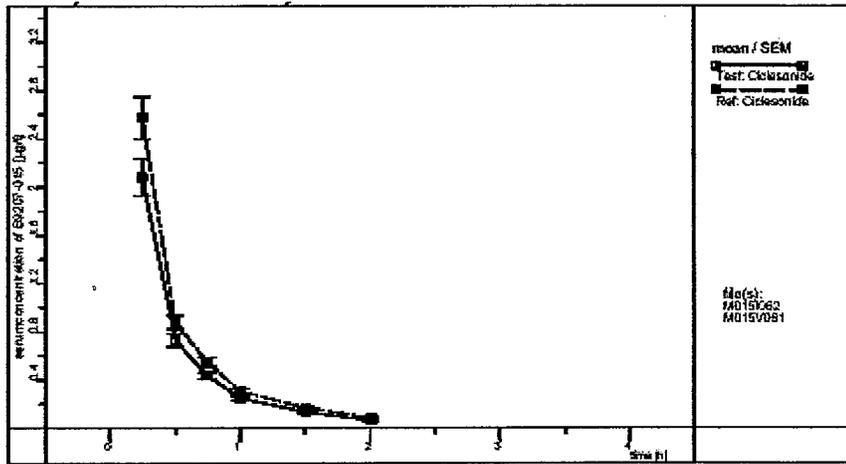


Figure 1. Mean serum concentrations of ciclesonide following single inhalation of ciclesonide with and without formoterol (reference).

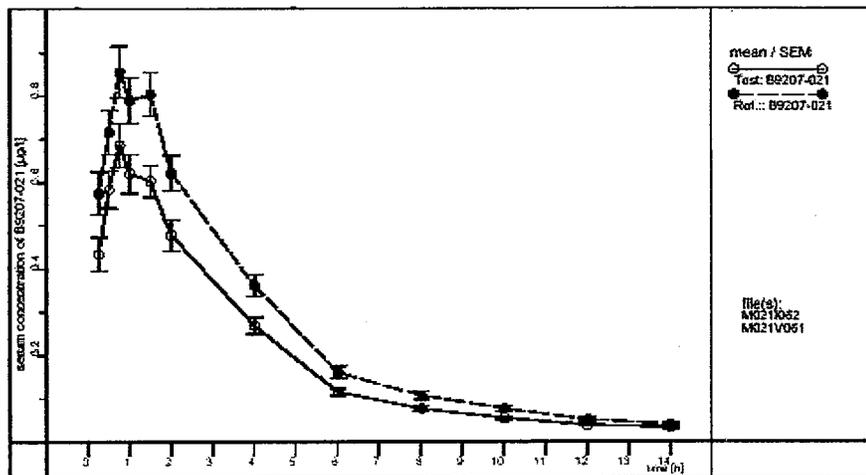


Figure 2. Serum concentrations of RM1 following single inhaled dose of 800 mcg ciclesonide with and without single inhalative dose of formoterol.

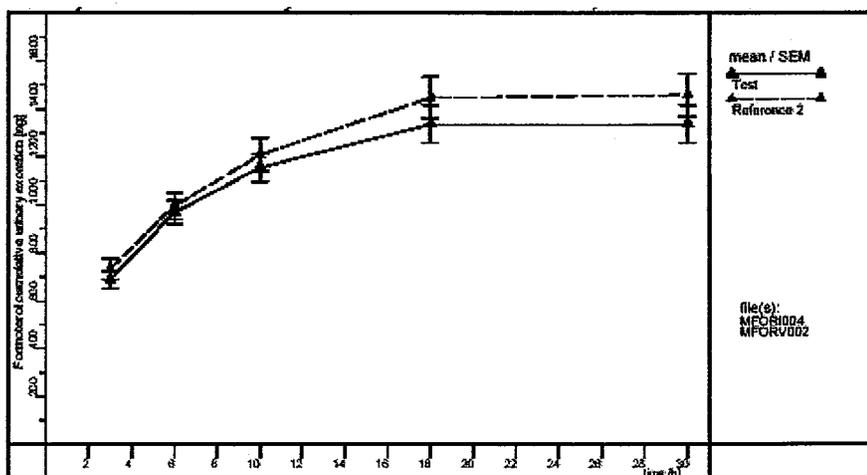


Figure 3. Mean cumulative excretion profile of formoterol in urine after inhalation of formoterol with (test) and without ciclesonide.

Table 1. PK characteristics of CIC and RM1 in healthy subjects following single administration of the treatments.

	Ciclesonide		RM1		Formoterol	
	Without formoterol	With formoterol	Without formoterol	With formoterol	Without CIC	With CIC
Cmax (µg/L)	2.58 (0.88)	2.03 (0.76)	0.89 (0.29)	0.70 (0.24)		
AUCinf (µg*hr/L)	1.32 (0.39)	1.04 (0.34)	3.75 (1.15)	2.88 (0.81)		
Tmax (hrs)	0.25 (0.0)	0.26 (0.05)	1.06 (0.36)	0.94 (0.33)		
T1/2 (hrs)	0.66 (0.21)	0.68 (0.29)	4.06 (1.23)	4.72 (1.73)		
Cumulative excretion (ng)					1456.5 (442.8)	1334 (391.8)

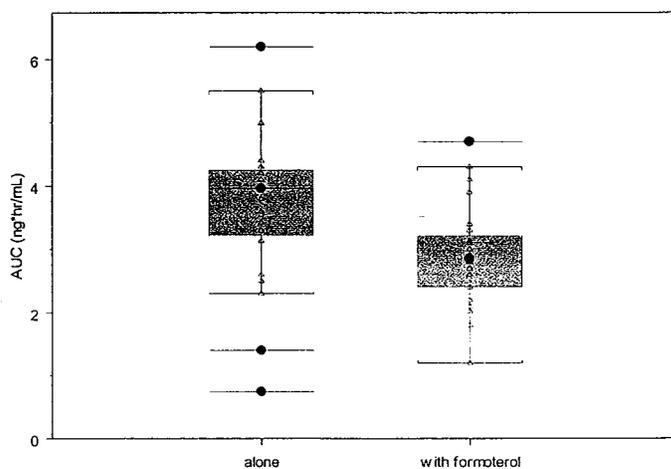
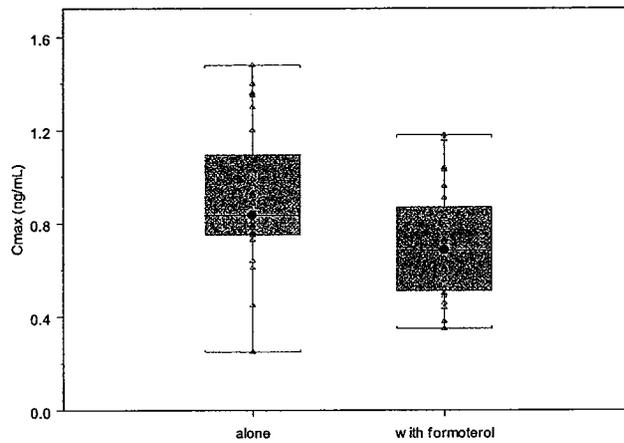


Figure 4. Individual AUCinf values for RM1 in healthy volunteers following single administration of ciclesonide with and without formoterol single dose of 24 mcg.



**Figure 5.** Individual C<sub>max</sub> values for RM1 in healthy volunteers following single administration of ciclesonide with and without formoterol 24 mcg.

**Table 2.** Geometric means, point estimates and 90% CI of the PK parameters of B9207-021 following single administration of 800 mcg B9207-015 to healthy subjects with and without formoterol.

Pharmacokinetic characteristic	Treatment A Ciclesonide 800 µg (Reference 1)	Treatment C Ciclesonide 800 µg/ Formoterol 24 µg (Test)	Equivalence ratio (Test/-Reference)
	geometric mean (68%-range)	geometric mean (68%-range)	Point estimate (90% confidence interval)
AUC <sub>0-inf</sub> [µg·h/l]	3.52 (2.32-5.33)	2.77 (2.08-3.69)	<b>0.79</b> (0.72, 0.86)
C <sub>max</sub> [µg/l]	0.840 (0.576-1.226)	0.665 (0.481-0.921)	<b>0.79</b> (0.73, 0.86)
t <sub>1/2</sub> [h]	3.91 (2.99-5.12)	4.47 (3.24-6.17)	<b>1.14</b> (1.04, 1.26)
t <sub>max</sub> [h] (additive statistical model, non-parametric analysis)	Median 1.00	Median 0.75	<b>-0.125</b> (-0.38, 0.00)

**Table 3.** Geometric means, point estimates and 90% CI of the PK parameters of formoterol following single administration of 24 mcg to healthy subjects with and without ciclesonide.

Pharmacokinetic characteristic	Treatment B Formoterol 24 µg (Reference 2)	Treatment C Ciclesonide 800 µg/ Formoterol 24 µg (Test)	Equivalence ratio (Test/-Reference)
	geometric mean (68%-range)	geometric mean (68%-range)	Point estimate (90% confidence interval)
A <sub>c</sub> [µg]	1.38 (1.04, 1.85)	1.28 (0.95, 1.73)	<b>0.93</b> (0.86, 1.00)
t <sub>1/2ER</sub> [h]	6.35 (5.20, 7.74)	5.63 (4.15, 7.63)	<b>0.89</b> (0.77, 1.02)

#### SUMMARY OF FINDINGS

- The arithmetic mean C<sub>max</sub> and AUC of ciclesonide decreased in the presence of formoterol 24 mcg by 21% and 22%, respectively following single administration of the treatments.
- The arithmetic mean C<sub>max</sub> and AUC of the active metabolite B9207-021 decreased in the presence of formoterol 24 mcg by 21 % and 23%, respectively following single administration of the treatments.
- The mean cumulative excretion of formoterol decreased in the presence of ciclesonide by 8% following single administration of the treatments.

#### GENERAL COMMENTS

- This study was conducted as a single dose. However, because little accumulation of the metabolite and drug product occurs (<50%) single dose PK may predict multiple dose PK.
- In the assessment of this DDI study with formoterol the sponsor did not use the maximum planned dose (1240 mcg) of ciclesonide to be administered to patients with asthma

#### CONCLUSION

- The systemic exposure of ciclesonide and its metabolite in healthy subjects receiving a single dose of ciclesonide 800 mcg was not statistically significantly altered when coadministered with formoterol 24 mcg single dose.
- The systemic exposure of formoterol in healthy subjects receiving a single dose of 24 mcg was not statistically significantly altered when coadministered with ciclesonide 800 mcg single dose.

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**"A Pilot study on the PK of the new topical steroid R-ciclesonide as compared to baseline and to budesonide following repeated dose inhalation in 12 healthy male volunteers"**

Clinical Study Report no.: 223/97  
Protocol No.: BY9010/FHP012  
Development Phase of Study: Phase I  
Study Initiation Date: 04/97  
Study Completion Date: 05/97  
Chief Investigator: H. Bliesath, MD,

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### **Objectives**

- to evaluate the potential effects of inhaled ciclesonide and budesonide on the HPA-axis function in healthy volunteers.

### **Study Design**

This was a randomized, 2 period, crossover design with placebo baseline phase prior to each study period.

### **Treatments**

Patients were randomized to receive one of the following treatments:

- Ciclesonide 200 mcg puff, 4 inhalations BID (800 mcg BID)
- Budesonide (Pulmicort) in turbohaler 200 mcg per puff, 4 inhalations BID (800 mcg BID)
- Matching placebo BID 4 inhalations BID.

In each of the two periods all subjects underwent a placebo run-in phase (days 1 and 2 of each period) in which the baseline profiles of cortisol in serum and urine were determined before the respective period of drug administration (days 3-9 of each period). There was at least a 14-day wash-out period.

### **Population**

Thirteen volunteers were screened and participated in this study (=intention to treat). Eleven healthy male volunteers (median age~ 30 years, median body weight: 74 kg) completed the study per protocol. Subject No. 09 terminated the study prematurely due to reasons not related to the study medication (infection of the urinary tract). Subject No. 14 was regarded as a protocol violator as he did not receive budesonide per protocol

### **Pharmacodynamic data**

periods  $t_1$  and  $t_2$ :

- Determination of the baseline 24-h profile of cortisol in serum under treatment with placebo; blood samples were taken at 8.00 h, 10.00 h, 12.00 h, 14.00 h, 16.00 h, 18.00 h, 20.00 h, on day 1 and at 6.00 h and 8.00 h on day 2.
- determination of the baseline amount of cortisol excreted in urine under treatment with placebo; urine was collected in the following intervals: 8.00 h - 12.00 h, 12.00 h - 16.00 h, 16.00 h - 20.00 h, 20.00 h - 24.00 h on day 1 and 0.0h - 8.00 on day

2.
  - ACTH-test at 800 h on day 2
  - determination of the 24-h profile of cortisol in serum on the 7th day of treatment with the active compound; blood samples were taken at predose (dose to morning inhalation that was performed at 8.00 h), 2 h, 4 h, 6 h, 8h, 10 h, 12 h, 22 h and 24 h after morning inhalation.
  - determination of the amount of cortisol excreted in urine on the 7th day of treatment with the active compound; urine was collected in the following intervals:
    - predose (close to morning inhalation that was performed at 8.00 h) - 12.00 h, 12.00 h - 16.00 h. 16.00 h - 20.00 h, 20.00 h -24.00h, 0.00 h -8.00 h (day 10)
  - ACTH-test at 5.00 h on day 10

### **Pharmacokinetics**

Blood sampling for determination of the serum concentrations of ciclesonide and its pharmacodynamically active metabolite B9207-021 was performed on day 9 in the ciclesonide treatment period, and blood sampling for determination of the serum concentrations of budesonide was performed on day 9 in the budesonide treatment period at the following time points:

- predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after morning inhalation.

### **Safety data**

Safety was evaluated based on physical examination results, vital signs, and clinical laboratory values collected at Visits 2 and 9; oropharyngeal examination results at Visits 2 through 9; and adverse events collected at all visits.

### **Statistical procedures**

Serum cortisol levels, time-averaged during 12-hours (mesor), were analyzed for treatment-related decreases by means of the one-sided paired t-tests after logarithmic transformation; this included for the characteristics themselves, geometric means and geometric 68%-range corresponding to mean  $\pm$  SD after logarithmic transformation. The tests were based on the log-transformed ratios versus the respective baselines. Geometric means as well as 90%- and 95%-confidence limits - using a logarithmic transformation - were given for the respective ratios ciclesonide/baseline and budesonide/baseline. Comparison between treatments based on these baseline-adjusted ratios were performed by means of standard analysis of variance for the crossover design using a multiplicative model. Geometric means and 90%- and 95%-confidence limits - using a Logarithmic transformation - were given for the respective ratios "ciclesonide/baseline / budesonide/baseline".

Apart from the mesor, the amplitude was approximated by half the difference between the maximum and minimum cortisol serum level during 24 hours.

The cortisol serum levels under ciclesonide and budesonide treatment were expressed as percentage of the baseline-values:

$$S(t) = \left( 1 - \frac{C_{t,DX}}{C_{(8,DX)}} \div \frac{C_{t,P}}{C_{(8,P)}} \right) \times 100\%$$

S(t)= Cortisol suppression (%) compared to baseline

Ct,p= Cortisol level at time t at baseline

Ct, DX= Cortisol level at time t after inhalation of ciclesonide or budesonide

C(8, P)= Cortisol level at time 8 hat baseline

C(8,DX)= Cortisol level at time B h after inhalation of ciclesonide or budesonide

The suppression indices were presented descriptively according to treatment. Means and 90%-confidence limits were given for the respective differences.

#### **Cortisol in urine**

The free cortisol in urine was presented as raw values and standardized for creatinine in urine. The 24-hour excretion of cortisol was calculated using the fraction from 8.00 (day 9) to 8.00 (day 10). The 24-hour cortisol excretions in urine was compared by means of standard analysis of variance for the crossover design.

#### **ACTH-test**

In addition to the descriptive and graphic presentation of the cortisol levels, the areas under the cortisol vs. time curve AUC(0-90min) were calculated by means of the trapezoidal rule. The AUC(0-90min) values following stimulation with tetracosactid were compared using the standard analysis of variance for the crossover design..

### **RESULTS**

#### **Analytical Method**

Levels of ciclesonide (B9207-015) and its metabolite (B9207-021) in serum were determined using \_\_\_\_\_ and HPLC with mass spectrometry detection. In addition, a similar method was used to determine budesonide in serum. The method had a lower limit of quantification (LLOQ) of 0025 mcg/mL for ciclesonide and its metabolite using 1 ml human serum and of 0.025 mcg/mL for budesonide using 1 ml human serum.

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#### **Pharmacodynamic Results**

According to the sponsor, the two placebo profiles were equivalent, both for the 12-h mesor and the 24-h mesor. For ciclesonide there was a 20% reduction (95%-confidence limits 14%-27%) versus placebo in the 12h mesor compared with a 42% (31%-51%) reduction for budesonide versus placebo. This difference between treatments was statistically significant at the 5%-level. Geometric mean and two-sided 95%-confidence interval (or the baseline-adjusted ratio ciclesonide/budesonide were 1.38 (113-1.67). This means that after adjustment for the baseline values, the 12-h cortisol mesor was 38% higher for ciclesonide than for budesonide.

The corresponding results for the 24-h serum cortisol mesor are as follows: For ciclesonide there was a 10% reduction (95%-confidence limits 2%-17%) versus placebo in the 24-h mesor compared with a 24% (18%-29%) reduction for budesonide versus placebo. This difference between treatments was statistically significant at the 5%-level. Geometric mean and two-sided 95%-confidence interval for the baseline-adjusted ratio ciclesonide/budesonide were 1.20 (1.08-1.33). This means that after adjustment (or the baseline values, the 24-h cortisol mesor was 20% higher for ciclesonide than for budesonide.

The ACTH test did not reveal a cortisol suppression when the active compounds and placebo were compared 12 hours after the last inhalation. Determination of cortisol in urine did not lead to plausible results, because according to the sponsor, there were discrepancies and doubts about the collection of urine which may have led to lower cortisol in urine following the ciclesonide treatment compared to that after budesonide.

#### **This Reviewer's Comments**

The 12h AUC serum cortisol measurements is usually not recommended for evaluating differences in cortisol suppression, since there is a high probability to miss the peak cortisol unless sampling is done very often and really early in the morning. The sponsor started the sampling at 8:00 AM, therefore, it may be better to use the 24 h data instead of the 12 h for making comparison between the 2 treatments, despite the sponsor's opinion.

The method used for calculating the degree of suppression relative to placebo and active comparator is questionable. The degree of cortisol suppression is usually determined as the difference in change from baseline to endpoint rather than the ratio of the geometric means between end point to placebo as determined in this study.

#### **Safety and tolerability:**

Repeated implementation of safety measurements (ECG, blood pressure heart rate, clinical laboratory investigation, physical examination, continuous recording of adverse events) did not reveal clinically relevant findings.

#### **CONCLUSION**

- Ciclesonide 1600 mcg/day produce a 10% reduction (95%-confidence limits 2%-17%) versus placebo in the AUC24-h serum cortisol mesor compared with a 24% (18%-29%) reduction for budesonide versus placebo. This difference from placebo among treatments may not be clinically relevant.

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**"Study on the circadian rhythm of cortisol in serum after repeated inhalation of 800 mcg ciclesonide in the morning, 800 mcg ciclesonide in the evening, and 400 mcg ciclesonide bid, as compared to placebo in healthy male volunteers"**

Clinical Study Report no.: 151/98  
Protocol No.: BY9010/FHP013  
Development Phase of Study: Phase I  
Study Initiation Date: 04/97  
Study Completion Date: 05/97  
Chief Investigator: W. Siegmund, MD, Germany

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### **Objectives**

#### **Primary**

- Investigation of the systemic bioactivity of ciclesonide after repeated inhalation of 800 mcg in the morning, 800 mcg in the evening, and 400 mcg bid, as compared to placebo

#### **Secondary**

- Safety and local tolerability

### **Medication:**

- Metered dose inhalers containing placebo (Batch No.: 172397)
- Metered dose inhalers with 100 mcg ciclesonide per puff (Batch No.: 174397)
- Metered dose inhalers with 200 mcg ciclesonide per puff (Batch No.: 173397)

### **Subjects**

Twelve male healthy subjects (median age 24 years, median weight 77 kg) participated in the study.

### **Treatments**

- Treatment A: at 7.00 am.: placebo (4 puffs)  
at 7.00 pm.: placebo (4 puffs)
- Treatment B: at 7.00 am.: 800 mcg ciclesonide (4 puffs of 200 pg each)  
at 7.00 p.m.: placebo (4 puffs)
- Treatment C: at 7.00 am.: placebo (4 puffs)  
at 7.00 p.m.: 800 mcg ciclesonide (4 puffs of 200 pg each)
- Treatment D: at 7.00 am.: 400 mcg ciclesonide (4 puffs of 100 pg each)  
at 7.00 p.m.: 400 mcg ciclesonide (4 puffs of 100 pg each)

### **Study Design**

The study was conducted according to a randomized, placebo-controlled, double-blind, 4-period change-over design. The washout period between two subsequent study periods was at least 7 days, but no more than 14 days.

### **Pharmacodynamic Measurements**

Twenty four hour-cortisol profiles were determined on the 7th day of treatment in each study period. Blood was taken at 7.00 am., 8.00 am., 9.00 am, 10.00 am., 12.00 am., 2.00 p.m., 4.00 p.m., 6.00 p.m., 7.00 p.m., 8.00 pm., 9.00 p.m., 10.00 p.m. on day 7, and at 0.00 am., 2.00 am., 4.00 am., 6.00 am. and 7.00 am on day 8 of each study period.

**Safety and local tolerability:**

EGG, blood pressure, heart rate, E.N.T.-examination, clinical laboratory, urinalysis at predefined time points

**Statistical Analysis**

Analysis of variance was performed for the 4-period change-over design after logarithmic transformation. Geometric means and 90%-confidence limits were given for the respective Test/Reference ratios.

**RESULTS**

**Analytical Method**

The concentrations of cortisol in serum were determined by a fluorescence-polarisation-immuno-assay.

**Pharmacodynamic Results**

No subjects dropped out during the study and according to the sponsor, all subjects terminated the study according to the protocol. Figure 1 shows the mean serum cortisol levels time profiles following multiple administration of the treatments for 7 days. Table 1 summarizes the cortisol geometric means and 90% confidence intervals of the ratio of the geometric means of test/placebo.

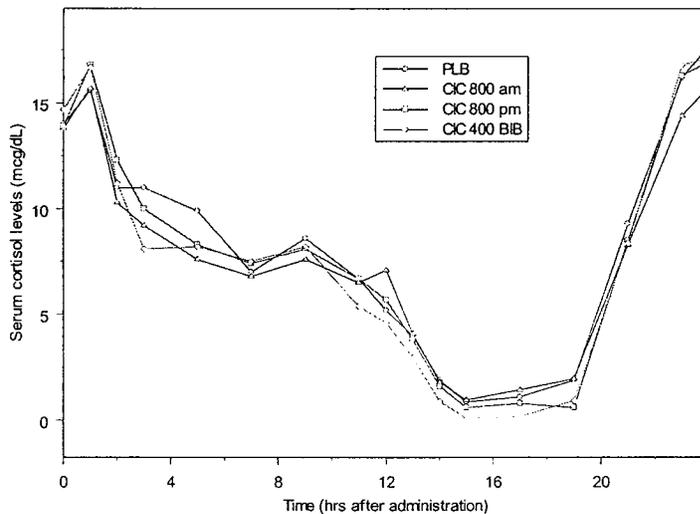


Figure 1. Mean serum cortisol time-profiles (day 7) following multiple administration.

**Table 1.** Geometric means of AUC/24 and 90%confidence intervals of the ratio of test/placebo

Product ID/Batch # (NME)	Treatments (Dose)	Reference	Serum cortisol	
			geometric mean cortisol mesor	point estimate to reference (90% confidence interval)
173397	800µg sid in the morning	placebo	6.75	0.94 (0.86-1.02)
173397	800µg sid in the evening	placebo	7.08	0.98 (0.90-1.07)
174397	400µg bid	placebo	6.75	0.93 (0.86-1.02)
172397	placebo	xxxxx	7.22	xxxxxx

**SUMMARY OF FINDINGS**

- In each of the four study periods, the mean 24-hour profile of cortisol in serum showed a typical circadian course.
- The mean cortisol profiles obtained with the different ciclesonide treatment regimens were similar to the mean cortisol profile obtained with placebo.

**GENERAL COMMENTS**

- This study did not include the assessment of 24 hr serum cortisol at baseline and therefore, geometric means and 90%-confidence for the Test/Reference ratios were calculated without correction from baseline.
- A one to two week washout period used in this study may not be sufficient to eliminate any carry over for the previous treatment.

**CONCLUSION**

- Since serum cortisol levels at baseline were not determined and the washout period between treatments is rather short, a statement that mean cortisol profiles obtained with the different ciclesonide treatment regimens are similar to that obtained with placebo is inconclusive.

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**"A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel Group, Multiple-Dose Study of the Potential Effects of Ciclesonide and Fluticasone Propionate on HPA-Axis in Adult Asthma Patients"**

Protocol No.: XRP1526B-102  
Development Phase of Study: Phase I  
Study Initiation Date: 15 February 2001  
Study Completion Date: 13 August 2001 **b(4)**  
Chief Investigator: 

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Aventis Pharmaceuticals Inc.  
Bridgewater, NJ 08807 USA

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### **Objectives**

- to evaluate the potential effects of inhaled ciclesonide and fluticasone propionate on the HPA-axis function in asthmatic adults.

### **Study Design**

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study; adult patients with mild to moderate were treated with ciclesonide either once daily or twice daily, fluticasone propionate twice daily, or placebo for 12 weeks.

### **Treatments**

Patients were randomized at Visit 3 (Day 1) to receive one of the following double-blind treatments:

- Ciclesonide 400 mcg once daily (in the evening)
- Ciclesonide 400 mcg twice daily
- Fluticasone propionate 440 mcg twice daily
- Matching placebo.

Following randomization, there were six additional visits, for a total of nine visits during the study. At 6 and 12 weeks of treatment (Visits 6 and 9), HPA-axis function was again assessed prior to and following cosyntropin stimulation testing. In addition to randomized treatment, patients were provided albuterol MDIs for use as rescue medication.

### **Population**

The patient population consisted of adults who had a 6-month history of mild-to-moderate persistent asthma, who used  $\beta_2$ -agonists on demand at least twice weekly for 6 months, who had an FEV<sub>1</sub> 70% of predicted, and who demonstrated normal HPA-axis function at baseline. There were 164 patients randomized to receive one of four double-blind treatments: 41 patients were randomized to placebo, 40 to ciclesonide 400  $\mu$ g q.d. (administered in the evening), 42 to ciclesonide 400  $\mu$ g b.i.d. (800  $\mu$ g/day), and 41 to fluticasone 440  $\mu$ g b.i.d. (880  $\mu$ g/day). The table below summarizes the demographic characteristics of the subjects.

Demographic characteristic	Ciclesonide			Fluticasone propionate 880 µg/day N=41	Overall total N=164
	Placebo N=41	400 µg/day N=40	800 µg/day N=42		
Age (years)					
N	41	40	42	41	164
Mean±SD	36.3±12.16	36.9±11.48	38.2±12.74	36.4±11.12	37.0±11.81
Range	18-78	18-60	18-72	18-68	18-78
Age group (years) – N (%)					
<65	40 (97.6)	40 (100.0)	40 (95.2)	40 (97.6)	160 (97.6)
≥65	1 (2.4)	0 (0.0)	2 (4.8)	1 (2.4)	4 (2.4)
Sex – N (%)					
Male	16 (39.0)	23 (57.5)	20 (47.6)	20 (48.8)	79 (48.2)
Female	25 (61.0)	17 (42.5)	22 (52.4)	21 (51.2)	85 (51.8)
Race – N (%)					
White	35 (85.4)	35 (87.5)	37 (88.1)	33 (80.5)	140 (85.4)
Black	5 (12.2)	3 (7.5)	4 (9.5)	4 (9.8)	16 (9.8)
Asian/Oriental	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.4)	2 (1.2)
Multiracial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (2.4)	2 (5.0)	0 (0.0)	3 (7.3)	6 (3.7)
Oral contraceptive/HRT use (females) – N (%)					
Yes	8 (32.0)	7 (41.2)	8 (36.4)	6 (28.6)	29 (34.1)
No	17 (68.0)	10 (58.8)	14 (63.6)	15 (71.4)	56 (65.9)

### Pharmacodynamic data

Pharmacodynamic parameters were based on serum cortisol concentrations before and after low-dose and high-dose cosyntropin stimulation testing at Visits 2, 6, and 9 (or early termination); and urine cortisol measurements (urine free cortisol corrected for creatinine) over a 24-hour period collected at Visits 2, 6, and 9 (or early termination). The primary pharmacodynamic endpoint was the peak serum cortisol level measured within 60 minutes after the low-dose (1 mg) cosyntropin stimulation injection (the maximum of the three serum cortisol values measured at 20, 30, and 60 minutes after stimulation).

### Efficacy data

Efficacy parameters were based on measurements of pulmonary function tests (FEV<sub>1</sub>, FVC, and FEF<sub>25-75%</sub>) collected at all visits or early termination.

### Safety data

Safety was evaluated based on physical examination results, vital signs, and clinical laboratory values collected at Visits 2 and 9; oropharyngeal examination results at Visits 2 through 9; and adverse events collected at all visits.

### Statistical procedures

The primary pharmacodynamic analysis for the intent-to-treat (ITT) population was conducted using an analysis of covariance (ANCOVA) model of the change from baseline in the post-low-dose cosyntropin- stimulation peak serum cortisol level at end of study (Week 12 or early termination). A stepwise comparison was conducted of the ciclesonide and fluticasone treatment groups. The primary comparison between ciclesonide 400 µg/day and fluticasone 880 µg/day was tested at the  $\alpha=0.05$  level of significance. If that comparison was significant, then the comparison between ciclesonide 800 µg/day and fluticasone 880 µg/day was to be performed at the  $\alpha=0.05$  level of significance. The remaining four pairwise comparisons were formed at a significance level of  $\alpha=0.05$  for descriptive purposes. In addition to pairwise statistical tests, two-sided 95% confidence intervals for the treatment difference were also constructed for each of the six treatment comparisons. Low-dose peak serum cortisol was also analyzed using the per-protocol population.

Secondary pharmacodynamic endpoints were analyzed for the ITT population using ANCOVA models. In addition, change from baseline in the post-low-dose-cosyntropin-stimulation peak serum cortisol values at Week 6 and Week 12 were analyzed using the per-protocol population. Efficacy endpoints were analyzed using the ITT population for FEV1. Additional post-hoc ANCOVA analyses (not specified in the SAP) were conducted using the ITT population excluding females on oral contraceptives or HRT.

## **RESULTS**

### **Analytical Method**

#### **In-Study Validation**

The sponsor mentioned that a radioimmunoassay (RIA) was used to quantitatively measure the serum/urine concentration of cortisol in the study samples from clinical PK/PD studies. The LLOQ was 20 nM using 50 µL study samples. The calibration range was from 10 - 1280 nM. However, in study validation data was not provided.

#### **Pharmacodynamic Results**

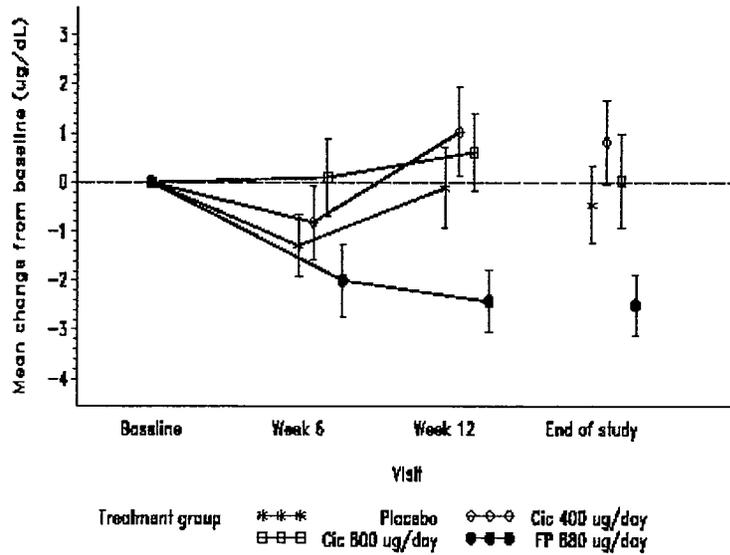
The primary PD endpoint was the change from baseline to end of study in peak serum cortisol value measured within 60 minutes after the low-dose (1 mg) cosyntropin stimulation (i.e., the highest of the three serum cortisol levels measured at 20, 30, and 60 minutes after stimulation). Low-dose-cosyntropin-stimulation peak cortisol levels at baseline and end of study, as well as change from baseline at end of study, for the ITT population are summarized in the Table 1. A graphic presentation of these mean changes in low-dose peak serum cortisol throughout the study is provided in the Figure 1. Analysis of change from baseline in low-dose peak cortisol levels (mg/dL) at end of study – ITT population is summarized in Table 2. Figure 2 shows the individual change from baseline in low-dose peak cortisol at week 6, end of study, early termination, and week 12 following multiple administration of the treatments.

The ANCOVA analysis of change from baseline at end of study in low-dose peak serum cortisol for the ITT population excluding females taking oral contraceptives or on HRT is summarized in the Table 3. The number of female patients in the study treated with oral contraceptives or HRT was small (29/159). Baseline mean low-dose peak serum cortisol levels for these female patients were higher than “all other patients” within each treatment group. At end of study, the female patients using oral contraceptives/HRT in the ciclesonide 400 µg/day and fluticasone 880 µg/day treatment groups exhibited positive changes in mean low-dose peak cortisol levels in relation to “all other patients” in the same treatment group who exhibited either no change or a decreases in mean cortisol levels.

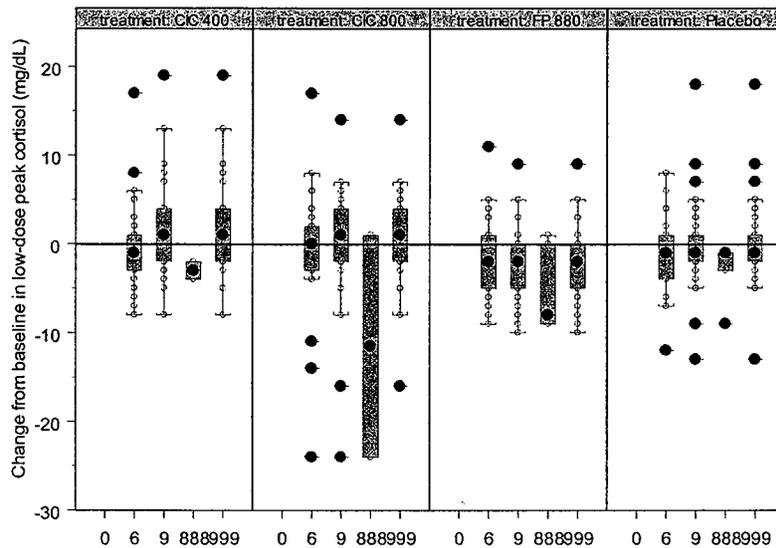
Figure 3 is a plot of the individual change from baseline in low-dose peak cortisol as a function of gender following multiple administration of the treatments. Figures 4 and 5 show the individual change from baseline urine free cortisol as a function of study visit for uncorrected and corrected for creatinine levels, respectively. The end-of-study analysis (ITT population) of treatment group comparisons of change from baseline in 24-hour urine free cortisol corrected for creatinine is summarized in Table 4.

**Table 1.** Low-dose-stimulation peak serum cortisol levels (mg /dL) at baseline, end of study (week 12 or early termination), and change from baseline at end of study – ITT population

Time point	Placebo N=39	Ciclesonide			Fluticasone propionate 880 µg/day N=40
		400 µg/day N=39	800 µg/day N=41	Total N=80	
<b>Baseline</b>					
N	39	39	41	80	40
Mean±SD	25.2±5.26	23.7±4.41	23.3±5.18	23.5±4.79	24.6±5.10
<b>End of study</b>					
N	39	39	41	80	40
Mean±SD	24.7±7.09	24.5±5.64	23.3±4.51	23.9±5.09	22.1±6.25
<b>Change from baseline at end of study</b>					
N	39	39	41	80	40
Mean±SD	-0.5±4.89	0.8±5.42	0.0±6.11	0.4±5.76	-2.5±3.88



**Figure 1.** Mean change (±SE) from baseline in low-dose peak cortisol (mg/dL)



**Figure 2.** Individual change from baseline in low-dose peak cortisol at week 6 (6), end of study (9), early termination (888) and week 12 (999) following multiple administration of the treatments

**Table 2.** Analysis of change from baseline in low-dose peak cortisol levels (mg/dL) at end of study – ITT population

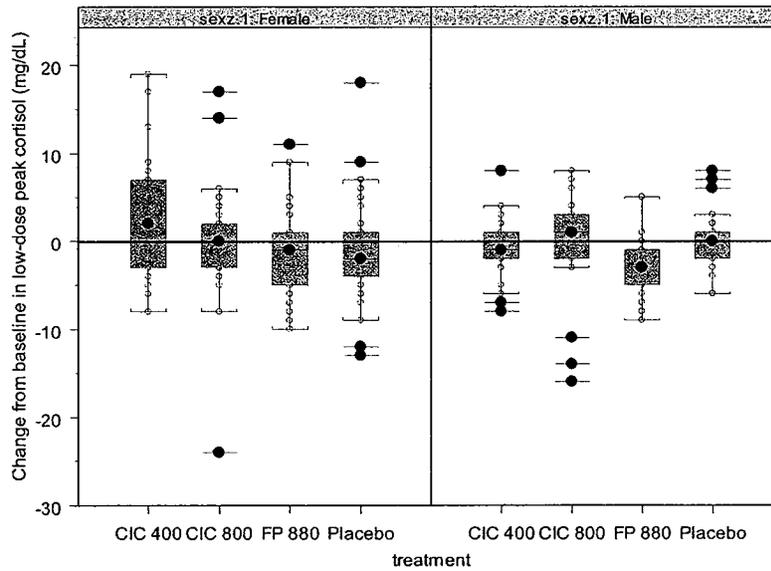
Treatment group	N	Baseline mean	Change from baseline		
			Adjusted mean	SE	95% CI
Placebo	39	25.18	-0.37	0.790	(-1.94; 1.19)
Cic 400 µg/day	39	23.69	0.60	0.779	(-0.94; 2.14)
Cic 800 µg/day	41	23.32	-0.50	0.764	(-2.01; 1.01)
FP 880 µg/day	40	24.63	-2.28	0.777	(-3.82; -0.74)

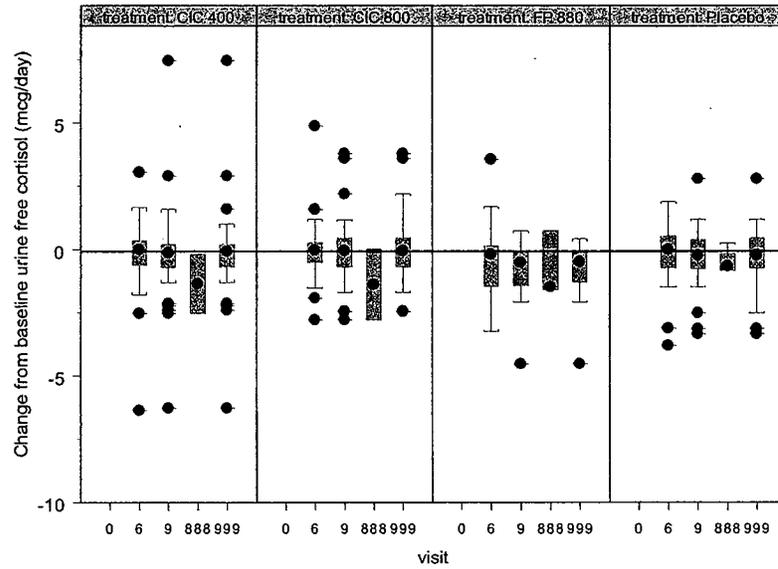
Pairwise comparisons:	Adjusted means				
	Difference	SE	95% CI	p-value	
Cic 400 µg/day – FP 880 µg/day	2.88	1.090	(0.73; 5.04)	0.0091	
Cic 800 µg/day – FP 880 µg/day	1.78	1.074	(-0.34; 3.91)	0.0991	
Placebo – Cic 400 µg/day	-0.98	1.117	(-3.18; 1.23)	0.3834	
Placebo – Cic 800 µg/day	0.12	1.096	(-2.04; 2.29)	0.9106	
Placebo – FP 880 µg/day	1.91	1.101	(-0.27; 4.08)	0.0854	
Cic 400 µg/day – Cic 800 µg/day	1.10	1.082	(-1.04; 3.24)	0.3112	

**Table 3.** Analysis of change from baseline in low-dose peak cortisol levels (mg/dL) at end of study – ITT population excluding females on oral contraceptives or HRT

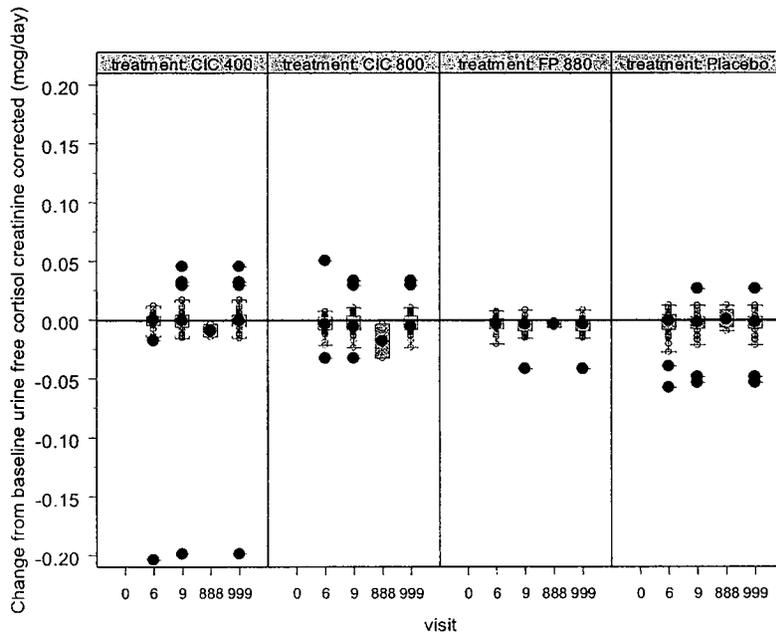
Treatment	N	Baseline mean	Adjusted mean change from baseline	Comparison with placebo		Comparison with fluticasone propionate	
				95% CI	p-value	95% CI	p-value
Placebo	31	23.77	-0.22	-	-	(1.05; 4.23)	0.0013
Cic 400 µg/day	32	23.09	0.01	(-1.88; 1.41)	0.7802	(1.33; 4.41)	0.0004
Cic 800 µg/day	33	22.82	0.35	(-2.20; 1.06)	0.4899	(1.68; 4.74)	0.0001
FP 880 µg/day	34	23.32	-2.86	(1.05; 4.23)	0.0013	-	-



**Figure 3.** Individual change from baseline in low-dose peak cortisol as a function of gender following multiple administration of the treatments



**Figure 4.** Individual change from baseline urine free cortisol following multiple administration of the treatments



**Figure 5.** Individual change from baseline urine free cortisol creatinine corrected following multiple administration of the treatments

**Table 4.** Analysis of change from baseline in 24-hour urine free cortisol corrected for creatinine (mg/mg creatinine) at end of study – ITT population

Treatment group	N	Baseline Mean	Change from baseline				p-value
			Raw Mean	Adjusted Mean	Standard Error	95% Confidence Interval	
Placebo	33	0.0182	-0.0045	-0.0036	0.00148	(-0.0085; -0.0007)	-
Ciclesonide 400 µg/day	39	0.0200	-0.0037	-0.0011	0.00145	(-0.0061; 0.0037)	-
Ciclesonide 800 µg/day	41	0.0171	-0.0035	-0.0037	0.00141	(-0.0065; -0.0009)	-
Fluticasone 880 µg/day	39	0.0143	-0.0061	-0.0087	0.00145	(-0.0115; -0.0059)	-
<b>Pairwise comparisons:</b>							
Cic 400 µg/day - FP 880 µg/day				0.0076	0.00204	( 0.0036; 0.0117)	0.0003
Cic 800 µg/day - FP 880 µg/day				0.0050	0.00199	( 0.0011; 0.0090)	0.0127
Placebo - Cic 400 µg/day				-0.0025	0.00207	(-0.0066; 0.0016)	0.2373
Placebo - Cic 800 µg/day				0.0001	0.00203	(-0.0039; 0.0041)	0.9519
Placebo - FP 880 µg/day				0.0052	0.00205	( 0.0011; 0.0092)	0.0111
Cic 400 µg/day - Cic 800 µg/day				0.0026	0.00201	(-0.0014; 0.0066)	0.1998

## SUMMARY OF FINDINGS

### Pharmacodynamics:

#### Low-dose peak serum cortisol:

- The change from baseline at end of study in low-dose peak serum cortisol (ITT population) for the comparison of ciclesonide 400 µg/day to fluticasone 880 µg/day was statistically significant difference (p=0.0091). The fluticasone 880 µg/day group had a 9.3% decrease in the mean, whereas the ciclesonide 400 µg/day group had an increment of 0.60 mg/dL (2.5% increase in the mean). However, when compared to placebo, both treatments were not statistically significant different.
- The pairwise comparison of ciclesonide 800 µg/day to fluticasone 880 µg/day was not statistically different (p=0.0991). However, the change from baseline in low-dose peak cortisol was more variable for ciclesonide 800 µg/day with a tendency of higher number of outlier (negative values). When compared to placebo ciclesonide 800 µg/day was also not statistically significant different.
- The pairwise comparison of ciclesonide 400 µg/day to ciclesonide 800 µg/day was NOT statistically different (p=0.31).
- The change from baseline in low-dose peak cortisol was more variable in female subjects than that in male subjects with a tendency of higher positive values.

#### Urine cortisol

- There were statistically significant differences in three pairwise comparisons: ciclesonide 400 µg/day versus fluticasone 880 µg/day, ciclesonide 800 µg/day versus fluticasone 880 µg/day, and placebo versus fluticasone 880 µg/day. In all three comparisons, the fluticasone 880 µg/day treatment group exhibited a change in mean 24-hour urine free cortisol corrected for creatinine of -45.8% compared to changes in the mean of 7.2%, -12.2%, and -8.6% for ciclesonide 400 mg/day, ciclesonide 800 mg/day, and placebo, respectively. However, the minimum and maximum values for the change from baseline in urine cortisol for the fluticasone 880 µg/day were within those observed for placebo and for ciclesonide 400 µg/day.

## CONCLUSION

- There is a tendency for the FP 880 µg/day treatment to produce higher degree of cortisol

suppression (mean values) than that observed for the ciclesonide 400 µg/day, ciclesonide 800 µg/day and placebo treatments. However, this difference may not be clinically relevant since the variation in change from baseline in low-peak cortisol and change from baseline in urine cortisol creatinine corrected is within that observed across treatment.

**GENERAL COMMENTS**

- The sponsor did not provide data for the validation of the analytical method used to analyze cortisol.

**APPEARS THIS WAY  
ON ORIGINAL**

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**"A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel Group, Multiple-Dose Study of the Potential Effects of Ciclesonide and Fluticasone Propionate on HPA-Axis in Adult Asthma Patients"**

Protocol No.: XRP1526B-103  
Development Phase of Study: Phase Ib  
Study Initiation Date: 31 July 2001  
Study Completion Date: 6 Oct 2001  
Chief Investigator: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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**Objectives**

- to evaluate the effects of high doses of inhaled ciclesonide compared with fluticasone propionate and placebo on the HPA-axis function in asthmatic patients.

**Study Design**

This was a randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study; patients were treated with ciclesonide, fluticasone propionate, or placebo twice daily for 29 days.

**Treatments**

Patients were treated for 29 days with:

- ciclesonide 400 µg twice daily,
- ciclesonide 800 µg twice daily,
- fluticasone propionate 440 µg twice daily,
- fluticasone propionate 880 µg twice daily, or
- placebo matching one of the active treatments.

All treatments were delivered as metered dose inhalations.

**Population**

The patient population consisted of adults who had a  $\geq 3$ -month history of moderate-to-severe persistent asthma, who had an FEV1  $\geq 40\%$  and  $\leq 80\%$  of predicted, who demonstrated or had a documented history of reversibility of FEV1 of  $\geq 12\%$ , and who demonstrated a normal HPA-axis function at screening. A total of 77 adult patients were screened, of which 60 were randomized and treated with double-blind study medication: 12 patients each received placebo, ciclesonide 400 µg b.i.d. (800 µg/day), ciclesonide 800 µg b.i.d. (1600 µg/day), fluticasone 440 µg b.i.d. (880 µg/day), or fluticasone 880 µg b.i.d. (1760 µg/day). All 60 randomized and treated patients completed the full 29-day treatment period.

Except for one patient in the placebo treatment group, all patients were  $\leq 65$  years of age. There were two-fold differences in the distribution of males and females in individual treatment groups, but the overall distribution of males (45.0%) and females (55.0%) was similar. All patients were either white (55.0%) or black (45.0%). Eight of the 33 randomized females (24.2%) in the study were using oral contraceptives or hormone replacement therapy at baseline.

### Pharmacodynamic data

Pharmacodynamic parameters were based on serum cortisol AUC0-24h levels at Day -1 (prior to randomization) and Days 8, 15, 22, and 29 (or early termination); serum cortisol measurements before and after low-dose (1 µg) cosyntropin stimulation testing at screening and Day 30 (or early termination); and urine cortisol measurements (urine cortisol corrected for creatinine and urinary free cortisol) over a 24-hour period collected at Days 1 and 29 (or early termination). The primary pharmacodynamic endpoint was serum cortisol AUC0-24h.

### Serum cortisol testing

#### Area under the curve (AUC0-24h)

Serum cortisol concentrations over 24 hours were to be measured on Days -1, 8, 15, 22, and 29 at the times indicated below:

#### Sampling Times for AUC0-24h Serum Cortisol Testing

Sampling Time	7 AM	8 AM	9 AM	10 AM	12 PM	2 PM	4 PM	6 PM	8 PM	10 PM	12 AM	2 AM	4 AM	6 AM	7 AM	8 AM
Collect Serum for Cortisol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Twenty-four hour serum cortisol was analyzed using electrochemiluminescence immunoassay methodology.

### Cosyntropin stimulation

Serum cortisol measurements were obtained 15 minutes prior to and 20, 30, and 60 minutes following a low-dose cosyntropin stimulation test (1 µg). Serum cortisol testing was to be performed at Visit 2 (screening) prior to treatment with study medication and on Day 30 (or upon early termination).

### Urine cortisol testing

For each patient, urine was collected for 24 hours beginning on the morning of Day -1 and Day 29 (or early termination). The patient was empty the contents of his or her bladder prior to 8:00 AM the morning of Day -1 and Day 29 and then collect all subsequent urine for 24 hours, until 8:00 AM the following morning (Days 1 and 30). Urine cortisol was analyzed using high-performance liquid chromatography.

### Efficacy data

Efficacy parameters were based on measurements of pulmonary function tests (FEV1, FVC, and FEF25-75%) collected at screening and Day 30 (or early termination).

### **Safety data**

Safety was evaluated based on physical examination results, vital signs, body weight, and clinical laboratory values collected at screening and Day 30 (or early termination); oropharyngeal examination results at screening and Days 1, 8, 22, and 30 (or early termination); and adverse events collected throughout the study.

### **Statistical procedures**

The primary pharmacodynamic analysis for the intent-to-treat (ITT) population was conducted using an analysis of covariance (ANCOVA) model of the change from baseline in serum cortisol AUC<sub>0-24h</sub> levels at end of study (Day 29 or early termination). Ten pairwise differences between the treatment groups were assessed, with primary emphasis on the ciclesonide 1600 µg/day versus fluticasone 1760 µg/day and the ciclesonide 800 µg/day versus fluticasone 880 µg/day comparisons. The primary comparison between ciclesonide 1600 µg/day and fluticasone 1760 µg/day was tested at the  $\alpha=0.05$  level of significance. The remaining eight pairwise comparisons were formed at a significance level of  $\alpha=0.05$  for descriptive purposes. In addition to pairwise statistical tests, two-sided 95% confidence intervals for the treatment difference were also constructed for each of the ten treatment comparisons. Change from baseline in serum cortisol AUC<sub>0-24h</sub> at end of study was also conducted using the per-protocol population. Secondary pharmacodynamic endpoints were analyzed for the ITT population using ANCOVA models. In addition, selected secondary pharmacodynamic endpoints were analyzed using the per protocol population. Efficacy endpoints were analyzed using the ITT population for FEV<sub>1</sub>.

## **RESULTS**

### **Analytical Method**

Twenty-four hour serum cortisol was analyzed using electrochemiluminescence immunoassay methodology. Urine cortisol was analyzed using high-performance liquid chromatography.

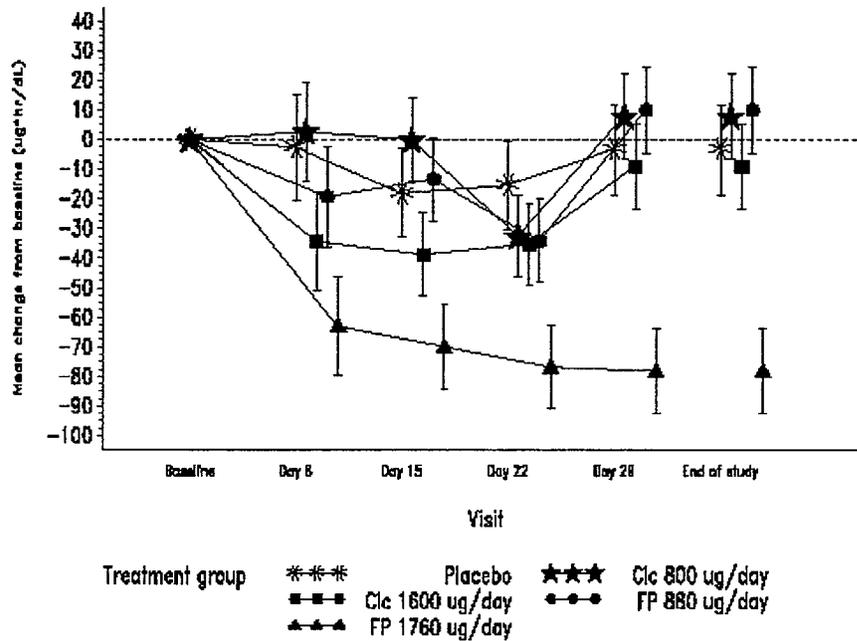
### **Pharmacodynamic Results**

Analysis of mean change from baseline in 24-hour serum cortisol AUC for ITT population are summarized in the Table 1. A graphic presentation of these mean changes in serum cortisol throughout the study is provided in the Figure 1. A pairwise comparisons of change from baseline in 24-hour serum cortisol AUC at Day 29 – ITT population is summarized in Table 2. Figure 2 shows the individual percent change from baseline in cortisol 24hr AUC and cortisol AUC change from baseline following multiple administration of the treatments. Figure 3 shows the individual change from baseline in low-dose peak cortisol following multiple administration of the treatments. Table 3 summarizes the change from baseline in low-dose peak cortisol following multiple administration of the treatments-end of study.

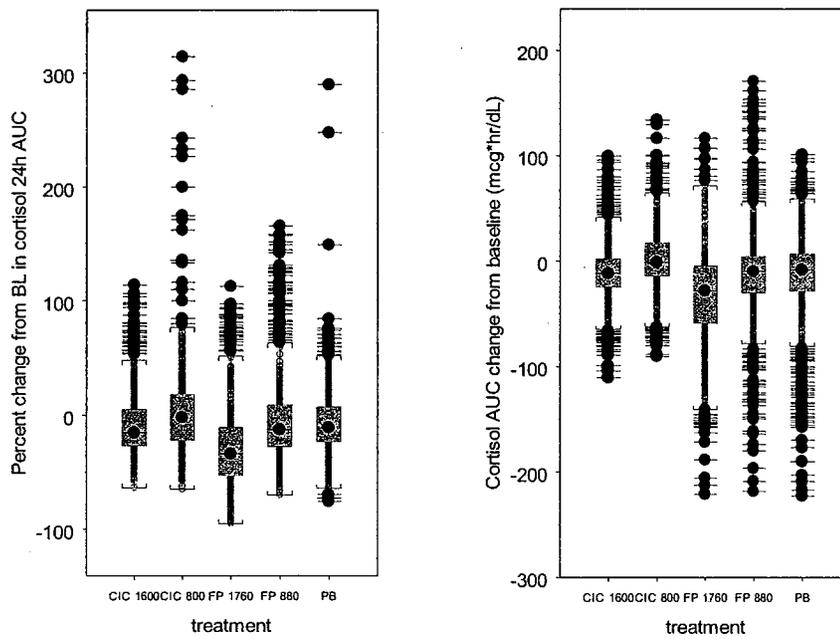
Table 4 shown an analysis of change from baseline in 24-hour urine free cortisol corrected for creatinine at Day 29 – ITT population. Table 5 presents pairwise comparisons of change from baseline in 24-hour urine free cortisol corrected for creatinine at Day 29 for the ITT population. Figure 4 shows the individual change from baseline in 24-hour urine free cortisol uncorrected and corrected for creatinine at Day 29 for the ITT population.

**Table 1.** Analysis of 24-hour serum cortisol AUC ( $\mu\text{g}\cdot\text{hr}/\text{dL}$ ) at Day 29 – ITT population

Treatment	N	Baseline mean	Mean at Day 29	Mean change from baseline (SD)	Adjusted mean change from baseline	95% confidence interval
Placebo	12	246.4	226.8	-19.6 (77.1)	-3.3	(-33.75; 27.24)
C1c 800 $\mu\text{g}/\text{day}$	12	192.0	210.5	18.5 (45.8)	8.0	(-20.50; 36.41)
C1c 1600 $\mu\text{g}/\text{day}$	12	195.8	191.7	-4.1 (44.1)	-8.9	(-37.39; 19.53)
FP 880 $\mu\text{g}/\text{day}$	12	209.3	210.0	0.7 (54.4)	10.0	(-18.90; 38.85)
FP 1760 $\mu\text{g}/\text{day}$	12	196.2	137.6	-58.6 (85.2)	-78.1	(-107.05; -49.11)



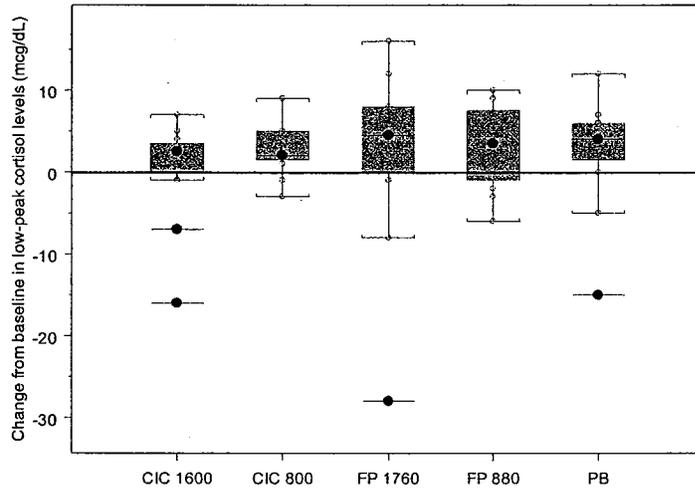
**Figure 1.** Mean change ( $\pm\text{SE}$ ) in 24-hour serum cortisol AUC from baseline over time – ITT population.



**Figure 2.** Individual percent change from baseline in cortisol 24hr AUC (right panel) and cortisol AUC change from baseline following multiple administration of the treatments

**Table 2.** Selected pairwise comparisons of change from baseline in 24-hour serum cortisol AUC ( $\mu\text{g}\cdot\text{hr}/\text{dL}$ ) at Day 29 – ITT population

Treatment comparison	p-value	Difference in adjusted means	95% confidence interval
Cic 1600 $\mu\text{g}/\text{day}$ vs FP 1760 $\mu\text{g}/\text{day}$	0.0013	69.2	( 28.34; 109.96)
Cic 800 $\mu\text{g}/\text{day}$ vs FP 880 $\mu\text{g}/\text{day}$	0.9209	-2.02	( -42.67; 38.63)
FP 1760 $\mu\text{g}/\text{day}$ vs placebo	0.0009	-74.8	(-117.51; -32.13)
Cic 1600 $\mu\text{g}/\text{day}$ vs placebo	0.7854	-5.7	( -47.29; 35.94)
FP 880 $\mu\text{g}/\text{day}$ vs placebo	0.5412	13.2	( -29.94; 56.40)
Cic 800 $\mu\text{g}/\text{day}$ vs placebo	0.5972	11.2	( -31.10; 53.52)



**Figure 3.** Individual change from baseline in low-dose peak cortisol following multiple administration of the treatments

**Table 3.** Change from baseline in low-dose peak cortisol (mcg/dL) following multiple administration of the treatments-end of study

Treatment	Mean	minimum	maximum	median
Placebo	2.5			4.0
Cic 800 µg/day	2.75			2.0
Cic 1600 µg/day	0.41			2.5
FP 880 µg/day	3.16			3.5
FP 1760 µg/day	2.17			4.5

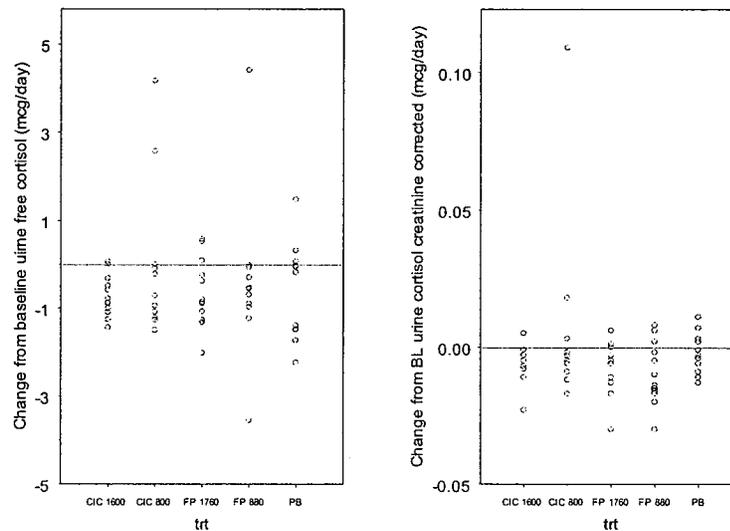
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**Table 4.** Analysis of change from baseline in 24-hour urine free cortisol corrected for creatinine (mg/mg creatinine) at Day 29 – ITT population

Treatment	N	Baseline mean	Mean at Day 29	Mean change from baseline (SD)	Adjusted mean change from baseline	95% confidence interval
Placebo	11	0.016	0.014	-0.002 (0.0075)	-0.010	(-0.0194; -0.0001)
Cic 800 µg/day	12	0.017	0.022	0.005 (0.0339)	0.006	(-0.0030; 0.0140)
Cic 1600 µg/day	12	0.018	0.011	-0.007 (0.0068)	-0.008	(-0.0163; 0.0006)
FP 880 µg/day	12	0.022	0.012	-0.009 (0.0114)	-0.002	(-0.0110; 0.0067)
FP 1760 µg/day	12	0.017	0.009	-0.008 (0.0097)	-0.010	(-0.0188; -0.0016)

**Table 5.** Selected pairwise comparisons of change from baseline in 24-hour urine free cortisol corrected for creatinine (mg/mg creatinine) at Day 29 – ITT population

Treatment comparison	p-value	Difference in adjusted means	95% confidence interval
Cic 1600 µg/day vs FP 1760 µg/day	0.6977	0.002	(-0.0098; 0.0146)
Cic 800 µg/day vs FP 880 µg/day	0.2120	0.008	(-0.0045; 0.0199)
FP 1760 µg/day vs placebo	0.9413	-0.001	(-0.0133; 0.0124)
Cic 1600 µg/day vs placebo	0.7649	0.002	(-0.0108; 0.0146)
FP 880 µg/day vs placebo	0.2770	0.008	(-0.0063; 0.0214)
Cic 800 µg/day vs placebo	0.0224	0.015	( 0.0023; 0.0283)



**Figure 4.** Individual change from baseline in 24-hour urine free cortisol uncorrected and corrected for creatinine (mg/mg creatinine) at Day 29 – ITT population

## SUMMARY OF FINDINGS

### Pharmacodynamics:

#### Serum Cortisol AUC0-24h

- The change from baseline at end of study in serum cortisol AUC0-24 for the comparison of ciclesonide 1600 µg/day to fluticasone 1760 µg/day was statistically significant difference (p=0.0013). The fluticasone 1760 µg/day group had a 28% decrease in the mean from baseline, whereas the ciclesonide 1600 µg/day group had a 7.5% decrease in the mean).
- The change from baseline at end of study in serum cortisol AUC0-24 for fluticasone 1760 µg/day was the only one statistically significant different from placebo (p=0.0018). However, placebo treatment had as low and high values as those observed for fluticasone 1670 µg/day.

- The change from baseline at end of study in serum cortisol AUC<sub>0-24</sub> for the comparison of ciclesonide 800 µg/day to fluticasone 880 µg/day was NOT statistically significant difference (p=0.92)

#### **Low-dose peak serum cortisol:**

- The mean change from baseline in low-dose peak cortisol was similar across treatments. ANCOVA analyses of low-dose peak cortisol levels at Day 30, change from baseline in degree of stimulation in low-dose peak cortisol levels at Day 30, and change from baseline in serum cortisol levels pre- and post-stimulation at Day 30 all revealed no statistically significant differences between treatment groups (data not shown).

#### **Urine cortisol**

- For Day 29 analyses of 24-hour urine cortisol corrected for creatinine (ITT population), the comparison of ciclesonide 1600 mg/day to fluticasone 1760 mg/day did not demonstrate statistical significant difference. Also when compared to placebo both treatment groups demonstrated reductions in urine cortisol corrected for creatinine, but the difference was not statistically significant.

#### **CONCLUSION**

- There is a tendency for the FP 1760 µg/day treatment to produce higher degree of cortisol suppression (measured as serum cortisol AUC<sub>0-24</sub> mean values) than that observed for the ciclesonide 1600 µg/day and placebo treatments. However, this difference may not be clinically relevant since the individual variation in change from baseline in serum cortisol AUC<sub>0-24</sub> for the FP 1760 µg/day treatment was similar to that observed for placebo treatment.

#### **GENERAL COMMENTS**

- The sponsor did not provide data for the validation of the analytical method used to analyze cortisol.
- The mean values of change from baseline in 24h AUC cortisol at end of study calculated by this reviewer using individual data provided by the sponsor do not agree to those calculated by the sponsor (e.g. -35.7 vs. ~ -59 mcg/dL for fluticasone 1760 µg/day).

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“Effect of inhaled ciclesonide on cortisol levels and hypersensitivity to AMP in subjects with bronchial asthma”

Clinical Study Report no.: 49/2000  
Protocol No.: BY9010/FK1 107  
Development Phase of Study: Phase 2  
Study Initiation Date: 01/04/98  
Study Completion Date: 09/28/1999  
Chief Investigator: \_\_\_\_\_

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b(4)

### Objectives

#### Primary

- To study the effect ciclesonide vs. fluticasone propionate and placebo, respectively, on HPA axis as well as on AMP (adenosine-5-monophosphate) induced bronchoconstriction and on lung function in asthmatic subjects.

#### Secondary

- Safety and local tolerability

#### Medication:

- Metered dose inhalers containing placebo (Batch No.: 172397)
- Metered dose inhalers with 100 mcg ciclesonide per puff (Batch No.: 174397)
- Metered dose inhalers with 200 mcg ciclesonide per puff (Batch No.: 173397)

### Subjects

A summary of the demographic characteristics of the subjects participated in the study is presented in the table below:

Parameter		itt	pp
Patients	n	26	23
Sex			
Male / Female	n	20 / 6	17 / 6
Age	yrs	25 (20 - 47)	25 (20 - 47)
Smoking (never/ ex/current)	n	12 / 6 / 8	10 / 6 / 7
FEV <sub>1</sub>	L	3.64 ± 0.62	3.68 ± 0.62
FEV <sub>1</sub>	%pred. (range)	88 (67 - 114)	90 (73 - 114)
PC <sub>20</sub> FEV <sub>1</sub>	mg/ml	15.3 (10.0 - 23.5)	15.1 (9.3 - 24.4)

### Treatments

The supplied medications were MDIs containing either

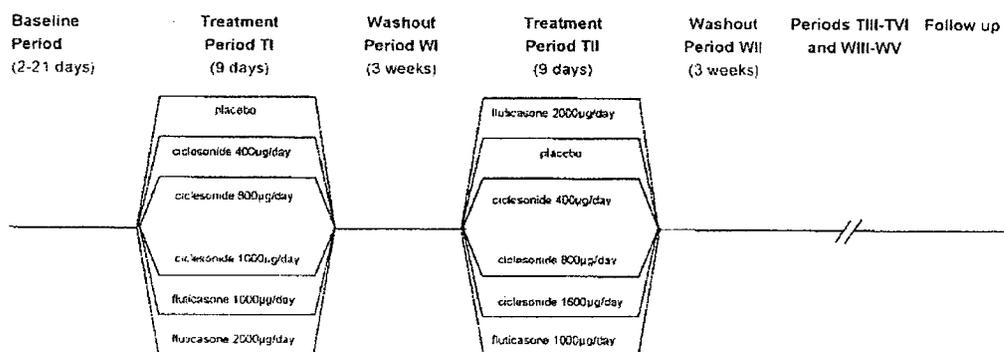
- placebo (batch No.: 97J01/1, CT970132/1) or

- 100 mcg ciclesonide/puff (batch 2BG001/1, CT970134/1) or
- 200 mcg ciclesonide/puff (batch Nos. 46G003/2, CT970135/1) or
- 125 mcg FP/puff (batch Nos.: 7L561/1, 8N203/1) or
- 250 pg FP/puff (batch Nos. 8N206/1, 7M216/1).

### Study Design

The trial was designed as a randomized, placebo-controlled six period changeover study using the double-observer technique. The ciclesonide/placebo study parts were double-blind; the FP parts were partially blinded. The trial consisted of the following periods:

- baseline period (2-14 days)
- treatment periods TI to TVI (9 days each) separated by washout periods WI to WI (3-12 weeks each)
- follow up,



Eligible patients were randomly assigned to one of six treatment sequences occurring in a Latin square. Each patient inhaled the following drugs and doses:

- placebo,
- ciclesonide 400 mcg in the evening,
- ciclesonide 800 mcg in the evening,
- ciclesonide 800 mcg bid,
- FP 500 mcg bid
- FP 1000 mcg bid.

Eligible subjects underwent the following investigations at visit BO:

- medical history
- routine physical examination including resting ECG (12 leads),
- laboratory work-up,
- pulmonary function test (FEV<sub>1</sub>, FVC),
- AMP challenge

- Pregnancy test

### **Pharmacodynamic Measurements**

Twenty four hour-cortisol profiles were recorded at visits T1, T4, T7, T10, T13, and T16. Blood was taken in 2-hour intervals starting from 8PM on the study day up to 8 PM the next day. 24-hr urine was collected at the same visits as listed above. Creatinine was also measured in urine to allow for correction.

### **Safety and local tolerability:**

EGG, blood pressure, heart rate, E.N.T.-examination, clinical laboratory, urinalysis at predefined time points

### **Statistical Analysis**

Primary variable for confirmative biostatistical analysis was the plasma cortisol mesor, i.e. the 24-h time average of plasma cortisol, which was calculated as  $AUC(0-24h)/24h$ .

**Primary variable:** The comparison of the 24h-time average of plasma cortisol was done by means of the corresponding analysis of variance (ANOVA) after logarithmic transformation. Prespecified pairwise comparisons were analyzed by corresponding contrasts.

**Secondary variables:** Urinary cortisol excretion was analyzed by ANOVA after logarithmic transformation.

### **Data Sets Analyzed**

Twenty six subjects were included in the ITT efficacy analysis. For the ITT-analysis of the primary variable plasma cortisol AUC all n=26 patients of this ITT population were included. As patient no. 51 completed only 3 treatment periods (800 and 1600 mcg ciclesonide, 1000 mcg/day FP), 153 instead of 156 (=26 x 6) observations were available for the ITT analysis.

N=23 patients form the pp population (population of valid cases). For the pp analysis of the primary variable plasma cortisol AUC all n=23 patients of the pp population were included.

## **RESULTS**

### **Analytical Method**

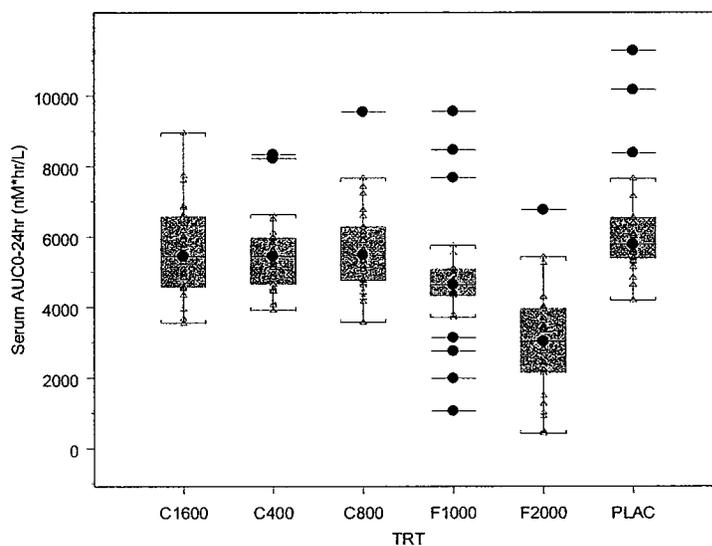
The concentrations of cortisol in serum were determined using a RIA kit.

### **Pharmacodynamic Results**

Figure 1 shows the individual AUC0-24 serum cortisol (nmol/L) following administration of the treatments. and 95% confidence limits for the ITT. A summary of plasma cortisol (AUC0-24Hr/24Hr) and 95% confidence intervals is given in Table 1. Table 2 gives the between-treatment comparison of plasma cortisol mesor expressed as point estimate and 95% CI for the respective treatment rations-IIT analysis. Figure 2 shows the plasma cortisol mesor referenced to placebo (mean ratio- ITT). Table 2 summarizes the urinary cortisol excretion adjusted for creatinine (nmol/mmol creatinine)-ITT analysis

**Table 1.** Plasma cortisol (AUC0-24Hr/24Hr) and 95% confidence intervals

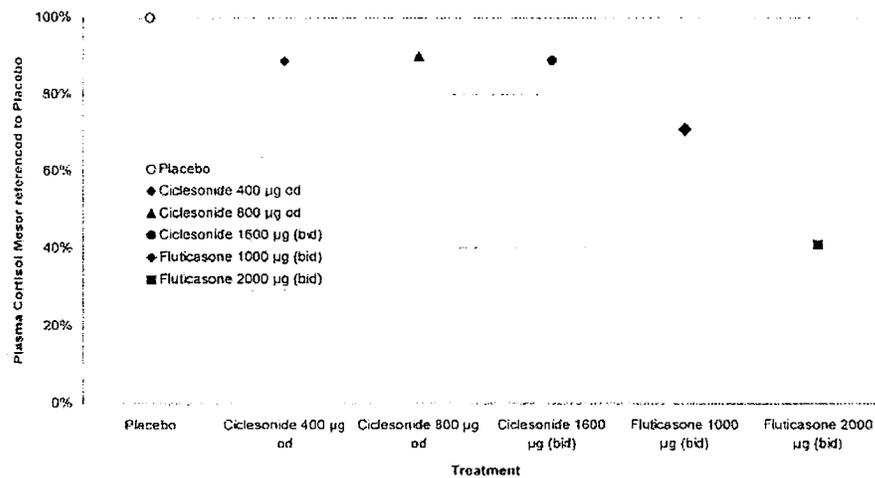
Treatment	Plasma Cortisol Mesor exp(LS-Mean) (nmol/l)	Lower 95%-CL (nmol/l)	Upper 95%-CL (nmol/l)
Placebo	257.53	225.74	293.80
Ciclesonide 400 µg od	228.38	200.18	260.54
Ciclesonide 800 µg od	231.91	203.82	263.86
Ciclesonide 1600 µg (bid)	228.81	201.10	260.33
Fluticasone 1000 µg (bid)	182.60	160.49	207.76
Fluticasone 2000 µg (bid)	105.52	92.50	120.39



**Figure 1.** Individual AUC0-24 serum cortisol levels following administration of the treatments (ITT)

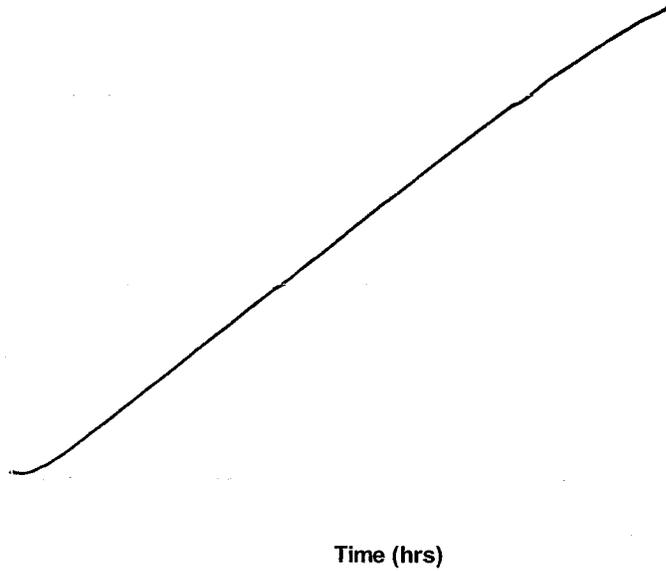
**Table 2.** Between-treatment comparison of plasma cortisol mesor expressed as point estimate and 95% CI for the respective treatment ratios-IIT analysis

Test	Reference	Test/Reference Point estimate	Test/Ref. Lower 95%-CL	Test/Ref. Upper 95%-CL
Ciclesonide 400 µg	Placebo	0.89	0.74	1.07
Ciclesonide 800 µg	Placebo	0.90	0.75	1.08
Ciclesonide 1600 µg	Placebo	0.89	0.74	1.07
Fluticasone 1000 µg	Placebo	0.71	0.59	0.85
Fluticasone 2000 µg	Placebo	0.41	0.34	0.49
Ciclesonide 800 µg	Ciclesonide 400 µg	1.02	0.84	1.22
Ciclesonide 1600 µg	Ciclesonide 400 µg	1.00	0.83	1.20
Ciclesonide 1600 µg	Ciclesonide 800 µg	0.99	0.82	1.18
Ciclesonide 800 µg	Fluticasone 1000 µg	1.27	1.06	1.52
Ciclesonide 800 µg	Fluticasone 2000 µg	2.20	1.83	2.64
Fluticasone 2000 µg	Fluticasone 1000 µg	0.58	0.48	0.69
Ciclesonide 400 µg	Fluticasone 1000 µg	1.25	1.04	1.50
Ciclesonide 1600 µg	Fluticasone 1000 µg	1.25	1.04	1.50
Ciclesonide 400 µg	Fluticasone 2000 µg	2.16	1.80	2.61
Ciclesonide 1600 µg	Fluticasone 2000 µg	2.17	1.80	2.61



**Figure 2.** Plasma cortisol mesor referenced to placebo (mean ratio- ITT)

Cortisol concentration (nM/L)

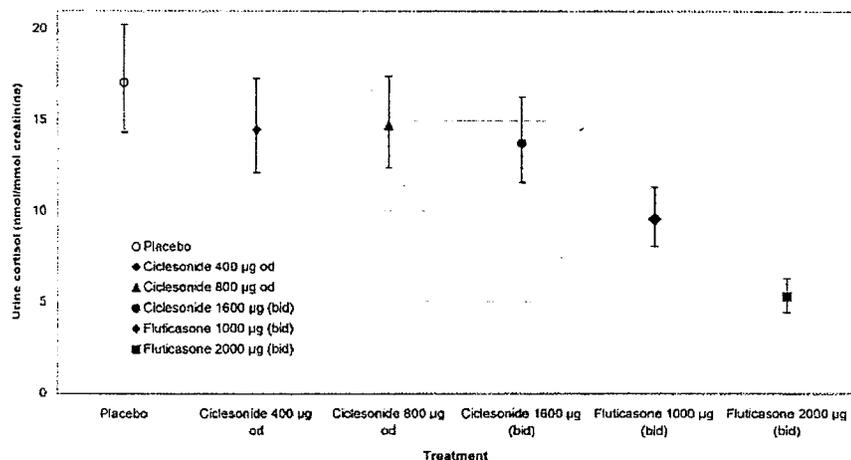


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Figure 3. Individual serum cortisol levels following administration of the treatments

**Table 3.** Urinary cortisol excretion adjusted for creatinine (nmol/mmol creatinine)-ITT analysis

Treatment	Urine Cortisol corrected for creatinine exp(LS-Mean) (nmol/mmol creat.)	Lower 95%-CL (nmol/mmol creat.)	Upper 95%-CL (nmol/mmol creat.)
Placebo	17.06	14.37	20.25
Ciclesonide 400 µg od	14.49	12.15	17.28
Ciclesonide 800 µg od	14.70	12.43	17.39
Ciclesonide 1600 µg (bid)	13.73	11.61	16.24
Fluticasone 1000 µg (bid)	9.59	8.11	11.35
Fluticasone 2000 µg (bid)	5.31	4.47	6.30



**Figure 3.** Urinary cortisol excretion corrected by creatinine-ITT analysis

### SUMMARY OF FINDINGS

- The 24-h plasma cortisol mesor following administration of 400- 800- and 1600 mcg/day CIC was reduced by 11%, 10% and 11%, respectively with respect to placebo treatment.
- Ciclesonide showed no dose dependency on cortisol suppression as based on 24hr serum cortisol levels
- The 24-h plasma cortisol mesor under following administration of 1000- and 2000 mcg/day fluticasone was reduced by 29% and 59%, respectively with respect to placebo which was statistically significant different.
- The effect of all doses of CIC was significantly different from the two fluticasone doses.
- Urinary cortisol excretion following CIC was reduced by 15%-20% versus placebo.
- Urinary cortisol excretion following FP was reduced by 44% and 59%, respectively. The respective confidence intervals were completely below 1, reflecting significant and dose dependant reductions of urinary cortisol excretion under fluticasone versus placebo.
- Cortisol values under fluticasone were significantly lower than under ciclesonide.

### GENERAL COMMENTS

- This study did not include the assessment of 24 hr serum cortisol at baseline and therefore, 95%-confidence for the Test/Reference ratios were calculated without correction from baseline.

### CONCLUSION

- Ciclesonide 400 µg/day and 1600 µg/day given for 9 days reduced serum cortisol levels by 11% compared to placebo.
- Ciclesonide produced no dose dependency on cortisol suppression in the range of 400-1600 µg/
- Fluticasone 1000 µg/day and 2000 µg/day reduced both 24-h plasma cortisol (and 24-h urinary cortisol excretion significantly compared to placebo, with the effects of fluticasone 2000 µg/day being more apparent than those of fluticasone 1000 µg/day.

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**“Population Pharmacokinetic / Pharmacodynamic Analysis of RM1 (Active Metabolite M1 of Ciclesonide) - Phase I and Phase III Data”**

**Technical Report:** DMPK/USA/2003-0019  
**Date of Final Report:** October 6, 2003  
**Phase:** I and III

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## **INTRODUCTION**

The population pharmacokinetics of RM1 were characterized in healthy and asthmatic patients receiving ciclesonide inhaled doses of 50- up to 3600 mcg. Data from 12 clinical Phase I studies (FHP009, FHP012, FHP015, FHP018, FHP019, FHP022, FHP023, FHP025, FHP026, FHP027, BTR-15/001, BTR-15/002), 3 clinical Phase III studies in adults (XRP1526B/321, XRP1526B/322, XRP1526B/323/324) and 2 Phase III studies in pediatrics (XRP1526B/341, XRP1526B/342) were used for population pharmacokinetic / pharmacodynamic (PK/PD) analysis. Phase I studies with extensive PK/PD data after administration of ciclesonide *via* metered dose inhalation (MDI) and Phase III studies with sparse PK/PD samples were included in the analysis. The influence of various demographic factors, co-existing disease states and concomitant medications on the disposition of RM1 was assessed using appropriate techniques.

## **OBJECTIVES**

- To estimate the population pharmacokinetics of the active metabolite of ciclesonide (RM1).
- To characterize the circadian rhythm of endogenous cortisol release (or production) and the relationship between systemic exposure of RM1 and endogenous cortisol concentrations.
- To explore the influence of covariates on RM1 pharmacokinetics including factors such as body weight, gender, age, race, liver status and disease state.

## **Formulation**

Ciclesonide solution formulation in a pressurized meter dose inhaler (MDI) available in doses of ~~50~~, 80 µg, and 160 µg /puff were used for the population analysis. Table 1 shows a detail of study treatments.

**b(4)**

**Table 1. Study Treatments**

Protocol	Batch Number	Dosage Form/Strength (Ex-valve)	Dosage Form/Strength (Ex-actuator)	REF
FHP009-117E97	CT9608010/1	Metered Dose inhalers 50 µg per puff	Metered Dose inhalers 40 µg per puff	9
	CT9608011/1	Metered Dose inhalers 100 µg per puff	Metered Dose inhalers 80 µg per puff	
	CT9608012/1	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	
FHP012-223/97	092197	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	10
FHP015-172/97	053297	Metered Dose inhalers 400 µg per puff	Metered Dose inhalers 320 µg per puff	11
FHP018-210/2000	034498	Metered Dose inhalers 400 µg per puff	Metered Dose inhalers 320 µg per puff	12
FHP019-304/98	015298	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	13
FHP022-307/98	149298	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	14
FHP023-563/99	090398	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	15
FHP025-253E/99	179498	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	16
FHP026-128/2000	033499	Metered Dose inhalers 100 µg per puff	Metered Dose inhalers 80 µg per puff	17
FHP027-211/2000	4BG003	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	18
BTR-15001	BTRX920A	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	19
BTR-15002	BTRX920A	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	20
XRP 1526B 321 & XRP 1526B 322	1BG010, 1BGA001	Metered Dose inhalers 50 µg per puff	Metered Dose inhalers 40 µg per puff	21, 22
	2BG005, 2BGA001	Metered Dose inhalers 100 µg per puff	Metered Dose inhalers 80 µg per puff	
	4BG009, 4BGA001	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	
XRP 1526B 323 & XRP 1526B 324	2BG005, 2BGA001	Metered Dose inhalers 100 µg per puff	Metered Dose inhalers 80 µg per puff	23
	4BG009, 4BGA001	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	
	0BG002	Metered Dose inhalers 400 µg per puff	Metered Dose inhalers 320 µg per puff	
XRP 1526B 341	1BG010	Metered Dose inhalers 50 µg per puff	Metered Dose inhalers 40 µg per puff	24
	2BG005	Metered Dose inhalers 100 µg per puff	Metered Dose inhalers 80 µg per puff	
	4BG009	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	
XRP 1526B 342	1BG011	Metered Dose inhalers 50 µg per puff	Metered Dose inhalers 40 µg per puff	25
	2BG006	Metered Dose inhalers 100 µg per puff	Metered Dose inhalers 80 µg per puff	
	4BG010	Metered Dose inhalers 200 µg per puff	Metered Dose inhalers 160 µg per puff	

**Subject Demographics**

There were a total of 635 subjects in this analysis with 2750, 5238 and 4470 observation records for ciclesonide, RM1 and cortisol concentrations, respectively. The mean (%CV) body weight and height were 78.7 kg (23.8%) and 171 cm (6.0%) for adults and 38.7 kg (39.3%) and 137.9 kg (9.2%) for pediatrics, respectively. The demographic profiles of these patient cohorts were comparable (see Table below).

**Table 2. Data description for discrete covariates across studies**

Covariate	Category	Distribution N (%)
Gender	Male	300 (47.2%)
	Female	310 (48.8%)
Population	Healthy	180 (28.3%)
	Mild -Moderate Asthmatics	253 (39.8%)
	Severe Asthmatics	105 (16.5%)
Race	Whites	471 (74.2%)
	Japanese	72 (11.3%)
	Blacks	20 (3.1%)
	Others	72 (11.3%)
Age	Pediatrics (<12 years)	53 (8.3%)
	Adults (12 - 65 years)	536 (84.4%)
	Elderly (>65 years)	21 (3.3%)

## Dosing Regimen and treatment

Table 3 shows a description of the dose regimen, disease state of the ITT population included in the study. The pediatric trials (341 and 342) were conducted as double-blind, placebo-controlled, parallel-group, multicenter, efficacy, safety and dose response studies of ciclesonide 50-, 100- and 200 µg/day for 12 weeks in approximately 500 children 4 to 11 years of age (125 per study) with persistent asthma

Table 3. Dosing regimen and treatment

Study	Subjects	Dose (ex-actuator) (MDI)	Age (yrs)	Weight (kg)	Height (cms)	Males/Females	REF
FHP009	Healthy subjects	400 µg	30.25 (5.94)	79.75 (8.41)	182.17 (5.29)	12/0	9
FHP009	Healthy subjects	1200 µg	30.25 (5.94)	79.75 (8.41)	182.17 (5.29)	12/0	9
FHP009	Healthy subjects	3600 µg	30.25 (5.94)	79.75 (8.41)	182.17 (5.29)	12/0	9
FHP009	Healthy subjects	250 µg	31 (5.9)	80 (14)	183 (11.2)	12/0	9
FHP009	Healthy subjects	1000 µg	31 (5.9)	80 (14)	183 (11.2)	12/0	9
FHP012	Healthy subjects	1600 µg	31 (4.9)	76 (6.7)	185 (7.6)	13/0	10
FHP015	Healthy subjects	1600 µg	32.00 (6.49)	75.44 (8.93)	180.58 (8.58)	12/0	11
FHP018	Subjects with liver cirrhosis	1600 µg	48.50 (2.14)	83 (8.67)	176.75 (5.90)	7/1	12
FHP019	Healthy subjects	800 µg	31.47(4.53)	65.82 (10.26)	172.76 (9.10)	9/9	13
FHP022	Healthy subjects	800 µg (4 x 200 µg)	29.37 (6.74)	70.62 (10.47)	174.25 (14.71)	16/8	14
FHP022	Healthy subjects	800 µg (16 x 50 µg)	29.37 (6.74)	70.62 (10.47)	174.25 (14.71)	16/8	14
FHP023	Healthy subjects	1600 µg	36.00 (10.94)	78.5 (11.30)	173.67 (8.54)	8/4	15
FHP023	Asthmatic patients	1600 µg	36.00 (10.94)	78.5 (11.30)	173.67 (8.54)	8/4	15
FHP025	Elderly healthy subjects	1600 µg	71.75 (3.89)	79.17 (6.89)	171.58 (7.04)	12/0	16
FHP026	Healthy subjects	800 µg (4 x 200 µg)	29.21(6.43)	72.46 (8.76)	177.04 (7.50)	20/4	17
FHP026	Healthy subjects	800 µg (8 x 100 µg)	29.21 (6.43)	72.46 (8.76)	177.04 (7.50)	20/4	17
FHP027	Healthy subjects	400 µg	30.67 (6.64)	77.06 (10.69)	178.61 (7.15)	15/3	18
BTR-15001	Healthy subjects	200 µg	24.2 (5.0)	58.28 (5.81)	168.31 (4.90)	12/0	19
BTR-15001	Healthy subjects	400 µg	22.9 (1.8)	64.10 (10.35)	170.77 (7.56)	12/0	19
BTR-15001	Healthy subjects	800 µg	21.3 (1.2)	58.78 (6.87)	169.08 (4.81)	12/0	19
BTR-15001	Healthy subjects	1600 µg	23.9 (3.9)	64.04 (5.83)	173.43 (4.56)	12/0	19
BTR-15002	Healthy subjects	800 µg/day	21.1 (1.4)	58.94 (3.08)	169.38 (6.89)	9/0	20
BTR-15002	Healthy subjects	1600 µg/day	21.9 (1.5)	63.39 (8.35)	170.79 (5.34)	9/0	20
XRP 1526B 321	Asthmatic patients	80 µg	35.7 (13.6)	79.5 (21.7)	168.7 (10.5)	50/78	21
XRP 1526B 321	Asthmatic patients	160 µg	36.8 (15.2)	79.1 (18.0)	168.2 (9.8)	56/72	21
XRP 1526B 321	Asthmatic patients	320 µg	37.1 (15.0)	79.2 (19.7)	168.9 (10.4)	53/78	21
XRP 1526B 322	Asthmatic patients	80 µg	36.8 (14.8)	80.9 (23.9)	167.4 (10.3)	50/74	22
XRP 1526B 322	Asthmatic patients	160 µg	35.9 (13.2)	77.5 (20.5)	166.9 (9.1)	42/81	22
XRP 1526B 322	Asthmatic patients	320 µg	36.5 (13.9)	80.9 (18.4)	169.3 (9.0)	59/65	22
XRP 1526B 323/324	Asthmatic patients	320 µg	43.5 (15.1)	84.4 (21.1)	168.4 (10.3)	52/75	23
XRP 1526B 323/324	Asthmatic patients	640 µg	43.1 (14.0)	84.7 (21.6)	168.8 (9.7)	55/75	23
XRP 1526B 341	Asthmatic patients	40 µg	8.2 (2.2)	34.8 (12.0)	133.1 (14.2)	78/46	24
XRP 1526B 341	Asthmatic patients	80 µg	8.0 (2.1)	33.2 (12.7)	131.1 (14.1)	83/51	24
XRP 1526B 341	Asthmatic patients	160 µg	8.0 (1.9)	33.1 (13.1)	131.3 (13.5)	62/57	24
XRP 1526B 342	Asthmatic patients	40 µg	8.1 (2.1)	31.5 (10.7)	131.6 (13.8)	82/46	25
XRP 1526B 342	Asthmatic patients	80 µg	8.4 (2.1)	33.7 (12.5)	134.5 (13.0)	86/39	25
XRP 1526B 342	Asthmatic patients	160 µg	8.6 (1.9)	34.0 (12.6)	134.2 (12.6)	92/42	25

### **Sparse Sample Collection**

Phase III studies included sparse PK samples (-1.5, 1, 2.5 and 6-10 hours following administration).

### **Methods for Data Analysis**

Data were analyzed *via* non-linear mixed-effects modeling with the NONMEM software. Various estimations methods (first-order, first-order conditional and hybrid) were evaluated during the model building process to select the most stable estimation method. Plasma/Serum concentration-time (PK/PD) data from all the subjects (adults and pediatrics) were simultaneously fitted to obtain the final population model. Population PK/PD models were developed using an iterative process in an attempt to define the best (most useful) model for the data. The selection of an appropriate pharmacostatistical model was based on a significant reduction in the objective function value, point and interval estimates of parameters, diagnostic plots, including weighted residuals vs. predictions and observed vs. predicted values. The principle of parsimony was applied to the model development.

For pharmacokinetics, structural models including one or two compartment models with first order absorption with/without lag times were evaluated to describe RM1 concentration-time data. The evaluation of covariates was performed in a sequential approach where body weight was considered the primary predictor followed by age, gender, race, disease state and liver status as additional predictors for clearance (CL), volume of distribution (V2) and F (bioavailability), wherever appropriate. Identification of relevant covariates was based on step-wise backward elimination method.

For pharmacodynamic analysis (endogenous cortisol concentrations), a one-compartment model with first-order elimination and first order input (i.e. rate constant of cortisol release to the system) was fitted to plasma/serum cortisol concentrations. Apparent clearance was the parameter controlling exposure (cortisol AUC). In addition, individual trough plasma/serum cortisol concentrations (C<sub>trough</sub>) at dose interval were estimated. Cortisol “dose” (i.e. total daily endogenous cortisol release) was arbitrarily set to 100 µg and with an hypothetical dosing time for this cortisol dose at 10 PM for all subjects to allow estimation of administration time (i.e. onset of endogenous cortisol production) using the parameter lag-time. Ciclesonide dose (*ex-valve*) and AUC was included in the cortisol model as a covariate on cortisol CL to assess the effect of exogenous corticosteroid on cortisol concentrations. Also, IPRED RM1 plasma/serum concentrations (CRM1) obtained from the final pharmacokinetic model for RM1 were used to describe the direct effect of RM1 concentrations on plasma/serum cortisol concentrations using an E<sub>max</sub> model. Residual variability was modeled as proportional and additive for both pharmacokinetic and pharmacodynamic models.

## **RESULTS**

### **Pharmacokinetic structural model development**

There were a total of 635 subjects in this analysis with 2750, 5238 and 4470 observation records for ciclesonide, RM1 and cortisol concentrations, respectively. RM1 is the major circulating species in humans, the present analysis focused on the characterization of RM1.

A one-compartment body model with first order absorption adequately described the RM1 concentration-time profile. Although there were measurable RM1 concentrations at 24

hours post dose, the limited number of samples collected during the night prevented further improvement in goodness of fit using a two-compartment model.

The population estimates of CL, V and Ka were 318 L/h, 1320 L and 8.3 h<sup>-1</sup>, respectively. The inter-individual variability (%CV) of CL, V, and Ka were estimated to be 58.1%, 45.2% and 80.1%, respectively. The proportional (%CV) and additive components of the residual errors were 19.5% and 0.045 ng/mL, respectively.

#### Pharmacokinetic covariate model development

The evaluation of covariates included body weight, age (pediatrics, geriatrics), race, gender, disease state and liver status. The application of the weight-based power (PWR) model to the base model resulted in a significant reduction (69.6 points) in the NONMEM objective function. However, inspection of the weighted residual (WRES) versus prediction (PRED) plot for pediatrics only indicated a bias. The model was further modified by applying separate weight effects for pediatrics and adults. This resulted in no weight adjustment for pediatrics and the PWR exponent for adults was close to the allometric values for CL and V (0.70 for CL and 0.95 for V) (Table 4). Thus, the final model has an allometric effect of weight on CL and V for adults only. Since children may inhale less amount of drug probably due to lower lung capacity, resulting in lower systemic exposure and their clearance could be lower, the allometric function was applied to the entire population with an additional covariate for bioavailability in pediatrics. The resulting model suggested a bioavailability of 60% relative to adults, but lower clearance and volume based on allometric principle. There was no change in objective function with minor improvement in goodness-of fit plots.

**Table 4.** Evaluation of Body Weight as a Covariate of RM1 Clearance and Volume of Distribution

Control File (nm*.con)	Model Description	Data	Objective Function	Parameter <sup>1</sup>	Estimate	RSE of Estimate (%)	Inter-Individual Variability (%CV) <sup>1</sup>	WRES versus PRED plot for pediatrics	DV versus PRED plot for pediatrics	Comment
001BASE	Base model	Adults and Pediatrics	-20670.0	CL (L/h) V2 (L) KA (h <sup>-1</sup> )	307 1310 8.0	2.7 2.5 6.6	49.1 45.9 76.8			No bias in diagnostic plots
001BASE_WT	PWR estimated	Adults and Pediatrics	-20739.6	CL (L/h) V2 (L) KA (h <sup>-1</sup> ) WTCL WTV	309 1530 8.0 0.56 0.84	2.7 15.2 6.2 19.6 15.1	51.4 46.9 74.3			Delta OF -69.6; significant bias in diagnostic plots
001BASE_WTADULTS	PWR estimated	Allometric model on Adults only	-20755.4	CL (L/h) V2 (L) KA (h <sup>-1</sup> ) WTCL WTV	289 1310 7.9 0.70 0.95	2.7 10.8 6.2 18.6 10.7	51.1 47.2 74.3			Delta OF -85.4; no bias in diagnostic plots

Control File (nm. *.con)	Model Description	Data	Objective Function	Parameter <sup>1</sup>	Estimate	RSE of Estimate (%)	Inter-Individual Variability (%CV) <sup>2</sup>	WRES versus PRED plot for pediatrics	DV versus PRED plot for pediatrics	Comment
001BASE WTADUL TS-A	Allometric model PWR fixed to 0.75 for CL and 1 for V2	Allometric model on Adults only	-20754.5	CL (L/h) V2 (L) KA (h <sup>-1</sup> ) WTCL WTV	289 1250 7.95 0.75 fix 1 fix	2.7 2.5 6.2	51.3 47.2 74.5			Delta OF -84.5; no bias in diagnostic plots

1. Modeled as Log-normal distribution; %CV calculated by taking the square root of the variance estimate and multiplying by 100
2. Parameter Units: CL: L/h; V2: L; KA: per h
3. WRES is weighted residuals, PRED is the population predicted values, DV is the dependent variable, i.e. observed RMI concentrations.
4. The black filled circles represent the observed data. The solid gray and black lines represent the line of identity at zero (y=x) for the DV versus PRED and slope of 0 for WRES versus PRED.

Following the selection of the appropriate weight-based model, other (age, gender, race, disease state and liver status) covariate-parameter relationships were explored for CL/F and V2/F and F (bioavailability), wherever appropriate. As CL/F and V2/F estimates are confounded by bioavailability term, the effect of race, disease state and liver status was explored on F. Since it is reasonable to expect physiological influence of age and gender on clearance of the drug rather than on volume, these two covariates were tested on CL/F only. The results from the base, full and final models are summarized in Table 5

Table 5. Parameter Estimates from Base, Full and Final Models for RMI Concentrations

Control File (nm. *.con)	Model	Objective Function	Parameter <sup>1</sup>	Estimate	RSE of Estimate (%)	Inter-Individual Variability (%CV) <sup>2</sup>	DV versus PRED plot	Residual Variability <sup>4</sup> Y1 (%CV) Y2 (ng/mL)
001BASE	Base	-20670.0	CL (L/h) V2 (L) KA (h <sup>-1</sup> )	302 1310 8.0	2.7 2.5 6.6	49.1 45.9 76.8		RMI: Y1: 19.0 Y2: 0.038
006FULL	Full	-20853.7	CL (L/h) V2 (L) KA (h <sup>-1</sup> ) WTCL WTV DISS (MILD-MOD) DISS (SEVERE) RACE (ASIAN) RACE (BLACK) LVST (MILD-MOD) LVST SEVERE AGE (PEDIATRICS) AGE (ELDERLY) SEX (FEMALE)	290 1250 7.8 0.75 FIX 1 FIX 1.04 1.19 1.01 0.96 0.55 0.48 1.28 1.17 0.996	4.4 3.8 6.6 - - 6.3 8.0 10.8 12.9 15.9 36.8 8.5 8.3 4.5	50.5 43.9 72.8		RMI: Y1: 18.7 Y2: 0.038
006FULL-6-DISS2	Final	-20838.5	CL (L/h) V2 (L) KA (h <sup>-1</sup> ) WTCL WTV LVST (MILD-MOD) LVST (SEVERE)	283 1220 7.78 0.75 FIX 1 FIX 0.54 0.48	2.7 2.5 6.4 - - 16.2 37.2	51.0 44.8 72.5		RMI: Y1: 18.3 Y2: 0.038

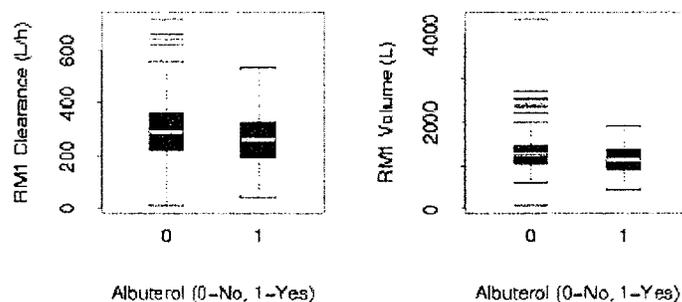
### Individual pharmacokinetic parameter estimates

Descriptive statistics of the pharmacokinetic parameter estimates from NONMEM's individual estimates for various sub-populations of interest are shown in Table 6. There were no trends for differences in these parameters based on severity of asthma, age, gender or race. For pediatric subjects there was modest decrease in clearance values of 20% as compared to healthy adults, which was also associated with a similar decrease in volume of distribution of approximately 17%. These changes do not result in any noticeable changes in the systemic exposure in pediatric subjects. Similarly, there were no noticeable changes in the plasma/serum

concentrations of elderly subjects. There was sufficient number of subjects (98) that had matching pharmacokinetic information following co-administration of ciclesonide with albuterol (Figure 1). The RM1 clearance and volume of distribution values for subjects with and without coadministration of albuterol were similar. The only significant covariates were patients with mild to moderate and severe liver impairment with bioavailability estimates of 54% and 48%, respectively, relative to subjects with healthy liver function. These results are in contrast to data from study FHP018, where concentrations were 2.73 and 1.77 fold-higher in subjects with mild to moderate and severe liver impairment, respectively (see individual report for more details).

**Table 5. Descriptive Statistics of Individual Parameter Estimates for RM1 from Final Model**

Parameter	Healthy	Mild to moderate Asthmatics	Severe Asthmatics	Pediatrics	Elderly	Male	Female	Japanese	Adults
<b>Clearance (L/h)</b>									
N	255	172	65	37	18	246	233	65	444
Mean	339.7	301.0	282.9	267.3	271.9	316.8	316.3	310.1	319.9
Median	304.7	293.5	248.1	262.6	250.0	272.9	293.9	308.7	285.3
Min	91.8	53.7	110.6	94.1	155.4	65.3	53.7	91.8	53.7
Max	1933.9	748.7	626.5	513.8	487.1	1933.9	974.3	631.7	1933.9
CV	58.2%	40.0%	44.8%	38.0%	35.6%	61.9%	42.1%	37.3%	40.2%
<b>Volume (L)</b>									
N	255	172	65	37	18	246	233	65	444
Mean	1426.6	1333.9	1313.7	1133.1	1113.0	1401.2	1342.5	1261.4	1326.7
Median	1247.2	1274.5	1209.3	1114.7	982.3	1223.9	1247.2	1211.2	1223.2
Min	492.9	390.4	643.1	450.3	580.6	476.4	390.4	492.9	390.4
Max	7636.0	3249.3	2848.3	2068.1	2218.0	7636.0	3480.2	2603.0	3480.2
CV	54.7%	38.8%	39.5%	33.5%	40.8%	55.6%	40.1%	34.3%	40.1%
<b>KA (h)</b>									
N	255	172	65	37	18	246	233	65	444
Mean	8.6	7.5	7.3	7.7	9.9	7.8	6.3	10.8	7.4
Median	7.1	7.6	7.1	7.7	7.9	7.2	7.6	9.5	7.3
Min	1.7	0.8	4.2	5.7	2.7	0.8	1.4	3.5	0.8
Max	27.8	14.2	9.6	9.1	26.0	27.8	24.9	24.9	27.8
CV	58.3%	18.6%	14.5%	9.8%	56.5%	47.4%	46.4%	52.7%	38.4%



**Figure 1. Box Plot of RM1 Clearance and Volume of Distribution Values for Subjects With and Without Co-Administration of Albuterol**

## Pharmacodynamic Results

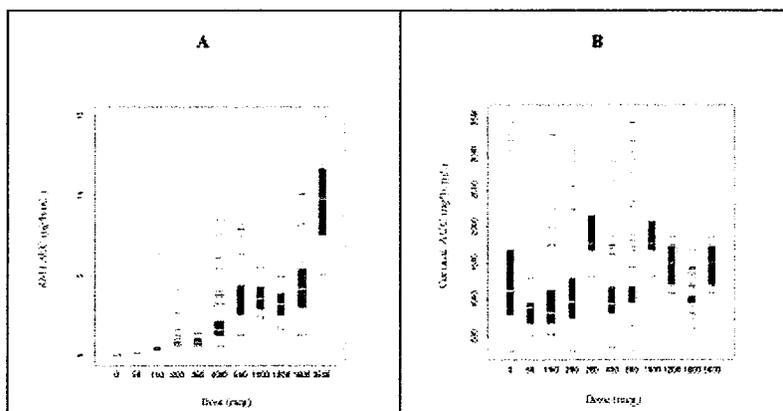
### Baseline cortisol model

In final cortisol baseline model, inter-individual variability was included on the cortisol parameters CL and V and on endogenous cortisol concentration  $C_{trough}$ . As there were limited cortisol samples collected during the nighttime, inter-individual variability on input rate (i.e. rate constant of endogenous cortisol release) was fixed at 20% and inter-individual variability on lag-time was set to 0%.

The goodness of fit statistics of the final baseline model suggests that the model reasonably describes measured plasma/serum cortisol concentrations at trough and the circadian rhythm of endogenous cortisol release. The estimated half-life of cortisol ( $0.693 V/CL$ ) was short 0.56 h. This agrees with the short half-life previously reported for cortisol of 1.5 h (35, 36).

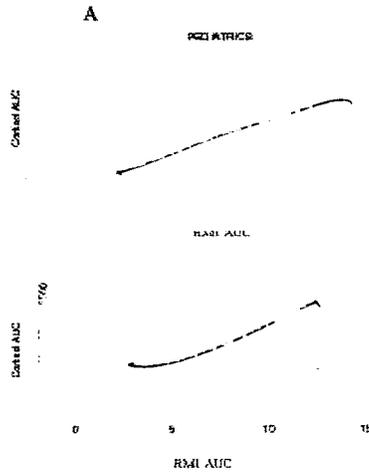
### Effect of dose on cortisol concentrations

Following inclusion of ciclesonide dose as a covariate in the cortisol model, a significant decrease in objective function was observed. The results indicate a decrease of only 13% and 8% in cortisol AUC for ciclesonide doses of 800 to 1200 mcg and 1600 mcg, respectively. Furthermore, a decrease of 49% was observed for the 3600 mcg. As individual cortisol AUC was derived from individual cortisol CL estimate and inter-individual variability of CL was high (55%), these differences are of no clinical significance. Figure 2 shows that there is a linear increase in RM1 AUC with dose but no clear change of cortisol AUC with increasing dose.



**Figure 2.** A. RM1 Area Under the Curve (AUC) versus Dose Box Plot. B. Cortisol Area Under the Curve (AUC) Versus Dose Box Plot

Figure 3 shows that there was no significant trend for change in cortisol AUC with increasing RM1 AUC in children or adults.



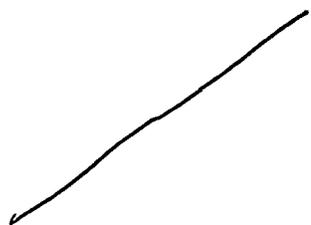
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Figure 3. A. Cortisol Area Under the curve (AUC) Versus RM1 AUC for Pediatric Subjects. B. Cortisol Area Under the Curve (AUC) Versus RM1 AUC for Adult Subjects

**Emax model**

The direct effect of individual predicted systemic RM1 concentrations as obtained from the final pharmacokinetic model on cortisol concentrations at a given time was assessed with an  $E_{max}$  model. There was a significant decrease in the objective function with estimated  $E_{max}$  value and also when  $E_{max}$  was fixed to 100% (i.e. reduction of measured cortisol plasma/serum concentration to 0 ng/mL). When  $E_{max}$  was fixed at 100% it expresses the maximum possible effect by any corticosteroid. This is based on findings that high doses can completely suppress cortisol plasma/serum concentrations. For the current model  $EC_{50}$  for ciclesonide was 1.96 ng/mL with fixed  $E_{max}$ . This  $EC_{50}$  value is similar to the 90th percentile of RM1 concentrations for the 1600  $\mu$ g dose. Less than 1% (28 and 37 out of 5288 records for IPRED and DV, respectively) of the RM1 concentrations were above 1.96 ng/mL (Figure 4). The highest IPRED and measured RM1 concentrations were 2.5 ng/mL and 3.5 ng/mL, respectively.

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b(4)

Figure 4. Cortisol Concentration Versus IPRED RM1 Concentrations

Furthermore, IPRED RM1 plasma/serum concentrations ( $C_{RM1}$ ) obtained from the final pharmacokinetic model for RM1 were used to describe the direct effect of RM1 concentrations on plasma/serum cortisol concentrations using a direct  $E_{max}$  model where  $E_{max}$  value was also estimated. The  $EC_{50}$  value was estimated to be 0.59 ng/mL. The  $E_{max}$  value was estimated to be 41% where 100% refers to reduction of measured cortisol plasma/serum concentration to 0 ng/mL. This agrees with the estimated 49% decrease for the 3600 mcg dose with the AUC covariate cortisol model. This suggests that even at the highest doses (more than double of therapeutic clinically relevant doses) complete (i.e. 100%) suppression of cortisol concentrations is not possible.

#### **REVIEWER'S REMARKS**

Dr. Yaning Wang (pharmacometric reviewer) ran the control files provided by the sponsor to confirm the above findings. In general, he agreed with the model performance and acknowledged the effort put by the sponsor in assessing the PK/PD of the drug. In general the models used performed well as shown by the significant reduction in the objective function values, point and interval estimates of parameters, diagnostic plots, including weighted residuals vs. predictions and observed vs. predicted values.

This reviewer used the reported post-hoc AUC given by the sponsor to create Figures 5 to 8. Figure 5 is a matrix plots showing the effect of covariates on AUC. Figure 6 shows the close superposition between observed and predicted concentrations suggesting the adequacy of the models used. Figure 7 confirms that the systemic exposure in children 5 to 11 years of age and the elderly is the same as that in adults receiving the same dose of inhaled ciclesonide. Figure 8 shows that race has an effect on the AUC of the drug. The mean (SD)  $AUC_{pop}$  was 2.07- (2.12), 2.5- (1.7), 0.85- (1.5), 0.59 (0.47) ng\*hr/mL in the White, Asian, Black, and other populations, respectively.



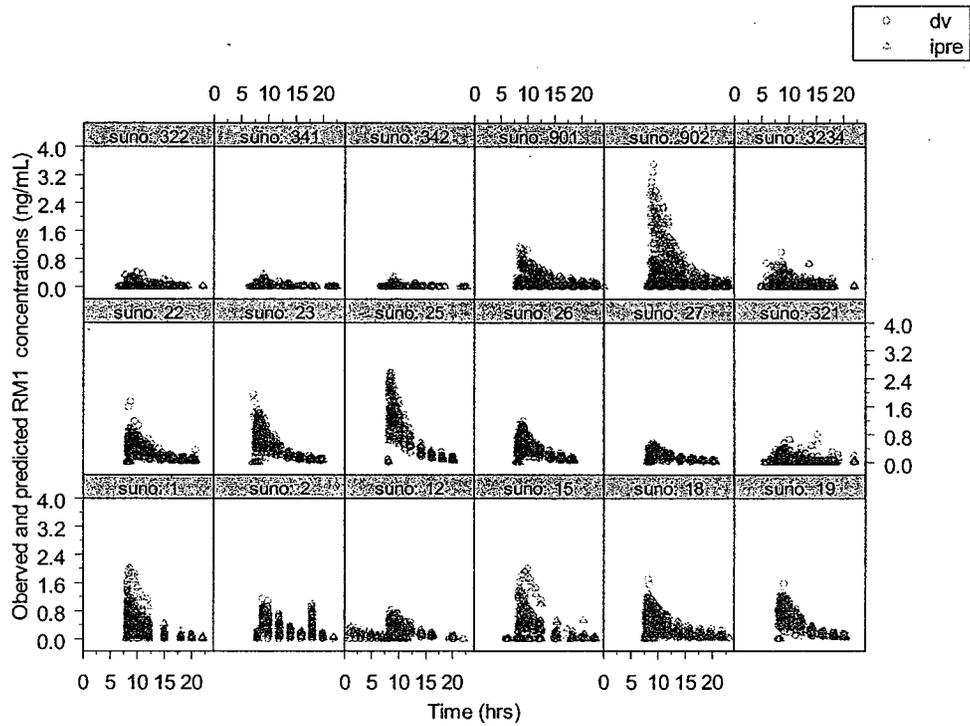


Figure 6. RM1 observed and predicted concentration versus time

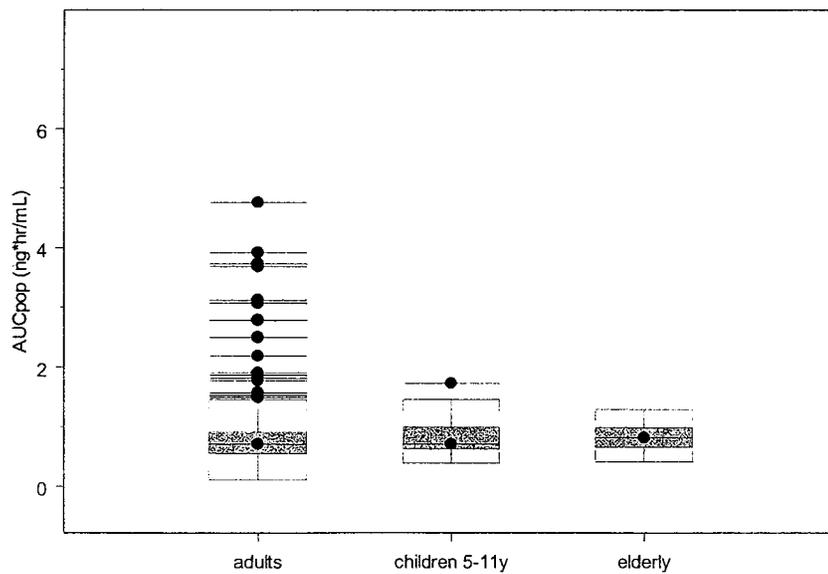
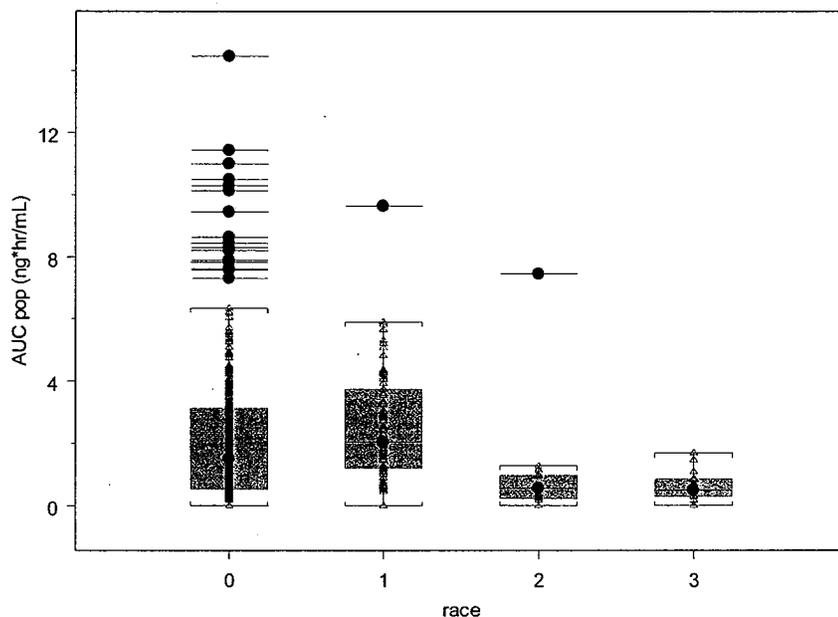


Figure 7. Individual post-hoc AUC (ng\*hr/mL) (normalized to 200 mcg) as a function of age (n= 444, 37 and 18 for adults, children and elderly, respectively) (data from population PK/PD analysis).



**Figure 8.** Effect of race on the AUC of RM1 (0: White, 1: Asian/Orientals; 2: Blacks; 3: others)

## CONCLUSIONS

- The population PK parameters were estimated across populations.
- Gender, asthma severity, age and body weight did not have a significant effect on the PK of RM1.
- The mean systemic exposure (AUC<sub>pop</sub>) in the Black and Others population was significantly lower (60% and 70%, respectively) than that in the White population. These results may be confounded due to uneven distribution of sample size, gender, body weight and other factors. This difference may also not be clinically relevant since the dose-exposure response was flat in the range of doses tested.
- The systemic exposure (AUC<sub>pop</sub>- dose normalized to 200 mcg) was similar in children 5 to 11 years of age, adults and elderly.
- The effect of ciclesonide at therapeutic doses on endogenous cortisol concentrations (suppression) was less than 13% as compared to baseline in the subpopulations investigated.

**Office of Clinical Pharmacology and Biopharmaceutics**

*New Drug Application Filing and Review Form*

General Information About the Submission			
	Information		Information
NDA Number	21-658		Brand Name Alvesco
OCPB Division (I, II, III)	II		Generic Name Ciclesonide
Medical Division	DPADP		Drug Class glucocorticoid
OCPB Reviewer	Sandra Suarez-Sharp		Indication(s) Treatment of asthma
OCPB Team Leader	Emmanuel Fadiran		Dosage Form MDI
PM Reviewer			Dosing Regimen Adults and adolescents: 80- mcg / up to 320 mcg /
Date of Submission	Dec 22, 2003		Route of Administration Oral Inhalation
Estimated Due Date of OCPB Review	Aug, 2004		Sponsor Aventis, Inc.
PDUFA Due Date	Oct 22, 2004		Priority Classification Standard
Division Due Date	Sep 22, 2004		

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**3 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:	x	1	1	
Isozyme characterization:	x	7	3	
Blood/plasma ratio:		1	1	
Plasma protein binding:	x	3	3	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	10	8	
multiple dose:	x	6	2	
Patients-				
single dose:	x	2	2	
multiple dose:		2	2	
Dose proportionality -				
fasting / non-fasting single dose:	x	3	1	
fasting / non-fasting multiple dose:			1	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	2	2	
In-vivo effects of primary drug:	x	2	1	
In-vitro:	x	2	1	
Subpopulation studies -				
ethnicity:	x	3		
gender:				
pediatrics:		2	2	
geriatrics:	x	1	1	
renal impairment:				
hepatic impairment:	x	1	1	
PD:				
Phase 2:	x	6	6	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:	x	3		
<b>Population Analyses -</b>				
Data rich:		2	1	
Data sparse:	x	2	1	
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>	x	1	1	
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:	x	1	1	
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
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>		54	37	
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
<b>QBR questions (key issues to be considered)</b>	<ol style="list-style-type: none"> <li>1. Dose proportionality</li> <li>2. Metabolic pathway</li> <li>3. Inhibition/induction of drug of CYP enzymes</li> <li>4. Drug-drug interaction</li> <li>5. Effect of hepatic impairment on PK of drug</li> <li>6. Gender, race, age, effect on the PK of the drug</li> <li>7. Lung residence time</li> <li>8. Pulmonary deposition/systemic BA</li> <li>9. Protein binding</li> <li>10. Dose-response</li> <li>11. Cortisol suppression</li> <li>12. QT prolongation</li> </ol>			
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>				
<b>Secondary reviewer Signature and Date</b>				

CC: NDA 21-658, HFD-870 (Electronic Entry or Lee), HFD-570 (Jackson), HFD-870 (Fadiran, Hunt, Malinowski), CDR (B. Murphy)

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this page is the manifestation of the electronic signature.**  
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/s/

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Sandra Suarez  
9/20/04 02:05:16 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
9/20/04 02:49:55 PM  
BIOPHARMACEUTICS  
I concur

## Clinical Pharmacology and Biopharmaceutics Review

### “Ciclesonide MDI HFA for the Treatment of Asthma”

**NDA 21-658**

**IND: 53-391**

**Sponsor: Aventis, Inc.**

**Type: NDA filing package**

**Drug: Ciclesonide**

**Submission date: Dec 22, 2003**

**Draft review: Jan 09, 2004**

**Review date:**

**Reviewer: Sandra Suarez-Sharp, Ph.D.**

### INTRODUCTION

Ciclesonide, a novel non-halogenated glucocorticoid developed for treatment of asthma, is administered by inhalation as a metered dose aerosol with ethanol and HFA-134a as propellant. According to the sponsor, the ester moiety attached to carbon position 21 is enzymatically cleaved *in vivo* to provide the active metabolite, RM1, also known as desciclesonide, which is considered to be the active principle.

Ciclesonide is a solution formulation in a pressurized metered dose inhaler (MDI) available in three strengths with *ex-actuator* doses of 80 µg, 80 µg, and 160µg per actuation corresponding to *ex-valve* doses of 100µg and 200µg/puff.

The development of ciclesonide started with the use of an epimeric mixture of R- and S-ciclesonide. However, according to the sponsor, further clinical development was only continued with the R-epimer because

The sponsor stated that as ciclesonide has only 1/100 of the binding affinity to the glucocorticoid receptor as compared to RM1 and RM1 is the major circulating species, human *in vivo* and *in vitro* pharmacology studies focused on the pharmacokinetic and pharmacodynamic characterization of the metabolite RM1. Ciclesonide concentrations were analyzed in a limited number of studies due to variable and transient concentrations of ciclesonide.

The clinical pharmacology program included the following key studies (see Table 1 for more detail):

- 12 human biomaterial studies that according to the sponsor, suggested high plasma protein binding for ciclesonide and RM1, similar metabolic profile across various species, lack of drug-drug interaction potential, and low glucocorticoid receptor binding of ciclesonide and other metabolites, except RM1 that is the active metabolite.
- 11 clinical pharmacokinetic studies in healthy subjects that according to the sponsor suggested high clearance, high volume of distribution, short half-life, low oral bioavailability, high inhaled bioavailability, dose proportional RM1 pharmacokinetics after single and multiple MDI dose administration, and lack of potential for R to S interconversion. The sponsor stated that these studies also

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showed high lung deposition, low oropharyngeal deposition, and bioequivalence of the 3 inhaler strengths.

- 8 clinical pharmacokinetic studies describing extrinsic and intrinsic factors that according to the sponsor, suggested no clinically relevant influence of covariants such as severity of asthma, age (pediatric and elderly), liver impairment, and race on the RM1 pharmacokinetics.
- 6 clinical pharmacology studies where cortisol responses were evaluated to investigate the pharmacodynamic effects of ciclesonide in healthy volunteers and asthmatics that according to the sponsor, did not demonstrate any clear effect on cortisol concentrations and excretion at doses up to 1280 µg.
- 2 population meta-analyses of the PK/PD were also conducted that according to the sponsor indicated no influence of covariates on the pharmacokinetics of RM1 and also suggested no trend in changes in cortisol concentrations for the doses tested.

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**Table 1:** Overview of the human biomaterial, clinical pharmacokinetic, clinical pharmacology, and ancillary studies included in this NDA submission.

Research Report-No.	Study title / objective	cf. Section	Comments
<b>Human Biomaterial Studies (2.7.2.2.1)</b>			
DMPK/USA 2003-0001 2.7.2.6.1.1 Human Biomaterial Studies	RM1 protein binding in plasma of various species and in isolated human plasma proteins.	2.7.2.2.1.1	Preclinical Protein Binding
246/2001 2.7.2.6.1.2 Human Biomaterial Studies	Serum protein binding of ciclesonide in different species, including humans	2.7.2.2.1.2	Preclinical Protein Binding
79/2001 (DMPK/USA 01-046) 2.7.2.6.1.3 Human Biomaterial Studies	Plasma protein binding in different species, blood cell/plasma partitioning in human blood and drug interaction in human plasma	2.7.2.2.1.3	Preclinical Protein Binding
DMPK/USA 2002-0014 2.7.2.6.1.4 Human Biomaterial Studies	<i>In vitro</i> metabolism by human hepatocytes	2.7.2.2.1.4	Metabolism
71/98 2.7.2.6.1.5 Human Biomaterial Studies	<i>In vitro</i> metabolism of <sup>14</sup> C-ciclesonide by animal and human liver microsomes (Altana)	2.7.2.2.1.5	Metabolism
241E/98 2.7.2.6.1.6 Human Biomaterial Studies	Investigation of enzymology of metabolism by human liver microsomes.	2.7.2.2.1.6	Metabolism
238/2001 2.7.2.6.1.7 Human Biomaterial Studies	<i>In vitro</i> formation of fatty acid esters of the ciclesonide metabolite B9207-021 by human lung and liver precision-cut slices.	2.7.2.2.1.7	Metabolism-fatty acid conjugation
266/99 2.7.2.6.1.8 Human Biomaterial Studies	Binding affinities of ciclesonide metabolites 1, 2, 3 in the glucocorticoid receptor binding assay.	2.7.2.2.1.8	Receptor binding assay
237/2001 2.7.2.6.1.9 Human Biomaterial Studies	Binding affinities of RM1 fatty acid conjugate 1, 2, 3 in the glucocorticoid receptor binding assay.	2.7.2.2.1.9	Receptor binding assay
123E/93 2.7.2.6.1.10 Pharmacokinetics: Human Biomaterial Studies	Binding affinities of ciclesonide analogs to the glucocorticoid receptor of rat lung Glucocorticoid receptor binding affinity Rat lung preparation <i>In vitro</i>	2.7.2.2.1.10	Receptor binding assay
DMPK/USA 2002-0145 2.7.2.6.1.11 Human Biomaterial Studies	<i>In vitro</i> CYP450 enzyme inhibition study of ciclesonide RM1 in human liver microsomes, determination of IC50 values and screening for metabolism- based inhibition	2.7.2.2.1.11	Drug-drug interaction potential
DMPK/USA 2003-078 2.7.2.6.1.12 Pharmacokinetics: Human Biomaterial Studies	Assessment of <i>in vitro</i> cytochrome P450 induction potential of ciclesonide to CYP1A2, 2C9, 2C19 and 3A4 in primary cultures of human hepatocytes	2.7.2.2.1.12	Drug-drug interaction potential

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Research Report-No.	Study title / objective	cf. Section	Comments
<b>Clinical Pharmacokinetic Studies (2.7.2.2.2)</b>			
FHP021 308E/98 2.7.2.6.2.1 Clinical Pharmacokinetic Studies	A study to investigate the pharmacokinetics and metabolism of ciclesonide after single intravenous and oral administration of <sup>14</sup> C-ciclesonide to six healthy volunteers.	2.7.2.2.2.1	Clinical ADME study
FHP015 172/97 2.7.2.6.2.2 Clinical Pharmacokinetic Studies	Systemic availability of the active metabolite RM1 after administration of R-ciclesonide as powder capsules p. o., inhalation via MDI, and powder inhalation via Cyclohaler® as compared to intravenous administration, and pharmacodynamics (cortisol in serum and urine) in healthy male volunteers.	2.7.2.2.2.2	Absolute bioavailability for oral and inhaled administration
FHP009 117E/97 2.7.2.6.2.3 Clinical Pharmacokinetic Studies	Safety, tolerability and pharmacodynamics of the new topical steroid ciclesonide in healthy male volunteers following ascending single dose and repeated dose inhalations.	2.7.2.2.2.3	Single and multiple dose MDI PK
FHP027 211/2000 2.7.2.6.2.4 Clinical Pharmacokinetic Studies	Pharmacokinetics of ciclesonide and its metabolite RM1 after single and repeated once-daily inhalation of ciclesonide 400 µg using MDI device.	2.7.2.2.2.4	Single and multiple dose MDI PK
FHP028 201/2001 2.7.2.6.2.5 Clinical Pharmacokinetic Studies	Investigation of the epimeric stability of ciclesonide following inhalation of 1800µg ciclesonide	2.7.2.2.2.5	Lack of R/S interconversion
FHP014 74/2001 2.7.2.6.2.6 Clinical Pharmacokinetic Studies	Study assessing lung deposition of <sup>99</sup> Tc-labelled ciclesonide in healthy volunteers	2.7.2.2.2.6	Lung deposition
FHP024 239/99 2.7.2.6.2.7 Clinical Pharmacokinetic Studies	Comparative investigation of the oropharyngeal deposition of ciclesonide, its active metabolite RM1 and budesonide	2.7.2.2.2.7	Oropharyngeal deposition
FK1 112 35/2001 2.7.2.6.2.8 Clinical Pharmacokinetic Studies	Comparison of the oropharyngeal deposition of an inhaled dose of ciclesonide (800 µg) and fluticasone propionate (1000 µg) in patients with asthma	2.7.2.2.2.8	Oropharyngeal deposition
FHP022 307/98 2.7.2.6.2.9 Clinical Pharmacokinetic Studies	Study on the bioequivalence of two different ciclesonide dosing regimen using different inhaler strengths (4 puffs of 200 µg vs. 16 puffs of 50 µg)	2.7.2.2.2.9	Bioequivalence
FHP026 128/2000 2.7.2.6.2.10 Clinical Pharmacokinetic Studies	Study on the bioequivalence of two different ciclesonide dosing regimen using different inhaler strengths (8 puffs of 100 µg vs. 4 puffs of 200 µg)	2.7.2.2.2.10	Bioequivalence
CP030 41/2003 2.7.2.6.2.11 Clinical Pharmacokinetic Studies	Comparison of the pharmacokinetics (active metabolite M1 and parent compound) of inhaled ciclesonide when administered via a MDI with and without AeroChamber Plus™ spacer	2.7.2.2.2.11	Bioequivalence

Research Report-No.	Study title / objective	cf. Section	Comments
<b>Effect of Intrinsic and Extrinsic Factors (2.7.2.2.3)</b>			
FHP023 56E/99 2.7.2.6.3.1 <i>Effect of Intrinsic and Extrinsic Factors</i>	Investigation of the pharmacokinetics of the active metabolite B9207-021 in asthmatic patients and healthy subjects after single dose inhalation of 1600 µg ciclesonide	2.7.2.2.3.1	PK in Asthmatics
FHP018 210/2000 2.7.2.6.3.2 <i>Effect of Intrinsic and Extrinsic Factors</i>	Influence of liver cirrhosis on the pharmacokinetics of the active metabolite RM1 of ciclesonide in comparison to a control group of healthy subjects.	2.7.2.2.3.2	Influence of Liver Impairment
FHP025 253E/99 2.7.2.6.3.3 <i>Effect of Intrinsic and Extrinsic Factors</i>	Investigation of the pharmacokinetics of the active metabolite RM1 after single inhalation of 1600 µg ciclesonide in healthy elderly subjects.	2.7.2.2.3.3	Influence of Age (Elderly)
BTR-15/001 49/2000 2.7.2.6.3.4 <i>Effect of Intrinsic and Extrinsic Factors</i>	Single administration of ciclesonide in healthy adult male volunteers – Phase I clinical study.	2.7.2.2.3.4	Single Dose PK in Japanese
BTR-15/002 60/2000 2.7.2.6.3.5 <i>Effect of Intrinsic and Extrinsic Factors</i>	Repeated dose study of ciclesonide in healthy male volunteers – Phase I clinical study.	2.7.2.2.3.5	Multiple Dose PK in Japanese
200/2000 2.7.2.6.3.6 <i>Effect of Intrinsic and Extrinsic Factors</i>	Comparison of the pharmacokinetic of ciclesonide metabolite RM1 in Caucasian and Japanese subjects following single inhalation of ciclesonide using the MDI device.	2.7.2.2.3.6	Comparison of PK in Japanese and Caucasians
FHP019 304/98 2.7.2.6.3.7 <i>Effect of Intrinsic and Extrinsic Factors</i>	Investigation of a possible pharmacokinetic interaction between ciclesonide and erythromycin in healthy subjects.	2.7.2.2.3.7	Lack of drug-drug interaction with erythromycin
CPC29 215/2002 2.7.2.6.3.8 <i>Effect of Intrinsic and Extrinsic Factors</i>	Investigation of the pharmacokinetic interactions between inhaled formoterol and inhaled ciclesonide	2.7.2.2.3.8	Lack of drug-drug interaction with formoterol
<b>Clinical Pharmacodynamics (2.7.2.2.4)</b>			
FHP012 223/97 2.7.2.6.4.1 <i>Clinical Pharmacodynamics</i>	Pharmacodynamics of ciclesonide as compared to baseline and to budesonide following repeated dose inhalations in 12 healthy male volunteers	2.7.2.2.4.1	PD (cortisol suppression) in healthy
FHP013 151/98 2.7.2.6.4.2 <i>Clinical Pharmacodynamics</i>	Study on the circadian rhythm of cortisol in serum after repeated inhalation of 800 µg ciclesonide in the morning, 800 µg ciclesonide in the evening, and 400 µg ciclesonide o.d. as compared to placebo in healthy male volunteers.	2.7.2.2.4.2	PD (cortisol suppression) in healthy

Research Report-No.	Study title / objective	cf. Section	Comments
K2001CLN0012 XRP1526B-102 2.7.2.6.4.3 <i>Clinical Pharmacodynamics</i>	A randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study of the potential effects of ciclesonide and fluticasone propionate on HPA-axis in adult asthma patients.	2.7.2.2.4.3	PD (cortisol suppression) in Asthmatics
K2001CLN0013 XRP1526B-103 2.7.2.6.4.4 <i>Clinical Pharmacodynamics</i>	A randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study of the potential effects of ciclesonide and fluticasone propionate on HPA-axis in adult asthma patients.	2.7.2.2.4.4	PD (cortisol suppression) in Asthmatics
FK1 103 2.7.2.6.4.5 <i>Clinical Pharmacodynamics</i>	Effect of inhaled ciclesonide on hypersensitivity to AMP in subject with bronchial asthma.	2.7.2.2.4.5	PD (cortisol suppression) in Asthmatics
FK1 107 2.7.2.6.4.6 <i>Clinical Pharmacodynamics</i>	Effect of inhaled ciclesonide on cortisol levels and hypersensitivity to AMP in subject with bronchial asthma.	2.7.2.2.4.6	PD (cortisol suppression) in Asthmatics
DMPK/USA 01-085 2.7.2.6.4.7 <i>Clinical Pharmacodynamics</i>	Population Pharmacokinetic and Pharmacodynamic (PK/PD) Analysis of RM1 (Metabolite M1 of Ciclesonide)-Phase I Data.	2.7.2.2.4.7	Population PK/PD-Phase I
DMPK/USA 2003-0019 2.7.2.6.4.8 <i>Clinical Pharmacodynamics</i>	Population Pharmacokinetic and Pharmacodynamic (PK/PD) Analysis of RM1 (Metabolite M1 of Ciclesonide) Phase I, Phase IB/II and Phase III Data	2.7.2.2.4.8	Population PK/PD-Phase I and III

#### Ancillary Studies (2.7.2.2.5)

6EMU8761 170E/93 2.7.2.6.5.1 <i>Ancillary Studies</i>	A single-dose, rising dose level, placebo-controlled study in human volunteers to evaluate the tolerance of ciclesonide (epimeric mixture of ciclesonide)	2.7.2.2.5.1	PK of racemic ciclesonide
6EMU8762 58E/94 2.7.2.6.5.2 <i>Ancillary Studies</i>	A single dose study of the metabolism and pharmacokinetics of (1H)-Ciclesonide after intravenous, oral and inhalation administration (study with epimeric mixture of ciclesonide)	2.7.2.2.5.2	Trium label was used and hence superceded with 14C study (30EE/96, 2.7.2.6.2.1 <i>Clinical Pharmacokinetic Studies</i> )
FHP001 138/97 2.7.2.6.5.3 <i>Ancillary Studies</i>	Safety, tolerability and pharmacodynamics of the new steroid ciclesonide in healthy male volunteers following its intravenous, oral and inhalation administration	2.7.2.2.5.3	Superceded by Study (172/97, 2.7.2.6.2.2 <i>Clinical Pharmacokinetic Studies</i> ) and described PK after intravenous oral and Cyclohexer administration (Not intended route or formulation)
FHP007 192/95 2.7.2.6.5.4 <i>Ancillary Studies</i>	Pilot study to assess the pharmacokinetics of the new steroid R-ciclesonide in healthy male volunteers following administration of a single oral dose	2.7.2.2.5.4	PK after oral administration (Not the intended route)
FHP005 187E/95 2.7.2.6.5.5 <i>Ancillary Studies</i>	Safety and tolerability of the new steroid R-ciclesonide in healthy male volunteers following ascending single-dose oral administration.	2.7.2.2.5.5	Safety and tolerability after oral administration (Not the intended route)

Research Report-No.	Study title / objective	cf. Section	Comments
FHP020 305/98 2.7.2.6.5.6 <i>Auxiliary Studies</i>	Pilot study on the systemic bioactivity (cortisol in serum) and the pharmacokinetics of metabolite RM1 after single oral administration of a ciclesonide powder formulation	2.7.2.2.5.6	PK/PPD and safety after oral administration (Not the intended route)
FHP011 171E/97 2.7.2.6.5.7 <i>Auxiliary Studies</i>	Placebo-controlled study on the safety and local tolerability of ascending dose levels of R-ciclesonide (0.4 mg, 0.8 mg, 1.2 mg) administered as a new infusion solution on the basis of human serum albumin to healthy male volunteers.	2.7.2.2.5.7	PK after intravenous administration (Not the intended route)
FHP002 110E/95 2.7.2.6.5.8 <i>Auxiliary Studies</i>	Safety and tolerability of the new topical steroid R-ciclesonide in healthy male volunteers following ascending single-dose inhalations	2.7.2.2.5.8	PK after single dose administration of Cyclohaler <sup>®</sup> (Not the intended formulation/ device)
FHP006 181/96 2.7.2.6.5.9 <i>Auxiliary Studies</i>	Safety, tolerability and pharmacodynamics of the new topical steroid R-ciclesonide in healthy male volunteers following ascending repeated-dose inhalations over 5 days	2.7.2.2.5.9	PK after multiple dose administration of Cyclohaler <sup>®</sup> (Not the intended formulation/ device)
FHP101 90/2002 2.7.2.6.5.10 <i>Clinical Pharmacokinetic Studies</i>	Comparison of the pharmacokinetics of the active metabolite B9207-021 using different ciclesonide inhalation devices (2 Ultrahalers TM with different puff strength versus the Metered Dose Inhaler)	2.7.2.2.5.10	PK after single dose administration of MDI and Ultrahaler <sup>®</sup> (Not the intended formulation/ device)
FHP003 156E/95 2.7.2.6.5.11 <i>Auxiliary Studies</i>	Topical potency of the new steroid R-ciclesonide in healthy men compared to placebo and budesonide.	2.7.2.2.5.11	Safety after topical (skin) administration (Not the intended indication)
FHP017 152/98 2.7.2.6.5.12 <i>Auxiliary Studies</i>	Pilot study on the efficacy of ciclesonide nasal spray after allergen provocation in subjects with allergic rhinitis – A randomized placebo-controlled, double blind crossover study.	2.7.2.2.5.12	Safety/efficacy after intranasal administration (Not the intended indication)
278E/98 2.7.2.6.5.13 <i>Auxiliary Studies</i>	<i>In vitro</i> formation of fatty acid esters of the ciclesonide metabolite B9207-021 by human lung and liver microsomes as compared to budesonide.	2.7.2.2.5.13	Metabolism-fatty acid conjugation
FHP021 267/99 2.7.2.6.5.14 <i>Auxiliary Studies</i>	A study to investigate serum sample for metabolite identification collected in study B9010/FHP021	2.7.2.2.5.14	Metabolism

### **This reviewer's Comments**

The following table summarizes the overall content of the clinical pharmacology and biopharmaceutics information (electronic submission) provided by the sponsor to support the request for the approval of this NDA. Phase I PK studies were conducted using a different container closure than that in the to-be marketed formulation. The impact of this difference in the lung deposition and PK of the drug is not known. The sponsor will be requested to provide and in vitro and/or in vivo link. It appears that all the pivotal PK/PD studies were conducted using the to-be marketed formulation. The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues.

<b>Study Title/Description</b>	<b>Tabular listing/PKPD summary</b>	<b>Analytical method</b>	<b>PK/PD parameters</b>	<b>Statistical analysis</b>
All PK/PD studies	√	√	√	√

### **COMMENT TO THE SPONSOR**

- Valves in early Phase I PK studies used a moving bottle emptier, after which a modification was made to replace the moving bottle emptier with a fixed bottle emptier in order to improve performance of the product. Please indicate if an in vitro or/and in vivo link was provided in this submission and the location of it.

### **RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceutics, the Division of Pharmaceutical Evaluation II (OCPB/DEP-II) has reviewed the NDA package submission (NDA 21-658) for Ciclesonide received on Dec 22, 2003. The OCPB/DEP-II is aware of the series of pharmacokinetic, pharmacodynamics and PK/PD population studies that the sponsor included in this NDA submission. The NDA is filable from a CPB stand point. The above comment should be conveyed to the sponsor.

Sandra Suarez-Sharp, Ph.D.  
Pharmacokinetics Reviewer, DPEII, OCPB

Concurrence:

Emmanuel Fadiran Ph. D.  
Team Leader, DPEII, OCPB

cc:

HFD-570 Div., Bosken, Gilbert-McClain, Jackson  
HFD-870 Malinowski, Hunt, Fadiran, Suarez-Sharp, Wang

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

General Information About the Submission

	Information		Information
NDA Number	21-658	Brand Name	
OCPB Division (I, II, III)	II	Generic Name	Ciclesonide
Medical Division	DPADP	Drug Class	glucocorticoid
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	Treatment of asthma
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	MDI
PM Reviewer		Dosing Regimen	Adults and adolescents: 80- mcg <del>upto 320 mcg</del>
Date of Submission	Dec 22, 2003	Route of Administration	Oral Inhalation
Estimated Due Date of OCPB Review	July 22, 2004	Sponsor	Aventis, Inc.
PDUFA Due Date	Oct 22, 2004	Priority Classification	Standard
Division Due Date	Aug, 2004		

**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:	x	1		
Isozyme characterization:	x	7		
Blood/plasma ratio:				
Plasma protein binding:	x	3		
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	x	10		
multiple dose:		6		
	X			
<b>Patients-</b>				
single dose:	x	1		
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	x	3		
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	x	2		
In-vivo effects of primary drug:	x	2		
In-vitro:	x	2		
<b>Subpopulation studies -</b>				
ethnicity:	x	3		

gender:				
pediatrics:				
geriatrics:	x	1		
renal impairment:				
hepatic impairment:	x	1		
<b>PD:</b>				
Phase 2:	x	6		
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	3		
<b>Population Analyses -</b>				
Data rich:				
Data sparse:	x	2		
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>	x	1		
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
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>		54		
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<b>Application filable ?</b>	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) 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>NONE at this time</b>		
<b>QBR questions (key issues to be considered)</b>	<ol style="list-style-type: none"> <li>1. Dose proportionality</li> <li>2. Metabolic path-way</li> <li>3. Inhibition/induction of drug of CYP enzymes</li> <li>4. Drug-drug interaction</li> <li>5. Effect of hepatic impairment on PK of drug</li> <li>6. Gender, race, age, effect on the PK of the drug</li> <li>7. Lung residence time</li> <li>8. Pulmonary deposition/systemic BA</li> <li>9. Protein binding</li> <li>10. Dose-response</li> <li>11. Cortisol suppression</li> <li>12. QT prolongation</li> </ol>			

<b>Other comments or information not included above</b>	
<b>Primary reviewer Signature and Date</b>	
<b>Secondary reviewer Signature and Date</b>	

CC: NDA 21-658, HFD-870 (Electronic Entry or Lee), HFD-570 (Yu), HFD-870 (Fadiran, Hunt, Malinowski), CDR (B. Murphy)

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Shinja Kim  
2/23/04 03:52:59 PM  
BIOPHARMACEUTICS  
i'm checking this review into DFS on behalf of Sandra Suarez

Emmanuel Fadiran  
2/23/04 03:56:37 PM  
BIOPHARMACEUTICS  
I concur