

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-658

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

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-658 (Complete Response)
Proprietary Drug Name:	ALVESCO
Generic Name:	Ciclesonide
Indication:	Treatment of asthma
Dosage Form:	MDI
Strength:	80 μg and 160 μg
Route of Administration:	Oral Inhalation
Applicant:	Sanofi- Aventis, Inc.
Clinical Division:	DPAP (HFD-570)
Submission Dates:	July 10, 2007
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader (acting):	Wei Qiu, Ph. D.

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1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCP) has reviewed the complete response to NDA 21-658 submitted on July 10, 2007. We found the complete response to the approvable letter dated October 21, 2004, acceptable from a Clinical Pharmacology standpoint provided that the sponsor agrees with the **Agency's label recommendations. The labeling comments (page 15) and comments listed on section 1.3 below should be conveyed to the sponsor as appropriate.**

1.2 Phase IV Commitments

None

1.3 Comments to Sponsor

1. The results from the HPA axis suppression in children **assessed as part of Study XRP1526B – 343 (A Phase III, multicenter, double-blind, placebo-controlled, non-inferiority study assessing the effects of ciclesonide metered dose inhaler 50 µg/day and 200 µg/day (ex-valve) administered once daily on growth in children with mild persistent asthma), are not acceptable for the following reasons:**
 - The criteria for urine volume, creatinine excretion, and collection duration were not met. More than 40% of the subjects included in this study had collection of 24 hr urine volume of less than 250 mL.
 - Analytical methodology and in-study validation information for the analysis of urinary cortisol was not submitted.
 - Patient compliance could not be assured.
2. We recommend that the effect of Alvesco MDI on HPA axis suppression be evaluated in children 4 to 11 years of age by assessing 24 hr serum and 24hr urinary free cortisol levels in a dedicated pharmacodynamic study. Please **submit protocol in a timely manner for Agency's recommendations.**

1.4 Comment to Medical Reviewers

- The data and results of HPA axis assessment made as part of the growth study are not acceptable. Please see Comments to Sponsor. Therefore, HPA axis data should not be included in the label.

1.5 SUMMARY OF CLINICAL PHARMACOLOGY

Alvesco® inhalation aerosol (pMDI) contains ciclesonide, a non-halogenated glucocorticoid delivered as the R-epimer. Ciclesonide is a pro-drug that is hydrolyzed by esterases to its active metabolite, RM1 (a glucocorticoid). RM1 has approximately 100-fold greater affinity for the glucocorticoid receptor than the parent drug. Alvesco is proposed for the treatment of asthma in adults and [] years and older. The proposed dosage regimen for Alvesco is: 80 µg BID, 160 µg BID, 320 µg BID, [] depending on [] use of other drugs for asthma in adolescent and adults. The proposed dosage regimen in []

The original NDA submission for Alvesco was received on December 2003. The efficacy and safety of Alvesco® in asthma patients was primarily assessed in seven double-blind, placebo-controlled, multicenter studies. The clinical pharmacology program contained 44 studies. The original NDA submission was found acceptable from a Clinical Pharmacology standpoint¹.

On October 21, 2004, the Agency issued an approvable letter for Alvesco. This letter included mainly Clinical and CMC deficiencies (see Clinical and CMC reviews for more detailed information). The Agency requested the sponsor to demonstrate the efficacy of ciclesonide MDI in adults and adolescents with mild to moderate asthma who had been treated previously with bronchodilators alone, to demonstrate the efficacy of ciclesonide MDI administered once daily relative to the same total daily dose administered twice daily, and to demonstrate the efficacy of ciclesonide MDI in patients less than 12 years of age. In addition, further data were required to demonstrate the replicated efficacy of ciclesonide MDI at the lower dose of 160 µg QD AM.

The present submission is a complete response to the approvable letter issued to the sponsor on October 21, 2004. It contains the results of two new efficacy/safety studies and two Clinical Pharmacology studies (CP-036 and CP-031). The clinical pharmacology studies are as follows:

Study CP-036: an open-label, non-randomized, repeated-dose investigation of the steady state PK of ciclesonide MDI (320 µg QD) and active metabolite with and without co-administration of ketoconazole (400 mg QD), a potent CYP3A4 inhibitor.

Study CP-031: an open-label, non-randomized, single-dose (320 µg) study to assess the lung deposition of ^{99m}Tc-labeled ciclesonide MDI in adults with mild asthma.

Study CP-036 was originally submitted and reviewed as part of NDA 22-004 (Ciclesonide Nasal Spray) on December 21, 2005. Ketoconazole had no effect on the PK of ciclesonide, the parent compound. However, the C_{max} and AUC of RM1 metabolite increased by approximately 2.2 and 3.7 fold after co-administration with ketoconazole, respectively.²

Results from Study CP-031 showed that the percentage of delivered dose from Alvesco MDI was highest in the whole lung as compared with the oropharynx, esophagus, stomach, and exhaled air filter. The whole lung deposition represented 52.0% of the ex-actuator ciclesonide dose. The 3D SPECT data obtained in the right lung showed the highest deposition of ciclesonide in the outermost 2 shells, which comprise small airways and alveoli.

¹ Clinical Pharmacology Review for NDA 21-658 (original submission) entered in DFS on by Dr. Sandra Suarez

² Clinical Pharmacology review for NDA 22-004 entered on DFS by Sayed Al-Habet, Ph.D. on 9/8/2006.

This submission also included the results of the HPA axis suppression assessed in children 5 to 8 years of age as part of a new phase III growth study (XRP1526B - 343) entitled "A Phase III, multicenter, double-blind, placebo-controlled, non-inferiority study assessing the effects of ciclesonide metered dose inhaler 50 µg/day and 200 µg/day (ex-valve) administered once daily on growth in children with mild persistent asthma". Results showed that the mean change from baseline in 10 hr overnight and 24 hr urinary free cortisol at the end of study treatment (12 months) with either ciclesonide 50 µg/day or 200 µg/day was not different from placebo. The mean (LS mean) (SE) differences from placebo for the change from baseline in 24 hr urinary cortisol were 0.54 (1.07) µg/day and -0.46 (1.11) µg/day for the 50 µg/day or 200 µg/day treatments, respectively. The mean percentage change from baseline in 24 hr urinary free cortisol was 0% and -7% for the ciclesonide 50 µg/day and 200 µg/day treatments, respectively compared to -2% in the placebo group. It is noted that the statistical analysis included the entire data set on cortisol generated in this study and only about 13% of children enrolled in the study met the criteria for urine volume, creatinine excretion, and collection duration. The 24 hr urine volume in children 5 to 8 years of age is about 250 to 500 mL, however, more than 40% of the subjects included in this study had 24 hr urine volume less than 250 mL. In addition, analytical methodology and validation information for the analysis of urinary cortisol were not submitted. Therefore, this study is not acceptable.

The HPA axis data from two phase 1 studies in adults included in the original submission (Studies XRP1526B-102 and XRP1526B-103) are reanalyzed to include the change from baseline in 24hr urinary free cortisol uncorrected for creatinine. The original clinical pharmacology review (date in DFS) included an analysis of change from baseline in 24hr urinary cortisol corrected for creatinine. Study XRP1526B-103 was a randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study. Twenty-four-hour urinary free cortisol was assessed in a total of 59 adults with mild asthma who were randomized to 400 µg or 800 µg Alvesco twice daily, placebo or active comparator. At the end of 29 days of treatment, the mean (SE) change from baseline in 24 hr urinary free cortisol was -8.69 (5.6) mcg/day, -4.01 (5.03) mcg/day, and -8.84 (5.02) mcg/day for the placebo, Alvesco 800 mcg/day, and Alvesco 1600 mcg/day, respectively. The difference from placebo for the change from baseline in 24 hr urinary cortisol was +4.7 mcg/day [95% CI: -10.58; 19.93] and -0.16 mcg/day [95% CI: -15.20; 14.89] for the 800 mcg/day or 1600 mcg/day treatments, respectively. In comparison, the mean (SE) change from baseline in 24 hour urinary cortisol was -8.57 (5.13) mcg/day and -14.17 (5.13) mcg/day for the the inhaled corticosteroid comparator 880 mcg/day and 1760 mcg/day, respectively and the difference from placebo was +0.12 mcg/day [95% CI: -15.79; 16.02] and -5.48 mcg/day [95% CI: -20.65; 9.69], respectively.

The adequacy of Study XRP1526B-102 is questionable since mean urinary free cortisol levels at baseline were in the range of 1.5 to 1.8 µg/day (normal values range from 10-100 µg/day) and the individual urinary free cortisol for placebo treatment range from 0.5 to 4 µg/day at week 12. Therefore, this study is not acceptable.

A summary of the Clinical Pharmacology findings is described below. The majority of this information has been previously reported in the Clinical Pharmacology review for the original submission of this NDA.

Pharmacokinetics in Healthy Volunteers

Single Dose

Following oral inhalation of ciclesonide 360 µg, the mean C_{max} of RM1 and ciclesonide occurred at 1.1 hr and 0.25 hr, respectively. The mean AUC_{0-∞} of RM1 (1.72 ng*hr/mL) ranged from 2.5- to 3-fold higher than that observed for the parent drug. However, the C_{max} (0.3 ng/mL) was 3.5-fold lower for RM1. No significant interconversion (<0.6%) of R-ciclesonide to S- ciclesonide occurs in vivo. In vivo studies showed that when the same dose (800 µg) of ciclesonide is delivered by inhalation from either strength (40, 80, or 160 µg), 90% confidence intervals applied to AUC and C_{max} geometric mean ratios of RM1 were within 80-125% limit. The systemic exposure (C_{max} and AUC) of RM1 was not affected by the used of [] spacer. The post-hoc AUC of RM1 was linear and dose-proportional in the range of 40 to 3520 µg. After inhaled administration of ^{99m}Tc (technetium)-labeled ciclesonide to healthy volunteers, ex-actuator lung deposition was 52 ± 11% with mouth-pharynx deposition of 38 ± 14%. Lung deposition did not change in asthmatic patients.

Repeat Dose

The mean C_{max} (0.369 ng/mL) and AUC_{0-∞} (2.18 ng*hr/mL) of RM1 following multiple administration of ciclesonide 360 µg QD increased up to 26% compared to those after single dose administration. Time to reach steady-state was not addressed; however, it is expected to be achieved within 2 to 3 days of repeated once daily dosing. The mean accumulation ratio for RM1 was 1.4 (range: 1.1-1.8). RM1 T_{max} was similar to that after single dose administration. The RM1 half-life increased from 5.2 to 6.7 hrs. The mean RM1 AUC was about 3-fold higher than that observed for the parent drug. However, C_{max} was similar. Following multiple administration of ciclesonide (250 and 1000 µg BID), C_{max} and AUC of both ciclesonide and RM1 increased proportionally to the dose.

Bioavailability

Inhaled bioavailability of ciclesonide + RM1 following inhalation of ciclesonide *via* MDI was 41%. Absolute oral and inhaled bioavailability of ciclesonide (measured as RM1), was 1.1% and 26%, respectively.

Absorption

Ciclesonide and RM1 are absorbed fairly rapidly. Based on population PK analysis, K_a values ranged from 7.3-10.8 h⁻¹ across sub-populations (asthmatics, healthy, adults, children, male, female etc.).

Distribution

The V_d following IV administration was 207 L and 898 L for ciclesonide and RM1, respectively. Based on population PK analysis, RM1 V_d values ranged from 1113.1-1426.8 L across sub-populations. The protein binding for RM1 and ciclesonide was higher than 98.5%; however this value should be interpreted with caution because of the relatively high non-protein binding reported in the study.

Elimination

Following IV administration, the half-lives and plasma clearance of ciclesonide and RM1 were 0.94 hr and 2.8 hr, and about 152 and 228 L/h, respectively indicating high extraction ratio drugs. Based on population PK analysis, mean CL ranged from 267.3-339.7 L/h across tested sub-populations.

Radioactive ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) and after IV (65.95%) administration, indicating that excretion through bile is the major route of elimination. The biotransformation of ciclesonide is likely to be catalyzed by an esterase enzyme which has not been identified. It appears that RM1 is the major active metabolite that results from the biotransformation of ciclesonide. However, this hypothesis is inconclusive since mass balance studies showed that only 20% of total plasma radioactivity corresponds to RM1. In addition, the metabolite M9, whose pharmacological potency is unknown, was as abundant as RM1 in plasma samples. The cleavage of ciclesonide starts in the lungs where RM1 forms ester conjugates with fatty acids. The biotransformation of RM1 appears to be predominately catalyzed by CYP3A4 (83%), although CYP2D6 (~30%), and to a lesser extent CYP2C8 (11%) are also involved. A major involvement of CYP3A4 in the metabolism of RM1 is inconclusive due to contradictory findings. RM1 does not produce significant inhibition (<25%) of major cytochrome CYP450 enzymes. The potential of ciclesonide to act as an inhibitor of CYP enzymes was not evaluated. Ciclesonide at therapeutic serum concentrations is not likely to induce the enzymes tested (CYP1A2, CYP2C9, CYP2C19, and CYP3A4).

Pharmacokinetics in Asthmatic Patients

The systemic exposure of ciclesonide and RM1 in asthmatic patients receiving a single dose of ciclesonide 1600 µg was similar to that observed in healthy subjects. The C_{max} and AUC_{0-∞} of RM1 increased in patients with asthma by <12%. The half-life and T_{max} remained unchanged. The C_{max} and AUC_{0-∞} of ciclesonide decreased in patients with asthma by <25%. Based on population PK analysis, the estimated CL/F values were 339.7 L, 301 L, and 283 L for healthy adults, mild to moderate asthmatics, and severe asthma patients, respectively.

Pharmacokinetics in Special Populations

Age, Gender, Weight, Race

Based on population PK analysis, there were no clinically relevant differences in RM1 pharmacokinetics due to race (74% whites, 11% Japanese, 3% Black and 11% others), gender (47% males, 49% females), weight, and age (8%

pediatrics, 84% adults, and 3% elderly). The mean AUC_{pop} normalized to 200 µg in children and elderly was similar to that in adults (0.82 ng*hr/mL±0.3 and 0.82 ng*hr/mL ± 0.2 vs. 0.76 ng*hr/mL ± 0.4).

The mean systemic exposure (AUC_{pop}) 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.

A meta-analysis of data from healthy young Caucasian and Japanese subjects revealed that the ratio of geometric means for C_{max} and AUC_{0-∞} of RM1 following single inhalation of 800 µg ciclesonide yielded point estimates and 90% CI of 0.87 (0.77, 0.99) and 0.90 (0.77, 1.05), respectively, indicating no clinically relevant differences in the systemic exposure.

Renal Impairment

The effect of renal impairment on the PK of ciclesonide and RM1 was not evaluated. The rationale provided is that ciclesonide (and RM1) is an inhaled drug with a wide therapeutic index that is mainly eliminated by the hepatic and/or biliary route. In addition, plasma protein binding was not altered when plasma from subjects with renal impairment was spiked with RM1 (at a concentration of 5.0 ng/mL, the protein binding of RM1 in the predose plasma samples varied between 97.5-99%).

Hepatic Impairment

The effect of hepatic impairment (HI) on the PK of a single inhaled dose of ciclesonide 1600 µg was examined in 24 subjects with different degrees of HI (8 healthy, 8 with severe HI and 8 with moderate HI). The C_{max} and AUC_{0-∞} of ciclesonide and RM1 in patients with moderate and severe HI increased in the range of 1.4-fold to 2.7 fold compared to that in healthy subjects. Also, the T_{1/2} of RM1 increased in patients with moderate and severe HI by 2.3 hr and 4.6 hr, respectively, as compared to that in healthy controls. No dose adjustment is needed in patients with moderate and severe HI. Caution should be exercised when administering ciclesonide in patients with severe hepatic impairment.

Drug/Drug Interactions (DDI)

In-vitro metabolism studies indicated that RM1 is likely to be metabolized by CYP3A4 although CYP2D6 is also involved to a lesser extent. The sponsor did not conduct DDI studies to assess the effect of CYP2D6 inhibitors on the PK of ciclesonide. No in vivo DDI studies were conducted with drugs that displace binding to proteins.

The systemic exposure of ciclesonide and RM1 in healthy subjects receiving a single dose of ciclesonide 800 µg was not statistically significantly altered by its coadministration with a single dose of erythromycin 500 mg. The arithmetic mean C_{max} and AUC_{0-∞} of RM1 increased in the presence of erythromycin by < 12%.

The systemic exposure (AUC_{0-∞} and C_{max}) of ciclesonide and RM1 in healthy subjects receiving a single dose of ciclesonide 800 µg was not statistically significantly altered (<23 % decreased) when coadministered with a single dose of formoterol 24 µg. The cumulative urinary excretion of formoterol was not statistically significantly altered (8% decreased) when coadministered with ciclesonide. Based on population PK analysis, the RM1 CL and V_d values were similar for subjects with (98 subjects) and without (512 subjects) coadministration of albuterol.

The systemic exposure (C_{max} and AUC) of ciclesonide and RM1 in healthy subjects receiving ciclesonide MDI (320 µg QD) with and without co-administration of ketoconazole (400 mg QD) was evaluated in a multiple dose (7 days) study. Ketoconazole had no effect on the PK of ciclesonide. However, the C_{max} and AUC of RM1 metabolite increased by approximately 2.2 and 3.7 fold after ketoconazole, respectively.

Dose-Response (Efficacy and Safety) Relationships

The dose-response relationship of RM1 was evaluated in three adult and two pediatric phase III, efficacy and safety studies. The ciclesonide doses evaluated in adults were: 80-, 160- and 320 µg QD for 12 weeks in patients with mild to moderate asthma, and 160, and 320 µg BID in patients with severe persistent asthma. The doses evaluated in children were 40, 80 and 160 µg QD for 12 weeks in approximately 500 children 4 to 11 years of age (125 per study) with persistent asthma.

The primary efficacy variable was the change from baseline to Week 12 in FEV₁. Suppression of endogenous cortisol release (HPA-axis function) was included as one of the safety variables.

For the efficacy variable considered, significant difference from placebo (p<0.05) was replicated in all doses tested in adults, except for the 160 µg/day. At higher doses (BID regimen), there was a trend for better dose-response; however, dose-ordering response for efficacy was not observed as has been shown for other glucocorticoids. Ciclesonide doses of 320 and 640 µg BID were tested in subjects with persistent asthma requiring oral corticosteroid; however the primary end point was other than FEV₁.

The potential systemic effect of Alvesco on HPA axis was assessed in adults with mild asthma in a 29-day placebo controlled study. Twenty-four-hour urinary free cortisol was assessed in a total of 59 adults with mild asthma who were randomized to 400 µg or 800 µg ALVESCO twice daily, placebo or active comparator. At the end of 29 days of treatment the mean (LS mean) differences from placebo for the change from baseline in 24 hr urinary cortisol were +4.7 µg/day and -0.16 µg/day for the 800 µg/day or 1600 µg/day treatments, respectively. The mean percentage change from baseline in 24 hr urinary free cortisol were -16 % and -29% for the ciclesonide 800 µg/day and 1600 µg/day treatments, respectively compared to -32% in the placebo group.

Based on population PK/PD analysis using data from phase I and Phase III Studies, there was a trend for higher doses of ciclesonide to produce a higher cortisol suppression (13%, 8%, and 49% decrease in serum cortisol AUC for doses of 800 to 1200 µg and 1600 µg, and 3520 µg, respectively); however, due to the great variability on the data, a clear relationship was not observed. Nevertheless, the degree of cortisol suppression caused by ciclesonide in the range of proposed therapeutic doses is not higher than that observed for fluticasone propionate at therapeutic doses for the treatment of asthma. It should be noted that if equipotent doses of these two drug products were to be administered, the previous statement about ciclesonide causing less cortisol suppression than fluticasone may not hold true.

No dose-response for efficacy was observed in children. The starting dose in children is uncertain since the effect of the 80 µg/day or 160 µg/day dose was not replicated. The extend of HPA axis suppression was assessed in a phase III growth study in children 5 to 8 years of age. This study was found not acceptable since the criteria for urine volume, creatinine excretion, and collection duration was not met.

Based on data from one Phase I study (NOT a thorough QT study) in healthy males, RM1 did not significantly affect QT or QTc at single doses up to 3520 µg.

Reviewer

Sandra Suarez-Sharp, Ph.D. _____
Office of Clinical Pharmacology
Division of Clinical Pharmaceutical Evaluation II

Final version signed by Qiu Wei, Ph.D., Acting Team leader _____

cc
DCPII: Sahajwalla, Doddapaneni, Qiu
HFD-570: Bosken, Gilbert-MCclain, Chowdhury, Jackson

2. QUESTION BASED REVIEW

This section focuses on a “question base review approach” considering mainly the clinical pharmacology information submitted in the complete response. A comprehensive question base review done for the original submission can be found in the appendix.

2.1 What is the effect of ketoconazole on the PK of Alvesco?

The original submission did not include a DDI with ketoconazole despite the Agency’s recommendations during the development phase of Alvesco. Study CP-036 was originally submitted and reviewed under NDA 22-004 (Ciclesonide Nasal Spray) on December 21, 2005. This study was an open-label, non-randomized, repeated-dose investigation of the steady state PK of ciclesonide MDI (320 µg QD) and active metabolite with and without co-administration of ketoconazole (400 mg QD), a potent CYP3A4 inhibitor. Ketoconazole had no effect on the PK of ciclesonide. However, the C_{max} and AUC of RM1 metabolite increased by approximately 2.2 and 3.7 fold after ketoconazole, respectively.¹

2.2 What is the effect of the proposed Alvesco doses on HPA axis suppression in children?

HPA axis suppression was assessed as part of a phase 3 growth evaluation in children entitled “A Phase III, multicenter, double-blind, placebo-controlled, non-inferiority study assessing the effects of ciclesonide metered dose inhaler 50 µg/day and 200 µg/day (ex-valve) administered once daily on growth in children with mild persistent asthma”. HPA axis suppression was assessed by measuring 10 hr (overnight) or 24 hr free urinary cortisol in about 100 children/treatment arm ages 5 to 8 years. Urine samples were collected during the last 2 weeks of the run-in period (the qualifying phase) to provide a baseline reference. Samples were collected again at the end of double-blind treatment (Visit 13, month 12) and at the follow-up visit (Visit 14). The 24-hour and 10-hour urinary cortisol endpoints included the change from baseline at Month 12.

The mean change from baseline in 10 hours (overnight) and 24-hour urine cortisol for ITT population are summarized in the Table 2.2.1 and 2.2.2, respectively. A graphic presentation of these mean changes in 10 hr urine cortisol (corrected for creatinine) and 24 hr urine cortisol (uncorrected for creatinine) at the end of the study treatment is provided in the Figure 2.2.1 and 2.2.22, respectively. Results from this study showed that the mean change from baseline in 10 hr overnight and 24 hr free urinary cortisol corrected or uncorrected for creatinine at the end of study treatment with either ciclesonide 50 µg/day or 200 µg/day was not different from placebo. The mean (LS mean) (SE) differences from placebo for the change from baseline in 24 hr urinary cortisol uncorrected for creatinine were 0.54 (1.07) µg/day and -0.46 (1.11) µg/day for the 50 µg/day or 200 µg/day treatments, respectively. These results are in agreement with previously reported information in about 32 children 4 to 11 years of age (Study 341) on change from baseline in 24 hr urinary cortisol following administration of ciclesonide 50 µg/day or 200 µg/day for 12 weeks. The mean percentage change from baseline in 24 hr urinary free cortisol was 0% and -7% for the ciclesonide 50 µg/day and 200 µg/day treatments, respectively compared to - 2% in the placebo group. It is noted that the statistical analysis included the entire data set on cortisol generated in this study and only about 13% of children enrolled in the study met the criteria for urine volume, creatinine excretion, and collection duration. The average 24 hr urine volume in children 5 to 8 years of age is about 250 to 500 mL, however, urine volume collected in this study ranged from 75 mL to 2 L. More than 40% of the subjects included in this study had 24 hr urine volume less than 250 mL (Figure 2.2.3). In addition, analytical methodology and validation information for the analysis of urinary cortisol was not included. Therefore, this study is not acceptable.

Table 2.2.1. Change from baseline to end of double-blind treatment period in 10-hour overnight urinary free cortisol levels (safety population)*

Parameter Treatment	N	Baseline mean ^a	Change from baseline ^b LS mean ± SE	Difference vs. placebo	
				LS mean ± SE	2-sided 95% CI
10-hour overnight urinary free cortisol corrected for creatinine (µg/mg creatinine)					
Placebo	75	0.020	-0.000 ± 0.0023	-	-
Ciclesonide 40 µg/day	71	0.023	-0.001 ± 0.0024	-0.001 ± 0.0030	(-0.007, 0.005)
Ciclesonide 160 µg/day	91	0.020	-0.003 ± 0.0021	-0.003 ± 0.0028	(-0.008, 0.003)
10-hour overnight urinary free cortisol (µg/10 h)					
Placebo	75	5.09	1.20 ± 0.826	-	-
Ciclesonide 40 µg/day	71	4.65	1.39 ± 0.847	0.18 ± 1.089	(-1.96, 2.33)
Ciclesonide 160 µg/day	91	3.82	-0.03 ± 0.749	-1.23 ± 1.026	(-3.26, 0.79)

CI = confidence interval; LS = least squares; N = safety population at participating sites; SE = standard error.

^aBaseline means are raw means. ^bEnd of double-blind treatment period.

Differences vs. placebo are calculated as ciclesonide minus placebo

*Based on sponsor's analysis

Table 2.2.2. Change from baseline to end of double-blind treatment in 24-hour urinary free cortisol levels (safety population)*

Parameter Treatment	N	Baseline mean ^a	Change from baseline ^b LS mean ± SE	Difference vs. placebo	
				LS mean ± SE	2-sided 95% CI
24-hour urinary free cortisol corrected for creatinine (µg/mg creatinine)					
Placebo	102	0.023	-0.002 ± 0.0014	-	-
Ciclesonide 40 µg/day	109	0.022	-0.002 ± 0.0014	-0.001 ± 0.0016	(-0.004, 0.002)
Ciclesonide 160 µg/day	97	0.022	-0.003 ± 0.0014	-0.001 ± 0.0016	(-0.004, 0.002)
24-hour urinary free cortisol (µg/day)					
Placebo	102	11.37	-0.24 ± 0.938	-	-
Ciclesonide 40 µg/day	109	10.56	0.31 ± 0.962	0.54 ± 1.072	(-1.57, 2.66)
Ciclesonide 160 µg/day	97	10.08	-0.70 ± 0.972	-0.46 ± 1.112	(-2.65, 1.72)

CI = confidence interval; LS = least squares; N = safety population at participating sites; SE = standard error.

^aBaseline means are raw means.

^bEnd of double-blind treatment period Differences vs. placebo are calculated as ciclesonide minus placebo.

*Based on sponsor's analysis

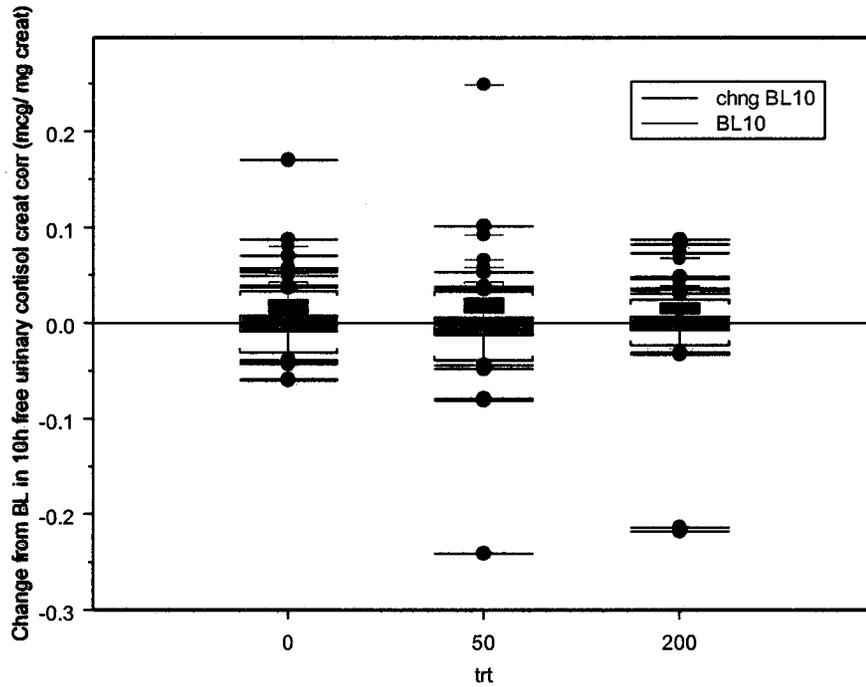


Figure 2.2.1. Change from baseline in 10 hr overnight urinary free cortisol corrected for creatinine following 1-year administration (visit 13) of ciclesonide 50 µg QD (50), ciclesonide 200 µg QD (200) or placebo (0) to asthmatic children. N=97-109.

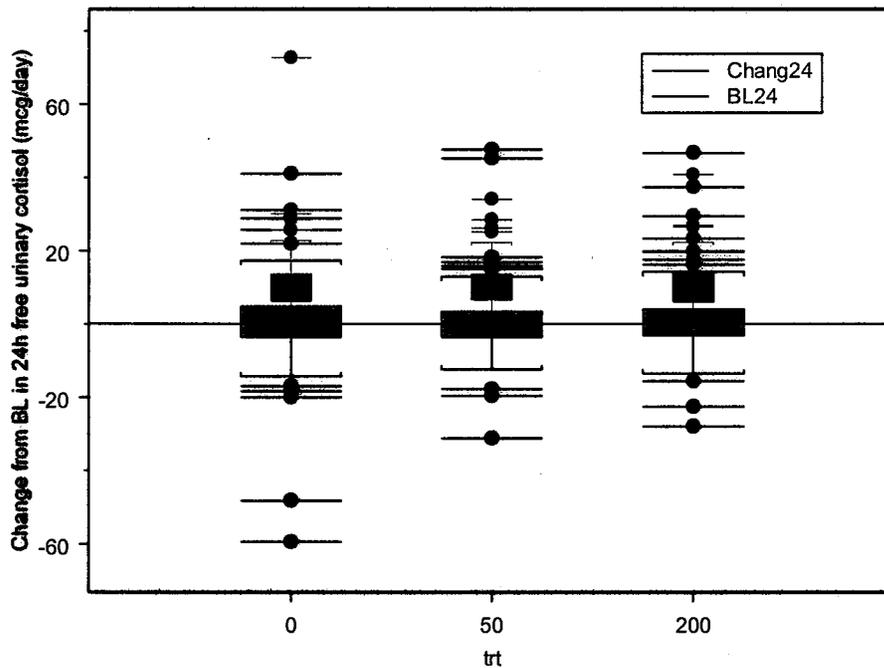


Figure 2.2.2. Change from baseline in 24 hr urinary free cortisol following 1-year administration (visit 13) of ciclesonide 50 µg QD (50), ciclesonide 200 µg QD (200) or placebo (0) to asthmatic children. N=71-91

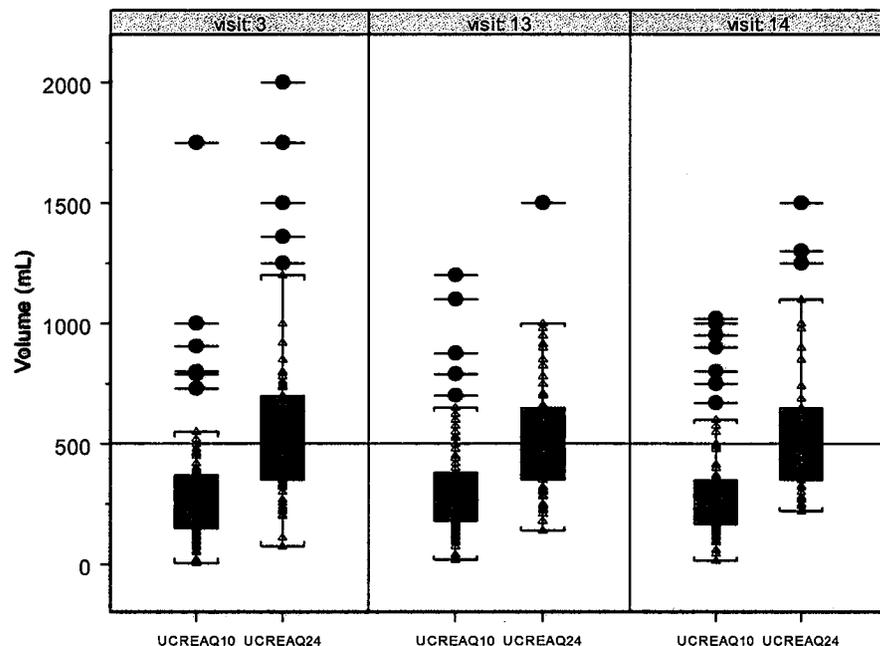


Figure 2.2.3. Urine volume collected from children 5 to 8 years of age at baseline (visit 3), end of study (visit 13) and follow-up (visit 14) for 10 hr overnight (UCRWAQ10) and 24 hr (UCREAQ10) urinary free cortisol analysis. Data from study 343.

2.3 What is the effect of Alvesco on HPA axis suppression in Adults?

The effect of Alvesco on HPA axis suppression in adults asthmatics was assessed in several phase I (Study BY9010/FHP012; Study FHP013; Study XRP1526B-102; Study XRP1526B-103; and Study BY9010/FK1 107) and phase 3 studies (321 and 322) which evaluated different doses (400 µg/day -3600 µg/day) and dosage regimens (QD vs. BID). The information from these studies was included and reviewed in the original NDA submission for Alvesco¹. Studies BY9010/FHP012, FHP013 and BY9010/FK1 107 were found not acceptable due to deficiencies in the study design (such as lack of information on urinary free cortisol at baseline) and data analysis. A reanalysis of HPA axis information from two phase 1 studies in adults included in the original submission (Studies XRP1526B -102 and -103) has been done in here to include the change from baseline in 24hr urinary cortisol uncorrected for creatinine. The original review included change from baseline in 24hr urinary cortisol corrected for creatinine.

Study XRP1526B-103 was a randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study. In this study patients were treated with ciclesonide, fluticasone propionate, or placebo twice daily for 29 days. Twenty-four-hour urinary free cortisol was assessed in a total of 59 adults with mild asthma who were randomized to 400 µg or 800 µg ALVESCO twice daily, placebo or active comparator. At the end of 29 days of treatment the mean (SE) changes from baseline in 24 hr urinary free cortisol were -8.69 (5.6) µg/day, -4.01 (5.03) µg/day, and -8.84 (5.02) µg/day for the PLB, CIC 800 µg/day, and CIC 1600 µg/day, respectively. The mean (LS mean) differences from placebo for the change from baseline in 24 hr urinary cortisol were +4.7 µg/day and -

0.16 µg/day for the 800 µg/day or 1600 µg/day treatments, respectively. The mean percentage change from baseline in 24 hr urinary free cortisol were -16 % and -29% for the ciclesonide 800 µg/day and 1600 µg/day treatments, respectively compared to -32% in the placebo group (Tables 2.3.1 and 2.3.2).

Table 2.3.1. Analysis of change from baseline in 24 hr urinary free cortisol (µg/day) at Day 29*

Treatment group	N	Mean Baseline (µg/day)	Change from baseline at Day 29		
			Adjusted mean (µg/day)	SE	95% CI
PLB	11	27.31	-8.69	5.6	(-19.96; 2.58)
CIC 800 µg/day	12	23.72	-4.01	5.03	(-14.12; 6.10)
CIC 1600 µg/day	12	30.09	-8.84	5.021	(-18.93; 1.25)
FP 880 µg/day	12	31.87	-8.57	5.13	(-18.89; 1.74)
FP 1760 µg/day	12	22.79	-14.17	5.13	(-24.47; -3.86)

* Adapted from sponsor's reported data.

Table 2.3.2 Analysis of difference from placebo (mean; SE) for 24hr urinary free cortisol change from baseline at Day 29*

Treatment group	Change from Baseline at Day 29		
	Mean difference from placebo (µg/day)	95% CI	Percentage change from baseline
PLB	--		-32
CIC 800 µg/day	4.68 (7.6)	(-10.58; 19.93)	-16
CIC 1600 µg/day	-0.16 (7.5)	(-15.20; 14.89)	-29
FP 880 µg/day	0.12 (7.9)	(-15.79; 16.02)	-27
FP 1760 µg/day	-5.48 (7.6)	(-20.65; 9.69)	-62

* Adapted from sponsor's reported data.

The highest difference from placebo was observed for the fluticasone 1600 µg/day treatment group. However, a conclusion that fluticasone causes greater cortisol suppression can not be drawn since equipotent doses were not tested. Although urine volumes were not provided, the 24 hr free cortisol baseline levels were within normal ranges in the adult population (10-100 µg/day) suggesting that the criteria for urine volume and creatinine excretion may have been met. This study also included the results of low dose cosyntropin stimulation (1 µg) and change from baseline in 24hr serum cortisol. The serum cortisol data is not being considered since the decrease trend in cortisol levels observed with Alvesco at earlier times was not observed at the end of the treatment (Figure 2.3.1).

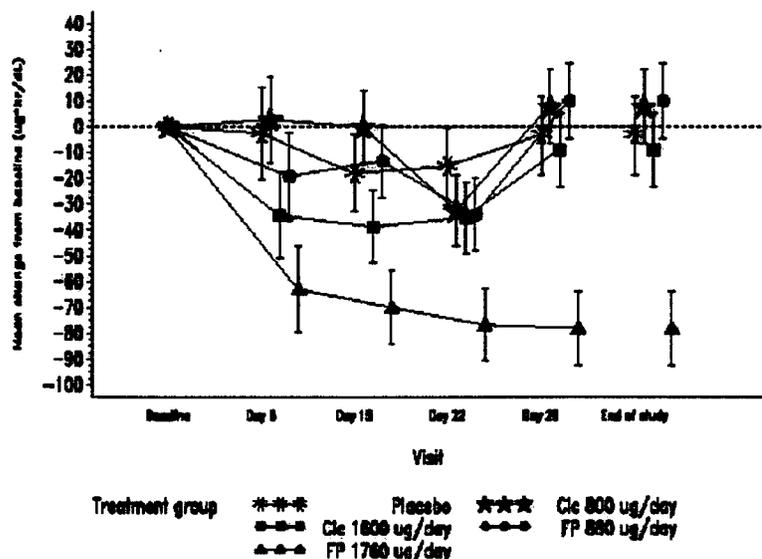


Figure 2.3.1. Mean change (\pm SE) in 24-hour serum cortisol AUC from baseline over time.

Study XRP1526B-102 was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study. Twenty-four-hour urinary free cortisol was assessed at week 6 and week 12 in a total of 158 adults with mild asthma who received either 400 μ g QD, 400 μ g BID ALVESCO, placebo or active comparator for 12 weeks. At the end of 6 weeks of treatment the mean difference from placebo for the change from baseline in 24 hr urinary cortisol were -0.14 μ g/day and +0.11 μ g/day for the 400 μ g QD and 400 μ g BID treatments, respectively. The mean percentage change from baseline in 24 hr urinary free cortisol were -15.6 % and -1.3% for the ciclesonide 400 μ g QD and 400 μ g BID treatments, respectively compared to -7.7% in the placebo group (Tables 2.33 and 2.35). The results at week 12 had the same trend (Tables 2.3.4 and 2.3.5). Urine volumes were not provided.

The adequacy of this study is questionable since mean urinary free cortisol levels at baseline were in the range of 1.5 to 1.8 μ g/day and the individual urinary free cortisol for placebo treatment range from 0.5 to 4 μ g/day at week 12. Therefore, this study is not acceptable.

Table 2.3.3. Analysis of change from baseline in 24 hr urinary free cortisol (μ g/day) at Week 6

Treatment group	N	Mean Baseline (μ g/day)	Change from baseline at week 6		
			Mean (μ g/day)	SE	95% CI
PLB	41	1.73	-0.133	0.0998	(1.54-1.92)
CIC 400 μ g/day	40	1.79	-0.28	0.11	(1.59-1.99)
CIC 800 μ g/day	42	1.55	-0.020	0.087	(1.41-1.7)
FP 800 μ g/day	41	1.73	-0.48	0.098	(1.58-1.87)

Table 2.3.4. Analysis of change from baseline in 24 hr urinary free cortisol (μ g/day) at Week 12

Treatment group	N	Baseline mean	Change from baseline at week 12		
			mean	SE	95% CI
PLB	41	1.73	-0.23	0.097	(1.43-1.85)
CIC 400 μ g/day	40	1.79	-0.19	0.16	(1.56-1.98)
CIC 800 μ g/day	42	1.55	-0.027	0.099	(1.38-1.67)
FP 800 μ g/day	41	1.73	-0.8	0.08	(1.52-1.86)

Table 2.3.5. Analysis of placebo difference (mean) in 24hr urinary free cortisol change from baseline at Day 29*

Treatment group	At week 6		At week 12	
	Difference from placebo	Percentage change from baseline	Difference from placebo	Percentage change from baseline
PLB	-	-7.7	-	-13.3
CIC 400 µg/day	-0.14	-15.6	0	-10.6
CIC 800 µg/day	+ 0.11	-1.29	0	-1.74
FP 800 µg/day	-0.35	-27.4	-0.57	-46

This study also included the results of low dose cosyntropin stimulation and change from baseline in 24hr serum cortisol. The serum cortisol data is not being considered also in this study since the decrease trend in cortisol levels observed with Alvesco at earlier times was not observed at the end of the treatment just like it was shown in Study 103.

2.4 What was the degree of pulmonary deposition following inhalation of ciclesonide from the MDI device?

Following single-dose (2 puffs x 160 µg =320 µg) inhalation of ^{99m}Tc-labeled ciclesonide MDI in adults with mild asthma the percentage of delivered dose was highest in the whole lung as compared with the oropharynx, esophagus, stomach, and exhaled air filter (Table 2.3.1). The whole lung deposition represented 52.0% of the ex-actuator ciclesonide dose (Table 2.3.3). The 3D SPECT data obtained in the right lung showed the highest deposition of ciclesonide in the outermost 2 shells, which comprise small airways and alveoli (see appendix).

Table 2.3.1. Mean and SD percentage distribution of ex-device (delivered) dose

Whole lung	Oropharynx	Oesophagus,	Stomach	Exhaled air filter
52.0 ± 9.0	32.9 ± 13.3	6.2 ± 3.8	5.2 ± 5.3	3.7 ± 3.1

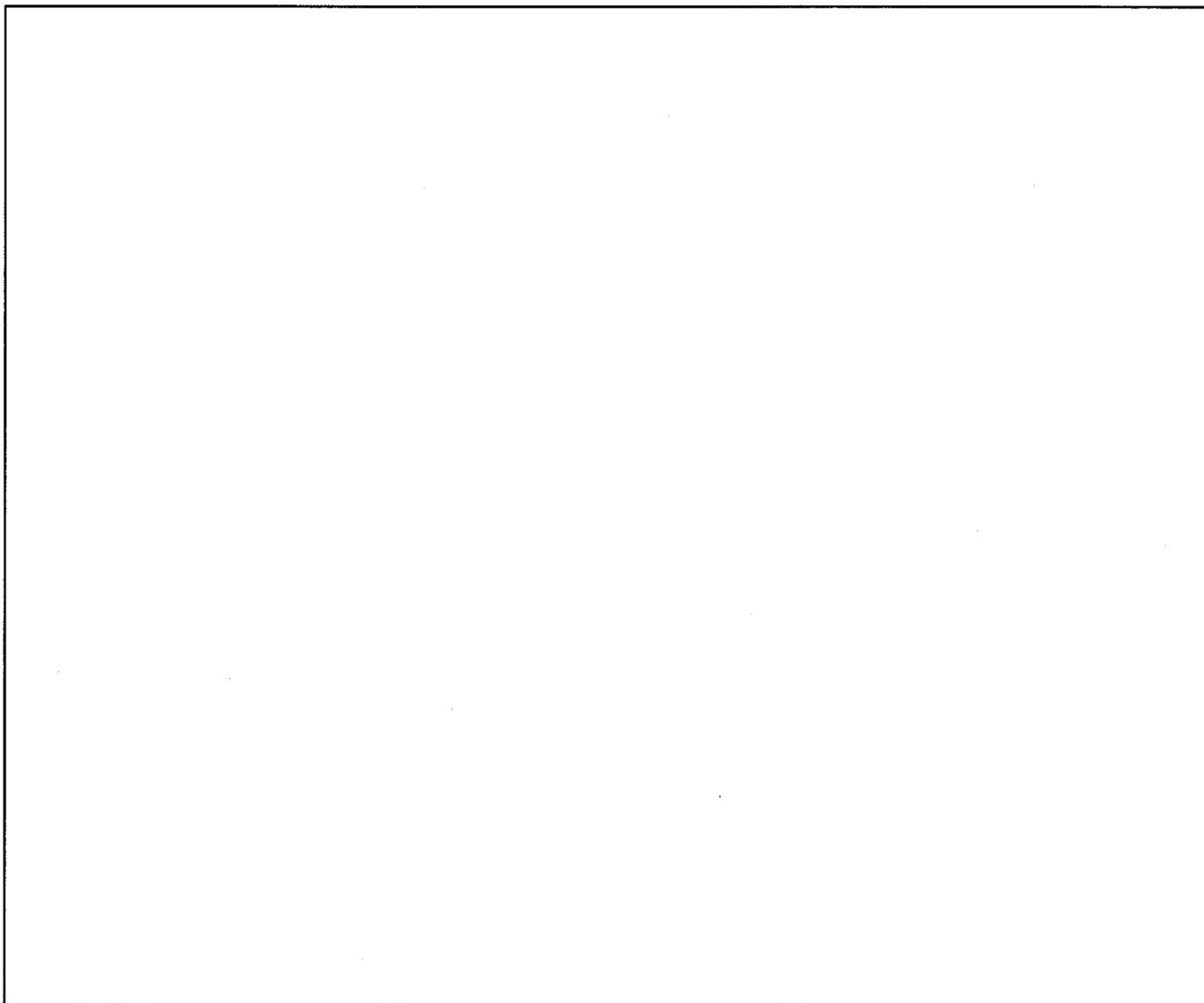
Table 2.3.2. Percentage distribution of ex-device (delivered) dose

Patient number	Whole lung	Oropharynx, oesophagus, and stomach	Exhaled air filter
0001	[Empty Box]	[Empty Box]	[Empty Box]
0002			
0003			
0004			
0005			
0006			
0007			
0008			
0009			
0010			
0011			
0012			
Mean	52.0	44.3	3.7
SD	9.0	8.1	3.1
Median	52.2	44.5	2.9
N	12	12	12

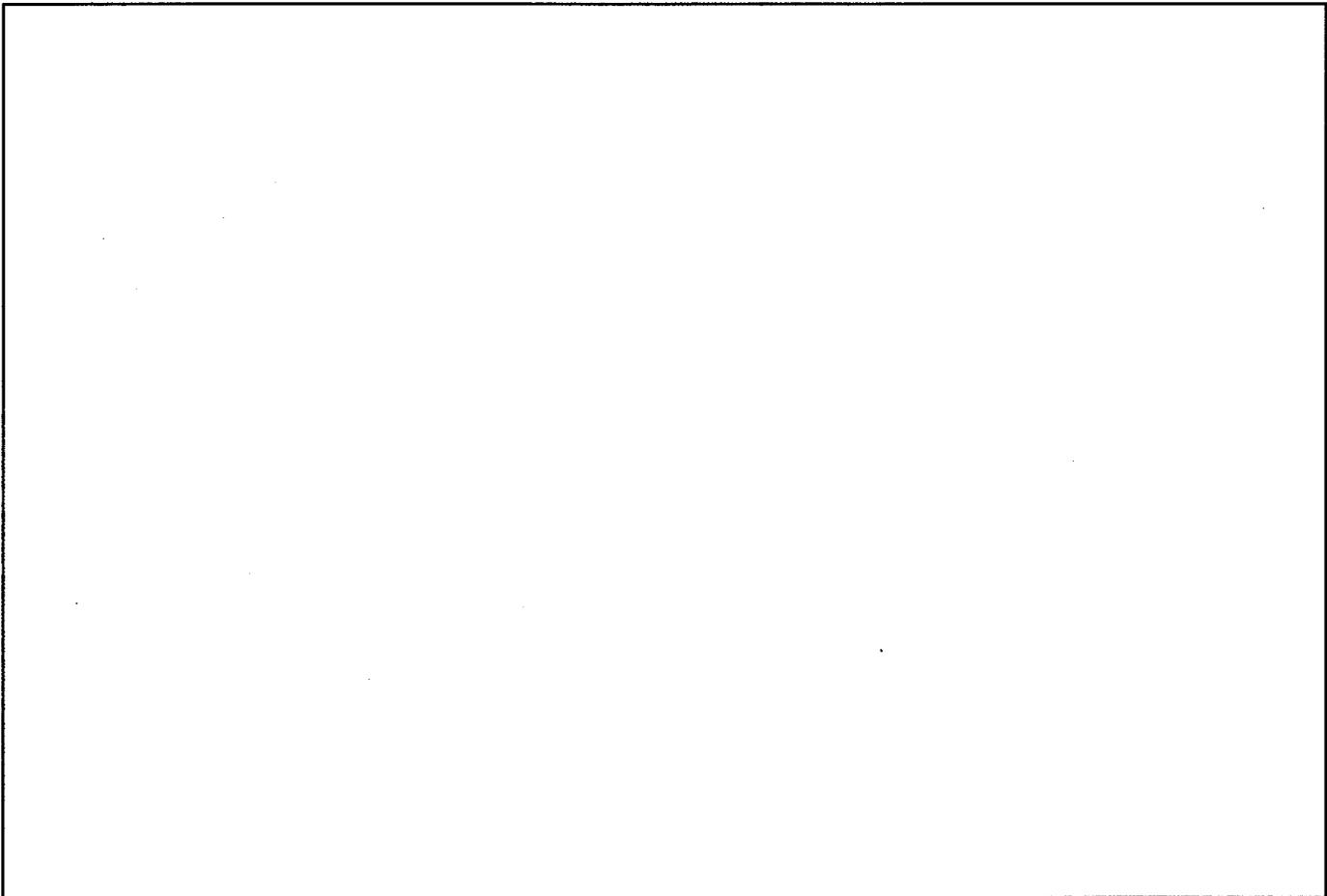
The lung deposition of the ciclesonide HFA-MDI solution aerosol was shown to be about 50 % (mean) in healthy volunteers. It could be possible that the lung deposition in patients with asthma be different than that in healthy volunteers due to the reduced diameter of their airways. It seems not to be the case with Alvesco. In fact, the systemic exposure of ciclesonide and its metabolite, RM1 in asthmatic patients receiving a single dose of ciclesonide 1600 µg was similar to that observed in healthy subjects.

3. LABELING RECOMMENDATIONS

The following changes (underlined) are recommended for the Clinical Pharmacology/Pharmacodynamic/Pharmacokinetic (section 12) sections of the label:

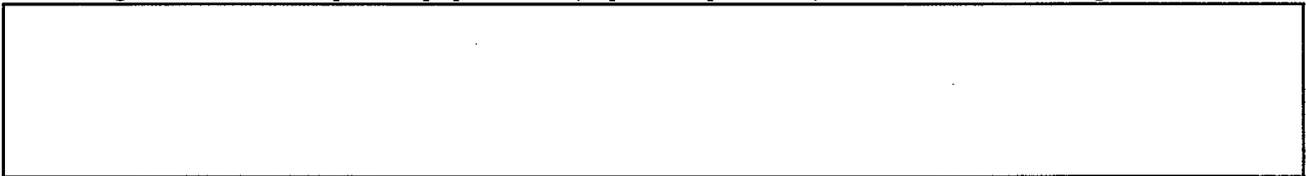


Page 16 redacted for the following reason:



Reviewer's Remarks

The following Clinical Pharmacology recommendations (cautionary statements) were made initially under the drug interaction and specific populations (hepatic impairment) sections of the labeling:



During an internal labeling meeting with the medical team, it was determined that the 3-fold increases in concentrations under these conditions are not deemed to be a safety concern based on available clinical data. Therefore, these cautionary statement were not included in the Alvesco labeling.

4. Appendix

4.1 Individual Study Reports

"A study to assess the lung deposition of ^{99m}Tc labeled ciclesonide administered via the HFA MDI in asthma patients - An open, nonrandomized, single dose study (320 µg exactuator corresponding to 400 µg ex-valve)"

Clinical Study Report no.: 316/2003
Protocol No.: BY9010/CP-031
Development Phase of Study: Phase I

Introduction

The lung deposition of the ciclesonide HFA-MDI solution aerosol was shown to be more than 50 % (mean) in healthy volunteers. However, it could be possible that the lung deposition of the device is different in patients with asthma due to the reduced diameter of their airways. Thus, the characterization of the lung deposition of ciclesonide via the HFA-device in the asthma population is of clinical importance.

Objectives

- to assess the lung deposition characteristics of ^{99m}Tc ciclesonide inhaled orally via the HFA-MDI in patients with asthma

Secondary:

- to characterize the single dose pharmacokinetics after inhalation of ^{99m}Tc-ciclesonide and
- To determine the amount of ciclesonide and active metabolite in the oral and pharyngeal region.
- To investigate the safety and tolerability of ^{99m}Tc-ciclesonide.

Study Population

A total of 12 patients with asthma (7 men and 5 women) entered and completed the study.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

Methods

This was an open, single dose (2 puffs of 160 mcg each), non-randomized study without control group. The study consisted of a screening visit, a study day, where the deposition characteristics and PK after administration of orally inhaled ^{99m}Tc-ciclesonide were investigated, and a post-study examination. During the course of the study day, blood and mouth rinsing samples were taken for PK analysis and scintigraphic images were acquired for lung deposition characterization. Blood samples for the PK evaluation were taken pre-dose and at the following times after inhalation: +15 min (+0.25 h), +30 min (+0.5 h), +45 min (+0.75 h), +60 min (+1 h), +90 min (+1.5 h), +120 min (+2 h), +3 h, +4 h, +5 h, +6 h, +8 h, +10 h, +12 h, and +14 h. The samples were analyzed by using a validated LC/MS/MS assay. The lower limit of quantitation (LLOQ) for the active metabolite (B9207-021) was 10 pg/mL, the LLOQ for the parent compound (B9207-015) was 25 pg/mL. Mouth rinsing was performed at approximately 7 to 12 min post-dose (i.e. directly after the oropharyngeal imaging) using 2-times 30 mL of a 50% (v/v) aqueous/ethanolic solution, which was expelled into a sampling tube.

Patients were able to leave the clinical unit on the study day after completion of study specific procedures at 14 h post-dose. The primary variables were analyzed from gamma scintigraphic image data (2D) to assess whole lung deposition, oropharyngeal deposition, and radioaerosol in exhaled air (given as percentage

of ex-actuator dose) as lung penetration profiles and dose percentage within 6 concentric lung-shaped regions. Single Photon Emission Computed Tomography (SPECT) images in 3D were analyzed to quantify deposition in 6 concentric lung shaped shells centered on the hilum.

Test Drugs

- ^{99m}Tc Ciclesonide HFA-MDI 320 µg (2 puffs of 120 µg each), ex-actuator batch number 131299

RESULTS

Scintigraphic Analysis

Two-dimensional Analysis

The results of the 2D analysis are presented in Table 1-2. The summary data for the distribution of the ex-device (delivered) dose are presented below in Table 3.

Table 1. Percentage of the ex-device (delivered) dose deposited in the 6 lung regions (2D analysis) and in the whole lung							
Patient number	2D Lung region						Whole lung
	1	2	3	4	5	6	
0001							
0002							
0003							
0004							
0005							
0006							
0007							
0008							
0009							
0010							
0011							
0012							
Mean	14.8	6.9	8.3	9.1	8.0	5.0	52.0
SD	3.2	1.5	1.4	1.7	1.7	1.0	9.0
Median	15.0	7.0	8.5	8.9	7.6	4.8	53.2
N	12	12	12	12	12	12	12

Table 2. Percentage distribution of ex-device (delivered) dose			
Patient number	Whole lung	Oropharynx, oesophagus, and stomach	Exhaled air filter
0001			
0002			
0003			
0004			
0005			
0006			
0007			
0008			
0009			

0010			
0011			
0012			
Mean	52.0	44.3	3.7
SD	9.0	8.1	3.1
Median	53.2	44.5	2.9
N	12	12	12

Table 3. Mean and SD percentage distribution of ex-device (delivered) dose

Whole lung	Oropharynx	Oesophagus,	Stomach	Exhaled air filter
52.0 ± 9.0	32.9 ± 13.3	6.2 ± 3.8	5.2 ± 5.3	3.7 ± 3.1

The percentage of delivered dose was highest in the whole lung compared with the oropharynx, esophagus, stomach, and exhaled air filter. The whole lung deposition represented 83/160 µg (52.0%) of the ex-actuator ciclesonide dose. A total of 32.9% was recorded in the oropharynx, 6.2% in the esophagus, and 5.2% in the stomach.

Three-dimensional Analysis

Analyses of the 3D data in 6 concentric shells of the right lung are presented in Table 4. Thus, deposition of ciclesonide was greater in the outer shells than for the inner shells of the lungs. The highest deposition was in the two outmost shells (shells 5 and 6).

Table 4. Mass of drug deposited in each shell (µg per puff)

Patient number	Shell						Total mass in the right lung (µg)
	1	2	3	4	5	6	
0001							47.2
0002							43.0
0003							46.1
0004							54.2
0005							61.3
0006							43.7
0007							35.4
0008							49.0
0009							44.0
0010							31.7
0011							34.7
0012							32.2
Mean	0.3	2.9	7.3	8.8	11.5	12.8	
SD	0.3	1.3	2.8	2.6	2.6	2.7	

Pharmacokinetics

The mean PK parameters of ciclesonide and its metabolite are shown in Table 5. Figure 1 shows the mean concentration-time profile of ciclesonide and its metabolite following single administration of the radiolabel compound. Maximum serum concentrations of the parent compound ciclesonide (B9207-015) were attained at the first available blood sampling time point at 0.25 h; at this time point, the mean C_{max} value was 1.361 µg/L. After inhalation, the distribution and elimination of B9207-015 was fast. The mean t_{1/2} as estimated from serum concentration between 1.0 h after inhalation and the last concentration that was above LLOQ resulted in values of about 0.57 h. The maximum serum concentrations of the active metabolite were attained mostly at about 1 h after ciclesonide inhalation and individual C_{max} spanned the range between 0.282 and 0.684 µg/L. The mean C_{max} value of the active metabolite was 0.406 µg/L. For the active metabolite (B9207-021), the mean elimination t_{1/2} was 6.02 h; the AUC(0,inf) had a mean value of 1.87 µgxh/L.

The parent compound ciclesonide and the main pharmacologically active metabolite were detected in all mouth rinsing solutions obtained at 8.9 min mean time point. At this time, the mean concentration of ciclesonide) was 118.7 µg/L and of active metabolite 18.6 µg/L. Molar concentrations are used to allow evaluations. The active metabolite represent on average 14.9% of the total molar concentration detected in the mouth rinsing solutions.

Compound	Mean	SD	SEM	Median	min	max	Geom. Mean	68%-range	
AUC _{inf} (µgxh/L)									
B9207-015	0.68	0.26	0.07	0.60	0.44	1.32	0.65	0.47	0.90
B9207-021	1.87	0.66	0.20	1.66	1.36	3.63	1.79	1.34	2.39
C _{max} [µg/L]									
B9207-015	1.361	0.526	0.152	1.221	0.664	2.540	1.276	0.881	1.849
B9207-021	0.406	0.108	0.031	0.407	0.282	0.684	0.395	0.309	0.504
t _{max} [h]									
B9207-015	0.25	0.00	0.00	0.25	0.25	0.25			
B9207-021	0.94	0.39	0.11	0.88	0.50	1.50			
t _{1/2} [h]									
B9207-015	0.57	0.08	0.02	0.56	0.46	0.76	0.56	0.50	0.64
B9207-021	6.02	1.55	0.47	5.88	3.88	8.52	5.84	4.48	7.60

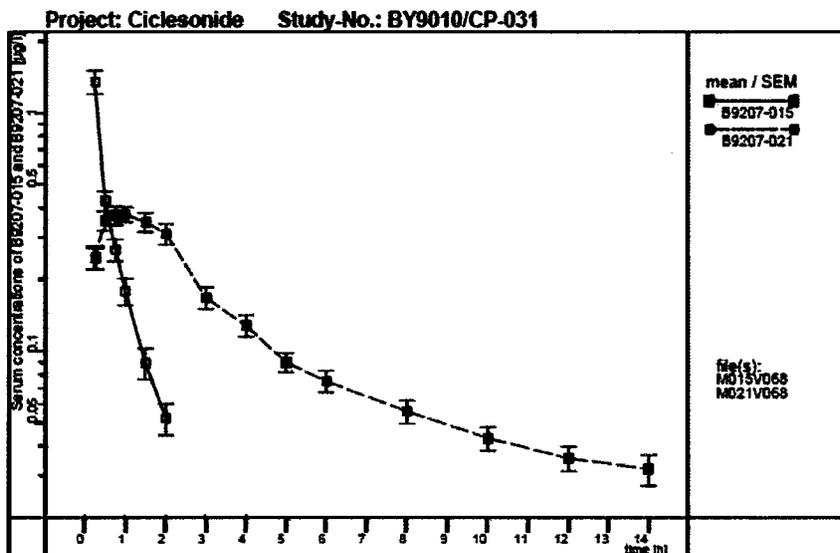


Figure 1. Mean (SEM) serum concentrations of the parent compound ciclesonide (B9207-015) and the active metabolite (B9207-021) in 12 asthma patients after inhalation of 320 µg ciclesonide.

Conclusions

- The 2D gamma scintigraphy data showed high deposition of ciclesonide in the *whole* lung of asthmatics (83 mg from a 160 mg ex-actuator dose of ciclesonide, representing 52.0% of the exactuator dose).
- The 3D SPECT data were based on the evaluation of the right lung. Of the 6 concentric shells of the lung, the outermost 2 shells (which comprise small airways and alveoli) showed the highest deposition of ciclesonide.
- Data from this study revealed very similar pharmacokinetics in serum compared with previous studies using a dose of 320 µg.
- The investigation of the mouth rinsing samples showed that the activation of the ciclesonide within the upper oropharynx was low. Only 14.9% of the active metabolite was present in mouth rinsing solutions as compared with the molar sum of ciclesonide and active metabolite.
- The mean oropharyngeal deposition of inhaled ciclesonide was 32.9% (scintigraphy data).

"A Phase III, multicenter, double-blind, placebo-controlled, non-inferiority study assessing the effects of ciclesonide metered dose inhaler 50 µg/day and 200 µg/day (ex-valve) administered once daily on growth in children with mild persistent asthma"

Protocol No.: **XRP1526B - 343**

Development Phase of Study: **Phase III**

Study Initiation Date: **29 December 2000**

Study Completion Date: **15 September 2004**

Objectives

Primary: To determine if ciclesonide metered dose inhaler (MDI) 50 µg/day or 200 µg/day (exvalve) (40 µg/day or 160 µg/day [ex-actuator]) administered once daily in the morning is noninferior to placebo with respect to growth velocity in children with mild persistent asthma following a 12-month treatment period.

Secondary: To investigate changes in growth in terms of bone age (wrist X-ray), and to investigate maintenance of asthma control and safety, after administration of ciclesonide MDI 40 µg/day or 160 µg/day (ex-actuator), compared to placebo.

One of the secondary endpoints was the assessment of HPA axis suppression by measuring 10 hr or 24 hr free urinary cortisol in children 5 to 8 years of age. This report summarizes the finding of this study in terms of HPA axis suppression only.

Study Design

This was a randomized, double-blind, parallel-group study including 2 dose groups of ciclesonide, 40 µg/day or 160 µg/day (ex-actuator), and a matching placebo group. Following a 6-month run-in period, eligible subjects were randomized to one of the 3 treatment groups. The dosages within these groups were fixed for the duration of the study. All subjects also received albuterol to be used as needed throughout the study.

The study consisted of 3 periods: run-in (including screening/baseline and qualification phases), double-blind treatment, and follow-up. The run-in period consisted of a 6-month observation period during which stadiometer measurements were collected.

Subjects who met the enrollment criteria were then randomized to approximately 12 months of double-blind treatment. This period included periodic clinic visits to perform stadiometry and collect safety information.

Population

A sample size of 135 subjects (Females aged 5 to 7.5 years and males aged 5 to 8.5 years at screening) per treatment (i.e., a total of 405 subjects) was required for the primary analysis of growth velocity. A total of 661 subjects were randomized to receive double blind treatment so as to ensure at least 405 evaluable subjects.

Pharmacodynamic data

24-hour urinary cortisol and 10-hour overnight cortisol tests

A total of 39 study sites were assigned to conduct 24-hour urine cortisol tests, and 36 sites were assigned to conduct 10-hour overnight urine cortisol tests (5 sites conducted both types of test).

Urine samples were collected in about 100 patients per treatment arm during the last 2 weeks of the run-in period (the qualifying phase) to provide a baseline reference. Samples were collected again at the end of

double-blind treatment (Visit 13) and at the follow-up visit (Visit 14). Urine cortisol values were analyzed as corrected and uncorrected for creatinine clearance.

Statistical analysis of 24-hour and 10-hour overnight urinary cortisol endpoints was based on the safety population. Tables of descriptive statistics at relevant visits were generated for 24-hour urinary cortisol corrected for creatinine, for 10-hour urinary cortisol corrected for creatinine, for 24-hour urinary free cortisol, and for 10-hour urinary free cortisol. Descriptive statistics were computed using the observed data. The analysis of change from baseline to end of double-blind treatment for these 4 endpoints at Visit 13 was conducted using an ANCOVA model that included terms for treatment, center (pooled), gender, age, baseline growth velocity, and the corresponding baseline cortisol variable.

Logarithmic transformation was applied to the dependent variable and all covariates in the ANCOVA model for pairwise treatment comparison and estimation of the 95% confidence interval for the geometric mean ratio for 24-hour urinary free cortisol and 10-hour urinary free cortisol. Resulting estimates and confidence interval limits were exponentiated in order to obtain adjusted means and confidence intervals. For each pairwise treatment comparison, a two-sided 95% confidence interval was constructed for the difference in least-squares means and ratios of geometric means.

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

According to the sponsor, the treatment compliance in this study was high. Overall, the percentage of subjects with a compliance of >85% was slightly higher in the placebo group (99.1%) than in the ciclesonide groups (ciclesonide 40 µg, 93.7%; ciclesonide 160 µg, 96.8%). However, compliance can not be assured since systemic exposure was not assessed.

Refer to the MO's review for discussion on the results of growth suppression. Analysis of mean change from baseline in 10 hours and 24-hour urine cortisol for ITT population are summarized in the Table 1 and 2, respectively. A graphic presentation of these mean changes in 10 hr urine cortisol (corrected for creatinine) and 24 hr urine cortisol (uncorrected for creatinine) at the of the study treatment is provided in the Figure 1 and 2, respectively. Mean 24-hour urinary free cortisol levels (corrected and uncorrected for creatinine) remained relatively unchanged between baseline and end of double-blind treatment in all 3 treatment groups, and there was no statistically significant difference between either ciclesonide group and placebo. These results are consistent with the geometric mean data for 24-hour urinary free cortisol levels

Table 1. Change from baseline to end of double-blind treatment in 24-hour urinary free cortisol levels (safety population)

Parameter Treatment	N	Baseline mean ^a	Change from baseline ^b LS mean ± SE	Difference vs. placebo	
				LS mean ± SE	2-sided 95% CI
24-hour urinary free cortisol corrected for creatinine (µg/mg creatinine)					
Placebo	102	0.023	-0.002 ± 0.0014	-	-
Ciclesonide 40 µg/day	109	0.022	-0.002 ± 0.0014	-0.001 ± 0.0016	(-0.004, 0.002)
Ciclesonide 160 µg/day	97	0.022	-0.003 ± 0.0014	-0.001 ± 0.0016	(-0.004, 0.002)
24-hour urinary free cortisol (µg/day)					
Placebo	102	11.37	-0.24 ± 0.938	-	-
Ciclesonide 40 µg/day	109	10.56	0.31 ± 0.962	0.54 ± 1.072	(-1.57, 2.66)
Ciclesonide 160 µg/day	97	10.08	-0.70 ± 0.972	-0.46 ± 1.112	(-2.65, 1.72)

CI = confidence interval; LS = least squares; N = safety population at participating sites; SE = standard error.

^a Baseline means are raw means.

^b End of double-blind treatment period Differences vs. placebo are calculated as ciclesonide minus placebo.

Table 2. Change from baseline to end of double-blind treatment period in 10-hour overnight urinary free cortisol levels (safety population)

Parameter Treatment	N	Baseline mean ^a	Change from baseline ^b LS mean ± SE	Difference vs. placebo	
				LS mean ± SE	2-sided 95% CI
10-hour overnight urinary free cortisol corrected for creatinine (µg/mg creatinine)					
Placebo	75	0.020	-0.000 ± 0.0023	-	-
Ciclesonide 40 µg/day	71	0.023	-0.001 ± 0.0024	-0.001 ± 0.0030	(-0.007, 0.005)
Ciclesonide 160 µg/day	91	0.020	-0.003 ± 0.0021	-0.003 ± 0.0028	(-0.008, 0.003)
10-hour overnight urinary free cortisol (µg/10 h)					
Placebo	75	5.09	1.20 ± 0.826	-	-
Ciclesonide 40 µg/day	71	4.65	1.39 ± 0.847	0.18 ± 1.089	(-1.96, 2.33)
Ciclesonide 160 µg/day	91	3.82	-0.03 ± 0.749	-1.23 ± 1.026	(-3.26, 0.79)

CI = confidence interval; LS = least squares; N = safety population at participating sites; SE = standard error.

^a Baseline means are raw means. ^b End of double-blind treatment period.

Differences vs. placebo are calculated as ciclesonide minus placebo

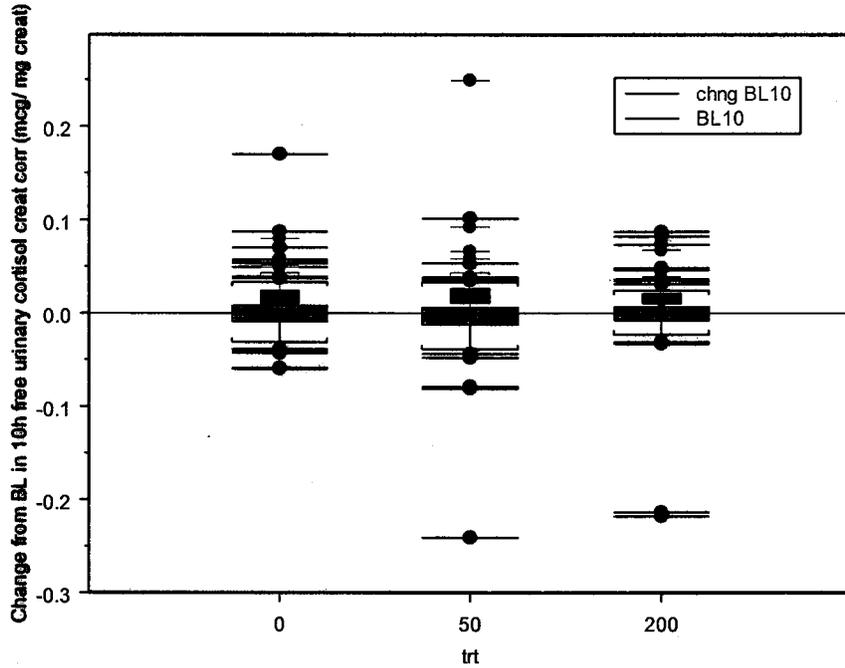


Figure 1. Change from baseline in 10 hr overnight urinary free cortisol corrected for creatinine following 1-year administration (visit 13) of ciclesonide 50 µg qd (50), ciclesonide 200 µg qd (200) or placebo (0) to asthmatic children. N=97-109.

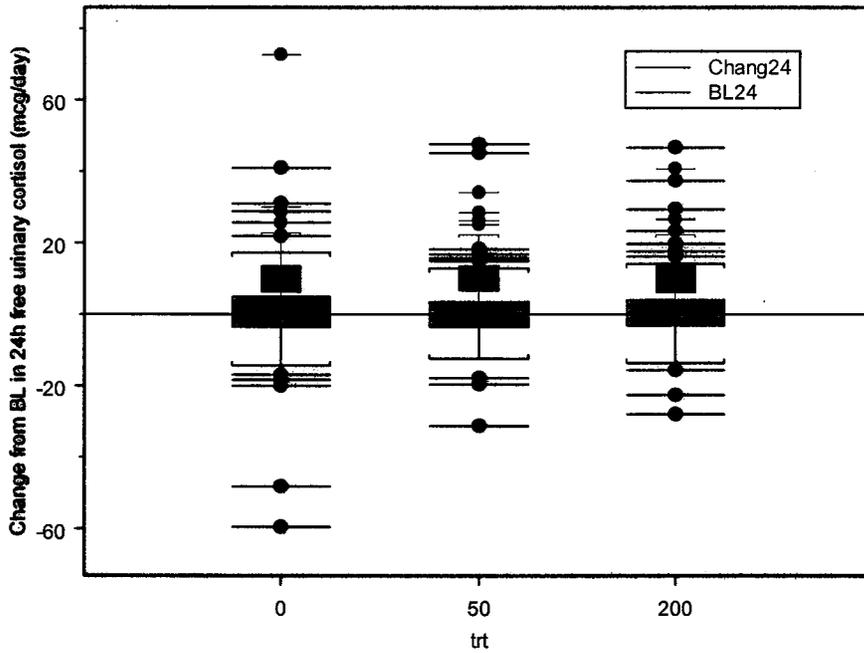


Figure 2. Change from baseline in 24 hr urinary free cortisol following 1-year administration (visit 13) of ciclesonide 50 µg qd (50), ciclesonide 200 µg qd (200) or placebo (0) to asthmatic children. N=71-91

SUMMARY OF FINDINGS

- The mean change from baseline in 10 hr urine free cortisol corrected or uncorrected for creatinine at the end of study treatment with ciclesonide 40 µg/day or 160 mcg/day was not different from placebo. Following administration of ciclesonide 40 mcg/day, the mean percentage change from baseline in 10 hr urine cortisol was +30% and -5% for the uncorrected and corrected values, respectively. Following administration of ciclesonide 160 mcg/day, the mean percentage change from baseline in 10 hr urine cortisol was -1% and -15% for the uncorrected and corrected values, respectively.
- The change from baseline in 24 hr urine free cortisol corrected or uncorrected for creatinine at the end of study treatment with ciclesonide 40 µg/day or 160 µg/day was not different from placebo. Following administration of ciclesonide 40 mcg/day, the mean percentage change from baseline in 24 hr urine cortisol was 3% and -9% for the uncorrected and corrected values, respectively. Following administration of ciclesonide 160 mcg/day, the mean percentage change from baseline in 24 hr urine cortisol was -7% and -13% for the uncorrected and corrected values, respectively.
- The change from baseline in 10 hr and 24 hr urine free cortisol corrected or uncorrected for creatinine at the end of study treatment with Placebo ranged from -10 to +23%.

GENERAL COMMENTS

- The sponsor did not provide data for the validation of the analytical method used to analyze cortisol.
- The following individual values were not included in the present submission:
 - 10 hr urinary free cortisol uncorrected for creatinine baseline values
 - Change from baseline in 10 hr urinary free cortisol uncorrected for creatinine
 - 24 hr urinary free cortisol corrected for creatinine baseline values
 - Change from baseline in 24hr urinary free cortisol corrected for creatinine

CONCLUSION

Ciclesonide given at either 40 mcg or 160 mcg/day to children older than 4 years olds appears not to affect their HPA axis function. It should be noted however, that the statistical analysis included the entire data set on cortisol generated in this study and only about 13% of patients met the criteria for urine volume, creatinine excretion, and collection duration originally set for adults. Therefore, this study is not acceptable.

4.2 Question based review for original submission

2.1 General Attributes

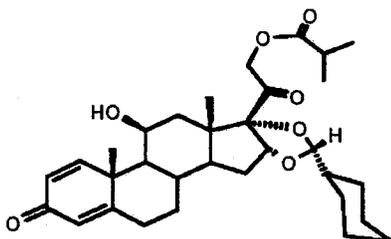
2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The active component of ALVESCO Inhalation Aerosol is ciclesonide, a non-halogenated glucocorticoid delivered as the R-epimer.

Chemical name:

pregna-1,4-diene-3,20-dione,16,17-[[[R]-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-(11β,16α).

Structural formula:



Molecular formula: C₃₂H₄₄NO₇

Molecular weight: 540.7

Solubility: Ciclesonide is a white to yellow-white powder. It is soluble in dehydrated alcohol, acetone, dichloromethane, and chloroform.

FORMULATION

Alvesco 80-, and 160 µg Inhalation Aerosol, are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a solution of ciclesonide in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. ALVESCO 80 µg delivers 100 µg from the valve and 80 µg of ciclesonide from the actuator. Alvesco 160 µg delivers 200 µg from the valve and 160 µg of ciclesonide from the actuator. This product delivers 50 microliters (59.3 milligrams) of solution as a fine particle mist from the valve with each actuation.

Table 1. Composition of Ciclesonide 160-, 80-, and Inhaler

Name of Ingredient	Quantity (% w/v)		Quantity (% v/v)
	160 µg inhaler	80 µg inhaler	
Ciclesonide	<input type="text"/>	<input type="text"/>	<input type="text"/>
Dehydrated Alcohol, <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
HFA-134a	<input type="text"/>	<input type="text"/>	<input type="text"/>
Total quantity	<input type="text"/>	<input type="text"/>	<input type="text"/>

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Ciclesonide is a pro-drug that is hydrolyzed by esterases to its active metabolite, RM1 (a glucocorticoid), which has approximately 100-fold greater affinity for the glucocorticoid receptor than the parent drug. According to the sponsor, RM1 has potent anti-inflammatory activity with affinity for glucocorticoid receptors that is 12 times greater than dexamethasone.

The precise mechanism of corticosteroid action in asthma is unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types and mediators involved in allergic- and non-allergic mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

INDICATION (as per proposed label)

Alvesco is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and patients years of age and older.
 Alvesco is NOT indicated for the relief of acute bronchospasm.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed route of administration is by oral inhalation.

DOSAGE AND ADMINISTRATION (as per proposed label)

	<input type="text"/>	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents:			
<input type="text"/>	Bronchodilators alone	<input type="text"/>	<input type="text"/>
	Inhaled Corticosteroids	<input type="text"/>	<input type="text"/>
	Inhaled Corticosteroids	<input type="text"/>	320 mcg twice daily
	Oral Corticosteroids	320 mcg twice daily	320 mcg twice daily
<input type="text"/>			

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology data?

The primary efficacy variable in the pivotal efficacy studies was the change from baseline to Week 12 (or end of study) in FEV₁ (forced expiratory volume in one second) in adults and adolescents, or in FEV₁ percent predicted in children. Although FEV₁ is a well established and validated clinical endpoint of efficacy in asthma, it does not, by itself, fully describes the level of overall asthma control. Therefore, key secondary endpoints reflecting asthma control, including AM PEF (morning peak expiratory flow), symptom scores, and rescue β₂-agonist use, were measured. Since systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and because there is uncertainty about the site of absorption along the respiratory tract/airways, plasma concentrations cannot be correlated to efficacy (FEV₁).

One of the major systemic side effects of therapeutic corticosteroids is the suppression of endogenous cortisol production. In the case of topical corticosteroid therapy such as in the lungs, it is attempted to minimize the systemic contribution by the absorbed corticosteroids in favor of primarily local effects. In this case, the suppression of endogenous cortisol release (HPA-axis function) assessed by cortisol concentrations measurements is a suitable marker to quantify the degree of systemic steroid activity of a drug. Ciclesonide however, showed no clear dose dependency (doses ranging from 360- to 1600µg/day) in serum cortisol levels measured as AUC_{0-24h}.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The basis for selecting the response endpoints was described in the previous question. The change from baseline to Week 12 in FEV₁ was measured prior to the morning dose (i.e., trough measurement) at the end of the 24-h dosing interval. Spirometry was performed according to standards for adults, adolescents, and children [1995 ATS Standardization of Spirometry guidelines].

As regards to cortisol suppression, the marked circadian rhythm in cortisol release makes the precise quantification of this cortisol suppression quite complex and therefore there is not a clear cut consensus about the ideal method for determining the effect on HPA-axis function. Suppression of endogenous cortisol release (HPA-axis function) was assessed by determining the AUC_{0-24h} serum cortisol corrected or uncorrected for baseline, 24 hr urine cortisol excretion corrected and uncorrected for creatinine, and peak cortisol levels following cosyntropin stimulation relative to placebo administration in either case.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Concentrations of ciclesonide and RM1 were determined in serum samples from all human pharmacokinetic studies using [] HPLC with tandem mass spectrometric detection (LC/MS/MS) with lower limits of quantification (LLOQ) of 25 pg/mL and 10 pg/mL for ciclesonide and its metabolite, respectively. The upper calibration limit for both analytes was 2000 pg/mL.

For Phase I studies, quantitative assay of serum cortisol was measured using a commercially available fluorescence polarization immunoassay. The lower limit of quantitation was 2.5 µg/dL (25 ng/mL). For Phase III studies, quantitative assay of serum cortisol was conducted using radio immunoassay (RIA). The LLOQ was 20 nM. See analytical section for details.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

As mentioned before, plasma concentrations cannot be correlated to efficacy for inhaled drugs. In the case of dose-response for efficacy, dose-ordering was not observed at lower doses. Studies 321 and 322 evaluated the efficacy, safety and dose response of ciclesonide 80-, 160- and 320 µg/day QD for 12 weeks in patients with mild to moderate asthma. In study 321, the middle dose had a lower mean change from baseline in FEV₁ values compared to the other 2 doses (Figure 1), while in study 322 the middle dose had the highest value in delta FEV₁. At higher doses (BID regimen), there was a trend for better response (Table 2, Figure 2); however no clear dose-response relationship was observed as has been shown for other glucocorticoids. According to the sponsor, all doses tested were significantly different from placebo (p<0.05), except the 160 µg dose in Study 321.

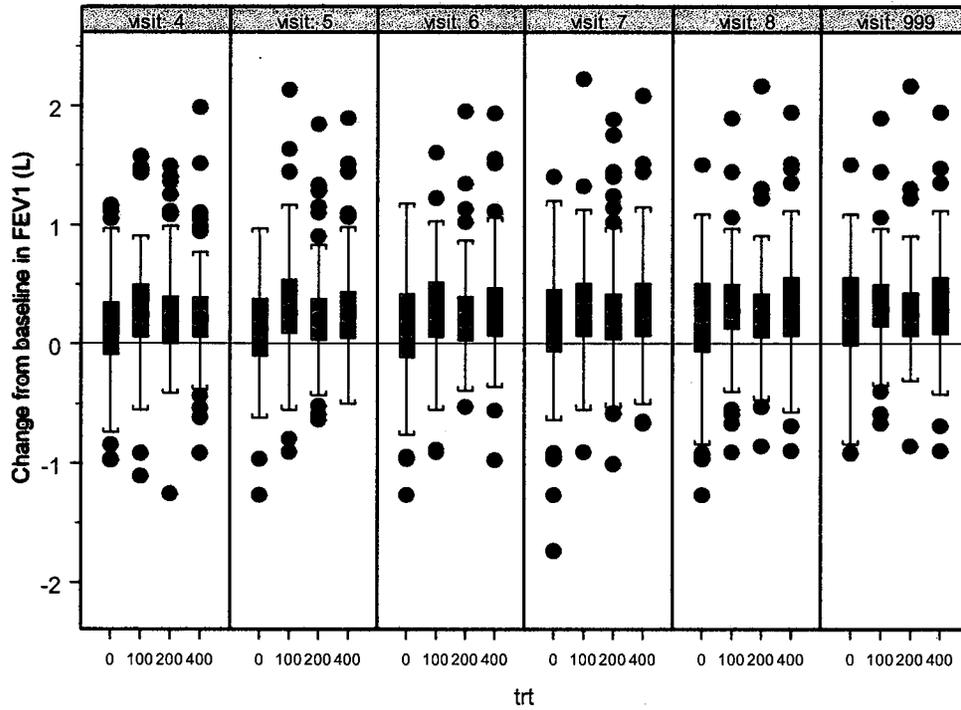


Figure 1. Change from baseline in FEV₁ (L) as a function of visit [time 4 (week 1), time 5 (week 2), time 6 (week 4), time 7 (week 8), time 8 (end point), time 999 (week 12)] following once daily administration of the treatments (ciclesonide 80, 160, and 320 µg QD) in adult patients with mild persistent to moderate persistent asthma (n=125 per treatment group). Data from study 321.

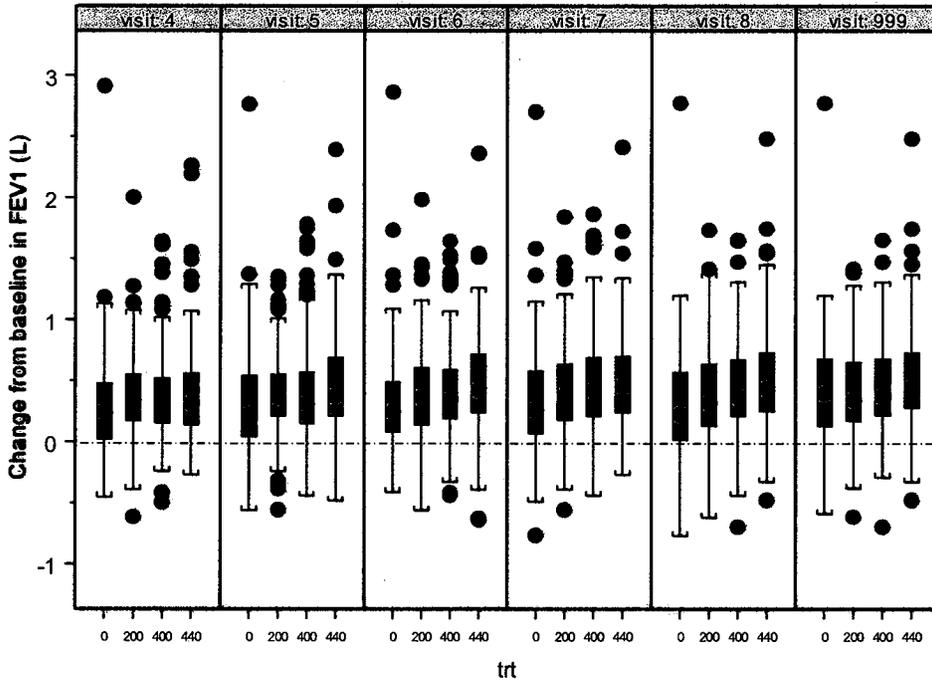


Figure 2. Change from baseline in FEV₁ (L) as a function of visit [time 4 (week 1), time 5 (week 2), time 6 (week 4), time 7 (week 8), time 8 (end point), time 999 (week 12)] following administration of the treatments (0=PLB; 200=ciclesonide 160 µg BID; 400= 320 µg BID; and 440= FP 440 BID) in adult patients with severe persistent asthma (n=125 per treatment group). Data from study 323/324.

Table 2 - Change from baseline to Week 12 in FEV¹ (L) – ITT population following administration of the treatments (ciclesonide 160-, and 320 µg BID and FP 440 BID) in adult patients with severe persistent asthma (n=125 per treatment group) (Study 323/324) (data reported by the sponsor)

Treatment	N	Baseline mean ^a (L)	Change from baseline			Treatment comparison vs. placebo		
			LS mean	SE	95% CI	LS mean difference	95% CI	P-value
Placebo	134	1.77	0.25	0.037	(0.18, 0.33)	-	-	-
Ciclesonide-320	127	1.78	0.36	0.038	(0.29, 0.44)	0.11	(0.01, 0.21)	0.0374
Ciclesonide-640	130	1.82	0.43	0.037	(0.36, 0.50)	0.18	(0.07, 0.28)	0.0008
Fluticasone-880	136	1.77	0.50	0.037	(0.43, 0.57)	0.24	(0.14, 0.35)	0.0001

^a Baseline means are raw means.
LS = least-squares, SE = standard error.

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

The existence of dose-response (HPA-axis function/cortisol suppression) relationship based on Phase I/II studies (doses tested ranged from 400 – 1600 µg /day) is difficult to be established due to the great variability on the data and because of the inconsistency on the method used to assess/calculate the degree of cortisol suppression. In general, there appears not to be a relationship between dose and degree of cortisol suppression in this range of doses tested (conclusion from studies 102, 49-2000, and 013). Study (FHP009) was the only study that showed a clear dose dependency decrease in cortisol levels measured as AUC_{0-24h}/24 hr serum cortisol (single doses of: 400, 1200, and 3600 µg ex-valve) (Table 3).

Table 3. Geometric means and point estimates for AUC 0-24h/24 serum cortisol levels following single and multiple administration of the treatments in healthy volunteers (from study FHP009)

Treatment (Dose)	Reference (Dose)	Serum Cortisol (µg/dL)	
		Geometric mean	PS (90% CI)
400 µg	placebo	9.8	0.94 (0.85-1.05)
1200 µg	placebo	8.8	0.83 (0.76-0.92)
3600 µg	placebo	7.3	0.62 (0.56-0.69)
Placebo		10.6	
250 µg bid	placebo	10.2	1.11 (1.03-1.2)
1000 bid	placebo	7.9	0.92 (0.85-0.99)
placebo		8.9	

Data from four phase III studies (studies 321, 322, 323/324: range of doses 80- to 640 µg/day) showed no correlation between dose and degree of cortisol suppression (see Table 4).

Table 4 - Change from baseline to Week 12 in low-dose peak serum cortisol levels (from study 323/324)

Variable	Treatment	N	Baseline mean ^a	Least-squares mean (SE)		P-value ^b
				Change from baseline	Treatment difference vs. placebo	
Low-dose peak serum cortisol (µg/dL)						
	Placebo	30	21.87	-0.44 (0.925)	-	-
	Ciclesonide-320	29	25.07	-2.06 (0.947)	-1.63 (1.256)	0.1988
	Ciclesonide-640	31	23.45	0.75 (0.871)	1.19 (1.209)	0.3261
	Fluticasone-180	30	24.53	-1.05 (0.931)	-0.61 (1.234)	0.6210

^a Baseline means are raw means.

^b P-values are for treatment comparisons versus placebo.

N = randomized population at selected centers, SE = standard error, - = not applicable.

Based on population pharmacokinetic/pharmacodynamic analysis using data from Phase I and Phase III studies, there was a trend for higher doses of ciclesonide to produce a higher cortisol suppression (13%, 8%, and 49% in cortisol AUC for doses of 800 to 1200 µg and 1600 µg, and 3600 mg, respectively); however, due to the great variability in the data, a clear relationship was not observed (Figure 4).

The direct effect of individual predicted systemic RM1 concentrations on cortisol concentrations at a given time was assessed with an Emax model. When Emax was fixed to 100%, EC50 (RM1 concentration to produce 50% of the maximum suppression) for ciclesonide was 1.96 ng/mL. This EC50 value is similar to the 90th percentile of RM1 concentrations for the 1600 µg dose. When Emax was estimated using a direct Emax model, the EC50 value was estimated to be 0.59 ng/mL and the Emax value was estimated to be 41%. This means that in the range of doses studied (up to 3520 µg) the maximum suppression of cortisol with ciclesonide is 41% and the EC50 is similar to the mean Cmax of RM1 observed following 1600 µg (maximum therapeutic dose) administration of ciclesonide (0.875 ng/mL, from study 56E/99). Refer to section 2.3.1.2 for efficacy- and safety-relationships in children.

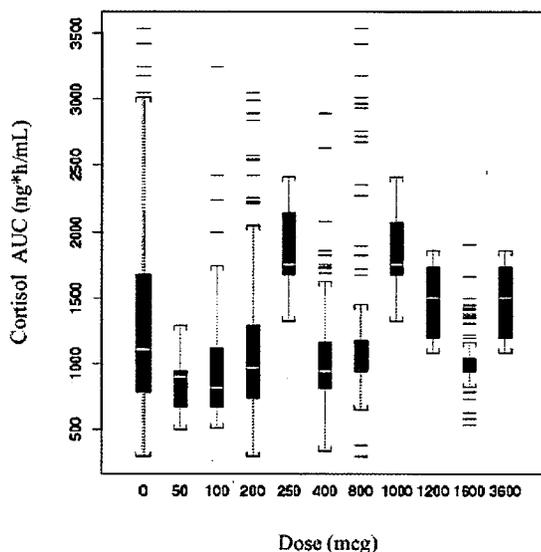


Figure 4. Effect of RM1 AUC0-24h on cortisol concentrations (data from population PK/PD analysis).

2.2.4.3 Does this drug prolong the QT or QTc interval?

Based on data from one Phase I (NOT thorough) study, RM1 did not significantly affect QT or QTc at single doses up to 3520 µg. This data should be interpreted with caution since it is based on single dosing, male subjects, and lack of robustness of the data provided.

Table 5 shows the statistics about QTb change from baseline as a function of time following single administration of ciclesonide. ECGs (12-lead) were recorded at -1 day, predose, 1 h, 6 h, 12 h and 23.5 h after morning inhalation in 12 healthy males (Study 117E/97). A summary of the findings from this study are as follows:

- The maximum mean QT change from baseline using **Bazett's correction** was observed at 23.5 hrs post administration for the placebo group (3.8 msec).
- There were 2 subjects from the placebo group, one subject in the 320 µg dose and one subject in the 3520 µg dose whose QTb change from baseline was greater than 30 msec. The highest QTb individual change from baseline was 53 msec following placebo treatment.
- The highest QTb absolute value was 447.12 following placebo treatment
- The mean of maximum QTb change from baseline was highest for the placebo group (10.05 msec ± 16)

Table 5. Mean (SD) QTb change from baseline as a function of dose and time following ciclesonide administration (Data from study 117E-97) (n=12 males)

Time	Delta QTc (msec) Based on Bazett's correction			
	Placebo	320	1200	3520
0	0 (2.3)	0 (1.8)	0 (7.3)	0 (4.48)
1	1.28 (10.2)	1.4 (4.7)	-2.7 (6)	0.84 (6.6)
6	-1.9 (8.2)	2.5 (4.3)	-0.4 (6)	2.8 (8.5)
12	-3.6 (8.6)	1.3 (4)	-1.6 (5)	-2.1 (10.9)
23.5	3.8 (15.9)	2.9 (15.9)	-1.6 (10.9)	0.7 (11.9)
maximum	3.8	2.9	0	2.8

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? What are the characteristics of drug distribution? How do the PK parameters change with time following chronic dosing?

Single Dose

In general, the systemic concentrations of ciclesonide were variable or transient following inhaled administration. Ciclesonide was not detected in plasma at inhaled doses lower than 400 µg/day. On the other hand, the PK of RM1 were well characterized and predictable.

The pharmacokinetics of RM1 were investigated in 15 healthy volunteers after single oral administration of ciclesonide (10 mg) as powder capsules, single oral inhalation of 1600 µg, ciclesonide via the MDI, and single intravenous administration. Table 6 summarizes the PK parameters for ciclesonide and RM1.

Following oral administration, the concentration of ciclesonide was detected only in 4 samples of two volunteers, with concentrations being close to the LOQ. The clearance of ciclesonide (152 L/h) and the apparent clearance of RM1 (228 L/h) exceeded the hepatic blood flow, suggesting a high extraction ratio drugs. The Vd of ciclesonide (2.9 L/kg) and the apparent volume of distribution of RM1 (12.1 L/kg) exceeded the total body water volume in humans (0.6 L/kg).

The protein binding for RM1 was higher than 98.5%; however this value should be interpreted with caution because of the relatively high non-protein binding reported in the study and because the hematocrit reported was much lower than normal blood. The protein binding of ciclesonide appears to be (98.9 to 99.8%) in various species including humans.

Inhaled relative bioavailability of ciclesonide + RM1 following inhalation of ciclesonide *viz* MDI was 41 %. Absolute oral and inhaled bioavailability of RM1, was 1.1% (n=10) and 26% (n=6), respectively.

Table 6. Mean (SD) PK parameters of ciclesonide and RM1 in serum of healthy subjects following single administration of the treatments (Data from study FH015-172-95)

	Intravenous (800 µg)		Oral (10 mg)		MDI (1280 µg)	
	ciclesonide	RM1	ciclesonide	RM1	ciclesonide	RM1
AUC (µg*hr/L)	5.6 (1.5)	3.27 (0.85)	-	1.18 (0.89)	2.19 (1.3)	3.67 (2.27)
Cmax (µg/L)	23.6 (9.4)	1.132 (0.36)	-	0.203 (0.22)	5.61 (2.6)	0.83 (0.53)
Tmax (hr)	0.17 (0)	0.43 (0.46)	-	3.92 (4.11)	0.18 (0.05)	1.04 (0.5)
T1/2 (hr)	0.94 (0.53)	2.8 (0.51)	-	-	0.71 (0.45)	2.8 (0.3)
CL (L/hr)	152.3 (37.3)	227.7 (65.01)	-	-	-	-
Vdarea (L)	206.8 (149.9)	897.7 (236.8)	-	-	-	-

Multiple Dose

The AUC and Cmax geometric means of ciclesonide increased by 28% and 30%, respectively following multiple administration of ciclesonide compared to that after single administration. The half-life of ciclesonide remained unchanged (Table 7). The AUC and Cmax geometric means of the RM1 increased by 44% and 38%, respectively following multiple administration of ciclesonide compared to that after single administration. The half-life of the metabolite increased by 1.6 hr (from 5.23 hr to 6.72 hr) following multiple administration. The accumulation ratio ranged from 1.1 to 1.8.

The data described above comes from Study 211-200. This was an open, non-controlled, one-period, single-center Phase I study in 18 healthy subjects. The study consisted of a screening examination, a treatment period of 7 days, and a post-study examination. During the treatment period all subjects received 400 µg ciclesonide in the morning on each study day.

Table 7. Mean (S.D.) RM1 PK parameters following single and repeat administration of ciclesonide (data from study 211-200)

	Regimen	Mean (SD)	Point estimate And 90% CI (single/multiple)
Cmax (µg/L)	Single	0.299 (0.13)	1.38 (1.09-1.76)
	Repeat	0.37 (49)	
AUC(0-inf) (µg.h/L)	Single	1.72 (0.73)	1.44 (1.13-1.84)
	Repeat	2.18 (0.42)	
T1/2 (h)	Single	5.23 (1.28)	1.32 (1.18-1.48)
	Repeat	6.72 (1.04)	
Tmax (h)	Single	1.08 (0.62)	
	Repeat	0.94 (0.44)	

2.2.5.2 Are the PK and PD of ciclesonide linear and dose-proportional?

Based on post hoc AUC values from population PK analysis, the pharmacokinetics of RM1 were linear and dose proportional in the range of 40- to 3520 µg ($R^2=0.65$) (Figure 5). Following single dose administration of ciclesonide (doses: 320-, 1200-, and 3520 µg) to healthy volunteers, the AUC and Cmax of both ciclesonide and RM1 increased more than dose-proportional (3-fold increased in the dose produced a 4 to 5-fold increased in the exposure) (Table 8). However, this conclusion should be interpreted with caution since high variability on the data was seen at higher doses. In the repeated dose study (250- and 1000- µg BID) Cmax and AUC increased in proportion with the dose.

The mean 24 h-profiles of cortisol in serum decreased less than proportional to the dose. The point estimates and 90% CI for test/placebo were 0.94 (0.85-1.05), 0.83 (0.76-0.92), and 0.62 (0.56-0.69), for the 400-, 1200-, and 3600 µg of ciclesonide, respectively (Table 3).

The data presented above comes from study 114E_97 (or FHP009). This study was a single dose/multiple dose

study with a wash-out period of 2 weeks between treatments of two subsequent periods conducted in 24 healthy volunteers. For assessing the effect on the HPA-axis, serum cortisol was determined at the following time points: predose, 2, 4, 6, 8, 10, 12, 14, 24 hrs, after administration on day 1 following single dose and on day 7 on the repeated doses.

Table 8. Mean (min-max) AUC and Cmax values following single and multiple administration of the treatments (data from FHP009)

Dose (µg/day)	Single Dose			
	Ciclesonide		RM1	
	AUC (µg*hr/L)	Cmax (µg/L)	AUC (µg*hr/L)	Cmax (µg/L)
400	0.24 (0.21-0.27)	0.215 (0.11-0.29)	0.72 (0.52-1.01)	0.153 (0.12-0.26)
1200	1.03 (0.33-2.4)	1.01 (0.34-2.1)	2.5 (1.1-4.8)	0.51 (0.28-0.94)
3600	4.4 (2.1-7.8)	4.9 (2.8-7.5)	10.5 (5.1-17.05)	2.5 (1.5-3.5)
	Multiple Dose			
500	0.23 (0.14-0.28)	0.19 (0.098-0.3)	0.85 (0.53-1.4)	0.17 (0.12-0.256)
2000	1.14 (0.5-1.9)	0.87 (0.38-1.5)	3.4 (2.15-5.4)	0.74 (0.49-1.11)

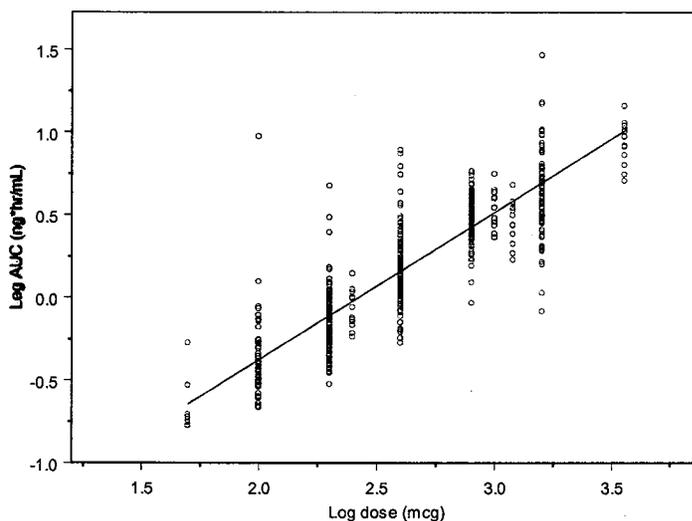


Figure 5. Individual RM1 AUC (log values) as a function of log-Dose (fitted line from power model: $AUC = e^{-2.15} * (dose)^{0.9}$). Data from population PK analysis.

2.2.5.3 What are the mass balance characteristics of the drug?

Radioactive ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) as after intravenous (65.95%) administration, indicating that excretion through bile is the major route of elimination. This information comes from study FHP021, which was a mass balance study conducted in 6 male healthy volunteers to investigate the disposition and routes of elimination following single oral 8 mg capsule ciclesonide and single intravenous 0.64 mg/20 mL as a 10-minute infusion. Blood samples were collected up to 168 hours for total radioactivity and up to 2 h for metabolite identification. Urine and feces were collected up to 168 hrs. The findings from this study can be summarized as follows:

- The excretion of radioactivity following a single oral dose of 6.9 mg ciclesonide and single intravenous administration of 0.64 mg ciclesonide was almost complete (total average recovery 91.4% and 85.95% respectively). Ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) as after intravenous (65.95%) administration (Table 9).

- Ciclesonide showed no accumulation in red blood cells, as could be concluded from the high plasma/whole blood ratio.
- The absorption of ¹⁴C-ciclesonide was 24.5% based on dose-normalized for radioactivity.
- Oral bioavailability based on AUCs of RM1 could only be determined for one subject and was about 1.8%.
- Parent compound ciclesonide and its metabolite RM1 constitute 19.3% of radioactivity found in plasma; approximately 80% of the ¹⁴C radioactivity AUC may be resulting from one or more yet unknown metabolites.

Table 9. Mean cumulative excretion of ¹⁴C-radioactivity (% of dose) after administration of ¹⁴C-ciclesonide as an i.v. solution and single oral dose

PARAMETER	6.9 mg of ¹⁴ C-ciclesonide p.o.		
	mean	min	max
A _{urine} (% of dose)	13.5	11.1	14.7
A _{faeces} (% of dose)	77.9	67.1	81.4
A _{total} (% of dose)	91.7	81.8	94.4
0.64 mg of ¹⁴ C-ciclesonide i.v.			
A _{urine} (% of dose)	20	9.1	23.5
A _{faeces} (% of dose)	65.95	55.9	75
A _{total} (% of dose)	85.95	78.5	98.3

2.2.5.5 What are the characteristics of drug metabolism and excretion?

Data from the in-vitro metabolism of ¹⁴C-Ciclesonide and RM1 in human hepatocytes and profiling of plasma and urine samples from ¹⁴C-ciclesonide clinical study showed that RM1 appears to be the mayor product of metabolism of ciclesonide. However, the existence of other metabolites cannot be ruled out since the sponsor has not adequately characterized the metabolic profiling of ciclesonide. The following summarizes the findings about the in-vitro metabolism and in vivo metabolic profiling:

- Ciclesonide was almost completely metabolized within the first hr of incubation with human hepatocytes.
- Approximately 50% of RM1 was metabolized within the first hr of incubation with human hepatocytes.
- Metabolite Profiling of ¹⁴C-Ciclesonide in Human Hepatocytes (4-Hr Incubation) showed that RM1 (17.75% of total radioactivity), M7 (15.27%), M4 (9.89%), M1 (6.35%), M2 (6.39%) were the major metabolites present.
- Metabolite Profiling of ¹⁴C-RM1 in Human Hepatocytes (4-Hr Incubation) showed that RM1 (14.22%), M7 (12.77%), M3-4 (21.14%), M1 (6.72%), M2 (7.62%), and M5-6 (9.61%) were the major metabolites present.
- Hippuric acid (M1) was the only major metabolite found in 0-4-hr interval of urine collection after oral (61%) and IV (38.7%) administration.
- Ciclesonide (22.36%), RM1 (11.93%) and M9 (5.53%) were the major components found in the 0.25 hr IV plasma sample.
- In the 0.5-hr IV plasma sample, RM1 was the mayor peak (10.34% of total radioactivity). Other components in the 0.5-hr plasma sample also eluted at the retention time regions of hydroxylated RM1 (the major one contributed 7.47%) of the total radioactivity.

2.2.5.4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

The CV% (intersubject variability) for the C_{max} and AUC of RM1 in healthy volunteers and asthmatics patients was as low as 38% and as high as 68%. Disease stage did not change the degree of variability.

2.3 Intrinsic Factors

2.3.1 Does age affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 ELDERLY

The mean C_{max} and AUC of ciclesonide increased in elderly subjects by 3-fold and 2.5 fold, respectively, as compared with that observed in young healthy adults. The mean C_{max} and AUC of RM1 increased in healthy elderly

subjects by 2.4-fold and 2-fold respectively (following single inhalative doses of 1600 µg ciclesonide), as compared to that in the young healthy controls (Figure 6). These findings should be interpreted with caution since the observations are based on cross-study comparisons and the lack of robustness on the analysis of plasma samples. This study in the elderly (56E/99) 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.

On the other hand, the population PK/PD analysis using data from phase I and III revealed that age did not influence the PK of the drug (see below for more details on the population PK/PD analysis). The mean posthoc AUC_{pop} (dose-normalized to 200 µg) in the elderly was 10% higher compared to that in adults (Figure 7). Therefore, dose adjustment in the elderly based on these PK findings may NOT be necessary since the dose-response curve for ciclesonide was flat in the range of 80-640 µg/day and the relative good safety profile based on cortisol suppression effect.

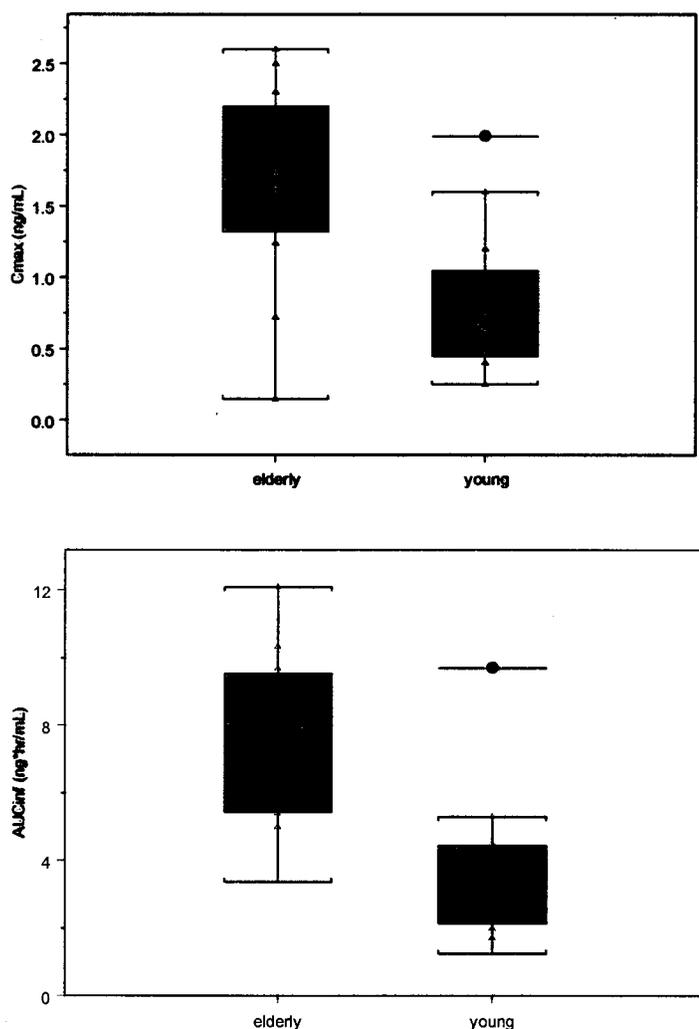


Figure 6. Individual C_{max} and AUC_{0-∞} values for RM1 in healthy elderly volunteers (Study 56E/99) and in young volunteers (data from study 253E/99) following single inhalative doses of 1600 µg ciclesonide (n=12 elderly).

2.3.1.2 PEDIATRICS

No dose-response was observed in the range of 40- to 160 µg/day (Table 10). In addition, cortisol suppression measured as change from baseline to Week 12 in low-dose peak serum cortisol levels showed no dose-order in the degree of suppression and it was no different from placebo treatment (Table 11). The starting dose in children is uncertain since the effect of the 80 µg/day or 160 µg/day dose was not replicated.

This information comes from two Phase III clinical studies conducted in children. These pediatric trials (341 and 342) were conducted as double-blind, placebo-controlled, parallel-group, multicenter, efficacy, safety and dose-response studies of ciclesonide 40-, 80- and 160 µg/day for 12 weeks in approximately 500 children 4 to 11 years of age (125 per study) with persistent asthma. In the primary efficacy analysis of change from baseline to Week 12 in FEV₁ percent predicted, the 40- and 160 µg daily dose did not reach significance when compared with the placebo treatment group at Week 12, and only the 80 µg daily dose showed significant improvement in the change from baseline in FEV₁ percent predicted compared to placebo (data reported by sponsor from Study 341). An integrated analysis of efficacy combining data from this study with an identically designed study (Study 342) showed that treatment with ciclesonide 80- (p=0.0239 versus placebo) or ciclesonide 160 µg /day (p=0.0069 versus placebo) administered once daily for 12 weeks increased FEV₁ percent predicted.

Table 10. Magnitude of treatment differences versus the placebo treatment group from baseline to Week 12 (LOCF) - ITT population in asthmatic children (Data from study 341)

Variable	Treatment difference at Week 12 versus placebo (p-value)		
	Ciclesonide 40 µg/day	Ciclesonide 80 µg/day	Ciclesonide 160 µg/day
FEV ₁ percent predicted	1.15 (0.5634)	3.93 (0.0460)	3.34 (0.1005)
FEV ₁ (L)	0.03 (0.3621)	0.08 (0.0259)	0.05 (0.1760)
AM PEF (L/min)	4.27 (0.3420)	16.34 (0.0003)	9.70 (0.0343)
Total Asthma Severity Rating Score	-0.14 (0.4003)	-0.73 (0.0001)	-0.80 (0.0006)
Daily albuterol use (puffs/day)	-0.23 (0.3134)	-0.82 (0.0002)	-0.76 (0.0011)

Blood samples were collected for the measurement of serum cortisol before and after stimulation with low-dose (1 mg) cosyntropin. Data for both baseline and Week 12 were available in 32 patients. The change from baseline to week 12 in low-dose peak serum cortisol levels following administration of the 3 doses was not greater (0.62,- -0.40 and 1.44- µg/dL, respectively) than that observed for placebo treatment (-2.35 µg/dL) (Table 11)

Table 11 - Change from baseline to Week 12 in low-dose peak serum cortisol levels (Data from study 341)

Variable	Treatment	N	Baseline Mean ^a	Least-squares mean (SE)
				Change from baseline
Low-dose peak serum cortisol (µg/dL)				
	Placebo	7	21.29	-2.35 (1.757)
	Ciclesonide-40	6	22.83	0.62 (1.766)
	Ciclesonide-80	10	24.10	-0.40 (1.282)
	Ciclesonide-160	9	23.56	1.44 (1.568)

^a Baseline means are raw means.
N = randomized population at selected centers, SE = standard error, - = not applicable.

In the population PK/PD analysis weight seemed to affect the PK of RM1. Inspection of the weighted residual (WRES) versus prediction (PRED) plot for pediatrics only indicated a bias. The application of separate weight effects for pediatrics and adults resulted in no weight adjustment for pediatrics, which may be expected since CL clearance varied less than 20% over a weight range of 50 to 100 kg. Then, it seems that weight does not affect the PK of the drug;

however, these results should be interpreted with caution since the estimated AUC in adults was highly variable (Figure 7).

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 Vd based on allometric principle. According to the sponsor, this resulted in similar predicted concentrations between children and adults when same dose is given. Figure 7 shows that the mean AUCpop normalized to 160 µg in children was similar to that in adults (0.82 ng*hr/mL±0.3 vs. 0.76 ng*hr/mL ± 0.4).

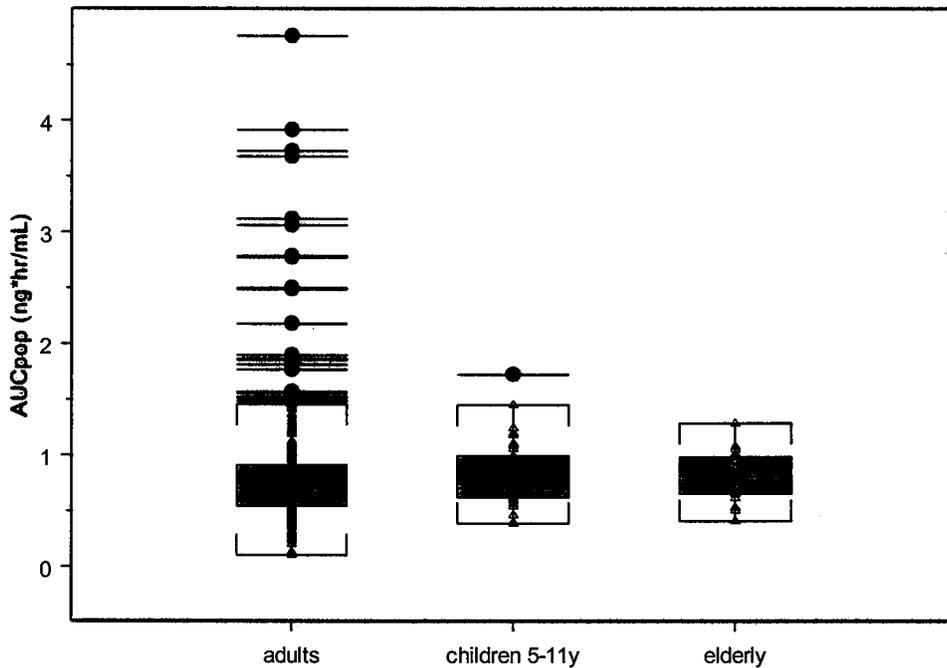


Figure 7. Individual post-hoc AUC (ng*hr/mL) (normalized to 160 µg) as a function of age (n= 444, 37 and 18 for adults, children and elderly, respectively) (data from population PK/PD analysis).

2.3.1.3 Do race, gender, and disease status affect the PK and PD of the drug? What dosage regimen adjustments are recommended for each of these subgroups?

Race

A meta-analysis of data from healthy young Caucasian and Japanese subjects was conducted using data from 11 studies. Statistical evaluation of the ratio of geometric means for Cmax and AUC_{0-∞} values of RM1 in Caucasians and Japanese following single inhalation of 800 µg ciclesonide yielded point estimates (90% confidence interval) of 0.87 (0.77, 0.99) and 0.90 (0.77, 1.05), respectively, indicating no clinically relevant difference in the systemic exposure. Based on population PK analysis, the mean systemic exposure (AUCpop) in the Black population (3.1%) and Others population (11.3%) was significantly lower (60% and 70%, respectively) than that in the White (74.2%) population. This difference may not be clinically relevant since the dose-exposure response was flat in the range of doses tested. The AUCpop in the Japanese population (11.3%) was 20% higher than that in the White population.

Gender, Height, and Asthma Severity

Based on population pharmacokinetic analysis, asthma severity, and gender did not influence RM1 pharmacokinetics. Also, there was no trend of change in cortisol AUC with respect to RM1 AUC for healthy subjects and asthmatics. 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 section 2.3.1.5 for more details about the effect of liver impairment on the PK of the drug).

The above mentioned population PK/PD analysis of ciclesonide and RM1 included data from 12 Phase I, 3 Phase III studies in adults, and 2 Phase III studies in pediatrics. Phase I studies had extensive PK/PD data after administration of ciclesonide. Phase III studies included sparse PK samples (-1.5, 1, 2.5 and 6-10 hours following administration). There were a total of 635 subjects in this analysis with 2750, 5238 and 4470 observation records for ciclesonide, RM1 and cortisol concentrations, respectively. A one-compartment body model with first order absorption adequately described the RM1 concentration-time profile. The estimates of CL and Vd when standardized to a 70 kg subject were 302 L/h and 1310 L, respectively. 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 CL, Vd and F (bioavailability), wherever appropriate. Identification of relevant covariates was based on step-wise backward elimination method. For 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_{trough}) at dose interval were estimated.

2.3.1.4. Does renal impairment affect the PK of the drug and its major metabolite? Is dosage regimen adjustment recommended?

The effect of renal impairment on the PK of ciclesonide and RM1 was not evaluated. The rationale provided by the sponsor is that ciclesonide (and its metabolite, RM1) is an inhaled drug with a wide therapeutic index that is mainly eliminated by the hepatic and/or biliary route. In fact, in a mass balance study total radioactivity was predominantly excreted through the feces, both after oral (77.9%) and after intravenous (65.95%) administration suggesting urinary excretion may not be an important route of elimination. In addition, plasma protein binding was not altered when plasma from subjects with renal impairment was spiked with RM1 (at a concentration of 5.0 ng/mL, the protein binding of RM1 in the predose plasma samples varied between 97.5-99%).

2.3.1.5 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The C_{max} and AUC_{0-∞} of ciclesonide and its metabolite in patients with moderate and severe hepatic impairment (HI) increased in the range of 1.4-fold to 2.7 fold compared to that observed in healthy subjects (Figure 8). Also, the T_{1/2} of RM1 increased in patients with moderate and severe HI by 2.3 hr and 4.6 hr, respectively, as compared to that in healthy controls. This data should be interpreted with caution due to the inconsistency of results in moderate and severe HI patients. Dose adjustment in this population is not needed.

The above findings come from study 210/2000. This was an open label, single dose, 3-parallel-group study comparison in 24 subjects with different degrees of HI (8 healthy, 8 with severe HI and 8 with moderate HI). Patients received 1600 µg of ciclesonide.

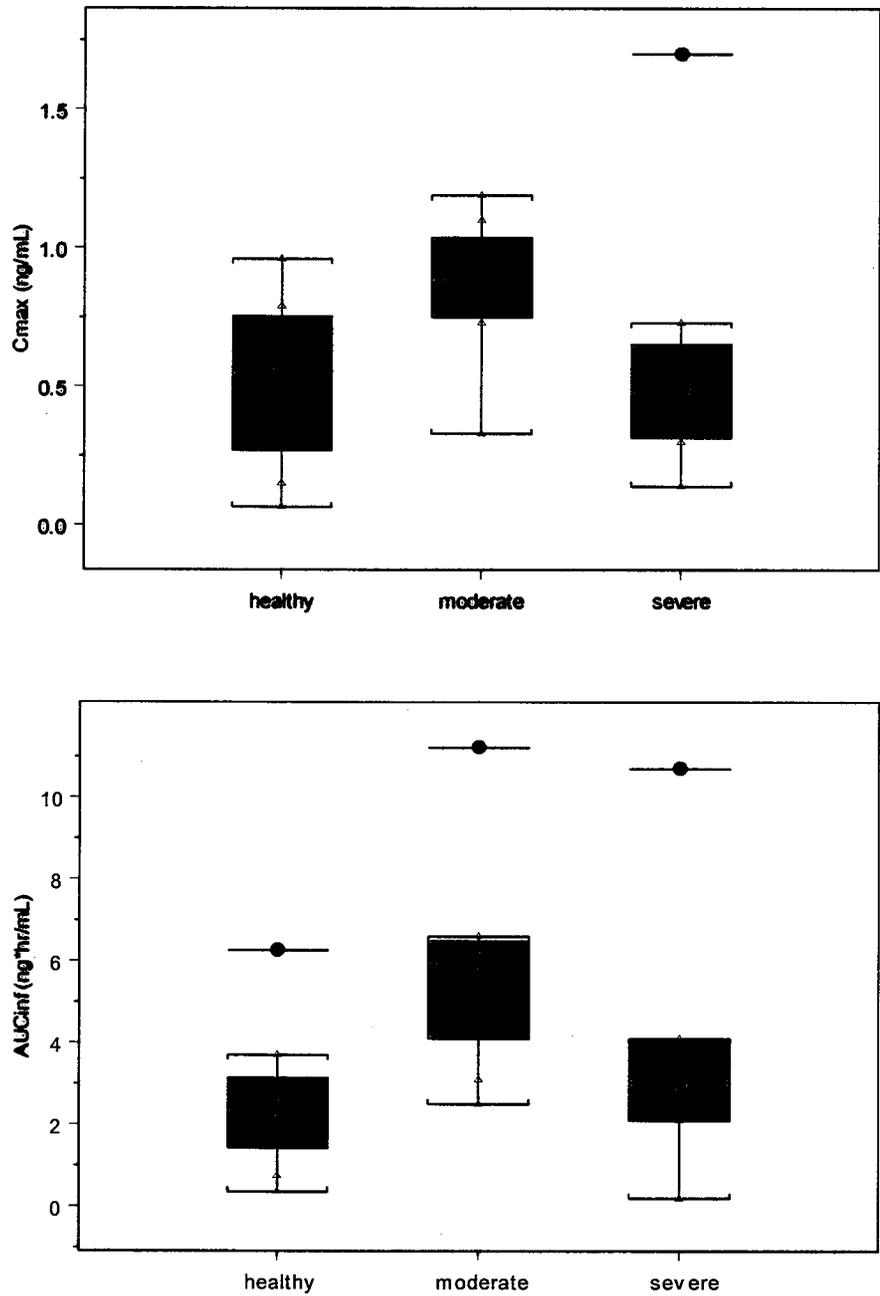


Figure 8. Individual C_{max} and AUC_{0-∞} values for RM1 in healthy volunteers and in patients with moderate and severe HI following single inhalative doses of ciclesonide 1600 µg (data from study 210/200)

2.3.1.6 What pregnancy and lactation use information is there in the application? None

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of herbal products, diet, smoking and alcohol used was not evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

In-vitro metabolism studies using human microsomes indicated that RM1 is mainly metabolized by CYP3A4 although CYP2D6 is also involved. Therefore, substrates, inhibitors or inducers of these enzymes may affect the PK of RM1. The sponsor did not conduct DDI studies to assess the effect of such drugs on the PK of RM1, except the effect of erythromycin.

Ciclesonide and RM1 did not affect the activity of the major CYP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Therefore, no major effects of ciclesonide should be expected on the PK of other drugs.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Yes. The following is a summary of the findings related to the investigation of the metabolism of ciclesonide (Figure 9) by human liver microsomes (incubation with pooled human liver microsomes, incubation with microsomes of individual donors, in the presence of chemical inhibitors, and with supersomes containing expressed human P450s):

- The biotransformation of ciclesonide is likely to be catalyzed by an esterase enzyme which has not been identified.
- It appears that RM1 is the major active metabolite that results from the biotransformation of ciclesonide. However, this hypothesis is inconclusive since mass balance studies showed that only 20% of total radioactivity corresponds to RM1. In addition, the metabolite M9, which pharmacological potency is unknown, was as abundant as RM1 in plasma samples.
- The biotransformation of RM1 appears to be predominately catalyzed by CYP3A4 (83%), although CYP2D6 (~30%), and to a lesser extent CYP2C8 (11%) are also involved. However, a major involvement of CYP3A4 on the metabolism of M1 is inconclusive since the correlation data failed to indicate the extent of CYP3A4 involvement in the biotransformation of M1, although inhibition studies showed the contrary. On the other hand, CYP4A11 correlated more strongly with rates of M3 formation than any of the other major human P450 isoforms, but inhibition studies showed the contrary.

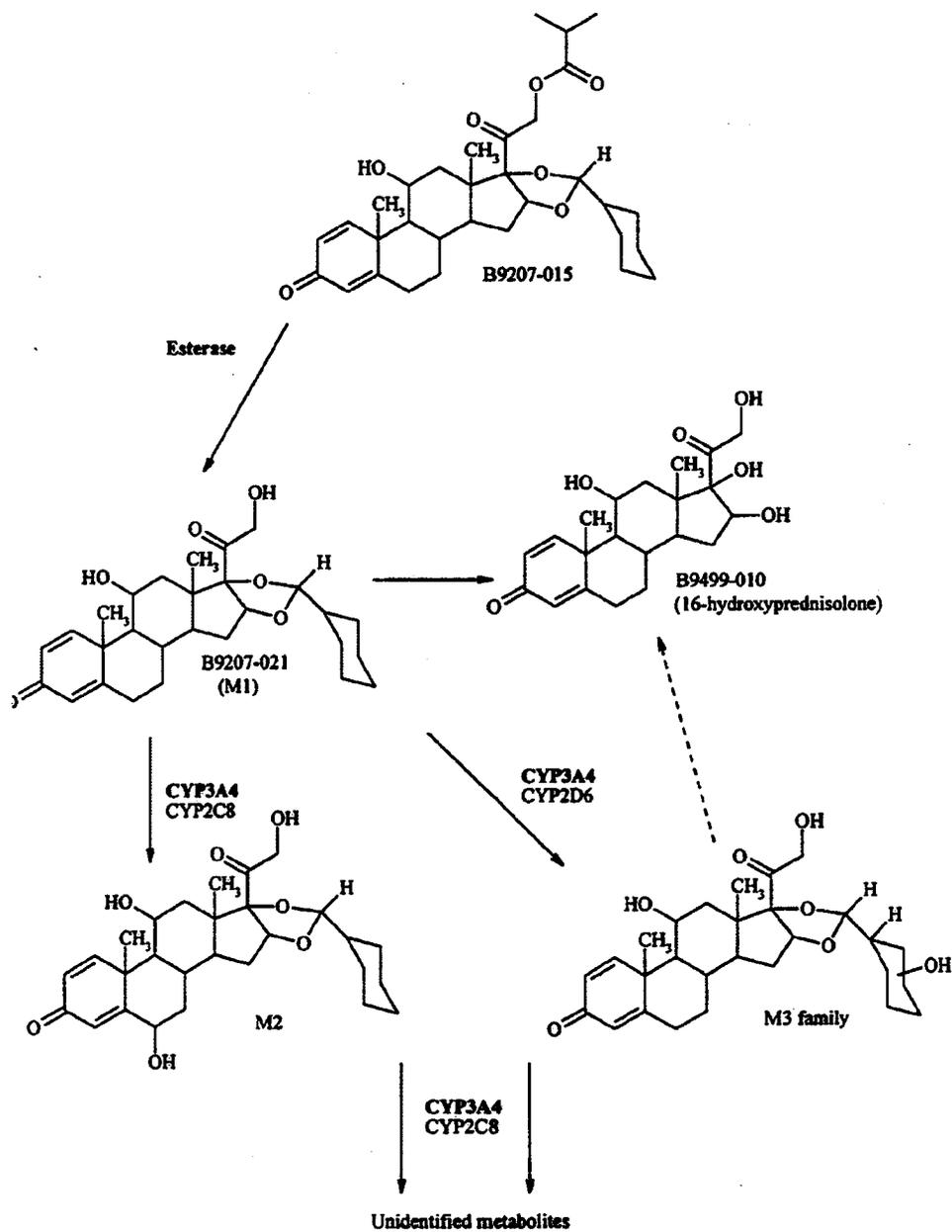


Figure 9. Sponsor's proposed metabolic pathway of ciclosonide

2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

At concentrations as high as 3 μM , RM1 failed to produce significant direct or metabolism-based inhibition of cytochrome CYP450s in pooled human liver microsomes (Tables 12, 13). The potential of ciclosonide to act as an inhibitor of CYP enzymes was not evaluated.

Table 12. Results of metabolism-based inhibition potential of RM1 on CYP450 enzyme expressed as percent remaining enzyme activities in HLM

CYP450 Enzyme	RM1 Metabolite of Ciclesonide (Ciclesonide RM1)	
	Pre-incubation w/o NADPH	Pre-incubation with NADPH
CYP1A2	100	88
CYP2A6	100	99
CYP2C9	100	100
CYP2C19	100	98
CYP2D6	100	80
CYP2E1	100	103
CYP3A4 (Midazolam)	100	114
CYP3A4 (Testosterone)	100	102

Table 13. Results of direct inhibition potential of RM1 on CYP450 enzymes expressed as percent remaining enzyme activities in HLM

CYP450 Enzyme	RM1 Metabolite of Ciclesonide (Ciclesonide RM1)					Positive Control
	0.3 nM	3.0 nM	30 nM	300 nM	3000 nM	
CYP1A2	99	100	99	98	96	8.5
CYP2A6	101	88	88	97	87	22
CYP2C9	97	95	90	94	89	9.1
CYP2C19	101	97	96	90	80	56
CYP2D6	95	90	80*	98	96	1.3
CYP2E1	97	98	100	98	99	58
CYP3A4 (Midazolam)	99	97	76	88	86	<5.4
CYP3A4 (Testosterone)	94	97	88	78	89	6.4

*Outlier, not used for calculation.

Ciclesonide at therapeutic serum concentrations is not likely to induce CYP1A2, CYP2C9, and CYP 3A4. The lack of effect of ciclesonide on CYP2C19 reported is questionable since lower concentration (25 µM) than those recommended for rifampin were used.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

This was not evaluated by the sponsor.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes. Ciclesonide may be administered concomitantly with other glucocorticoids and beta agonists. DDI with other glucocorticoids was not determined. The DDI interaction with formoterol was evaluated (see below) and the effect of albuterol was evaluated using population PK analysis.

2.4.2.7 What is the effect of ciclesonide on the PK of other drugs? What is the effect of other drugs on the PK of ciclesonide?

In-vitro metabolism studies using human microsomes indicated that RM1 is mainly metabolized by CYP3A4 although CYP2D6 (30%), and to a lesser extent CYP2C8 (11%) are also involved. Therefore, inhibitors or inducers of

these enzymes may affect the PK of RM1. The sponsor did not conduct drug-drug interactions to assess the effect of CYP2D6 inhibitors on the PK of ciclesonide.

DDI with Albuterol

Based on population PK analysis, the RM1 clearance and volume of distribution values for subjects with (98 subjects) and without (512 subjects) coadministration of albuterol were similar.

DDI with Erythromycin

- The systemic exposure of ciclesonide and its metabolite in healthy subjects receiving a single dose of ciclesonide 800 µg was not statistically significantly altered by its coadministration with erythromycin 500 mg oral single dose. The arithmetic mean Cmax and AUC of ciclesonide decreased in the presence of erythromycin by 17% and 5%, respectively. The arithmetic mean Cmax and AUC of RM1 increased in the presence of erythromycin by 5% and 12%, respectively.
- The systemic exposure of erythromycin in healthy subjects receiving a single dose of 500 mg was not statistically significantly altered by its coadministration with ciclesonide 800 µg single dose. The arithmetic mean Cmax and AUC of erythromycin decreased in the presence of ciclesonide by 24 % and 21%, respectively.

The above findings come from study 56E/99. This study was conducted according to a randomized, open, 3-period change-over design. In one study period, the subjects (18) received ciclesonide alone and in another study period, the subjects received erythromycin alone. In a third study period, both drugs were given together.

DDI with formoterol

- The systemic exposure (AUC and Cmax) of ciclesonide and its metabolite in healthy subjects receiving a single dose of ciclesonide 800 µg was not statistically significantly altered (<23% decreased) when coadministered with formoterol 24 µg single dose.
- The cumulative urinary excretion of formoterol in healthy subjects receiving a single dose of 24 µg was not statistically significantly altered (8% decreased) when coadministered with ciclesonide 800 µg.

These findings come from study 56E/96, which was an open, randomized, 3-period-cross-over study in 24 healthy volunteers

DDI with Ketoconazole

The original submission did not include a DDI with ketoconazole despite the Agency’s recommendations during the development phase of Alvesco.

2.4.2.8 What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for ciclesonide?

This information was not provided by the sponsor. Also, this information may not be relevant since this is not a solid dosage form.

2.5.2 Was the to-be-marketed formulation used in the PK/clinical trials?

Yes. Clinical and PK studies were carried out using identical formulations of ciclesonide inhalers as those proposed for marketing, as the formulation remained unchanged throughout development. The actuator performance

remained unchanged throughout development. The container closure system for ciclesonide inhalers underwent minor changes during the development process, and according to the chemistry reviewer, these changes must likely do not have an impact on the PK of the drug. However, in vitro dose proportionality data was not provided to support this statement.

2.5.3 Are the method and dissolution specifications supported by the data provided by the sponsor?

This does not apply for orally inhaled drugs.

2.5.4 What is the effect of food on the BA of the drug?

This was not assessed. Generally, the effect of food on the PK of orally inhaled drugs is not evaluated since the effect of these drugs is local. However, food may increase the systemic exposure of these drugs which may change its safety profile.

2.5.5 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product? Does the use of spacers affect the PK of the drug?

In vivo studies showed that when the same dose is delivered by inhalation, i.e. 4 puffs of the 160 µg strength, 8 puffs of the 80 µg strength and 16 puffs of the 40 µg strength, the AUC and Cmax of the metabolite were within BE standards. In addition, the systemic exposure (Cmax and AUC) of the active metabolite was not affected by the used of [redacted] spacer.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

Bioanalytical methods for Ciclesonide and RM1

Yes. The metabolite selected for analysis was RM1, which appears to be the major circulating metabolite and active moiety measured in plasma. The sponsor did not mention if free, bound or total drug was measured. Therefore, it is assumed that total drug was measured. Concentrations of ciclesonide and RM1 were determined in serum samples from all human pharmacokinetic studies using [redacted] HPLC with tandem mass spectrometric detection (LC/MS/MS). Internal standard was added to serum samples [redacted]

[redacted] Samples of the Phase I studies FHP018, FHP026 and FHP027 and all the Phase III studies were analyzed using this method. The new method also uses [redacted] [redacted] The accuracy, intra- and inter-day precision were acceptable for all the methods (<15% Bias or %CV) for in-study validation information

Cortisol Determination

For Phase I studies, quantitative assay of serum cortisol was measured using a commercially available fluorescence polarization immunoassay [redacted]. The lower limit of quantitation was 2.5 µg /dL (25 ng/mL). For Phase III studies, quantitative assay of serum cortisol was conducted using radio immunoassay (RIA). This assay was used to measure the cortisol level in human serum/urine in all clinical Phase III PK/PD studies. The LLOQ was 20 nM. The calibration range was from 10 - 1280 nM. The cortisol concentrations in human serum samples were determined using radioimmunoassay (RIA) with the calibration range from 10 to 1280 nM.

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Sandra Suarez
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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-658
Proprietary Drug Name:	ALVESCO
Generic Name:	Ciclesonide
Indication:	Treatment of asthma
Dosage Form:	MDI
Strength:	—, 80-, and 160 µg
Route of Administration:	Oral Inhalation
Applicant:	Aventis, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	December 22, 2003, August 12, 2004
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

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1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-658 submitted on December 22, 2003. We found this NDA acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's label recommendations. The comments below and labeling comments (page 27) should be conveyed to the sponsor.

1.1.1 Comments to Sponsor

A response to the following comments will help to clarify the metabolism and lung residence time of the drug. However, these comments could be addressed in the product labeling.

- Evaluate the potential for drug-drug interaction between ciclesonide/RM1 and potent CYP2D6 inhibitors in vivo settings.
- The involvement of CYP3A4 as a major enzyme responsible for the metabolism of RM1 is inconclusive. Conduct in vivo drug-drug interaction studies with potent CYP3A4 inhibitor such as ritonavir and ketoconazole.
- Provide data on the claim that the lung formation of esters with fatty acids increases the lung residence time of RM1 in humans.

1.2 Phase IV Commitments

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Alvesco® inhalation aerosol (pMDI) contains ciclesonide, a non-halogenated glucocorticoid delivered as the R-epimer. Alvesco is proposed for the treatment of asthma in adults _____ years and older. Ciclesonide is a pro-drug that is hydrolyzed by esterases to its active metabolite, RM1 (a glucocorticoid), which has approximately 100-fold greater affinity for the glucocorticoid receptor than the parent drug.

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Alvesco has been evaluated in 77 Phase I, II and III clinical studies by Aventis, Inc. and Altana Pharma. The efficacy and safety of Alvesco in asthma patients was primarily assessed in seven double-blind, placebo-controlled, multicenter studies. The sponsor assessed the clinical pharmacology of Alvesco inhalation aerosol in 44 studies, including three dose-response studies in adults and 2 in pediatrics. Some of these studies included: in vitro studies to assess protein binding and metabolism of the drug (8), PK studies in healthy volunteers (8), PK studies in special populations (6), drug-drug interaction studies (2), studies in asthma patients (6, which were used in population PK/PD analysis and exposure-response analysis) and PD (cortisol suppression studies, 6). The majority of these studies were reviewed (37). The remaining studies were not reviewed because they did not provide additional information. Alvesco inhalation aerosol will be available in _____ strengths: _____, 80-, and 160 µg per puff. The orally inhaled doses (ex-actuator) studied in adults were: 320- to 3520 µg single dose in healthy adults; 250-, 320- and 1000 µg BID in healthy adults; 80-, 160-, 320 µg QD; and 160-, 320- and 640 µg BID in asthmatics. In asthmatic children the doses tested were: 40-, 80-, and 160 µg QD.

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Pharmacokinetics in Healthy Volunteers

Single Dose

Following oral inhalation of ciclesonide 360 µg, the mean C_{max} of RM1 and ciclesonide occurred at 1.1 hr and 0.25 hr, respectively. The mean AUC_{0-∞} of RM1 (1.72 ng*hr/mL) ranged from 2.5- to 3-fold higher than that observed for the parent drug. However, the C_{max} (0.3 ng/mL) was 3.5-fold lower for RM1. No significant interconversion (<0.6%) of R-ciclesonide to S- ciclesonide occurs in vivo. In vivo studies showed that when the same dose (800 µg) of ciclesonide is delivered by inhalation from

either strength (40-, 80- or 160 µg), the AUC and Cmax of RM1 were within BE standards. The systemic exposure (Cmax and AUC) of RM1 was not affected by the used of AeroChamber Plus spacer. The post-hoc AUC of RM1 was linear and dose-proportional in the range of 40- to 3520 µg.

Repeat Dose

The mean Cmax (0.369 ng/mL) and AUC_{0-∞} (2.18 ng*hr/mL) of RM1 following multiple administration of ciclesonide 360 µg QD increased up to 26% compared to those after single administration. Time to reach steady-state was not addressed; however, it is expected to be achieved within 2 to 3 days of repeated once daily dosing. The mean accumulation ratio for RM1 was 1.4 (range: 1.1-1.8). RM1 Tmax was similar to that after single dose administration. The RM1 half-life increased from 5.2- to 6.7 hrs. The mean RM1 AUC was about 3-fold higher than that observed for the parent drug. However, Cmax was similar. Following multiple administration of ciclesonide (250- and 1000- µg BID), Cmax and AUC of both ciclesonide and RM1 increased proportionally to the dose.

Bioavailability

Inhaled bioavailability of ciclesonide + RM1 following inhalation of ciclesonide *via* MDI was 41%. Absolute oral and inhaled bioavailability of ciclesonide (measured as RM1), was 1.1% and 26%, respectively.

Absorption

Ciclesonide and RM1 are absorbed fairly rapidly. Based on population PK analysis, KA values ranged from 7.3-10.8 h⁻¹ across sub-populations (asthmatics, healthy, adults, children, male, female etc.).

Distribution

The Vd following IV administration was 207 L and 898 L for ciclesonide and RM1, respectively. Based on population PK analysis, RM1 Vd values ranged from 1113.1-1426.8 L across sub-populations. The protein binding for RM1 and ciclesonide was higher than 98.5%; however this value should be interpreted with caution because of the relatively high non-protein binding reported in the study.

Elimination

Following IV administration, the half-lives and plasma clearance of ciclesonide and RM1 were 0.94 hr and 2.8 hr, and about 152- and 228 L/h, respectively indicating high extraction ratio drugs. Based on population PK analysis, mean CL ranged from 267.3-339.7 L/h across tested sub-populations.

Radioactive ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) and after IV (65.95%) administration, indicating that excretion through bile is the major route of elimination. The biotransformation of ciclesonide is likely to be catalyzed by an esterase enzyme which has not been identified. It appears that RM1 is the major active metabolite that results from the biotransformation of ciclesonide. However, this hypothesis is inconclusive since mass balance studies showed that only 20% of total plasma radioactivity corresponds to RM1. In addition, the metabolite M9, whose pharmacological potency is unknown, was as abundant as RM1 in plasma samples. The cleavage of ciclesonide starts in the lungs where RM1 forms ester conjugates with fatty acids. The biotransformation of RM1 appears to be predominately catalyzed by CYP3A4 (83%), although CYP2D6 (~30%), and to a lesser extent CYP2C8 (11%) are also involved. A major involvement of CYP3A4 in the metabolism of RM1 is inconclusive due to contradictory findings. RM1 does not produce significant inhibition (<25%) of major cytochrome CYP450 enzymes. The potential of ciclesonide to act as an inhibitor of CYP enzymes was not evaluated. Ciclesonide at therapeutic serum concentrations is not likely to induce the enzymes tested (CYP1A2, CYP2C9, CYP2C19, and CYP3A4).

Pharmacokinetics in Asthmatic Patients

The systemic exposure of ciclesonide and RM1 in asthmatic patients receiving a single dose of ciclesonide 1600 µg was similar to that observed in healthy subjects. The C_{max} and AUC_{0-∞} of RM1 increased in patients with asthma by <12 %. The half-life and T_{max} remained unchanged. The C_{max} and AUC_{0-∞} of ciclesonide decreased in patients with asthma by <25%. Based on population PK analysis, the estimated CL/F values were 339.7 L, 301 L, and 283 L for healthy adults, mild to moderate asthmatics, and severe asthma patients, respectively.

Pharmacokinetics in Special Populations

Age, Gender, Weight, Race

Based on population PK analysis, there were no clinically relevant differences in RM1 pharmacokinetics due to race (74% whites, 11% Japanese, 3% Black and 11% others), gender (47% males, 49% females), weight, and age (8% pediatrics, 84% adults, and 3% elderly). The mean AUC_{pop} normalized to 200 µg in children and elderly was similar to that in adults (0.82 ng*hr/mL±0.3 and 0.82 ng*hr/mL ± 0.2 vs. 0.76 ng*hr/mL ± 0.4).

The mean systemic exposure (AUC_{pop}) 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.

A meta-analysis of data from healthy young Caucasian and Japanese subjects revealed that the ratio of geometric means for C_{max} and AUC_{0-∞} of RM1 following single inhalation of 800 µg ciclesonide yielded point estimates and 90% CI of 0.87 (0.77, 0.99) and 0.90 (0.77, 1.05), respectively, indicating no clinically relevant differences in the systemic exposure.

Renal Impairment

The effect of renal impairment on the PK of ciclesonide and RM1 was not evaluated. The rationale provided is that ciclesonide (and RM1) is an inhaled drug with a wide therapeutic index that is mainly eliminated by the hepatic and/or biliary route. In addition, plasma protein binding was not altered when plasma from subjects with renal impairment was spiked with RM1 (at a concentration of 5.0 ng/mL, the protein binding of RM1 in the predose plasma samples varied between 97.5-99%).

Hepatic Impairment

The effect of hepatic impairment (HI) on the PK of a single inhaled dose of ciclesonide 1600 µg was examined in 24 subjects with different degrees of HI (8 healthy, 8 with severe HI and 8 with moderate HI). The C_{max} and AUC_{0-∞} of ciclesonide and RM1 in patients with moderate and severe HI increased in the range of 1.4-fold to 2.7 fold compared to that in healthy subjects. Also, the T_{1/2} of RM1 increased in patients with moderate and severe HI by 2.3 hr and 4.6 hr, respectively, as compared to that in healthy controls. No dose adjustment is needed in patients with moderate and severe HI.

Drug/Drug Interactions (DDI)

In-vitro metabolism studies indicated that RM1 is likely to be metabolized by CYP3A4 although CYP2D6 is also involved to a lesser extent. The sponsor did not conduct DDI studies to assess the effect of CYP2D6 inhibitors on the PK of ciclesonide. Also the effect of ketoconazole, a potent CYP3A4 inhibitor was not evaluated despite FDA recommendations. No in vivo DDI studies were conducted with drugs that displace binding to proteins.

The systemic exposure of ciclesonide and RM1 in healthy subjects receiving a single dose of ciclesonide 800 µg was not statistically significantly altered by its coadministration with a single dose of erythromycin 500 mg. The arithmetic mean C_{max} and AUC_{0-∞} of RM1 increased in the presence of erythromycin by < 12%.

The systemic exposure (AUC_{0-∞} and C_{max}) of ciclesonide and RM1 in healthy subjects receiving

a single dose of ciclesonide 800 µg was not statistically significantly altered (<23 % decreased) when coadministered with a single dose of formoterol 24 µg. The cumulative urinary excretion of formoterol was not statistically significantly altered (8% decreased) when coadministered with ciclesonide. Based on population PK analysis, the RM1 CL and Vd values were similar for subjects with (98 subjects) and without (512 subjects) coadministration of albuterol.

Dose-Response (Efficacy and Safety) Relationships

The dose-response relationship of RM1 was evaluated in three adult and two pediatric phase III, efficacy and safety studies. The ciclesonide doses evaluated in adults were: 80-, 160- and 320 µg QD for 12 weeks in patients with mild to moderate asthma, and 160-, and 320 µg BID in patients with severe persistent asthma. The doses evaluated in children were 40-, 80- and 160 µg QD for 12 weeks in approximately 500 children 4 to 11 years of age (125 per study) with persistent asthma.

The primary efficacy variable was the change from baseline to Week 12 in FEV₁. Suppression of endogenous cortisol release (HPA-axis function) was included as one of the safety variables.

For the efficacy variable considered, significant difference from placebo (p<0.05) was replicated in all doses tested in adults, except for the 160 µg/day. At higher doses, there was a trend for better response; however, dose-ordering response for efficacy was not observed as has been shown for other glucocorticoids. Ciclesonide doses of 320- and 640 µg BID were tested in subjects with persistent asthma requiring oral corticosteroid; however the primary end point was other than FEV₁.

Based on population PK/PD analysis using data from phase I and Phase III Studies, there was a trend for higher doses of ciclesonide to produce a higher cortisol suppression (13%, 8%, and 49% decrease in serum cortisol AUC for doses of 800- to 1200 µg and 1600 µg, and 3520 µg, respectively); however, due to the great variability on the data, a clear relationship was not observed. Nevertheless, the degree of cortisol suppression caused by ciclesonide in the range of proposed therapeutic doses is not higher than that observed for fluticasone propionate at therapeutic doses for the treatment of asthma.

No dose-response for efficacy was observed in children. In addition, cortisol suppression showed no dose-order in the degree of suppression and it was not different from that in the placebo treatment. The starting dose in children is uncertain since the effect of the 80 µg/day or 160 µg/day dose was not replicated.

Based on data from one Phase I study (NOT thorough study) in healthy males, RM1 did not significantly affect QT or QTc at single doses up to 3520 µg.

Reviewer

Sandra Suarez-Sharp, Ph.D. _____

Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader _____

cc

NDA 21-658 : Division File

HFD-870: Malinowski, Hunt

HFD-570: Fadiran, Bosken, Chowdhury, Jackson, Gilbert-MCClaine, Suarez-Sharp

2. QUESTION BASED REVIEW

2.1 General Attributes

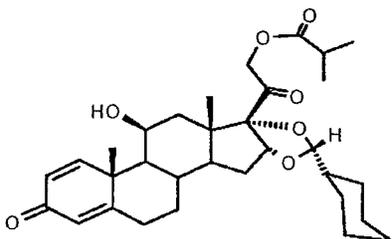
2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The active component of ALVESCO Inhalation Aerosol is ciclesonide, a non-halogenated glucocorticoid delivered as the R-epimer.

Chemical name:

pregna-1,4-diene-3,20-dione,16,17-[[[(R)-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11 β ,16 α).

Structural formula:



Molecular formula: C₃₂H₄₄NO₇

Molecular weight: 540.7

Solubility: Ciclesonide is a white to yellow-white powder. It is soluble in dehydrated alcohol, acetone, dichloromethane, and chloroform.

FORMULATION

Alvesco 80-, and 160 μ g Inhalation Aerosol, are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a solution of ciclesonide in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. Alvesco 80 μ g delivers 80 μ g from the valve and 80 μ g of ciclesonide from the actuator. ALVESCO 80 μ g delivers 100 μ g from the valve and 80 μ g of ciclesonide from the actuator. Alvesco 160 μ g delivers 200 μ g from the valve and 160 μ g of ciclesonide from the actuator. This product delivers 50 microliters (59.3 milligrams) of solution as a fine particle mist from the valve with each actuation.

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Table 1. Composition of Ciclesonide 160-, 80-, and 80 μ g Inhaler

Name of Ingredient	Quantity (% w/w)		
	160 μ g inhaler	80 μ g inhaler	80 μ g inhaler
Ciclesonide			
Dehydrated Alcohol, USP			
HFA-134a			
Total quantity			

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2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Ciclesonide is a pro-drug that is hydrolyzed by esterases to its active metabolite, RM1 (a glucocorticoid), which has approximately 100-fold greater affinity for the glucocorticoid receptor than the parent drug. According to the sponsor, RM1 has potent anti-inflammatory activity with affinity for glucocorticoid receptors that is 12 times greater than dexamethasone.

The precise mechanism of corticosteroid action in asthma is unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types and mediators involved in allergic and non-allergic mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

INDICATION (as per proposed label)

Alvesco is indicated for the maintenance treatment of asthma as prophylactic therapy in adult years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma management. Alvesco is NOT indicated for the relief of acute bronchospasm.

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2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed route of administration is by oral inhalation.

DOSAGE AND ADMINISTRATION (as per proposed label)

	Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents:	Bronchodilators alone	80 - mcg	
	Inhaled Corticosteroids	80 - mcg	320 mcg
		twice daily	320 mcg twice daily
	Oral Corticosteroids	320 - mcg twice daily	twice daily

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2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

The primary efficacy variable in the pivotal efficacy studies was the change from baseline to Week 12 (or end of study) in FEV₁ (forced expiratory volume in one second) in adults and adolescents, or in FEV₁ percent predicted in children. Although FEV₁ is a well established and validated clinical endpoint of efficacy in asthma, it does not, by itself, fully describes the level of overall asthma control. Therefore, key secondary endpoints reflecting asthma control, including AM PEF (morning peak expiratory flow), symptom scores, and rescue β₂-agonist use, were measured. Since systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and because there is uncertainty about the site of absorption along the respiratory tract/airways, plasma concentrations cannot be correlated to efficacy (FEV₁).

One of the major systemic side effects of therapeutic corticosteroids is the suppression of endogenous cortisol production. In the case of topical corticosteroid therapy such as in the lungs, it is attempted to minimize the systemic contribution by the absorbed corticosteroids in favor of primarily local effects. In this case, the suppression of endogenous cortisol release (HPA-axis function) assessed by cortisol concentrations measurements is a suitable marker to quantify the degree of systemic steroid activity of a drug. Ciclesonide however, showed no clear dose dependency (doses ranging from 360- to 1600µg/day) in serum cortisol levels measured as AUC_{0-24h}.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The basis for selecting the response endpoints was described in the previous question. The change from baseline to Week 12 in FEV₁ was measured prior to the morning dose (i.e., trough measurement) at the end of the 24-h dosing interval. Spirometry was performed according to standards for adults, adolescents, and children [1995 ATS Standardization of Spirometry guidelines].

As regards to cortisol suppression, the marked circadian rhythm in cortisol release makes the precise quantification of this cortisol suppression quite complex and therefore there is not a clear cut consensus about the ideal method for determining the effect on HPA-axis function. Suppression of endogenous cortisol release (HPA-axis function) was assessed by determining the AUC_{0-24h} serum cortisol corrected or uncorrected for baseline, 24 hr urine cortisol excretion corrected and uncorrected for creatinine, and peak cortisol levels following cosyntropin stimulation relative to placebo administration in either case.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Concentrations of ciclesonide and RM1 were determined in serum samples from all human pharmacokinetic studies using _____ HPLC _____ (LC/MS/MS) with lower limits of quantification (LLOQ) of 25 pg/mL and 10 pg/mL for ciclesonide and its metabolite, respectively. The upper calibration limit for both analytes was _____ pg/mL.

For Phase I studies, quantitative assay of serum cortisol was measured using a commercially available fluorescence polarization immunoassay. The lower limit of quantitation was 2.5 µg/dL (25 ng/mL). For Phase III studies, quantitative assay of serum cortisol was conducted using radio immunoassay (RIA). The LLOQ was 20 nM. See analytical section for details.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

As mentioned before, plasma concentrations cannot be correlated to efficacy for inhaled drugs. In the case of dose-response for efficacy, dose-ordering was not observed at lower doses. Studies 321 and 322 evaluated the efficacy, safety and dose response of ciclesonide 800-, 160- and 320 µg/day QD for 12 weeks in patients with mild to moderate asthma. In study 321, the middle dose had a lower mean change from baseline in FEV₁ values compared to the other 2 doses (Figure 1), while in study 322 the middle dose had the highest value in delta FEV₁. At higher doses, there was a trend for better response (Table 2, Figure 2); however no clear dose-response relationship was observed as has been shown for other glucocorticoids. According to the sponsor, all doses tested were significantly different from placebo (p<0.05), except the 160 µg dose in Study 321.

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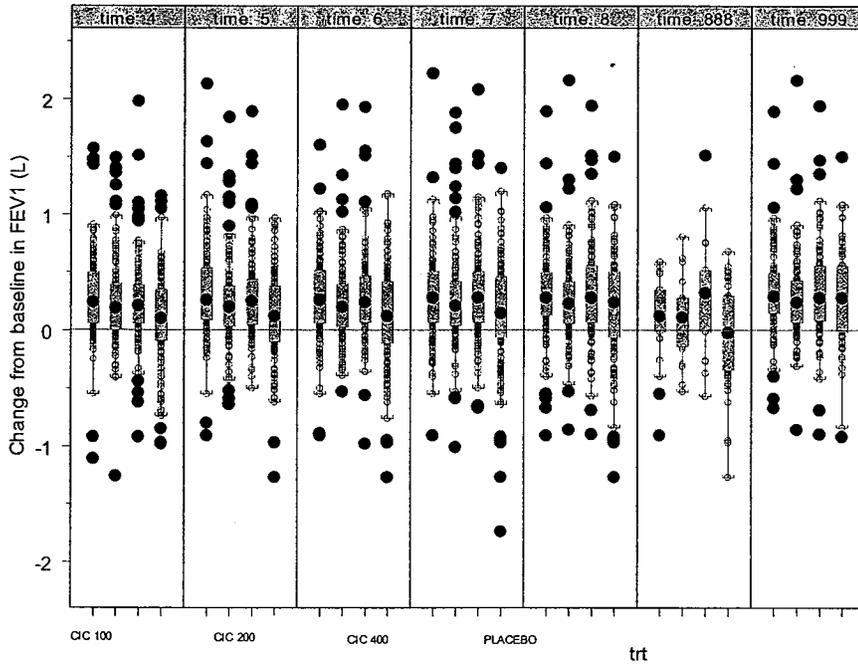


Figure 1. Change from baseline in FEV₁ (L) as a function of visit [time 4 (week 1), time 5 (week 2), time 6 (week 4), time 7 (week 8), time 8 (end point), time 888 (early termination), time 999 (week 12)] following once daily administration of the treatments (ciclesonide 80, 160, and 320 µg QD) in adult patients with mild persistent to moderate persistent asthma (n=125 per treatment group). Data from study 321.

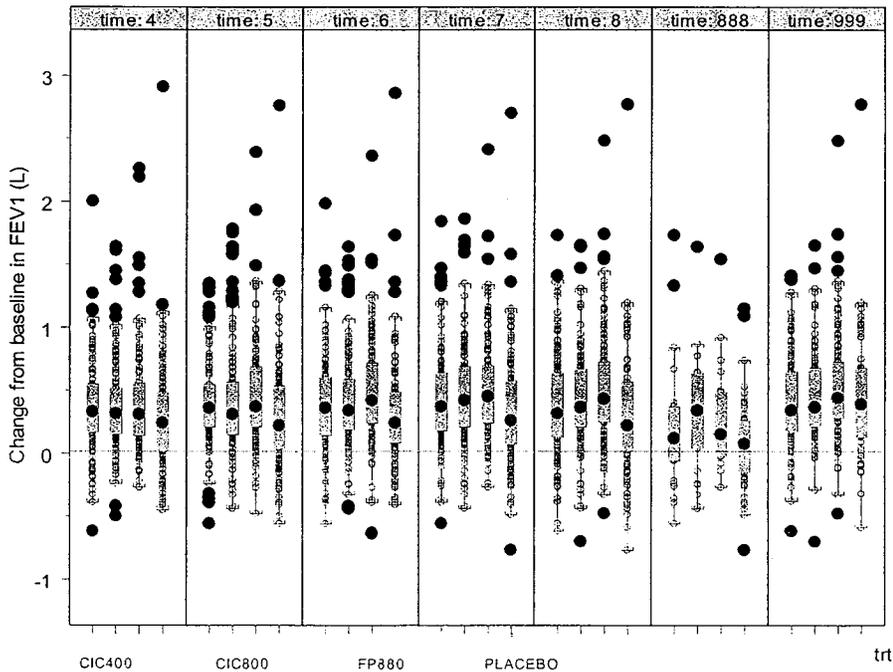


Figure 2. Change from baseline in FEV₁ (L) as a function of visit [time 4 (week 1), time 5 (week 2), time 6 (week 4), time 7 (week 8), time 8 (end point), time 888 (early termination), time 999 (week 12)] following administration of the treatments

(ciclesonide 160-, and 320 µg BID and FP 440 BID) in adult patients with severe persistent asthma (n=125 per treatment group). Data from study 323/324.

Table 2 - Change from baseline to Week 12 in FEV¹ (L) – ITT population following administration of the treatments (ciclesonide 160-, and 320 µg BID and FP 440 BID) in adult patients with severe persistent asthma (n=125 per treatment group) (Study 323/324) (data reported by the sponsor)

Treatment	N	Baseline mean ^a (L)	Change from baseline			Treatment comparison vs. placebo		
			LS mean	SE	95% CI	LS mean difference	95% CI	P-value
Placebo	134	1.77	0.25	0.037	(0.18, 0.33)	-	-	-
Ciclesonide-320	127	1.78	0.36	0.038	(0.29, 0.44)	0.11	(0.01, 0.21)	0.0374
Ciclesonide-640	130	1.82	0.43	0.037	(0.36, 0.50)	0.18	(0.07, 0.28)	0.0008
Fluticasone-880	136	1.77	0.50	0.037	(0.43, 0.57)	0.24	(0.14, 0.35)	0.0001

^a Baseline means are raw means.
LS = least-squares, SE = standard error.

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

The existence of dose-response (HPA-axis function/cortisol suppression) relationship based on Phase I/II studies (doses tested ranged from 400 – 1600 µg /day) is difficult to be established due to the great variability on the data and because of the inconsistency on the method used to assess/calculate the degree of cortisol suppression. In general, there appears not to be a relationship between dose and degree of cortisol suppression in this range of doses (conclusion from studies 102, 49-2000, and 013). Study 103 showed that ciclesonide 1600 µg/day produced a greater suppression than the 800 µg/day dose (see Figure 3) and only one study (FHP009) showed a clear dose dependency decrease in cortisol levels measured as AUC_{0-24h}/24 hr serum cortisol (single doses of: 400, 1200, and 3600 µg ex-valve) (Table 3).

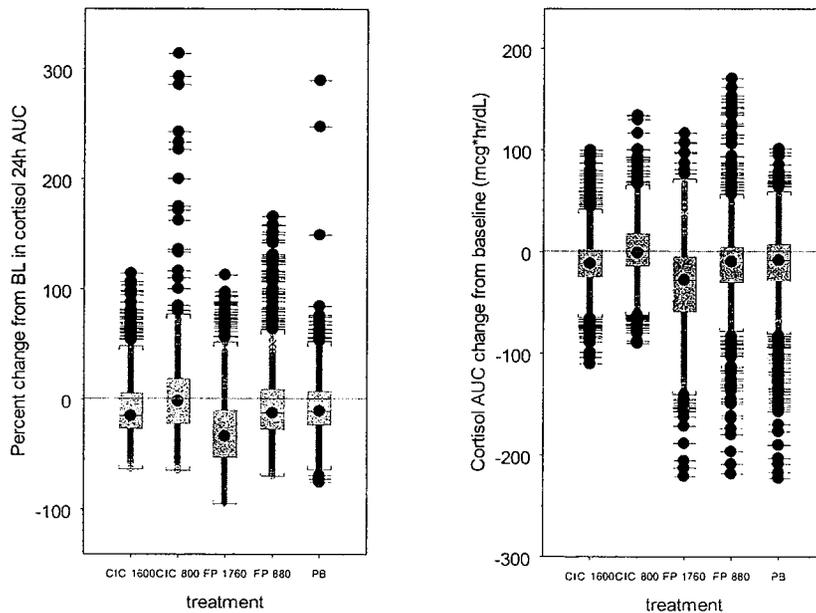


Figure 3. Individual % change from baseline in AUC_{0-24h} serum cortisol (left panel) and AUC_{0-24h} serum cortisol change from baseline (right panel) following multiple administration of ciclesonide 320 µg bid, ciclesonide 640 µg bid, FP 440 µg bid, FP 8880 µg bid, or placebo (data from study 103).

Table 3. Geometric means and point estimates for AUC 0-24h/24 serum cortisol levels following single and multiple administration of the treatments in healthy volunteers (from study FHP009)

Treatment (Dose)	Reference (Dose)	Serum Cortisol (µg/dL)	
		Geometric mean	PS (90% CI)
400 µg sid	placebo	9.8	0.94 (0.85-1.05)
1200 µg sid	placebo	8.8	0.83 (0.76-0.92)
3600 µg sid	placebo	7.3	0.62 (0.56-0.69)
Placebo		10.6	
250 µg bid	placebo	10.2	1.11 (1.03-1.2)
1000 bid	placebo	7.9	0.92 (0.85-0.99)
placebo		8.9	

Data from four phase III studies (studies 321, 322, 323/324: range of doses 80- to 640 µg/day) showed no correlation between dose and degree of cortisol suppression (see Table 4).

Table 4 - Change from baseline to Week 12 in low-dose peak serum cortisol levels (from study 323/324)

Variable	Treatment	N	Baseline mean ^a	Least-squares mean (SE)		P-value ^b
				Change from baseline	Treatment difference vs. placebo	
Low-dose peak serum cortisol (µg/dL)						
	Placebo	30	21.87	-0.44 (0.925)	-	-
	Ciclesonide-320	29	25.07	-2.06 (0.947)	-1.63 (1.256)	0.1988
	Ciclesonide-640	31	23.45	0.75 (0.871)	1.19 (1.200)	0.3261
	Fluticasone-880	30	24.53	-1.05 (0.931)	-0.61 (1.234)	0.6210

^a Baseline means are raw means.

^b P-values are for treatment comparisons versus placebo.

N = randomized population at selected centers, SE = standard error, - = not applicable.

Based on population pharmacokinetic/pharmacodynamic analysis using data from Phase I and Phase III studies, there was a trend for higher doses of ciclesonide to produce a higher cortisol suppression (13%, 8%, and 49% in cortisol AUC for doses of 800 to 1200 µg and 1600 µg, and 3600 mg, respectively); however, due to the great variability in the data, a clear relationship was not observed (Figure 4). Nevertheless, the degree of cortisol suppression caused by ciclesonide in the range of proposed therapeutic doses is not higher than that observed for fluticasone propionate at therapeutic doses for the treatment of asthma (Figure 3, Table 4). In addition, no significant effect of individual systemic drug exposure (RM1) on serum cortisol (AUC) was found.

Also, the direct effect of individual predicted systemic RM1 concentrations on cortisol concentrations at a given time was assessed with an Emax model. When Emax was fixed to 100%, EC50 (RM1 concentration to produce 50% of the maximum suppression) for ciclesonide was 1.96 ng/mL. This EC50 value is similar to the 90th percentile of RM1 concentrations for the 1600 µg dose. When Emax was estimated using a direct Emax model, the EC50 value was estimated to be 0.59 ng/mL and the Emax value was estimated to be 41%. This means that in the range of doses studied (up to 3520 µg) the maximum suppression of cortisol with ciclesonide is 41% and the EC50 is similar to the mean Cmax of

RM1 observed following 1600 µg (maximum therapeutic dose) administration of ciclesonide (0.875 ng/mL, from study 56E/99).

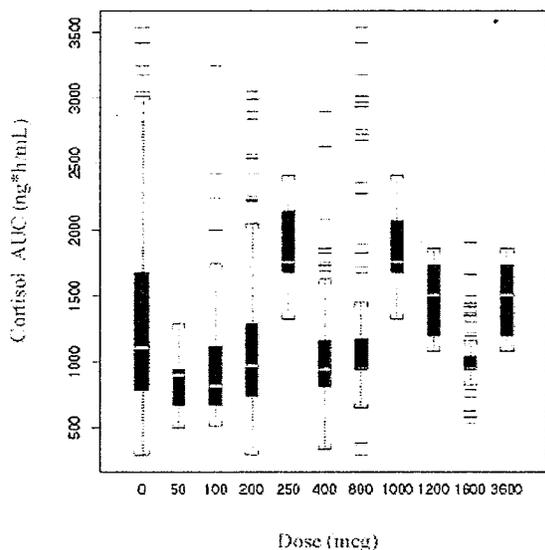


Figure 4. Effect of RM1 AUC0-24h on cortisol concentrations (data from population PK/PD analysis).

2.2.4.3 Does this drug prolong the QT or QTc interval?

Based on data from one Phase I (NOT thorough) study, RM1 did not significantly affect QT or QTc at single doses up to 3520 µg. This data should be interpreted with caution since it is based on single dosing, male subjects, and lack of robustness of the data provided.

Table 5 shows the statistics about QTb change from baseline as a function of time following single administration of ciclesonide. ECGs (12-lead) were recorded at -1 day, predose, 1 h, 6 h, 12 h and 23.5 h after morning inhalation in 12 healthy males (Study 117E/97). A summary of the findings from this study are as follows:

- The maximum mean QT change from baseline using Bazett’s correction was observed at 23.5 hrs post administration for the placebo group (3.8 msec).
- There were 2 subjects from the placebo group, one subject in the 320 µg dose and one subject in the 3520 µg dose whose QTb change from baseline was greater than 30 msec. The highest QTb individual change from baseline was 53 msec following placebo treatment.
- The highest QTb absolute value was 447.12 following placebo treatment
- The mean of maximum QTb change from baseline was highest for the placebo group (10.05 msec ± 16)

Table 5. Mean (SD) QTb change from baseline as a function of dose and time following ciclesonide administration (Data from study 117E-97) (n=12 males)

Time	Delta QTc (msec) Based on Bazett’s correction			
	Placebo	320	1200	3520
0	0 (2.3)	0 (1.8)	0 (7.3)	0 (4.48)
1	1.28 (10.2)	1.4 (4.7)	-2.7 (6)	0.84 (6.6)
6	-1.9 (8.2)	2.5 (4.3)	-0.4 (6)	2.8 (8.5)
12	-3.6 (8.6)	1.3 (4)	-1.6 (5)	-2.1 (10.9)
23.5	3.8 (15.9)	2.9 (15.9)	-1.6 (10.9)	0.7 (11.9)
maximum	3.8	2.9	0	2.8

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The recommended doses of ciclesonide in adults depend on the severity of the disease and concomitant therapy and ranges from 80 µg/day to 1280 µg/day. Dose-response was not observed for 80, 160-, and 320 µg/day QD. At higher doses (160, and 320 µg BID), there was a trend for better response, however no clear dose-response relationship was observed as has been shown for other glucocorticoids. Because of this, the right dose/dosing regimen need to be based on safety outcomes other than the effect on the HPA axis since the proposed doses of ciclesonide do not appear to produced higher cortisol suppression compared to those from approved glucocorticoids on the market. The starting dose in the children population is uncertain since the effect of the 80 µg/day or 160 µg/day dose was not replicated.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? What are the characteristics of drug distribution? How do the PK parameters change with time following chronic dosing?

Single Dose

In general, the systemic concentrations of ciclesonide were variable or transient following inhaled administration. Ciclesonide was not detected in plasma at inhaled doses lower than 400 µg/day. On the other hand, the PK of RM1 were well characterized and predictable.

The pharmacokinetics of RM1 were investigated in 15 healthy volunteers after single oral administration of ciclesonide (10 mg) as powder capsules, single oral inhalation of 1600 µg, ciclesonide via the MDI, and single intravenous administration. Table 6 summarizes the PK parameters for ciclesonide and RM1.

Following oral administration, the concentration of ciclesonide was detected only in 4 samples of two volunteers, with concentrations being close to the LOQ. The clearance of ciclesonide (152 L/h) and the apparent clearance of RM1 (228 L/h) exceeded the hepatic blood flow, suggesting a high extraction ratio drugs. The Vd of ciclesonide (2.9 L/kg) and the apparent volume of distribution of RM1 (12.1 L/kg) exceeded the total body water volume in humans (0.6 L/kg).

The protein binding for RM1 was higher than 98.5%; however this value should be interpreted with caution because of the relatively high non-protein binding reported in the study and because the hematocrit reported was much lower than normal blood. The protein binding of ciclesonide appears to be (98.9 to 99.8%) in various species including humans.

Inhaled relative bioavailability of ciclesonide + RM1 following inhalation of ciclesonide *via* MDI was 41 %. Absolute oral and inhaled bioavailability of RM1, was 1.1% (n=10) and 26% (n=6), respectively.

Table 6. Mean (SD) PK parameters of ciclesonide and RM1 in serum of healthy subjects following single administration of the treatments (Data from study FH015-172-95)

	Intravenous (800 µg)		Oral (10 mg)		MDI (1280 µg)	
	ciclesonide	RM1	ciclesonide	RM1	ciclesonide	RM1
AUC (µg*hr/L)	5.6 (1.5)	3.27 (0.85)	-	1.18 (0.89)	2.19 (1.3)	3.67 (2.27)
Cmax (µg/L)	23.6 (9.4)	1.132 (0.36)	-	0.203 (0.22)	5.61 (2.6)	0.83 (0.53)
Tmax (hr)	0.17 (0)	0.43 (0.46)	-	3.92 (4.11)	0.18 (0.05)	1.04 (0.5)
T1/2 (hr)	0.94 (0.53)	2.8 (0.51)	-	-	0.71 (0.45)	2.8 (0.3)
CL (L/hr)	152.3 (37.3)	227.7 (65.01)	-	-	-	-
Vdarea (L)	206.8 (149.9)	897.7 (236.8)	-	-	-	-

Multiple Dose

The AUC and Cmax geometric means of ciclesonide increased by 28% and 30%, respectively following multiple administration of ciclesonide compared to that after single administration. The half-life of ciclesonide remained unchanged (Table 7). The AUC and Cmax geometric means of the RM1 increased by 44% and 38%, respectively following multiple administration of ciclesonide compared to

that after single administration. The half-life of the metabolite increased by 1.6 hr (from 5.23 hr to 6.72 hr) following multiple administration. The accumulation ratio ranged from 1.1 to 1.8.

The data described above comes from Study 211-200. This was an open, non-controlled, one-period, single-center Phase I study in 18 healthy subjects. The study consisted of a screening examination, a treatment period of 7 days, and a post-study examination. During the treatment period all subjects received 400 µg ciclesonide in the morning on each study day.

Table 7. Mean (S.D.) RM1 PK parameters following single and repeat administration of ciclesonide (data from study 211-200)

	Regimen	Mean (SD)	Point estimate And 90% CI (single/multiple)
Cmax (µg/L)	Single	0.299 (0.13)	1.38 (1.09-1.76)
	Repeat	0.37 (49)	
AUC(0-inf) (µg.h/L)	Single	1.72 (0.73)	1.44 (1.13-1.84)
	Repeat	2.18 (0.42)	
T1/2 (h)	Single	5.23 (1.28)	1.32 (1.18-1.48)
	Repeat	6.72 (1.04)	
Tmax (h)	Single	1.08 (0.62)	
	Repeat	0.94 (0.44)	

2.2.5.2 Are the PK and PD of ciclesonide linear and dose-proportional?

Based on post hoc AUC values from population PK analysis, the pharmacokinetics of RM1 were linear and dose proportional in the range of 40- to 3520 µg ($R^2=0.65$) (Figure 5). Following single dose administration of ciclesonide (doses: 320-, 1200-, and 3520 µg) to healthy volunteers, the AUC and Cmax of both ciclesonide and RM1 increased more than dose-proportional (3-fold increased in the dose produced a 4 to 5-fold increased in the exposure) (Table 8). However, this conclusion should be interpreted with caution since high variability on the data was seen at higher doses. In the repeated dose study (250- and 1000- µg BID) Cmax and AUC increased in proportion with the dose.

The mean 24 h-profiles of cortisol in serum decreased less than proportional to the dose. The point estimates and 90% CI for test/placebo were 0.94 (0.85-1.05), 0.83 (0.76-0.92), and 0.62 (0.56-0.69), for the 400-, 1200-, and 3600 µg of ciclesonide, respectively (Table 3).

The data presented above comes from study 114E_97 (or FHP009). This study was a single dose/multiple dose study with a wash-out period of 2 weeks between treatments of two subsequent periods conducted in 24 healthy volunteers. For assessing the effect on the HPA-axis, serum cortisol was determined at the following time points: predose, 2, 4, 6, 8, 10, 12, 14, 24 hrs, after administration on day 1 following single dose and on day 7 on the repeated doses.

Table 8. Mean (min-max) AUC and Cmax values following single and multiple administration of the treatments (data from FHP009)

Dose (µg/day)	Single Dose			
	Ciclesonide		RM1	
	AUC (µg*hr/L)	Cmax (µg/L)	AUC (µg*hr/L)	Cmax (µg/L)
400	0.24 (0.21-0.27)	0.215 (0.11-0.29)	0.72 (0.52-1.01)	0.153 (0.12-0.26)
1200	1.03 (0.33-2.4)	1.01 (0.34-2.1)	2.5 (1.1-4.8)	0.51 (0.28-0.94)
3600	4.4 (2.1-7.8)	4.9 (2.8-7.5)	10.5 (5.1-17.05)	2.5 (1.5-3.5)
	Multiple Dose			
500	0.23 (0.14-0.28)	0.19 (0.098-0.3)	0.85 (0.53-1.4)	0.17 (0.12-0.256)
2000	1.14 (0.5-1.9)	0.87 (0.38-1.5)	3.4 (2.15-5.4)	0.74 (0.49-1.11)

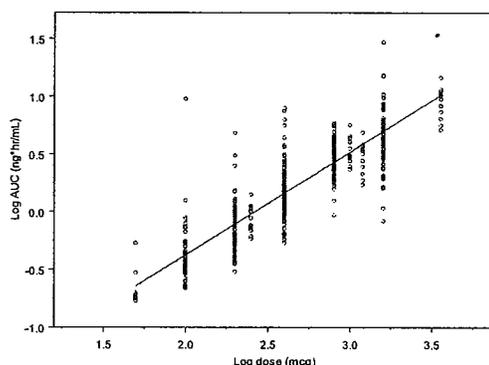


Figure 5. Individual RM1 AUC (log values) as a function of log-Dose (fitted line from power model: $AUC = e^{-2.15*} (dose)^{0.9}$). Data from population PK analysis.

2.2.5.3 What are the mass balance characteristics of the drug?

Radioactive ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) as after intravenous (65.95%) administration, indicating that excretion through bile is the major route of elimination. This information comes from study FHP021, which was a mass balance study conducted in 6 male healthy volunteers to investigate the disposition and routes of elimination following single oral 8 mg capsule ciclesonide and single intravenous 0.64 mg/20 mL as a 10-minute infusion. Blood samples were collected up to 168 hours for total radioactivity and up to 2 h for metabolite identification. Urine and feces were collected up to 168 hrs. The findings from this study can be summarized as follows:

- The excretion of radioactivity following a single oral dose of 6.9 mg ciclesonide and single intravenous administration of 0.64 mg ciclesonide was almost complete (total average recovery 91.4% and 85.95% respectively). Ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) as after intravenous (65.95%) administration (Table 9).
- Ciclesonide showed no accumulation in red blood cells, as could be concluded from the high plasma/whole blood ratio.
- The absorption of ^{14}C -ciclesonide was 24.5% based on dose-normalized for radioactivity.
- Oral bioavailability based on AUCs of RM1 could only be determined for one subject and was about 1.8%.
- Parent compound ciclesonide and its metabolite RM1 constitute 19.3% of radioactivity found in plasma; approximately 80% of the ^{14}C radioactivity AUC may be resulting from one or more yet unknown metabolites.

Table 9. Mean cumulative excretion of ^{14}C -radioactivity (% of dose) after administration of ^{14}C -ciclesonide as an i.v. solution and single oral dose

PARAMETER	6.9 mg of ^{14}C -ciclesonide p.o.		
	mean	min	max
A_{urine} (% of dose)	13.5	11.1	14.7
A_{faeces} (% of dose)	77.9	67.1	81.4
A_{total} (% of dose)	91.7	81.8	94.4
	0.64 mg of ^{14}C -ciclesonide i.v.		
A_{urine} (% of dose)	20	9.1	23.5
A_{faeces} (% of dose)	65.95	55.9	75
A_{total} (% of dose)	85.95	78.5	98.3

2.2.5.5 What are the characteristics of drug metabolism and excretion?

Data from the in-vitro metabolism of ¹⁴C-Ciclesonide and RM1 in human hepatocytes and profiling of plasma and urine samples from ¹⁴C-ciclesonide clinical study showed that RM1 appears to be the mayor product of metabolism of ciclesonide. However, the existence of other metabolites cannot be ruled out since the sponsor has not adequately characterized the metabolic profiling of ciclesonide. The following summarizes the findings about the in-vitro metabolism and in vivo metabolic profiling:

- Ciclesonide was almost completely metabolized within the first hr of incubation with human hepatocytes.
- Approximately 50% of RM1 was metabolized within the first hr of incubation with human hepatocytes.
- Metabolite Profiling of ¹⁴C-Ciclesonide in Human Hepatocytes (4-Hr Incubation) showed that RM1 (17.75% of total radioactivity), M7 (15.27%), M4 (9.89%), M1 (6.35%), M2 (6.39%) were the major metabolites present.
- Metabolite Profiling of ¹⁴C-RM1 in Human Hepatocytes (4-Hr Incubation) showed that RM1 (14.22%), M7 (12.77%), M3-4 (21.14%), M1 (6.72%), M2 (7.62%), and M5-6 (9.61%) were the major metabolites present.
- Hippuric acid (M1) was the only major metabolite found in 0-4-hr interval of urine collection after oral (61.%) and IV (38.7%) administration. The presence of this product was thought to originate from initial aromatization of the cyclohexane moiety to form benzoic acid.
- Ciclesonide (22.36%), RM1 (11.93%) and M9 (5.53%) were the major components found in the 0.25 hr IV plasma sample.
- In the 0.5-hr IV plasma sample, RM1 was the mayor peak (10.34% of total radioactivity). Other components in the 0.5-hr plasma sample also eluted at the retention time regions of hydroxylated RM1 (the major one contributed 7.47%) of the total radioactivity.

2.2.5.4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

The CV% (intersubject variability) for the C_{max} and AUC of RM1 in healthy volunteers and asthmatics patients was as low as 38% and as high as 68%. Disease stage did not change the degree of variability.

2.3 Intrinsic Factors

2.3.1 Does age affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 ELDERLY

The mean C_{max} and AUC of ciclesonide increased in elderly subjects by 3-fold and 2.5 fold, respectively, as compared with that observed in young healthy adults. The mean C_{max} and AUC of RM1 increased in healthy elderly subjects by 2.4-fold and 2-fold respectively (following single inhalative doses of 1600 µg ciclesonide), as compared to that in the young healthy controls (Figure 6). These findings should be interpreted with caution since the observations are based on cross-study comparisons and the lack of robustness on the analysis of plasma samples. This study in the elderly (56E/99) 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.

On the other hand, the population PK/PD analysis using data from phase I and III revealed that age did not influence the PK of the drug (see below for more details on the population PK/PD analysis). The mean posthoc AUC_{pop} (dose-normalized to 200 µg) in the elderly was 10% higher compared to that in adults (Figure 7). Therefore, dose adjustment in the elderly based on these PK findings may NOT be necessary since the dose-response curve for ciclesonide was flat in the range of 80-640 µg/day and the relative good safety profile based on cortisol suppression effect.

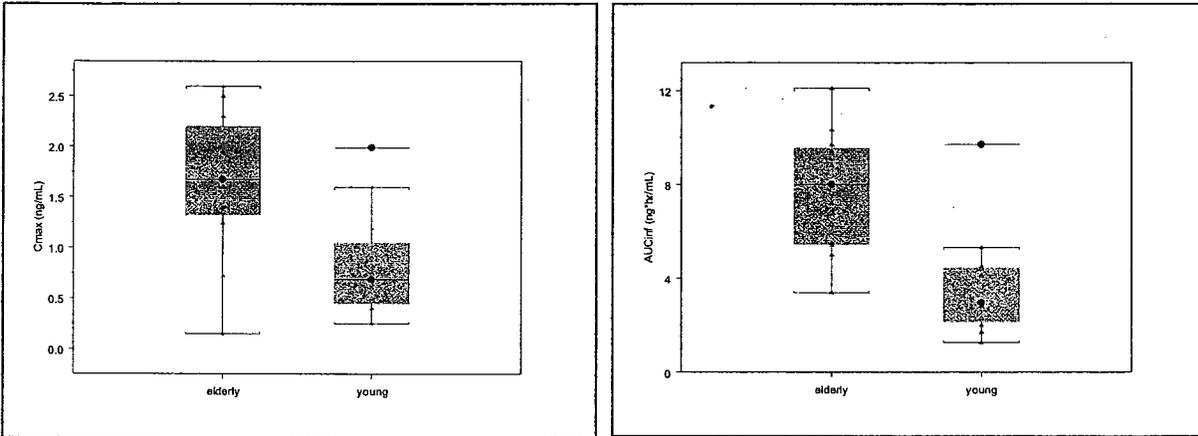


Figure 6. Individual C_{max} and AUC_{0-∞} values for RM1 in healthy elderly volunteers (Study 56E/99) and in young volunteers (data from study 253E/99) following single inhalative doses of 1600 µg ciclesonide (n=12 elderly).

2.3.1.2 PEDIATRICS

No dose-response was observed in the range of 40- to 160 µg/day (Table 10). In addition, cortisol suppression measured as change from baseline to Week 12 in low-dose peak serum cortisol levels showed no dose-order in the degree of suppression and it was no different from placebo treatment (Table 11). The starting dose in children is uncertain since the effect of the 80 µg/day or 160 µg/day dose was not replicated.

This information comes from two Phase III clinical studies conducted in children. These pediatric trials (341 and 342) were conducted as double-blind, placebo-controlled, parallel-group, multicenter, efficacy, safety and dose-response studies of ciclesonide 40-, 80- and 160 µg/day for 12 weeks in approximately 500 children 4 to 11 years of age (125 per study) with persistent asthma. In the primary efficacy analysis of change from baseline to Week 12 in FEV₁ percent predicted, the 40- and 160 µg daily dose did not reach significance when compared with the placebo treatment group at Week 12, and only the 80 µg daily dose showed significant improvement in the change from baseline in FEV₁ percent predicted compared to placebo (data reported by sponsor from Study 341). An integrated analysis of efficacy combining data from this study with an identically designed study (Study 342) showed that treatment with ciclesonide 80- (p=0.0239 versus placebo) or ciclesonide 160 µg /day (p=0.0069 versus placebo) administered once daily for 12 weeks increased FEV₁ percent predicted.

Table 10. Magnitude of treatment differences versus the placebo treatment group from baseline to Week 12 (LOCF) - ITT population in asthmatic children (Data from study 341)

Variable	Treatment difference at Week 12 versus placebo (p-value)		
	Ciclesonide 40 µg/day	Ciclesonide 80 µg/day	Ciclesonide 160 µg/day
FEV ₁ percent predicted	1.15 (0.5634)	3.93 (0.0460)	3.34 (0.1005)
FEV ₁ (L)	0.03 (0.3621)	0.08 (0.0259)	0.05 (0.1760)
AM PEF (L/min)	4.27 (0.3420)	16.34 (0.0003)	9.70 (0.0343)
Total Asthma Severity Rating Score	-0.14 (0.4003)	-0.73 (0.0001)	-0.60 (0.0006)
Daily albuterol use (puffs/day)	-0.23 (0.3134)	-0.82 (0.0002)	-0.76 (0.0011)

Blood samples were collected for the measurement of serum cortisol before and after stimulation with low-dose (1 mg) cosyntropin. Data for both baseline and Week 12 were available in 32 patients. The change from baseline to week 12 in low-dose peak serum cortisol levels following administration of the 3

doses was not greater (0.62,- -0.40 and 1.44- $\mu\text{g/dL}$, respectively) than that observed for placebo treatment (-2.35 $\mu\text{g/dL}$) (Table 11)

Table 11 - Change from baseline to Week 12 in low-dose peak serum cortisol levels (Data from study 341)

Variable	Treatment	N	Baseline Mean ^a	Least-squares mean (SE)
				Change from baseline
Low-dose peak serum cortisol ($\mu\text{g/dL}$)				
	Placebo	7	21.29	-2.35 (1.757)
	Ciclesonide-40	6	22.83	0.62 (1.766)
	Ciclesonide-80	10	24.10	-0.40 (1.282)
	Ciclesonide-160	9	23.56	1.44 (1.568)

^a Baseline means are raw means.
N = randomized population at selected centers, SE = standard error, - = not applicable.

In the population PK/PD analysis weight seemed to affect the PK of RM1. Inspection of the weighted residual (WRES) versus prediction (PRED) plot for pediatrics only indicated a bias. The application of separate weight effects for pediatrics and adults resulted in no weight adjustment for pediatrics, which may be expected since CL clearance varied less than 20% over a weight range of 50 to 100 kg. Then, it seems that weight does not affect the PK of the drug; however, these results should be interpreted with caution since the estimated AUC in adults was highly variable (Figure 7).

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 Vd based on allometric principle. According to the sponsor, this resulted in similar predicted concentrations between children and adults when same dose is given. Figure 7 shows that the mean AUC_{pop} normalized to 160 μg in children was similar to that in adults (0.82 $\text{ng}\cdot\text{hr}/\text{mL}\pm 0.3$ vs. 0.76 $\text{ng}\cdot\text{hr}/\text{mL} \pm 0.4$).

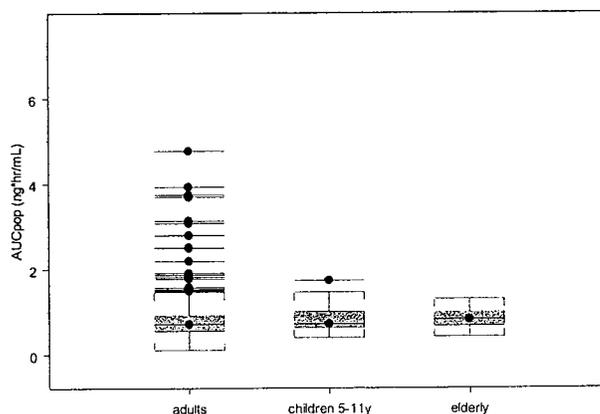


Figure 7. Individual post-hoc AUC (ng*hr/mL) (normalized to 160 μg) as a function of age (n= 444, 37 and 18 for adults, children and elderly, respectively) (data from population PK/PD analysis).

2.3.1.3 Do race, gender, and disease status affect the PK and PD of the drug? What dosage regimen adjustments are recommended for each of these subgroups?

Race

A meta-analysis of data from healthy young Caucasian and Japanese subjects was conducted using data from 11 studies. Statistical evaluation of the ratio of geometric means for C_{max} and AUC_{0-∞} values of RM1 in Caucasians and Japanese following single inhalation of 800 µg ciclesonide yielded point estimates (90% confidence interval) of 0.87 (0.77, 0.99) and 0.90 (0.77, 1.05), respectively, indicating no clinically relevant difference in the systemic exposure. Based on population PK analysis, the mean systemic exposure (AUC_{pop}) in the Black population (3.1%) and Others population (11.3%) was significantly lower (60% and 70%, respectively) than that in the White (74.2%) population. This difference may not be clinically relevant since the dose-exposure response was flat in the range of doses tested. The AUC_{pop} in the Japanese population (11.3%) was 20% higher than that in the White population.

Gender, Height, and Asthma Severity

Based on population pharmacokinetic analysis, asthma severity, and gender did not influence RM1 pharmacokinetics. Also, there was no trend of change in cortisol AUC with respect to RM1 AUC for healthy subjects and asthmatics. 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 section 2.3.1.5 for more details about the effect of liver impairment on the PK of the drug).

The above mentioned population PK/PD analysis of ciclesonide and RM1 included data from 12 Phase I, 3 Phase III studies in adults, and 2 Phase III studies in pediatrics. Phase I studies had extensive PK/PD data after administration of ciclesonide. Phase III studies included sparse PK samples (-1.5, 1, 2.5 and 6-10 hours following administration). There were a total of 635 subjects in this analysis with 2750, 5238 and 4470 observation records for ciclesonide, RM1 and cortisol concentrations, respectively. A one-compartment body model with first order absorption adequately described the RM1 concentration-time profile. The estimates of CL and V_d when standardized to a 70 kg subject were 302 L/h and 1310 L, respectively. 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 CL, V_d and F (bioavailability), wherever appropriate. Identification of relevant covariates was based on step-wise backward elimination method. For 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_{trough}) at dose interval were estimated.

2.3.1.4. Does renal impairment affect the PK of the drug and its major metabolite? Is dosage regimen adjustment recommended?

The effect of renal impairment on the PK of ciclesonide and RM1 was not evaluated. The rationale provided by the sponsor is that ciclesonide (and its metabolite, RM1) is an inhaled drug with a wide therapeutic index that is mainly eliminated by the hepatic and/or biliary route. In fact, in a mass balance study total radioactivity was predominantly excreted through the feces, both after oral (77.9%) and after intravenous (65.95%) administration suggesting urinary excretion may not be an important route of elimination. In addition, plasma protein binding was not altered when plasma from subjects with renal impairment was spiked with RM1 (at a concentration of 5.0 ng/mL, the protein binding of RM1 in the predose plasma samples varied between 97.5-99%).

2.3.1.5 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The C_{max} and $AUC_{0-\infty}$ of ciclesonide and its metabolite in patients with moderate and severe hepatic impairment (HI) increased in the range of 1.4-fold to 2.7 fold compared to that observed in healthy subjects (Figure 8). Also, the $T_{1/2}$ of RM1 increased in patients with moderate and severe HI by 2.3 hr and 4.6 hr, respectively, as compared to that in healthy controls. This data should be interpreted with caution due to the inconsistency of results in moderate and severe HI patients. Dose adjustment in this population is not needed.

The above findings come from study 210/2000. This was an open label, single dose, 3-parallel-group study comparison in 24 subjects with different degrees of HI (8 healthy, 8 with severe HI and 8 with moderate HI). Patients received 1600 μ g of ciclesonide.

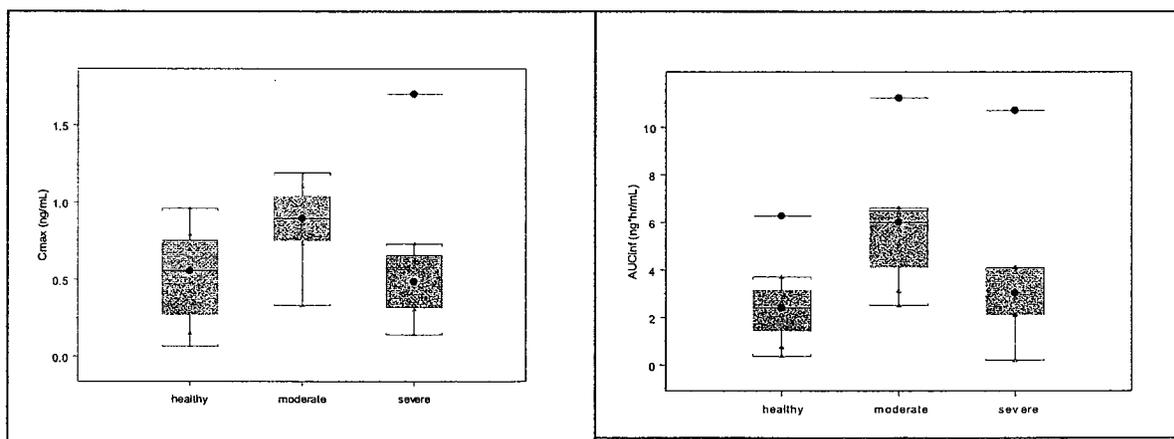


Figure 8. Individual C_{max} and $AUC_{0-\infty}$ values for RM1 in healthy volunteers and in patients with moderate and severe HI following single inhalative doses of ciclesonide 1600 μ g (data from study 210/200)

2.3.1.6 What pregnancy and lactation use information is there in the application? None

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of herbal products, diet, smoking and alcohol used was not evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

In-vitro metabolism studies using human microsomes indicated that RM1 is mainly metabolized by CYP3A4 although CYP2D6 is also involved. Therefore, substrates, inhibitors or inducers of these enzymes may affect the PK of RM1. The sponsor did not conduct DDI studies to assess the effect of such drugs on the PK of RM1, except the effect of erythromycin.

Ciclesonide and RM1 did not affect the activity of the major CYP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Therefore, no major effects of ciclesonide should be expected on the PK of other drugs.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Yes. The following is a summary of the findings related to the investigation of the metabolism of ciclesonide (Figure 9) by human liver microsomes (incubation with pooled human liver microsomes, incubation with microsomes of individual donors, in the presence of chemical inhibitors, and with supersomes containing expressed human P450s):

- The biotransformation of ciclesonide is likely to be catalyzed by an esterase enzyme which has not been identified.
- It appears that RM1 is the major active metabolite that results from the biotransformation of ciclesonide. However, this hypothesis is inconclusive since mass balance studies showed that only 20% of total radioactivity corresponds to RM1. In addition, the metabolite M9, which pharmacological potency is unknown, was as abundant as RM1 in plasma samples.
- The biotransformation of RM1 appears to be predominately catalyzed by CYP3A4 (83%), although CYP2D6 (~30%), and to a lesser extent CYP2C8 (11%) are also involved. However, a major involvement of CYP3A4 on the metabolism of M1 is inconclusive since the correlation data failed to indicate the extent of CYP3A4 involvement in the biotransformation of M1, although inhibition studies showed the contrary. On the other hand, CYP4A11 correlated more strongly with rates of M3 formation than any of the other major human P450 isoforms, but inhibition studies showed the contrary.

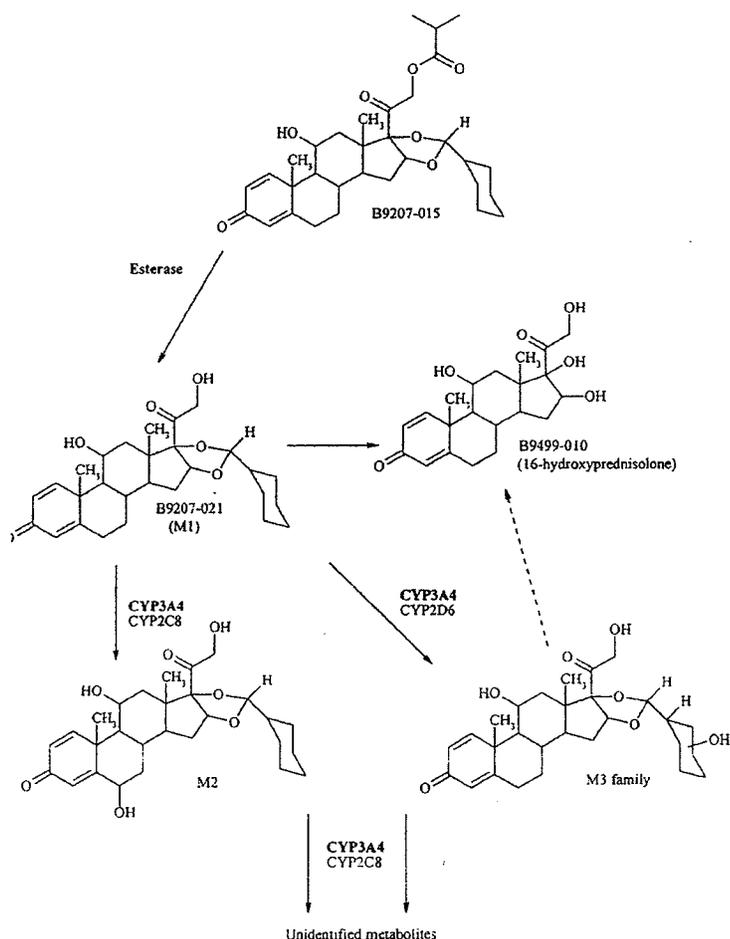


Figure 9. Sponsor's proposed metabolic pathway of ciclesonide

2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

At concentrations as high as 3 μ M, RM1 failed to produce significant direct or metabolism-based inhibition of cytochrome CYP450s in pooled human liver microsomes (Tables 12, 13). The potential of ciclesonide to act as an inhibitor of CYP enzymes was not evaluated.

Table 12. Results of metabolism-based inhibition potential of RM1 on CYP450 enzyme expressed as percent remaining enzyme activities in HLM

CYP450 Enzyme	RM1 Metabolite of Ciclesonide (Ciclesonide RM1)	
	Pre-incubation w/o NADPH	Pre-incubation with NADPH
CYP1A2	100	88
CYP2A6	100	99
CYP2C9	100	100
CYP2C19	100	96
CYP2D6	100	80
CYP2E1	100	103
CYP3A4 (Midazolam)	100	114
CYP3A4 (Testosterone)	100	102

Table 13. Results of direct inhibition potential of RM1 on CYP450 enzymes expressed as percent remaining enzyme activities in HLM

CYP450 Enzyme	RM1 Metabolite of Ciclesonide (Ciclesonide RM1)					Positive Control
	0.3 nM	3.0 nM	30 nM	300 nM	3000 nM	
CYP1A2	99	100	99	98	98	8.5
CYP2A6	101	88	88	97	87	22
CYP2C9	97	95	90	94	89	9.1
CYP2C19	101	97	96	90	80	56
CYP2C6	95	90	60*	98	98	1.3
CYP2E1	97	98	100	98	99	58
CYP3A4 (Midazolam)	99	97	76	85	86	<5.4
CYP3A4 (Testosterone)	94	97	88	76	89	6.4

*Outlier, not used for calculation.

Ciclesonide at therapeutic serum concentrations is not likely to induce CYP1A2, CYP2C9, and CYP 3A4. The lack of effect of ciclesonide on CYP2C19 reported is questionable since lower concentration (25 μ M) than those recommended for rifampin were used.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

This was not evaluated by the sponsor.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes. Ciclesonide may be administered concomitantly with other glucocorticoids and beta agonists. DDI with other glucocorticoids was not determined. The DDI interaction with formoterol was evaluated (see below) and the effect of albuterol was evaluated using population PK analysis.

2.4.2.7 What is the effect of ciclesonide on the PK of other drugs? What is the effect of other drugs on the PK of ciclesonide?

In-vitro metabolism studies using human microsomes indicated that RM1 is mainly metabolized by CYP3A4 although CYP2D6 (30%), and to a lesser extent CYP2C8 (11%) are also involved. Therefore, inhibitors or inducers of these enzymes may affect the PK of RM1. The sponsor did not conduct drug-drug interactions to assess the effect of CYP2D6 inhibitors on the PK of ciclesonide. As an

3A4 inhibitor, the sponsor choose to use erythromycin, despite our recommendation for the use of ketoconazole.

DDI with Albuterol

Based on population PK analysis, the RM1 clearance and volume of distribution values for subjects with (98 subjects) and without (512 subjects) coadministration of albuterol were similar.

DDI with Erythromycin

- The systemic exposure of ciclesonide and its metabolite in healthy subjects receiving a single dose of ciclesonide 800 µg was not statistically significantly altered by its coadministration with erythromycin 500 mg oral single dose. The arithmetic mean C_{max} and AUC of ciclesonide decreased in the presence of erythromycin by 17% and 5%, respectively. The arithmetic mean C_{max} and AUC of RM1 increased in the presence of erythromycin by 5% and 12%, respectively.
- The systemic exposure of erythromycin in healthy subjects receiving a single dose of 500 mg was not statistically significantly altered by its coadministration with ciclesonide 800 µg single dose. The arithmetic mean C_{max} and AUC of erythromycin decreased in the presence of ciclesonide by 24 % and 21%, respectively.

The above findings come from study 56E/99. This study was conducted according to a randomized, open, 3-period change-over design. In one study period, the subjects (18) received ciclesonide alone and in another study period, the subjects received erythromycin alone. In a third study period, both drugs were given together.

DDI with formoterol

- The systemic exposure (AUC and C_{max}) of ciclesonide and its metabolite in healthy subjects receiving a single dose of ciclesonide 800 µg was not statistically significantly altered (<23% decreased) when coadministered with formoterol 24 µg single dose.
- The cumulative urinary excretion of formoterol in healthy subjects receiving a single dose of 24 µg was not statistically significantly altered (8% decreased) when coadministered with ciclesonide 800 µg.

These findings come from study 56E/96, which was an open, randomized, 3-period-cross-over study in 24 healthy volunteers

2.4.2.8 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Yes. The sponsor claims that RM1 is the major product of ciclesonide metabolism and that it is the major circulating metabolite in plasma. However, data from in vitro studies using human hepatocytes and metabolite profiling in human plasma of subjects who received ciclesonide showed the existence of other metabolites which radioactivity accounts for more than 80% of the total radioactivity. M9 and RM1 appear to be the mayor circulating metabolites in plasma 0.25 hr following administration. However, metabolic profiling was conducted up to 0.5h, therefore, the existence of other metabolites beyond this period is unknown. In addition, no metabolic profiling was conducted in faeces which is the mayor route of elimination of ciclesonide.

In-vitro metabolism studies using human microsomes indicated that RM1 is mainly metabolized by CYP3A4 although CYP2D6 (30%), and to a lesser extent CYP2C8 (11%) are also involved. The sponsor did not conduct drug-drug interactions to assess the effect of CYP2D6 inhibitors on the PK of ciclesonide, and the effect of ketoconazole, a potent CYP3A4 inhibitors is unknown.

The protein binding for RM1 was higher than 98.5%; however this value should be interpreted with caution because of the relatively high non-protein binding reported in this study and because the hematocrit reported was much lower than normal blood. Also, DDI studies with drugs that displace binding to proteins were not conducted.

FHP018, FHP026 and FHP027 and all the Phase III studies were analyzed using this method. The new method also uses [redacted] that can inhibit the esterase activity and hence lower the conversion of ciclesonide into ciclesonide metabolite during [redacted]. The lower limit of quantification was set at 25 pg/ml for ciclesonide and 10 pg/mL for RM1. The upper calibration limit for both analytes was [redacted] pg/mL. Calibration curve range from [redacted] pg/mL for ciclesonide and [redacted] pg/mL for RM1. The calibration curves for ciclesonide and RM1 were linear with a coefficient of correlation equal or better than [redacted] for ciclesonide and equal or better than [redacted] for RM1. QC nominal concentrations were [redacted] and [redacted] pg/mL for ciclesonide and [redacted] and [redacted] pg/mL for RM1.

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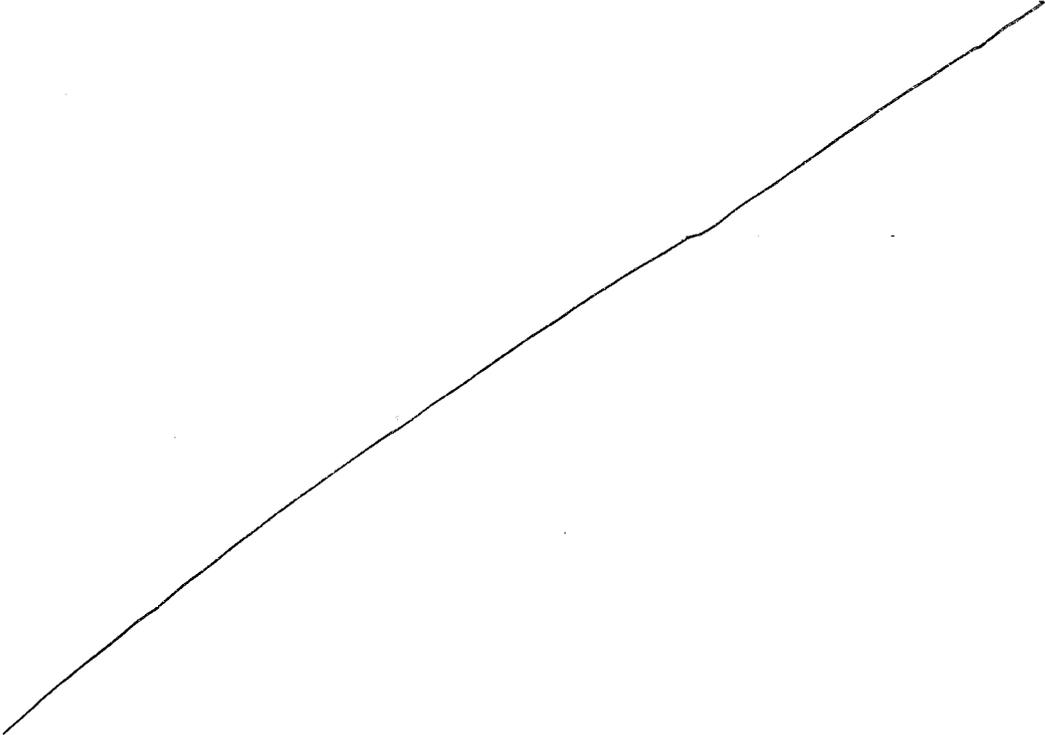
The accuracy, intra- and inter-day precision were acceptable for all the methods (<15% Bias or %CV) for in-study validation information

Cortisol Determination

For Phase I studies, quantitative assay of serum cortisol was measured using a commercially available fluorescence polarization immunoassay [redacted]. The lower limit of quantitation was 2.5 µg /dL (25 ng/mL). For Phase III studies, quantitative assay of serum cortisol was conducted using radio immunoassay (RIA). This assay was used to measure the cortisol level in human serum/urine in all clinical Phase III PK/PD studies. The LLOQ was 20 nM. The calibration range was from [redacted] nM. The cortisol concentrations in human serum samples were determined using radioimmunoassay (RIA) with the calibration range from [redacted] nM.

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3. LABELING COMMENTS



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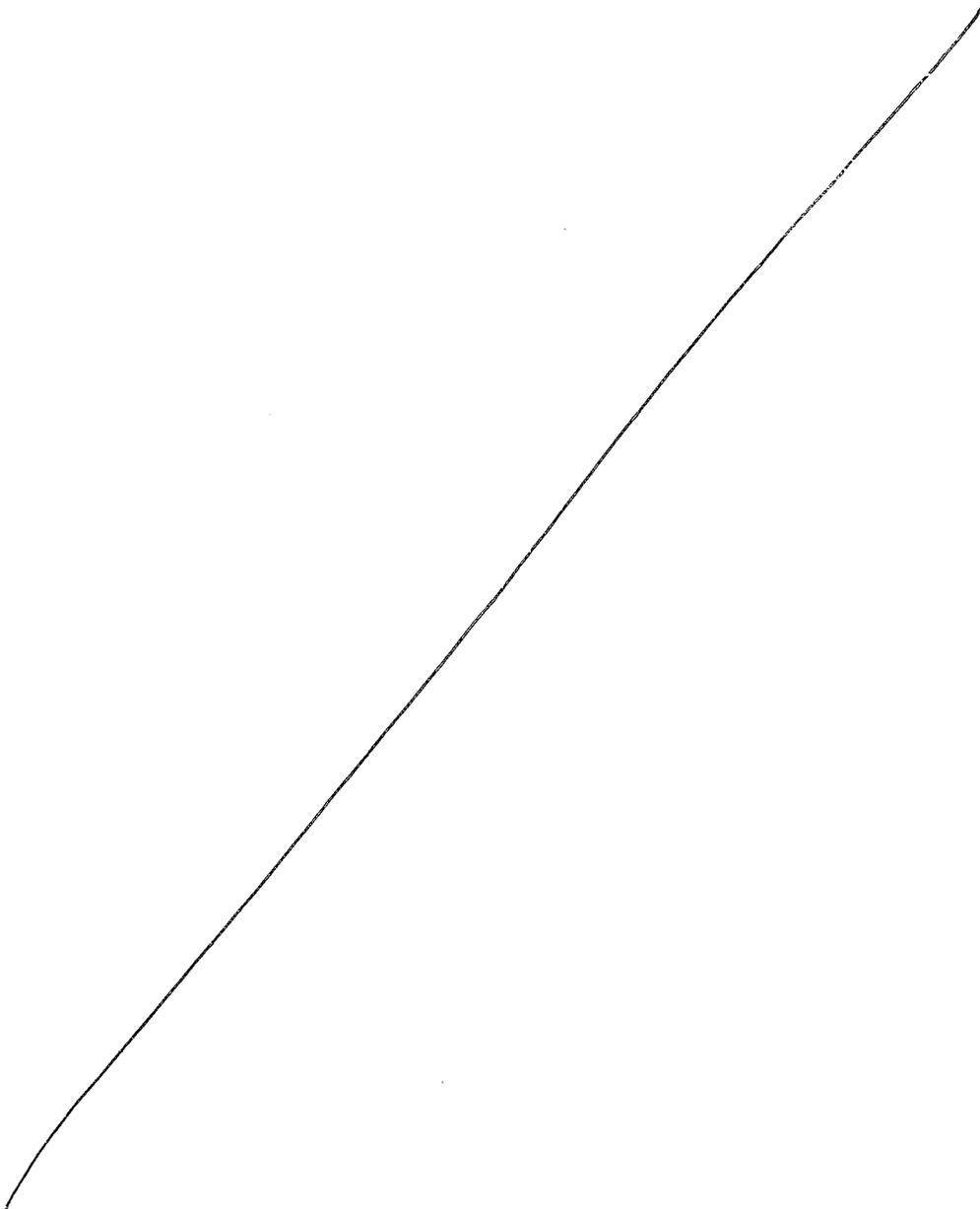
20 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)



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4.2 Individual Study Review

“A study to investigate the pharmacokinetics and metabolism of ciclesonide after single intravenous and oral administration of ^{14}C -B9207-015 to six healthy volunteers”

Study No.

BY9010/FHP021

Investigator(s) and Center(s): _____

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Report date:

22/06/99

OBJECTIVE

- to investigate the absorption, pharmacokinetics and metabolism of ¹⁴C-radiolabelled B9207-015 (ciclesonide) after single intravenous and oral administration to six healthy volunteers.

METHODOLOGY

This was a single-centre, single dose, open-label, two-way crossover study in six healthy young male volunteers with a washout of at least 14 days between drug administrations.

Eligibility screening and follow-up:

Clinical laboratory, full physical examination, ECG; at eligibility screening: drug screening, HBsAg, anti-HCV and anti-HIV 1/2 .

Observation period

In clinic from -17 h up to 176 h (afternoon day 8); the stay in the clinic was to be prolonged by maximally 3 days in case total ¹⁴C-radioactivity was >50 dpm/mL in urine or >75 dpm per 400 mg homogenized faeces sample.

No. of Subjects.

Six (6) healthy young male volunteer, ages 18-45 yrs. (mean 27.3 ± 7.4 yrs., range: 19-40 yrs.) and weight within 15% deviation from normal range (mean: 72.6 ± 6.2 kg, range: 66-84 kg)

Test product:

After a 10-hour overnight fast, a single oral dose of ciclesonide 8 mg (1.48 MBq/40 mCi; target dose) as a capsule or a single intravenous dose of 0.64 mg per 20 mL (1.48 MBq/40 mCi) as a 10-minute infusion was to be administered.

The Batch No. for human serum albumin solution for intravenous infusion was FH/2/64 and for the capsule for oral administration was FH/2/57.

Blood sampling

- Plasma for ¹⁴C-total radioactivity: pre-dose and at 10, (iv. in addition: 15) and 20 min and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 30, 36, 48, 72, 96, 120, 144 and 168 h after drug administration;
- whole blood for ¹⁴C-total radioactivity: pre-dose and 0.5, 1, 3, 6, 10 and 24 h after drug administration;
- serum for parent compound and principal metabolite: pre-dose, 10, (i.v. in addition: 15) and 20 min and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 30 h after drug administration;
- serum for metabolite(s) identification: 0.5 and 2 h after drug administration

Urine Sampling

- pre-dose and 0-4, 4-8, 8-12 and 12-24 h after drug administration; thereafter in 24-hour intervals until discharge

Faeces sampling

- blank and quantitatively in 24-hour pooled fractions up to 168 h after dosing

Safety assessments

- adverse events, vital signs and ECG: daily during the stay in the clinic

Analytical Method

The plasma, whole blood, urine and faeces samples were analyzed for total radioactivity using a liquid scintillation counting method.

Serum concentrations of ciclesonide and metabolite were determined using an automated for sample preparation and high pressure liquid chromatography with spectrometric detection.

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DATA ANALYSIS

ADME Assessments

Individual and mean excretion and metabolism data were presented in this report. Statistical analysis was been limited to calculation of means and standard deviations only. The total radioactivity in each collection of urine and faeces has been expressed as a percentage of the total administered radioactive dose. The total radioactivity in plasma has been expressed as ng equivalents per mL of plasma.

The drug-related components in urine and faeces have been quantified in terms of a percentage of the administered radioactive dose. The drug-related components in plasma were quantified in terms of the percentage of total plasma radioactivity, and as ng equivalents of ciclesonide per mL.

Pharmacokinetic Data Analysis

For total radioactivity: C_{max}, t_{max}, k_{el}, t_{1/2}, AUC_{last}, and AUC_{inf}, A_{urine}, A_{faeces} and A_{total} were determined.

For ciclesonide and its metabolite C_{max}, t_{max}, k_{el}, t_{1/2} AUC_t and AUC_{inf} were calculated using non-compartmental analysis.

RESULTS

Assay Performance

For the faeces samples, the mean (±SD) t-combustion factor was 1.05 (0.04). The precision (CV%) for the oral medication and intravenous medication quality control samples was ~~—~~ and ~~—~~ %, respectively. The accuracy (bias) was ~~—~~ and ~~—~~ % respectively. The precision for the plasma level, based on the quality control results, was 3.5%, 3.4% and 5.4%, respectively. The accuracy was 3.5%, -1.1% and -1.0%, respectively.

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The precision for the whole blood was 6.7%, 5.1% and 2.8%, respectively. The accuracy was -5.0%, -4.1% and -5.4%, respectively.

The precision for the urine was 4.6%, 2.0% and 2.5%, respectively. The accuracy was -4.7%, 2.4% and -5.1%, respectively. Results of duplicate assays of randomly selected samples compared to original results gave a mean relative difference of 3.8%.

The precision for the faeces was 7.1 %, 1.4% and 1.6%, respectively. The accuracy was 3.0%, 2.3% and -2.8%, respectively.

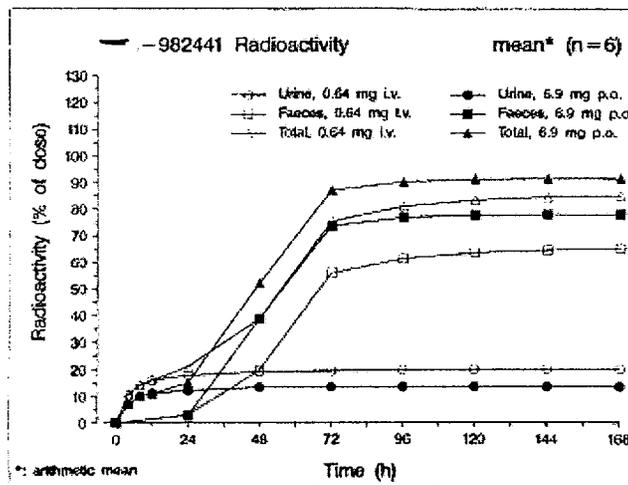
ADME Evaluation

Results on excretion of total ¹⁴C-radioactivity in urine and faeces

The mean cumulative excretion profiles of radioactivity in urine, faeces and of total radioactivity are presented in Figure 1. Data of mean cumulative amounts of excreted radioactivity are summarized in Table 1.

Table 1. Mean cumulative excretion of ¹⁴C-radioactivity (% of dose) after administration of ¹⁴C-ciclesonide as an i.v. solution and single oral dose

PARAMETER	6.9 mg of ¹⁴ C-ciclesonide p.o.		
	mean	min	max
A _{urine} (% of dose)	13.5	11.1	14.7
A _{faeces} (% of dose)	77.9	67.1	81.4
A _{total} (% of dose)	91.7	81.8	94.4
	0.64 mg of ¹⁴ C-ciclesonide i.v.		
A _{urine} (% of dose)	20	9.1	23.5
A _{faeces} (% of dose)	65.95	55.9	75
A _{total} (% of dose)	85.95	78.5	98.3



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Figure 1. Mean cumulative excretion of radioactivity in urine and faeces after administration of ¹⁴C-ciclesonide as an i.v. solution of 0.64 mg and single oral dose of 69 mg.

Results Total Radioactivity on Plasma and Whole Blood

Mean plasma radioactivity concentration profiles are presented in Figures 2. As the whole blood radioactivity concentrations were above the limit of detection from 0.5 until 6 hours after intravenous administration and below the limit of detection at all time points after the oral administration, these data were not plotted. Comparison of the total radioactivity concentrations for plasma and whole blood indicates that there is (almost) no accumulation in blood cells: plasma concentrations between 0.5 - 6 hours post-dose following the intravenous administration

are approximately a factor 1.5-1.6 higher than for whole blood, as can be expected on the basis of the plasma/whole blood volume ratio.

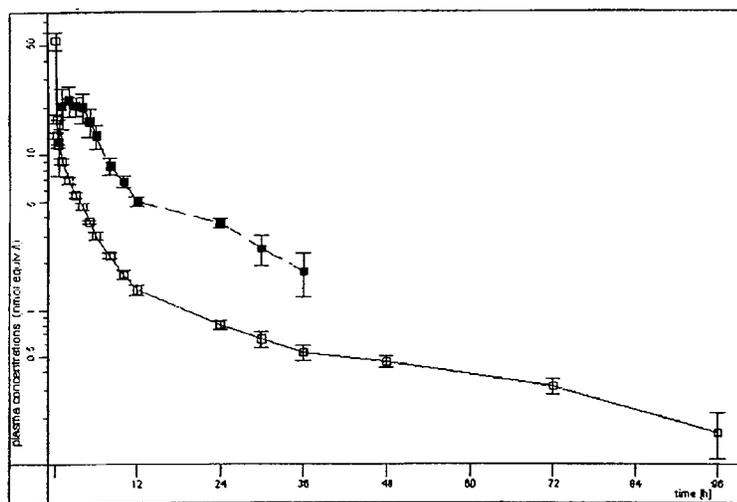


Figure 2. Mean plasma concentrations of total radioactivity in 6 healthy subjects following a single oral dose (close squares) of 6.9 mg or single i.v. (open squares) dose of 0.64 mg of C14-ciclesonide.

The geometric mean for C_{max} of total radioactivity following oral administration was 30.1 nmol equiv/L (range 12.8-41.9 nmol/L) with a t_{max} ranging from 1.0-4.0 h. Radioactivity in plasma could be measured up to 48 h after oral treatment, whereas for the i.v. treatment, radioactivity in plasma was profiled up to 120 h. However, due to the low specific radioactivity of the oral dose, the plasma concentration is higher at 48 h post-dose as compared to the intravenous treatment (Figure 2).

Based on geometric mean plasma AUC of total radioactivity adjusted to dose, about 24.5% of the administered dose was absorbed following oral administration of ¹⁴C-B9207-015. Results from the ANOVA on bioavailability are summarized in Table 2.

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Table 2. Summary table of ANOVA results on absorption

parameter	treatment*	mean**	point estimate	90% confidence interval of ratio (%)***
AUC _{0-∞} (ng equiv.mL ⁻¹ .h)	A	16.02****	0.25	0.22 - 0.29
	B	63.90		
A [*] _{intrc} (% of dose)	A	13.50	0.68	0.40 - 0.95
	B	20.00		

* A = 6.9 mg p.o. ¹⁴C Ciclesonide, B = 0.64 mg i.v. ¹⁴C Ciclesonide

** geometric mean for AUC; arithmetic mean for A^{*}_{intrc}

*** 90% confidence interval for the ratio of (geometric) means of A (test) and B (reference) (from ANOVA on log-transformed data)

**** dose adjusted with 0.64 mg as reference dose (uncorrected value: 172.69 ng equiv.mL⁻¹.h)

Pharmacokinetics of Ciclesonide (B9207-015) and its Metabolite (RM1:B9207-021)

For the metabolic profiling data sets of serum ¹⁴C-89201-015 and ¹⁴C-89207-021 and plasma total radioactivity were analyzed.

Bioanalytical Performance

Calibration data, quality control data and chromatograms indicated that the method performed acceptably during the sample analyses. However, the LLQ for B9207-015 was raised to 50 ng/L due to an interfering peak. Intra-batch precision values, based upon coefficients of variation of quality control samples (60, 800, 1600 pg/mL), were less than or equal to 15% for B9207-015 and 10% for B9207-021. Intra-batch accuracy of quality control samples ranged from 95% to 105% for B9207-015 and from 95% to 105% for B9207-021.

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Following oral administration of ciclesonide powder capsules, B9207-015 was not detected in any of the serum samples. Serum concentrations of B9207-021 following oral doses of 6.9 mg were mostly below or near the LLQ. Only in one case (Subject 02), an expected serum concentration vs. time profile was obtained with an individual C_{max} of 0.32 nmol/L (0.153 µg/L).

Mean (SFM) serum concentration vs. time profiles of the parent compound and the metabolite following single intravenous administration of ciclesonide are shown in Figure 3. For a summary of mean pharmacokinetic parameters see Table 2. The sum of the AUCs of the parent compound and the metabolite amounts to 19.3% of the total AUC. Therefore, approximately 80% may be resulting from one or more yet unknown metabolites.

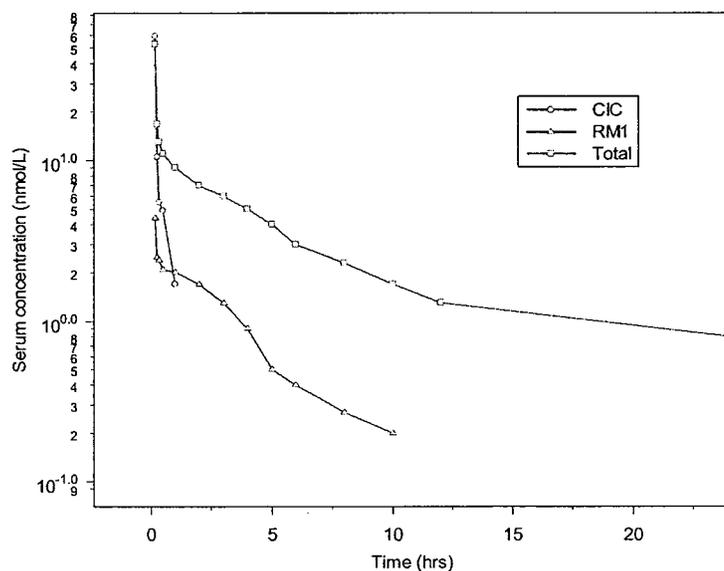


Figure 3. Mean serum concentrations for ciclesonide and RM1 and concentration of total radioactivity in plasma in 6 healthy subjects following a single i.v. dose of radioactive ciclesonide.

Table 3. Geometric mean serum PK parameters of ciclesonide and its metabolite after single i.v. of radioactive ciclesonide

Parameter (units)	B9207-015			B9207-021			Sum of both
	geometric mean	min	max	geometric mean	min	max	
c_{max} (nmol.L ⁻¹)	53.87	23.70	89.25	4.05	2.04	7.44	57.92**
t_{max} (h)	0.17	0.17	0.17	0.31	0.17	1.00	
AUC _{0-∞} (nmol.L ⁻¹ .h)	11.63	7.63	16.81	9.70	7.25	12.31	21.33
$t_{1/2}$ (h)	0.36	0.20	0.63	3.40	2.30	4.90	

* mean for t_{max}

** c_{max} at different time

Calculation of AUC of B9207-021 was possible only for Subject 02 for both treatments. A ratio comparison of the AUC of B9207-021 following oral and intravenous administration resulted in an oral bioavailability of about 1.8% for this subject. This value represents an estimation of the maximum oral bioavailability. For all other subjects, the oral bioavailability is probably considerably below 1.

SUMMARY OF FINDINGS

- The excretion of radioactivity following a single oral dose of 6.9 mg ciclesonide and single intravenous administration of 0.64mg ciclesonide was almost complete (total average recovery 91.4% and 85.95% respectively). ¹⁴C-B9207-015 was predominantly excreted through the faeces, both after oral (77.9%) as after intravenous (65.95%) administration, indicating that excretion through bile is the major route of elimination.
- B9207-015 showed no accumulation in red blood cells, as could be concluded from the high plasma/whole blood ratio.

- The absorption of ¹⁴C-ciclesonide was 24.5% based on dose-normalized for radioactivity.
- Oral bioavailability based on AUCs of RM1 could only be determined for one subject and was about 1.8%.
- Parent compound ciclesonide and RM1 constitute 19.3% of radioactivity found in plasma; approximately 80% of the ¹⁴C radioactivity AUC may be resulting from one or more yet unknown metabolites.

COMMENTS

- a) Validation of the analytical methods used in this study is incomplete. No raw data, including calibration curves and examples of chromatograms were submitted. For a description on current FDA thinking on assay validation, you are referred to: V.P. Shah, et al. *Pharm Res.* Vol 9, No. 4, 1992 and to the bioanalytical methods validation guidance for industry.
- b) The sum of the AUCs of the parent compound and the metabolite accounts for 19.3% of the total AUC. Provide metabolic profiling of the remaining 80% of AUC.

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“Metabolism of ¹⁴C-Ciclesonide and Its Metabolite in Human Hepatocytes and Profiling of Plasma and Urine Samples from ¹⁴C-Ciclesonide Clinical Study”

Report No.: — 01827
Protocol No.: 2002 0014
Study Director: _____
SB Document Number: SB-207499/RSD-100G26/
NDA Section: 5A Pharmacology studies (Drug Metabolism)
Pages: 1-83
Completion Date: 05 February 2002

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Objective

- to determine the metabolic rates and the preliminary *in vitro* biotransformation profiles of ¹⁴C-ciclesonide (BYK20426) and its metabolite ¹⁴C-RM1 (BYK20432) in human hepatocytes and,
- to profile and identify or characterize the prominent metabolites of ciclesonide in urine and plasma samples from subjects following oral and/or IV administration of ciclesonide

Materials

Analytes and Chemicals

- ¹⁴C-ciclesonide; purity: >98.4%; lot No: B9207-015
- ¹⁴C-RM1; purity: >98.3%; lot No: B9207-021
- A cold reference chemical of metabolite RM1 was also provided by the Sponsor.
- hippuric acid
- reference chemical was purchased from ~~_____~~ for identification of one metabolite.
- **Incubation System: Buffer:** Krebs-Henseleit (K-H) buffer, pH 7.4.

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Biomaterials

- Cryopreserved hepatocytes from humans (pooled from 2-4 males) were obtained from —

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Human Hepatocyte Incubation Mixtures

¹⁴C-Ciclesonide and its metabolite ¹⁴C-RM1 (BYK20432), at a concentration of 10 μM in incubation media, were separately incubated with human hepatocytes. Incubation mixtures were harvested at 0-, 1-, 2-, and 4-hr intervals for metabolic rate determination. The 4-hr incubation mixtures were also used for metabolite identification.

Human Urine and Plasma Samples

A total of 35 urine samples, collected from six subjects at intervals of 0-4 hr, 4-8 hr, and 8-12 hr after dosing, were supplied to — by the sponsor.

A total of 48 plasma samples were collected from each of the six subjects at 4 different intervals. The sample collection intervals ranged from 0.17 to 4 hr for IV dosing subjects and 0.5 to 8 hr for oral dosing subjects. However, only the 0.25 and 0.5 hr samples from IV dosing subjects contained sufficient radioactivity to merit analysis (samples from study: — 982441).

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Negative Control Incubation: Test articles (~10 μM) in Krebs-Henseleit buffer (pH 7.4) were incubated (in 1 well) in a 37 °C, 5% CO₂ and ~95% humidity incubator for 4 hr to determine the stability of the test articles in the buffer.

Positive Control Incubations: Two positive control incubations at 100 μM , one with 7-ethoxycoumarin (7-EC) and one with 7-hydroxycoumarin (7-HC) were carried out (1 well each). Each positive control substrate was separately incubated with rat, dog, monkey and human hepatocytes (~1 x 10⁶ viable cells/mL in Krebs-Henseleit buffer) in a 37 °C, 5% CO₂ and ~95% humidity incubator for 4 hr. At 0 and 4 hr, duplicate aliquots (0.1 mL) of the incubation mixture were transferred to separate containers and extracted with 0.4 mL of acetonitrile. The extracts were analyzed for the parent compound by HPLC.

METHODS

Hepatocyte Incubation

¹⁴C-Ciclesonide and its metabolite ¹⁴C-RM1 (BYK20432), at a concentration of 10 μM in incubation media, were separately incubated with human hepatocytes in a 37°C, 5% CO₂, and 95% humidity incubator. Incubations were carried out in ~~24~~ 24-well cell culture clusters with each well containing 0.5 mL of the incubation mixture.

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Metabolic Rate Determination

At 0, 1, 2, and 4 hr, duplicates of incubation mixture were harvested and mixed with acetonitrile. After centrifugation, each resulting supernatant was aliquotted for liquid scintillation counting to check recovery. Methanol was added to the mixture to obtain quantitative recoveries. The final mixture was re-centrifuged and the supernatant was analyzed for both ciclesonide and RM1 metabolite by LC/MS/MS. The HPLC system was interfaced to a ~~LC/MS/MS~~ Mass Spectrometer.

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Metabolite Profile

Wells containing ¹⁴C-ciclesonide or ¹⁴C-RM1 4-hr human hepatocyte incubation mixtures, were combined by test article for metabolite profiling and identification. The 0-4 hr interval urine samples from each subject were pooled according to oral and IV dosing group. Each pooled urine sample was directly analyzed by HPLC for metabolite profiling.

The amount of radioactivity in plasma samples was determined by liquid scintillation counting. Only the 0.25-hr and 0.5-hr IV dosing plasma samples contained enough radioactivity for metabolite profiling. Each pooled plasma samples was first acidified with formic acid and loaded onto an HLBTM cartridge. The loaded cartridge was washed and then air dried. Retained radioactivity was eluted from its respective cartridge with ~3.4 mL of acetonitrile. The resulting acetonitrile eluate was concentrated and reconstituted into methanol for analysis.

RESULTS

Enzymatic Activities in Human Hepatocytes

The metabolism of 7-EC and 7-HC was used to determine the enzymatic activities in human hepatocytes. After 4 hr of incubation, 45.6% of 7-EC and 47.5% of 7-HC was metabolized by human hepatocytes (Table 1). Thus, the human hepatocyte preparations used in this study were enzymatically active.

Table 1. Metabolism of 7-Ethoxycoumarin (7-EC) and 7-Hydroxycoumarin (7-HC) by Human Hepatocytes

Compound	PA (0 hr)	PA (4 hr)	% Metabolized
7-EC	715229	389303	45.6%
7-HC	576911	302853	47.5%

PA: Peak Area at 254 nm

Metabolic Rate of ¹⁴C-Ciclesonide and 14C-RM1 in Human Hepatocytes

The metabolic rates of ciclesonide and metabolite RM1 in the incubation mixtures were determined by LC/MS/MS using the multiple reaction monitoring (MRM) mode. The ion transitions were obtained and the collision energies were optimized to obtain suitable sensitivity. Ciclesonide was almost completely metabolized, mostly to RM1, within the first hr of incubation. Approximately 50% of RM1 was metabolized within the first hr of incubation (Figures 1 and 2).

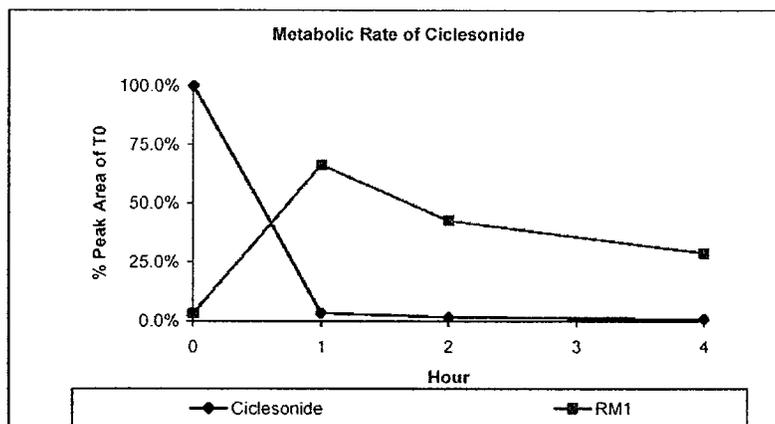


Figure 1. Metabolic rate of ciclesonide in human hepatocytes

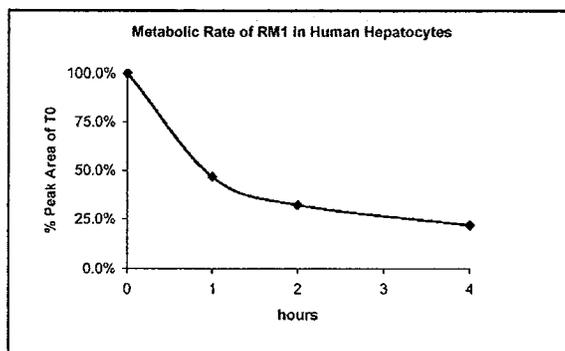
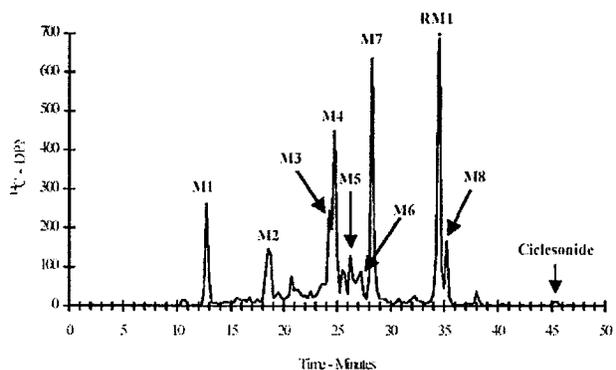


Figure 2. Metabolic rate of RM1 in human hepatocytes

Metabolite Identification

The metabolite identification and characterization were accomplished using 4-hr ^{14}C -ciclesonide incubation sample and 0-4 hr oral dose urine sample. Metabolite identification was focused on metabolites M1-M8 found in hepatocyte incubation samples (Figures 3 and 4) and metabolite M1 found in the urine samples (Tables 2 and 3).



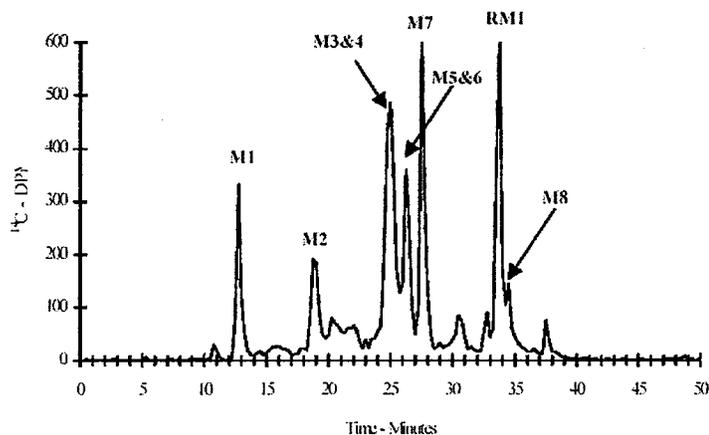
Run #: 01827006.D04

^{14}C Data

Peak	Start	Stop	R _t	dpm	%RUI	%Total	Peak	Start	Stop	R _t	dpm	%RUI	%Total
1	10.5	10.8	10.5	32	0.54%	0.52%	13	25.5	26.0	25.5	206	3.51%	3.32%
M1	12.3	14.0	12.8	394	6.71%	6.35%	M5	26.3	26.8	26.3	257	4.38%	4.14%
3	14.3	15.3	14.5	47	0.80%	0.76%	M6	27.0	27.8	27.3	212	3.61%	3.41%
4	15.5	16.8	16.8	106	1.81%	1.71%	M7	28.0	30.0	28.3	948	16.14%	15.27%
M2	18.0	19.0	18.5	397	6.76%	6.39%	17	30.8	30.8	30.8	20	0.34%	0.32%
6	19.3	20.0	19.5	100	1.70%	1.61%	18	31.3	31.3	31.3	10	0.17%	0.16%
7	20.3	21.0	20.8	166	2.83%	2.67%	19	31.8	33.3	32.3	103	1.75%	1.66%
8	21.3	21.8	21.3	104	1.77%	1.68%	RM1	33.5	35.0	34.5	1102	18.77%	17.75%
9	22.0	22.8	22.5	110	1.87%	1.77%	M8	35.3	35.8	35.3	194	3.30%	3.13%
10	23.0	23.8	23.5	176	3.00%	2.84%	22	38.0	38.3	38.0	52	0.89%	0.84%
M3	24.0	24.5	24.3	498	8.48%	8.02%	Cicl-	45.3	45.5	45.3	24	0.41%	0.39%
M4	24.8	25.3	24.8	614	10.46%	9.89%							

Total ^{14}C 6298 in RUIs 5872

Figure 3. Metabolite Profile of ^{14}C -Ciclesonide in Human Hepatocytes (4-Hr Incubation)



Run#: 01827007.D01

Peak	Start	Stop	R _f	dpm	%ROI	%Total	Peak	Start	Stop	R _f	dpm	%ROI	%Total
1	5.3	5.3	5.3	7	0.08%	0.07%	M7	27.3	28.5	27.5	1199	13.07%	12.77%
2	10.5	11.3	10.8	60	0.65%	0.64%	13	28.8	29.3	29.0	83	0.90%	0.88%
M1	12.3	14.0	12.8	631	6.88%	6.72%	14	29.5	31.3	30.5	368	4.01%	3.92%
4	14.3	14.8	14.5	42	0.46%	0.45%	15	31.5	32.0	31.5	63	0.69%	0.67%
5	15.0	17.3	16.0	200	2.18%	2.13%	16	32.3	33.0	32.8	206	2.25%	2.19%
M2	17.5	19.8	18.8	716	7.80%	7.62%	RM1	33.3	34.3	33.8	1336	14.56%	14.22%
7	20.0	21.3	20.3	371	4.04%	3.95%	M8	34.5	36.0	34.5	347	3.78%	3.69%
8	21.5	22.8	22.0	303	3.30%	3.23%	19	36.3	37.0	36.5	66	0.72%	0.70%
9	23.0	23.3	23.0	63	0.69%	0.67%	20	37.3	39.5	37.5	193	2.10%	2.05%
MB-4	23.5	25.8	25.0	1985	21.63%	21.14%	21	40.5	41.0	40.5	15	0.16%	0.16%
MS-6	26.0	27.0	26.3	903	9.84%	9.61%	22	48.5	49.0	48.8	18	0.20%	0.19%
Total ¹⁴ C:			9392	m ROIs:			9175						

Figure 4. Profile of ¹⁴C-RM1 in Human Hepatocytes (4-Hr Incubation)

Table 2. Metabolite Profile of Ciclesonide in Pooled IV Urine (peak no. 5 corresponds to M1)

Sample Name: 01827008.D02

Name	Start	Stop	R _f	dpm	%ROI	%Total
1	6.8	7.3	7.0	31	1.28%	1.15%
2	7.8	8.3	7.8	17	0.70%	0.63%
3	8.5	9.5	9.0	54	2.23%	2.01%
4	10.0	11.3	10.8	139	5.73%	5.17%
5	11.5	14.0	12.8	1042	42.97%	38.72%
6	14.3	14.8	14.8	64	2.64%	2.38%
7	15.0	15.5	15.3	123	5.07%	4.57%
8	15.8	16.3	15.8	101	4.16%	3.75%
9	16.5	17.3	16.5	78	3.22%	2.90%
10	17.5	19.3	18.8	197	8.12%	7.32%
11	19.5	20.3	19.5	64	2.64%	2.38%
12	20.5	21.5	21.0	70	2.89%	2.60%
13	21.8	22.5	22.0	79	3.20%	2.91%
14	22.8	23.8	23.3	132	5.11%	4.91%
15	24.0	24.3	24.0	61	2.52%	2.27%
16	24.5	25.0	24.5	68	2.80%	2.53%
17	25.3	26.3	26.0	69	2.85%	2.56%
18	27.8	28.5	28.3	76	3.18%	2.91%
Total ¹⁴ C:	2691		m ROIs:		2425	

Table 3. Metabolite Profile of Ciclesonide in Pooled Oral Urine (peak 5 corresponds to M1)

Sample Name: 01827008.D03							
Name	Start	Stop	R _t	dpm	%ROI	%Total	
1	7.0	8.0	7.0	32	1.86%	1.63%	
2	8.8	9.5	9.0	33	1.92%	1.68%	
3	9.8	10.3	10.0	16	0.93%	0.82%	
4	10.5	11.8	10.8	76	4.42%	3.87%	
5	12.3	14.0	12.8	1198	69.69%	61.06%	
6	14.3	17.0	15.3	131	7.62%	6.68%	
7	17.5	20.8	18.5	101	5.88%	5.15%	
8	21.0	21.5	21.3	20	1.16%	1.02%	
9	21.8	23.8	22.0	56	3.26%	2.85%	
10	24.0	24.3	24.0	18	1.05%	0.92%	
11	24.5	25.0	24.5	19	1.11%	0.97%	
12	25.3	26.0	25.8	19	1.11%	0.97%	
Total C:			1962	mROIs:		1719	

Ciclesonide, RM1, and the unidentified metabolite M9 were the major components found in the 0.25-hr plasma sample, with ciclesonide being the most abundant (Figure 5). In contrast, in the 0.5-hr sample RM1 predominated over ciclesonide, and many minor metabolites were found in the retention time region of M2-M7 (Figure 6).

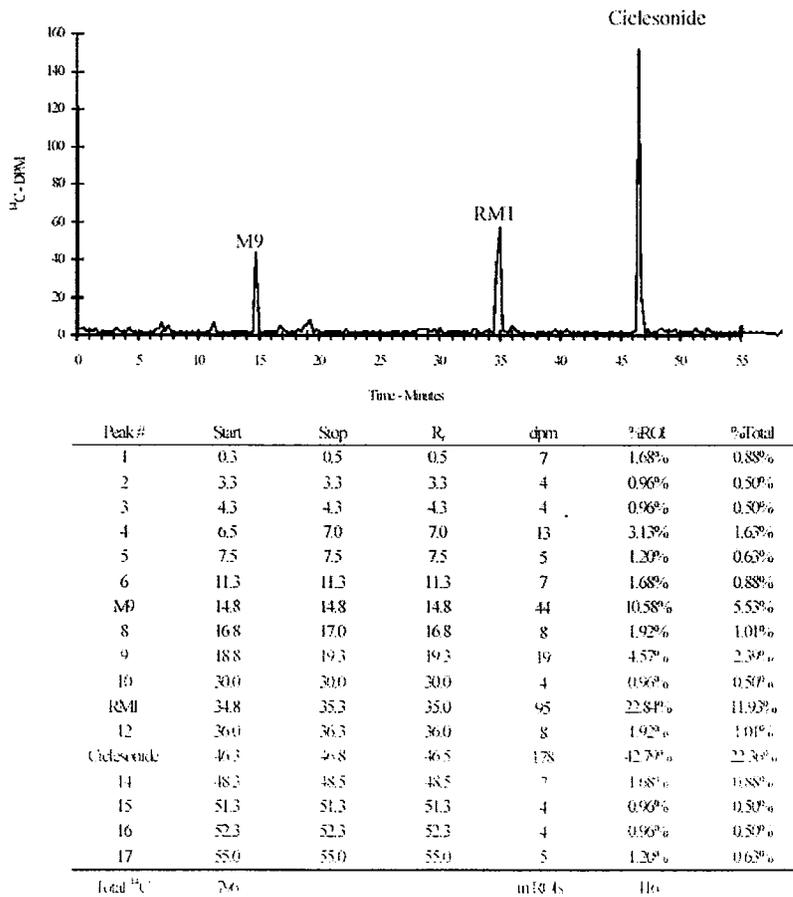
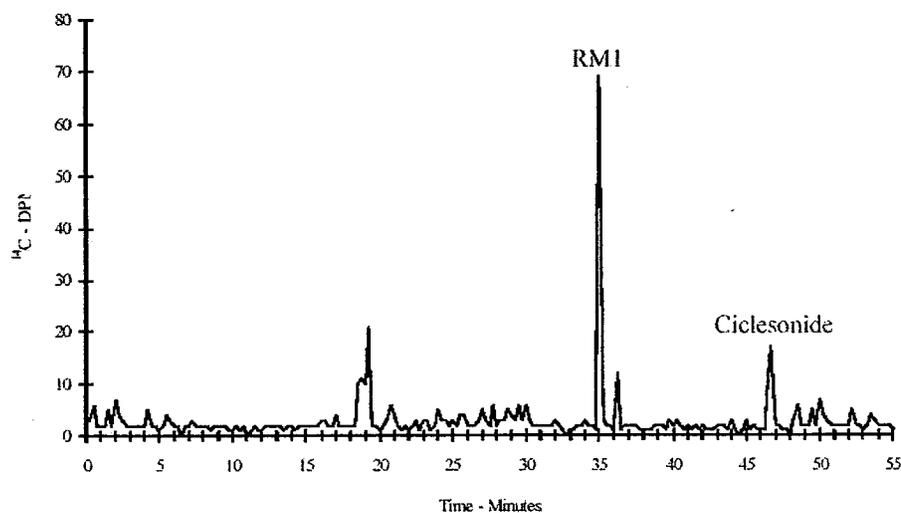


Figure 5. Metabolite Profile of ¹⁴C-Ciclesonide in Human Plasma (IV 0.25 Hr)



¹⁴ C Data																
Peak	Start	Stop	R _f	dpm	%ROI	%Total	Peak	Start	Stop	R _f	dpm	%ROI	%Total			
1	0.3	0.5	0.5	9	2.38%	1.29%	19	29.5	29.8	29.5	9	2.38%	1.29%			
2	1.5	1.5	1.5	5	1.32%	0.72%	20	30.0	30.3	30.0	9	2.38%	1.29%			
3	2.0	2.5	2.0	14	3.70%	2.01%	21	32.0	32.0	32.0	3	0.79%	0.43%			
4	4.3	4.3	4.3	5	1.32%	0.72%	22	34.0	34.0	34.0	3	0.79%	0.43%			
5	5.5	5.8	5.5	7	1.85%	1.01%	23	35.0	35.3	35.0	72	19.05%	10.34%			
6	7.3	7.3	7.3	3	0.79%	0.43%	24	36.3	36.3	36.3	12	3.17%	1.72%			
7	16.0	16.3	16.3	6	1.59%	0.86%	25	39.8	39.8	39.8	3	0.79%	0.43%			
8	17.0	17.0	17.0	4	1.06%	0.57%	26	40.3	40.3	40.3	3	0.79%	0.43%			
9	18.5	19.3	19.3	52	13.76%	7.47%	27	44.0	44.0	44.0	3	0.79%	0.43%			
10	20.5	21.0	20.8	13	3.44%	1.87%	28	45.0	45.0	45.0	3	0.79%	0.43%			
11	22.5	22.5	22.5	3	0.79%	0.43%	29	46.5	46.8	46.8	28	7.41%	4.02%			
12	23.0	23.3	23.3	6	1.59%	0.86%	30	48.3	48.5	48.5	9	2.38%	1.29%			
13	24.0	24.5	24.0	11	2.91%	1.58%	31	49.5	49.5	49.5	5	1.32%	0.72%			
14	25.0	25.0	25.0	3	0.79%	0.43%	32	50.0	50.5	50.0	14	3.70%	2.01%			
15	25.5	25.8	25.8	8	2.12%	1.15%	33	52.3	52.3	52.3	5	1.32%	0.72%			
16	26.8	27.3	27.0	11	2.91%	1.58%	34	53.5	53.8	53.5	7	1.85%	1.01%			
17	27.8	27.8	27.8	6	1.59%	0.86%	35	56.8	56.8	56.8	3	0.79%	0.43%			
Total ¹⁴ C:		696												in ROIs:		378

Figure 6. Metabolite Profile of ¹⁴C-Ciclesonide in Human Plasma (IV 0.5 Hr)

The proposed structures of metabolites M1- M7 are shown in Table 4. Metabolites M3 to M7 eluted at retention times of ~24-28 min. All of the ¹⁴C-peaks exhibited a common ¹⁴C-MH⁺ ion at *m/z* 489 suggesting a common ¹⁴C-molecular weight indicating that metabolites M3-M7 are mono-hydroxylated derivatives of RM1. M2 appears to be a di-hydroxylated metabolite of RM1.

According to the sponsor, metabolite M1 found in the hepatocyte samples exhibited the same retention time as that of the major component found in urine samples. Metabolite M1 from both hepatocyte and urine samples was isolated and purified by HPLC. The retention times and MS spectra of metabolite M1 and its methyl ester agree with those of hippuric acid and hippuric acid methyl ester. While radioactive M1 co-eluted with the hippuric acid reference chemical,

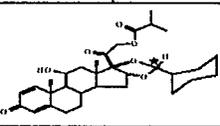
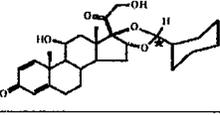
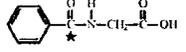
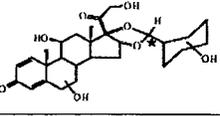
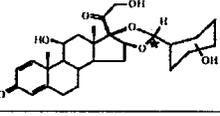
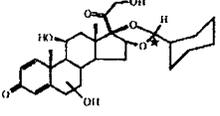
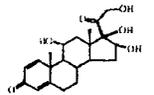
additional information from the hepatocytes yielded convincing evidence to support that M1 is indeed hippuric acid.

Metabolite Profiles

The ^{14}C -metabolite profiles of ciclesonide and RM1 human hepatocyte incubation mixtures are similar (Figures 3 and 4). Ciclesonide was metabolized to RM1, monohydroxylated RM1 (M3-M7), dihydroxylated RM1 (M2), and hippuric acid (M1).

The ^{14}C -metabolite profiles of IV and oral dosing urine samples contained one major metabolite (M1, hippuric acid). Identification of other minor metabolites was not attempted. According to the sponsor, the byproduct of the cleavage of ciclesonide to (ultimately) form hippuric acid would be 16-hydroxyprednisolone and this compound has been reported to be formed from ciclesonide by human liver microsomes. Thus, it is possible that 16-hydroxyprednisolone was present in these matrices but could not be detected by the radiodetection methods employed. There was insufficient MS information to confirm the presence of 16-hydroxyprednisolone in the incubation mixtures.

Table 4. Metabolites of Ciclesonide and RM1

ID	R _t (min)	MW	Structure or Proposed Structure
Ciclesonide	~46	540	
Metabolite RM1	~35	470	
Metabolite M1	~13	179	
Metabolite M2	~19	504	
Metabolite M3-M6	24-28	488	
Metabolite M7	29	488	
16-Hydroxy-Prednisolone (possible metabolite but not detected)	NA	376	

SUMMARY OF FINDINGS

- Ciclesonide was almost completely metabolized within the first hr of incubation with human hepatocytes.

- Approximately 50% of RM1 was metabolized within the first hr of incubation with human hepatocytes.
- Both CIC and RM1 were metabolized to mono- and di-hydroxylated forms of RM1. Hydroxylation occurred at the cyclohexane moiety and/or steroid moiety of the molecule.
- Metabolite Profiling of ¹⁴C-Ciclesonide in Human Hepatocytes (4-Hr Incubation) showed that RM1 (17.75% of total radioactivity), M7 (15.27%), M4 (9.89%), M1 (6.35%), M2 (6.39%) were the major metabolites present.
- Metabolite Profiling of ¹⁴C-RM1 in Human Hepatocytes (4-Hr Incubation) showed that RM1 (14.22%), M7 (12.77%), M3-4 (21.14%), M1 (6.72%), M2 (7.62%), and M5-6 (9.61%) were the major metabolites present.
- Hippuric acid (M1) was the only major metabolite found in 0-4-hr oral (61.%) and IV (38.7%) dose urine. The presence of this product was thought to originate from initial aromatization of the cyclohexane moiety to form benzoic acid.
- Ciclesonide (22.36%), RM1 (11.93%) and M9 (5.53%) were the major components found in the 0.25 hr IV plasma sample.
- In the 0.5-hr IV plasma sample, RM1 was the mayor peak (10.34% of total radioactivity). Other components in the 0.5-hr plasma sample also eluted at the retention time regions of hydroxylated RM1 (the major one contributed 7.47%) of the total radioactivity.

DISCUSSION

The assessment of the metabolic rate of ciclesonide in human hepatocytes showed that it is almost completely metabolized within the first hour. The sponsor claims that RM1 is the mayor product of ciclesonide metabolism and that it is the mayor circulating metabolite in plasma. However, data from in vitro studies using human hepatocytes and metabolite profiling in human plasma of subjects who received ciclesonide showed the existence of other metabolites which radioactivity accounts for more than 80% of the total radioactivity. M9 and RM1 appear to be the mayor circulating metabolites in plasma 0.25 hr following administration. Metabolic profiling was conducted up to 0.5h, therefore, the existence of other metabolites beyond this period is unknown. In addition, no metabolic profiling was conducted in faeces which are the mayor route of elimination of ciclesonide.

CONCLUSION

Ciclesonide is completely metabolized within the first hour of administration. RM1 appears to be the mayor product of metabolism of ciclesonide. However, the existence of other metabolites cannot be ruled out since the sponsor has not adequately characterized the metabolic profiling of ciclesonide.

"Investigation of the enzymology of metabolism by human liver microsomes"

DMPK Report No.: 241E/98
Protocol No.: BYG 010
Study Director: Nave, R.
Pages: 1-62
Issue Date: 24 Jan 2002

Objective

- To investigate the enzymes involved in the metabolism of ciclesonide by human liver microsomes

Materials

- [¹⁴C]B9207-015 (lot numbers FH/1/262 and FH/2/53), with a specific activity of _____, and [¹⁴C]B9207-021 (lot numbers L.J.1.1,17-50 and FH/2/105), with a specific activity of _____, were provided by the Study Sponsor, Byk Gulden Lomberg Chemische Fabrik GmbH.

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The sponsor also provided the following reference standards;

- B9207-015 (lot R01950),
- B9499-010 (16-hydroxyprednisolone. lot G139/1 77),
- B9207-021 (MI, lot R02043)
- M2,
- RL33, RL34 M3, and RL3I.
- The radiochemical purity of [¹⁴C]B9207-015 and [¹⁴C]B9207-021 were checked at _____ using TLC methods and when the purity was found to be <97%, the Sponsor's consent was sought to continue using the same batch of [¹⁴C]substrate prior to the incubation being conducted.

b(4)

Human Liver Microsomes

- Pooled human liver microsomes used for incubations with [¹⁴C]B9207-015 were supplied by the _____
- The 16 individual donor liver microsomes used for the correlation analysis were obtained from _____ and comprised of microsomes from individual donors 2, 7, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25. All of the microsomes were stored at -75°C until they were used in incubations with [¹⁴C]B9207-015, [¹⁴C]B9207-021 or substrates selective for CYP2C8, CYP2D6, CYP3A4 and CYP4A11.
- Microsomes containing expressed human P450 reductase and Cytochrome b5 and either CYP2C8, CYP2D6, CYP3A4 or CYP4A11 using baculovirus as a vector were obtained from the _____
- Insect cell control _____TM (P201) prepared from insect cells (BTI-TN-5BI-4) infected with wild type baculovirus were used by _____ to prepare these microsomes.

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b(4)

Measurement of microsomal protein concentration

Protein concentration in the pooled human liver microsomes and microsomes containing expressed human CYP2C8, CYP2D6, CYP3A4, CYP4A11 and control ~~_____~~ were determined by the method of Lowry *et al.*

b(4)

Measurement of microsomal cytochrome P450

Cytochrome P450 was assayed essentially as described by Rutten *et al.* (1987), a standardized protocol procedure derived from the original method of Omura and Sato (1964).

MICROSOMAL INCUBATIONS

Preliminary incubation of [¹⁴C]B9207-015 with pooled human liver microsomes

The preliminary incubations of [¹⁴C]B9207-015 with pooled human liver microsomes were undertaken to determine the optimum conditions to be used in subsequent incubations with microsomes from 16 individual donors and inhibitors. All reaction mixtures contained Na/K phosphate buffer, microsomal protein (0.5 mg/mL) and NADPH (2 mM) in a total volume of 990 μL.

Incubation of [¹⁴C]B9207-015 with microsomes from 16 individual donors

Conditions, components and methods were as for preliminary incubation, except reactions were started by the addition of 7.8 μL of [¹⁴C]B9207-015 to give a final concentration of 10 μM, and denatured control incubations contained pooled microsomes which had been denatured by heating to 80°C for 10 minutes. Reactions were terminated after 60 minutes by transferring the incubation mixture from the incubation vial to a 4.5 ml ~~_____~~ tube which was capped and dropped into liquid nitrogen. All incubations were conducted in duplicate.

b(4)

Incubation of [¹⁴C]B9207-015 with pooled human liver microsomes in the presence of inhibitors

Incubations with [¹⁴C]B9207-015 were also conducted in the presence of inhibitors of esterase (bis-p-nitrophenylphosphate), cytochrome P450 (SKF 525-A) and individual P450 isoforms; CYP3A (troleandomycin), CYP2C8 (sulphaphenazole), CYP2D6 (quinidine) and CYP4A11 (diethyldithiocarbamate, DEDC). Final concentrations and solvents of inhibitors were as follows; SKF 525-A (1 mM), bis-p-nitrophenylphosphate (1 mM), troleandomycin (100 μM, acetone), sulphaphenazole (20 μM, ethanol), quinidine (10 μM, acetone) and DEDC (300 μM, super-pure water).

All reaction mixtures contained Na/K phosphate buffer, pooled human microsomal protein (0.5 mg/ml), 5 μL of either 200 mM SKF 525-A, 200 mM bis-p-nitrophenylphosphate, 20 mM troleandomycin, 4 mM sulphaphenazole, 2 mM quinidine, 60 mM DEDC, super-pure water, ethanol or acetone and NADPH. Following a pre-incubation of 3 minutes (except samples containing troleandomycin and DEDC, which had a 15 minute pre-incubation) at 37°C, the reactions were started by addition of 5 μL of [¹⁴C]B9207-015 (2 mM, dissolved in acetone) to give a final substrate concentration of 10 μM. Positive control incubations for CYP3A, CYP2C8, CYP2D6 and CYP4A11 in which [¹⁴C]Testosterone (final concentration 175 μM in methanol), [¹⁴C]Tolbutamide (final concentration 100 μM in Na/K phosphate buffer), [¹⁴C]Debrisoquine (final concentration 500 μM in Na/K phosphate buffer, and [¹⁴C]Lauric acid (final concentration 100 μM in Na/K phosphate buffer, replaced [¹⁴C]B9207-015 as substrate.

incubation or [¹⁴C]B9207-021 with microsomes containing expressed human CYP2C8, CYP2D6, CYP3A4 and CYP4A11

All reaction mixtures contained Na/K phosphate buffer, microsomes containing expressed human CYP2C8, CYP2D6, CYP3A4 or CYP4A11 and NADPH (2 mM). Following a pre-incubation of 3 minutes at 37°C, the reactions were started by addition of 10 mcL of [¹⁴C]B9207-021 (1 mM, dissolved in acetone) to give a final substrate concentration of 10 mcM. Control incubations for CYP3A, CYP2C8, CYP2D6 and CYP4A11 in which [¹⁴C]Testosterone (final concentration 175 mcM in methanol), [¹⁴C]Tolbutamide (final concentration 100 mcM in Na/K phosphate buffer), [¹⁴C]Debrisoquine (final concentration 500 mcM in Na/K phosphate buffer, and [¹⁴C]Lauric acid (final concentration 100 mcM in Na/K phosphate buffer, replaced [¹⁴C]B9207-015 as substrate.

Sample Processing

The rates of formation of M1 and/or the metabolites M2 and M3 were measured by TLC analysis. In addition, quantification of a further potential metabolite, 16-hydroxy-prednisolone, was done by LC-MS/MS. Positive control were analyzed by HPLC.

DATA PROCESSING

The metabolism data were derived from evaluations of TLC lanes or HPLC chromatograms using either software system for TLC and HPLC, respectively. This enabled the amount of radioactivity attributed to each region of interest (ROI) to be expressed as a percentage of total lane or chromatogram radioactivity. The % ROI were subsequently used to determine the percentage metabolism of [¹⁴C]B9207-015 or [¹⁴C]B9207-015 and positive control substrates and the formation of M1, M2 and M3 and major metabolites of the positive control substrates. Control values (% metabolism in the presence of denatured microsomal protein or control Supersomes™) were taken into account in this respect. The % metabolism of substrates and formation of metabolites was then used to calculate the rate of metabolism/formation, using the formula:

$$\text{Rate (nmol/min/mg protein)} = \frac{\frac{\% \text{ metabolism/formation}}{100} \times \text{concentration (nmoles)}}{\text{time (min)} \times \text{protein (mg)}}$$

RESULTS

PRELIMINARY INCUBATION OF [¹⁴C]B9207-015 WITH POOLED HUMAN LIVER MICROSOMES

The preliminary incubation with [¹⁴C]B9207-015 was conducted at two substrate concentrations and using either acetone or dimethylsulfoxide (DMSO) as the solvent. Incubations proceeded for up to 1 hour, to enable the optimal conditions to be used in future experiments.

The metabolism of [¹⁴C]B9207-015 was rapid and progressive over time. Three metabolite fractions were quantified on the basis of their respective Rt values being comparable

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to those of authentic standards of M1 (B9207-021), M2 and M3. M2 was formed in slightly greater quantities than M3, but each accounted for ~20% of lane radioactivity after 30 minutes incubation. The profiles suggest that M1 was the primary metabolite, which served as a precursor to M2 and M3. According to the sponsor, it is likely that these compounds were then metabolized further by human liver microsomes, as other bands of radioactivity were observed in the lower portion of the plate in a time-dependent manner.

On the basis of this incubation a substrate concentration of 10 μM [^{14}C]B9207-015 (or [^{14}C]B9207-021), dissolved in acetone, was used in all of the subsequent incubations. This concentration is much higher than the C_{max} in human serum (0.01 μM), which has been measured previously *in vivo*.

INCUBATION OF [^{14}C]B9207-015 WITH MICROSOMES FROM INDIVIDUAL DONORS

The activities of [^{14}C]B9207-015 metabolism showed very variable results within the 16 donors, although with the exception of donors 20 and 24, [^{14}C]B9207-015 had been almost completely metabolized within 1 hour (>90%). Significant quantities of M1 were remaining only following incubations with pooled human microsomes and with microsomes prepared from donors 14, 19, 20 and 24 (<25%). According to the sponsor, the data supplied by _____ showed that these donor microsomes contained the lowest CYP3A4/5 activity which supports the hypothesis that CYP3A4/5 is involved in the formation of the secondary metabolites.

b(4)

M2 was generally present in lower quantities than M3 and the amount of M2 formed varied 10-fold (mean values of 19% in donor 17 to 19.5% in donor 20). Formation of M3 was less variable, the extent of variation being approximately 1.5-fold (mean values of 12.8% in donor 20 to 19.6% in donor 22). Numerous other metabolite bands were present in all of the samples, none of which have been positively identified to date.

The rates for the selective substrates were compared to those for the rates of M2 and M3 formation for each human donor to determine the extent and statistical significance of any correlations between the two data sets. None of the correlations for M3 formation were statistically significant within 95% confidence limits and the highest r value was 0.47 (CYP4A11) followed by $r=0.27$ (CYP2C8) and $r=0.26$ (CYP2D6). The formation of M2 was significantly negatively correlated with CYP3A4/5 ($r=-0.96$), CYP2C8 ($r=-0.71$) and CYP2B6 ($r=-0.71$ and -0.79).

INCUBATION OF B9207-015 WITH POOLED HUMAN LIVER MICROSOMES IN THE PRESENCE OF CHEMICAL INHIBITORS

These inhibitors included the non-selective P450 inhibitors carbon monoxide and SKF 525-A, the carboxyesterase inhibitor bis-p-nitrophenylphosphate, and inhibitors which are effective against CYP2C8/9 (sulphaphenazole), CYP2D6 (quinidine), CYP3A4 (troleanomycin) and CYP4A11(diethyldithiocarbamate).

The results of control incubations with denatured microsomes (without NADPH) showed negligible formation of metabolites. When NADPH was omitted from an incubation mixture containing native microsomes, metabolism of the parent did occur, but only M1 (and negligible M2 or M3) was formed (~ 60%). Uninhibited controls contained super-pure water, acetone, and ethanol (which were used as solvents for the inhibitors) and the profiles and extents of metabolite formation were very similar: ~70% metabolism of [^{14}C]B9207-015 and 35%, 12% and 9% formation of M1, M2 and M3, respectively, after 15 minutes incubation, rising to ~95%

metabolism of [¹⁴C]B9207-015 and 26%, 19%, and 15-18% formation of M1, M2 and M3, respectively after 30 minutes incubation.

Bubbling carbon monoxide through the incubation mixture for 1 minute prior to initiating the reaction had little effect on metabolism of [¹⁴C]B9207-015 or production of its metabolites. SKF 525-A was a more potent inhibitor of M2 and M3 formation (~88%) than M1 production (~49%) or biotransformation of the parent compound (~71%). Bis-p-nitrophenylphosphate reduced formation of all three metabolites to a similar extent (82-84%), whilst it had less effect on total [¹⁴C]B9207-015 metabolism (reduced by 62%).

Of the more selective inhibitors, troleandomycin had little effect on the metabolism of [¹⁴C]B9207-015 or formation of M1, whilst formation of M2 and M3 was significantly reduced (83-85%). Consequently, CYP3A4/5 would be expected to play a major role in the formation of secondary metabolites of [¹⁴C]B9207-015.

Sulphaphenazole had very little inhibitory effect on M2 (6%) or M1 (2%) formation and no effect on M3, while quinidine had a similar minor inhibitory effect on M3 (7%), but none on M1 or M2 formation. This suggests that both CYP2C8/9 and CYP2D6 may play a minor role in the formation of secondary metabolites from M1.

Diethyldithiocarbamate had more effect on M2 and M3 production (43-47%), but this inhibition may have been due to non-selective inhibition of CYP3A4, CYP2C8/9 and CYP2D6, which were all implicated in production of M2 and M3 to varying degrees. Only 12% inhibition of lauric acid 12-hydroxylase activity (CYP4A11 marker) was elicited by diethyldithiocarbamate in parallel incubations.

INCUBATION OF [¹⁴C]B9207-021 (M1) WITH _____ ^{CM} CONTAINING EXPRESSED HUMAN P450s

The percentage metabolism by microsomes containing human expressed CYP2C8 was less than 11% after 60 minutes irrespective of the P450 concentration, and was progressive over time. The sponsor believes that as only one band was evident in the M2/M3 region of the samples chromatographed on these plates, coupled with differences in the R₁-values of the metabolite and [¹⁴C]B9207-021 bands of radioactivity, this band may correspond to M2 on the 20 pmole plate and M3 on the 100 pmole plate.

[¹⁴C]B9207-021 was more rapidly metabolized by microsomes containing expressed human CYP2D6, 13% and 30% by 20 pmole and 100 pmole P450, respectively, after 60 minutes. M3 was the major metabolite fraction produced, although very low amounts of M2 were also formed by this enzyme (<2%) in a time-dependent manner, irrespective of P450 concentration. No metabolites additional to M2 and M3 were produced in significant quantities.

Microsomes containing expressed human CYP3A4 metabolized [¹⁴C]B9207-021 very extensively to at least 9 metabolites. At the lower P450 concentration, M3 formation and [¹⁴C]B9207-021 metabolism was progressive over time, whereas M2 formation remained constant over time. In 100 pmole P450 samples, the extent of [¹⁴C]B9207-021 metabolism remained constant and M2 and M3 formation decreased with increasing incubation periods. The amounts of M2 and M3 formed from [¹⁴C]B9207-021 decreased over time in 100 pmole CYP3A4 samples which suggests that both of these secondary metabolites are further metabolized to other products. As formation of M3 increased over time in 20 pmole CYP3A4 samples, this would suggest either that [¹⁴C]B9207-021 is preferentially metabolized to M2 (but not M3), or that M2

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is further metabolized more rapidly than M3, at lower CYP3A4 concentrations.

[¹⁴C]B9207-021 was not transformed to M2 or M3 by microsomes containing expressed human CYP4A11, even under conditions with high P450 content and long incubation periods (<2%).

INCUBATION OF [¹⁴C]B9207-021 (M1) WITH POOLED HUMAN LIVER MICROSOMES

[¹⁴C]B9207-021 was extensively metabolized after 60 minutes incubation (~69%) with most of this transformation occurring within the first 15 minutes (~50%) B9207-021 was extensively metabolized after 60 minutes incubation (~69%) with most of this transformation occurring within the first 15 minutes (~50%) M2 and M3 were produced in similar quantities in all of the time points and also reached maximal concentration after 15 minutes incubation (~15% and 21%, respectively). Levels of these metabolites decreased steadily in all of the subsequent time point. A number of other more polar metabolites were also formed in a time-dependent manner. These results are quantitatively and qualitatively similar to previous incubations which were performed using the same human liver microsomal pool where [¹⁴C]B9207-015 was used as the substrate, rather than [¹⁴C]B9207-021. Very small quantities of M2 and M3 were also present in control incubations which were conducted in the absence of NADPH or in the presence of denatured microsomes (~1 %).

When these samples were assayed using LC-MS/MS methods, 16-hydroxyprednisolone was formed in a time dependent manner over the time course. Formation of this metabolite appeared to be linear for 30 minutes, and reached maximal concentration after 60 minutes (11.3 ng/100 mL) which is equivalent to a maximal concentration of 0.1 mcM (approximately 2% of initial [¹⁴C]B9207-021 concentration).

Table 1. Metabolism of M1

Study system: Human liver microsomes.				
Time	Mean % metabolism formation ¹			
	0	15 minutes 10 µM	30 minutes 10 µM	60 minutes 10 µM
Concentration : 10 µM				
Compound:				
RM1	3	50	64	69
B-ring-hydroxylated RM1	0	15	17	16
4,5 dihydro RM1	0	21	20	17
16OH-prednisolone	0	1	1	2
Additional information: ¹ Based on respective mean control values, ROI values quoted				

SUMMARY OF FINDING

- [¹⁴C]B9207-021 was extensively metabolized after 60 minutes incubation (~69%) with most of this transformation occurring within the first 15 minutes (~50%). M2 and M3 were produced in similar quantities in all of the time points and also reached maximal concentration after 15 minutes incubation (~15% and 21%, respectively). A number of other more polar metabolites were also formed in a time-dependent manner
- Bis-p-nitrophenylphosphate inhibited the transformation of [¹⁴C]B9207-015 by ~82%, which supports the hypothesis that the transformation of [¹⁴C]B9207-015 is catalyzed by an unidentified carboxylesterase(s) which have not been identified.
- The non-selective inhibitor of P452, SKF 525-A (1 mM) inhibited biotransformation of M1 90%. 2KP 525-A (at 300 mcM concentration) has been shown to inhibit all of the major P450 families of enzymes (except 1A) by more than 50%. Consequently several

individual P450 isoforms were investigated here for their involvement in the metabolism of M1.

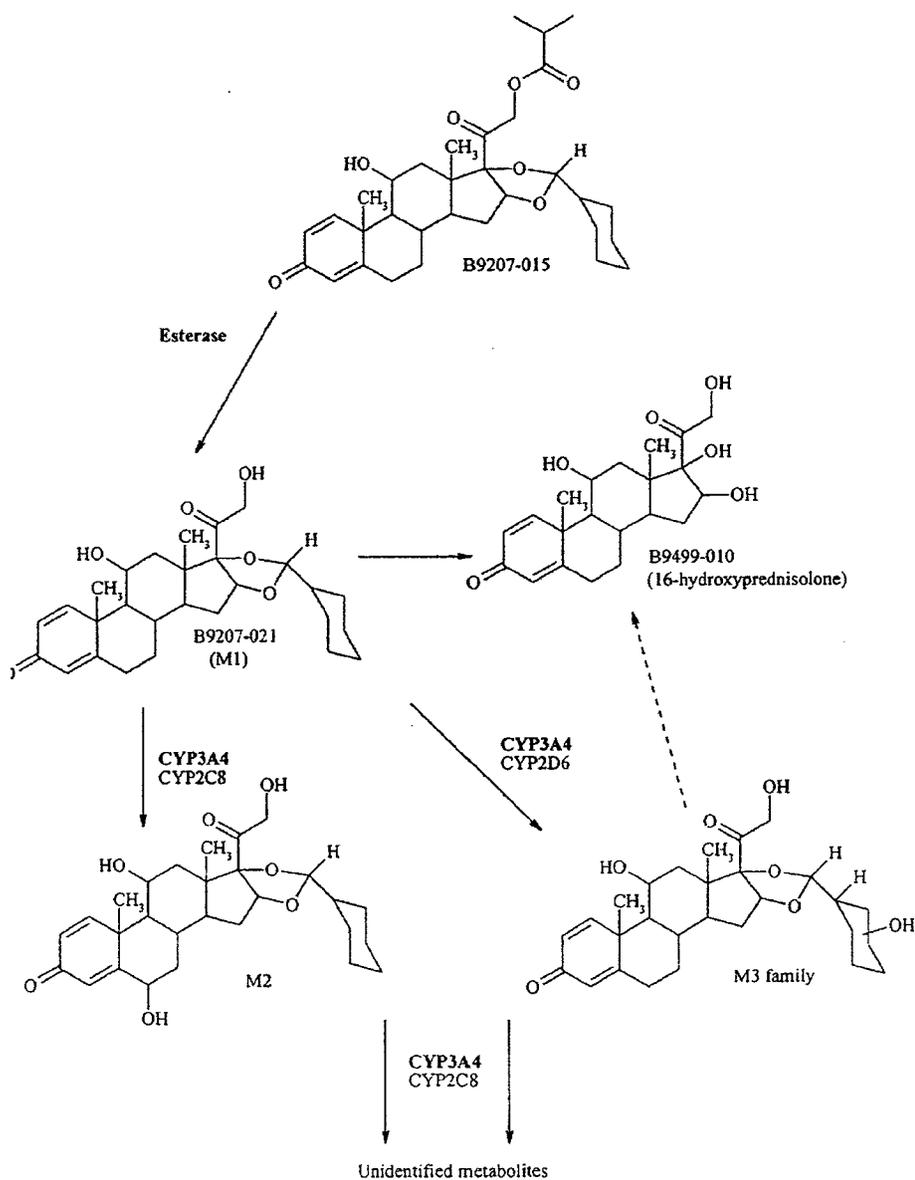
- The expressed enzyme and inhibition data implied that CYP4A11 was unlikely to be significantly involved in the production of M3 from [¹⁴C]B9207-015. However, this was contradicted by the data from the correlation analysis, where CYP4A11 correlated more strongly with rates of M3 formation than any of the other major human P450 isoforms.
- Troleandomycin had little effect on the metabolism of [¹⁴C]B9207-015 or formation of M1, whilst formation of M2 and M3 was significantly reduced (83-85%). However, the correlation data also failed to indicate the extent of CYP3A4 involvement in the biotransformation of M1 to M3 and other products. The sponsor stated that the reasons for these anomalies remain unknown.
- The percentage metabolism by microsomes containing human expressed CYP2C8 was less than 11% after 60 minutes irrespective of the P450 concentration, and was progressive over time.
- [¹⁴C]B9207-021 was more rapidly metabolized by microsomes containing expressed human CYP2D6, 13% and 30% by 20 pmole and 100 pmole P450, respectively, after 60 minutes. M3 was the major metabolite fraction produced, although very low amounts of M2 were also formed by this enzyme (<2%) in a time-dependent manner, irrespective of P450 concentration. No metabolites additional to M2 and M3 were produced in significant quantities.
- Microsomes containing expressed human CYP3A4 metabolized [¹⁴C]B9207-021 very extensively to at least 9 metabolites. M3 formation and [¹⁴C]B9207-021 metabolism was progressive over time, whereas M2 formation remained constant over time. The amounts of M2 and M3 formed from [¹⁴C]B9207-021 decreased over time which suggests that both of these secondarily metabolites are further metabolized to other products. As formation of M3 increased over time, this would suggest either that [¹⁴C]B9207-021 is preferentially metabolized to M2 (but not M3), or that M2 is further metabolized more rapidly than M3, at lower CYP3A4 concentrations.
- Low levels of 16-hydroxyprednisolone were formed from B9207-015 in a time-dependent manner by unidentified human P450 enzyme(s).
- The proposed pathway of [¹⁴C]B9207-015 metabolism by human liver microsomes on the basis of this study is shown in Figure 1.

Conclusions/Reviewer's Comments

- RM1 has a molecular weight of 540.7. At a dose of 400 µg, the mean C_{max} was 0.4 ng/mL. The RM1 final concentrations in the incubates were 10 µM. Thus, the concentrations used in this study were at least 100 times the minimum concentrations achieved *in vivo*.
- Optimal substrate concentrations were used for preferred substrate reactions in this study.
- The biotransformation of B9207-015 (ciclesonide) is likely to be catalyzed by an esterase enzyme which has not been identified.
- It appears that M1 is the major active metabolite that results from the biotransformation of ciclesonide. However, this hypothesis is inconclusive since mass balance studies showed that only 20% of total radioactivity corresponds to M1. In addition, the

metabolite M9, which pharmacological potency is unknown, was as abundant as M1 in plasma samples.

- The biotransformation of M1 appears to be predominately catalyzed by CYP3A4, although CYP2D6, and to a lesser extent CYP2C8 are also involved (see figure below).
- A major involvement of CYP3A4 on the metabolism of M1 is inconclusive since the correlation data failed to indicate the extent of CYP3A4 involvement in the biotransformation of M1, although inhibition studies showed the contrary. On the other hand, CYP4A11 correlated more strongly with rates of M3 formation than any of the other major human P450 isoforms, but inhibition studies showed the contrary. This data indicate that CYP 3A4 may be responsible for the production of M3 and M2 metabolites and CYP4A11 may be responsible for the production of other metabolites that were not identified.



COMMENTS

The following comments can be addressed in the labeling:

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APPEARS THIS WAY ON ORIGINAL