# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 21-067 SE5-003 | Submission Date(s): March 30, 2007; Aug. 13, 2007; Sept 6, 2007; Oct 29, 2007 |
| Brand Name | Asmanex® Twisthaler® |
| Generic Name | Mometasone furoate inhalation powder |
| Reviewer | Wei Qiu, Ph.D. |
| Secondary Review | Chandrahas Sahajwalla, Ph.D. |
| OCP Division | DCPII |
| OND division | DPAP |
| Sponsor | Schering |
| Submission Type | Efficacy Supplement |
| Formulation; Strength(s) | Inhalation powder; 110 mcg |
| Indication | Maintenance treatment of asthma in children 4-11 years of age |

## Table of Contents



## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology /Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 21-067 SE5-003 submitted on March 30, 2007, Aug. 13, 2007, Sept 6, 2007 and Oct 29, 2007 and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the agency regarding the language in the package insert. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

### 1.2 Phase IV Commitments

None.

## 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The effect of mometasone furoate (MF) on HPA axis function was assessed in a 29-day randomized, double-blind, placebo-controlled, and parallel group study involving 50 asthmatic children 6 to 11 years of age. HPA axis function was primarily evaluated by 12-hour plasma cortisol AUC0-12h and 24-hour urinary free cortisol levels with additional analysis on plasma cortisol Cmin, Cmax, 8 AM levels, and Tmax.

Following a 29 days of treatment, the mean changes in plasma cortisol AUC0-12h from baseline were -0.11, -19.5, -21.3, and -3.47 mcg.hr/dL for the treatment groups of ASMANEX TWISTHALER 110 mcg BID (n = 12), 220 mcg BID (n = 12), 430 mcg BID (n = 11) and placebo (n = 7), respectively. The mean difference from placebo in AUC0-12h changes from baseline for the 110 mcg BID, 220 mcg BID and 430 mcg BID treatment groups were 3.4 mcg.hr/dL (95% CI: -14.0, 20.7), -16.0 mcg.hr/dL (95% CI: -33.9, 1.9), and -17.9 mcg.hr/dL (95% CI: -35.8, 0.0), respectively. For the 24-hour urinary free cortisol excretion, the mean changes from baseline were -1.53, -1.33, -6.70, and -4.68 mcg/day for the groups treated with ASMANEX TWISTHALER 110 mcg BID (n = 12), 220 mcg BID (n = 12), 430 mcg BID (n = 12), and placebo (n = 10), respectively. The mean placebo corrected differences in changes from baseline for the 100 mcg BID, 200 mcg BID, and 400 mcg BID treatment groups were 3.1 mcg/day (95% CI: -3.3, 9.6), 3.3 mcg/day (95% CI: -3.0, 9.7), and -2.0 mcg/day (95% CI: -8.6, 4.6), respectively.

The plasma cortisol Cmin and Cmax values for all doses showed a trend towards dose-dependent decreases from baseline compared to placebo. The 8 AM cortisol concentrations are generally consistent with the AUC0-12h findings where only the 200 mcg BID and 400 mcg BID groups showed dose related decreases from baseline compared to placebo.

Optional Intra-Divisional Briefing was held on Nov. 21, 2007. Attendees: Ting Eng Ong and Drs. Chandrahas Sahajwalla, Badrul Chowdhury, Banu Karimi-Shah, and Sandra Suarez-Sharp

# 2 Question Based Review

## 2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of mometasone furoate?

Asmanex® Twisthaler® 220 mcg (mometasone furoate inhalation powder) was approved for the maintenance treatment of asthma in patients 12 years of age and older on March 30, 2005. The sponsor's deferred pediatric studies required under the Pediatric Research Equity Act (PREA) for the maintenance treatment of asthma as prophylactic therapy in patients 4 to 11 years of age were considered required post-marketing study commitments.

To fulfill this commitment, the sponsor submitted a total of eight clinical studies to support the use of mometasone furoate dry powder inhaler for the treatment of asthma in this age group, including efficacy and safety assessments, growth and HPA Axis studies, and long-term safety data up to one year in this efficacy supplement. The sponsor intends to obtain approval of MF DPI 110 mcg QD PM dosing in patients 4 to 11 years of age.

HPA axis function was assessed in three studies, a 29-day study (C96-361) in asthmatic children 6 to 11 years of age, and two one-year studies in asthmatic children 4 to 9 years of age (growth study C97-384 and safety study C97-385). In study C96-361, standard measurements including plasma cortisol AUC and 24-hour urinary free cortisol levels were assessed. For the purpose of HPA axis assessment, the two one-year studies are not adequate since only AM plasma cortisol

and 12-hour urinary cortisol were assessed and they are not generally considered as sensitive parameters for detecting systemic effect on HPA axis function.

## 2.2 General Clinical Pharmacology

1. What is the effect of mometasone furoate on HPA axis function in asthmatic children 6-11 years old?

The effect of various doses of mometasone furoate (100 mcg BID, 200 mcg BID, and 400 mcg BID) on HPA axis function was assessed in 50 asthmatic children 6 – 11 years old in a 29-day HPA Axis study C96-361. This was a randomized, single-center, double-blind, placebo-controlled, and parallel-group study. The systemic effects of mometasone furoate on HPA axis function were primarily assessed by plasma cortisol AUC0-12h, Cosyntropin stimulation, and 24-hour urinary free cortisol. Additional analyses were performed on plasma cortisol Cmin, Cmax, 8 AM levels, and Tmax.

The Day-29 plasma cortisol AUC0-12h values and AUC0-12h change from baseline are shown in **Table 1**. Due to an imbalance in the baseline AUC0-12h values, an analysis of covariance (ANCOVA) was performed on the Day-29 AUC0-12h and change from baseline, with baseline AUC0-12h as a covariate. The 200 mcg group was not significantly different from placebo (p=0.078), and the 400 mcg BID group was marginally significant different from placebo (p=0.050). The mean Day-29 AUC0-12h value for the 200 mcg BID and 400 mcg BID groups were 24% and 27% less than the placebo AUC0-12h, respectively. The ANCOVA results for the AUC0-12h changes from baseline provide the same mean difference from placebo as the ANCOVA for Day-29 AUC0-12h.

**Table 1**. Day 29 12-hour plasma cortisol AUC0-12h[a] and difference from placebo

| Treatment | N | Days of treatment | Baseline (mcg.hr/dL) | Adjusted Day-29 Mean[b] (mcg.hr/dL) | Adjusted Mean change from baseline[b] (mcg.hr/dL) (95% CI) | Mean difference from placebo[b] (mcg.hr/dL) (95% CI) |
|---|---|---|---|---|---|---|
| 400 mcg bid | 11[c] | 29 | 73.15 | 49.23 | -21.3 (-32.3, -10.4) | -17.9 (-35.8, 0.0) |
| 200 mcg bid | 12[c] | 29 | 79.45 | 51.08 | -19.5 (-30.2, -8.8) | -16.0 (-33.9, 1.9) |
| 100 mcg bid | 12[c] | 29 | 66.85 | 70.47 | -0.1 (-10.6, 10.4) | 3.4 (-14.0, 20.7) |
| placebo | 7[c] | 29 | 57.70 | 67.11 | -3.5 (-17.5, 10.5) | -- |

[a] Blood samples were collected at 10 PM on Day -1 (and Day 28), and at 12 midnight, as well as 3 AM, 5 AM, 6 AM, 7 AM, 8 AM, 9 AM and 10 AM on Day 1 (and Day 29).
[b] adjusted for imbalance in baseline AUC value
[c] Four subjects (1 each in the MF DPI 100 mcg BID and MF DPI 200 mcg treatment groups and 2 in the placebo group) discontinued the study prior to scheduled completion. Three (3) subjects in the placebo group and 1 in the 400 mcg BID group had missing plasma cortisol measurements at three or more (>33%) of the time points and were excluded from all plasma cortisol analysis.

The Cmin, Cmax, 8 AM concentration and Tmax values are summarized in **Table 2**. There were no statistically significant differences between treatment groups in Cmin, Cmax, or 8 AM concentration. There were statistically significant differences among the treatment groups for Tmax.

**Table 2**. Mean Cmin, Cmax, 8 AM concentration, and Tmax of cortisol

| Parameters | Treatment | Baseline | Day 29 | Change from Baseline |
|---|---|---|---|---|
| Cmin (mcg/dL) | 400 mcg BID (n=12) | 0.73 | 0.00 | -0.73 |
| | 200 mcg BID (n=12) | 0.35 | 0.10 | -0.25 |
| | 100 mcg BID (n=11) | 0.51 | 0.42 | -0.09 |
| | Placebo (n=7) | 0.00 | 0.00 | 0.00 |
| Cmax (mcg/dL) | 400 mcg BID (n=12) | 18.16 | 14.62 | -3.55 |
| | 200 mcg BID (n=12) | 18.95 | 16.32 | -2.63 |
| | 100 mcg BID (n=11) | 17.46 | 16.19 | -1.27 |
| | Placebo (n=7) | 17.03 | 16.27 | -0.76 |
| 8 AM Cortisol (mcg/dL) | 400 mcg BID (n=12) | 12.34 | 10.33 | -2.01 |
| | 200 mcg BID (n=12) | 13.16 | 12.13 | -0.74 |
| | 100 mcg BID (n=11) | 11.34 | 12.56 | 1.22 |
| | Placebo (n=7) | 11.60 | 11.91 | 0.31 |
| Tmax* (hours:minutes after dose) | 400 mcg BID (n=12) | 8:38 | 7:51 | -0:47 |
| | 200 mcg BID (n=12) | 7:00 | 8:25 | 1:25 |
| | 100 mcg BID (n=11) | 8:16 | 7:32 | -0:43 |
| | Placebo (n=7) | 7:37 | 8:00 | 0:23 |

*Tmax is the exact clock time of collection.

Individual urinary cortisol measurements were highly variable, and there were no statistically significant changes from baseline between treatment groups (**Table 3**).

**Table 3**. 24-hr Urinary free cortisol* and statistical analysis results

| Treatment | N | days of Treatment | Baseline (mcg/day) | Adjusted Day-29 value** (mcg/day) | Adjusted mean change from baseline** (mcg/day) (95% CI) | Mean difference from placebo (mcg/day)** (9%%CI) |
|---|---|---|---|---|---|---|
| 400 mcg bid | 12 | 4 | 21.26 | 10.01 | -6.7 (-11.0, -2.4) | -2.0 (-8.6, 4.6) |
| 200 mcg bid | 12 | 4 | 14.28 | 15.38 | -1.3 (-5.6, 2.9) | 3.3 (-3.0, 9.7) |
| 100 mcg bid | 12 | 4 | 19.02 | 15.18 | -1.5 (-5.8, 2.7) | 3.1 (-3.3, 9.6) |
| placebo | 10 | 4 | 11.41 | 12.03 | -4.7 (-9.4, 0.1) | -- |

* Urine was collected over a 24-hr period beginning at 10 AM on Day -1 (and Day 28) and ending at 10 AM on Day 1 (and Day 29)
** adjusted for imbalance in baseline

Changes in plasma cortisol concentration in response to Cortrosyn® stimulation was evaluated at baseline and on Day 29. One subject treated with 400 mcg BID had an abnormal response to Cortrosyn® stimulation at Day 29. Low pre-stimulation plasma cortisol concentrations (i.e., < 5 mcg/dL) were reported in 2/12 subjects in the placebo group, 4/13 subjects in the 100 mcg BID group, 4/13 in the 200 mcg BID group and 4/12 subjects in the 400 mcg BID group. Sponsor concluded that there were no statistically significant differences between treatment groups at either time point (**Table 4**).

**Table 4**. Mean AM plasma cortisol concentration (mcg/dL) (All treated subjects with both pre and post-Cortrosyn® plasma cortisol values.

| | MF DPI 100 mcg BID | | MF DPI 200 mcg BID | | MF DPI 400 mcg BID | | Placebo | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | N | Mean | N | Mean | N | Mean |
| **Screening** | | | | | | | | |
| Pre-Cortrosyn® | 13 | 9.72 | 12 | 9.08 | 12 | 8.28 | 10 | 7.60 |
| Post-Cortrosyn® | 13 | 27.92 | 12 | 26.12 | 12 | 26.63 | 10 | 25.26 |
| Difference Between Pre and Post | 13 | 18.19 | 12 | 17.05 | 12 | 18.35 | 10 | 17.66 |
| **Day 29** | | | | | | | | |
| Pre-Cortrosyn® | 13 | 8.47 | 12 | 7.80 | 11 | 6.33 | 10 | 9.47 |
| Post-Cortrosyn® | 12 | 26.14 | 12 | 24.89 | 11 | 24.43 | 10 | 25.46 |
| Difference Between Pre and Post | 12 | 17.75 | 12 | 17.09 | 10 | 18.14 | 10 | 15.99 |
| Change from Screening (Post-Pre) | 12 | -0.72 | 12 | 0.04 | 10 | -0.14 | 10 | -1.67 |

*Cortrosyn® testing was done on screening and Day 29. An IV injection of 0.25 mg of cosyntropin (Cortrosyn®) solution was administered after the last blood sample was taken at 10 AM. A second blood sample was taken 30 minutes after the injection for the measurement of plasma cortisol.

Plasma mometasone furoate concentrations were generally below or only slightly above the limit of quantitation (LOQ = 50 pg/mL) immediately before and following dosing with mometasone furoate (**Table 5**). In addition, trough plasma mometasone furoate concentrations tended to increase in a dose-related manner, with values remaining close to the LOQ.

**Table 5**. Plasma Mometasone Furoate concentration

| | Day 28 2-hr post 8 PM Dose | Day 29 Pre 8 AM Dose | Day 29 1-hr post 8 AM Dose | Day 29 2-hr post 8 AM Dose |
|---|---|---|---|---|
| MF DPI 100 mcg BID (n=13) | | | | |
| No. Samples Reportable[a] | 12 | 11 | 11 | 11 |
| No. Samples Above LOQ | none | 1 | 4 | none |
| Mean (pg/mL) | 0 | 4.97 | 19.6 | 0 |
| Minimum Value (Above LOQ) (pg/mL) | none | 54.7 | 50.2 | none |
| Maximum Value (pg/mL) | 0 | 54.7 | 58.5 | 0 |
| MF DPI 200 mcg BID (n=13) | | | | |
| No. Samples Reportable[a] | 12 | 11 | 9 | 11 |
| No. Samples Above LOQ | 2 | 4 | 4 | 4 |
| Mean (pg/mL) | 10.4 | 28.9 | 46.8 | 30.1 |
| Minimum Value (Above LOQ) (pg/mL) | 51.8 | 64.4 | 77.0 | 59.1 |
| Maximum Value (pg/mL) | 72.7 | 91.0 | 117 | 109 |
| MF DPI 400 mcg BID (n=12) | | | | |
| No. Samples Reportable[a] | 11 | 9 | 9 | 9 |
| No. Samples Above LOQ | 4 | 2 | 4 | 3 |
| Mean (pg/mL) | 32.5 | 49.0 | 56.8 | 39.3 |
| Minimum Value (Above LOQ) (pg/mL) | 50.7 | 83.1 | 88.2 | 96.7 |
| Maximum Value (pg/mL) | 140 | 358 | 188 | 135 |

LOQ = limit of quantification = 50 pg/mL; levels below LOQ were reported as 0.

a: Reportable samples were those samples for which a value, either above or below the LOQ, was reported.

The sponsor concluded that there was no evidence in the mometasone furoate 100 mcg BID treatment group of HPA axis suppression based on mean plasma cortisol AUC0-12h parameters and the response to Cortrosyn® stimulation. Plasma cortisol AUC0-12h results suggest that there is a potential for systemic exposure in children given 200 mcg BID or 400 mcg BID.

**Reviewer's Comments:**

Overall, this 29-day HPA axis study is adequate for the purpose of evaluating HPA axis function. In this study, relatively sensitive methods for detecting systemic effects on HPA axis function (e.g., plasma cortisol AUC and 24-hour urinary free cortisol) were utilized. Patients were confined during the days for plasma sampling and urine collection. Urine collections seem adequate. Compliance could be assured by the PK samplings showing detectable concentration in some patients although most of the mometasone furoate levels were below the assay sensitivity. Forty-five of the 50 subjects used at least 75% of their prescribed investigational study medication. This study included three doses of mometasone furoate and dose-related trends in HPA axis effects further support the compliance. Duration of this study is 4 weeks which is shorter than the recommended 6 weeks. Furthermore, the BID dosing regimens (100 mcg BID, 200 mcg BID, and 400 mcg BID) were assessed although a QPM dosing of 100 mcg was proposed for children.

The ANCOVA analysis on actual Day-29 plasma cortisol AUC0-12h values or changes in AUC0-12h from baseline, using baseline AUC0-12h as a covariate, resulted in the same treatment difference from placebo. The mean changes in plasma cortisol AUC0-12h from baseline were -0.1, -19.5, -21.3, and -3.5 mcg.hr/dL for the 100 mcg BID, 200 mcg BID, 400 mcg BID, and placebo, respectively. The mean difference from placebo (95% CI) were 3.4 (-14.0, 20.7), -16.0 (-33.9, 1.9), and -17.9 (-35.8, 0.0) mcg.hr/dL for 100 mcg BID, 200 mcg BID, and 400 mcg BID, respectively. For the plasma cortisol AUC0-12h calculation, the sponsor used the nominal time instead of actual time of sample collection. In addition to the 4 subjects who discontinued the study, 4 subjects who had 3 or more missing plasma cortisol measurements were also excluded from the final analysis. Considering the limited sample size of this study, the sponsor was requested to perform the analysis by including and excluding these subjects.

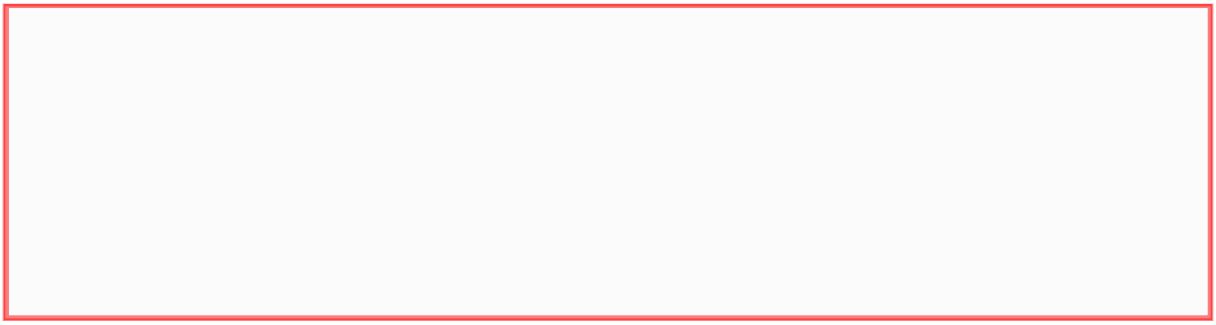
For 24-hour urinary free cortisol, the mean changes from baseline were -1.5, -1.3, -6.7, and -4.7 mcg/day for the groups treated with 100 mcg BID, 200 mcg BID, 400 mcg BID and placebo, respectively. The mean differences from baseline compared to placebo were 3.1 (95% CI: -3.3, 9.6), 3.3 mcg/day (95% CI: -3.0, 9.7), and -2.0 (95% CI: -8.6, 4.6) mcg/day for the groups treated with 100 mcg BID, 200 mcg BID, and 400 mcg BID, respectively. The 400 mcg BID group showed a numerical decrease in urinary free cortisol level compared to placebo. The other two groups showed a numerical increase compared to placebo.

The plasma cortisol Cmin and Cmax values for all doses showed dose-dependent numerical decreases compared to placebo. The 8 AM cortisol concentrations are generally consistent with the AUC0-12h finding where only the 200 mcg BID and 400 mcg BID groups showed dose related decreases compared to placebo. The sponsor calculated the mean Tmax values using actual Tmax data. However, generally, the Tmax data should be summarized with median and range.

The conventional high-dose Cosyntropin stimulation test is not generally accepted as a sensitive method to detect systemic effect. Clinically, this test is useful in determining severe adrenocortical insufficiency, however, it has been deemed inadequate for detecting mild or short-term adrenal gland suppression or for detecting isolated central adrenal insufficiency.

An issue was raised during filing meeting with regards to the re-assurance of in vitro dose proportionality between the 220 mcg [redacted] devices. [redacted] The batch number for the [redacted] used in this study is 36809-039. Dr. Craig Bertha had reviewed the in vitro data for other [redacted] batches made at the same time as this clinical batch (see chemistry review by Dr. Craig Bertha dated March 23, 1999). It was found that dose delivery of the [redacted] batches were reasonable close to target and was able to meet the Agency's promoted acceptance criterion of 85-115% of label claim emitted dose.

## 3 Detailed Labeling Comments



# 4 Appendix

## 4.1 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology

*New Drug Application Filing and Review Form*

***General Information About the Submission***

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | **21-067** | **Brand Name** | **Asmanex Twisthaler** |
| **OCP (I, II, III)** | **II** | **Generic Name** | **Mometasone Furoate** |
| **Medical Division** | **DPADP** | **Drug Class** | Corticosteroid |
| **OCPB Reviewer** | Sayed (Sam) Al Habet, RP.h, Ph.D. | **Indication(s)** | Asthma |
| **OCPB Team Leader** | **Emmanuel (Tayo) Fadiran, RP.h., Ph.D.** | **Dosage Form** | **Oral Inhalation Dry Powder** |
| **PM Reviewer** | | **Dosing Regimen** | **Once daily in children 4 to 11 years of age** |
| **Date of Submission** | **March 30, 2007** | **Route of Administration** | **Oral Inhalation** |
| **Estimated Due Date of OCP Review** | **October 30, 2007** | **Sponsor** | **Schering** |
| **PDUFA Due Date** | **December 30, 2007** | **Priority Classification** | Standard |
| **Division's Due Date** | November 30, 2007 | | |

***Clin. Pharm. and Biopharm. Information***

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **x** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| *Healthy Volunteers-* | | | | |
| single dose: | **x** | **3** | | |
| multiple dose: | X | **3** | | |
| **Patients-** | | | | |
| single dose: | **x** | **3** | | |
| multiple dose: | | **3** | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | **x** | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |

| | | | | |
|---|---|---|---|---|
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **8 (including clinical studies)** | | |
| | | | | |

**Filability and QBR comments**

| | "X" if yes | Comments |
|---|---|---|
| **Application filable ?** | X | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? |
| **Comments sent to firm ?** | **No Comments at this time.** | Comments have been sent to firm (or attachment included). FDA letter date if applicable. NONE at this time |
| **QBR questions (key issues to be considered)** | **The sponsor conducted c8 clinical studies. Three studies are most relevant to clinical pharmacology to determine the HPA axis (see attached slides). The three main studies are:** | |
| | **1) HPA axis x 29 days (study # 361).**<br>**2) Safety, efficacy, HPA axis and growth study x 52 weeks (Study # 384)**<br>**3) Safety, efficacy, HPA axis and growth study x 52 weeks (Study # 385)**<br><br>**See attached filing slides for details.** | |

| | |
|---|---|
| **Other comments or information not included above** | **Inspection Recommendation:**<br><br>DSI inspection is not recommended for this NDA because the drug was minimally detected in the plasma. In most of the samples, the concentration was below LLOQ (50 ng/ml.). |
| **Primary reviewer Signature and Date** | |
| **Secondary reviewer Signature and Date** | |

4.2 Study Synopsis



## 2. SYNOPSIS

| | | |
|---|---|---|
| **Title of the Study:** | **Multiple Dose Safety Study of Mometasone Furoate (SCH 32088) Dry Powder (MF DPI) in Asthmatic Children (Protocol C96-361)** | |
| **Investigator(s):** | | |
| **Study Center:** | Single center in the USA | |
| **Publication(s):** | None | |
| **Studied Period:** | June 1997 to September 1997 | **Clinical Phase:** I |

**Objective(s):**

- to determine the systemic effects of MF DPI lactose-mix on HPA-axis function in pediatric subjects as assessed by 12-hour multiple nocturnal plasma cortisol measurements, cosyntropin stimulation, and 24-hour urinary free cortisol concentrations.

**Methodology:** Randomized, single-center, double-blind, placebo-controlled, parallel groups.

**Number of Subjects:** 50 total, 31 males and 19 females, aged 6 to 11 y; 13 in MF DPI 100 mcg BID group, 13 in MF DPI 200 mcg BID group, 12 in MF DPI 400 mcg BID group, and 12 in placebo group. Four subjects did not complete the study.

**Diagnosis and Criteria for Inclusion:** Subjects of either sex and any race, age 6 to 11, with mild childhood asthma of at least 6 months duration were eligible for enrollment.

- Subjects must have been using inhaled $\beta_2$ adrenergic agonists on an as-needed basis only, and must not have required any regular controlling therapy.
- The subject's Screening $FEV_1$ must have been greater or equal to 80% of predicted when all restricted medications had been withheld for the specified intervals.
- Clinical laboratory tests (CBC, blood chemistries, urinalysis) must have been within normal limits or clinically acceptable to the investigator/sponsor.
- Subjects must have had normal growth development within the preceding year.
- At Screening, the subjects must have had an unstimulated Baseline plasma cortisol concentration of ≥5 mcg/dL, and must have demonstrated an increase in cortisol level of at least 7 mcg/dL, 30 minutes after Cortrosyn® injection, with an absolute stimulated plasma cortisol value exceeding 18 mcg/dL.

**Test Product, Dose, Mode of Administration, Batch No(s):** MF DPI 100 mcg BID (Batch No. 36809-093), MF DPI 200 mcg BID (36809-057), MF DPI 400 mcg BID (36809-039), all administered by oral inhalation.

**Duration of Treatment:** 29 days

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** MF Placebo BID (Batch No. 36809-056) administered by oral inhalation.

**Criteria for Evaluation:** The primary parameter for this study was the Day-29 12-hour area under the plasma cortisol concentration-time curve (AUC). Other parameters included plasma cortisol response to cosyntropin stimulation, and 24-hour urinary free cortisol concentrations. Safety variables included adverse events, laboratory tests, vital signs, and physical examination. Although efficacy variables were measured, e.g., $FEV_1$, PEFR, symptoms, and response to therapy, they were secondary evaluations as this study was designed specifically to evaluate the safety of MF DPI in pediatric patients. Peak inspiratory flow rates were evaluated using a functional model of the dry powder inhaler. Office visits were Screening, Baseline (Day -2/1), Days 8, 15, and 27/29. Subjects were confined on Days -2/1 and 27/29.

**Statistical Methods:** The primary safety variable at Day 29 was analyzed for all treated subjects using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) with effects due to treatment (and baseline covariate in ANCOVA) because of a large (but not significant) imbalance among the treatment groups at Baseline. Since the highest dose should have the greatest potential to show an effect on HPA-axis function, the primary pairwise comparison was between MF DPI 400 mcg BID and placebo. The Day-29 24-hour (Day 28 -- 10 AM to Day 29 -- 10 AM) AUC of urinary free cortisol was analyzed by ANOVA.

**Title of the Study: Multiple Dose Safety Study of Mometasone Furoate (SCH 32088) Dry Powder (MF DPI) in Asthmatic Children (Protocol C96-361)**

**SUMMARY-CONCLUSIONS:**

**RESULTS:** .

**Efficacy:** Pulmonary function was evaluated primarily to ensure that subjects did not experience a worsening of asthma. There were no significant differences among the treatment groups in $FEV_1$, percent predicted $FEV_1$, or PEFR.

Results obtained for peak inspiratory flow rates through a functional model of the dry powder inhaler revealed that subjects achieved adequate flow rates to provide functional drug delivery using the DPI.

**Safety:** The mean Baseline and change from Baseline at Day 29 in 12-hour plasma cortisol AUC (mcg.hr/dL) are shown below:

| | MF DPI 100 mcg BID | MF DPI 200 mcg BID | MF DPI 400 mcg BID | Placebo |
|---|---|---|---|---|
| Baseline | 66.85 | 79.45 | 73.15 | 57.70 |
| Change from Baseline | 1.83 | -24.11 | -20.69 | 3.23 |

The Baseline values of the AUC showed large, although not statistically significant, differences among the treatment groups. For this reason, an analysis of covariance (ANCOVA) was done on the Day-29 AUC data, with baseline AUC as a covariate. For the primary parameter, 12-hour plasma cortisol AUC at Day 29, the 100 mcg BID treatment was comparable to placebo. The 200 mcg group was not significantly different from placebo (p=0.078), and the 400 mcg BID group was marginally significantly different from placebo (p=0.050). The mean AUCs for the 200 mcg BID and 400 mcg BID groups were 24% and 27% less than the placebo mean AUC, respectively.

There were no statistically significant differences between treatment groups in $C_{min}$, $C_{max}$ , or 8 AM plasma cortisol concentration. Change in plasma cortisol concentration in response to Cortrosyn® stimulation was evaluated at Baseline and at Day 29. Although all subjects had responses to Cortrosyn® stimulation that were >7 mcg/dL, individual plasma cortisol concentrations were occasionally abnormal, i.e., prestimulation values <5 mcg/dL or poststimulation values ≤18 mcg/dL. Most abnormalities were low prestimulation plasma cortisol concentrations (i.e., <5 mcg/dL) which were reported in 2/12 subjects in the placebo-treatment group, 4/13 subjects in the MF DPI 100 mcg BID-treatment group, 4/13 subjects in the MF DPI 200 mcg BID-treatment group, and 4/12 subjects in the MF DPI 400 mcg BID-treatment group. Of the 14 subjects with abnormal cortisol values, all except one (treated with MF DPI 400 mcg BID, with a poststimulation plasma cortisol concentration <18 mcg/dL) had a normal response to Cortrosyn® stimulation at Day 29.

Individual urinary cortisol measurements were highly variable, and there were no statistically significant changes from Baseline between treatment groups.

All adverse events were mild or moderate in severity. The most common adverse event, headache, was reported more often by subjects who received MF DPI 400 mcg BID (25%) than those who received MF DPI 100 BID (0%) or 200 mcg BID (8%) or placebo (8%). There was no apparent dose relationship for the remaining adverse events. Adverse events characterized as aggravated allergy, chest pain, fever and pharyngitis each were reported by ≤17% of the subjects in any group. Overall, treatment-emergent adverse events were reported for 38% to 62% of subjects in the MF DPI treatment groups compared with 42% of subjects in the placebo treatment group. The adverse events that were reported during this study were typical of those that have previously been reported with other inhaled corticosteroids. There was no issue related to other measures of safety, including vital signs or results of laboratory tests or physical examinations.

Plasma mometasone furoate concentrations were generally below or only slightly above the limit of quantitation (LOQ=50 pg/mL) immediately before and following dosing with MF, indicating minimal systemic exposure following oral inhalation. In addition, baseline plasma MF concentrations tended to increase in a dose-related manner, with values remaining close to the LOQ. There was no evidence of drug accumulation in either the MF DPI 100 mcg BID or 200 mcg BID treatment groups.

**Title of the Study: Multiple Dose Safety Study of Mometasone Furoate (SCH 32088) Dry Powder (MF DPI) in Asthmatic Children (Protocol C96-361)**

**CONCLUSIONS:**

- There was no evidence in the MF DPI 100 mcg BID treatment group of hypothalamic-pituitary-adrenal (HPA)-axis suppression based on mean plasma cortisol AUC parameters and the response to Cortrosyn® stimulation. Plasma cortisol AUC results suggest that there is a potential for systemic exposure in children given MF DPI 200 mcg BID or MF DPI 400 mcg BID.

- The primary parameter for this study was the Day-29 12-hour plasma cortisol AUC. Based on ANCOVA results, the 100 mcg BID treatment was comparable to placebo. The 200 mcg group was not significantly different from placebo (p=0.078), and the 400 mcg BID group was marginally significantly different from placebo (p=0.050). The mean AUCs for the 200 mcg BID and 400 mcg BID groups were 24% and 27% less than the placebo mean AUC, respectively.

- Individual urinary free cortisol measurements were highly variable, and there were no statistically significant differences in changes from Baseline between treatment groups.

- Plasma MF concentrations were generally below or only slightly above the limit of quantitation (50 pg/mL) immediately before and following dosing with MF, indicating minimal systemic exposure following oral inhalation. Baseline plasma MF concentrations tended to increase in a dose-related manner, with values remaining close to the LOQ, and there was no evidence of drug accumulation in either the MF DPI 100 mcg BID or 200 mcg BID treatment groups.

- All mometasone furoate treatments were well tolerated, and no unusual or unexpected adverse events were reported.

- Because this study was primarily designed and powered to investigate safety and not to show differences between treatments in efficacy measurements, statistically significant differences across treatment groups in pulmonary function parameters, i.e., $FEV_1$, percent predicted $FEV_1$, and PEFR, were not identified in response to 29 days of treatment.

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12/5/2007 01:24:20 PM
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