OFFICE OF CLINICAL PHARMACOLOGY: CLINICAL PHARMACOLOGY REVIEW

NDA	205641
Submission Date:	June 26, 2013
Brand Name:	Asmanex® HFA
Generic Name:	Mometasone furoate
Clinical Pharmacology Reviewer:	Dinko Rekić, M.Sc., Ph.D.
Clinical Pharmacology Team Leader:	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Reviewer:	Dinko Rekić, M.Sc., Ph.D.
Pharmacometrics Team Leader:	Liang Zhao, Ph.D.
OCP Division:	DCP2
OND Division:	DPARP (OND-570)
Sponsor:	Merck
Application type	505 (b)(1) non-NME
Dosing regimen:	Two inhalations twice daily (morning and evening)
Dosage form	Metered Dose Inhaler (MDI)
Strengths:	100 or 200 µg BID
Indication:	Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older

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1 EXECUTIVE SUMMARY

The sponsor is seeking approval for a new formulation (metered dose inhaler [MDI]) of the inhaled corticosteroid mometasone furoate (MF) with the proposed trade name Asmanex HFA®. MF formulated in a dry powder inhaler (DPI) is an approved product with the trade name Asmanex Twistinhaler®.

Studies supporting efficacy of Asmanex HFA have been conducted as part of the Dulera® program where MF MDI was used as active control. Dulera (NDA 22518) is an approved combination product of MF and formoterol fumarate (F), formulated in a MDI. Clinical pharmacology studies supporting the application where conducted using Dulera (MF/F MDI), Asmanex Twistinhaler (MF DPI) or Asmanex HFA (MF MDI).

This review has determined that there is no evidence of formulation or metabolic interaction between MF and F when formulated in a MDI. Hence, the clinical pharmacology studies conducted with co-formulated MF and F in a MDI are relevant to this application. The sponsor has fulfilled the clinical pharmacology requirements of a NDA and no further clinical pharmacology studies are warranted.

Reviewer's independent analysis of the FEV 1 endpoint, using phase II trials from the Dulera program, shows that the two treatments (Asmanex HFA and Asmanex Twistinhaler) have equivalent response when administered at the same dose.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 205641and 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.

1.2 Phase IV commitments

None

2 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The focus of this review is to determine if the clinical pharmacology studies conducted during the Dulera program (MF, MF/F MDI) and the Asmanex Twistinhaler program (MF DPI) are relevant to this application.

Additionally, dose finding phase II trials from the Dulera program and the Asmanex Twistinhaler program are re-analyzed to compare the treatment effect of Asmanex Twistinhaler (MF DPI) and Asmanex HFA (MF MDI).

2.1 Regulatory background

The proposed product is an inhaled corticosteroid (mometasone furoate [MF]) indicated for maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The proposed doses are 200 µg and 400 µg BID delivered by two actuations. Each actuation delivers one dose of 100 µg or 200 µg, depending on the presentation. Mometasone furoate is currently approved for treatment of asthma in two formulations: 1) a dry powder inhalation (DPI) device with the trade name Asmanex Twistinhaler® and 2) as part of a combination product with the long-acting β2-agonist formoterol fumarate (F) with the trade name Dulera®. MF, delivered by a metered dose inhaler (MDI), was used as an active control in development of Dulera. The sponsor is seeking approval for MF MDI formulation, with the proposed trade name Asmanex HFA, based on the studies conducted during the Dulera program as well as the Asmanex Twistinhaler program.
Clinical pharmacology findings

2.1.1 Clinical pharmacology bridging

There are no statistically or clinically relevant differences in mometasone plasma exposure, following Asmanex HFA (MF MDI) or Dulera (MF/F MDI) administration. No pharmacokinetic or formulation interactions between formoterol and mometasone have been found, therefore, results from clinical pharmacology studies of mometasone when co-formulated with formoterol are relevant and applicable to this application.

Mometasone plasma exposure is significantly lower when administered by a MDI (Asmanex HFA) device compared to a DPI (Asmanex Twistinhaler) device. Based on difference in systemic exposure, Asmanex Twistinhaler represents worst case scenario of Asmanex HFA in regards to concentration dependent systemic safety profile. Below is a list of items that are supported by findings from the Dulera program and the Asmanex Twistinhaler program.

Items supported by Dulera program (MF/F, MDI):

- HPA axis (Study PO3705)

Items supported by Dulera program (MF, MDI):

- Dose and dose regimen (phase II and Phase III trials)
- Oral prednisone reduction in subjects with severe asthma (Study C97-224)
- Efficacy and safety in geriatrics and pediatrics (Phase III trials)

Items supported by Asmanex Twistinhaler program (MF, DPI):

- Drug-Drug interaction with the CYP3A4 inhibitor ketoconazole (Study I98-216)
- Growth inhibition in pediatrics (Study C98-384)
- Hepatic Impairment (Study C98-291)
- Reduction in bone mineral density (Study C98-302)

Some studies supporting this application where conducted more than 15 years ago. Consequently, the systemic exposure of mometasone was not measurable with technology available at that time. The hepatic impairment study was only able to measure increased number of observations above lower limit of detection (LOQ) with increasing level of hepatic impairment. The ketoconazole interaction study applied a similar approach. However, in addition to increased exposure to mometasone, a higher degree of cortisol suppression was detected. Because systemic mometasone exposure following Asmanex HFA is significantly lower than following Asmanex Twistinhaler administration, it is possible that reduction in bone mineral density as well as growth inhibition in pediatrics will be less severe with the new product. Sponsor's choice to reference studies conducted with Asmanex Twistinhaler is appropriate as they can represent a worst case scenario.

2.1.2 Comparison of efficacy with Asmanex Twistinhaler

A reviewer initiated analysis of phase II Asmanex HFA trials (trials (I97-200, C97-225, C97-224, C97-208) and Asmanex Twistinhaler phase II trial (C96-134) has determined that the mean treatment effect for the two regimens is not expected to be different when administered at the same dose.

3 QUESTION BASED REVIEW

3.1 General Attributes/Background

3.2 What is the pertinent regulatory background of ASMANEX HFA?

The active ingredient of the product has previously been approved as a single ingredient product in Asmanex Twistinhaler (DPI) as well as part of a combination product with formoterol (Dulera) MDI. Relevant products to this review are listed in **Table 1.**

Asmanex HFA is essentially the same product as Dulera but without the formoterol component.

Table 1. Table of products related to this submission.

Product	Active ingredients	Patient Population	Device	Date
Asmanex Twistinhaler	mometasone furoate	Asthma in patients of 12 years and older	DPI	Approved 03/ 30/ 2005
Asmanex Twistinhaler	mometasone furoate	Asthma in patients of 4 years and older	DPI	Approved 02/ 01/ 2008
Dulera	mometasone furoate and formoterol	Asthma in patients of 12 years and older	MDI	Approved 06/ 22/ 2010
Dulera	mometasone furoate and formoterol	COPD	MDI	Complete response 01/ 27/ 2012

3.3 What are the proposed mechanism of action and therapeutic indications?

Mometasone furoate is a corticosteroid with anti-inflammatory effects. The precise mechanism of action in asthma is unknown. The proposed indication is maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

3.4 What are the proposed dosages and routes of administration?

Asmanex HFA is an inhaled corticosteroid delivered via a hydrofluoroalkane (HFA)-propelled pressurized metered dose inhaler (pMDI). Two dosage strengths are proposed: 100 µg and 200 µg administered as 2 inhalations twice daily (BID). This review refers to the dose strengths 100 µg and 200 µg. The dose strength correspond to doses of 200 µg and 400 µg delivered by two actuations. The starting dose is dependent on previous corticosteroid therapy. The proposed dosages are summarized in **Table 2.**

Table 2. Recommended dosages for Asmanex HFA

Previous Therapy	Recommended dose	Total delivered dose
Inhaled medium-dose corticosteroids	100 µg 2 inhalations BID	200 µg BID
Inhaled high-dose corticosteroids	200 µg 2 inhalations BID	400 µg BID
Oral corticosteroids	200 µg 2 inhalations BID	400 µg BID

3.5 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

No new studies have been submitted in this application. For complete list of clinical pharmacology studies in the Dulera program please see the clinical pharmacology review of Dulera (NDA 22518) by Drs. Fan and Zhao dated May 21, 2009.

Sponsor is referencing studies in Dulera and the Asmanex Twistinhaler program. Below is a list of studies supported by the two programs.

Items supported by Dulera program (MF/F, MDI):

- HPA axis (Study PO3705)

Items supported by Dulera program (MF, MDI):

- Dose and dose regiment (phase II and Phase III trials)
- Oral prednisone reduction in Subjects with severe asthma (Study C97-224)
- Efficacy and safety in geriatrics and pediatrics (Phase III trials)

Items supported by Asmanex Twistinhaler program (MF, DPI):

- Drug-Drug interaction with CYP3A4 inhibitor: ketoconazole (Study I98-216)
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- Hepatic Impairment (Study C98-291)
- Reduction in bone mineral density (Study C98-302)

3.6 General Clinical Pharmacology

3.7 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Reference is made to Dr. Limb's review dated May 21, 2010 as well as **sections 3.8.1 to 3.8.4.**

3.8 What is the basis for selecting the product dose?

Dose selection for mometasone is based on trials performed in the Dulera program as well as the doses in the Asmanex Twistinhaler program. The following studies are

invoked by the sponsor in support of the proposed doses: C97208, C97225, I97200 and, C97224. These studies have been reviewed previously by Dr. Limb in her clinical review dated May 21, 2010. **Table 3** lists number of subjects and doses tested in the trials.

Table 3. List of studies supporting the proposed dose strengths of MF MDI, with the number of subjects per dose group

Trial ID	50 µg BID	100 µg BID*	200 µg BID*	400 µg BID	600 µg BID	800 µg BID	Placebo
C97-208**	71		73	74	73		72
C97-225**	58		57				59
I97-200**		176	182	176			
C97-224				42		43	38
Total number of subjects	129	176	312	292	73	43	169

The doses are delivered by two actuations BID.

** The proposed strengths.*

*** An additional active control arm was included in this trial.*

3.8.1 Study C97-208

Randomized, active and placebo controlled, parallel group, double blind trial in patient with moderate to severe asthma ages 12 to 81. Number of subjects in each arm is shown in **Table 3**. In addition to arms shown in **Table 3**, beclomethasone dipropionate MDI 168 µg was used as an active control. The main efficacy point was FEV1, which was not a trough value. Sponsor claims these values to be comparable to trough values because of majority of measurements were performed within 1 to 4 hours of the AM dose. All active treatments were superior compared to placebo, supporting the efficacy of MF 50 µg, 200 µg, 400 µg, and 600 µg dose strengths against placebo. FEV1 increased by 6.5% from baseline for the active control arm at week 12. In order to compare efficacy across trials, week 12 FEV1 values were used in **Figure 1.**

3.8.2 Study C97-225

Randomized, active and placebo controlled, parallel group, double blind trial in patient with moderate to severe asthma ages 12 years and older. In addition to those in **Table 3**, beclomethasone dipropionate MDI 168 µg was used as an active control. The primary efficacy endpoint was FEV1. All active treatments were superior compared to placebo, supporting the efficacy of MF 50 µg, 200 µg dose strengths against placebo. In order to compare efficacy across trials, week 12 FEV1 values were used in **Figure 1.** FEV1 increased by 8.2% from baseline for the active control arm at week 12.

3.8.3 Study I97-200

Randomized, active-control, evaluator blind, parallel group, phase III trial in patients with moderate to severe asthma. Fluticasone propionate MDI 250 µg was included as active comparator. The study did not include a placebo arm. The main efficacy point was FEV1, which was not a trough value. In order to compare efficacy across trials, week 12 FEV1 values were used in **Figure 1.**

3.8.4 Study C97-224

Randomized, placebo controlled, double-blind, parallel group, phase III trial in patients with moderate to severe asthma. The main efficacy endpoint was change in daily prednisolone requirement. FEV1 was evaluated as a secondary endpoint. All active treatments were superior compared to placebo, supporting the efficacy of MF 400 µg, 800 µg dose strengths against placebo. In order to compare efficacy across trials, week 12 FEV1 values were used in **Figure 1.**

The studies chosen by the sponsor to support the proposed doses have some important differences: 1) Not all studies were placebo-controlled (i.e., I97-200); 2) two different active comparators were used in studies C97-225 and C97-208 (beclomethasone dipropionate) and in study I97-200 (fluticasone propionate); 3) Studies C97-208, C97-225, and I97-200 were conducted in patients with moderately severe asthma while study C97-224 was conducted in patients with severe asthma; 4) The primary endpoint was FEV1 in studies C97-208, C97-225, and I97-200 while FEV1 was designated as secondary endpoint in study I97-200; 5) It is uncertain if all FEV1 values are considered trough values; 6) study I97-200 is essentially a corticosteroid reduction study while studies C97-208, C97-225, and I97-200 are dose ranging studies.

FEV1 change from baseline at week 12 is plotted verses dose strength for all studies, **Figure 1.**

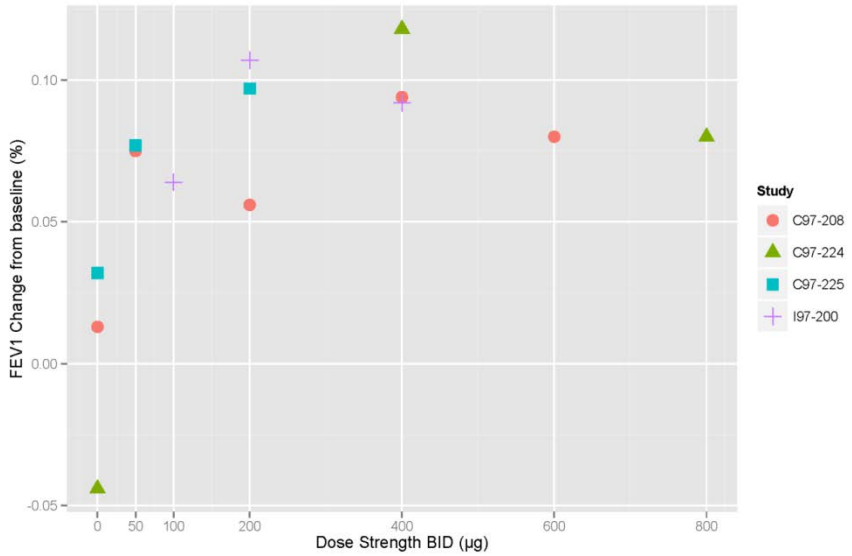


Figure 1. Integrated visualization of dose-response relationship for studies C97-208, C97-224, C97-225, and I97-200. Dose zero refers to placebo arm. Effect is defined as improvement in FEV1 at week 12. Dose strengths of 100 µg and 200 µg proposed for marketing in this submission. The doses are delivered by two actuations, BID.

3.8.5 Reviewer's analysis of dose-response relationship

Purpose

The purpose of this analysis is to compare the efficacy of Asmanex Twistinhaler and Asmanex HFA utilizing data from different studies and drug development programs.

Data: Asmanex HFA

Mean percent FEV1 change from baseline at week 12 was extracted from Section 2.7.3 – Summary of Clinical Efficacy for studies C97-208, C97-224, C97-225, and I97-200. The respective studies are summaries in **section 3.8.** The data is based on the per protocol population.

Data: Asmanex Twistinhaler

Mean percent FEV1 change from baseline at week 12 was extracted from Table 1, page 13 for study C96-134 from Dr. Gebert's statistical review of NDA 21067 (dated September 14, 1999). It is assumed that the data is based on the per protocol population.

Methods

Statistical software R (2.15.2) and the package "Dose-Finding" (0.9-9) was used to estimate the dose-response relationship[1]. Model selection for non-hierarchical as well as hierarchical models was based on Akaike information Criterion (AIC). Evaluated models and their corresponding AIC values are shown in **Table 4**.

[1] Björn B *et al*. Journal of Statistical Software (2009).

Statistical uncertainty in model selection should be accounted for when making inferences. If ignored, this uncertainty may lead to over-confident predictions and riskier decisions than initially believed[2]. Model averaging is a method where a number of pre-specified models are fit to the data and evaluated based on either the Akaike Information Criteria (AIC) or Bayesian information criterion (BIC). Predictions from each model are weighted against their respective AIC_i or BIC_i according to **Equation 1.** The final model average prediction will be based on all models in proportion to the individual model weight (w_i). Individual model weights are shown in **Table 4**.

$$w_i = \frac{\exp(-0.5\ AIC_i)}{\sum_i\ (\exp(-0.5 AIC_i))} \qquad \textbf{Equation 1}$$

The mean estimate and confidence intervals for the model average predictions were obtained by repeating the following steps for all models:

1. Fit all models to the data;
2. Sample 10,000 model parameters based on the estimated variance-covariance matrix;
3. Simulate 10,000 trials with the sampled model parameters;
4. Sample x number of trials where x is the product of w_i and number of simulated trials.

The 50th, the 10th, and the 90th percentile were obtained based on the weighted combined simulations.

This meta-analysis was based on reported mean change in FEV1 at week 12. Data from multiple studies (C97-208, C97-224, C97-225, and I97-200) was pooled. Although, dose-arm sample size ranged from 38 to 182 subjects, all study arms were given equal weighting. No attempt was made to estimate inter study variability. Homoscedastic variance and normally distributed data are assumed. Based on the purpose of this analysis, these assumptions are found acceptable.

Results

Based on AIC, the Linear in log model was chosen as the final model. Parameter estimates of the final model with their associated estimates of uncertainty are shown in **Table 5. Figure 2** and **Figure 3** illustrate the estimated dose-effect relationship based on the final model, and the model averaging approach. Parameter estimates and their respective relative standard error, based on the variance -covariance matrix, were used to generate the confidence interval for the predicted response.

Table 6 summarizes the estimated treatment effect with the final model and the model averaging approach. Effect is measured as percent change in FEV1 from baseline at week 12. The distributions of the predicted effect stratified by dose (based on the model averaging approach) are shown in **Figure 4.** The probability to show an improvement over baseline (2.31 L) of 140 mL or more is 93.59 and 95.95 percent for the 100 µg and

[2] Buckland, *et al.*, Biometrics (1997).

the 200 µg dose strengths, respectively. There is no evidence of dose separation between the 100 and the 200 µg dose.

In **Figure 3,** mean treatment effect at week 12 following Asmanex Twistinhaler (study C96-134) administration is shown as triangles. The data from study C96-134 was not used for model building purposes; it is plotted in figure 3 for illustrative purposes only. The derived dose-response relationship for Asmanex HFA appears to be representative of the Asmanex Twistinhaler dose-response observations, suggesting that the mean treatment effect for the two regimens is not expected to be different when administered at the same dose.

Conclusions

Asmanex Twistinhaler response is not expected to be significantly different from Asmanex HFA response, if not equivalent.

Similar conclusions can be made regardless of the approach employed (model averaging or parametric modeling). The higher dose strength shows a numerical superiority compared to the lower dose. However, confidence intervals of the mean effect are overlapping and dose separation appears to be minimal if at all present. In fact, the second best model (based on AIC) suggests a complete flat dose response curve for all doses.

Table 4. Evaluated dose-response models

Model	Equation	AIC	Model weight
Linear Model	$f(d,\theta) = E_0 + \delta d$	-48.14	0.00
Quadratic Model	$f(d,\theta) = E_0 + \beta_1 d + \beta_2 d^2$	-53.62	0.00
Logistic Model	$f(d,\theta) = E_0 + E_{\max} / \{1 + \exp[(ED_{50} - d)/\delta]\}$	-58.38	0.05
Sigmoid E_{max} Model	$f(d,\theta) = E_0 + E_{max}\frac{d^h}{ED_{50}^h + d^h}$	-58.89	0.06
Beta model	$f(d,\theta) = E_0 + E_{max}B(\delta_1,\delta_2)(d/scal)^{\delta_1}(1-d/scal)^{\delta_2}$ $B(\delta_1,\delta_2) = (\delta_1+\delta_2)^{\delta_1+\delta_2}/(\delta_1^{\delta_1}\delta_2^{\delta_2})$	-59.78	0.09
E_{max} model	$f(d,\theta) = E_0 + E_{max}\frac{d}{ED_{50} + d}$	-60.88	0.16
Piesewise flat dose response model	$if\ dose = placebo: f(d,\theta) = E_p$ $if\ dose \neq placebo: f(d,\theta) = E_t$	-61.79	0.26
Linear in log Model*	$f(d,\theta) = E_0 + \delta\log(d + off)$	-62.55	0.38

*AIC: Akaike information criterion (lower is better), d: dose variable, E0: placebo effect, Emax: maximum effect (for Beta model: within tested dose range), ED50: Dose giving half of the maximum effect, h, Hill parameter, determining the steepness of the model at the ED50, off: fixed value used to avoid problems with dose=0. Scal: fixed scale parameter, β: parameter of the quadratic model, δ: for exponential model: Parameter, controlling the convexity of the model, for Linear and lin-log model: Slope parameter, Logistic model: Parameter controlling determining the steepness of the curve. E1 Slope parameter for exponential model. * Selected as the final model.*

Table 5. Parameter estimates and their associated precision for the final (linear in log)

Parameter	Linear in log model (AIC -62.55)	
	Estimate	**Relative Standard error (%)**
E_0 (%)	0.064	9.46
δ (%/log(µg))	0.00398	17.11
Residual standard error	0.0226	NA

E0 is the estimated placebo effect at week 12 measured as change in FEV1 from baseline in percent, δ is the slope parameter estimating change in effect with increasing dose.Doses are delivered by two actuations, BID. Effect is measured as percent change in FEV1 from baseline at week 12

Table 6. Estimates of treatment effect based on parametric models and model averaging approach.

Method	Mean estimated effect (CI: 90%)			
	100 µg BID		**200 µg BID**	
Model Averaging	8.20% (6.81-9.20)	189.42 mL	8.51% (7.29-9.46)	196.58 mL
Final model (lin-log [AIC: -62.55])	8.24% (7.16-9.31)	190.34 mL	8.51% (7.40-9.62)	196.58 mL

Mean estimated effect is measured as percent change from baseline. Absolute change from baseline is calculated from the combined mean baseline value of 2.31 L from studies: C97-208, C97-224, C97-225, and I97-200.

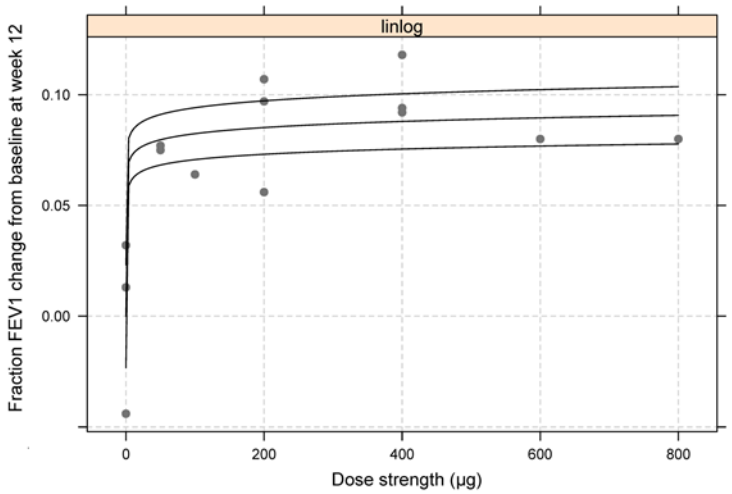


Figure 2. Estimated dose-response relationship based on the final model. Dose refers to dosage strength in µg. Response is defined as fraction FEV1 change from baseline. Grey circles represent the mean change from baseline for a dose group at week 12 of the study. Lines represent the mean predicted response with confidence interval (CI: 90%).

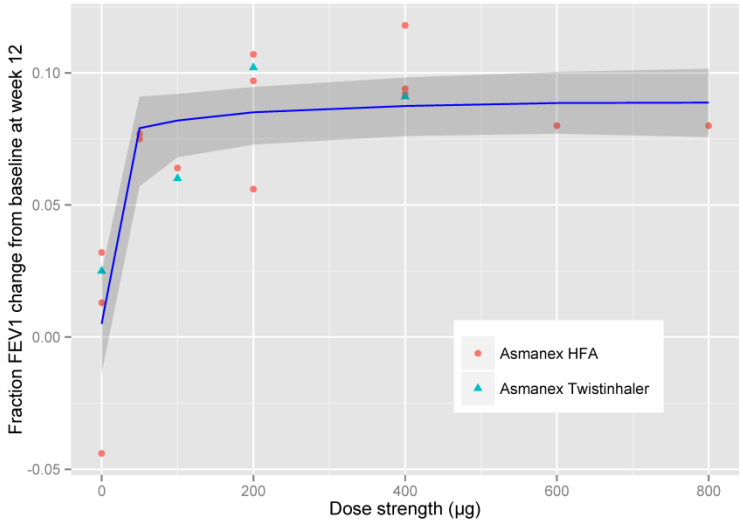


Figure 3. Estimated dose-response relationship based on the model averaging approach. Dose refers to dosage strength in µg. Response is defined as fraction FEV1 change from baseline. Circles represent the mean change from baseline for a dose group at week 12 for in a study. Lines and the shaded grey area represent the mean predicted response with confidence interval (CI: 90%). Data from Study C96-134 (Asmanex Twistinhaler) are superimposed in the plot (teal triangles) but where not used in generation of the model.

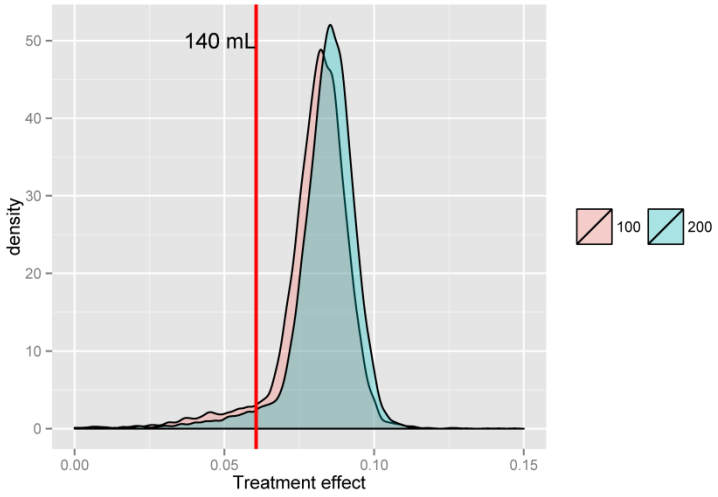


Figure 4. Weighted distributions of treatment effect for the 100 µg and the 200 µg dose strength. The red line indicates an improvement over baseline of 6.06 % or 140 mL. The probability to reach a treatment effect of 140 mL or greater is 93.59 and 95.95 percent forth the 100 µg and the 200 µg dose strengths, respectively.

3.9 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Systemic exposure of mometasone is of unknown importance to treatment effect. Dose selection based on efficacy is currently only informed by dose-response analysis.

3.10 What is previously known about the pharmacokinetics of MF

Oral bioavailability of mometasone has been determined to be less than 1%. Systemic exposure following inhalation is therefore likely to originate from local lung absorption. Following 28 days of inhaled administration of 400 µg mometasone BID, mean plasma concentrations at steady state ranged from 94 to 114 pg/mL and mean time to maximum concentrations ranged from 1 to 2.5 hours.

Intravenous administration of mometasone displays bi-phasic disposition with a mean terminal half-life of 5 hours. Steady state volume of distribution is estimated to 152 liters. Plasma protein binding was reported to be ~98% in the concentration range of 5 to 500 ng/mL.

In vitro studies have identified CYP3A4 as the major route of metabolism. However, no major metabolites have been identified. Radioactive mometasone is mainly excreted in feces (74%) and do some extend in urine (8%). Unchanged mometasone was not associated with radioactivity in urine, i.e. it is unlikely that un-metabolized mometasone is excreted in urine.

For detailed clinical pharmacology summary, the reader is referred to the clinical pharmacology review of Dulera (NDA 22518) by Drs. Fan and Zhao dated May 21, 2009.

3.11 What is the impact of chronic MF dosing on cortisol suppression

As no new clinical studies have been conducted and the sponsor is referring to the corticosteroid suppression studies submitted under the Dulera applications; detailed review of those studies can be found in the clinical pharmacology review of Dulera (NDA 22518) by Drs. Fan and Zhao dated May 21, 2009.

There is a lack of interaction between MF and F when they are administered together. Because of this, results of corticosteroid suppression studies conducted with MF/F MDI (Dulera) device are meaningful to this application. Please see section **3.12.1** for discussion on relative bioavailability between MF MDI and MF/F MDI.

3.12 General Biopharmaceutics

3.12.1 What is the relative bioavailability of the proposed product and Dulera

There are no statistically or clinically relevant differences in mometasone plasma exposure, following Asmanex HFA (MF MDI) or Dulera (MF/F MDI) administration. Because no pharmacokinetic or formulation interaction between formoterol and mometasone has been found, results from clinical pharmacology studies of mometasone when formulated with formoterol are relevant and applicable to this application.

The current submission does not include new clinical studies. For general discussion about the studies' design, please see clinical pharmacology review of Dulera (NDA 22518) by Drs. Fan and Zhao dated May 21, 2009.

The sponsor is supporting this application by making reference to the following studies in the Dulera program: P03658 and P05644. In addition to those trials the reviewer has identified trial PO4275, also from the Dulera program, to be relevant to this application **Table 7**.

Clinical pharmacology trials supporting this interaction intend to show the following:

- Lack of pharmacokinetic interaction between MF and F (PO3658)
- Lack of formulation interaction on MF when MF and F are formulated (MDI), (PO3658)
- MF systemic exposure is not dosage-form proportional (P05644)

Figure 5 summarizes the above-mentioned studies in an integrated forest plot. The implication of the results in study PO3658 are that pharmacokinetic characteristics of MF when delivered via MDI as a single ingredient product are similar to MF when co-formulated with F in a metered dose inhaler. These results provide the necessary bridge that allows the sponsor to rely on the studies conducted with MF/F in the Dulera program.

Study PO3658 suggest that 4 inhalations of 100/5 µg MF/F and 2 inhalations of 200/10 µg MF/F result in different exposure of MF. These results are relevant for single ingredient MF MDI because trial PO4275 established that there is no pharmacokinetic interaction between F and MF. These results may indicate that the 100 µg and the 200 µg dose strength may not be used interchangeably when adjusted by number of inhalations. One possible explanation to these finding is that the relative absorption surface increases

following four verses versus two inhalations. The increase relative absorption area would result in increased bioavailability.

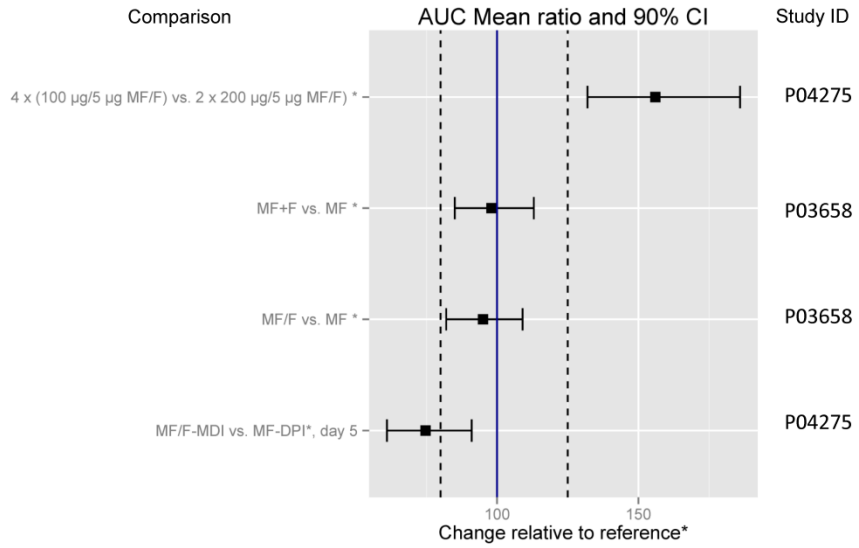
The original Dulera program relied, in part, on safety and efficacy of the approved Asmanex Twistinhaler program. The clinical pharmacology trials in the Dulera submission aimed to provide a link between the Asmanex Twistinhaler and Dulera. Trial PO4275 investigated the relative bioavailability of MF when administered via a single ingredient DPI device and via a MF/F MDI device. The results of trial PO4275 suggest that systemic exposure of MF is significantly lower following MDI administration compared to DPI administration **Table 7.** These results suggest that the two formulations MDI and DPI fail to deliver a bioequivalent dose of MF. Because of the findings in trial PO3658, the results are believed to be a due to formulation and/or device and not due to a metabolic interaction between F and MF.

Table 7. Formulation and drug interaction trials relevant to this submission.

Trial ID	Treatments arms	Population	Results
PO3658[1]	1) MF 800 µg MDI 2) F 20 µg MDI 3) MF 800 µg MDI+F 20 µg MDI 4) MF 800 µg/F 20 µg MDI	Healthy volunteers	There is a lack of interaction between MF and F when they are administered concomitantly via a MDI device.
P04275[1]	1) MF 800 µg/F 20 µg MDI 2) MF 800 µg DPI	Healthy volunteers	MF $AUC_{(0\text{-}12hr)}$ is approximately 52% to 25% lower following MDI administration compared with DPI administration.
PO5644[1]	1) 8 puffs x (50 µg/5 µg MF/F) MDI[2] 2) 4 puffs x (100 µg/5 µg MF/F) MDI[2] 3) 2 puffs x (200 µg/5 µg MF/F) MDI[2]	Healthy volunteers	MF dosage form proportionality could not be concluded. Treatment 1) resulted in 75% (95%CI: [48-108]) higher exposure compared of MF compared to treatment 3). Treatment 2) and 3) resulted in 56% difference in exposure.

MF: mometasone furoate, F: formoterol, AUC: area under the concentration-time curve, MDI: metered dose inhaler, DPI: dry powder inhaler. [1] Reference is made to clinical pharmacology review by Drs. Fan and Zhao dated May 21, 2009. [2] Total dose of MF was 800 µg in all treatments.

a)



b)

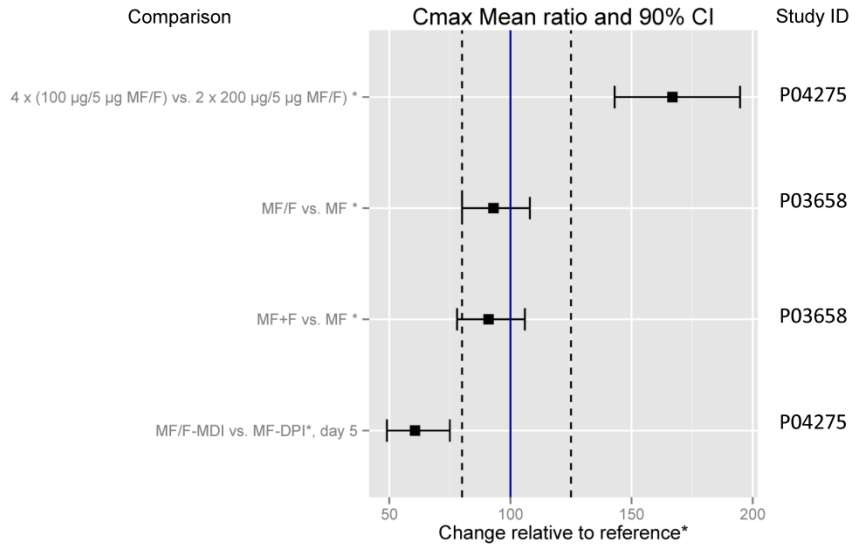


Figure 5. Integrated summary of results from studies P03658, P05644, and P04275. Figure 5a) shows the mean AUC ratio with 90% confidence intervals, figure 5b) shows the mean Cmax ration with 90% confidence intervals.

4 PRELIMINARY LABELING RECOMMENDATIONS

4.1 Clinical Pharmacology

The proposed label is acceptable form a clinical pharmacology perspective.

5 APPENDIX

5.1 Proposed Package insert from the sponsor

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

12.2 Pharmacodynamics

HPA Axis Effects

The effects of inhaled mometasone furoate administered via ASMANEX HFA on adrenal function have not been directly evaluated. However, the effects of inhaled mometasone furoate administered (b) (4) on adrenal function were evaluated in two clinical trials in patients with asthma. As no evidence of a pharmacokinetic drug interaction between mometasone furoate and formoterol was observed when the two drugs were administered (b) (4), the HPA axis effects from (b) (4) are applicable to ASMANEX HFA. (b) (4) Although both these trials have open-label design and contain a small number of subjects per treatment arm, results from these trials taken together demonstrated suppression of 24-hour plasma cortisol AUC for (b) (4) 200 mcg/5 mcg compared to placebo consistent with the known systemic effects of inhaled corticosteroid.

In a 42-day, open-label, placebo- and active-controlled study, the mean change from baseline plasma cortisol $AUC_{(0\text{-}24\ hr)}$ was 8%, 22% and 34% lower compared to placebo for the (b) (4) 100 mcg/5 mcg (n=13), (b) (4) 200 mcg/5 mcg (n=15) and fluticasone propionate/salmeterol xinafoate 230 mcg/21 mcg (n=16) treatment groups, respectively.

In a 52-week, open-label safety study, the mean plasma cortisol $AUC_{(0\text{-}24\ hr)}$ was 2.2%, 29.6%, 16.7%, and 32.2% lower from (b) (4) 100 mcg/5 mcg (n=18), (b) (4) 200 mcg/5 mcg (n=20), fluticasone propionate/salmeterol xinafoate 125/25 mcg (n=8), and fluticasone propionate/salmeterol xinafoate 250/25 mcg (n=11) treatment groups, respectively.

The potential effect of mometasone furoate via a dry powder inhaler (DPI) on the HPA axis was assessed in a 29-day study. A total of 64 adult patients with mild to moderate asthma were randomized to one of 4 treatment groups: mometasone furoate DPI 440 mcg twice daily, mometasone furoate DPI 880 mcg twice daily, oral prednisone 10 mg once daily, or placebo. The 30-minute post-Cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 mcg/dL for the mometasone furoate DPI 440 mcg twice daily group and 20.8 mcg/dL for the mometasone furoate DPI 880 mcg twice daily group, compared to 14.5 mcg/dL for the oral prednisone 10 mg group and 25 mcg/dL for the placebo group. The difference between mometasone furoate DPI 880 mcg twice daily (twice the maximum recommended dose) and placebo was statistically significant.

12.3 Pharmacokinetics

As no evidence of a pharmacokinetic drug interaction between mometasone furoate and formoterol was observed when the two drugs were administered from (b) (4), the pharmacokinetics information from (b) (4) is applicable to ASMANEX HFA.

Absorption

Healthy Subjects: Following oral inhalation of single doses of ASMANEX HFA, mometasone furoate was absorbed in healthy subjects with median T_{max} values ranging from 0.50 to 2 hours. Following single-dose administration of higher than recommended dose of ASMANEX HFA (4 inhalations of ASMANEX HFA 200 mcg) in healthy subjects, the arithmetic mean (CV%) C_{max} and $AUC_{(0\text{-}tf)}$ values for mometasone furoate were 53 (102) pg/mL and 992 (80) pg•hr/mL, respectively. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of mometasone furoate is negligible (<1%).

Asthma Patients: Following oral inhalation of single and multiple doses of the (b) (4), mometasone furoate was absorbed in asthma patients with median T_{max} values ranging from 1 to 2 hours. Following single-dose administration of (b) (4) 400 mcg/10 mcg, the arithmetic mean (CV%) C_{max} and $AUC_{(0\text{-}12\ hr)}$ values for mometasone furoate were 20 (88) pg/mL and 170 (94) pg•hr/mL, respectively, while the corresponding estimates following twice daily dosing of (b) (4) 400 mcg/10 mcg at steady-state were 60 (36) pg/mL and 577 (40) pg•hr/mL.

Distribution

Based on the study employing a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder in humans, no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an intravenous 400 mcg dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean steady-state volume of distribution of 152 liters. The *in vitro* protein binding for mometasone furoate was reported to be 98% to 99% (in a concentration range of 5 to 500 ng/mL).

Metabolism

Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. *In vitro* studies have confirmed the primary role of human liver CYP3A4 in the metabolism of this compound; however, no major metabolites were identified. Human liver CYP3A4 metabolizes mometasone furoate to 6-beta hydroxy mometasone furoate.

Excretion

Following an intravenous dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine. Absorbed mometasone furoate is cleared from plasma at a rate of approximately 12.5 mL/min/kg, independent of dose. The effective $t_{½}$ for mometasone furoate following inhalation with DULERA was 25 hours in healthy subjects and in patients with asthma.

Special Populations

Hepatic/Renal Impairment: There are no data regarding the specific use of ASMANEX HFA in patients with hepatic or renal impairment.

A study evaluating the administration of a single inhaled dose of 400 mcg mometasone furoate by a dry powder inhaler to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pg/mL). The observed

peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels were few.

Gender and Race: Specific studies to examine the effects of gender and race on the pharmacokinetics of ASMANEX HFA have not been specifically studied.

Geriatrics: The pharmacokinetics of ASMANEX HFA have not been specifically studied in the elderly population.

Drug-Drug Interactions

A single-dose crossover study was conducted to compare the pharmacokinetics of 4 inhalations of the following: mometasone furoate MDI, formoterol MDI, (b) (4) (mometasone furoate/formoterol fumarate MDI), and mometasone furoate MDI plus formoterol fumarate MDI administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between mometasone furoate and formoterol.

Inhibitors of Cytochrome P450 Enzymes: Ketoconazole: In a drug interaction study, an inhaled dose of mometasone furoate 400 mcg delivered by a dry powder inhaler was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pg/mL on Day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pg/mL on Day 9 (211-324 pg/mL). Mometasone furoate plasma levels appeared to increase and plasma cortisol levels appeared to decrease upon concomitant administration of ketoconazole.

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/s/

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