CLINICAL REVIEW

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Division / Office	DPARP, ODE II, OND
Reviewer Name(s)	Kimberly A. Witzmann, MD
Review Completion Date	March 21, 2014
Established Name	Mometasone furoate
(Proposed) Trade Name	Asmanex HFA
Therapeutic Class	Inhaled corticosteroid (ICS)
Applicant	Merck
Formulation(s)	Inhaled via MDI
Dosing Regimen	2 inhalations of 100- or 200mcg BID
Indication(s)	“maintenance treatment of asthma”
Intended Population(s)	≥12 years with asthma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommended regulatory action is Approval of mometasone furoate HFA metered dose inhaler (MDI) for the twice daily treatment of asthma in patients 12 years of age and older for both proposed doses, mometasone furoate (MF) 100 mcg, two actuations (therapeutic dose 200 mcg), and mometasone furoate 200 mcg, two actuations (therapeutic dose 400 mcg).

1.2 Risk Benefit Assessment

The proposed indication for mometasone furoate HFA MDI is "for the maintenance treatment of asthma as prophylactic therapy in (b) (4) 12 years of age and older." Two dose strengths are proposed in this NDA: MF 100 and 200mcg (ex-mouthpiece dose) administered as two inhalations twice daily. This review refers to the therapeutic dose of MF delivered by two actuations, i.e., MF 200 and MF 400, respectively. This clinical review concludes that the application provides adequate information to support the indication for the maintenance treatment of asthma in patients 12 years and older for the two proposed doses.

The support for efficacy of both the MF 200 and MF 400 doses is demonstrated in clinical trials originally conducted for the combination therapy application, Dulera (mometasone furoate/formoterol fumarate (MF/F) [NDA 22-518]. The combination product was approved in 2010, at which time the Sponsor agreed to develop a mometasone furoate monotherapy MDI for treatment of asthma. As agreed upon by the FDA, this application includes clinical trials conducted under the combination product development program.

In terms of benefit, support for the efficacy of MF 200 is provided in the factorial design Study P04334, which included evaluation of MF 200, and provided a statistically significant comparison against placebo. The efficacy of MF 400 is provided in Study P04431, which demonstrated numerical separation of the mometasone furoate/formoterol fumarate (MF/F) 400/10 combination product over the 200/10 dose, in terms of trough FEV1. Additional studies from a related, older MF MDI program (which evaluated a similar MF MDI HFA) provide additional support for both doses. While there are other inhaled corticosteroid (ICS) products available, an important benefit of MF MDI to patients and clinicians lies within this drug-device; offering MF as an MDI will provide more effective step-down therapy for patients with moderate to severe asthma who are prescribed the Dulera combination. Currently, patients using Dulera transition to either mometasone furoate in a different device, Asmanex Twisthaler dry powder inhaler (DPI), or to a different inhaled corticosteroid (ICS)

altogether, which could potentially interrupt asthma control due to these differences. With the availability of the mometasone monotherapy as an HFA MDI, patients potentially will be able to wean to the corresponding ICS medium- or high-dose inhaled corticosteroid monotherapy, when deemed clinically appropriate to trial off of a LABA-containing combination, as is recommended in clinical practice guidelines for asthma, and labeling of combination ICS-LABA products.

In terms of risk, the common adverse event profiles for MF 200 and 400 are comparable to those for Asmanex Twisthaler (mometasone furoate dry powder inhaler (DPI)). There were no appreciable differences in events based on dose level. No asthma-related deaths or intubations were reported, and there were few hospitalizations related to exacerbations within the program; seven total events were evenly distributed across MF doses (including those in combination with formoterol), active comparator arms, and placebo groups. Given the extensive known safety profile of mometasone furoate, and data from this MDI HFA program, no REMS are deemed necessary.

In summary, the benefit-risk assessment for MF 200 and MF 400 is favorable, and supports approval of these two dose levels for the treatment of asthma indication. In addition, the availability of an MF MDI HFA monotherapy provides an important tool in the clinician's armamentarium of asthma therapies, to allow for appropriate step-down therapy from the combination Dulera (MF/F) HFA product. No additional evaluations of post-marketing safety are deemed necessary at this time; any risks can be mitigated through professional labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Clinical review recommends no additional postmarketing risk evaluation and mitigation strategies. At this time, the Division of Risk Management (DRISK) concurs that risk mitigation measures beyond professional labeling are not warranted for Asmanex HFA (MF). They note that MF MDI has proven efficacy for maintenance treatment of asthma as demonstrated by the clinical program, the safety profile is consistent with the known safety profile for comparable approved products, and thus, the benefit-risk profile for MF MDI is favorable and the risks can be mitigated through professional labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

The Clinical review recommends no additional postmarketing requirements. At this time, the Division of Risk Management (DRISK) concurs that risk mitigation measures beyond professional labeling are not warranted for Asmanex HFA (MF). They note that MF MDI has proven efficacy for maintenance treatment of asthma as demonstrated by the clinical program, the safety profile is consistent with the known safety profile for

comparable approved products, and thus, the benefit-risk profile for MF MDI is favorable and the risks can be mitigated through professional labeling.

Pediatric Studies
The Sponsor is currently evaluating the safety and efficacy of mometasone furoate in patients 5 to 11 years of age, under the Written Request for the combination mometasone furoate/ formoterol fumarate (Dulera) program, issued on July 23, 2012. Under that WR, the Sponsor is required to complete an efficacy and safety study in children aged 5-11 years, "with the goal of determining the appropriate dose or doses of mometasone HFA in the intended pediatric population," as well as a second study to assess combination therapy against the corresponding monotherapy, such that "doses chosen must be doses that could be safe and efficacious as single-ingredient HFA formulation." A third long-term safety study is also required.

The Pediatric Review Committee met on January 15, 2014, and agreed that the PREA requirements for Asmanex HFA are being met by those described in the Written Request for the combination mometasone furoate/ formoterol fumarate MDI product, and that no additional pediatric studies are required.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product is mometasone furoate (MF) metered-dose inhaler (MDI), which is an inhaled corticosteroid (ICS). The proposed trade name is Asmanex HFA®. Two dosage strengths are proposed: 100mcg per inhalation, and 200mcg per inhalation (ex-mouthpiece dose) to be given as 2 inhalations twice daily (BID). This review refers to the therapeutic dose of mometasone delivered by two actuations, i.e., MF 200mcg and 400mcg, respectively. Mometasone is also approved to treat asthma in a dry powder inhaler formulation, as Asmanex Twisthaler®.

Mometasone is also available as part of the Dulera® MDI product [NDA# 22-518], approved in 2010, which consists of two dosage strengths of mometasone furoate ICS, in combination with formoterol fumarate, a long-acting beta-agonist (LABA): 100/5mcg per inhalation (200/10mcg BID), and the 200/5mcg per inhalation (400/10mcg BID). (b) (4) During the review of Dulera, the Applicant agreed to bring forward a mometasone MDI monotherapy, because there is no other MDI formulation available for mometasone to use as step-down therapy from the combination ICS-LABA, as recommended in national and international asthma guidelines. No new studies have been conducted to

support this NDA; the pivotal data is the same as was used in the Dulera registration program.

The proposed indication is the maintenance treatment of asthma in (b) (4) 12 years and older, which is in line with the labeled indication for the mometasone DPI product (Asmanex Twisthaler).

2.2 Currently Available Treatments for Proposed Indications

In general, the main drugs approved for the treatment of asthma include short-acting and long-acting beta-agonists, inhaled corticosteroids (ICS), and long-acting beta-agonist/ ICS combination products. According to NHLBI and GINA guidelines, ICS are first-line treatment for persistent asthma, with ICS/LABA combination products recommended for moderate to severe persistent asthma. Other classes of drug approved for the treatment of asthma include leukotriene inhibitors, inhaled cromolyn, theophylline, and anti-IgE therapy (omalizumab).

Mometasone furoate, a 17-heterocyclin glucocorticosteroid, has been marketed in the US since 2005 as a multiple dose dry powder inhalation (DPI) formulation [NDA 21-067, Asmanex Twisthaler®]. Asmanex Twisthaler was approved for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is available in a 110 and 220 mcg DPI formulation (100 and 200 mcg ex-mouthpiece, respectively). The recommended dose ranges from 110 mcg QD in children 4 to 11 years of age and 220 mcg QD to 440 mcg BID in patients 12 years and older. Efficacy and safety information for mometasone furoate are summarized in the current approved package insert for Asmanex Twisthaler.

Other ICS products approved for the treatment of asthma include:

- Alvesco MDI (ciclesonide)
- Asmanex DPI twisthaler (mometasone furoate)
- Flovent MDI and DPI (fluticasone)
- Pulmicort DPI (budesonide)
- Pulmicort respules (budesonide)
- QVAR MDI (beclomethasone diproprionate)

Combination ICS plus LABA products to treat asthma include the following:

- ADVAIR MDI and DPI (fluticasone/salmeterol)
- Dulera MDI (mometasone furoate/ formoterol fumarate)
- Symbicort MDI (budesonide/ formoterol fumarate)

2.3 Availability of Proposed Active Ingredient in the United States

Mometasone furoate is available in DPI form as Asmanex Twisthaler, and as the ICS component of the combination therapy, Dulera, as described in section 2.2. The moiety is also approved as Nasonex nasal spray [NDA 20-762], for use in seasonal and perennial rhinitis in adults and children down to age 2, and is available for the treatment of steroid-responsive dermatoses as Elocon, in ointment, cream, and lotion forms [NDAs 19-543, 19-625, and 19-796, respectively].

2.4 Important Safety Issues with Consideration to Related Drugs

The safety issues related to the use of inhaled corticosteroids are well-characterized in both the clinical literature, and in Prescribing Information of FDA-approved products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

(b) (4)

MF as a dry powder inhaler (DPI) was approved in 2005, and Schering-Plough developed Dulera, the mometasone furoate/ formoterol fumarate combination metered-dose inhaler HFA product, which was approved in 2010. Pertinent details of the development programs and regulatory history are described below:

- December 23, 1996- Opening of IND 52,214, mometasone furoate MDI (original MDI program)
- March 30, 2005- Asmanex Twisthaler DPI Approved for ≥12 years of age in asthma [NDA 21-067]
- March 28, 2006- Dulera MDI pre-IND meeting to discuss program design
- February 01, 2008- Asmanex Twisthaler DPI supplemental NDA approved to extend indication to ≥4 years of age
- April 11, 2010- Response to IR under Dulera NDA review, in which Sponsor agrees to develop a mometasone furoate monotherapy MDI for treatment of asthma
- June 22, 2010- Dulera MDI Approved for ≥12 years of age in asthma [NDA 22-518]
- September 09, 2011- Pre-IND pre-meeting comments for mometasone furoate monotherapy MDI product submission [IND 112,669] agreed that no additional clinical trials would be necessary for mometasone furoate MDI approval, due to the factorial design of the combination program, in that the approval of combination inherently agrees that each of the monotherapies provides appropriate efficacy. However, FDA raised two issues:
    - Support for the 400mcg MF dose did not have a placebo comparator

    - Labeling concerns with regard to data from a related, older MDI formulation
- June 27, 2013- NDA 205-641 submitted for mometasone furoate HFA

2.6 Other Relevant Background Information

The pivotal studies for this NDA are two of the 3 studies originally submitted to the Dulera HFA MDI program [NDA 22-518]. No new studies have been conducted to support this MF monotherapy application, as agreed upon in the pre-NDA meeting in 2011. The Applicant has also submitted supportive data from the related, older mometasone furoate MDI program, which utilized a somewhat different MF MDI product. (b) (4) The older MF program, however, did provide the dose-ranging studies in support of Dulera, and the review team concluded that the products were similar enough to inform appropriate dose selection for the Dulera product, which employed the currently marketed formulation in its Phase 3 program. The MF single-agents used in the Dulera Phase 3 program are those currently proposed for registration as MF monotherapy in this NDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The original NDA dated June 27, 2013, was submitted in electronic common technical document (eCTD) format, well-organized, and easily navigated by this reviewer. There were no issues with respect to submission quality and/or integrity.

No OSI reviews were requested for this NDA, because an OSI review was already completed for the same pivotal studies submitted under the Dulera review, NDA 22-518. Under that application, in September to October of 2009, clinical sites 12 and 16 were inspected. Site 12 had minor variances noted and a Voluntary Action Indicated (VAI) letter was sent. For site 16, although several regulatory violations were noted on a form 483 that was issued (temperature logs for storage areas were not reviewed by the Monitor at monitoring visits, but no temperatures out-of-range were found), these findings were deemed unlikely to affect the data integrity of the clinical trial, and OSI concluded that the studies appeared to have been adequately conducted, and the data submitted by the Applicant was appropriate to use in support of the indication sought.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each clinical study report, within the electronic submission.

3.3 Financial Disclosures

The financial disclosure information for the two pivotal trials was already submitted as part of the review for the Dulera product, under NDA 22-518, and which revealed three investigators with disclosable financial interests or agreements (honoraria from $16,500 to $50,000) with the Applicant):

- (b) (6) $30,000 honoraria (b) (6)
- (b) (6) $50,000 honoraria and consulting fees (b) (6)
- (b) (6) $16,500 honoraria for presentations in reference to Nasonex and Asmanex (b) (6)

The Applicant has therefore submitted the required financial disclosure information.

The Applicant has also submitted a Debarment statement to Module 1.3.3 of this NDA submission, certifying that no debarred individuals were used in the conduct of the trials included in this NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The MF MDI product proposed here by the Applicant is essentially the same as the approved mometasone furoate/ formoterol fumarate MDI combination product (Dulera) but without the formoterol component, and the same as the mometasone furoate (MF) monotherapy comparator used for the Dulera Phase 3 clinical trials. The MF 100 mcg and 200 mcg MDIs utilize an hydrofluoroalkane (HFA-227: 1,1,1,2,3,3,3-heptafluoropropane) propelled pressurized metered dose inhaler containing sufficient amount of drug for 120 actuations. After priming, each actuation of the inhaler delivers 115 or 225 mcg of mometasone furoate in 69.6 mg of suspension from the valve and delivers 100 or 200 mcg of mometasone furoate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. The MF MDI also contains ethanol as a co-solvent, and oleic acid as a surfactant. The container

closure system for the drug products consists of a16 mL aluminum canister [redacted] closed with a 50 µL metering valve. A [redacted] press and breathe actuator with the mouthpiece cap is provided with the pressurized canister to deliver a dose to the patient. The [redacted] actuator [redacted] dose counter.

It is worth noting that the MF product used in the original MF MDI program, which provided the MF dose ranging trials used in support of Dulera, differed somewhat from the MF product used in the Phase 3 program. [redacted] This was evaluated by the CMC reviewers during the review of the Dulera NDA, and overall the Dulera team concluded that the differences in the products were not considered to have a significant effect on the program, [See the CDTL Review for Dulera NDA 22-518, dated June 22, 2010, page 10].

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval; see the primary CMC review by Dr. Xiaobin Shen, dated March 18, 2014, for further details..

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

There are no non-clinical studies submitted that were not already reviewed under NDA 22-518 for the approved Dulera combination product. Therefore, there are no clinical implications based on new non-clinical data. For a summary of the non-clinical program, please see the Asmanex Pharmacology Toxicology review dated March 07, 2014, by Dr. Timothy Robison. The non-clinical recommendation is for approval.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Mometasone furoate (MF) is an inhaled corticosteroid that acts as an anti-inflammatory. The precise mechanism of action in asthma is not known, but is believed to involve inhibition of multiple cell types in the lungs, including mast cells, eosinophils, neutrophils, macrophages, and lymphocytes), and release of inflammatory mediators from these cells.

4.4.2 Pharmacodynamics

Clinical Pharmacology Program
The Clinical Pharmacology review has determined that 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 [Refer to Dr. Dinko Rekic's Clinical Pharmacology review under this NDA 205-641, dated March 14, 2014]. The assessment of the clinical pharmacology review is that the application is acceptable, and final recommendations are for approval.

HPA Axis Effects
The effects of MF MDI monotherapy on adrenal function have not been directly evaluated; however, these were evaluated under both the Dulera (MF/F) and Asmanex Twisthaler (MF DPI) programs, and are described in the Twisthaler and Dulera labels. Mometasone plasma exposure is significantly lower when administered by a MDI (Asmanex HFA) device compared to a DPI (Asmanex Twisthaler) device. The potential effect of MF DPI on the HPA axis was assessed in a 29-day study of 64 adult patients with mild to moderate asthma, who were randomized to one of 4 treatment groups: MF DPI 440 mcg BID, MF DPI 880 mcg BID, 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 MF DPI 440 mcg BID group and 20.8 mcg/dL for the MF DPI 880 mcg BID 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 MF DPI 880 mcg BID and placebo was statistically significant.

Because systemic MF exposure following MF MDI is significantly lower than following MF DPI administration, reduction in bone mineral density as well as growth inhibition in pediatrics would presumably be less severe with the new product. Therefore, the Applicant's choice to reference studies conducted with MF DPI is appropriate, as this would represent a "worst case scenario" [Refer to Dr. Dinko Rekic's Clinical Pharmacology review under this NDA 205-641, dated March 14, 2014].

Dose selection
The dose selection program for MF MDI is the same as that for the combination Dulera program. It was based on approved doses for the Asmanex Twisthaler (MF DPI) product and additional trials performed in the related, older MF MDI monotherapy program. These trials were submitted as part of the New Drug Application for Dulera [NDA 22-518], and have been evaluated by the previous review team. Four trials conducted with the related MF MDI were found to support the MF dose selection and provide confirmatory evidence of efficacy for the MF monocomponent; studies C97-208, C97-225, I97-200, and C97-224 have been re-submitted to this current application. Studies C97-208, C97- 225, and C97-224 were 12-week, placebo-controlled dose ranging trials, and I97-200 was active controlled. Of these trials, C97-208 and C97-225

provided replicate evidence of efficacy for MF 200 compared to placebo based on the change from mean baseline FEV1. C97-208 and C97-224 provided replicate evidence of efficacy for MF 400 compared to placebo. These will be briefly described below. In the related, older MF monotherapy program, the FEV1 value used was not a trough measurement, which is what is typically used to assess the efficacy of an ICS product. This issue was discussed at length in the primary Dulera review [NDA 22-518], and while the use of trough values would be preferable, the results of these trials were felt to provide adequate support for the Dulera application, and therefore are acceptable in this application as well.

The applicant did not conduct a relative bioavailability study in patients with asthma, but it was determined under the Dulera review that, since the pharmacokinetic profiles of mometasone furoate and formoterol fumarate by inhalation route are well known, the program is adequate [See Division Director Summary Review of Regulatory Action for Dulera NDA 22-518, dated June 22, 2010, page 3].

The Dulera review also included a relevant fifth trial, P04275, which was not re-submitted in this current NDA, but is described briefly here for its relevance to safety of the mometasone product. P04275 was an open-label, crossover study conducted in 12 healthy subjects intended to compare the pharmacokinetic exposures from MF MDI formulation to the approved MF DPI formulation, Asmanex Twisthaler. It showed that systemic exposure of MF from Dulera was lower compared to that from Asmanex Twisthaler (MF DPI) at the same nominal dose (AUC was approximately 52% and 25% lower on day 1 and day 5, respectively). Studies using oral dosing of labeled and unlabeled mometasone have demonstrated that systemic bioavailability of mometasone is negligible (less than 1%). The lower exposure for mometasone from the MDI product compared to Asmanex Twisthaler (MF DPI) assures systemic safety, such as HPA axis effect, for the mometasone component in Dulera. It was also determined that the Applicant has adequately assessed the HPA axis effect of Dulera in separate studies; see “HPA Axis Effects,” above. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 24-25, as well as the Division Director Summary Review of Regulatory Action for Dulera NDA 22-518, dated June 22, 2010, page 3].

The drug product used in the dose-selection studies is not the same as the to-be-marketed MF MDI (as noted in Section 4.1 Chemistry Manufacturing and Controls, above). This difference in products was considered in the Dulera review, because studies conducted under the related, older MF MDI program were used in support of dose selection for Dulera, as well as are proposed here. The differences in the products were not considered to have a significant effect on the program, given the flat dose response from 200-600mcg of MF, and the doses chosen from these older studies were carried forward into the Phase 3 program for Dulera, which then utilized the new formulation of MF MDI. Ultimately the MF 200 and 400mcg BID doses were approved as part of the Dulera combination product [See the CDTL Review for Dulera NDA 22-518, dated June 22, 2010, page 10].

Study C97-208

Study C97-208 was a 12-week, randomized, active- and placebo-controlled, parallel group, double-blind, double dummy trial in 435 patients aged 12 to 81 years with moderately severe asthma. The primary objective of the trial was to compare 4 dose levels of MF MDI (50, 200, 400, and 600 mcg BID) to placebo. Beclomethasone dipropionate MDI (Vanceril) 168 mcg BID was included as an active control. The main efficacy endpoint was the change in FEV1 from baseline to the last visit. These measurements were not trough FEV1 measurements, but study sites were encouraged to schedule spirometry at the same time of day throughout the trial to reduce diurnal variation, with specific timing of PFTs in relation to dosing not prescribed. (According to the Applicant, the majority of assessments were performed within 1 to 4 hours after the AM dose). As the ICS is not expected to have an acute effect, the Applicant has posited that these values would be expected to be comparable to trough values. All active treatments showed statistically significant increases in FEV1 from baseline compared to placebo ($p<0.01$). However, there was no separation among the MF doses and no lowest effective dose was identified in terms of the change in FEV1. See Table 1, below.

Table 1: MF Dose-Ranging Studies vs. Placebo: Change in mean FEV1 from Baseline (L)

Dose	N	Baseline FEV1 (L)	Change from Baseline	Difference from Placebo	P
Study C97-208					
MF 50	71	2.49	0.12	0.21	<0.01
MF 200	73	2.51	0.14	0.23	<0.01
MF 400	74	2.61	0.12	0.21	<0.01
MF600	73	2.52	0.13	0.22	<0.01
Beclomethasone 168	72	2.57	0.02	0.11	<0.01
Placebo	72	2.38	-0.09		
Study C97-225					
MF 50	58	2.49	0.13	0.31	<0.01
MF 200	57	2.66	0.16	0.34	<0.01
Beclomethasone 168	58	2.73	0.18	0.36	<0.01
Placebo	59	2.53	-0.18		

MF= Mometasone furoate MDI; Beclomethasone= beclomethasone diproprionate (Vanceril)

Source: Modified from Table 2, Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 26, and from original study reports C97-208 and C97-225 in Module 5.3.5.4.

Secondary efficacy variables assessed included AM and PM PEFR, nocturnal awakenings, SABA use, and clinical asthma exacerbations. For PEFR, all doses of MF were statistically better than placebo ($p\leq0.02$). Treatment with MF 200 resulted in a change from baseline of 21.64 L/min compared to -15.63 L/min for placebo ($p<0.01$). Similarly, all doses of MF showed greater decreases in the number of daily inhalations of Proventil compared to placebo ($p<0.01$) and in the number of nocturnal awakenings

(p<0.01). For the purposes of this trial, a clinical asthma exacerbation was defined as a worsening of asthma that resulted in emergency treatment, hospitalization or treatment with additional asthma medications (other than SABA). Overall, the number of patients with an asthma exacerbation during the trial was low (n=23) and no major differences were noted among treatment groups (MF 50, n=3; MF 200, n=2; MF 400, n=3; MF 600, n=4; BDP 168, n=5, and placebo, n=4).
In summary, the results of C97-208 support the efficacy of MF 50, 200, 400, and 600 against placebo, but do not show a clear separation in terms of efficacy for this MF dose range. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 25-26].

Study C97-225

Study C97-225 was a 12-week randomized, double blind, double dummy, placebo controlled, parallel group trial in 232 patients age 12 years and older with asthma. The main objective was to compare the efficacy of MF 50 and 200 to placebo with beclomethasone dipropionate 168 mcg (Vanceril) as an active comparator. The MF 50 mcg dose level was included with the intention of demonstrating a “no effect” dose. As in Study C97-208, the primary endpoint was the change in FEV1 from baseline to Endpoint (last study visit). As shown in Table 1, the MF 50 and 200 mcg dose levels showed a similar, statistically significant difference from placebo. Numerically, MF 200 showed a greater increase over placebo than MF 50 with a treatment difference of 30mL. Like C97-208, secondary efficacy variables included AM and PM PEFR, SABA use, nocturnal awakenings, and clinical asthma exacerbations. Both doses of MF displayed statistically greater changes in AM and PM PEFR from baseline compared to placebo (p<0.01) with a numerical trend favoring MF 200 (20.90 L/min) over MF 50 (15.2 L/min). Similarly, MF 50 and 200 demonstrated greater decreases in the number of SABA puffs used per day; -0.69 and -1.16 puffs/day, respectively, compared to +0.83 puffs/day for placebo (p<0.01). The number of nocturnal awakenings was also decreased for both MF 50 (-0.02) and MF 200 (-0.05) compared to placebo (p<0.01). Clinical asthma exacerbations, defined as in C97-208, were infrequent in the trial. A total of 13 patients reported an exacerbation during the 12 weeks: 7 in the placebo arm compared to 2 patients in the MF 200 arm and none in the MF 50 arm. In summary, the results of C97-225 support the efficacy of MF 50 and 200 against placebo, with MF 200 demonstrating a numerical advantage over MF 50 in terms of the primary efficacy endpoint, mean change from baseline FEV1, and several of the secondary efficacy endpoints. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 26-27].

Study I97-200

Study I97-200 was a phase 3, 12 week, randomized, active-controlled, evaluator blind, parallel group trial in 715 patients with moderately severe asthma. The main objective was to compare the efficacy and safety of 3 dose levels of MF MDI (100, 200, and 400). Fluticasone propionate CFC MDI 250 mcg was included as an active comparator. The primary efficacy variable was the change in FEV1 from baseline to Endpoint (last visit). The values obtained were not trough values, and there was no placebo arm. Similar changes from baseline were observed for MF 200 and 400 and FP 250 (Table 2); there was no clear numeral separation between the MF 200 and 400 mcg dose levels but there was a treatment difference of 90 mL between MF 100 and MF 200. The increases observed for MF 200 and 400 well as FP 250 were statistically significantly greater than the change from baseline observed for the MF 100 ($p<0.04$).

Table 2: Study I97-200: Change in meanFEV1 from Baseline to Endpoint (L)

Dose	N	Baseline FEV1 (L)	Change from Baseline	Difference from MF 100	P
Study I97-200					
MF 100	176	2.45	0.10	---	---
MF 200	182	2.41	0.19	0.09	<0.01
MF 400	176	2.49	0.18	0.08	<0.01
Fluticasone 250	176	2.49	0.21	0.11	<0.01

MF= Mometasone furoate MDI; Fluticasone= fluticasone propionate CFC MDI

Source: Modified from Table 3, Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 28, and from original study reports I97-200 in Module 5.3.5.4.

Numerical separation among the 3 MF doses (MF 100, 200, 400) was observed for several secondary endpoints, including the following:

- Wheezing scores: -0.04, -0.14, and -0.19, respectively. FP 250: -0.19.
- Difficulty breathing: -0.04, -0.15, and -0.19, respectively. FP 250: -0.17
- Number of nocturnal awakenings: -0.01, -0.02, -0.15, respectively FP 250: -0.05

For SABA use and clinical asthma exacerbations, results were similar in magnitude to FP 250 but no clear separation was observed among the 3 MF dose levels. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 27-28].

Study C97-224

Study C97-224 was a Phase 3, randomized, double-blind, placebo-controlled efficacy and safety trial in patients ages 12 to 83 years with severe asthma. The primary objective was to evaluate the safety and efficacy of MF MDI 400 and 800 BID in reducing oral prednisone use. A total of 123 patients initially enrolled in a 3-month phase in which they were randomized to MF 400 (n=42), MF 800 (n=43), or placebo (n=38). Subsequently, patients entered a 9-month phase during which they were

treated with open-label, variable doses of MF (400 mcg BID to 800 mcg BID) as oral prednisone therapy was withdrawn. The primary efficacy endpoint was the percent change from Baseline at Endpoint (last available 3-month data) in daily prednisone requirement. FEV1 was evaluated as a secondary endpoint. In terms of the steroid reduction primary endpoint, MF 400 and 800 performed similarly and were statistically significantly different from placebo ($p<0.01$). A -39% and -31% prednisone dose reductions were reported for MF 400 and MF 800, respectively, compared to a 107% increase in placebo. As noted in Table 3, for the secondary endpoint of change from baseline FEV1, both MF treatment arms had a change from baseline of +0.08 L compared to -0.17L for placebo (treatment difference 0.25 L), supporting the efficacy of MF 400 and 800 over placebo while indicating that the MF 800 did not appear to provide additional efficacy benefit. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 28-29].

Table 3: Study C97-224: Change in Mean FEV1 from Baseline (L) at 3 Months

Dose	N	Baseline FEV1 (L)	Change from Baseline	Difference from Placebo	P
Study C97-224					
MF 400	42	1.79	0.08	0.25	<0.01
MF 800	43	1.71	0.08	0.25	<0.01
Placebo	38	1.71	-0.017		

MF= Mometasone furoate MDI;

Source: Modified from Table 3, Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 29, and from original study reports C97-224 in Module 5.3.5.4.

4.4.3 Pharmacokinetics

Pharmacokinetic studies supporting efficacy of Asmanex HFA have been conducted as part of the Dulera program where MF MDI was used as a monotherapy comparator to allow for a factorial design program. The Absorption, Distribution, Metabolism, and Excretion (ADME) data for MF were evaluated under the Dulera program, and the proposed language for MF MDI labeling is taken directly from the Dulera label. Data from special populations, including those with hepatic and renal impairment, is also the same as is described in the Dulera label [Dulera package Insert, Section 12.3, Pharmacokinetics]. MF is noted to have increased plasma levels when given concomitantly with inhibitors of Cytochrome P450 enzymes; a drug interaction study conducted under the Dulera program administering MF concomitantly with ketoconazole noted increased MF peak plasma levels over MF administered alone.

With regard to drug-drug interactions, the Clinical Pharmacology 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. They conclude that the

Applicant has fulfilled the clinical pharmacology requirements of a NDA and no further clinical pharmacology studies are warranted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies relevant to clinical decision making for this application are listed in Table 4, below. The Applicant's drug development program for MF MDI is unusual, in that the pivotal efficacy and safety trials were conducted as part of the program for the combination MF/F MDI product, Dulera. Additional studies conducted by the Applicant in the late 1990's using a slightly different MDI product than the to-be-marketed one, are also provided in support of MF MDI. Specifically, studies beginning with "C97" and "I97" are from the original MDI program conducted in the 1990's; one of the Phase 3 trials for that program failed to meet its primary efficacy endpoint (Study C97-226), but was included as additional support of safety for the MF MDI. Even though they do not utilize the to-be-marketed formulation, these studies from the related, older MF MDI program are relevant, in that they used the same non-CFC propellant as the to-be-marketed formulation (and that used in the marketed Dulera product), and the older MDI product was assessed during the Dulera review, and was found to have comparable product performance [See Cross-Discipline Team Leader Review for Dulera NDA 22-518, dated June 22, 2010, pages 3-4].

Table 4: Studies Relevant to Clinical Regulatory Decision Making

Study #/ *Year*	Study Design	Study Duration	Age	Baseline FEV1	Asthma severity	N	Treatment Arms	Primary efficacy
Efficacy and Safety Asthma Trials								
P04334 US, Canada, EU, Asia, South America *2008*	R, DB, PC Safety Efficacy	26 week	12-76	60-90% predicted	Mod to severe; medium ICS [MF run-in]	781	MF/F 200/10 BID MF 200 BID F10 BID Placebo	Post-dose FEV1 (exacerbation)
P04431 US, Europe, South America *2008*	R, DB Safety Efficacy	12 week	12-84	50-85% predicted	Mod to severe; High dose ICS	728	MF/F 200/10 BID MF/F 400/10 BID MF 400 BID	Post-dose FEV1 (exacerbation)
Dose Selection Studies								
C97-208 US *1998*	PC, AC, Dose-range	12 week	12-81	60-90% predicted	Mod; ICS	435	MF-MDI 50 BID MF-MDI 200 BID MF-MDI 400 BID MF-MDI 600 BID BDP 168 BID	1-4 hr post-dose FEV1

							Placebo	
C97-224 US *1999*	PC Efficacy, Safety	12 wk +9mo OLE	12-83	40-85% predicted	Severe; Oral CS	123	MF-MDI 400 BID MF-MDI 800 BID Placebo	% change in daily prednisone requirement
C97-225 US *1998*	PC Efficacy, Safety	12 week	12-72	60-90% predicted	Mod; ICS	232	MF-MDI 50 BID MF-MDI 200 BID BDP 168 BID Placebo	1-4 hr post-dose FEV1
I97-200 EU, South America, South Africa *1998*	AC Efficacy, Safety	12 week	12-76	55-90% predicted	Mod; ICS	715	MF-MDI 100 BID MF-MDI 200 BID MF-MDI 400 BID FP MDI 250 BID-CFC	1-4 hr. post-dose FEV1
Other Supportive Studies								
C97-222 US *1999*	R, AC, OL LT safety	52 week	12-70	60-90% predicted	Mod.; ICS	308	MF MDI 200 BID MF MDI 600 BID BDP 168 BID	none
C97-223 *1999*	R, DB,PC Efficacy, Safety	12 wk +9mo OLE	12-79	55-85% predicted	Asthma; SABA only	251	MF MDI 200 Qam MF MDI 400Qam Placebo	Change in FEV1
C97-226 US *1998*	R, DB, PC Phase 3	12 week	12-68	55-85% predicted	Mild to mod; SABA only	330	MF-MDI 100 QDam MF-MDI 400 QDam MF-MDI 200 BID Placebo	Change in FEV1 (Supportive safety; failed to meet 1ry)
C97-227 US *1998*	R, DB,PC Phase 3 Dose interval	12 wk [+4wk MFrun-in]	12-71	60-90% predicted	Mod; ICS [MF run-in]	245	MF-MDI 200 QDam MF-MDI QDpm MF-MDI 400 QDpm MF-MDI 200 BID Placebo	Change in FEV1
P04139	R, OL, AC Long-term safety HPA axis	52 weeks	12-75	60-90% predicted	Mod to severe, on ICS	404	MF/F 200/10 BID MF/F 400/10 BID F/SC 250/50 BID F/SC 500/50 BID	Long-term safety study
P03418	Bone Mineral density	52 weeks	18-49	--	Asthma never treated with ICS	277	MF 200 QD/ML pcb MF 400 QD/ML pcb FP 250 BID/MLpcb ML 10 QD/DPI pcb ML 10 QD/MDI pcb	Bone Mineral density
P03705 US *2008*	HPA Axis	6 week	18-64	>60% predicted	Mild to moderate	66	MF/F200/10 BID MF/F 400/10 BID Advair 500/100 BID placebo	none

a= P04075 was closed early at the completion of 12 weeks' treatment, for non-safety reasons

MF=mometasone furoate; F=formoterol fumarate; MF/F=mometasone + formoterol; BDP= beclomethasone diproprionate; F/SC= fluticasone + salmeterol; ML= montelukast; FP= fluticasone propionate; pcb=placebo; QD= once daily; BID= twice daily

5.2 Review Strategy

This clinical review will focus on the demonstration of benefit of the MF monotherapy component from the pivotal Phase 3 efficacy and safety trials from the combination Dulera program, Studies P04431 and P04334, which will be discussed in detail in Section 6, Clinical Efficacy. Section 5.3 below will discuss the endpoints from each of these studies with regard to the protocol-defined primary and secondary endpoints, as well as supportive endpoints. Other studies from the Dulera review are briefly discussed, but do not provide primary support of the efficacy of the MF doses here (Studies P04139, P04073, P04705); these will be described briefly for their support of safety. In addition, trials utilizing a related, older formulation of the MF MDI were reviewed, to support dose selection, as well as to provide additional supportive efficacy and safety. Most of these studies were reviewed under the Dulera submission [NDA 22-518], and have been summarized as applicable.

Section 4.4.2 addresses the design, conduct, and major pharmacodynamic results of the Phase 2 pharmacokinetic and pharmacodynamic trials, including the studies used for dose selection. Section 5.3 briefly describes the design, conduct, and pertinent efficacy results for the individual Phase 3 trials, as well as provides brief review of supportive studies, including those from the older MF development program. Discussion of the pivotal trial designs, including endpoint selection and major efficacy conclusions from these trials, and how they relate to the efficacy of the MF MDI product as a whole, is presented in Section 6. Safety information from the pivotal trials (including long-term safety), is described in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Studies P04334 and P04431: Design and Conduct

Two studies from the Dulera adult and adolescent asthma program utilized the proposed, to-be-marketed formulation of MF MDI as monotherapy arms in the clinical development program These studies, P04334 and P04431, are considered pivotal Phase 3 studies for the current application in support of efficacy and safety of the MF 200 and 400 monotherapy products. These studies have been thoroughly reviewed under NDA 22-518 for Dulera, and therefore will be only briefly discussed here. [For detailed description of these trials, refer to Dr. Limb's Primary Clinical Review of Dulera, NDA 22-518, Section 5.3].

Study P04334 was a 26-week, randomized, double-blind, double-dummy, placebo-controlled study of 781 patients 12 years and older with persistent asthma (FEV1 60-90% predicted), who were not well-controlled despite medium does of ICS, alone or in combination with LABA. Patients underwent a screening period followed by a 2 to 3 week open-label run-in period with MF 200 mcg BID and then a 26-week double-blind

treatment period. Patients were randomized 1:1:1:1 to 1 of 4 possible treatment groups: MF/F 200/10 BID, MF 200 BID, formoterol fumarate (F) 10 BID, and placebo. This was a full-factorial design study for the combination Dulera, and as such, it captured the use of MF MDI 200 against the combination MF 200/F 10 product, and against placebo.

Study P04431 was a 12-week, randomized, double-blind, parallel-group, controlled trial in 728 patients 12 years and older with severe persistent asthma (FEV1 50-85% predicted), who required high-dose ICS or ICS/LABA therapy and had a history of exacerbations. Patients underwent a screening period followed by a 2 to 3 week open-label run-in period with MF 400 mcg BID and then a 12-week double-blind treatment period. Patients were randomized 1:1:1 to 1 of 3 possible treatment groups: MF/F 400/10 BID, MF/F 200/10 BID, and MF 400 BID. The study did not include a placebo arm because it was considered unethical to withhold controller therapy from patients with severe persistent asthma. Instead, the two (now approved) doses of combination therapy were compared with the higher dose MF 400 monoproduct.

The studies shared a number of similarities in design, and all study treatments were given twice daily. Enrolled patients had to be 12 years of age and older, have a documented history of asthma for ≥ 12 months and demonstrate response to bronchodilator (reversibility with a ≥ 12% increase in FEV1 following albuterol administration or PEF variability >20% or PEF diurnal variations >20%). The required FEV1 percent predicted varied depending upon the asthma severity (>60% or >50%). Baseline use of ICS was required. Patients in Study P04431 must have had at least one asthma exacerbation requiring oral glucocorticosteroids 2 to 12 months prior to screening. Patients with ≥ 10 pack year smoking history or current smokers were excluded. Prohibited medications and washout periods for both studies were similar.

A 2-3 week run in period was followed by the randomized treatment period (12 or 26 weeks). Clinic visits occurred at Baseline, Weeks 1, 4, 8, 12, (and 16, 20, and 26, for Study P04334) during which pulmonary function tests (PFTs) were measured. PFTs were conducted according to ATS criteria. At baseline, Week 1, Week 12, and the final visit, PFTs were measured 30 minutes and immediately prior to the morning dose (pre-dose or trough) and then 5, 15, 30 minutes, 1, 2, 3, 4, 6, 8, 10, 11, and 12 hours post-dose.

Both studies were designed to support registration and approval of the MF/F combination product, Dulera, as noted by the choice of primary efficacy endpoints. Study P04334 had two primary efficacy variables: change in FEV1 AUC 0-12 hours from baseline to week 12 (to show the contribution of the formoterol fumarate component of the combination), and time to first severe asthma exacerbation (to show the contribution of the mometasone furoate component of the combination). In Study P04431, because there is no formoterol monotherapy or placebo group, the FEV1 AUC 0-12 hours is the single primary efficacy endpoint. Because the endpoint of FEV1 AUC 0-12 hours assesses the contribution of formoterol, and not the contribution MF

monotherapy, it will not be discussed in detail [refer to Dr. Limb's Primary Clinical Review of Dulera, NDA 22-518, for details].

In the Dulera program, to evaluate the efficacy of MF, time to first severe asthma exacerbation was identified as a co-primary endpoint in Study P04334, and was assessed as a secondary variable in P04431. However, the Division identified concerns regarding the definition of asthma exacerbation when the Phase 3 protocols were initially submitted, since correlation of pulmonary function parameters with symptoms was not included (patients could qualify based on FEV1 or PEFR results alone), and duration of symptoms was not specified. Because of concerns with this definition, the Division noted that for the contribution of the MF, the secondary endpoint, trough FEV1, would be closely reviewed [see Cross-Discipline Team Leader Review for Dulera NDA 22-518, dated June 22, 2010, page 11, and Dr. Limb's Primary Clinical Review of Dulera, NDA 22-518].

For this reason, change in mean trough FEV1 from baseline to endpoint will be assessed for the demonstration of efficacy in this MF MDI program [see Section 6 Review of Efficacy, for more detail]. The Applicant notes that although the study protocols specified pre-dose (trough) FEV1 as an additional secondary endpoint, it was elevated to a key secondary endpoint in their statistical data analysis plan, prior to database lock, in response to FDA concerns [Module 2.7.3, Summary of Clinical Efficacy, section 2.7.3.1.4.2].

Other pertinent efficacy variables assessed in these studies were the Asthma Quality of Life Questionnaire (AQLQ), the Asthma Control Questionnaire (ACQ), peak expiratory flow rates (PEFR), symptom scores, and nocturnal awakenings. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory evaluations, ECGs, and CXR.

Study P04334: Specific Results

Protocol Changes and Deviations

Clarifications and changes in the Study P04334 protocol were unlikely to have impacted the efficacy findings of the trial. A total of 360 randomized patients were reported as having at least one protocol deviation. The most commonly reported protocol deviations included the following: no acceptable PFT curve after 3 attempts, incomplete ACQ/AQLQ entries, and dose taken outside the protocol-specified time window. The protocol deviations appear to have been distributed across all treatment arms and do not indicate any gross systematic bias [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 55].

Patient Disposition

A total of 781 patients from 152 sites worldwide were randomized. One of the 781 patients was randomized but did not receive at least one dose of double-blind study medication. Of the 781 patients, 551 (71%) completed the protocol specified double-blind treatment period while 230 (29%) discontinued early from the trial; see Table 5 below. Treatment failure was cited at the main reason for early discontinuation (n=114, 15% overall), with a greater proportion occurring in the F and placebo treatment arms. Few patients discontinued due to AEs.

Table 5: Study P04334: Disposition

Disposition (N, %)	MF/F 200/1 N=191	MF 200 N=192	F 10 N=202	Placebo N=196
Randomized	191 (100)	192 (100)	202 (100)	196 (100)
Early discontinuation	35 (18)	33 (17)	85 (42)	77 (39)
Adverse event	4 (2)	6 (3)	9 (4)	7 (4)
Treatment failure	8 (4)	15 (7)	47 (23)	46 (23)
Lost to follow-up	3 (2)	---	---	2 (1)
Withdrawal of consent, unrelated	6 (3)	3 (2)	8 (4)	8 (4)
Withdrawal of consent, related	---	1 (1)	3 (1)	5 (3)
Noncompliance	4 (2)	5 (3)	9 (4)	6 (3)
Did not meet protocol eligibility	9 (5)	4 (2)	9 (4)	3 (2)
Administrative	1 (1)	1 (1)	---	---
Completed	156 (82)	159 (83)	117 (58)	119 (61)

MF= Mometasone furoate MDI; F= formoterol fumarate

Source: Modified from Dulera Primary Clinical Review, Table 17, and original study report P04334, Table 3 in Module 5.3.5.4.

Demographics and Baseline Characteristics

Overall, the gender, age, and race distribution across the four treatment groups were comparable. The patient population had a mean age of 42 years, and was 59% female and 72% white, with pediatric patients ages 12 to <18 years (n=63).

Relevant demographic data and baseline characteristics are further described in Table 6, below.

Table 6: Study P04334: Patient Demographics and Baseline Characteristics

	MF/F 200/10 N=191	MF 200 N=192	F 10 N=202	Placebo N=196	Total N=781
Sex (n, %)					
Female	97 (51)	112 (58)	129 (64)	122 (62)	460 (59)
Male	94 (49)	80 (42)	73 (36)	74 (38)	321 (41)
Race (n, %)					
White	136 (71)	135 (70)	146 (72)	143 (76)	560 (72)
Non-white	55 (29)	57 (30)	56 (28)	53 (27)	221 (28)
Asian	31 (16)	28 (14)	24 (12)	26 (13)	112 (14)
Black	8 (4)	11 (5)	9 (4)	7 (4)	30 (4)
Multi-racial	16 (8)	21 (10)	23 (11)	19 (10)	78 (10)
Pacific Islander	-	2 (1)	-	1 (<1)	3 (<1)
Age (years)					
Overall					
Mean (SD)	43 (16)	43 (15)	42 (15)	42 (15)	42 (15)
Median	46	45	44	44	45
Range	12-70	12-73	12-76	12-69	12-76
12 to <18 years					
N	19	10	18	16	63
Mean (SD)	14 (2)	14 (2)	14 (2)	14 (2)	14 (2)
Median	14	14	14	14	14
Range	12-17	12-17	12-17	12-17	12-17
18 to <65 years					
N	161	173	174	169	577
Mean (SD)	45 (13)	42 (13)	43 (12)	43 (13)	43 (13)
Median	48	45	45	45	46
Range	18-64	18-64	18-64	18-64	18-64
≥65 years					
N	11	9	10	11	41
Mean (SD)	67 (2)	68 (3)	70 (4)	66 (1)	68 (3)
Median	67	68	70	67	67
Range	65-70	65-73	65-76	65-69	65-76
Asthma Duration (years)					
Mean (SD)	16 (14)	17 (15)	16 (13)	15 (14)	16 (14)
Median	12	15	12	11	12
Baseline FEV1 (mean, SD)					
L	2.4 (0.6)	2.4 (0.7)	2.3 (0.6)	2.3 (0.6)	2.3 (0.7)
% predicted	72.4	72.6	73.2	72.4	72.6
% reversibility (screen)	18.9	18.2	19.0	19.1	18.8
FEV1/FVC	0.73	0.73	0.73	0.72	0.73
Questionnaire Score					
ACQ	1.54 (0.75)	1.49 (0.77)	1.51 (0.78)	1.50 (0.75)	1.51 (0.76)
AQLQ	5.31 (1.05)	5.37 (1.08)	5.41 (1.05)	5.46 (0.99)	5.38 (1.04)

MF= Mometasone furoate MDI; F= formoterol fumarate MDI; ACQ= Asthma Control Questionnaire; AQLQ= Asthma Quality of Life Questionnaire

Source: Modified from Table 18, Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 57, and from Summary of Clinical Efficacy in Module 2.7.3.2.1.1.1., Table 12

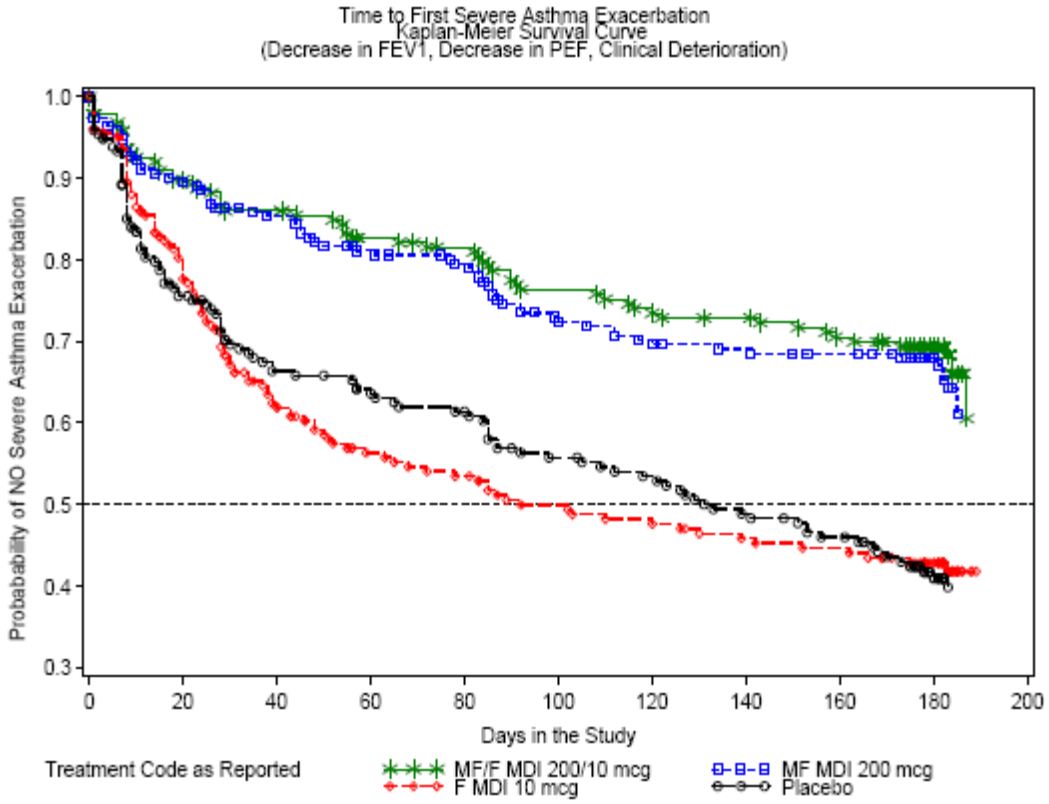
Co-Primary Efficacy Variable: Change in Mean FEV1 AUC0-12 hours from Baseline to Week 12

Under the original Dulera application for which these efficacy studies were designed, the change in mean FEV1 AUC 0-12 hours endpoint was an appropriate endpoint for assessing the bronchodilatory effects of the MF/F combination product, and evaluating the contribution of the F monocomponent to the combination. The current package is evaluating the efficacy of the MF monotherapy, so this endpoint does not provide direct support; however, in Study P0443, the numerical differences between MF/F 400/10 and MF/F 200/10 in the change in mean FEV1 AUC 0-12 hours clinically supported the justification of two dose levels for Dulera.

Co-Primary Efficacy Variable: Time to First Severe Asthma Exacerbation

The time to first asthma exacerbation over 26 weeks of treatment was the other primary endpoint, intended to demonstrate the contribution of the MF component to the MF/F combination. The primary treatment comparison was MF/F 200/10 mcg BID vs. F 10 mcg BID. Due to the overall lower than expected rate of exacerbations, a median time first exacerbation could not be established for the MF/F and MF treatment groups. For the F and placebo arms, the median times were Day 92 and Day 131, respectively. A total of 341 patients experienced an asthma exacerbation at some point during the treatment period. The majority qualified on the basis of PEF decreases and a smaller group qualified on the basis of FEV1 decreases. Few patients reported clinical deterioration as a feature of the first severe asthma exacerbation, although the majority of those attributed to clinical deterioration occurred in the F treatment group (n=18) and the placebo group (n=9) compared to the MF/F and MF treatment arms (n=3 and n=5, respectively), supporting the efficacy of the MF component. Over the course of the trial, a total of 79 patients experienced some kind of clinical deterioration. The clinical deteriorations were mainly unscheduled visits and/or treatment with systemic corticosteroids or other medications (n=46). Three patients were hospitalized and 10 patients received emergency treatment for asthma during the trial. A Kaplan-Meier survival curve illustrating the time to first severe asthma exacerbation is shown below in Figure 1. MF was statistically superior to placebo ($p<0.001$) and MF/F was statistically superior to F ($p<0.001$). These results supported the efficacy of the MF component in the MF/F combination.

Figure 1: P04334: Time-to-First Severe Asthma Exacerbation (Kaplan-Meier)



[Source: Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, Figure 8, pg. 59, and from Summary of Clinical Efficacy in Module 2.7.3.2.1.1.3., Figure 1]

Supportive Efficacy

None of the secondary endpoints in this study were pre-specified to determine a statistically-significant change in MF 200 over placebo, and therefore did not adequately control for Type I error. So while the true statistical significance of these endpoints is considered nominal, the demonstration of p-values within the generally-accepted range of <0.05 are from a clinical perspective, considered reassuring and supportive of the overall efficacy of MF.

Trough FEV1

Trough FEV1 was designated as a key secondary efficacy endpoint as an additional assessment of the MF contribution to the MF/F combination within the Dulera program. While the main comparison was MF/F vs. F, all pairwise comparisons were evaluated. There was a greater increase in the mean change in trough FEV1 between the MF/F and F treatment arms and the results were statistically significant (0.13 vs. <0.01; p<0.001; treatment difference = 0.13), which provided support for the Dulera product.

For the MF MDI program, the change in mean trough FEV1 from baseline to endpoint comparing MF 200 against placebo, provides the treatment difference of interest which

supports the efficacy of the MF 200 dose. The comparison of MF 200 over placebo was statistically significant (difference of 0.12, p<0.001). These results provide support for the efficacy of MF 200. This will be discussed further in Section 6.

Table 7: Study P04334: Trough FEV1 (L) at Week 12

	MF/F 200/10 (A)		MF 200 (B)		F 10 (C)		Placebo (D)	
	N	LS mean (% change)	N	LS mean (% change)	N	LS mean (% change)	N	LS mean (% change)
Baseline	187	2.33	190	2.36	197	2.29	191	2.30
Week 12	167	0.13 (5.5)	175	0.07 (2.9)	141	0.00 (1.7)	145	-0.05 (-1.1)
Pairwise comparisons			**A-B**	**A-C**	**A-D**	**B-C**	**B-D**	**C-D**
P			0.119	<0.001	<0.001	0.058	<0.001	0.170
95% CI			-0.01, 0.13	0.05, 0.20	0.11, 0.25	-<0.01, 0.14	0.05, 0.20	-0.02, 0.13

MF= Mometasone furoate MDI; F= formoterol fumarate MDI

Source: Modified from Table 20, Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 60, and from Study P04334 CSR, Module 5.3.5.1, Section 11.4.1.3, Table 13

Other Secondary Endpoints

Other key secondary endpoints included change from baseline to endpoint in ACQ score, change from baseline to endpoint in AQLQ score, and change from baseline across the 26-week treatment period in the proportion of nights with nocturnal awakenings. All showed a statistically significant difference for the MF/F group over placebo, which was the main comparison. These endpoints also assessed pairwise comparisons of MF 200 versus placebo.

The proportion of nocturnal awakenings for those receiving MF 200 showed a 60% decrease from baseline, with a p-value of <0.05 when compared against placebo. This result supports the efficacy of MF 200.

For the AQLQ, the score at endpoint for MF 200 group was statistically significantly greater than that of the placebo group, but the change did not reach the established Minimal Clinically Important Difference (MCID) of $\geq$0.5 (0.38, p<0.05). For the ACQ, the difference in MF 200 versus placebo was 0.38 (p<0.05), but no MCID has been established for the ACQ score. These statistically significant changes have unclear clinical relevance, but are generally supportive of efficacy of MF 200 over placebo.

Additional secondary variables were evaluated, including AM and PM peak expiratory flow rates (PEFR), morning and evening asthma symptom scores, and rescue medication usage. Pairwise comparisons of MF 200 compared to placebo met statistical significance, and are generally supportive of the efficacy of MF 200 over placebo, as shown in Table 8, below. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 60-63; Source: Module 2.7.3.2.1.1.2, Summary of Clinical Efficacy, Tables 13-14, and Module 5.3.5.1, CSR for Study P04334].

Table 8: Study P04334: Supportive Efficacy Endpoints

Secondary Variable	Baseline Value	Change from Baseline	Difference from Placebo	P
Proportion of Nights with Nocturnal Awakenings				
MF 200 (N=192)	0.16	-0.05	60%	<0.05
Placebo (N=196)	0.15	0.00		
AQLQ Score				
MF 200	5.40	0.37	0.38	<0.05
Placebo	5.56	-0.01		
ACQ Score				
MF 200	1,46	-0.23	0.37	<0.05
Placebo	1.41	0.14		
AM PEFR (Liters/min)				
MF 200	369.5	1.7	30.1	<0.05
Placebo	367.5	-28.4		
AM/PM Asthma Symptom Score				
MF 200	1.30	-0.41	0.50	<0.05
Placebo	1.29	0.09		
Total SABA Rescue Use				
MF 200	1.64	-0.24	1.32	<0.05
Placebo	1.95	1.08		

MF= Mometasone furoate MDI; AQLQ= Asthma Quality of Life Questionnaire; ACQ= Asthma Control Questionnaire; SABA= short-acting beta-2 agonist

Source: Modified from Tables 13-14 in Module 2.7.3.2.1.1, Summary of Clinical Efficacy; original study report C97-226 in Module 5.3.5.1; and Modified from Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 60-63,.

Efficacy Evaluation for Patient Subgroups

As noted in the primary clinical review of Dulera, gender, race, and BMI did not appear to impact results of the trial. Overall, in terms of age, patients 12 to <18 years of age (n=63) had comparable results to the patients 18 to <65 years of age. "Patients >65 years of age had less robust results than the rest of the cohort, although MF/F still performed numerically better to each of the monocomponents and placebo. The reduced efficacy may reflect a greater prevalence of fixed airway disease in older individuals or may be partly due to the small number of evaluable patients >65 years at Week 12 included in this subgroup (n=33 at Week 12)." [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 63]

With regard to the MF component alone, specific subgroup analysis was not evaluated, due to the small number of patients in each age cohort (n=10 for patients 12 to <18 years, and n=9 for patients>65 years in the MF 200 group, respectively). These small numbers preclude any meaningful interpretation of the data; however, the larger MF/F program overall, as well as the Asmanex Twisthaler [NDA 21-067] provide reassurance for efficacy across age groups.

Study P04334 Summary Conclusions

Study P04334 was designed as a full-factorial study to assess the efficacy of MF/F 200/10 mcg BID over each of its mono-components, F 10 mcg BID and MF 200 mcg BID, as well as over placebo. The study met that goal, and provided support for approval of the MF/F combination product. For the MF MDI monotherapy program, the key secondary efficacy variable, trough FEV1, demonstrates the efficacy contribution of the MF200 component over placebo, which provides the basis for support of the MF 200 dose in this application. Other secondary efficacy endpoints, including rescue medication use, nocturnal awakenings, ACQ, AQLQ, and AM and PM PEFs were generally supportive and statistically significant in most instances for the comparison of MF to placebo, although these analyses were not pre-planned and do not adequately control for Type I error.

Study P04431: Specific Results

Protocol Changes and Deviations

Clarifications and changes in the Study P04431 protocol were unlikely to have impacted the efficacy findings of the trial. A total of 469 randomized patients were reported as having at least one protocol deviation. The most commonly reported protocol deviations included the following: trial visit outside of the protocol-specified window, no acceptable PFT curve after 3 attempts, incomplete ACQ/AQLQ entries, and dose taken outside the protocol-specified time window. The protocol deviations appear to have been distributed across all treatment arms and do not indicate any gross systematic bias [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 68].

Patient Disposition

A total of 728 patients from 115 sites worldwide were randomized. All randomized patients received at least one dose of double-blind study medication. Of the 728 patients, 643 (88%) completed the protocol specified double-blind treatment period, while 85 (12%) discontinued early from the trial, as seen in Table 9, below. Treatment failure was cited at the main reason for early discontinuation (n=32, 4% overall). Few patients discontinued due to AEs. The distribution of patients who discontinued early in each category was similar across the three treatment groups.

Table 9: Study P04431: Disposition

Disposition (N, %)	MF 200/10	MF 400/10	MF 400
Randomized	233 (100)	255 (100)	240 (100)
Early discontinuation	25 (11)	27 (11)	33 (14)
Adverse event	2 (1)	2 (1)	5 (2)
Treatment failure	11 (5)	8 (3)	13 (5)
Lost to follow-up	1 (<1)	---	1 (<1)
Withdrawal of consent, unrelated	1 (<1)	2 (1)	4 (2)
Withdrawal of consent, related	---	---	1 (<1)
Noncompliance	3 (1)	9 (4)	3 (1)
Did not meet protocol eligibility	7 (3)	5 (2)	5 (2)
Administrative	---	1 (<1)	1 (<1)
Completed	208 (89)	228 (89)	207 (86)

MF= Mometasone furoate MDI; F= formoterol fumarate

Source: Modified from Dulera Primary Clinical Review, Table 25, and clinical study report P04431, Table 3 in Module 5.3.5.4.10.1.

Demographics and Baseline Characteristics

Overall, the gender, age, and race distribution across the 3 treatment groups was comparable. The patient population had a mean age of 48 years, slightly older than the mean age in Trial P04334, and was 56% female and 89% white. There were similar numbers of pediatric patients ages 12 to <18 years (n=63) compared to Trial P04334. Thirty percent (n=218) of the population reported prior use of an ICS plus a LABA.

Table 10: Study P04431: Demographics and Baseline Characteristics

	MF/F 200/10 N=233	MF/F 400/10 N=255	MF 400 N=240	Total N=728
Sex (n, %)				
Female	135 (58)	138 (54)	136 (57)	409 (56)
Male	98 (42)	117 (46)	104 (43)	319 (44)
Race (n, %)				
White	209 (90)	227 (89)	215 (90)	651 (89)
Non-white	24 (10)	28 (11)	25 (10)	77 (11)
Asian	-	1 (<1)	-	1 (<1)
Black	3 (1)	4 (2)	3 (1)	10 (1)
Multi-racial	20 (9)	23 (9)	21 (9)	64 (9)
Native American	1 (<1)	-	1 (<1)	2 (<1)
Age (years)				
Overall				
Mean (SD)	48 (16)	48 (16)	48 (16)	48 (16)
Median	52	50	52	52
Range	12-84	12-77	12-80	12-84
12 to <18 years				
N	18	23	22	63
Mean (SD)	14 (2)	14 (2)	14 (2)	14 (2)
Median	15	13	14	14
Range	12-17	12-17	12-17	12-17
18 to <65 years				
N	189	200	189	578
Mean (SD)	49 (12)	48 (10)	48 (12)	48 (11)
Median	51	50	52	51
Range	18-64	18-64	18-64	18-64
≥65 years				
N	26	32	29	87
Mean (SD)	21 (5)	69 (4)	69 (4)	70 (4)
Median	70	68	69	68
Range	65-84	65-77	65-80	65-84
Asthma Duration (years)				
Mean (SD)	14 (12)	14 (11)	14 (12)	14 (12)
Median	11	10	11	10
Baseline FEV1 (mean, SD)				
L	2.06 (0.6)	2.04 (0.6)	2.04 (0.6)	2.05 (0.6)
% predicted	66.5	65.9	66.5	66.3
% reversibility (screen)	24.4	22.2	22.1	22.9
FEV1/FVC	0.67	0.67	0.67	0.67
Questionnaire Score				
ACQ	1.92 (0.81)	1.95 (0.86)	1.94 (0.88)	1.93 (0.85)
AQLQ	4.96 (1.03)	4.90 (1.15)	4.93 (1.07)	4.93 (1.08)

MF= Mometasone furoate MDI; F= formoterol fumarate MDI; ACQ= Asthma Control Questionnaire; AQLQ= Asthma Quality of Life Questionnaire

Source: Modified from Table 26, Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 70, and from Summary of Clinical Efficacy in Module 2.7.3.2.1.1.1., Table 15

Primary Efficacy Variable

Because Study P04431 was designed to support registration and approval of the MF/F combination product, the primary efficacy endpoint chosen was change in FEV1 AUC 0-12 hours from baseline to week 12. This endpoint primarily was chosen to assess the contribution of formoterol, and not the contribution of MF monotherapy. There was no placebo group or low-dose MF group included, due to safety and ethical considerations for patients with severe asthma. As such, there is no head-to-head comparison of the MF 200 to MF 400 monotherapy, or of the MF 400 to placebo. The primary efficacy endpoint, the change in mean FEV1 $AUC_{0\text{-}12h}$ from baseline to Week 12 (treatment difference = 0.54 L x h), supported the higher dose of combination under the Dulera program. However, this endpoint does not directly support the efficacy of MF monotherapy which is proposed in this application. In this circumstance, because Clinical Pharmacology reviewers have concluded that there is no drug-drug interaction between mometasone and formoterol [see Section 4.4 Clinical Pharmacology], it is possible to evaluate the relative benefit of the MF 400 dose over the MF 200 dose by comparing the differences between the two combination products studied in the more severe population, given that the effect of the F 10 component would be expected to exert the same effect in both dose cohorts. [Refer to Dr. Limb's Primary Clinical Review of Dulera, NDA 22-518, for details]. This comparison will be discussed further in Section 6 Review of Efficacy.

With regard to the Dulera program's pre-specified primary efficacy endpoint, change in FEV1 AUC 0-12 hours from baseline to week 12, there was a numerical difference favoring the MF/F 400/10 dose over 200/10, which provided justification of two different dose levels of the combination MF/F, as described in Table 11, below.

Table 11: Study P04431: FEV1 AUC 0-12h Change from Baseline to Week 12

Treatment group	N	FEV1 AUC $_{0\text{-}12h}$ change LS mean		
(A) MF/F 200/10	230	3.59		
(B) MF/F 400/10	251	4.19		
(C) MF 400	237	2.04		
Pairwise comparisons	A-B	A-C	B-C	
P	0.096	<0.001	<0.001	
95% CI	(-1.30, 0.11)	(0.82, 2.27)	(1.44, 2.85)	

MF= Mometasone furoate MDI; F= formoterol fumarate MDI

Source: Modified from Table 27, Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 71, and from Summary of Clinical Efficacy, Module 2.7.3.2.1.2.3, Table 16

Supportive Efficacy

Trough FEV1

Trough FEV1 was designated a key secondary efficacy endpoint to evaluate the relative differences between the MF/F 200/10 and 400/10 dose levels. There was a numerically greater increase in the mean change in trough FEV1 in the MF/F 400/10 group than in

the MF/F 200/10 treatment group (treatment difference = 0.04L; 95% CI -0.02, 0.01). The treatment difference provided justification for the higher dose level of the MF/F combination product, for use in the more severe asthma population. In addition, the original application provided subgroup analysis for this endpoint based on baseline percent predicted FEV1 below the median 66%, which indicated a greater treatment difference between the MF/F dose levels compared to patients with FEV1 values above the median (treatment difference = 0.08L v. 0.03 L, respectively). [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 72]. This endpoint will be explored further in terms of its support for the two doses of MF monotherapy, in Section 6.1.4 Analysis of Primary Endpoint(s).

Other Secondary Endpoints

Additional key secondary endpoints included change from baseline to endpoint in ACQ score, change from baseline to endpoint in AQLQ score, and change from baseline across the 26-week treatment period in the proportion of nights with nocturnal awakenings. Other endpoints included AM and PM peak expiratory flow rates (PEFR), time-to-first and number of exacerbations, and rescue medication usage. Change from baseline to week 12 for the MF/F 200/10 and 400/10 groups versus the MF 400 were evaluated; combination therapy groups achieved statistically significant changes over the MF 400 arm; see Table 12 below. When comparing the two combination doses, there were no apparent, clinically significant differences between them.

Time to first and number of asthma exacerbations

Severe asthma exacerbation was defined the same as in Trial P04334. A total of 104 patients experienced a severe exacerbation at some point in the trial: n=29 (12%) in the MF/F 200/10 arm, n=31 (12%) in the MF/F 400/10 arm, and n=44 (18%) in the MF 400 arm. The majority of these exacerbations qualified on the basis of decreased FEV1. No apparent differences were noted between the MF/F 200/10 and 400/10 treatment groups. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 74]

Table 12: Study P04431: Secondary Endpoints

Secondary Variable	MF/F 200/10 N=233	MF/F 400/10 N=255	MF 400 N=240
Proportion of Nights with Nocturnal Awakenings			
Baseline	0.21	0.23	0.19
Change Across 12-wk Treatment Period	-0.10 (-44%)	-0.10 (-48%)	0.05 (-32%)
AQLQ Score			
Baseline	5.05	5.00	5.05
Change at Week 12 Endpoint	0.58 (13%)	0.46 (12%)	0.41 (10%)
ACQ Score			
Baseline	1.83	1.87	1.85
Change at Week 12 Endpoint	-0.56 (-25%)	-0.51 (-20%)	-0.33 (-5%)
AM PEFR (Liters/min)			
Baseline	327.1	321.6	320.8

Change at Week 12 Endpoint	33.2 (12%)	34.0 (13%)	14.9 (7%)
AM/PM Asthma Symptom Score			
Baseline	1.90	1.94	1.94
Change at Week 12 Endpoint	-0.60	-0.55	-0.31
Total SABA Rescue Use			
Baseline	1.96	1.74	1.95
Change at Week 12 Endpoint	-0.78	-0.66	-0.21

MF= Mometasone furoate MDI; AQLQ= Asthma Quality of Life Questionnaire; ACQ= Asthma Control Questionnaire; SABA= short-acting beta-2 agonist

Source: Modified from Tables 16-17 in Module 2.7.3.2.1.1, Summary of Clinical Efficacy; original study report P04431 in Module 5.3.5.1; and Modified from Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pg. 70-73,.

Efficacy Evaluation for Patient Subgroups

As noted in the primary clinical review of Dulera, gender, race, and BMI did not appear to impact results of the trial. Overall, in terms of age, patients 12 to <18 years of age (n=63) had comparable results to the patients 18 to <65 years of age (n=578). Patients >65 years of age (n=87) had less robust results than the rest of the cohort, although MF/F still performed numerically better to MF alone. The reduced efficacy may reflect a greater prevalence of fixed airway disease in older individuals or may be partly due to the small number of evaluable patients >65 years at Week 12 included in this subgroup [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 74]

Study P04431 Summary Conclusions

Study P04431 provided justification for two different dose levels in the Dulera program, on the basis of differences between the two MF/F 400/10 and 200/10 doses from MF400. The primary endpoint, mean FEV1 $AUC_{0\text{-}12h}$ change from baseline to Week 12, also supported a numerical difference favoring the MF/F 400/10 dose level over the 200/10; this efficacy variable was intended primarily to measure the efficacy contribution of the F component to the combination. Other endpoints, such as rescue medication use, nocturnal awakenings, asthma exacerbations, and peak flows, did not indicate a clear difference in efficacy between these dose levels of the combination, which is not entirely unexpected, given the relatively flat dose response curve anticipated for most ICS products.

Additional Supportive Studies

The following studies utilizing the related, older MF MDI product were submitted to this NDA, as additional supportive efficacy and safety for the current MF MDI HFA submission. These studies did not utilize the to-be-marketed formulation; the study design and results are briefly described below.

Study C97-226

Study C97-226 was a Phase 3, 12-week, randomized, double-blind, placebo-controlled efficacy and safety study in patients 12 to 71 years of age with moderately severe asthma requiring maintenance on short-acting inhaled beta agonists. The primary objective was to evaluate efficacy and safety of MF MDI at doses of 100mcg Qam, 400mcg Qam, and 200mcg BID, as compared to placebo, to determine dose interval. A total of 330 patients were randomized to treatment, as follows: MF 100 Qam (n=82), MF 400 Qam (N=84), MF 200 BID (n=83), or placebo (n=81). The primary efficacy endpoint was the change from Baseline at Endpoint in FEV1. All active treatments showed statistically significant increases in FEV1 from baseline compared to placebo ($p \leq 0.03$). However, there was no separation among the MF doses, or differences between the Qam and BID regimen of the same total daily dose, as seen in Table 13 below.

Table 13: Study C97-226: Change in Mean FEV1 from Baseline (L)

Dose	N	Baseline FEV1 (L)	Change from Baseline	Difference from Placebo	P
Study C97-226					
MF 100 Qam	82	2.56	0.24	0.14	0.03
MF 400 Qam	84	2.67	0.32	0.22	<0.01
MF 200 BID	83	2.54	0.31	0.21	<0.01
Placebo	81	2.67	0.10		

MF= Mometasone furoate MDI; Qam= once daily each morning, BID= twice daily

Source: Modified from Table 20 in Module 2.7.3 Summary of Clinical Efficacy, page 63, and from original study report C97-226 in Module 5.3.5.4.

Secondary efficacy variables assessed included AM and PM PEFR, nocturnal awakenings, SABA use, time to first asthma worsening, and clinical asthma symptom scores. For PEFR, all doses of MF were numerically better than placebo, reflecting improvements of 7-15% over placebo. Treatment with MF 200 BID resulted in a statistically significant change from baseline for AM and PM values (p=0.03). The MF 100 Qam and 200BID doses of MF showed greater decreases in the number of daily inhalations of Proventil compared to placebo (with p=0.02 and p=0.01, respectively), but the 400 Qam dose failed to meet significance (p=0.15). For the number of nocturnal awakenings, all MF groups showed fewer events than placebo, but failed to reach statistical significance. For the purposes of this trial, asthma worsening was defined as a $\geq$20% decrease in FEV1 from baseline, $\geq$25% decrease in PEFR from baseline for 2 consecutive days, increase in bronchodilator use for 2 consecutive days, or worsening of asthma symptoms that resulted in hospitalization. Greater than 90% of treated and 85% of placebo patients did not meet criteria for worsening during the study period, so although numerical differences are noted, median time to worsening could not be determined (Of the 28 patients with worsening, treatments were as follows: MF 100 Qam= 5, MF 200 BID= 5, MF 400 Qam=6, placebo= 12). Similarly, the number of patients with a clinical asthma exacerbation during the trial was low (n=12) and no major

differences were noted among treatment groups (MF 100 Qam= 2, MF 200 BID= 1, MF 400 Qam=3, placebo= 6).
In summary, the results of C97-226 support the efficacy of the proposed MF 200 BID, or 400 Qam, against placebo. [Source: Module 5.3.5.4, CSR for C97-226, and Module 2.7.3, Summary of Clinical Efficacy, pages 60-70].

Study C97-227

Study C97-227 was a 12-week, randomized, double-blind, placebo-controlled efficacy and safety study in patients 36 to 46 years of age with moderately severe asthma requiring maintenance on ICS; all patients were treated in open-label fashion with MF 200mcg BID for 4 weeks prior to randomization. The primary objective was to evaluate efficacy and safety of MF MDI at doses of 200mcg Qam, 200mcg Qpm, 400 mcg Qam, and 200mcg BID, as compared to placebo, to determine dose interval/timing. A total of 245 patients were randomized to treatment, as follows: MF 200 Qam (n=48), MF 200Qpm (n=49); MF 400 Qam (N=49), MF 200 BID (n=49), or placebo (n=50). There was a significant amount of dropout, the greatest of which occurred in the placebo group (52%), and 12-29% dropout in the MF groups, the lowest of which was the MF 200 BID group (12%). The most common reason for dropout was treatment failure, especially in the placebo group. The primary efficacy endpoint was the change from Baseline at Endpoint in FEV1. All active treatments showed statistically significant increases in FEV1 from baseline compared to placebo ($p \leq 0.01$), as seen in Table 14, below.

Table 14: Study C97-227: Change in Mean FEV1 from Baseline (L)

Dose	N	Baseline FEV1 (L)	Change from Baseline	Difference from Placebo	P
Study C97-227					
MF 200 Qam	48	2.67	-0.13	0.29	<0.01
MF 200 Qpm	49	2.74	-0.13	0.29	<0.01
MF 400 Qam	49	2.67	-0.12	0.30	<0.01
MF 200 BID	49	2.76	0.07	0.49	<0.01
Placebo	50	2.74	-0.42		

MF= Mometasone furoate MDI; Qam= once daily each morning, Qpm= once daily each evening; BID= twice daily

Source: Modified from Table 22 in Module 2.7.3 Summary of Clinical Efficacy, page 74, and from original study report C97-227 in Module 5.3.5.4.

Secondary efficacy variables assessed included am and pm PEFR, nocturnal awakenings, SABA use, time to first asthma worsening, clinical asthma exacerbations, and clinical symptom scores. The primary comparison chosen for these statistical analyses was the 400mg Qam dose, which only met significance for changes in PEFR. For PEFR, 3 of the 4 MF doses met significance compared to placebo (200Qam did not), and AM and PM values were similar. Much of the change in PEFR was due to a decline in the placebo group (after randomization to placebo from 4 weeks' treatment of

MF 200 BID). All other secondary endpoints noted trends in pairwise comparisons demonstrating improvement for the MF-treated patients over the placebo group, but did not meet the predefined statistical criteria for significance. Greater than 75% of patients did not meet criteria for worsening during the study period, so although numerical differences are noted, median time to worsening could not be determined (Of the 61 patients with worsening, treatments were as follows: MF 200 Qam= 10, MF 200 Qpm= 10, MF 400 Qam=11, MF 200 BID= 3, placebo= 27). Similarly, the number of patients with a clinical asthma exacerbation during the trial was low (n=18) and no major differences were noted among treatment groups (MF 200 Qam= 3, MF 200 Qpm= 2, MF 400 Qam=5, MF 200 BID= 0, placebo= 8).
In summary, the results of C97-227 support the efficacy of the proposed MF 200 BID against placebo. [Source: Module 5.3.5.4, CSR for C97-227,and Module 2.7.3, Summary of Clinical Efficacy, pages 71-84].

Study C97-223

Study C97-223 was similar in design to Study C97-224, discussed in Section 4.4.2, above. It was a Phase 3, randomized, double-blind, placebo-controlled efficacy and safety trial in patients ages 12 to 78 years with moderately severe asthma who requires maintenance on short-acting beta-agonists. The primary objective was to evaluate the safety and efficacy of two doses of MF MDI (200 or 400 Qday) compared to placebo. A total of 251 patients initially enrolled in a 3-month phase in which they were randomized to MF 200 Qam (n=80), MF 400 Qam (n=86), or placebo (n=85). Subsequently, 160 patients entered a 9-month dose-blind, randomized, uncontrolled phase during which they were treated with variable doses of MF (200 or 400 mcg) Qday, in either the am or pm. The primary efficacy endpoint was the change in FEV1 from Baseline at Endpoint (last available 3-month visit data). Secondary endpoints included PEFR, other spirometry measures, asthma symptom scores, rescue SABA use, nocturnal awakenings, discontinuations due to asthma worsening, and physician's evaluation of response. In terms of the primary endpoint, MF 200 and 400mcg Qday performed similarly and were statistically significantly different from placebo ($p<0.01$), see Table 15 below. The secondary endpoint of nocturnal awakenings demonstrated statistically significant improvements over placebo for both treatment groups ($p\leq0.05$), while the remainder of secondary endpoints showed numerical improvements over placebo, but did not consistently meet significance at all measured time points for both doses of MF.
In summary, the results of C97-223 support the efficacy of the proposed MF 200 BID (400mcg daily dose) against placebo. [Source: Module 5.3.5.4, CSR for C97-223, and Module 2.5, Clinical Overview].

Table 15: Study C97-223: Change in Mean FEV1 from Baseline (L) at 3 Months

Dose	N	Baseline FEV1 (L)	Change from Baseline	Difference from Placebo	P
Study C97-223					
MF 200 Qam	78	2.60	0.25	0.20	<0.01
MF 400 Qam	85	2.55	0.25	0.20	<0.01
Placebo	82	2.56	0.05		

MF= Mometasone furoate MDI; Qam= once daily each morning,

Source: Modified from original study report C97-224 in Module 5.3.5.4, Table 13.

Study C97-222

Study C97-222 was a 12-month, randomized, open-label, active-controlled safety study in patients 12 to 89 years of age with moderately severe to severe asthma requiring maintenance on ICS; all patients entered a run-in period for 2 weeks prior to randomization, during which they continued their usual ICS treatment. The primary objective was to characterize long-term safety of MF MDI at doses of 200mcg BID and 600mcg BID, with a secondary objective comparing the two doses of MF to beclomethasone diproprionate (BDP) 168mcg BID. A total of 308 patients were randomized to treatment, as follows: MF 200 BID (n=120), MF 600 BID (n=129); or BDP 168mcg BID (n=59). A total of 51 subjects (17%) discontinued the study, with incidence similar across treatment regimens. The most common reasons for dropout were adverse events (6%, n=19) and reasons unrelated to treatment (5%, n=15). Ten patients were excluded from efficacy analyses from a single center (Center 08) due to site termination due to non-adherence to good clinical practice (GCP). Although the study was not powered to demonstrate efficacy, a secondary efficacy endpoint was the change from Baseline at Endpoint in FEV1. The two MF treatments showed numerical increases in FEV1 from baseline compared to BDP, as seen in Table 16, below, which suggests compliance with regimen.

Table 16: Study C97-222: Change in Mean FEV1 from Baseline (L)

Dose	N	Baseline FEV1 (L)	Change from Baseline	Difference from BDP	P
Study C97-222					
MF 200	120	2.59	0.20	0.12	0.07
MF 600	128	2.58	0.29	0.21	<0.01
Beclomethasone 168	59	2.53	0.08	---	---

MF= Mometasone furoate MDI; Beclomethasone= beclomethasone diproprionate (Vanceril)

Source: Modified from original study report C97-222 in Module 5.3.5.4, Table 9.

Other secondary efficacy variables assessed included AM and PM PEFR, nocturnal awakenings, SABA use, time to first asthma worsening, clinical asthma exacerbations,

and clinical symptom scores. These endpoints suggest that MF doses were no worse than BDP.

In summary, Study C97-222 was intended primarily as a long-term safety trial; safety data are discussed in Section 7. In terms of efficacy information, data on trough FEV1 and secondary efficacy variables like SABA use and nocturnal awakenings are suggestive of compliance, although there is no placebo for control. The results of C97-222 generally support the efficacy and safety of the proposed MF 200 BID. [Source: Module 5.3.5.4, CSR for C97-222,and Module 2.7.3, Summary of Clinical safety, pages 36 and section 2.7.4.3.5].

Study P04139

Study P04139 was a 12-month, randomized, open-label, active-controlled safety study in 404 patients 12 to 75 years of age with moderately severe to severe asthma requiring maintenance on ICS. This study was conducted exclusively outside the US; the primary review of Dulera placed particular attention on the comparability of data from this to the other pivotal trials, since this provided the long-term safety information for the combination program [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 75-79].

The primary objective was to characterize long-term safety of combination MF/F MDI at doses of 200/10mcg BID and 400/10mcg BID, with a secondary objective comparing the two doses of MF/F to two doses of fluticasone/salmeterol (F/SC), 250/50 and 500/50 BID. An additional objective was to evaluate extrapulmonary effects of MF on 24-hour plasma cortisol AUC. A total of 404 patients were randomized 2:1 to treatment, as follows: MF/F 200/10 BID (n=141), MF/F 400/10 BID (n=130); F/SC 250/50 (n=68), or F/SC 500/50 BID (n=65). Allocation to medium- or high-dose ICS was based on prior ICS use. In addition to monitoring for AEs, ophthalmological assessments were performed as Visit 1, Week 26, and Week 52 or the final visit. HPA axis function was assessed by 24-hour cortisol performed at Baseline, Week 26, and Week 52. Compliance was monitored by efficacy measurements that included spirometry, SABA usage, nocturnal diaries, and symptom scoring. A total of 59 subjects (15%) discontinued the study, with incidence similar across treatment regimens. The most common reasons for dropout were adverse events (3%, n=13), non-compliance (4%, n=17), and reasons unrelated to treatment (2%, n=9). Although the study was not powered to demonstrate efficacy, a secondary efficacy endpoint was the change from Baseline at Endpoint in FEV1, which in this instance is useful as a surrogate for compliance. The mean changes in trough FEV1 (L) from baseline to week 12 and to endpoint are as follows: for MF/F 200/10= 0.24, 0.24; for MF/ 400/10= 0.20, 0.21; for F/SC 250/50= 0.32, 0.33; for F/SC 500/50= 0.37, 0.32. In addition, the proportion of patients with nocturnal awakenings requiring SABA use decreased similarly across treatment groups.

In summary, Study P04139 was intended primarily as a long-term safety trial; safety data are discussed in Section 7. In terms of efficacy information, data on trough FEV1 and secondary efficacy variables like SABA use and nocturnal awakenings are suggestive of compliance, although there is no placebo for control. The results of P04139 supported the efficacy and safety of the combination product, and as such support the proposed MF 200 and 400 BID. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 75-78; Module 5.3.5.4, CSR for P04139]

Study P04703

P4703 was an open-label, multi-center trial of MF/F 100/10 BID (2 actuations of MF/F 50/5 mcg) intended to assess the performance of the integrated dose counter. Of note, the 100/10mcg dose of MF/F did not receive approval, and the 100mcg dose of MF has not been submitted for this application; however, since dose counter information was not evaluated in the Phase 3 pivotal trials, a separate handling trial was conducted, and is relevant to this application. A total of 343 patients enrolled, of which 272 underwent treatment, and 233 completed the trial. Patients were stratified by age, so that 25% were 65 years of age or older, and the remaining 75% were 12-64 years of age. Eligible patients with asthma (FEV1 $\geq$70%, and low-dose ICS use) or COPD (FEV1 ≥50% and FEV1/FVC ≤0.70 (pre-bronchodilator)) received instructions for use and underwent a familiarization period of at least 3 days, during which time subjects were to become acquainted with the trial procedures. After the familiarization period, subjects underwent a 14-day Screening period to confirm correct MDI usage (MDI without integrated dose counter), stable asthma control, and at least 90% compliance with trial medication, diary completion, and Counterstrip usage (alternate dose counting log adhered to the MDI; patients instructed to scratch off a number on the Counterstrip for every actuation taken). Qualified subjects were then enrolled in a 30-day Treatment Period, during which time patients were to complete 120 labeled actuations of MF/F MDI 100/10 mcg BID with an integrated dose counter. Trial visits were scheduled for every 7 days. At each visit, protocol adherence was assessed by review of the e-diary/spirometry and Counterstrip data and correlation to the dose counter data. Efficacy was assessed as the number of discrepancies based on the difference between recorded number of actuations and counter readout across the 4-week treatment period, the quartile discrepancy rate per 100 actuations, the magnitude of discrepancies, and end-of-use agreement (patient-recorded actuations minus dose counter readout).

The disposition of the screened group is noted for 20% discontinuing (n=71) before the treatment period, the most common reasons for which included 12% (n=40) not meeting eligibility, followed by 6% non-compliance (n=19). An additional 4% (n=11) discontinued during the treatment period, with the most common reason being withdrawal unrelated to treatment (n=4). Baseline characteristics are noted for the

mean age being 47 years, with a range of 12 to 92 years. There were 35 pediatric patients aged 12 to <18 years old, and 65 patients ≥65 years old. The majority were female (n=178, 65%) and Caucasian (N=244, 90%). Eighty-two percent (n=222) were asthma patients and the remaining 50 patients (18%) had COPD.

In this study, 92% of patients were determined to be compliant with the regimen; the most common reason for non-compliance was forgetting a dose; compliance was better in patients >65 years of age. Counterstrip compliance was better than 95%, and e-dairy compliance was 75%. Older patients had a lower rate of compliance with the e-diary. Four inhalers were reported to be inoperative or malfunctioning during the Treatment Period. Quality control investigations to did not identify a cause for two of the reported incidents. One of the inhalers was returned for use after being deemed to be fully functional. Another inhaler showed signs of subject misuse, which the patient attributed to damage as a result of being thrown by a younger sibling. Endpoint results are listed below [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 79-84].

Dose counter discrepancy rate
The calculated dose counter discrepancy rate for the Treatment period population was 0.14 discrepancies per 100 actuations. The mean rate was lower in the older population >65 years (0.07 discrepancies per 100 actuations) compared to the patients <65 years (0.14 discrepancies per 100 actuations).

Nature of discrepancies
Over-counting (Count, Not Spray [n=17, 0.06 discrepancies per 100 actuations] or Count, Unknown Spray [n=10, 0.03 discrepancies per 100 actuations]) occurred more frequently than under-counting (Spray, Not Count [n=14, 0.05 discrepancies per 100 actuations]). In vitro and root cause analysis of the under-counting attributed the undercounts to sprays firing in advance of counting, which may have been due to incomplete depression of the canister during inhalation administration. The Applicant addressed this issue by improving the counter design in commercial units by adjustment of the Count Point-Fire Point Relationship so that the tendency will be for the counter to count an incomplete depression, potentially resulting in over-counting rather than under-counting, consistent with the *2003 Guidance for Industry: Integration of Dose-counting mechanisms into MDI Drug Products*, which stipulates that dose counters should be designed to avoid under-counting specifically. The over-counts were attributed to a variety of factors, including patient technique (re-actuation before fully releasing the canister), counting upon dropping, etc.

Dose counter discrepancy size
The maximum difference in end-of-use agreement was an undercount of 7. A total of 175 inhalers (76%) had perfect end-of-use agreement. Of the remaining 56 inhalers, 2/3 had overcounts and 1/3 had undercounts. The Applicant provided an additional analysis in the Dulera application to adjust for subject error and non-compliance. Based

on this adjusted analysis, the report claims that 92% of the inhaler tracked medication usage perfectly and states that most counting discrepancies are likely to be a function non-conventional handling of the MDI and non-compliance with the e-diary and Counterstrip. The mean size of the discrepancies was 1.2 for the completer population.

In summary, Study P04703 was planned to demonstrate accuracy and durability of the dose counter mechanism in MF/F, which is the same as that used in the MF monotherapy product proposed here. Original issues in 14 MDI devices causing under-counting (which posed a potential safety issue), were addressed prior to approval and marketing of the Dulera product. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 79-84; Module 5.3.5.4, CSR for P04703]

Study P04705

This was a randomized, multi-center, two-phase, evaluator-blind, active comparator-controlled, parallel-group study in subjects with persistent asthma previously treated with a medium daily dose of ICS, alone or in combination with a LABA, originally planned for 52 weeks. Overall, 722 subjects were randomized to receive study treatment. Of these, 371 subjects (12 to 82 years of age) were randomized to receive MF/F MDI (200/10 mcg BID) or F/SC DPI (250/50 mcg BID) for 14 to 16 weeks. There was a 2- to 4-week (approximately) open-label run-in period with MF MDI (200 mcg BID), followed by a 52-week, open-label, evaluator-blind treatment period that was shortened to 12 weeks prior to the unblinding of the database for administrative reasons other than safety. Patients received dosing for approximately 14 to 16 weeks; as such, the amount of support this study provides is negligible; safety will be briefly discussed in section 7. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 96; Module 5.3.5.4, CSR for P04705]

6 Review of Efficacy

Efficacy Summary

The proposed indication for MF MDI in this application is maintenance treatment of asthma as prophylactic therapy in (b) (4) 12 years of age and older. This language is consistent with the approved label for Asmanex Twisthaler (DPI formulation of MF), and is in line with other ICS monotherapies.

The Applicant provides support for the efficacy of both the MF 200 and MF 400 doses from studies conducted for the MF/F combination product (Dulera) development program. However, while the efficacy for each MF can be derived from the combination program efficacy data, the main efficacy variable(s) used to support the efficacy of the MF monoproducts are slightly different than those used to support the combination

product where endpoints must take into consideration the factorial design nature of Phase 3 trials used in combination product programs. With that clarification, change in mean trough FEV1 from baseline to endpoint was used for this MF program as the main efficacy endpoint to provide support for the MF indication. Support for the efficacy of the MF 200 dose is provided in the factorial design Study P04334, which included evaluation of MF 200 against placebo. For MF 200, the mean change in trough FEV1 compared to placebo was clinically and statistically significant (treatment difference from placebo = 0.12L; p<0.001). Additional support for efficacy was provided by demonstration of fewer/less asthma deteriorations, nocturnal awakenings, and SABA use as well as from supportive efficacy data obtained from a previous related MF MDI monoproduct development program.

Support for MF 400 is derived mainly from the pivotal efficacy trial, P04431, which provided a direct comparison of MF/F 400/10 and MF/F 200/10. This trial included MF 400 as a third treatment arm, but did not include a placebo control, given the severity of the asthma population enrolled. A numerical separation between MF/F 200/10 and 400/10 was demonstrated for the key secondary efficacy endpoint, trough FEV1 (treatment difference = 0.04 L) which supports an added benefit for the 400mcg MF dose over the 200mcg dose. Additionally, the efficacy of MF 400 compared to placebo is supported by replicate, 12-week dose ranging trials (C97-208 and C97-224) from the related MDI monoproduct development program.

In summary, taken as a whole, the submitted data provide evidence of efficacy for both the proposed MF 200 and MF 400 monotherapy doses.

6.1 Indication

Asmanex HFA is proposed for the maintenance treatment of asthma as prophylactic therapy in (b) (4) 12 years of age and older.

6.1.1 Methods

The trial design, conduct, and original efficacy results of the pivotal Phase 3 efficacy trials (P04334 and P04431) and trials for the MF monocomponent (C97-222, C97-223, C97-226, C97-227) are described in Section 5.3. The important dose-ranging trials (C97-208, C97-225, C97-224, I97-200) are described under Pharmacodynamics, Section 4.4.2.

These trials were adequately designed for the Dulera combination MF/F therapy program, to assess the efficacy of MF/F and the efficacy and contribution of MF and F to the combination. The pivotal trial P04334 had a full factorial design in order to demonstrate the contribution of MF and F to the combination, while P04431 had a partial factorial design (previously discussed with the Division and deemed appropriate given the more severe asthma population enrolled). For this MF monotherapy program,

the application did not provide replicate evidence of efficacy for MF 200 and MF 400 monoproducts against placebo; however, by providing a direct comparison of MF 200/10 and MF/F 400/10, we can estimate the additional effect of the 400 dose over MF 200 in the more severe asthma population for which it would be intended. In addition, the related, older MF MDI program provides support for the two proposed doses.

6.1.2 Demographics

Detailed demographic data from the pivotal Phase 3 trials and supportive studies are shown in Section 5.3, and the key dose-ranging trials are shown in Section 4.4.2. Patient inclusion/exclusion criteria for the various trials were appropriate for defining a patient population with a range of asthma severity, distinguished primarily by baseline ICS requirements. Trial P04431, which evaluated the highest proposed dose level of MF 400, was intended to assess patients with the most severe, persistent disease. In addition to higher baseline ICS requirements, patients in P04431 were also required to have had at least one severe exacerbation in the time preceding the trial and were permitted a lower threshold FEV1 at screening. Overall, recruitment appears to have been performed appropriately, and the patients enrolled in the clinical development program appear to be representative of a general asthma population.

6.1.3 Subject Disposition

Patient disposition for the Phase 3 trials is described in Section 5.3 in the individual study summaries. Overall, more early discontinuations from treatment were observed in F and placebo arms (when present), followed by MF alone, and then lastly, MF/F. The most common reason cited for early discontinuations was treatment failure, which occurred at a higher rate in the F and placebo arms. (Formoterol monotherapy arms in long-duration studies are no longer accepted in asthma development programs, but at the time of study conduct, this was still within the standards for acceptability). This differential pattern of early discontinuation among the treatment arms supports the efficacy of the proposed MF monotherapy, as it did for the MF/F combination.

6.1.4 Analysis of Primary Endpoint(s)

Trial P04334 had co-primary endpoints: 1) the change in mean FEV1 $AUC_{0\text{-}12h}$ from baseline to Week 12 and 2) time to first severe asthma exacerbation. Trial P04431 had a single primary endpoint, the change in mean FEV1 $AUC_{0\text{-}12h}$ from baseline to Week 12. Time to first severe asthma exacerbation was also assessed in Trial P04431, but it was specified as a secondary endpoint. To evaluate the data in terms of the MF monotherapy, the most appropriate endpoint is change in mean trough FEV1 from baseline to endpoint. Therefore, trough FEV1 will be described in this primary efficacy section, time to first exacerbation will be discussed with secondary endpoints, and change in mean FEV1 $AUC_{0\text{-}12h}$ from baseline to endpoint has been discussed under

each study individually in Section 5.3, since it does not provide additional support to the MF monotherapy.

Trough FEV1

The main efficacy evaluation for the MF monotherapy program is the change in mean trough FEV1 from baseline to endpoint. For Study P04334, trough FEV1 values of MF 200 over placebo are supportive, with a treatment difference of 120mL, and 95% confidence interval of (0.05, 0.20). Because the protocol did not pre-specify comparisons between MF 200 and placebo, calculation of p-values could potentially underestimate type 1 error; however, since this p-value was highly significant, ($p<0.001$), the likelihood of it being falsely significant is low [refer also to Dr. Robert Abugov's Primary Statistical Review of NDA 206-541, Section 3.2.4.1, page 15]. In addition, under the original Dulera review, trough FEV1 data comparing MF/F 200/10 over F 10 (treatment difference 130 mL; $p<0.001$), provided support of the contribution of MF to MF/F, and by extension, the efficacy of the MF product itself.

Study P04431 did not include a placebo group for comparison to MF 400, which was accepted by the Division for ethical considerations, given that it would be inappropriate to subject a severe asthma population to prolonged placebo treatment knowing the inherent morbidity and mortality risks. Because Study P04431 was designed to provide support of the combination over the monotherapy, it contains MF/F 200/10 and 400/10 combination arms, and a MF 400 monotherapy arm. To estimate the effect of the monotherapy itself requires additional consideration. The Clinical Pharmacology team has determined that there is no drug-drug interaction between mometasone and formoterol [see Section 4.4, Clinical Pharmacology], so therefore it is possible to evaluate the relative benefit of the MF 400 dose over the MF 200 dose by comparing the differences between the two combination products studied in the more severe asthma population, given that the effect of the F 10 component would be expected to exert the same effect in both dose cohorts. A numerical separation between MF/F 200/10 and 400/10 was demonstrated for trough FEV1 suggesting a modest increase in efficacy with the higher concentration of MF in the combination, albeit not statistically significant (treatment difference 40 ml; $p=0.14$; 95% CI -0.02, 0.10).

These data from the two clinical trials will be included in MF MDI labeling in Section 14, to provide primary support of efficacy. Description of these trials will be provided, given that the pre-specified primary efficacy endpoints and analyses of these studies were appropriate for the Dulera program, but were not designed for MF MDI monotherapy. Specific details of labeling are pending at the time of this review.

Reviewer's Comment:
The Applicant proposes in their package that demonstration of improvement in trough FEV1 from baseline to the week 12 endpoint provides efficacy for the higher MF 400 dose; because no control arm is included for comparison, it cannot be ruled out from

this analysis that such improvements were not due to placebo effect rather than a true treatment effect [refer also to Dr. Robert Abugov's Primary Statistical Review of NDA 206-541, Section 3.2.4.1, page 15]. While we do not believe that change from baseline itself provides primary efficacy support for the monotherapy, it does favor the durability of the MF 400 dose over time, and provides additional reassurance to the benefit between MF doses noted above.

6.1.5 Analysis of Secondary Endpoints(s)

This section provides analysis of these endpoints in relation to how they provide support to the MF MDI program. The individual results for these endpoints for each trial have been described in Section 5.3.

(b) (4)

Nocturnal awakenings
The proportion of nights disrupted by nocturnal awakenings requiring treatment with a SABA over the 26 week (P04334) and 12-week (P04431) treatment periods was assessed. In the 26-week placebo-controlled trial, a greater decrease in the proportion of nights with nocturnal awakenings was observed in the MF 200 compared to placebo (-0.05 vs. +0.0), and the results were statistically significant ($p<0.001$). In P04431, MF 400 had a decrease in the proportion of nocturnal awakenings by 32% from the baseline value. In general, the data for nocturnal awakenings supports the efficacy of MF over placebo but does not demonstrate a clear dose response. The proposed MF labeling includes decrease in proportion of nights with nocturnal awakenings over placebo (P04334) and over baseline (P04431) in Section 14, Clinical Studies section, which is generally supported by the application.

Rescue medication use
The proposed labeling for MF MDI does not include rescue SABA use as a specific claim in Section 14, Clinical Studies section. SABA use decreased in P04334 between MF 200 and placebo (-0.24 vs. +1.08 puffs/day), and in P04431 in MF 400 by 20% from the baseline value; these changes are less than one puff/day, and have limited clinical significance. It is agreed that this should not be included in labeling.

Peak expiratory flow
AM and PM PEF data was collected in both trials and are detailed in the respective trial summaries in Section 5. These data correlated closely with FEV1 measurements and were supportive of efficacy of MF over placebo in Study P04334 (difference of 30L/min over placebo), and improvement from baseline in Study P04431 (increase of 15L/min from baseline value). (b) (4)

Asthma Control Questionnaire (ACQ)

The application does not propose to include ACQ information in the label; this is appropriate, as ACQ information was not included in the Dulera labeling, and the clinical meaning of any changes is uncertain.

6.1.6 Other Supportive Data

The Applicant provided an overall efficacy summary based on change in trough FEV1 from baseline the week 12, including data from the Dulera combination product program, as well as that from the related, older MF MDI program. As such, the Applicant proposes that the benefit in change in FEV1 for the 200mcg dose is supported by 6 studies, five of which had a comparison to placebo [P04334, C97-208, C97-225, C97-226, C97-227, and I97-200]. They propose that the 400mcg dose is supported by 4 studies, two of which had a placebo arm for comparison [P04431, I97-200, C97-208, and C97-224]. It is noted that this comparison has limitations due to the following:

- not all studies were powered for these analyses,
- MF product proposed differs somewhat from that evaluated in the older MF program
- Studies evaluated different asthma severities, had different baseline medications, and different design/durations

However, these data are generally supportive of benefit, as shown in Table 17 and Table 18, below. For the MF 200 dose, there were positive results both in change from baseline and additionally, over placebo. For the MF 400 dose, the same is seen.

Although the changes were not greater for the higher dose, this is not unexpected due to the relatively flat dose-response curve for mometasone, and because the patients receiving a 400mg dose, in general, had more severe disease, and most received treatment after a run-in period on ICS (either MF or the previously prescribed ICS).

Table 17: Comparative Week 12 FEV1 Endpoint for MF 200

Study	MF 200 BID	Placebo	Difference	p-value
P04334				
N	190	191		
Baseline	2.36	2.30		
Change	0.06 (3.2%)	-0.08 (-3%)	0.14	<0.001
C97-208				
N	73	72		
Baseline	2.51	2.38		
Change	0.14 (6.1%)	-0.19 (-8.4%)	0.33	<0.01
C97-225				
N	57	59		
Baseline	2.66	2.53		
Change	0.16 (6.1%)	-0.18 (-8.0)	0.34	<0.01
C97-226				
N	83	81		
Baseline	2.54	2.67		
Change	0.31 (12.8%)	0.10 (4.2%)	0.21	<0.01
C97-227				
N	49	50		
Baseline	2.76	2.74		
Change	0.07 (1.7%)	-0.42 (-16.5%)	0.49	<0.01
I97-200				
N	182			
Baseline	2.41			
Change	0.19 (8.5%)			

MF= Mometasone furoate MDI;

Source: Module 5.3.5.1, Individual CSRs; Module 2.7.3 Summary of Clinical Efficacy, Table 39, pg. 134

Table 18: Comparative Week 12 FEV1 Endpoint for MF 400

Study	MF 400 BID	Placebo	Difference	p-value
P04431				
N	239			
Baseline	2.07			
Change	0.09 (4.1%)			
C97-208				
N	74	72		
Baseline	2.61	2.38		
Change	0.12 (5.3%)	-0.19 (-8.4%)	0.31	<0.01
C97-224				
N	42	38		
Baseline	1.79	1.71		
Change	0.08 (7.3%)	-0.17 (-4.8%)	0.25	<0.01
I97-200				
N	176			
Baseline	2.49			
Change	0.18 (7.7%)			

MF= Mometasone furoate MDI

Source: Module 5.3.5.1, Individual CSRs; Module 2.7.3 Summary of Clinical Efficacy, Table 38, pg. 132

6.1.7 Subpopulations

The application included subgroup analyses of the major efficacy variables by age, gender, and race for each pivotal trial. For the change in mean FEV1 $AUC_{0\text{-}12h}$ and trough FEV1, similar patterns of efficacy were observed for MF over placebo, and also supported the dose separation between MF/F 400/10 and 200/10 in P04431 in terms for FEV1 $AUC_{0\text{-}12h}$ and the trough FEV1. Although the sample sizes were not equally distributed across the subgroups and formal statistical analyses were not provided, the results do not suggest differential efficacy on the basis of age, gender, or race.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two dose strengths of MF are proposed in this application. Dose ranging of MF is discussed above in Section 4 and was also discussed at length in the combination product review [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 93-94]. Because the MF 200 and MF 400 doses were chosen as part of the combination product, it is reasonable that the same two dose strengths would be chosen for use as monotherapy, to allow for stepdown from the ICS-LABA combination when clinically appropriate. Within the Dulera program, dose ranging information for the mometasone component was not clear cut, which may reflect the relatively flat dose response curve expected for an ICS, but in general, did provide support for two dose levels of MF. In review of the Dulera clinical program, it was determined that adequate

support was provided for the dose selection of the MF 200 and MF 400 monocomponents (as well as the combination MF/F 200/10 and 400/10 dose levels). There is no information to contradict that determination for the monotherapy proposed here.

In addition, the importance to patients and clinicians lies within the drug-device, since offering MF as an MDI will provide more effective step-down therapy for patients with moderate to severe asthma, currently using the Dulera combination. Currently, patients using Dulera transition to either MF DPI (Asmanex Twisthaler), or to a different ICS altogether, which can potentially interrupt asthma control. With the availability of the mometasone monotherapy as an HFA MDI, patients potentially will be able to wean to the corresponding ICS medium- or high-dose inhaled corticosteroid monotherapy, when deemed clinically appropriate to trial off of a LABA-containing combination.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were observed in the pivotal efficacy trials, and examination of efficacy endpoints out to 26 weeks supported persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

This NDA submission contains adequate data to support the safety of MF 200 and 400 in patients 12 years of age and older for the treatment of asthma in (b) (4) 12 years of age and older. The evidence for safety for MF is based primarily on the assessments performed in the completed Phase 3 efficacy trials (P04334, and P04431) and the dedicated 1-year safety trial (P04139). These data are supplemented by data from Phase 2 clinical pharmacology trials, which indicated lower exposure for the mometasone monotherapy, Asmanex Twisthaler DPI. The safety profiles for mometasone furoate DPI (Asmanex Twisthaler) and the combination product mometasone furoate/ formoterol fumarate (Dulera) are established and are also supportive.

The most common adverse events reported for MF (alone or in combination with formoterol) included headache, nasopharyngitis, sinusitis, influenza and bronchitis. There was no apparent dose response for these common AEs. The nature and frequency of these are consistent with those reported for approved monotherapies. Other AEs which are associated with the monotherapies, including oral candidiasis and dysphonia, occurred in less than 2% of all patients. There were no apparent differences

in AE frequencies when subgroups divided by age, gender, and race were evaluated. Similar AE profiles were observed in the individual trials as well as in the pooled analyses.

No asthma-related deaths or intubations were reported. In terms of other serious asthma-related outcomes, 7 patients in the combination clinical program had serious asthma exacerbations resulting in hospitalization. Of these, 2 patients received MF/F 200/10 BID, 1 patient was taking MF/F 400/10 BID, 1 patient received MF 200 BID, and 1 patient was taking F 10 BID. The remaining 2 patients received comparator product fluticasone propionate/salmeterol MDI and DPI, respectively. Additional data from the related, older MF MDI program was reassuring, and further informed the safety profile. Pediatric data was determined to be adequate under the original Dulera review, and additional data from the older MF MDI program further supports the safety in this population. In addition, there is extensive safety information from both the Asmanex Twisthaler (MF DPI) and Dulera combination products.

In summary, the safety database for MF 200 and MF 400 is adequate to support approval in patients aged 12 and older. No additional post-marketing safety trials are necessary for this ICS monoproduct.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based on a total of 15 clinical trials that enrolled 5683 asthmatic subjects aged 12 to 92 years of age, who received at least one dose of study medication in the MF MDI development program, either alone or in combination with formoterol. These include studies from the combination Dulera program, as well as the related, older MF MDI program. Of these 5683 subjects, 4015 were treated with MF, alone or in combination with formoterol, and 1668 subjects were randomized to receive placebo or another active comparator. The program consisted of 2 pivotal safety and efficacy trials, including P04334 (the placebo-controlled 26-week efficacy and safety study), and P04431 (the non-placebo-controlled 12-week efficacy and safety study). The Dulera development program also included a 1-year long-term safety trial, P04139, as well as Study P04705, a non-inferiority trial of MF/F and fluticasone propionate/salmeterol (Advair 250/50 mcg), and Study P04703, a 4 week dose counter study. HPA axis effects were assessed in the long-term safety trial as well as Study P03705, which was a dedicated HPA axis study. This review focuses on the pooled analysis of the two pivotal efficacy and safety Phase 3 trials (n=1509) and the results of the long-term safety trial (n=404), supplemented by data from the other trials.

7.1.2 Categorization of Adverse Events

In all trials, patients were questioned about adverse events occurring since the previous visit up to 30 days after the stop of treatment. Investigators graded the AEs as mild (easily tolerable), moderate (interference with usual activity and may warrant intervention), severe (incapacitating, warrants intervention), or life-threatening. A serious adverse event (SAE) was defined as an event that was fatal, life-threatening, significantly or permanently disabling, a congenital anomaly or birth defect, or required hospitalization. For clinical laboratory tests following outside the laboratory's stated range of normal, investigators and the Applicant made a determination if the changes were clinically meaningful. Symptoms associated with asthma, including chest tightness or congestion, cough, difficulty breathing, and wheezing, were not included as AEs unless there was a clear temporal relationship with study drug administration, was associated with an SAE, associated with another underlying disease, or per investigator discretion.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the Integrated Summary of Safety, the Applicant provided a pooled analysis of the two pivotal Phase 3 trials, as well as analyses of the supportive studies classified by duration, placebo-control, blinding, and exposure. Studies conducted under the Dulera combination program are indicated by the prefix, "P," and studies beginning with "C97" and "I97" are from the original MDI program conducted by the Applicant in the late 1990's using a slightly different MDI product than the to-be-marketed one. The 15 studies are listed and pooled as follows:

- "Pivotal" Phase 3 Efficacy and Safety,
  - P04334: 26-week, placebo controlled
  - P04431: 12-week, non-placebo-controlled
- Supportive Phase 3 Efficacy and Safety, 12-week
  - C97-208
  - C97-226
  - C97-227
- Supportive Phase 3 Efficacy and Safety, 3-month + 9-month OL safety
  - C97-223
  - C97-224
- Supportive Phase 3 Non-placebo-controlled, 12-week
  - P04075
  - I97-200
- Supportive Phase 3, Non-placebo-controlled, 52-week safety
  - C97-222
  - P04139
- Supportive Phase 3 Open-label, 6 week dose-counter
  - P04703

- Supportive Phase 2/3, 12-week dose-ranging
  - C97-208
- Supportive Phase 1 extrapulmonary HPA axis function
  - P03705
- Supportive Phase 4 Bone mineral density
  - P03418

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The size of the safety database is adequate for this application. The Dulera combination product development program which utilized the to-be-marketed formulations of MF 200 and MF 400 HFA, included studies P04334, P04431, P04139, P04705, P04703, and P03705, as described in Section 7.1.1. Within those studies, 1781 patients received at least one dose of MF/F, and 618 received at least one dose of MF. Treatment duration of the Phase 3 program is summarized in Table 19, below.

When data from the older MF program are added, a total of 4015 asthmatic subjects (≥12 years of age) received MF MDI (at doses ranging from 50 to 100 mcg once daily, up to 800 mcg BID) or inhaled combination MF/F (at doses ranging from 100/10 mcg BID to 400/10 mcg BID) for up to 52 weeks. The Internal Conference on Harmonization of the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in the ICHE1A Guidance for Industry recommends that for a drug with chronic use generally recommends a safety database of 1500 patients with short-term exposure, 3-600 patients with 6-month exposure, and 100 patients exposed for one year for support. For this program, MF MDI numbers demonstrate adequacy of the safety database, with over 4,000 total exposures, 909 patients exposed for 6 months, and 227 patients with MF MDI exposure for at least one year. In addition, 277 subjects (18-49 years of age) received MF DPI (at doses of 200 mcg and 400 mcg QD) for 52 weeks in a Phase 4 study (P03418), which provides data on MF treatment effects on bone mineral density (BMD). Although this study used MF dry powder inhaler (DPI), rather than MF MDI, the systemic exposure of the former is known to be greater than equivalent doses of the latter; thus, the findings of this study in terms of BMD can be applied to MF MDI, as well.

Table 19: Duration of Exposure: Pooled Phase 3 Trials

Duration (day)	MF/F 100/10 N=465	MF/F 200/10 N=936	MF/F 400/10 N=385	MF 100 N=188	MF 200 N=192	MF 400 N=240	F 10 N=390	F/SC MDI 250/50 N=68	F/SC MDI 500/50 N=65	F/SC DPI N=351	Pbo N=384
Received any treatment	464	932	385	186	192	240	390	68	65	349	383
≥15	411	904	381	183	190	233	375	67	64	335	362
≥30	391	880	372	174	187	227	348	67	62	328	336
≥60	165	841	355	168	180	211	304	66	61	311	293
≥90	159	538	138	160	175	11	285	66	60	220	277
≥120	154	499	118	154	168	-	271	65	59	196	260
≥178	138	383	115	131	142	-	223	64	58	95	218
≥267	-	160	109	-	-	-	-	60	57	25	-
≥356	-	144	108	-	-	-	-	58	57	17	-
≥363	-	131	96	-	-	-	-	52	48	11	-
≥371	-	27	13	-	-	-	-	8	8	2	-
≥386	-	3	2	-	-	-	-	-	2	-	-
Unknown	6	-	-	-	-	-	-	-	-	-	-
Randomized, not treated	1	4	-	2	-	-	-	-	-	-	1

F/SC= fluticasone propionate/salmeterol
Source: Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 97, Table 39

7.2.2 Explorations for Dose Response

No new dose-response data was submitted in this application; all data was reviewed under the Dulera program [see Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 98].

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Routing clinical testing was performed at Screening and at Final Visit for all trials. Additional interim time points were assessed, depending on the individual protocol. The laboratory tests included the following:

- Chemistries: albumin, alkaline phosphatase, bicarbonate, blood urea, glucose, total bilirubin, BUN, cholesterol, creatinine, total protein, calcium, albumin, inorganic phosphorus, sodium, potassium, chloride, AST, ALT, LDH, and plasma cortisol, serum pregnancy tests (females of child-bearing potential at Screening)
- Complete blood count: WBC, differential, platelets, RBC, hematocrit, hemoglobin, eosinophils, neutrophils, lymphocytes, monocytes, and basophils
- Complete urinalysis: specific gravity, pH, blood, ketones, color, protein, glucose

In the phase 3 program, clinical relevant abnormalities were defined as follows: blood chemistry parameters ≥2.6 times the upper limit of normal (ULN), hemoglobin ≤9.4g/dl; platelet ≤74x10^3 cells/ml; white blood cell count ≤2.9x10^3 cells/ml. Serum glucose was not evaluated at every visit; only urinary glucose was tested.

7.2.5 Metabolic, Clearance, and Interaction Workup

Specific metabolic, clearance, and/or interaction safety studies were not conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

ICS

Given the known potential for HPA axis suppression with corticosteroids, plasma cortisol $AUC_{0\text{-}24hr}$ was assessed in the long-term safety study (P04139) and the designated HPA axis study (P03705). In addition, Study P03418 was a Phase 4 study on bone mineral density, completed after approval of Dulera. Also, given the potential risk of elevated intraocular pressures and cataract formation associated with corticosteroids, all subjects were examined by a certified ophthalmologist with additional assessments at Visits 1, 9, and 11 at a subset of study sites. Physical exams were performed at all visits to monitor for oral candidiasis and dysphonia, which are commonly reported with Asmanex Twisthaler and other ICS, and adverse events were assessed throughout the trial. Laboratory testing did not include routine evaluation for hyperglycemia, which would have been preferable, but did evaluate glucosuria.

7.3 Major Safety Results

7.3.1 Deaths

Four deaths were reported among patients who received MF/F in the Dulera program. In P04139, 2 patients died while on MF/F 200/10 BID; a 59 year-old male (Patient 0013/Site 17) was accidentally electrocuted at his place of employment, and a 50-year-old female (Patient 0139/Site 28) died of gastric cancer. In Study P04334, a 53-year-old woman (Patient 0012/Site 12) on MF/F 200/10 BID died from metastatic uterine leiomyosarcoma. In addition, there was a 26 year-old male subject receiving montelukast 10mg in the Phase 4 Study P03418 (Patient 26/742), who died as the result of a homicide.

Based on the nature and timing of these deaths, they do not appear to be related to study drug. There were no asthma-related deaths reported in the Dulera clinical program utilizing the to-be-marketed formulations of MF.

Within the related, older MF MDI program, two patients with severe, oral steroid-dependent asthma died during the course of Study C97-224, one in the blinded 3-month phase, and the other in the open-label 9-month phase. A 79-year-old (Patient C97-224-02/011) receiving MF 400mcg BID died from respiratory insufficiency and pneumonia, and a 60yo (Patient C97-224-24/005) receiving MF MDI variable dose died of myocardial infarction and septic shock, respectively. These events are confounded by patient age and disease severity, and do not represent a significant safety signal.

7.3.2 Nonfatal Serious Adverse Events

In the P04334 and P04431 studies, 22 subjects (MF/F 200/10 mcg BID group, 8 (1.9%) subjects (1.9%); MF/F 400/10 mcg BID, 2 (0.8%) subjects; MF 200 mcg BID, 3 (1.6%) subjects; MF 400 mcg BID, 3 (1.3) subjects; F 10 mcg BID, 3 (1.5%) subjects; and placebo, 3 (1.5%) subjects) reported a total of 25 SAEs, as shown in Table 20. All were considered unlikely related to treatment, except for hemoptysis and chest pain which occurred in a patient receiving MF 400 (Patient 114/002191) in Study P04431. Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in MF 200 and MF 400-treated patients included abdominal pain (2), chest pain (1), gastroenteritis (1), endometriosis (1), asthma (1), and hemoptysis (1); all events occurred at rates less than 1%.

Table 20: Serious Adverse Events by System, Pooled P04334 and P04431

	MF/F 200/10 N=424	MF/F 400/10 N=255	MF 200 N=192	MF 400 N=240	F 10 N=202	Placebo . N=196	Total . N=1509
Subjects reporting Any SAE	8 (1.9)	2 (0.8)	3 (1.6)	3 (1.3)	3 (1.5)	3 (1.5)	22 (1.5)
Gastrointestinal	1 (0.2)			2 (0.8)			3 (0.2)
General Disorders				1 (0.4)			1 (0.1)
Infections	1 (0.2)		1 (0.5)				2 (0.1)
Injury	1 (0.2)					1 (0.5)	2 (0.1)
Metabolism					1 (0.5)		1 (0.1)
Neoplasms	1 (0.2)				1 (0.5)		2 (0.1)
Nervous system	2 (0.5)						2 (0.1)
Pregnancy	1 (0.2)						1 (0.1)
Psychiatric	1 (0.2)						1 (0.1)
Renal		1 (0.4)					1 (0.1)
Reproductive	1 (0.2)		1 (0.5)				2 (0.1)
Respiratory		1 (0.4)	1 (0.5)	1 (0.4)	1 (0.5)		4 (0.3)
Skin	1 (0.2)					1 (0.5)	2 (0.1)
Surgical						1 (0.5)	1 (0.1)
Source: Module 2.7.4, Summary of Clinical Safety, Table 2.7.4.12.1.4							

Of the supportive studies, few patients reported SAE, with a wide range of non-asthma-related SAEs affecting various organ systems, the majority of which did not appear to be drug-related.

The long-term safety study, P04139, noted 21 patients with SAEs. Of note, there were 5 reported eye disorders, including ophthalmic lens disorders reported in 3 patients and ocular hypertension reported in 1 patient treated with MF/F 400/10, and an additional report in a patient receiving F/SC 250/50 mcg BID.

Asthma-related SAEs

Within the Dulera program previously reviewed, there were seven subjects who had serious asthma exacerbations during study treatment periods that led to hospitalization; 2 patients were one MF/F 200/10 BID, 1 patient was on MF/F 400/10 BID, 1 patient was on MF 200 BID, and 1 patient was on F 10 BID. None of these subjects were intubated or died. Six of the 7 subjects had asthma exacerbations that were considered unlikely related to study drug. In Study P04334, one subject in the F 10 mcg BID treatment group (Subject No. 4195) had a serious asthma exacerbation that was considered as possibly related to study drug. In three of the subjects with serious asthma exacerbations, the event was in conjunction with a reported infection. These cases were all reviewed in detail by Dr. Limb [see Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 100]. Based on the varying time courses reported and the underlying background of moderate to severe asthma, a determination of causality between the study treatments and asthma-related SAEs cannot be made.

Evaluating the data with the addition of the related, older MF MDI development program, a total of 18 patients with severe asthma-related events were identified [Applicant's Summary of Clinical Safety, Module 2.7.4.3.4.4.3.3, Table 12, page 106-07]. These events occurred within 8 studies, at multiple dose levels, and two of which were on active comparator F/SC 250/50 BID. Five of these events occurred in Study C97-224, during the open-label 9-month variable MF dose portion of the study, none of which were considered drug-related. As for SAEs, based on the varying time courses reported and the underlying background of moderate to severe asthma, a determination of causality between the study treatments and asthma-related severe AEs cannot be made.

7.3.3 Dropouts and/or Discontinuations

Within the Dulera program, 50 patients discontinued from study, comprised of the following dose regimens: MF/F 200/10 (6), MF/F 400/10 (2), MF 200 (7), MF400 (5), F 10 (17), and placebo (13). More patients in the formoterol alone and placebo group discontinued than those on active treatment. A total of 184 subjects discontinued from studies included in this summary due to AEs. One hundred twenty-nine of the 4015

(3%) subjects who received MF MDI or MF/F discontinued from the study due to the occurrence of AEs. In the two pivotal studies (P04334 and P04431), the primary reasons for early discontinuation were "Treatment failure," which occurred in higher percentages of subjects in either the placebo or F groups (P04334), or "Did not meet protocol eligibility." Relatively few subjects discontinued because of AEs across all treatment groups. The most frequently reported AEs cited for premature termination included upper respiratory tract infection, viral infection, and bronchitis. There was no clear association between these AEs and the study treatments, both in terms drug itself (MF v. F v. MF/F) and in respective doses. In these trials, the proportion of patients who prematurely discontinued study drug due to adverse reactions was 3% for MF 200 and 2% for MF 400mcg treated patients, and 4% for placebo-treated patients.

In the long-term safety trial for the Dulera combination program, 15 patients discontinued early due to AEs: 5 in the MF/F 200/10 group, 8 in the MF/F 400/10 group, and 2 in the fluticasone/salmeterol 250/50 group. No patients in the fluticasone/salmeterol 500/50 group discontinued early due to an AE. Notably, 4 patients on MF/F 400/10 discontinued early due to lens disorders and ocular hypertension, which are known potential adverse effects of other inhaled corticosteroids. These events were coded as SAEs and are described in the section above.

.7.3.4 Significant Adverse Events

Significant events associated with the use of inhaled corticosteroids are discussed in the next section, below.

7.3.5 Submission Specific Primary Safety Concerns

Specific concerns for mometasone include those that are regarded as class effects of ICS, namely HPA axis suppression and hypercorticism, reduction in bone mineral density, ocular issues, and dysphonia. These are discussed briefly below.

HPA axis suppression
The effects of MF/F on 24-hour plasma cortisol profiles were assessed in a designated clinical pharmacology trial, P03705, and in the long-term safety trial, P04139. These were reviewed in detail under the Dulera review; the results were consistent with dose-related HPA axis suppression, which is a known adverse effect of inhaled corticosteroids. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 101-102]. This is appropriately described in the draft prescribing information under (b) (4) 12.2, *Pharmacodynamics*, *HPA Axis Effects*.

Reduction in Bone Mineral Density

Decreases in bone mineral density have been observed with long-term administration of products containing inhaled steroids. The Applicant completed a Phase 4 study (P03418) on the effects of MF dry-powder inhaler on bone mineral density. Although this study used MF dry powder inhaler (DPI), rather than MF MDI, the systemic exposure of the former is known to be greater than equivalent doses of the latter; thus, the findings of this study in terms of BMD are applicable to MF MDI, as well. In this light, the effect of MF MDI should be no worse than that demonstrated with the DPI in terms of bone mineral density. These results are included in the Dulera prescribing information under *WARNINGS AND PRECAUTIONS* Section 5.12, and for the Asmanex Twisthaler under Section 5.7. Similar recommendations for the proposed MF MDI product are warranted, and are appropriately described in the draft prescribing information under the *WARNINGS AND PRECAUTIONS* Section 5.9.

Ocular disorders
Use of inhaled corticosteroids may lead to posterior subcapsular cataract formation as well as increased ocular pressure. In the overall safety database, 10 of 3664 patients (0.3%) reported a treatment-emergent AE in the SOC Eye Disorders, as reviewed in detail under the Dulera review [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 102-103]. Six of these reports were from patients who received MF/F 400/10, with lens disorder (n=3), vision blurred (n=2), and ocular hypertension (n=1) reported. One case of visual disturbance was reported for MF/F 200/10. In the fluticasone propionate/salmeterol (F/SC) 250/50 group, there was 1 case of lens disorder and reduced visual acuity, while in the F/SC 500/50 group, there was 1 reported of blurred vision. In the placebo group, there was one reported of blurred vision. No cases of posterior subcapsular cataracts were reported were reported in the safety database.

The current approved package inserts for MF DPI (Asmanex Twisthaler) and lists glaucoma and cataracts in Section 5.8 *WARNINGS AND PRECAUTIONS*, noting that increased intraocular pressure and cataracts were reported in 8 of 3007 patients in the clinical trials database. Similarly, Section 5.14 of the MF/F MDI (Dulera) label describes the warning for glaucoma and cataracts. The label recommends close monitoring of patients for a change in vision and in those with a history of increased intraocular pressure, glaucoma, and/or cataracts. Similar recommendations for the proposed MF MDI product are warranted, and are appropriately described in the draft prescribing information under the *WARNINGS AND PRECAUTIONS* Section 5.11.

Other ICS effects
As described in the Dulera review, Dysphonia was reported in 1.7% of the pooled Phase 3 database and 0.8% of all patients reported oral candidiasis (MF/F 100/10, n=1; MF/F 200/10, F 10 n=1, placebo n=1). In the long-term safety trial, oral candidiasis was reported in 2 patients (1.4%) receiving MF/F 200/10 and 1 patient (0.8%) in MF/F 400/10, compared to 1 patient (2%) receiving F/SC 250/50 and 2 patients (3%) who received F/SC 500/50. Overall, these frequencies are lower than those reported for the

approved Asmanex DPI. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, page 103]. Oral candidiasis is appropriately described in the draft prescribing information under the ADVERSE REACTIONS Section 6.1.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported AEs in the 2 pivotal trials (P04334 and P04431) were nasopharyngitis, upper respiratory tract infection, and headache. Observed AE event rates were similar across the treatment groups, including placebo.

Table 21: Common AE Occurring in >2% of Patients (P04334 and P04431)

	P04334 26 weeks			**P04331 12 weeks**		
	Placebo N=196 n (%)	ASMANEX 200mcg N=192 n (%)	MF/F 200/10 mcg N=191 n (%)	ASMANEX 400mcg N=240 n (%)	MF/F 200/10mcg N=233 n (%)	MF/F 400/10 mcg N=255 n (%)
Any AE	82 (42)	88 (46)	97 (51)	66 (28)	62 (27)	75 (29)
Nasopharyngitis	7 (4)	15 (8)	12 (6)	13 (5)	8 (3)	12 (5)
Upper Respiratory Tract Infection	17 (9)	16 (8)	11 (6)	4 (2)	4 (2)	8 (3)
Headache	7 (4)	10 (5)	9 (5)	8 (3)	10 (4)	5 (2)
Oropharyngeal Pain	7 (4)	4 (2)	6 (3)	---	---	---
Pharyngitis	6 (3)	6 (3)	8 (4)	---	---	---
Sinusitis	2 (1)	6 (3)	5 (3)	4 (2)	9 (4)	5 (2)
Pyrexia	1 (1)	5 (3)	6 (3)	---	---	---
Influenza	5 (3)	7 (4)	5 (3)	1 (1)	---	---
Chest pain	4 (2)	1 (1)	2 (1)	---	---	---
Bronchitis	4 (2)	3 (2)	5 (3)	6 (3)	2 (1)	7 (3)
Cough	4 (2)	4 (2)	3 (2)	---	---	---
Gastroenteritis	---	4 (2)	1 (1)	---	---	---
Rhinitis	4 (2)	3 (2)	5 (3)	---	---	---
Viral infection	1 (1)	---	6 (3)	---	---	---

Source: Modified from Module 5.3.5.1, CSR P04334, Table 34 and Module 5.3.5.1, CSR P04431, Section 14.3.1.2; Module 2.7.4, SCS Table8, page 57; Modified from Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, Table 42, p105

Because of the differences in the two trials, data was not pooled, and the formoterol only arm of Study P04334 is not shown. When comparing the 200/10 and 400/10 doses of MF/F, there is no evidence of significant dose-response in terms of AEs.

For safety labeling, a comparison of treatment emergent adverse reactions that occurred over placebo is typically included. Since Study P04431 did not have a placebo arm, a single table did not present data to provide a fair comparison across studies. Therefore, for labeling purposes, the common AE data will be presented separately for the two studies; Table 22 provides the safety information of treatment-related adverse reactions which occurred at a rate of 3% or greater and greater than placebo, over the 26-week treatment period of Study P04334. Table 23 describes the full safety data from all arms of Study P04431, because there was no placebo arm, and because it is important to evaluate the safety events from the lower, as compared to the higher, combination dose (since the determination of efficacy of the higher dose is based on this difference). These two tables provide support that the safety profile of MF 100 and 200 are good, and that the higher dose does not present more safety risk for the population of severe asthmatics studied.

Table 22: Trial 1: Treatment-Related Adverse Reactions Occurring in 3% or Greater and Over Placebo, Through 26 Weeks

	Placebo N=196 n (%)	ASMANEX 200mcg N=192 n (%)
Any AE	82 (42)	88 (46)
Nasopharyngitis	7 (4)	15 (8)
Headache	7 (4)	10 (5)
Sinusitis	2 (1)	6 (3)
Influenza	5 (3)	7 (4)

Source: Modified from Module 5.3.5.1, CSR P04334, Table 34; ; Module 2.7.4, SCS Table 8, page 57; Modified from Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, Table 42, p105

Table 23: TRIAL 2: Treatment-Related Adverse Reactions Occurring in 3% or Greater in any Treatment Group Through 12 Weeks

	ASMANEX 400mcg N=240 n (%)	MF/F 200/10 mcg N=233 n (%)	MF/F 400/10 mcg N=255 n (%)
Any AE	66 (28)	62 (27)	75 (29)
Nasopharyngitis	13 (5)	8 (3)	12 (5)
Headache	8 (3)	10 (4)	5 (2)
Sinusitis	4 (2)	9 (4)	5 (2)
Bronchitis	6 (3)	2 (1)	7 (3)

Source: Modified from Module 5.3.5.1, CSR P04431, Section 14.3.1.2; Module 2.7.4, SCS Table 8, page 57; Modified from Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, Table 42, p105

7.4.2 Laboratory Findings

In general, review of the laboratory test data did not identify any specific safety concerns. No clinically relevant changes in median values for hematology or chemistry parameters were noted; a relatively small number of outlier values were noted, and the majority of these were small elevations in AST/ALT, not clinically relevant, and distributed evenly across treatment groups. The second most common abnormality was low hemoglobin; no patients discontinued due to these abnormalities. Serum glucose was not serially assessed, as described in section 7.2.4. None of these findings would suggest a safety concern associated with the chronic use of inhaled corticosteroids, [For full details, see Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 106-109].

7.4.3 Vital Signs

In general, review of the vital signs data did not identify any specific safety concerns that would be associated with chronic use of inhaled corticosteroids such as hypertension. For more details, see data reviewed under the Dulera program [see Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 109-110].

7.4.4 Electrocardiograms (ECGs)

In general, review of the ECG data did not identify any specific safety concerns related to the use of inhaled corticosteroids; there were no clinically significant changes observed between baseline and follow-up in terms of ventricular rate, PR, QRS, QTc, and QT intervals, and no differences between treatment groups. For more details, see data reviewed under the Dulera program [see Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 109-110].

7.4.5 Special Safety Studies/Clinical Trials

Study P04703 was a designated dose counter handling study intended to assess the durability of the integrated dose counter, which was not used in the pivotal Phase 3 trials. The design, conduct, and major results for this trial are presented in Section 4. Overall, the results of the study support the use of the dose counter and do not raise any specific safety concerns. [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 79-84, 110].

7.4.6 Immunogenicity

Immunogenicity was not specifically assessed in the development program. Mometasone is a small molecular entity not known to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Overall, there was no clear dose dependency for adverse events observed in the pivotal safety and efficacy trials and the long-term safety trial. The most common adverse events, such as nasopharyngitis and headache, did not display any clear dose dependency.

Hypercorticism is expected to be dose-dependent, and this relationship is partly supported by the pattern of plasma cortisol suppression observed with higher doses described in Section 7.2. Likewise, adverse events associated hypercorticism, such as cataract formation or adrenal suppression, are expected to be dose-dependent. The adverse event data from the safety database did not yield specific examples of this type of dose-dependency, but these types of AEs may be seen more often with long-term, chronic use.

7.5.2 Time Dependency for Adverse Events

There was no apparent time dependency for the most commonly observed adverse events in the pivotal safety and efficacy trials and the long-term safety trial.

Adverse events associated with chronic corticosteroid use may be expected to be increased with prolonged use. This effect was not observed in the trials but with the caveat that the longest trial was the 1-year safety trial.

7.5.3 Drug-Demographic Interactions

Subgroup analyses of AE data by age, gender, and race do not indicate any apparent drug-demographic interactions, with the caveat that that not all subgroups were evenly represented. The overall rate of any AE was similar across age, gender, and race subgroups, without any clear patterns in relation to dose or treatment group. Similar conclusions were made regarding these subgroups and laboratory parameters and vital signs.

7.5.4 Drug-Disease Interactions

Comparison of AE data from Trial P04431, which presumably enrolled more severe asthmatics, to data from the other efficacy trials, do not indicate any apparent drug-disease interactions.

7.5.5 Drug-Drug Interactions

In these clinical trials, concurrent administration of MF or MF/F with other commonly-used drugs such as short-acting beta-2-agonists and intranasal steroids, did not result in an increased frequency of adverse events. No formal drug-drug interaction studies were performed for MF or MF/F MDI. Refer also to Section 4.4.3 for more detailed information regarding assessments of Drug-drug interactions for MF MDI.

Both the Dulera and Asmanex Twisthaler (DPI) labels contain information regarding inhibitors of Cytochrome P450 enzymes, noting that with concomitant administration of ketoconazole, mometasone furoate plasma levels increase and serum cortisol levels decrease. This same language is proposed for MF MDI label, under Section 12.2, Pharmacodynamics, Drug-drug Interactions, and is appropriate.

7.6 Additional Safety Evaluations

No additional safety evaluations were performed.

7.6.1 Human Carcinogenicity

Specific evaluations for carcinogenicity were not conducted for this application. Mometasone is a well-known chemical entity, which is not known to be carcinogenic.

7.6.2 Human Reproduction and Pregnancy Data

Specific evaluations of MF on reproduction and pregnancy have not been conducted. A total of 13 patients became pregnant while exposed to study treatment under the Dulera program, reviewed by Dr. Limb . [See Primary Clinical Review for Dulera NDA 22-518, dated Jan 22, 2010, pages 139-40], as below:

- Two of the 13 experienced miscarriages during the 1st trimester.
- One patient gave birth to a boy with a mild heart murmur which did not require any intervention.
- One patient (P03705) developed fetal distress syndrome, fetal growth retardation, and oligohydramnios 222 days after discontinuation from treatment. The baby was later delivered via cesarean section and both mother and baby were reported to be doing well.
- One patient (186/004257) on MF 200 delivered prematurely at <26 weeks due to ruptured membranes. The baby subsequently died of respiratory distress.

Given the background frequency of events expected in pregnancy, it is not possible to establish a causal relationship between the reported pregnancy outcomes and use of MF/F, MF, or F.

No other information on the use of MF in pregnancy or lactation in humans is available. The Asmanex label notes that hypoadrenalism may occur in infants of mothers treated with systemic steroids during pregnancy. It is not known whether MF is excreted in human milk, although it has been established that other corticosteroids are excreted in human milk. This information is adequately captured in the Applicant's draft labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Dulera (MF/F) combination program and the related, older MF MDI program combined enrolled a total of 658 patients aged 12 to <18 years, of whom 466 had exposure to MF/F or MF alone, as seen in Table 24 below. This level of exposure is comparable to the pediatric representation that has been seen in other ICS/LABA development programs.

Table 24: Patients 12 to <18 Years Old, Across Development Programs

	MF/F 100/10	MF/F 200/10	MF/F 400/10	MF 50	MF 100	MF 200	MF 400	MF 600	MF 800	F 10	pcbo	AC
Total	105	89	34	30	55	88	41	22	2	40	82	70
P04073	28				30					22	30	
P04334		19				10				18	16	
P04431		18	23				22					
P04139		30	11									21
P04703	77											
P04705		22										18
C97-208				8		10	11	9			10	5
C97-222						15		13				7
C97-223‡					7	11					11	
C97-224							1		2		1	
C97-225				8		6					4	7
C97-226‡				14		19					10	
C97-227‡					11	9						4
I97-200					7	8	7					8

‡= Studies with once daily dosing converted to total daily to be in line with BID dose regimen
Source: Module 5.3.5.1 and 5.3.5.4, Individual CSRs

As summarized in Section 7.5.3, no apparent differences in terms of adverse events related to age were observed. A specific assessment on growth velocity was not conducted for MF MDI, but reduction in growth velocity is considered a potential adverse effect for all orally inhaled corticosteroids. Based on a growth study conducted for MF DPI, the Asmanex DPI and Dulera package inserts include effects on growth in Section 5, WARNINGS AND PRECAUTIONS, and recommends titration to the lowest effective dose. The data from MF DPI covers the MF MDI program, given that the MDI has less systemic exposure than the DPI; the DPI data presents a "worst case scenario." A similar recommendation for MF HFA is warranted.

No serious asthma-related outcomes (hospitalization for asthma exacerbation, intubation, or death) were reported for pediatric patients who received any dose of MF as monotherapy or in combination.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose were reported. In most cases of overdosage, no intervention is likely to be required. Given the mode of administration, the low systemic bioavailability, and the nature of the drug, drug abuse potential, withdrawal, and rebound are not anticipated. If used at excessive doses for prolonged periods, hypercorticism may occur and abrupt stoppage of MF may theoretically precipitate an adrenal crisis.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 4-month safety update on October 22, 2013, as required by regulations. However, since these trials have all been completed and previously reviewed under the Dulera application, no new information was submitted.

8 Postmarket Experience

MF MDI has not been approved anywhere, so there is no post-marketing safety data available. (b) (4)

9 Appendices

9.1 Literature Review/References

The application included a list of 26 clinical references, including a list of 55 abstracts regarding the use of mometasone furoate. To supplement this list, the clinical review conducted a PubMed literature search [search terms: ("mometasone furoate asthma") limits: "English," "human"] which yielded 174 articles. These articles were briefly scanned in terms of their relevance to the current application. No new safety signals were identified from the literature.

9.2 Labeling Recommendations

Labeling negotiations are pending at the time of this review. The following discussion is limited to high-level recommendations for the proposed package insert.

Proposed package labeling was included in the original submission [Section 1.14] and updated labeling was submitted on June 27, 2013. The Applicant seeks an indication for the maintenance treatment of asthma as prophylactic therapy in (b) (4) 12 years of age and older.

In general, the proposed package insert supplied by the Applicant is a consolidation of the Asmanex Twisthaler (DPI) and Dulera HFA (MF/F MDI) labels. Most of the sections, including Sections 11 (chemical description), 7 and 12 (clinical pharmacology), and 13 (non-clinical toxicology) have been assessed by their respective review disciplines, and do not require substantial revision.

Section 4: CONTRAINDICATIONS, Section 5: WARNINGS AND PRECAUTIONS, Section 8: USE IN SPECIFIC POPULATIONS, and Section 10: OVERDOSAGE, are also very similar to previously approved package inserts and require little modification.

The majority of the changes from the Applicant's proposed package insert appear in sections 6: ADVERSE REACTIONS, and Section 14: CLINICAL TRIALS. For Section 6, the Applicant has proposed to (b) (4) Also, since Study P04431 provides support for the higher dose of MF by demonstration of difference in combination strengths, the data for these two groups is necessary to inform safety, as well as the MF 400 group. Because of the difficulty displaying this data in one summary table (as is usual when studies are

similar enough to allow for pooling), it was felt that two separate tables would provide a more accurate representation of the safety data to inform patients and providers. (b) (4)

Section 14 proposed by the Applicant also requires a number of revisions. (b) (4)

The "Other Studies" section would not normally be included in labeling, but since the two pivotal studies described do not provide replicate evidence of efficacy alone, it is important to note that 3 other studies from the Dulera program, as well as other studies from the related, older MF MDI program also provide support for both doses of MF as proposed.

9.3 Advisory Committee Meeting

Since mometasone is not a new molecular entity, and no new indications were proposed, an Advisory Committee Meeting was not warranted for this application.

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/s/

KIMBERLY A WITZMANN
03/21/2014

ANTHONY G DURMOWICZ
03/21/2014