CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-518
Priority or Standard	S
Submit Date(s)	May 21, 2009
Received Date(s)	May 21, 2009
PDUFA Goal Date	March 22, 2010
Division / Office	DPAP
Reviewer Name(s)	Susan Limb, MD
Review Completion Date	January 22, 2010
Established Name	Mometasone furoate and formoterol fumarate (MF/F)
(Proposed) Trade Name	Dulera Inhalation Aerosol
Therapeutic Class	Inhaled corticosteroid/long-acting beta-agonist
Applicant	Schering-Plough
Formulation(s)	Combination metered dose inhaler (MDI): MF/F (b) (4) 100/5 mcg, and 200/5 mcg
Dosing Regimen	2 inhalations twice daily
Indication(s)	Asthma
Intended Population(s)	12 years and older

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List of Commonly Used Abbreviations

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
AUC	Area under the curve
BDP	Budesonide propionate
DPI	Dry powder inhaler
F	Formoterol fumarate
F/SC	Fluticasone propionate/salmeterol combination
FEV1	Forced expiratory volume in 1 second
HFA	Hydrofluroalkane
HPA	Hypothalamic-pituitary axis
ICS	Inhaled corticosteroid
LABA	Long-acting beta-agonist
MF	Mometasone furoate
MF/F	Mometasone furoate/formoterol fumarate combination
PEFR	Peak expiratory flow rate
pMDI	Pressurized metered dose inhaler
PREA	Pediatric Research Equity Act
SABA	Short-acting beta-agonist

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommended regulatory action is Approval for the twice-daily treatment of asthma in patients 12 years of age and older for the following dose levels of mometasone furoate/formoterol fumarate (MF/F) combination inhalation aerosol: MF/F 100/5 mcg 2 actuations (therapeutic dose 200/10 mcg) twice daily and MF/F 200/5 mcg 2 actuations (400/10 mcg) twice daily.

1.2 Risk Benefit Assessment

The proposed indication for mometasone furoate/formoterol fumarate (MF/F) combination is "the (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older." (b) (4) separate MF/F dosage strengths are proposed: (b) (4) 100/5, and 200/5 mcg (ex mouthpiece dose) administered as 2 inhalations twice daily. This review refers to the therapeutic dose of MF/F delivered by 2 actuations, i.e. MF/F (b) (4) 200/10, and 400/10 mcg, respectively. The clinical review concludes that the application includes adequate information to support an indication for the treatment of asthma in patients 12 years of age and older for MF/F 200/10 and 400/10 administered twice daily. (b) (4)

In terms of benefit, the pivotal, factorial design trial P04334 provides statistically robust evidence of efficacy for MF/F 200/10 compared to placebo and demonstrates the contribution of the MF 200 and F 10 monocomponents to the combination. The efficacy of the individual MF 200 and F 10 monocomponents is also supported by replicate, statistically significant comparisons to placebo. The efficacy of MF/F 400/10 is supported by the numerical separation from MF/F 200/10 observed in the pivotal Phase 3 trial, P04431, as well as replicate, statistically significant comparisons to placebo for both the MF 400 and F 10 monocomponents.

In terms of risk, the common adverse event profiles for MF/F 200/10 and 400/10 were comparable to the known profiles for the related approved monotherapy products, Asmanex (mometasone furoate DPI) and Foradil (formoterol fumurate DPI). There was no appreciable difference in terms of MF/F dose level. In terms of serious, asthma-related adverse events, no deaths or intubations secondary to asthma were reported. Seven hospitalizations due to asthma exacerbations were reported and but were not associated with a particular treatment arm, with the cases evenly distributed across MF/F treatment arms, active comparator arms, and placebo. Overall, the safety profiles for MF/F 200/10 and 400/10 were acceptable. However, the clinical program was not

large enough to assess the risk of rare, serious asthma-related adverse events, including exacerbation-related death, which have been associated with LABAs. Therefore, a REMS program comprised of a Medication Guide and Communication Plan to address the risk of asthma-related death is recommended, in conjunction with a post-marketing requirement for a large, simple safety trial that will assess the risk of such events when a LABA is used in addition to an ICS. The REMS and large safety trial should be consistent with the REMS and safety trials planned for similar LABA-containing inhalation products approved for asthma.

(b) (4)

(b) (4) MF/F 200/10 is the lowest dose recommended for approval by the clinical review.

The wording for the recommended indication differs from the proposed indication (b) (4) (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older." While the proposed indication (b) (4) is consistent with previously approved long-acting beta-agonists (LABA), the current thinking within the Agency has shifted with an emphasis on the selective use of LABAs due to the risk of serious asthma-related adverse events. As a result, the role of LABAs (b) (4) (b) (4) is in question, and the clinical review considers a general asthma treatment indication as more appropriate. (b) (4)

(b) (4)

In summary, the benefit risk assessment for MF/F 200/10 and 400/10 is favorable and supports approval of these 2 dose levels for a modified indication of the treatment of asthma. (b) (4) The clinical recommendation for approval for the MF/F 200/10 and 400/10 dose levels is made with the provision that the Applicant and the Agency will agree upon an appropriate REMS

and post-marketing safety trial, both of which are the subject of ongoing review. The REMS and post-marketing safety trial are intended to further assess and manage the risk of serious asthma-related adverse events which have been associated with LABAs. The clinical recommendation for approval is also contingent on a satisfactory evaluation of the DSI audits, which also remains pending at the time of this review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The submission includes a proposed risk management plan with the following goals:

- (b) (4)

In addition to product labeling, the proposal includes a Medication Guide and a communication plan for HCP and patients through sales representatives and a website. The effectiveness of these measures will be assessed by periodic HCP/patient comprehension surveys at 18, 36, and 84 months and expedited AE reporting

The clinical review recommends a REMS with a Medication Guide and Communication Plan that addresses the risk of asthma-related death associated with LABA products. The goals of the REMS should be consistent with the goals for similar LABA products. Review of the proposed REMS in conjunction with the Office of Surveillance and Epidemiology (OSE) remains ongoing. Final recommendations regarding a REMS program is pending at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical review recommends postmarketing requirements for trials to assess the safety and efficacy of MF/F in pediatric patients 5 to <12 years of age and a large safety trial to assess the risk of serious asthma-related AEs for the addition of F to MF.

Pediatric studies
The clinical review recommends evaluation of safety and efficacy in patients 5 to <12 years of age as required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)). The Applicant has requested a deferral for submission of

data on patients 5 to <12 years of age. At a meeting on January 28, 2009, and the pre-NDA meeting on December 15, 2008, the Division and the Applicant discussed plans for a pediatric clinical program (b) (4) . In the interim, a Phase 2 trial (C2204) is currently ongoing at the time of this application. The application projects a 2010 start date for a Phase 3 trial in this age group. The clinical review finds the deferral request and proposed timeline reasonable. Details of the pediatric plan, including specific trial design and projected dates of protocol submission, trial initiation and completion, and submission of the complete study report have yet to be finalized at the time of this review.

The Applicant requested a waiver of studies in patients 4 years of age and younger, citing current practice guidelines which recommend treatment with ICS in this age group and noting that concerns about severe asthma-related adverse events with LABAs make the MF/F combination less appropriate for this age group. The waiver request also noted that alternative reliever and controller medications, including SABAs and leukotriene receptor antagonists, are available for patients 4 years of age and younger. The clinical review finds this rationale reasonable and recommends approval of the request for waiver.

LABA safety
The safety issue of severe, asthma-related adverse events, including asthma death, associated with chronic LABA use remains the subject of ongoing discussion within the Agency. The Applicant will be required to conduct a large safety trial as a post-marketing requirement evaluating the safety of MF/F in terms of serious asthma-related outcomes, e.g. exacerbations resulting in intubations, hospitalizations, and death. The purpose of the safety trial will be to evaluate the safety of formoterol added to mometasone in this combination product. The safety trial will be required as a post-marketing requirement since both mometasone and formoterol are currently marketed in the US.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product is a new inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination inhalation metered-dose inhaler (MDI), mometasone furoate and formoterol fumarate (MF/F). The proposed tradename is Dulera®. (b) (4) separate MF/F dosage strengths are proposed: (b) (4) 100/5, and 200/5 mcg (ex mouthpiece dose) administered as 2 inhalations twice daily. This review refers to the therapeutic dose of MF/F delivered by 2 actuations, i.e. MF/F (b) (4), 200/10, and 400/10 mcg, respectively. Both mometasone and formoterol are currently approved for

the maintenance treatment of asthma. Mometasone is approved in a dry powder inhaler formulation as Asmanex Twisthaler. Formoterol is approved as a dry powder inhaler as Foradil Aerolizer and Foradil Certihaler (not currently marketed). MF/F combination MDI is a new HFA formulation for both active pharmaceutical ingredients.

The proposed indication is the (b) (4) twice daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older. While the proposed indication (b) (4) is consistent with previously approved long-acting beta-agonists (LABA), the current thinking within the Agency has shifted with an emphasis on minimizing the chronic use of LABAs due to the risk of serious asthma-related adverse events. As a result, the role of LABAs (b) (4) (b) (4) is in question, and the clinical review considers a general asthma treatment indication as more appropriate.

While both mometasone and formoterol monotherapies are approved for the maintenance treatment of asthma, (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Mometasone furoate, a mid-strength to potent 17-heterocyclin glucocorticosteroid, has been marketed in the US since 2005 as a multiple dose dry powder inhalation (DPI) formulation (NDA 21-067, Asmanex®). Asmanex 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.

Formoterol fumarate has been marketed in the US since 2001 as a single dose DPI formulation (NDA 20-831, Foradil® Aerolizer) for the maintenance treatment of asthma and the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma. Efficacy and safety information for formoterol are summarized in the current approved package insert for Foradil Aerolizer. The recommended dose is 12 mcg BID. Foradil is also approved for the acute prevention of exercise-induced bronchospasm (EIB) in patients 5 years of age and older, and for the maintenance treatment of bronchoconstriction in patients with COPD.

Alternative forms of formoterol include Foradil Certihaler, which is another DPI formulation which was approved for the maintenance treatment of asthma in December

2006. The recommended dose of Foradil Certihaler is 10mcg BID. Foradil Certihaler is not currently marketed in the US. An inhalation solution of formoterol (Perforomist 20 mcg) administered by nebulization is approved for the maintenance treatment of COPD. Formoterol is also a component in the ICS/LABA combination product, budesonide/formoterol (Symbicort 80/4.5 and 160/4.5 mcg), which is approved for the maintenance treatment of asthma in patients 12 years of age and older and the maintenance treatment of airflow obstruction in patients with COPD.

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 such as the proposed MF/F product. 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).

2.3 Availability of Proposed Active Ingredient in the United States

The two monotherapy component active pharmaceutical ingredients have been previously approved as DPI formulations for the treatment of asthma and are described in the preceding Section 2.2. There is currently no mometasone/formoterol combination inhalation product marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety issue of serious, asthma-related adverse events associated with chronic LABA use remains the subject of ongoing discussion within the Agency. As a post-marketing requirement, the Applicant will be required to conduct a large safety trial evaluating the safety of MF/F in terms of serious asthma-related outcomes that include intubations, hospitalizations due to exacerbations, and death.

The submission also includes a proposed risk management plan with the following

(b) (4)

(b) (4)

The proposal includes a Medication Guide and a communication plan for HCP and patients through sales representatives and a website. The effectiveness of these measures will be assessed by periodic HCP/patient comprehension surveys at 18, 36, and 84 months and expedited AE reporting.

The clinical review recommends a REMS with a Medication Guide and Communication Plan that addresses the risk of asthma-related death associated with LABA products. The goals of the REMS should be consistent with the goals for similar LABA products. Review of the proposed REMS in conjunction with the Office of Surveillance and Epidemiology (OSE) remains ongoing. Final recommendations regarding a REMS program is pending at the time of this review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

MF/F is currently not marketed. The following timeline summarizes the regulatory history:

- June 11, 2003 – Preclinical development meeting
  - Design of multi-dose toxicity study focusing on cardiotoxicity and male reproductive toxicity discussed.
  - Genetic and teratology toxicology studies would not be required.
  - Juvenile animal study required only if planned use in children <2 yrs, which DPAP deemed was not likely to be an appropriate population for this fixed-dose combination.
- November 3, 2004 – Clinical pharmacology/clinical development meeting
  - Commercially available monotherapy comparators (Asmanex and Foradil) not appropriate reference controls for factorial design study to satisfy the Combination Rule.
  - Need to develop appropriate monotherapy comparators or provide evidence that pharmaceutical differences are not clinically relevant.
  - HPA axis assessment to be done in Study P03705, Study 2102, and additional assessments in P3 trials
- March 28, 2006 – Pre-IND meeting
  - Use of unapproved monotherapy comparators. Formoterol comparator will be an HFA-134a MDI previously studied under a separate IND (IND 64,719). Mometasone comparator will be an HFA-227 pMDI formulation of the MF/F combination minus the formoterol, which constitutes a small proportion of the total formulation.
  - Need for dose-ranging data with the MDI formulation. Only limited support from the DPI formulation would be relevant.
  - Program must show advantage of combination over the components.

  - HPA axis studies should include the highest to-be-marketed dose.
  - Need for formoterol monotherapy arm in P3 trials.
  - Placebo arm not necessary for trial with highest dose of MF/F in moderate to severe asthmatics; a lower dose of MF/F should be included to justify the higher dose.
  - Endpoints in the P3 trials should assess the contribution of each component. The change in FEV1 AUC_{0-12h} should be from baseline to Week 12, not Week 1.
  - "Asthma worsening" endpoint vague and would require clear pre-specified definitions if used as a co-primary endpoint.
- September 12, 2006 – CMC development meeting
- February 22, 2007 – Written communication
  - Limitations of proposed asthma exacerbation definition
- February 27, 2007 – Written communication
  - Limitation of proposed non-inferiority trial and labeling claims
- January 30, 2008 – Pediatric/clinical development meeting

(b) (4)

- April 23, 2008 – CMC meeting
- December 15, 2008 – pre-NDA meeting
  - Need replicate data to support the MF monotherapy comparator against placebo at each dose level. MF monotherapy comparator needs to be fully developed, even if approval for the single product is not sought.
  - Need for dose ranging data and appropriate bridging between the Foradil Aerolizer and the 10 mcg formoterol HFA134a MDI monotherapy comparator.
  - Justify the (b) (4) proposed dose levels: (b) (4) 100/5 and 200/5. No head-to-head comparison of (b) (4) to 100/5.
  - Proposed asthma exacerbation endpoint based on lung function and oral corticosteroid use with post hoc correlation to symptoms. The Division stated that a pre-specified definition including these elements was needed.
  - Inclusion of Asthma Control Questionnaire data in the product label would be a review issue.
  - Inclusion of AQLQ12+ product label may be appropriate.
  - No PK assessment of MF and F in adolescent populations would be viewed as a data gap.

2.6 Other Relevant Background Information

The application is a 505(b)(1) application submitted electronically. Schering Corporation and Novartis Pharmaceuticals co-developed the proposed MF/F combination. Schering is the NDA holder for mometasone DPI (NDA 21-067, Asmanex Twisthaler), and Novartis is the NDA holder for formoterol DPI (NDA 20-831, Foradil Aerolizer). Schering and Novartis have provided open right of reference to all sections of both NDAs. Cross-reference is made to these NDAs for CMC information on the drug substances, non-clinical data, and clinical data on bioavailability and pharmacodynamics.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is appropriately indexed and complete to permit review. Review of potential treatment center effects by the statistical reviewer did not show any clear discrepancies.

A DSI review was requested for Study Sites 16 and 12, which were the two US study sites that enrolled the highest numbers in the pivotal studies P04334 and P04037. The conclusions of the DSI consult are pending at the time of this review.

Site # and Contact Information	Protocol ID	Number of Subjects	Indication
Site #16 Nayak, Anjuli, MD Sneeze, Wheeze & Itch Associates, LLC 2010 Jacobssen Drive Normal, IL 61761 USA	P04334 P04037	21 20	Asthma
Site #12 Kerwin, Edward, MD Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Suite B Medford, OR 97504 USA	P04334 P04037	13 18	Asthma

Another investigator, Theodore Lee, MD, was terminated by the Applicant and cited for violation of GCP guidelines during the review period for this application (Inspection letter for Complaint #2602 dated December 8, 2009). This investigator enrolled 9 patients in the non-inferiority trial, P04705. The majority of violations were due to failure to meet and document the specified inclusion criteria. As the clinical review did not rely on

results from this trial for efficacy or safety support, data obtained from this investigator's site do not impact the conclusions of this review.

In addition, the Applicant submitted an amendment to the application on October 29, 2009, which included numerous corrections of discrepancies/errors in 9 eCTD subsection documents pertaining to CMC information. Although the nature of the corrections was minor and do not alter the content of the CMC information significantly, the number of errors noted raised some concern about data integrity. This issue of data integrity, in addition to results from the manufacturing site inspections, remains pending at the time of this review.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each complete study report and in the efficacy information amendment located in Module 1.11.3. One study investigator for P04705 was terminated due to violation of GCP guidelines (described above in Section 3.1).

3.3 Financial Disclosures

The Applicant has submitted a statement certifying that no debarred individuals were used in the conduct of the trials included in the NDA. The Applicant has submitted the following financial arrangements with investigators:

- (b) (6) $30,000 honoraria (b) (6) (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)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The preliminary recommendation of the CMC review is Approval. Details of the CMC review can be found in Dr. Alan Schroeder's review. Results of the manufacturing site inspections and final recommendations are pending at the time of this review.

The proposed drug product is a pressurized metered dose inhaler (pMDI) containing HFA 227 as the propellant. The drug products are white suspensions containing (b) (4) (b) (4) alcohol (b) (4) anhydrous (USP-NF), (b) (4) oleic acid (USP-NF), and active ingredients, mometasone furoate anhydrous and formoterol fumarate dehydrate. (b) (4) separate MF/F dosage strengths are proposed: (b) (4) 100/5, and 200/5 mcg administered as 2 inhalations twice daily. Each (b) (4) aluminum canister is closed (b) (4) Based on in vitro evaluations, dose counter performance appears adequate. The pMDI is designed to deliver a minimum of 120 actuations. One therapeutic dose is obtained from two single actuations.

The Applicant developed novel monotherapy MF and F products for use in the Phase 2 and Phase 3 trials. The MF product was the same as the HFA 227 MF/F combination formulation minus formoterol. The formoterol MDI formulation used in the dose-ranging trials was an HFA 134a product, not HFA 227, since it was not feasible to develop a F HFA 227 product (b) (4). As a result, the F MDI used as a monotherapy comparator in the Phase 2 and 3 trials was a formulated that used HFA 134a as a propellant (b) (4). This issue was previously discussing during the April 23, 2008, pre-NDA meeting.

The Applicant submitted an amendment to the application on October 29, 2009, which included numerous corrections of discrepancies/errors in 9 eCTD subsection documents pertaining to CMC information. Although the nature of the corrections was minor and do not alter the content of the CMC information significantly, the number of errors noted raised some concern about data integrity. This issue of data integrity, in addition to results from the manufacturing site inspections, remains pending at the time of this review.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the preclinical review is Approval. Details of the preclinical pharmacology/toxicology review can be found in Dr. Lawrence Sancilio's review.

The nonclinical safety program for MF/F relied on the nonclinical data available for mometasone furoate DPI (Asmanex, NDA 21-067) and formoterol fumarate DPI (Foradil, NDA 20-831), which included chronic, reproductive, genotoxicity, and carcinogenicity studies. In addition, the nonclinical bridging program consisted of 2- and 13-week inhalation toxicity studies in rats and dogs using co-administered MDI

formulations at a ratio of 50/5 and 200/5 MF/F. The observed findings were consistent with those expected after administration of the single agents, and no new toxicities were identified. This program was previously discussed during a pre-IND meeting with the Division on June 11, 2003.

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. Formoterol fumarate (F) acts by binding and activating beta-2 adrenergic receptors in the lungs, predominantly in bronchial smooth muscle, to promote bronchodilation.

The combination of MF and F in a single device is intended to enhance patient convenience and to promote compliance with concomitant use of a long-acting beta agonist with an inhaled corticosteroid.

4.4.2 Pharmacodynamics

Dose selection for the MF and F components was based on dosing for approved formulations of MF (Asmanex Twisthaler) and F (Foradil Aerolizer). Additional pharmacodynamic trials were conducted to provide clinical bridging data to the approved formulations and to support dose selection for the monocomponents and the proposed MF/F product. The following section summarizes the major pharmacodynamic endpoints from Phase 2 trials; pharmacokinetic parameters are discussed separately in Section 4.4.3. Detailed review of the clinical pharmacology trials can be found in Dr. Ying Fan's review.

Formoterol

Selection of the formoterol dose was based on an earlier formoterol DPI development program, which established Foradil Aerolizer 12 mcg DPI BID as safe and effective. The F MDI formulation that most closely matched the pharmacodynamic and pharmacokinetic profile of Foradil Aerolizer 12 mcg BID was selected for development in the MF/F combination. The formoterol MDI formulation used in the dose-ranging studies was an HFA 134a product, not HFA 227, since it was not feasible to develop a F HFA 227 product (b) (4). As a result, the F MDI with HFA 134a as a propellant (b) (4) was used as the monotherapy comparator in Phase

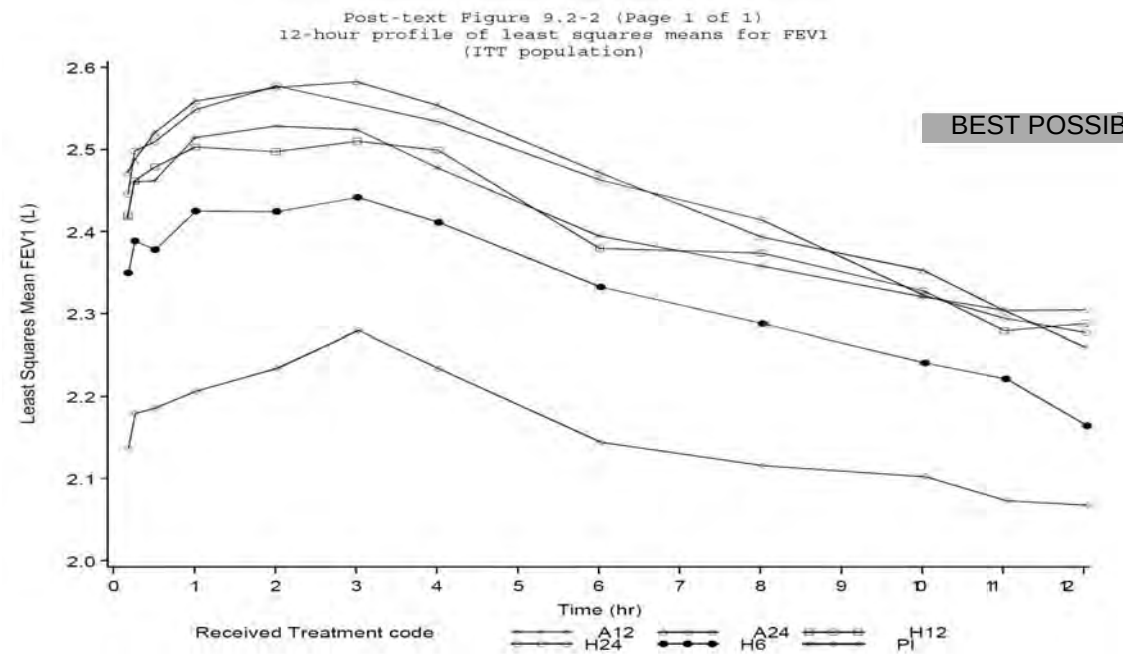
2 and Phase 3 trials. This issue was previously discussing during the April 23, 2008, pre-NDA meeting.

Dose selection for formoterol and a clinical bridge to Foradil Aerolizer were supported primarily by 3 pharmacodynamic trials: Study P06144, Study P05643, and Study P05642.

Study P06144

Study P06144 was a randomized, double-blind, double-dummy, placebo-controlled, single dose trial comparing F MDI 6, 12, and 24 mcg (amount in delivery chamber) to Foradil Aerolizer 12 and 24 mcg and placebo. The original CSR and figures describe the MDI doses in terms of the amount of drug in the delivery chamber. Later summary documents provide the total emitted dose (ex actuator dose) for each dose level. For example, "F MDI 6 mcg" as written in the CSR is equivalent to a 5 mg ex actuator dose. Twenty-six patients ages 18 to 67 years with persistent asthma were enrolled. The 6 treatment periods were separated by a washout of 2 to 7 days. This trial was conducted by Novartis as part of a separate F MDI monotherapy development program. Based on FEV1 $AUC_{0\text{-}12h}$, the F MDI 12 mcg dose (10 mcg total emitted dose) was similar to the Foradil12 mcg dose while the F MDI 24 mcg dose (20 mcg total emitted dose) approximated the Foradil 24 mcg dose (Figure 1). The Applicant concluded that the lowest dose, 6 mcg, was substandard, and the highest dose of 24 mcg offered no significant advantages over the 12 mcg dose level; therefore, F MDI 12 mcg (10 mcg ex actuator) was selected for further development. All doses of F MDI were statistically superior to placebo (p = 0.03 to <0.001).

Figure 1 Study P06144 12-hour profile of LS mean FEV1 over time

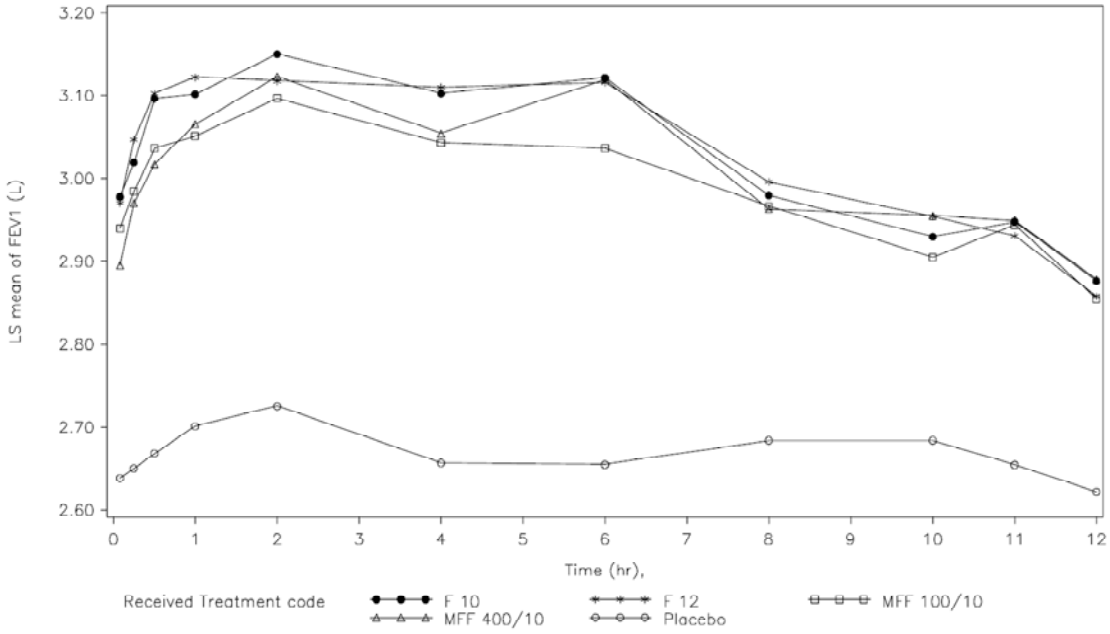


A12 = Foradil Aerolizer 12 mcg
A24 = Foradil Aerolizer 24 mcg
H6 = F MDI 6 mcg (5 mcg ex mouthpiece dose)
H12 =F MDI 12 mcg (10 mcg ex mouthpiece dose)
H24 = F MDI 24 mcg (20 mcg ex mouthpiece dose)
Source: Module 5, study-report-p06144.pdf

Study P05643

Study P05643 was a randomized, double-blind, double-dummy, placebo-controlled, single dose, 5-period crossover trial that provided additional comparison of the F MDI 10 mcg alone and in combination with MF to Foradil Aerolizer 12 mcg. In contrast to the CSR for Study P06144, the dose presented is the ex-actuator dose and not the amount of the drug in the delivery chamber. Twenty-five patients ages 20 to 64 years with mild to moderate asthma were treated with single doses of the following: MF/F 100/10, MF/F 400/10, F 10, Foradil Aerolizer 12 mcg, and placebo. In this trial, F MDI 10 mcg most closely approximated Foradil Aerolizer 12 mcg (Figure 2). The curves for MF/F 100/10 and 400/10 were somewhat lower but were not statistically significantly different from F MDI 10 or Foradil Aerolizer 12. All formulations of F MDI and MF/F were superior to placebo ($p<0.001$).

Figure 2 Study P05643 12 hour curve for LS mean FEV1 over time

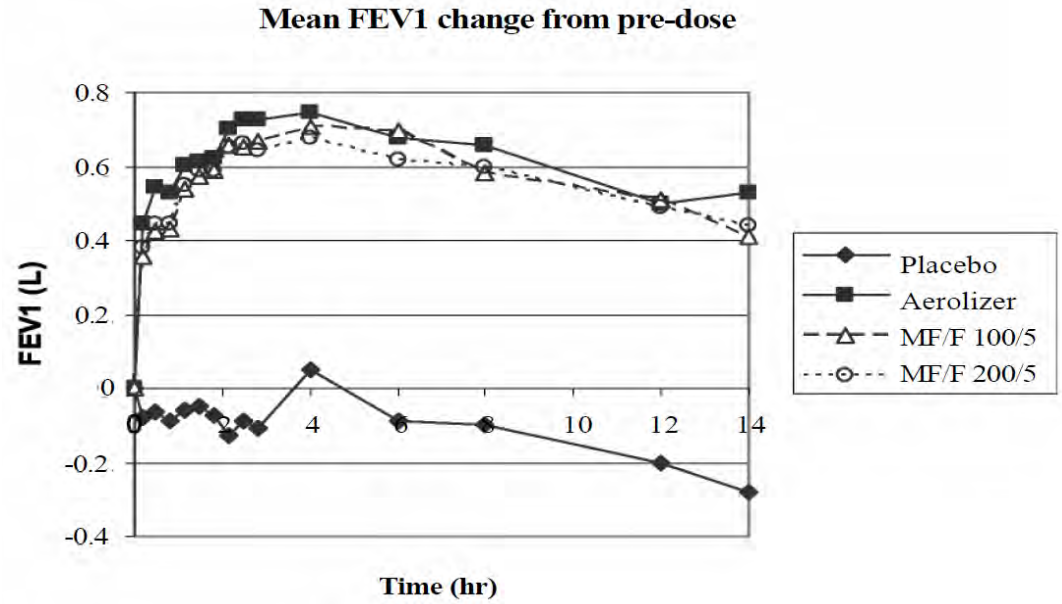


F 10 = F MDI 10 mcg
F 12 = Foradil Aerolizer 12 mcg
MFF 100/10 = MF 100 mcg/F 10 mcg combination (2 inhalations of MF/F 50/5 mcg ex mouthpiece)
MFF 400/10 = MF 400 mcg/F 10 mcg combination (2 inhalations of MF/F 200/5 mcg ex mouthpiece)
Source: Module 5, study-report-p05643.pdf

Study P05642

Additional comparison of the MF/F combination to Foradil Aerolizer was performed in Study P05642. Study P05642 was a randomized, open-label, 3-period crossover, cumulative dose trial in 19 patients with mild to moderate asthma that compared pharmacodynamic parameters between cumulative doses of MF/F 200/10 to 1600/40 mcg and Foradil Aerolizer 12 to 48 mcg. Cumulative doses were delivered over a 2 hour period. Based on FEV1 $AUC_{0\text{-}14h}$, doses delivered from MF/F 100/5 and 200/5 devices were similar to doses delivered from Foradil Aerolizer 12 mcg (Figure 3) and were superior to placebo.

Figure 3 Study P05642: Mean FEV1 change from pre-dose over 14 hours



Source: Module 5, study-report-p05642.pdf

Mometasone

Dose selection for mometasone was based on approved doses for the Asmanex Twisthaler DPI product and additional trials performed in the separate MF MDI monotherapy program. The Applicant states that they do not plan to seek product registration for the MF monotherapy. Four trials conducted with MF MDI were intended to support MF dose selection and provide confirmatory evidence of efficacy for the MF monocomponent: Studies C97-208, C97-225, I97-200, and C97-224. C97-208, C97-225, and C97-224 were 12-week, placebo-controlled dose ranging trials. I97-200 was active controlled. Of these trials, C97-208 and C97-225 provided replicated evidence of efficacy for MF 200 compared to placebo based on the change from mean baseline FEV1. C97-208 and C97-224 provided replicated evidence of efficacy for MF 400 compared to placebo. There was no replicated comparison of MF 100 to placebo in these dose-ranging trials, and this issue is discussed in further detail in Section 6. A fifth trial, 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 mometasone DPI formulation, Asmanex.

Study P04275

Study P04275 was a 5-day, randomized, open-label, multiple-dose, crossover trial in 12 healthy subjects that assessed the pharmacokinetics of MF MDI 800/200 mcg BID compared to MF DPI 800 mcg BID. The clinical pharmacology reviewer, Dr. Ying Fan, has concluded that systemic exposure to MF based on $AUC_{0\text{-}12h}$ was approximately 52% and 25% lower on Day 1 and Day 5, respectively, following MDI administration compared to DPI administration. It is worth noting that systemic absorption from inhaled

mometasone is almost exclusively from the lungs, with a negligible amount absorbed from the GI tract. These results support the safety of the proposed MF/F combination.

Table 1 Pharmacokinetic parameters for MF MDI compared to MF DPI: P04275

	Day	Cmax (pg/ml)	Tmax (h)	AUC012h (pg h/ml)	Accumulation index
MF/F MDI 800/20	1 5	67.8 241	4.00 1.00	650 2200	- 3.81
MF DPI 800	1 5	184 383	1.00 1.00	1270 2820	- 2.34

Source: Module 5, study-report-p04275.pdf

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 ages 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. Study sites were encouraged to schedule spirometry at the same time of day throughout the trial to reduce diurnal variation, but specific timing of PFTs in relation to dosing was 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.

Table 2 Dose ranging for MF: Change in mean FEV1 from baseline (L)

	N	Baseline	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
MF 600	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 186	58	2.73	0.18	0.36	<0.01
Placebo	59	2.53	-0.18		

Source: study-report-c97208.pdf, Table 10; study-report-c97225.pdf

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 ($p \leq 0.02$). 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.

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 186 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 2, 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 30 mL.

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.

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 3); 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 3 Study I97-200: Change in mean FEV1 from baseline (L) to Endpoint (last visit)

	N	Baseline	Change from baseline	Difference from MF 100	P
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

Source: study-report-i97200.pdf, Table 10

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.

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 patients 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. In terms of 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.

Table 4 C97-224: Change in mean FEV1 from baseline (L) at 3 months

	N	Baseline	Change from baseline	Difference from placebo	P
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	-0.17		

Source: study-report-c97224.pdf, Table 15

4.4.3 Pharmacokinetics

The preliminary assessment of the clinical pharmacology review is that the application is acceptable. Final recommendations are pending at the time of this review.

Details of the pharmacokinetic evalulation for MF/F can be found in Dr. Ying Fan's Clinical Pharmacology review. In addition to the PK assessments conducted in the dose-ranging trials described in the preceding Section 4.4.2, other PK assessment included evaluations of dose proportionaility (P05644) and drug interactions (P03658) in healthy subjects. The clinical pharmacology review has concluded that systemic exposure from F MDI 10 mcg is approximately the same as the exposure from Foradil Aerolizer 12 mcg. The exposure from MF MDI is approximately 25% less than the same nominal dose of Asmanex Twisthaler in healthy subjects and COPD patients; evaluation of exposure in asthmatic patients is not available and is considered a deficiency in the program. Based on the information provided, there appears to be dose proportionality for formoterol over a range of 20 to 40 mcg. Dose proportionality for MF could not be established due to a high degree of inter-individual variability. The clinical pharmacology review has concluded that there were no significant pharmacokinetic interactions between MF and F in the combination.

The clinical pharmacology review has noted that PK assessments were not performed in adolescents aged 12 to 17 years of age. This concern was previously communicated to the Applicant at the pre-NDA meeting on December 18, 2008, and again in the 74-day filing letter. The Applicant has stated plans for obtaining PK information in children 5 to 11 years of age and using population PK analysis to extrapolate information for adolescents. A review of safety and efficacy data for this age subgroup is included in Sections 7 and 6, respectively. Overall, a total of XX patients ages 12 to 17 years were included in the Phase 3 program and in the 12-week phase 2 trials, providing sufficient safety information for the age group.

Safety results from the designated HPA axis study, P03705, and the formoterol cumulative dose study, P05643, are discussed in Section 7.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant's drug development program is comprised of 14 major trials: 8 clinical pharmacology trials, 3 pivotal efficacy trials, 1 long-term safety trial, and 1 dose counter reliability trial. The Applicant also references 4 dose-ranging trials conducted with the MF monotherapy under a separate IND, and a phase 3 non-inferiority trial conducted with fluticasone/salmeterol (F/SC) as an active comparator. The clinical pharmacology trials are intended to support dose selection for the individual monocomponents and to establish a link between the new MF/F MDI solution formulation and the approved monotherapy DPI formulations. The MF MDI and F MDI monotherapies used in these trials were developed for the purposes of the MF/F development program and have not been approved for the treatment of asthma.

A total of 2659 patients were included in the 4 pivotal efficacy and safety trials (b) (4) P04334, P04431, and P04139): 1265 patients received MF/F, 620 received MF alone, 390 received F alone, and 384 received placebo.

The table below outlines the major clinical trials included in the application.

Table 5 Clinical development program for MF/F

Study	Subjects (age range)	Design	Dose	Duration	Notes
PK trials					
P05644	24 healthy (23-58)	R, OL, SD, XO	• MF/F 400/10 • MF/F 400/20 • MF/F 400/40	SD	• Dose proportionality
P03658	27 healthy (22-58)	R, OL, SD, XO	• MF/F 800/20 • MF 800 + F 20 • MF 800 • F 20	SD	• Drug interaction
P04275	12 healthy (18-57)	R, OL, MD, XO	• MF/F MDI 800/20 BID • MF DPI 800 BID	4.5 days	• New MF MDI compared to MF DPI (Asmanex)
P05643	25 asthma (20-64)	R, DB, DD, SD, XO	• MF/F 100/10 • MF/F 400/10 • F MDI 10 • F DPI 12 • Pbo	SD	• Onset of action and duration for F MDI compared to DPI (Foradil)
P05642	19 asthma (20-65)	R, OL, XO	• MF/F 100/5 device: 200/10 to 800/40 • MF/F 200/5 device: 400/10 to 1600/40 • F DPI: 12 to 48 mcg	Cumulative dose	• F PD in combination compared to DPI (Foradil)
P03705	66 asthma (18-64)	R, OL, PC, AC	• MF/F 200/10 BID • MF/F 400/`0 BID • F/SC 460/42	42 days	• HPA axis
P04689	14 COPD (45-72)	R, OL, MD, XO	• MF/F 400/10 BID • MF/F 400/10 BID w/spacer • MF DPI 400 BID	4.5 days	• MF PK in MDI vs DPI in COPD
P06144	26 asthma (18-67)	E, DB, DD, PC, XO	• F MDI 6, 12, and 24 mcg • F DPI 12 and 24 mcg • Pbo	SD	• Dose ranging for F MDI HFA 134a compared to DPI (Aerolizer)
C97-208	435 asthma	MC, PC	• MF 50 BID • MF 200 BID • MF 400 BID • MF600 BID • Beclomethasone 168 BID • Pbo	12 wks	• Dose ranging for MF MDI
C97-225	232 asthma	MC, PC, DD	• MF 50 BID • MF 200 BID • Beclomethasone 168 BID • Pbo	12 wks	• Dose ranging for MF MDI
I97-200	715 asthma	AC	• MF 100 BID • MF 200 BID • MF 400 BID • FP 250 BID	12 wks	• Dose ranging for MF MDI
C97-224	123 in 3mos phase; 120 in 9mos phase	PC, DB (3mos) and OL (9mos)	• MF 400 BID • MF 800 BID	DB (3mos) and OL (9mos)	• Steroid-reducing effects for MF MDI and long-term safety
Efficacy and safety asthma trials					
[redacted] (b) (4)					
P04334	781 (12-76)	R, DB, PC	• MF/F 200/10 BID • MF 200 BID • F 10 BID • Pbo BID	26 wks	Assess contribution of monocomponents

P04431	728 (12-84)	R, DB	• MF/F 400/10 BID • MF/F 200/10 BID • MF 400 BID	12 wks	• FEV1 AUC • ACQ, AQLQ, nocturnal awakenings
P04705	722 (12-82)	R, OL, AC	• MF/F 200/10 BID • F/SC 250/50 BID	12 wks	Non-inferiority compared to Advair
P04139	404 (12-75)	R, OL, AC	• MF/F 200/10 BID • MF/F 400/10 BID • F/SC 250/50 BID • F/SC 500/50	52 wks	Long-term safety study
P4703	343 asthma and COPD (12-82)	OL, MD	• MF/F 100/10 BID	4 wks	Dose counter study

The following table summarizes the pediatric patient population enrolled in the pivotal Phase 3 trials and in the pivotal Phase 2 dose-ranging trials.

Table 6 Pediatric enrollment in the Phase 3 trials and pivotal Phase 2 dose-ranging trials

Trial	Countries	# study sites	# patients 12 to <18 years (# received MF/F)
Phase 3 trials			
[redacted] (b) (4)			
P4334	USA Canada Colombia Costa Rica Croatia Denmark Ecuador Estonia Guatemala Hungary India Mexico Phillipines Poland Russia Thailand	152	63 (19)

	Ukraine		
P04431	USA Canada Chile Peru Colombia Honduras Argentina Denmark Poland Bulgaria Ukraine Russia Hungary	115	63 (41)
P04139	Argentina Peru Ecuador Guatemala Chile Mexico	27	62 (41)
P04703	US	56	42 (42)
P04705	US Canada Columbia Costa Rica Ecuador Czech Republic Estonia Finland Germany Latvia Lithuania Netherlands Romania Russia Serbia Slovak Republic Ukraine	164	40 (40)
Pivotal phase 2, 12-week trials			
I97-200	Argentina Austria Belgium Canada Chile Columbia Denmark Ecuador Finland France Germany Greece Guatemala Mexico Netherlands Norway Portugal South Africa Spain	77	30

	Sweden Switzerland United Kingdom Uruguay Venezuela		
C97-208	US	23	53
C97-225	US	15	25
C97-224	US	26	4

Source: Collated from individual CSRs in Module 5

5.2 Review Strategy

The clinical review focuses on the pivotal Phase 3 efficacy and safety trials, (b) (4) P04334, P04431, and P04139, and the long-term safety trial, P04139. The two 12-week, placebo-controlled dose-ranging trials, C97-208 and C97-225, were reviewed for additional efficacy support of the MF 200 monocomponent. Trial P4703, the dose counter study, was reviewed for support of the durability and reliability of the integrated dose counter device. Trial P04705, the non-inferiority trial comparing MF/F to a commercially marketed fluticasone/salmeterol combination (Advair), was reviewed briefly in terms of additional safety information but was not reviewed in detail for efficacy support. The other Phase 2 trials were reviewed primarily to support the dose selection of each monocomponent and to establish a clinical link to the related approved monotherapies, formoterol DPI (Foradil Aerolizer) and mometasone DPI (Asmanex Twisthaler).

Section 4.4.2 addresses the design, conduct, and major pharmacodynamic results of the Phase 2 pharmacokinetic and pharmacodynamic trials. Dose selection information is discussed in further detail in Section 6. Section 5.3 describes the design, conduct, and major efficacy results for the individual pivotal Phase 3 trials as well as the long-term safety trial and dose counter trial. Detailed discussion of the trial designs, including endpoint selection and major efficacy conclusions from these trials, is presented in Section 6. Safety information from these 3 trials in addition to the long-term safety study, designated HPA axis study, and cumulative dose study, are reviewed in detail in Section 7.

(b) (4) separate MF/F dosage strengths are proposed: (b) (4) 100/5, and 200/5 mcg (ex mouthpiece dose) administered as 2 inhalations twice daily. This review refers to the therapeutic dose of MF/F delivered by 2 actuations, i.e. MF/F (b) (4) 200/10, and 400/10 mcg, respectively.

5.3 Discussion of Individual Studies/Clinical Trials

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(b) (4)

TRIAL P04334
P04334: Study Protocol

Administrative Information

- **Study title:** A 26-week placebo controlled efficacy and safety study of MF/F compared with MF and F monotherapy in subjects with persistent asthma previously treated with medium-dose ICS
- **Study dates:** November 27, 2006 to October 10, 2008
- **Study sites:** 152 sites: 52 US, 4 Canada, 3 Colombia, 3 Costa Rica, 6 Croatia, 2 Denmark, 1 Ecuador, 3 Estonia, 3 Guatemala, 10 Hungary, 15 India, 4 Mexico, 8 Philippines, 2 Puerto Rico, 12 Poland, 10 Russia, 4 Thailand, 10 Ukraine
- **Study report date:** April 22, 2009

Objectives/Rationale

- Determine the efficacy of MF/F 200/10 mcg MDI BID compared to MF MDI 200 mcg BID in order to assess the added benefit of F MDI 10 mcg BID in combination
- Determine the efficacy of MF/F MDI 200/10 mcg MDI BID compared to F MDI 10 mcg BID to assess the benefit of the steroid component in the combination

Study Design and Conduct

Overview
Trial P04334 was a randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group, 26-week trial in 781 patients 12 years and older with moderate persistent asthma. The target population was patients on moderate doses of ICS +/- LABA, and the trial evaluated the MF/F 200/10 combination. These were the major differences that distinguished Trial P04334 from (b) (4). Otherwise, Trial P04334 was the same in design and conduct as Trial (b) (4). 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. The duration of the open-label treatment period was determined by the stability of the patient's asthma as defined by the inclusion criteria and the subject's ability to be switched to randomized treatment. Patients were randomized 1:1:1:1 to 1 of 4 possible treatment groups: MF/F 200/10 BID, MF 200 BID, F 10 BID, and placebo. To qualify, patients had to be on a moderate

daily dose of ICS as defined below in the inclusion/exclusion criteria. Patients on an ICS/LABA combination were also permitted to enroll.

At the start of the study (Screening), all patients were supplied with a SABA MDI and oral prednisone/prednisolone. Patients were advised not to take these medications unless warranted. Patients who required more than 8 inhalations of SABA per day were instructed to contact the investigator. Patients with severe asthma exacerbations were advised to obtain investigator approval prior to initiating therapy with the oral corticosteroids, if possible.

Spirometry
At the baseline visit, Week 1, Week 26, and the final visit, serial PFT measurements were taken at 30 minutes and immediately prior to the 1st dose and then at 5, 15, 30 minutes, and 1, 2, 3, 4, 6, 8, 10, 11, and 12 hours post dose. At all other visits (screening, pre-baseline, Weeks 4, 8, 16, and 20), a single spirometry assessment was performed immediately prior to the AM dose of study medication and at least 12 hours after the previous evening's dose. Reversibility, defined as an increase in FEV1 of at least 12% over the pre-SABA value and with an absolute volume increase of at least 200 ml, was evaluated at Visit 1. If reversibility criteria based on FEV1 was not met, a single repeat assessment could be performed at any time prior to the baseline visit (Visit 3) or by demonstration of PEF variability (see inclusion/exclusion criteria).

Table 16 Trial P04334: Schedule of assessments

	Visit 1 Screening Days -21 to -14	Visit 2 Pre-baseline Days -14 to -7	Visit 3 Baseline Day 1	Visit 4 Week 1	Visits 5 to 9 Weeks 4, 8, 12, 16, 20	Visit 10 Final Week 26
Informed consent	X					
Inclusion/exclusion	X	X	X			
Med Hx	X					
Concomitant meds	X	X	X	X	X	X
Physical exam	X					X
Oropharyngeal exam	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
PFT	X	X	X	X	X	X
Reversibility	X	X				
PEF variability		X	X			
Labs	X					X
Telephone contact		X				
Pharmacogenetic sampling (optional)	X					X
ECG	X					
Chest x-ray	X					
Dispense e-diary/spirometry device	X	X	X	X	X	X
Retrieve e-diary		X	X	X	X	X
Dispense/retrieve SABA PRN	X	X	X	X	X	X
Dispense/retrieve oral corticosteroids PRN	X	X	X	X	X	X
MDI training	X	X	X	X	X	
Dispense study drug			X			

Dispense/collect OL MF	X		X			
Review compliance		X	X	X	X	X
AQLQ			X		X	X
ACQ			X		X	X
Healthcare resource utilization	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Asthma exacerbation evaluation		X	X	X	X	X
Dispense/review asthma diary scale	X	X	X	X	X	X

Source: Module 5, study-report-p04334.pdf, Section 9.1, Table 2

Study Population
781 patients ages 12 years and older with persistent asthma and on a moderate daily dose of ICS +/- LABA. Patients were randomized using a central, computerized randomization system (IVRS).

- **Inclusion criteria**

  Inclusion criteria for P04334, including the enrolled age range (12 years and older) and the documented diagnosis of asthma and responsiveness to bronchodilators, were the same as for Trial (b) (4) The only differences were the requirement for pre-existing treatment with a moderate daily dose of ICS as defined below:
  - Moderate daily dose of ICS for at least 12 weeks and on a stable regimen for at least 2 weeks prior
    - >500 to 1000 mcg beclomethasone CFC
    - >250 to 500 mcg beclomethasone HFA
    - >600 to 1000 mcg budesonide DPI
    - >1000 to 2000 mcg flunisolide
    - >250 to 500 mcg fluticasone
    - 400 mcg MF
    - >1000 to 2000 mcg triamcinolone acetonide
    - >160 to 320 mcg ciclesonide

- **Exclusion criteria**

  Same as those previously defined for (b) (4)

Study Treatments
Treatment groups
- MF/F MDI 200/10 mcg (2 inhalations of 100/5 mcg inhaler) BID
- MF 200 mcg (2 inhalations of 100 mcg inhaler) BID
- F 10 mcg (2 inhalations of 5 mcg inhaler) BID
- Placebo inhaler BID

The trial was double dummy in design, so all patients received a second inhaler, either placebo F or placebo MF/F, depending on treatment allocation. Compliance with trial medications were handled similarly as in Trial (b) (4) with the use of an e-diary that

sounded twice-daily reminder alarms and recorded times and dates. Canister weights and dose counters were not used in the trial.

Prior and concomitant therapy
All concomitant therapy was to be recorded in the eCRF. Certain medications were prohibited during the study and required the specific minimum washout periods. These medications were the same as those specified for Trial (b) (4) and are described in Table 8.

Efficacy Parameters
Efficacy parameters were the same as those described for Trial (b) (4)

Co-primary efficacy endpoints
- The AUC_{0-12h} of the change from Baseline to Week 12 in FEV1 for MF/F 200/10 vs. MF 200
    - Intended to assess the contribution of the F component to the combination

- Time to first severe asthma exacerbation for MF/F 100/10 vs. F 10
    - Intended to assess the contribution of MF component to the combination

Secondary efficacy endpoints (MF/F vs. placebo comparisons)
- Change from baseline to Week 26 in AQLQ
- Change from baseline to Week 26 in ACQ score
- Change from baseline in proportion of nights across the treatment period with nocturnal awakenings due to asthma that required use of SABA (baseline = proportion of nights of Days -7 to Day 1 prior to first dose with nocturnal awakenings)

Secondary efficacy endpoints (MF/F vs. F comparison)
- Change from baseline to Week 12 in AM end-of-dosing interval FEV1 (trough FEV1)
    - Intended to assess the contribution of the MF component to the combination

Safety Parameters
Monitoring for safety included the same assessments described for Trial (b) (4)
Results of the safety assessments are discussed in Section 7.

Statistical Plan
(b) (4) the statistical plan specified that the MF 200 mcg and F 10 mcg monotherapy comparators be statistically significant over placebo in terms of time to first asthma exacerbation over 26 weeks and FEV1 AUC_{0-12h} at Week 12, respectively. An ANCOVA with treatment, study site, and Baseline as covariates was used for the

comparison of FEV1 AUC_{0-12h} for MF/F 200/10 vs. MF 200 and for the comparison of F 10 vs. placebo. The log-rank test for equality of survival curves were used to analyze responses for the time-to-first asthma exacerbation for the comparison of MF/F 200/10 vs. F 10 and for the comparison of MF 200 vs. Placebo.

Tests for 4 key secondary efficacy endpoints were performed sequentially on MF/F vs placebo: change in trough FEV1 at Week 12, change from baseline in AQLQ at Week 26, change from baseline to Week 26 in ACQ, and the proportion of nights with nocturnal awakenings due to asthma over the 26-week treatment period.

Sample size calculation and handling of missing data were the same (b) (4)

P04334: Results

Protocol Changes and Deviations

The original protocol was dated June 8, 2006. An amendment to the protocol was made on August 29, 2007. Amendment 1 added a screening period separate from the open-label run-in period and also added a telephone contact between Visit 1 and 2. The discontinuation criteria were clarified to ensure that patients requiring the use of oral corticosteroids during the study would be discontinued. A clarification memo was issued on December 13, 2007, to clarify a misprint in the study design diagram in the protocol. The changes to the protocol seem 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.

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. 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 17 P04334: Patient disposition

Disposition (N,%)	MF/F 200/10	MF 200	F 10	Placebo
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)	13 (7)	47 (23)	46 (23)
Lost to follow-up	3 (2)	-	-	2 (1)
Withdrawal of consent, reasons unrelated	6 (3)	3 (2)	8 (4)	8 (4)
Withdrawal of consent, reasons related	-	1 (1)	3 (1)	5 (3)
Noncompliance	4 (2)	5 (3)	9 (4)	6 (2)
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)

Source: Module 5, study-report-p04334.pdf, Section 10.1, Table 3

Datasets Analyzed

Datasets were defined (b) (4). A total of 275 patients were excluded from the efficacy evaluable dataset. The main reasons cited were "noncompliance with study treatment" (n=130) as self-reported in the e-diary and "did not meet entrance criteria" (n=141). The distribution of these patients across the 4 treatment arms was similar and appears unlikely to have impacted efficacy findings.

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, slightly older than the mean age in Trial (b) (4) and was 59% female and 72% white. There were fewer pediatric patients ages 12 to <18 years (n=63) (b) (4)

Table 18 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)
Multiracial	16 (8)	21 (10)	23 (11)	19 (10)	78 (10)
Native Hawaiian/Pacific Islander	-	2 (1)	-	1 (1)	1 (<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	12-16	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
Duration of asthma (years)					
Mean (SD)	16 (14)	17 (15)	16 (13)	15 (14)	16 (14)
Median	12	15	12	11	12
FEV1 (mean, SD) at baseline					
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 (at screening)	18.9	18.2	19.0	19.1	18.8
FEV1/FVC	0.73	0.73	0.73	0.72	0.73
Asthma Control Questionnaire	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)

Source: study-report-p040703.pdf, Section 14.1.1

Efficacy Endpoint Outcomes

Compliance

Based on the definition of treatment compliance (b) (4) 646 of 781 (83%) patients were compliant. Treatment compliance was similar across the four treatment groups (78 to 81%).

Co-primary efficacy variable: FEV1 mean AUC_{0-12h}

The co-primary efficacy endpoint, mean AUC_{0-12h} of the change from Baseline to Week 12 in FEV1, was intended to assess the LABA contribution to the MF/F combination, comparing MF/F 200/10 mcg BID vs. MF 200 mcg BID. MF/F demonstrated a statistically significant difference over MF alone ($p<0.001$), and the F monotherapy alone was statistically superior to placebo ($p=0.009$). The mean values are displayed in the Table 19. These results support the efficacy of MF/F and F and the contribution of F to the combination.

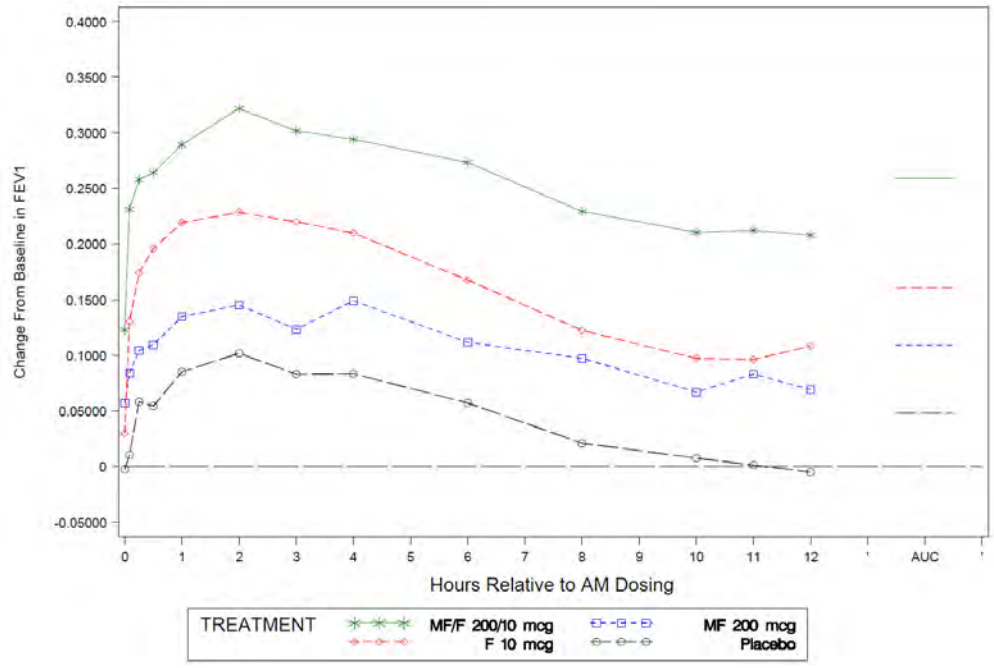
Table 19 P04334: Mean AUC0-12h of the change from baseline to Week 12 (L x h)

	Week 12		Week 26	
	N	LS mean	N	LS mean
MF/F 200/10	166	3.11	190	3.34
MF 200	169	1.30	190	1.47
F 10	135	1.93	202	2.40
Placebo	128	0.57	193	0.99

Source: Module 5, study-report-p04334.pdf, Section 11.4.1.1, Table 7

These AUCs correspond approximately to increases from baseline FEV1 of 0.26 L (12%) in for MF/F, 0.11 (6%) for MF, 0.16 (9%) for F, and 0.05 (4%) for placebo, averaged across the 12-hour serial evaluation. These curves are displayed graphically in Figure 7.

Figure 7 P04334: 12-hour serial evaluations of FEV1 at Week 12



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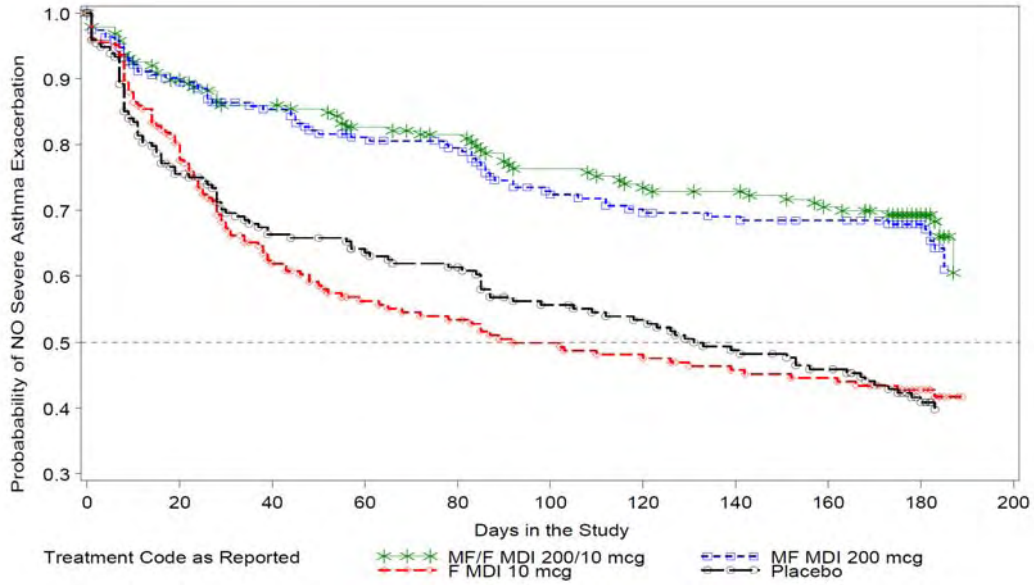
Co-primary efficacy variable: Time to first severe asthma exacerbation

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. MF was statistically superior to placebo ($p<0.001$) and MF/F was statistically superior to F ($p<0.001$). These results support the efficacy of the MF component in the MF combination.

Figure 8 P04334: Time to first asthma exacerbation



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Source: Module 5, study-report-p04334.pdf

Secondary efficacy variables

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. The main comparison was MF/F vs. F. 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). These results provide further support for the efficacy contribution of MF to the MF/F combination.

Table 20 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

Source: Module 5, study-report-p040334.pdf, Section 11.4.1.3, Table 13

AQLQ

The change from baseline AQLQ at Week 26 was assessed as a secondary efficacy endpoint. Statistically significant differences were demonstrated between MF/F and placebo, as well as MF/F versus F and MF versus F. The treatment difference of 0.25 between MF/F and placebo did not meet the threshold for the minimum clinically important difference of 0.5 for the AQLQ. While these results are supportive of the efficacy of MF/F and MF over placebo, they are not sufficient to support labeling claims.

Table 21 Study P04334: Change from baseline AQLQ at Week 26

	MF/F 200/10 (A)		MF 200 (B)		F 10 (C)		Placebo (D)	
	N	LS mean	N	LS mean	N	LS mean	N	LS mean
Baseline	183	5.38	189	5.40	187	5.51	189	5.56
Week 26	153	0.61	157	0.50	121	0.31	121	0.36
Pairwise comparisons			A-B	A-C	A-D	B-C	B-D	C-D
P			0.152	<0.001	<0.001	0.039	0.130	0.612

Source: Module 5, study-report-p04334.pdf, Section 11.4.1.4, Table 16

ACQ

The change from baseline to Week 26 in the total ACQ score was assessed as a secondary efficacy endpoint (Table 22). MF/F showed a statistically significant difference over placebo (p<0.001), as did each of the monotherapy comparators over placebo. As the MCID for the ACQ is not established, the clinical relevance of the

observed changes is not clear, although these results are generally supportive of efficacy for MF/F over placebo.

Table 22 Study P04334: Change from baseline to Week 26 in ACQ total score

	MF/F 200/10 (A)		MF 200 (B)		F 10 (C)		Placebo (D)	
	N	LS mean	N	LS mean	N	LS mean	N	LS mean
Baseline	179	1.47	186	1.46	184	1.43	187	1.41
Week 26	152	-0.52	154	-0.32	119	-0.20	121	-0.22
Pairwise comparisons			A-B	A-C	A-D	B-C	B-D	C-D
P			0.005	<0.001	<0.001	0.129	0.187	0.857

Source: Module 5, study-report-p04334.pdf, Section 11.4.1.5, Table 17

Nocturnal awakenings

The proportion of nights during the 26-week treatment period with nocturnal awakenings due to asthma requiring treatment with a SABA was assessed as a secondary efficacy endpoint (Table 23). The MF/F and MF treatment groups reported a decrease during the treatment period and the results were statistically significant in comparison to placebo and F alone. These results support the efficacy of both the combination as well as the MF monotherapy component.

Table 23 Study P04334: Proportion of nights with nocturnal awakenings due to asthma requiring SABA use

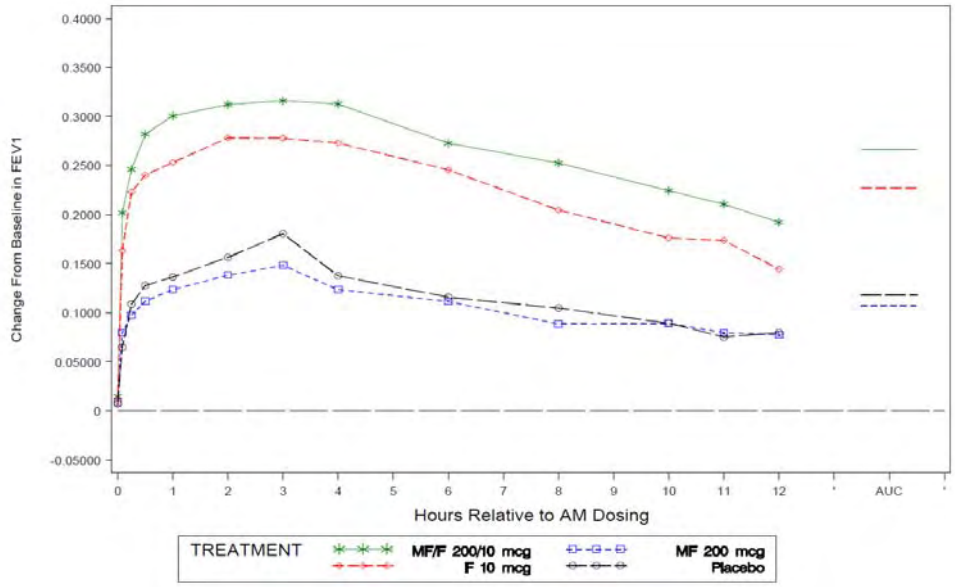
	MF/F 200/10 (A)		MF 200 (B)		F 10 (C)		Placebo (D)	
	N	LS mean	N	LS mean	N	LS mean	N	LS mean
Baseline period	186	0.18	191	0.16	199	0.16	194	0.15
26-week treatment period	186	-0.08	191	-0.05	199	0.01	194	-<0.01
Pairwise comparisons			A-B	A-C	A-D	B-C	B-D	C-D
P			0.063	<0.001	<0.001	<0.001	0.003	0.601

Source: Module 5, study-report-p04334.pdf, Section 11.4.1.6, Table 18

Onset of action

Onset of action was assessed by serial FEV1 measurements at Day 1, Week 1, Week 12, Week 28, and Endpoint. MF/F and F demonstrated statistically significant separation from placebo starting at 5 minutes which was maintained over the interval timepoints through 12 hours for MF/F ($p<0.001$) and 11 hours for F ($p\leq0.007$). The maximum effect in FEV1 was observed at 3 hours after dose administration: MF/F change from baseline = 0.32 L compared to placebo change from baseline = 0.19 L (treatment difference = 0.13 L). The relative FEV1 curves are displayed in Figure 9.

Figure 9 Trial P04334: Onset of action: Serial FEV1 (0-12h) on Day 1



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Source: Module 5, study-report-p04334.pdf, Section 11.4.1.8, Figure 6

Peak expiratory flow (PEF)
AM and PM PEFs were assessed as a secondary efficacy variable, in addition to being used in the definition of the co-primary efficacy variable, time to first asthma exacerbation. At Week 12, a statistically significant difference was observed between MF/F and placebo in AM PEF (change from baseline 27.9 vs. -16.2 L/min; p<0.001). Statistically significant differences were also observed for F (-2.6 L/min) and MF (6.2 L/min) when compared to placebo (p=0.016 and p<0.001, respectively). MF/F was also statistically superior to each of the monocomponents (p<0.001). Similar results were also observed for the mean change from baseline PM PEF. These results are supportive of the MF/F combination's efficacy and the efficacy of each monotherapy comparator.

Rescue medication usage
Patients were permitted the use of SABA as needed, and the number of inhalations used was recorded each day in the patient diaries. Baseline usage varied somewhat among the treatment arms, with the MF/F treatment group having the highest daily SABA use (2.02 puffs or nebulizer treatments/day). The MF, F, and placebo treatment groups averaged 1.64, 1.79, and 1.95 treatments/day, respectively. At Week 12, the MF/F group had the greatest decrease in mean SABA use with a mean change from baseline of -1.23, compared to -0.62, -0.34, and +0.07 for MF, F, and placebo, respectively. The comparison of MF/F to placebo at Week 12 was statistically significant (p<0.001). When averaged over the whole 26-week treatment period, the mean change in SABA use in the MF/F group was -0.67 compared to +0.70 in the placebo group (p<0.001). The change in MF monotherapy was also statistically

significant over placebo when averaged over the whole treatment period (-0.19 vs. +0.70; p=0.005). SABA use actually increased in the F treatment at several timepoints like in the placebo group and there were no statistically significant differences. These results support the efficacy of the MF/F combination and the contribution of the MF monocomponent.

Efficacy evaluation for patient subgroups
The Applicant included summary statistics for various subgroups of the co-primary endpoint FEV1 $AUC_{0\text{-}12h}$. Overall, gender, race, and BMI did not appear to impact the results. In terms of age, patients 12 to <18 years of age (n=X) 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).

P04334: Study summary and conclusions
P04334 supports the efficacy of MF/F 200/10 mcg BID, as well as providing evidence of efficacy for the MF 200 mcg BID and F 10 mcg BID monotherapy components, which are currently not marketed. Results for the co-primary efficacy endpoint, change from baseline to Week 12 in FEV AUC0-12h, demonstrate the contribution of the F component to the combination. The co-primary efficacy variable, time to first severe asthma exacerbation and the key secondary efficacy variable, trough FEV1, both convincingly demonstrated the efficacy contribution of the MF component. Other secondary efficacy endpoints, including rescue medication use, nocturnal awakenings, ACQ, AQLQ, and AM and PM PEFs were supportive and statistically significant in most instances for the comparison of MF/F to placebo and MF alone to placebo. No major differences in efficacy were noted based on age, gender, BMI, or race. In summary, P04334 supports the efficacy of the proposed MF/F 200/10 combination as well as the efficacy of the MF 200 mcg and F 10 mcg monocomponents and contribution of MF and F to the combination.

TRIAL P04331
P04331: Study Protocol
Administrative Information

- **Study title:** A 12-week efficacy and safety study of two doses of MF/F combination formulation (SCH 418131) compared with MF monotherapy in persistent asthmatics previously treated with high dose ICS
- **Study dates:** July 29, 2006 to February 29, 2008
- **Study sites:** 115 sites
- **Study report date:** March 20, 2009

Objectives/Rationale

- Compare the efficacy of MF/F 400/10 mcg MDI BID compared to MF MDI 400 mcg BID as measured by the mean AUC of the change from Baseline to Week 12 in FEV1
- Compare the efficacy of MF/F MDI 400/10 mcg MDI BID compared to MF MDI 400 mcg BID as measured by the ACQ, AQLQ, and proportion of nocturnal awakenings due to asthma that requires rescue SABA use

Study Design and Conduct

Overview
Trial P04431 was a randomized, multi-center, double-blind, parallel group, 12-week trial in 728 patients 12 years and older with asthma intended to compare the MF/F 400/10 BID to MF/F 200/10 BID combinations. To qualify, all patients had to have been previously treated with high doses of ICS +/- LABA as defined below in the inclusion/exclusion criteria. 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. The duration of the open-label treatment period was determined by the stability of the patient's asthma as defined by the inclusion criteria and the subject's ability to be switched to randomized treatment. 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. There was no F alone or placebo arm because these treatments were deemed inadequate therapy for the patient population under study. Efficacy was evaluated by spirometry at all visits as well as the completion of patient symptom and medication use diaries and questionnaires (ACQ and AQLQ).

At the start of the study (Screening), all patients were supplied with a SABA MDI and oral prednisone/prednisolone. Patients were advised not to take these medications unless warranted. Patients who required more than 8 inhalations of SABA per day were instructed to contact the investigator. Patients with severe asthma exacerbations were advised to obtain investigator approval prior to initiating therapy with the oral corticosteroids, if possible.

Spirometry
At the baseline visit, Week 1, and Week 12, serial PFT measurements were taken at 30 minutes and immediately prior to the 1st dose and then at 5, 15, 30 minutes, and 1, 2, 3, 4, 6, 8, 10, 11, and 12 hours post dose. At all other visits (screening, pre-baseline, Weeks 4 and 8), a spirometry assessment was performed immediately prior to the AM dose of study medication and at least 12 hours after the previous evening's dose. Reversibility, defined as an increase in FEV1 of at least 12% over the pre-SABA value and with an absolute volume increase of at least 200 ml, was evaluated at Visit 1. If reversibility criteria based on FEV1 was not met, a single repeat assessment could be performed at any time prior to the baseline visit (Visit 3) or by demonstration of PEF variability (see inclusion/exclusion criteria).

Table 24 Trial P04431: Schedule of assessments

	Visit 1 Screening Days -21 to -14	Visit 2 Pre-baseline Days -14 to -7	Visit 3 Baseline Day 1	Visit 4 Week 1	Visits 5 and 6 Weeks 4 and 8	Visit 7 Final Week 12
Informed consent	X					
Inclusion/exclusion	X	X	X			
Med Hx	X					
Concomitant meds	X	X	X	X	X	X
Physical exam	X					X
Oropharyngeal exam	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
PFT	X	X	X	X	X	X
Reversibility	X					
PEF variability		X	X			
Labs	X					X
Telephone contact		X				
Pharmacogenetic sampling (optional)	X					
ECG	X					X
Chest x-ray	X					
Dispense PEF meter	X	X	X	X	X	X
Dispense diary	X	X	X	X	X	
Retrieve diary		X	X	X	X	X
Dispense/retrieve SABA PRN	X	X	X	X	X	X
Dispense/retrieve oral corticosteroids PRN	X	X	X	X	X	X
MDI training	X	X	X	X	X	
Dispense study drug			X			
Dispense/collect OL MF	X		X			
Review compliance		X	X	X	X	X
AQLQ			X		X	X
ACQ			X		X	X
Healthcare resource utilization	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Asthma exacerbation evaluation		X	X	X	X	X
Dispense/review asthma symptom scale and diary comment cards	X	X	X	X	X	X

Source: Module 5, study-report-p04431.pdf, Section 9.1, Table 2

Study Population

728 patients ages 12 years and older with persistent asthma and on a high daily dose of ICS +/- LABA. Patients were randomized using a central, computerized randomization system (IVRS).

- **Inclusion criteria**
  - Age 12 years and older
  - High daily dose of ICS for at least 12 weeks and on a stable regimen for at least 2 weeks prior. No use of oral steroids within 30 days prior to Screening.
    - > 1000 mcg beclomethasone CFC

        - > 500 mcg beclomethasone HFA
        - > 1000 mcg budesonide DPI
        - > 2000 mcg flunisolide
        - > 500 mcg fluticasone
        - >400 mcg MF
        - > 2000 mcg triamcinolone acetonide
        - > 320 mcg ciclesonide
    - At least one severe exacerbation requiring oral steroids 20 to 12 months prior to Screening
    - Documented diagnosis of asthma between Screening and Baseline Visit by one of the following methods:
        - Increase in absolute FEV1 of at least 12% and at least 200 ml within 15 to 20 minutes after 4 puffs of SABA (albuterol/salbutamol)
        - PEF variability >20% expressed as a percent of the mean highest and lowest AM pre-bronchodilator PEF over at least 1 week
        - Diurnal variation in PEF >20% based on the difference between the pre-bronchodilator AM value and the post-bronchodilator value from the PM before, expressed as a percentage of the mean daily PEF value.
    - At Screening, FEV1 ≥50% predicted when all restricted medications withheld for the specified periods
    - At Baseline, FEV1 ≥50% and ≤85% predicted when all restricted medications withheld for the specified periods
    - Screening labs within acceptable limits per Investigator
    - Female subjects of childbearing potential had to use a medically acceptable, adequate form of birth control for at least 3 months prior to Screening and must agree to its use during the trial.

- **Exclusion criteria**

Same as those previously described for Trials (b) (4) and P04334.

Study Treatments

Treatment groups

- MF/F MDI 400/10 mcg (2 inhalations of 200/5 mcg inhaler) BID
- MF 400 mcg (2 inhalations of 200 mcg inhaler) BID
- MF/F 200/10 mcg (2 inhalations of 100/5 mcg inhaler) BID

Randomization, Blinding, and Compliance Assessment

Patients were randomized 1:1:1 to 1 of the 3 treatment groups described above according to an SPRI computer-generated randomization schedule. Study medications were double-blinded. Treatment assignment was revealed to the investigator and patient only in the event of an emergency. Compliance with treatment was assessed at each trial visit by review of diary cards and the return of unused medications. Dose

counter data and canister weights were not collected, which may have been a more reliable assessment of treatment compliance.

Prior and concomitant therapy
All concomitant therapy was to be recorded in the eCRF. Certain medications were prohibited during the study and required the specific minimum washout periods. These medications were the same as those specified for Trial (b) (4) and are described in Table 8.

Efficacy Parameters
Efficacy parameters were the same as those described (b) (4).

Primary efficacy endpoints
- The mean $AUC_{0\text{-}12h}$ of the change from Baseline to Week 12 in FEV1 for MF/F 400/10 vs. MF 400
    - Baseline FEV1 = average of the two pre-dose FEV1 measurements at 30 minutes and 0 hr immediately before dosing) at the Baseline visit
    - Assesses the contribution of the F component to the combination

Key secondary efficacy endpoints
- Change from baseline to Week 12 in AQLQ
- Change from baseline to Week 12 in ACQ score
- Change from baseline in proportion of nights across the treatment period with nocturnal awakenings due to asthma that required use of SABA (baseline = proportion of nights of Days -7 to Day 1 prior to first dose with nocturnal awakenings)

Other secondary efficacy endpoints
- Change from baseline to Week 12 in AM end-of-dosing interval FEV1 (trough FEV1)
    - Intended to assess the contribution of the MF component to the combination
- Daytime and nighttime SABA usage
- Change from baseline in PFTs
- Time to first asthma severe asthma exacerbation and total number of asthma exacerbations
    - Exacerbation defined by one of the following 3 criteria
        - Decrease in FEV1 below the Treatment Period stability limit (80% of average of the two pre-dose FEV1 measurements 30 min and 0h immediately before the first dose of randomized study medication
        - Decrease in AM or PM PEF of 30% or more on 2 consecutive days of treatment below the stability limit (70% of mean AM or PM PEF obtained over last 7 days immediately before randomization)

- Clinical deterioration resulting in emergency hospitalization due to asthma or treatment with excluded asthma medication, including oral corticosteroids

Safety Parameters
Monitoring for safety included the same assessments described (b) (4). Results of the safety assessments are discussed in Section 7.

Statistical Plan
The primary comparison was MF/F 400/10 versus MF 400 mcg BID. An ANCOVA with treatment, study site, and Baseline as covariates was used for the comparison of FEV1 $AUC_{0\text{-}12h}$ for MF/F 400/10 vs. MF 400. The three key secondary efficacy variables were examined in sequential order: ACQ, AQLQ, and then the proportion of nocturnal awakenings. Other secondary variables were evaluated without adjustment for multiplicity. Relative effect sizes of MF/F 400/10 and MF/F 200/10 were to be compared to justify a higher dosage level for the combination. A target sample size of 621 patients was calculated to provide the trial with 90% power to detect a difference of 2.4 L x hr between MF/F 400/10 and MF 400 in FEV1 change from baseline AUC0-12h at a 5% significance level. This difference is approximately equivalent to an average difference of 0.2L in FEV1 across a 12-hour time period, which would be a clinically meaningful difference.

Handling of missing data was the same (b) (4)

P04431: Results
Protocol Changes and Deviations
The original protocol was dated February 1, 2006. An amendment to the protocol was made on May 9, 2006, and a second amendment was issued on August 17, 2007. Amendment 1, made prior to the start of the trial, added an additional treatment arm, MF/F 200/10, and the primary analysis endpoint was changed from Week 1 to Week 12. The ACQ, AQLQ, and nocturnal awakenings were designated as key secondary endpoints. Amendment 2 added a screening period separate from the open-label run-in period and added a telephone contact between Visits 1 and 2. Additional clarifications were made of the inclusion/exclusion criteria and the early discontinuation of patients requiring treatment with oral corticosteroids. Based on the early timing and the nature of the amendments, the amendments are not likely to have biased the trial results.

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.

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. 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 25 P04431: Patient disposition

Disposition (N,%)	MF/F 200/10	MF/F 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, reasons unrelated	1 (<1)	2 (1)	4 (2)
Withdrawal of consent, reasons 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)

Source: Module 5, study-report-p04431.pdf, Section 10.1, Table 3

Datasets Analyzed

Datasets were defined as in Trials (b) (4) and P04334. A total of 123 patients were excluded from the efficacy evaluable dataset. The main reasons cited were "did not meet entrance criteria" (n=89). The distribution of these patients across the 3 treatment arms was similar and appears unlikely to have impacted efficacy findings.

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 Trials (b) (4) and P04334, and was 56% female and 89% white. There were fewer pediatric patients ages 12 to <18 years (n=63) compared to Trial (b) (4) (b) (4) Thirty percent (n=218) reported prior use of an ICS plus a LABA.

Table 26 P04431: Demographics and baseline characteristics

	MF/F 200/10 N=233	MF 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)
Multiracial	20 (9)	23 (9)	21 (9)	64 (9)
American Indian/Alaskan Native	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
Duration of asthma (years)				
Mean (SD)	14 (12)	14 (11)	14 (12)	14 (12)
Median	11	10	11	10
FEV1 (mean, SD) at baseline				
L	2.06	2.06	2.04	2.05
% predicted	66.5	65.9	66.5	66.3
% reversibility (at screening)	24.4	22.2	22.1	22.9

Source: study-report-p04431.pdf, Section 14.1.1

Efficacy Endpoint Outcomes

Compliance

Based on patient diary data, 721 of 728 (99%) patients were >75% compliant. Treatment compliance was similar across the four treatment groups.

Primary efficacy variable: FEV1 mean AUC_{0-12h}

The co-primary efficacy endpoint, mean AUC_{0-12h} of the change from Baseline to Week 12 in FEV1, was intended to assess the LABA contribution to the MF/F combination, comparing MF/F 400/10 mcg BID vs. MF 400 mcg BID. Both MF/F 400/10 and 200/10 demonstrated a statistically significant difference over MF alone ($p<0.001$). The mean

values are displayed in the Table 27. These results support the efficacy of the F component.

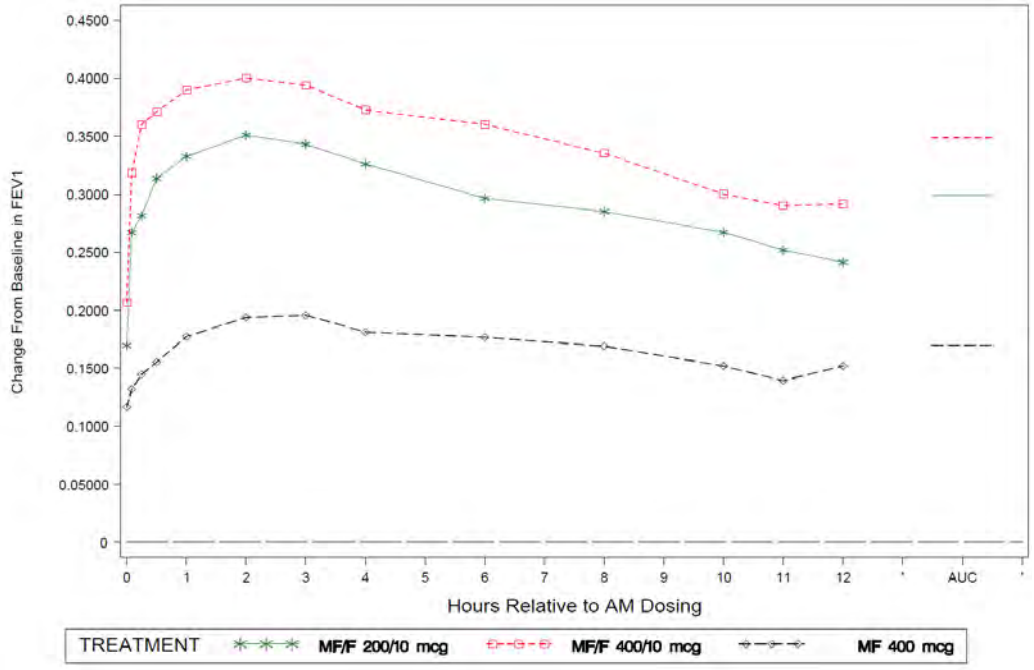
Table 27 P04431: FEV1 AUC_{0-12h} change from baseline to Week 12

Treatment group	N	LS mean		
(A) MF/F 200/10	230	3.59		
(B) MF 400/10	251	4.19		
(C) MF 400	237	2.04		
Pairwise comparisons		**A-B**	**A-C**	**B-C**
P-value		0.096	<0.001	<0.001
(95% CI)		(-1.30, 0.11)	(0.82, 2.27)	(1.44, 2.85)

Source: Module 5, study-report-p04431.pdf, Section 11.4.1.1, Table 7

These AUCs correspond approximately to increases from baseline FEV1 of 0.299 L for MF/F 200/10, 0.349 for MF/F 400/10, and 0.170 for MF 400 alone, averaged across the 12-hour serial evaluation. Numerically, there is greater efficacy observed for MF/F 400/10 over 200/10, providing justification for two different dose levels. These curves are displayed graphically in Figure 2.

Figure 10 P04431: 12-hour serial evaluations of FEV1 at Week 12



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Source: Module 5, study-report-p04431.pdf

Key secondary efficacy endpoint: Trough FEV1 at Week 12

Trough FEV1 was designated as a key secondary efficacy endpoint as an additional assessment of end of the dosing interval and to evaluate the relative differences

between the MF/F 400/10 and 200/10 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 = 0.05L; p=0.145). The treatment difference helps provide justification for the higher dose level. The application provides subgroup analysis for this endpoint based on baseline percent predicted FEV1 below the median 66%, which indicates 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).

Table 28 P04431: Change in trough FEV1 from baseline to Week 12

	MF/F 200/10 (A)		MF/F 400/10 (B)		MF 400 (C)	
	N	LS mean (% change)	N	LS mean (% change)	N	LS mean (% change)
Baseline	232	2.10	255	2.05	239	2.07
Week 12	212	0.14 (6.7)	230	0.19 (8.7)	210	0.10 (4.7)

Pairwise comparisons	A-B	A-C	B-C
P	0.145	0.195	0.006
95% CI	-0.10, 0.02	-0.02, 0.10	0.02, 0.14

Source: Module 5, study-report-p04431.pdf, Section 11.4.1.1, Table 8

Onset of action
Serial FEV1 was assessed on Day 1, Week1, Week12, and at Endpoint. Based on the least-square mean changes from baseline in FEV1, MF/F 400/10 and 200/10 was statistically superior to MF 400 starting at 5 minutes post-dose. This effect was sustained over the duration of the 12 hours ($p<0.001$ at all time points). There were no differences between the 400/10 and 200/10 dose levels.

AQLQ
The change from baseline AQLQ at Week12 was assessed as a secondary efficacy endpoint. All of the treatment groups demonstrated an improvement in the AQLQ of 0.5 or more. The greatest improvement was noted for MF/F 200/10, followed by MF/F 400/10. While these results are generally supportive of efficacy, they do not help distinguish between the MF/F 400/10 and 200/10 dose levels.

Table 29 P04431: Change from baseline to Week 12 in AQLQ score

	MF/F 200/10 (A)		MF/F 400/10 (B)		MF 400 (C)	
	N	LS mean	N	LS mean	N	LS mean
Baseline	224	5.05	250	5.00	234	5.05
Week 12	205	0.61	223	0.51	208	0.50

Pairwise comparisons	A-B	A-C	B-C
P	0.169	0.124	0.839
95% CI	-0.04, 0.23	-0.03, 0.25	-0.12, 0.15

Source: Module 5, study-report-p04431.pdf, Section 11.4.1.3, Table 13

ACQ

The change from baseline to Week 12 in the total ACQ score was assessed as a secondary efficacy endpoint (Table 30). As the MCID for the ACQ is not established, the clinical relevance of the observed changes is not clear, although these results are generally supportive of efficacy for MF/F over MF alone. However, there was no separation in terms of the two dose levels of MF/F, 400/10 and 200/10.

Table 30 P04431: Change from baseline to Week 12 in ACQ total score

	MF/F 200/10 (A)		MF/F 400/10 (B)		MF 400 (C)	
	N	LS mean	N	LS mean	N	LS mean
Baseline	224	1.83	250	1.87	233	1.85
Week 12	205	-0.59	222	-0.58	206	-0.42

Pairwise comparisons	A-B	A-C	B-C
P	0.821	0.008	0.014
95% CI	-0.14, 0.11	-0.30, -0.04	-0.28, -0.03

Source: Module 5, study-report-p04431.pdf, Section 11.4.1.2, Table 12

Nocturnal awakenings

The proportion of nights during the 12-week treatment period with nocturnal awakenings due to asthma requiring treatment with a SABA was assessed as a secondary efficacy endpoint (Table 31). All treatment groups were reported to have decreased awakenings. The treatment effect was the same for the MF/F 400/10 and 200/10 dose levels, which both had greater decreases than for MF 400 alone. These results are generally supportive of MF/F's efficacy but do not distinguish between the two dose levels for the combination.

Table 31 P04431: Change from baseline to endpoint in proportion of nights with nocturnal awakenings due to asthma requiring SABA use

	MF/F 200/10 (A)		MF/F 400/10 (B)		MF 400 (C)	
	N	LS mean	N	LS mean	N	LS mean
Baseline	233	0.21	255	0.23	239	0.19
Endpoint	233	-0.10	255	-0.10	239	-0.05

Pairwise comparisons	A-B	A-C	B-C
P	0.620	0.002	0.006
95% CI	-0.04, 0.02	-0.08, -0.02	-0.08, -0.01

Source: Module 5, study-report-p04431.pdf, Section 11.4.1.4, Table 14

Peak expiratory flow (PEF)

AM and PM PEFs were assessed as a secondary efficacy variable. At Week 12, a statistically significant difference was observed between MF/F and placebo in AM PEF (change from baseline 27.9 vs. -16.2 L/min; $p<0.001$). Statistically significant differences were observed for MF/F 200/10 (33.7 L/min) and MF/F 400/10 (37.9 L/min)

when compared to MF 400 (15.6 L/min) (p=0.001and p<0.001, respectively). Numerically, MF/F 400/10 was slightly better than MF/F 200/10, although the difference is likely not clinically significant. These results are generally supportive of MF/F's efficacy but do not distinguish between the two dose levels for the combination. Similar results were observed for PM PEFs.

Time to first and number of asthma exacerbations
Severe asthma exacerbation was defined the same as in Trials (b) (4) and 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.

Rescue medication usage
Patients were permitted the use of SABA as needed, and the number of inhalations used was recorded each day in the patient diaries. Baseline usage varied somewhat. The average baseline use among the 3 treatment arms were as follows: MF/F 200/10 1.96 puffs/day; MF/F 400/10 1.74 puff/day, and MF 400 1.95 puffs/day. At endpoint (the last 7 days of diary data for each patient), the change from baseline was as follows: -0.78, -0.66, and -0.21 puffs/day. These results support the efficacy of the MF/F combination but do not justify the need for two separate dose levels.

Efficacy evaluation for patient subgroups
The Applicant included summary statistics for various subgroups of the co-primary endpoint FEV1 $AUC_{0\text{-}12h}$. Overall, gender, race, and BMI did not appear to impact the results. 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 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).

P04431: Study summary and conclusions
P04431 supports the efficacy of MF/F over MF alone, and provides justification for two different dose levels, MF/F 400/10 and 200/10 on the basis of the key secondary endpoint, trough FEV1. 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 200/20, although this efficacy variable is intended primarily to measure the efficacy contribution of the F component to the combination. However, 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.

Trial P04139

P04139: Study Protocol

Administrative Information

- Title: A 1-year safety study of medium and high doses of MF/F combination formulation and medium and high doses of F/SC in persistent asthmatics previously treated with medium to high doses of inhaled glucocorticoids
- Study dates: June 30, 2006 to March 14, 2008
- Study report date: March 17, 2009
- Study sites: 27 centers (8 Argentina, 6 Peru, 4 Ecuador, 4 Guatemala, 3 Chile, 2 Mexico)

As the long-term trial was conducted exclusively outside the US, the clinical review placed particular attention was placed on the comparability of data obtained from this trial and the other pivotal trials. Comparison of the safety profiles observed is provided in Section 7.

Objectives/Rationale

- Evaluate the long-term safety of MF/F MDI 200/10 and 400/10 BID compared to F/SC 250/50 and 500/50 BID
- Evaluate extrapulmonary effects on 24-hour plasma cortisol AUC

Study design and conduct

P04139 was a randomized, multi-center, open-label, evaluator blind trial that enrolled 404 patients 12 years of age and older with a history of persistent asthma on medium to high doses of ICS. After a 1 to 2-week screening period, patients were randomized 2:1 to MF/F or F/SC. Allocation to medium or high dose 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. The Applicant states that neither F nor MF monocomponent was used as a control because these products were not intended for commercial development.

Table 32 P04139: Schedule of assessments

	Visit 1 Screening Days -14 to -7	Visit 2 Baseline Day 1	Visit 3 Week 1	Visits 4-10 Weeks 4, 8, 12, 16, 20, 26, and 39	Visit 11 Week 52
Inclusion/exclusion criteria	X	X			
Medical hx	X				
Concomitant medication review	X	X	X	X	X
Physical exam	X			X	X
Oropharyngeal exam	X				
Vital signs	X	X	X	X	X
PFT	X	X	X	X	X
Reversibility[b]	X	X			
Labs	X				X
Pharmacogenetic sample (optional)	X				
ECG	X				X
Chest x-ray	X				
AEs	X	X	X	X	X
Ophthalmological assessment	X			X[a]	X
24hr plasma cortisol[c]		X		X	X

[a] At 6-month visit
[b] If no historical documentation of reversibility
[c] Performed in subset of sites
Source: Module 5, study-report-p04139.pdf, Table 2

Study treatments

- MF/F 400/10 mcg BID
- MF/F 200/10 mcg BID
- F/SC 250/50 mcg BID
- F/SC 500/50 mcg BID

Study population

Pertinent inclusion criteria

- 12 years of age and older
- Medium or high daily dose of ICS for at least 12 weeks prior to screening and stable regimen for at least 2 weeks prior to screening
    - Medium doses
        - >500 to 1000 mcg beclomethasone CFC
        - >250 to 500 mcg beclomethasone HFA
        - >600 to 1000 mcg budesonide DPI
        - >1000 to 2000 mcg flunisolide
        - >250 to 500 mcg fluticasone
        - 400 mcg MF DPI
        - >1000 to 2000 mg triamcinolone
    - High doses
        - >1000 mcg beclomethasone CFC
        - >500 mcg beclomethasone HFA

  - >1000 mcg budesonide DPI
  - >2000 mcg flunisolide
  - >500 mcg fluticasone
  - >400 mcg MF DPI
  - >2000 mg triamcinolone
- Demonstrated reversibility within last 12 months prior to screening
  - FEV1 increase ≥12% and ≥200 ml
- Normal or clinically acceptable clinical laboratory tests, ECG, and chest x-ray
- Medically acceptable birth control in females of childbearing potential

Pertinent exclusion criteria

- Change in FEV1 >20% at any time from Screening to Baseline
- >12 inhalations of SABA or >2 nebulized SABA treatments during Screening period
- Clinical asthma exacerbation (deterioration of asthma resulting in emergency treatment, hospitalization due to asthma, or treatment with other excluded asthma medication) during Screening period
- Prior history of intubation/ventilator support for asthma
- Respiratory tract infection within 2 weeks prior to Screening
- Smoker or ex-emoker with cumulative history >10 pack-years
- Clinically significant abnormal vital sign
- Clinically significant oral candidiasis
- Comorbid medical conditions which may interfere with the trial
- Pregnancy or breastfeeding

Parameters assessed

The primary endpoint of the trial was the number and rate of reported adverse events. Secondary endpoints were: 1) 24-hour plasma cortisol AUCs; and 2) mean change in trough FEV1 from baseline to endpoint. Additional efficacy parameters that were assessed included AM/PM PEFRs, SABA usage, and nocturnal awakenings. Formal statistical testing was not conducted on these efficacy variables.

P04139: Study results

Demographic information, patient disposition, and efficacy results obtained as a measure of compliance are presented here. Safety data, including results of the HPA axis assessment and ophthalmological evaluations are presented in Section 7.

Patient disposition

Table 33 summarizes the patient disposition following the randomized treatment period. Discontinuation patterns were similar across the 4 treatment arms.

Table 33 P04139: Patient disposition

	MF/F 200/10 N=141	MF 400/10 N=130	F/SC 250/50 N=68	F/SC 500/50 N=65
Enrolled	141 (100)	130 (100)	68 (100)	65 (100)
Discontinued early	19 (13)	22 (17)	10 (15)	8 (12)
AE	5 (4)	6 (5)	2 (3)	-
Treatment failure	-	1 (1)	-	1 (2)
Lost to follow-up	3 (2)	3 (2)	2 (3)	-
Unrelated to study drug	-	3 (2)	4 (6)	2 (3)
Related to study drug	1 (1)	-	-	1 (2)
Noncompliance	8 (6)	6 (5)	2 (3)	1 (2)
Ineligibility	-	1 (1)	-	2 (3)
Administrative	2 (1)	2 (2)	-	1 (2)
Completed	122 (87)	108 (83)	58 (85)	57 (88)

Source: Module 5, study-report-p04319.pdf, Table 3

Patient demographic characteristics

Table 34 describes the demographic characteristics of the long-term safety trial population, which was generally consistent with the population enrolled in the other Phase 3 trials as well as comparable across the 4 treatment arms.

Table 34 Long-term safety trial P04139: Demographics and baseline characteristics

	MF/F 200/10 N=141	MF 400/10 N=130	F/SC 250/50 N=68	F/SC 500/50 N=65
Sex (n, %)				
Female	92 (65)	86 (66)	38 (56)	40 (62)
Male	49 (35)	44 (34)	30 (44)	25 (38)
Race (n,%)				
White	68 (48)	60 (46)	30 (44)	32 (49)
Non-white	73 (52)	70 (54)	38 (56)	33 (51)
Age (years)				
Mean (SD)	33 (15)	39 (15)	32 (15)	37 (15)
Median	31	41	29	36
Range	12-75	12-69	12-67	12-65
Age (n, %)				
12 to <18 years	30 (21)	11 (8)	13 (19)	8 (12)
18 to <65 years	109 (77)	113 (87)	54 (79)	56 (86)
≥65 years	2 (1)	6 (5)	1 (1)	1 (2)
Duration of asthma (years)				
Mean (SD)	15 (12)	19 (13)	16 (12)	18 (12)
Median	12	16	14	15
FEV1 (mean, SD) at baseline				
L	2.56	2.31	2.53	2.26
% predicted	80.5	74.5	78.1	72.2
% reversibility (historical)	20.6	23.3	23.4	23.6

Source: Module 5, P04139 CSR, Section 14.1.1 and Section 16.2.4

Efficacy parameters

Trough FEV1
Although P04139 was intended primarily as a safety trial, trough FEV1 measures provided a surrogate measure of compliance.

Table 35 P04139: Change in mean trough FEV1 from baseline to Week 12 and Endpoint

	MF/F 200/10 N=139		MF/F 400/10 N=129		F/SC 250/50 N=66		F/SC 500/50 N=65	
	Mean (L)	Mean change (L)	Mean (L)	Mean change (L)	Mean (L)	Mean change (L)	Mean (L)	Mean change (L)
Baseline	2.56		2.31		2.53		2.26	
Week 12		0.24		0.20		0.32		0.37
Endpoint		0.24		0.21		0.33		0.32

Source: Module 5, study-report-p04139.pdf, Table 7

SABA use
The proportion of patients reporting at least 2 consecutive days of high SABA use (>8 units of inhalations) was similar across the 4 treatment groups (17 to 22%). Likewise, the proportion of nights with nocturnal awakenings requiring SABA use decreased similarly in the 4 treatment groups (-0.15 to -0.17). The baseline number of nocturnal awakenings at night was low (0.3 to 0.4).

Safety parameters
Safety data from P04139 is presented in Section 7.

Study conclusions: P04139
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. Plasma cortisol measurements provide an added measure of compliance and are also discussed in Section 7.

TRIAL P04703

P04703: Study Protocol

Administrative Information
- Title: An open-label, multi-center, patient handling study of MF/F with an integrated dose counter in adolescent and adult subjects with asthma or COPD
- Trial dates: March 7, 2008 to November 20, 2008
- Study report date: April 24, 2009
- Study sites: 56 sites in the US (58 investigators)

Objectives/Rationale

- Evaluate the performance, including measures of accuracy and ruggedness, of the MF/F MDI dose counter in adolescent and adult subjects with persistent asthma or COPD
- Assess subject satisfaction with the dose counter

Study Design Overview
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. The dose counter information was not evaluated in the Phase 3 pivotal trials, so a separate handling trial was conducted. Eligible patients with asthma or COPD 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.

Study Population
A total of 343 patients were enrolled, of which 272 underwent the treatment period and 233 completed the trial. Patients were stratified by age as they were accrued so that a target of 25% were 65 years of age or older and the remaining 75% were 12 to 64 years of age.

Inclusion criteria
- ≥12 years of age with a diagnosis of asthma or COPD of at least 12 months
- At Screening:
  - Asthma patients: FEV1 ≥70%
  - COPD patients: FEV1 ≥50% and FEV1/FVS ≤0.70 (pre-bronchodilator)
- Asthma patients must have used a low or medium daily dose of ICS (±LABA) as defined in the pivotal trials P04334 (b) (4) for at least 12 weeks prior to Screening
- ≥90% compliance with e-diary, Counterstrip, and trial medication during 2-week screening
- At Baseline visit, asthma patients: FEV1 ≥80%
- Pre-screening laboratory parameters and ECG within normal limits or deemed clinically acceptable by the investigator/sponsor

- Females of childbearing potential must have a negative serum pregnancy test at pre-screening and using an adequate form of birth control for at least 3 months prior to pre-screening and during treatment period

Exclusion criteria

- Pregnancy
- Serious or life-threatening AE
- Use of systemic corticosteroids
- Asthma patients requiring >8 inhalations/day of SABA or >2 nebulized treatments/day on any 2 consecutive days during Screening
- COPD patients with exacerbations requiring emergent treatment, hospitalization, oral steroids, and/or at the discretion of the investigator

Study Treatments

- MF/F 100/10 mcg with and without an integrated dose counter twice daily (2 inhalations of 50/50 mcg inhaler BID)
- SABA and oral prednisone were also provided to patients at Pre-Screening. Patients were instructed to take the SABA and prednisone as rescue medications only. The prednisone was to be initiated only after investigator approval, if possible.

Efficacy Parameters

- Discrepancy rate per 100 actuations (# discrepancies based on the difference between the subject-recorded number of actuations and the subject-recorded counter readout across the 4-week treatment period)
- Quartile discrepancy rate per 100 actuations
- Magnitude of discrepancies
- End-of-use agreement (difference in the final MDI dose counter readout and the total number of recorded actuations at end of use)

Safety Parameters

- Adverse events
- Clinical tests**:** hematology, chemistry, urinanalysis, serum pregnancy test, ECG, and chest x-ray at pre-screening. Chest x-rays were only required at the discretion of the investigator.
- Physical examination (focused oropharyngeal exam and repetitive strain injury (RSI) exam at each visit)
- Pulmonary function testing
    - Spirometry at Screening, Baseline, and Final visit
    - Peak flows throughout
- Vital signs at each visit
- Rescue medication use
- Symptom scores

Statistical Plan
No formal hypothesis testing or sample size calculations were performed. Results were presented using descriptive statistics.

P4703: Results

Patient disposition
Of the 343 patients enrolled and who received at least one dose of trial medication, 272 continued through the Treatment Period and 233 completed at least 90% of labeled actuations (Completer population). Fifty-nine patients (25%) in the Completer population were 65 years or older. Disposition is summarized in Table 36.

Table 36 P4703 patient disposition

Disposition	All treated population N (%)	Treatment period population N (%)
Treated	343 (100)	272 (100)
Discontinued	82 (24)	11 (4)
Adverse event	6 (2)	2 (1)
Treatment failure	1 (<1)	1 (<1)
Lost to follow-up	1 (<1)	--
Withdrawal of consent for reasons unrelated to study treatment	12 (3)	4 (1)
Non-compliance	19 (6)	2 (1)
Did not meet protocol eligibility	40 (12)	1 (<1)
Administrative	3 (1)	1 (<1)
Completed	261 (76)	261 (96)

Source: Module 5, study-report-p04703, Section 10.1, Table 4

The clinical review focuses on the Completer population, as these are the patients who received the MDI with the integrated dose counter and provided the most information dose counter durability and performance over time.

Demographics and Baseline Characteristics
The mean age of the treatment period population was 47 years with a range of 12 to 92 years. A total of 35 pediatric patients 12 to <18 years and a total of 65 patients ≥65 years were included in the treatment period population. 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.

Treatment Compliance
Treatment compliance was assessed by the e-diary and Counterstrip readings. Canister weights were not used. According to Procedure Verification Forms completed for individual patients, 92% patients were reported to be compliant with the study medication regimen. The most common reason cited for non-compliance was subjects forgetting a dose. In general, compliance was greater in patients >65 years of age. For

the Counterstrip, the average compliance was greater than 95% during the treatment period and 75% compliance was reported for the e-Diary. In contrast to compliance with study medication, older patients appeared to have 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 date have not identified 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.

Efficacy Endpoint Outcomes

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 under-counts to sprays firing in advance of counting, which may have been due to incomplete depression of the canister during inhalation administration. To address the issue, the Applicant states that the counter design will be improved 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. This is more 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, keeping in mind that patients who used more than the labeled number of actuations (dose counter used beyond 0), were not fully included in the end-of-use assessment (n=2). The study report stated that data from these patients up until the point that the dose counter counted zero would be used. Data beyond zero were not included.

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 has provided an additional analysis 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.

Safety Outcomes
Safety outcomes for P4703 are discussed as part of the pooled analysis presented in Section 7.

P4703: Study summary and conclusions
P4703 was intended to demonstrate the accuracy and durability of the integrated dose counter mechanism in MF/F MDI. Although the majority of the inhalers tested in the protocol appeared to perform without problems, there were 14 reports of under-counting, which poses a potential safety concern if patients do not realize that they have run out of asthma medication. Root cause analysis indicated that MDIs were firing in advance of counting, most likely due to an incomplete depression of the canister. To address this issue, the Applicant has stated that the Count Point-Fire-Point Relationship will be adjusted so that the tendency will be for incomplete depression of the canister to result in a count.

6 Review of Efficacy

Efficacy Summary

The proposed indication is the (b) (4) treatment of asthma, (b) (4) (b) (4) in adults and adolescents 12 years of age and older. While the proposed indication for (b) (4) treatment of asthma" is consistent with previously approved long-acting beta-agonists (LABA), the current thinking within the Agency has shifted with an emphasis on minimizing the chronic use of LABAs due to the risk of serious asthma-related adverse events. As a result, the role of LABAs as a (b) (4) is in question, and the clinical review considers a general asthma treatment indication as more appropriate. (b) (4) separate MF/F dosage strengths are proposed: (b) (4) 100/5, and 200/5 mcg (ex mouthpiece dose) administered as 2 inhalations twice daily. This review refers to the therapeutic dose of MF/F delivered by 2 actuations, i.e. MF/F (b) (4), 200/10, and 400/10 mcg, respectively.

The application provides support for the efficacy of MF/F 200/10 and 400/10 mcg administered twice daily in the treatment of asthma in patients 12 years of age and older. (b) (4)

(b) (4)

Support for the efficacy of MF/F 200/10 is derived from the pivotal, factorial design trial P04334. MF/F 200/10 demonstrated a statistically significant, increased mean change from baseline to 12 weeks in FEV1 AUC_{0-12h} compared to placebo (3.25 vs. 0.88; p<0.001) and to MF 200 (1.71; p<0.001), which was the co-primary efficacy endpoint. This efficacy variable confirmed the efficacy of F 10 compared to placebo (2.42 vs 0.88; p<0.001) and demonstrated the contribution of the F 10 monocomponent to the MF/F combination. The other co-primary efficacy endpoint, time to first severe asthma exacerbation, was intended to assess the contribution of the MF component to MF/F. While MF/F 200/10 was shown to have a longer time to first severe asthma exacerbation than placebo (p<0.001), this endpoint was more difficult to interpret due to the shortcomings of the exacerbation definition and a low rate of events in all treatment groups. Therefore, trough FEV1 data was used as an additional evaluation of the efficacy of MF 200 and its contribution to the combination. For mean change from baseline to Week 12 in trough FEV1 was +0.13 for MF/F 200/10 compared to -0.05 for placebo (treatment difference = 0.18L; p<0.001) and 0 for F 10 (treatment difference = 0.13L; p<0.001). For MF 200, the mean change was +0.07 (treatment difference from placebo = 0.12L; p<0.001). These results support the efficacy of the MF 200 monocomponent as well demonstrating the contribution of MF 200 to the combination. The efficacy of the MF 200 monocomponent against placebo is replicated in the two 12-week, placebo-controlled dose ranging trials, C97-208 (treatment difference = 0.21L; p<0.01) and C97-225 (treatment difference = 0.31L; p<0.01). In these two trials, the change in mean FEV1 from baseline at Week 12 was assessed as the primary efficacy endpoint. Although this differs from the trough FEV1, this endpoint is acceptable since an ICS is not expected to have an acute onset of action and bronchodilators were appropriately held prior to spirometry. Other secondary efficacy variables evaluated in P04334, including AM and PM PEFR, nocturnal awakenings, and SABA use, were also supportive of the efficacy of MF/F 200/10.

Support for MF/F 400/10 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 3rd 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 primary efficacy endpoint, the change in mean FEV1 AUC_{0-12h} from baseline to Week 12 (treatment difference = 0.54 L x h), and the key secondary efficacy endpoint, trough FEV1 (treatment difference = 0.05 L). The trough FEV1 results support the contribution of the MF 400 moncomponent to combination. The efficacy of MF 400 compared to placebo is supported by replicate, 12-week dose ranging trials (C97-208 and C97-224). Although clear dose separation between MF 200 and MF 400 was not observed in the dose-ranging trials for the MF monocomponent, this may be due to differences in the trial populations' asthma severity and the relatively flat dose response curve for ICS in general. The dose-ranging trials assessed patients

with more moderate asthma, whereas the pivotal efficacy trial for MF/F 400/10 enrolled patients with more severe disease with a specific requirement for high doses of ICS at baseline and also a history of at least one severe exacerbation requiring oral corticosteroids within 20 months prior to screening. The application provides subgroup analysis for the trough FEV1 based on baseline percent predicted FEV1, which indicated a greater treatment difference between the MF/F dose levels for patients below the median value of 66% compared to patients with FEV1 values above the median (treatment difference = 0.08L v. 0.03 L, respectively). While there are limitations to this type of post hoc subgroup analysis, the analysis supports the theory that a more severe asthma population is likely to have provided better assay sensitivity for demonstrating dose separation between MF/F 200/10 and 400/10. Overall, the data from P04431 indicates that the MF/F 400/10 dose level may offer an efficacy benefit for some patients over the MF/F 200/10 dose level.

ICS/LABA combination products are generally considered combinations of convenience. Furthermore, ongoing concerns about the occurrence of serious asthma-related adverse events associated with LABA monotherapy have highlighted the requirement for robust evidence of efficacy and safety of the ICS monocomponent in an ICS/LABA combination. As a result, the clinical program was expected to demonstrate the efficacy and safety for each of the novel monocomponents in a well-controlled, replicated fashion and provide evidence of the contribution of each monocomponent to the combination. (b) (4)

In summary, the application provides evidence of efficacy for MF/F 200/10 and 400/10 for the treatment of asthma as well demonstrating the efficacy and contribution of the MF 200, MF 400, and F 10 monocomponents to the respective combinations. (b) (4)

(b) (4)

6.1 Indication

MF/F is proposed for the (b) (4) treatment of asthma (b) (4) in adults and children 12 years of age and older.

6.1.1 Methods

The trial design and conduct of the pivotal Phase 3 efficacy trials (b) (4) P04334, and P04431) and the pivotal dose-ranging trials for the F monocomponent (P06144, P05643) and MF monocomponent (C97-208, C97-225, I97-200) are described in Section 5.3. Overall, the trials were adequately designed to assess the efficacy of MF/F and the efficacy and contribution of MF and F to the combination. The pivotal trials (b) (4) and P04334 had a 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). (b) (4) The application did provide replicate evidence of efficacy for MF 200 and MF 400 against placebo as well as providing a direct comparison of MF 200/10 and MF/F 400/10.

6.1.2 Demographics

Detailed demographic data from the pivotal Phase 3 trials and the key dose-ranging trials are shown in Section 5.3. 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/F 400/10, 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 MF/F 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, 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. This differential pattern of early discontinuation among the treatment arms supports the efficacy of the proposed MF/F combination.

6.1.4 Analysis of Primary Endpoint(s)

Trials (b) (4) and 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. For the sake of maintaining parallel comparisons, the asthma exacerbation endpoint will be discussed for all 3 pivotal trials in this section.

Change in mean FEV1 $AUC_{0\text{-}12h}$ from baseline to Week 12

The change in mean FEV1 $AUC_{0\text{-}12h}$ endpoint was an appropriate endpoint for assessing the bronchodilatory effects of MF/F and evaluating the contribution of the F monocomponent to the combination. In (b) (4) and P04334, the changes in mean FEV1 $AUC_{0\text{-}12h}$ for (b) (4) 200/10, respectively, were greater than the change observed for placebo (Table 37, Figure 4, and Figure 7). P04431 did not include a placebo control; however, the changes in mean FEV1 $AUC_{0\text{-}12h}$ were greater in MF/F 400/10 and MF/F 200/10 compared to MF 400 alone, and the differences were statistically significant ($p<0.001$; Figure 10), supporting the contribution of F to the combination. Note that the values displayed in Table 37 are derived from the Agency's statistical reanalysis and vary slightly from the values provided in the application and in Section 5. The numerical differences are small and do no alter the conclusions.

Table 37 Change in mean FEV1 $AUC_{0\text{-}12h}$ from baseline to Week 12*

Trial	Treatment group	N	LS mean	Difference from	P-value compared to	Difference from MF	P-value compared to
(b) (4)							
P04334	MF/F 200/20	160	3.25	2.37	<0.001	1.54	<0.001
	MF 200	165	1.71	0.83	0.049		
	F 10	133	2.23	1.35	0.002	0.52	
	Placebo	135	0.88			-0.83	0.049
P04431	MF/F 200/10	207	3.64			1.72	<0.001
	MF 400/10	232	4.18			2.27	<0.001
	MF 400	211	1.91				

* Values taken from Dr. Robert Abugov's statistical review.

Time to first severe asthma exacerbation

The time to first severe asthma exacerbation endpoint was intended to assess the contribution of the MF component to MF/F. However, this endpoint was more difficult to interpret due to the shortcomings of the definition as well as a lower than expected rate

of events. While asthma exacerbations in general are considered a clinically meaningful endpoint, there is no standard, widely accepted definition. In the MF/F program, a severe asthma exacerbation was defined as 1 of the following: 1) ≥20% decrease in FEV1 from the treatment stability period; 2) a ≥30% decrease in PEF from the treatment stability period on 2 consecutive days; and 3) a clinical deterioration of asthma resulting in emergency treatment, hospitalization, or treatment with systemic corticosteroids. Although the definition of exacerbation was prespecified in the protocols, the definition did not correlate lung function parameters with clinical symptoms or duration, (b) (4). As defined, patients with a decrease in peak flow alone could qualify and the results from all 3 trials indicate that PEF decreases comprised the majority of asthma exacerbations that were reported.

The limitations of the asthma exacerbation endpoint were previously raised by the Division in a written communication dated February 22, 2007, and discussed during the April 28, 2008, pre-NDA meeting. The Applicant has submitted post hoc analysis that correlates lung function with symptoms and corticosteroid use. (b) (4)

In addition, due to a lower than expected rate of events, a median time to first severe exacerbation could not be established for any of the trials. In (b) (4) P04334, Kaplan-Meier survival curve analyses indicated that MF (b) (4) 200, respectively, were superior to placebo ($p<0.001$; Figure 5 and Figure 8), and MF/F (b) (4) 200/10, respectively, were superior to F alone. In P04431, there were no appreciable differences among the 3 treatment groups.

Therefore, while the results for the asthma exacerbation endpoint are generally supportive of the efficacy of MF/F, the clinical relevance of these results remains uncertain, (b) (4). Further support from secondary endpoints is required, particularly for assessment of the MF contribution to the combination.

6.1.5 Analysis of Secondary Endpoints(s)

Given the issues with the time to first severe asthma exacerbation endpoint, additional support from secondary endpoints is particularly critical. The clinical review focused on the trough FEV1, which was designated as a key secondary efficacy variable in all 3 efficacy trials and which has been used in similar development programs for asthma. Other important secondary endpoints which were assessed included the following: nocturnal awakenings, rescue medication use, PEFs, AQLQ and ACQ scores.

Trough FEV1

The main comparison for the trough FEV1 assessment was MF/F versus F, in order to evaluate the MF contribution to the combination. For P04334, the trough FEV1 data support the efficacy of the monocomponent MF 200 over placebo (treatment difference

120 mL; p<0.001), and the efficacy of MF/F 200/10 over F 10 (treatment difference 130 mL; p<0.001), supporting the contribution of MF to MF/F (Table 38). For the lower MF dose, a similar treatment effect is observed for the monocomponent (b) (4) over placebo (treatment difference 120 mL; p=0.001), but the comparison (b) (4) over F 10 is not statistically significant (treatment difference 70 ml; p=0.07). P04431 did not include a placebo group for comparison, but comparison of the MF/F 400/10 to MF 200/10 suggests a modest increase in efficacy with the higher concentration of MF in the combination, albeit not statistically significant (treatment difference 50 ml; p=0.14). The application provides subgroup analysis for this endpoint based on baseline percent predicted FEV1, which indicates a greater treatment difference between the MF/F dose levels for patients below the median value of 66% compared to patients with FEV1 values above the median (treatment difference = 0.08L v. 0.03 L, respectively).

Table 38 Change in trough FEV1 from baseline to Week 12

	N	Baseline (L)	Change from baseline at Week 12 (L)[b]	P-value (vs. Pbo)	Difference from Pbo	P-value (vs. F)
(b) (4)						
P04334						
MF/F 200/10 BID	167	2.33	0.10	<0.001	0.18	<0.001
MF 200 BID	175	2.36	0.06	0.002	0.12	0.058
F 10 BID	141	2.29	-0.04	0.170	0.03	
Placebo	145	2.30	-0.07			
P04431						
MF/F 400/10 BID	212	2.05	0.19			
MF/F 200/10 BID[a]	230	2.10	0.14			
MF 400 BID	210	2.07	0.10			

[a] P value for = 0.145 for MF/F 200/10 BID vs. MF 400/10 BID
[b] The values are obtained from Dr. Robert Abugov's statistical review and differ slightly from those presented in Section 5, which were derived from the application's various CSRs. The differences do not impact the conclusions.

Nocturnal awakenings

The proposed labeling includes rescue SABA use in Section 14, Clinical Studies section, which is supported by the application. The proportion of nights disrupted by nocturnal awakenings requiring treatment with a SABA over the 26 week (b) (4) P04334) and 12-week (P04431) treatment periods was assessed. In the two 26-week placebo-controlled trials, a greater decrease in the proportion of nights with nocturnal awakenings was observed in the (b) (4) 200/10 treatment groups (-0.08 vs. -0.01), respectively, compared to placebo, and the results were statistically significant in both trials (p<0.001). In P04431, both MF/F 400/10 and 200/10 had a decrease in the proportion of nocturnal awakenings by -0.10 compared to -0.05 to MF 400 alone (p=0.002 to 0.006). In general, the data for nocturnal awakenings

supports the efficacy of MF/F over placebo but does not demonstrate a clear dose response, particularly for the 2 highest dose levels.

Rescue medication use
In all Phase 3 trials, patients were permitted the use of SABA as needed, and the number of inhalations used was recorded daily in the patient diaries. In all 3 trials, the mean number of inhalations/day decreased the most in the MF/F treatment groups compared to MF alone, and in (b) (4) and P04334, F alone and placebo, but the clinical impact of the treatment difference was modest (<1 puff/day change). Similar to the data for nocturnal awakenings, while both MF/F 400/10 (-0.66 puffs/day) and 200/10 (-0.78 puffs/day) demonstrated greater decreases in daily SABA use compared to MF 400 alone (-0.21), the 2 dose levels of MF/F were not distinguishable. The proposed labeling includes rescue SABA use in Section 14, Clinical Studies section, which is supported by the application.

Peak expiratory flow
AM and PM PEF data was collected in all 3 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/F. The proposed labeling includes mention of AM PEF as a supportive endpoint, which is supported by the application.

Asthma Control Questionnaire (ACQ)
The application (b) (4) provided a Patient-Reported Outcome (PRO) dossier to support the clinical significance of the observed treatment differences. The psychometric properties of the ACQ were assessed through post-hoc analysis of data collected from P04073 and P04334.

(b) (4)

The change in ACQ from baseline to Week 26 (b) (4) P04334) and to Week 12 (P04431) in the total ACQ score was evaluated as a secondary endpoint. In the (b) (4) placebo-controlled trials, (b) (4) and MF/F 200/10 demonstrated a statistically significant decrease from baseline when compared to placebo ($p<0.001$) as did MF alone and F alone (Table 14 and Table 22). The magnitude of change was >0.5 for MF/F 200/10 and MF/F 400/10. However, the treatment difference from placebo was <0.5 for MF/F 200/10 and there was no comparison to placebo available for MF/F 400/10. (b) (4)

(b) (4)

(b) (4). In addition, certain elements of the ACQ are duplicated in other secondary endpoints, such as nocturnal awakenings, rescue SABA use, and

spirometry. It is unclear that a composite score like the ACQ provides added value to the examination of these individual efficacy variables

Asthma Quality of Life Questionnaire

(b) (4) The change from baseline to Week 26 (b) (4) and P04334) and to Week 12 (P04431) in the AQLQ score was evaluated as a secondary endpoint. (b) (4) (b) (4) (b) (4) Similarly, the treatment difference was less than 0.5 for MF/F 200/10 versus placebo in P04334. The AQLQ data is considered secondary support for the efficacy of MF/F (b) (4) In P04431, increases >0.5 were observed for all 3 treatment groups but no placebo was available for comparison.

6.1.6 Other Endpoints

Onset of action

In all 3 trials, onset of action was assessed by serial FEV1 measurements at Day 1. Demonstration of statistical separation from placebo was observed for (b) (4) 200/10 starting at 5 minutes and was maintained over the interval timepoints out to 12 hours. Similarly, in P04431, statistical separation from MF 400 was observed for both MF/F 200/10 and 400/10 at 5 minutes, reflecting the bronchodilatory action of formoterol in the combination. The application has not proposed an onset of action claim for the label.

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_{0-12h} and trough FEV1, similar patterns of efficacy were observed for (b) (4) 200/10 over placebo regardless of age sub-categories (12-17, 18-64, and >54 years), gender, and race (Caucasian vs. non-Caucasian). The subgroup analysis also supported the dose separation between MF/F 400/10 and 200/10 in P04431 in terms for FEV1 AUC_{0-12h} and the trough FEV1. Although the samples 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

(b) (4) separate MF/F dosage strengths are proposed: (b) (4) 100/5, and 200/5 mcg (ex mouthpiece dose) administered as 2 inhalations twice daily. This review refers to the therapeutic dose of MF/F delivered by 2 actuations, i.e. MF/F (b) (4) 200/10, and 400/10 mcg, respectively.

Individual dose ranging trials for the MF and F monocomponents are discussed in detail in Section 4. The information obtained from these trials is adequate to support the proposed formoterol MDI dose of 10 mcg (ex-actuator dose). P06144 demonstrated that F MDI 10 mcg corresponded most closely with the approved dose of Foradil Aerolizer 12 mcg. Comparison of F MDI 5, 10, and 20 mcg to Foradil Aerolizer 12 and 24 mcg demonstrated similar dose response curves between the two formulations of formoterol, supporting the selection of the F MDI 10 mcg dose for the MF/F combination. In the pivotal Phase 3 trials, the factorial trial design clearly demonstrated the contribution of F 10 to the MF/F combination and confirmed the efficacy of F 10 compared to placebo.

Dose ranging information for the mometasone component was less clear cut, which may reflect the relatively flat dose response curve expected for an ICS. Based on change in FEV1 from baseline, C97-208 was unable to demonstrate a clear separation in efficacy among MF 50, 200, and 400 mcg, even though the 50 mcg dose level had been included as an anticipated “no effect” level. C97-225 showed a 30 cc difference between 50 mcg BID and 200 mcg BID in favor of the 200 mcg BID dose. Neither of these trials included an intermediate 100 mcg BID dose, although based on these results, a similar effect might be expected. No doses below 50 mcg BID were evaluated. The Applicant contends that the 50 mcg BID did not demonstrate as consistent a benefit for the patient population as the 200 mcg BID dose; in C97-225, patients who had a baseline FEV1>75% did not show clear differences between the 50 and 200 mcg dose levels (270 and 230 ml, respectively), in contrast to patients with FEV1<75% (320 and 450 ml, respectively). Whether this explanation is the case remains uncertain, but given the relatively flat dose response curve for ICS, it may be that more severe patients would provide greater assay sensitivity.

In contrast, I97-200 did compare the 100 mcg BID to the 200 mcg BID dose directly, showing a treatment difference of 90cc in favor of the higher dose. This trial provides justification for having a MF 100 and 200 mcg dose level. (b) (4) . This result may be due in part to the lower exposure observed for MF MDI 100 compared to the related Asmanex DPI product at the same nominal dose. Given the information provided in the application as a whole, the lowest effective dose recommended for approval is the MF/F 200/10 dose level.

The clinical program does provide justification for the MF/F 400/10 dose level. Dose separation was observed in P04431, the pivotal Phase 3 trial that included both MF/F 200/10 and MF/F 400/10 in the terms of the primary efficacy endpoint, change in mean FEV1 AUC_{0-12h}, and the trough FEV1. Although clear dose separation between MF 200 and MF 400 was not observed in the dose-ranging trials for the MF monocomponent, this may be due to differences in the trial populations' asthma severity. The dose-ranging trials assessed patients with more moderate asthma, whereas the pivotal trial for MF/F 400/10, P04431, enrolled patients with more severe disease with a specific requirement for high doses of ICS at baseline and also a history of at least one severe exacerbation requiring oral corticosteroids within 20 months prior to screening. The application provides subgroup analysis for the trough FEV1 based on baseline percent predicted FEV1, which indicated a greater treatment difference between the MF/F dose levels for patients below the median value of 66% compared to patients with FEV1 values above the median (treatment difference = 0.08L v. 0.03 L, respectively). While there are limitations to this type of post hoc subgroup analysis, the analysis supports the explanation that a more severe asthma population is likely to have provided better assay sensitivity for demonstrating dose separation between MF/F 200/10 and 400/10.

In summary, the clinical program provides adequate support for the dose selection of the F10, MF 200, and MF 400 monocomponents and the combination MF/F 200/10 and 400/10 doses levels. (b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were observed in the pivotal efficacy trials for MF/F 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

The NDA submission contains adequate data to support the safety of MF/F (b) (4) 200/10, and 400/10 in patients 12 years of age and older for the treatment of asthma in adults and children 12 years of age and older. The evidence for safety for MF/F is based primarily on the assessments performed in the completed Phase 3 efficacy trials (b) (4) 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 comparable exposure to the approved formoterol monotherapy, Foradil, and probable lower exposure for the mometasone monotherapy, Asmanex. The safety profiles for mometasone furoate DPI (Asmanex Twisthaler) and formoterol fumarate (Foradil Aerolizer) are established and described in the current package inserts for each product.

The most common adverse events reported for MF/F included headache, nasopharyngitis, upper respiratory tract infection, and pharyngolaryngeal pain. 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 clinical program had serious asthma exacerbations resulting in hospitalization. Of the 7, 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. The remaining 2 patients were on fluticasone propionate/salmeterol MDI and DPI, respectively. While these results are consistent with the safety profiles observed in other clinical trial databases, concern remains regarding the risk of rare, serious asthma-related adverse events associated with long-term use of LABAs, which is the subject of ongoing discussion within the Agency. Whether concomitant pairing with an ICS mitigates this risk is unknown.

Given the lack of PK information in adolescents ages 12 to 17 years, adequate representation of this age group in the safety database is critical. The full Phase 3 program plus the 4 12-week dose-ranging trials enrolled 485 patients ages 12 to 17 years, of whom 186 were exposed to MF/F, which is comparable to the pediatric representation that has been seen in other ICS/LABA development programs. In addition, there is extensive safety information of the related monotherapies.

In summary, the safety database for MF/F (b) (4), 200/10, and 400/10 is adequate to support approval in patients 12 years of age and older. Additional characterization of the risk of rare, serious asthma-related adverse events in a post-marketing safety trial is warranted and would be consistent with the safety trials planned for other ICS/LABA combination inhalation products.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based on 7 Phase 2 (n=150) and 6 Phase 3 (n=3664) clinical trials that enrolled 3814 subjects ages 12 years and older. Of these 3814 subjects, 1961 were treated with MF/F. The Phase 3 program consisted of 3 pivotal safety and efficacy trials (b) (4) P04334, and P04431), the 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 designated HPA axis study. This review focuses on the pooled analysis of the 3 pivotal efficacy and safety Phase 3 trials (n=2,255) 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 all 6 phase 3 trials as well as analyses of the placebo-controlled trials pooled together and non-placebo-controlled trials pooled separately. The placebo-controlled trials were also pooled in terms of extent of exposure, adverse events, laboratory test results, and vital signs. The non-placebo controlled trials were pooled for extent of exposure and adverse events. The results of the formoterol dose-ranging trial (P06144), the long-term safety trial (P04139) and the dose counter trial (P04703) were presented separately. Of note, 14 COPD patients who participated in the PK study comparing MF to Asmanex Twisthaler (P04689) and 60 COPD patients who participated in the dose counter trial were not included.

7.2 Adequacy of Safety Assessments

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

Overall, the size of the safety database was adequate for this application. In the total Phase 3 program, 1781 patients received at least one dose of MF/F; 618 received at least one dose of MF, and 390 received at least one dose of F. The treatment duration ranged from 4 to 52 weeks, and all subjects had moderate to severe asthma. Treatment duration for the Phase 3 program is summarized in Table 39.

Table 39 Duration of exposure: Pooled Phase 3 trials

Duration (day) (b) (4)	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	932	385	186	192	240	390	68	65	349	383
≥15	904	381	183	190	233	375	67	64	335	362
≥30	880	372	174	187	227	348	67	62	328	336
≥60	841	355	168	180	211	304	66	61	311	293
≥90	538	138	160	175	11	285	66	60	220	277
≥120	499	118	154	168	-	271	65	59	196	260
≥178	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	-	-	-	-	-	-	-	-	-	-
Randomized, not treated	4	-	2	-	-	-	-	-	-	1

Source: Module 5.3.5.3, integrated-summary-safety.pdf, Section 7.1.1.1

In the Phase 2 program, a total of 151 patients received MF/F. As expected, the treatment duration was shorter and more variable in these Phase 2 trials. Additional short-term safety information from the dose ranging trials for the F and MF monocomponents was also available, although these were not included in the pooled analysis. Patient demographic information for each of the Phase 3 trials is presented in Section 5 and was generally comparable across the trials aside from the varying severity of asthma.

7.2.2 Explorations for Dose Response

The clinical program included a cumulative dose trial, which assessed the pharmacodynamics and safety of a cumulative dose of formoterol in the MF/F combination compared to F DPI (Foradil) administered alone in 19 adult patients with moderate persistent asthma. The trial evaluated the following cumulative doses:

- MF/F 1600/40 mcg (400/10, 400/10, and 800/20 administered at intervals of 60 minutes)
- MF/F 800/50 mcg (200/10, 200/10, and 400/20 administered at 60 minute intervals)
- Foradil up to a cumulative dose of 48 mcg (12 mcg dose x 3 administered at intervals of 60 minutes)

No SAEs, deaths, or significant AEs were reported in the cumulative dose trial. Fourteen of 19 (74%) reported at least one AE during the trial. The most commonly reported AE was headache. Tremor was reported in 1 patient during dosing with Foradil. In terms of laboratory parameters, serum potassium below the lower limit of normal (3.5 mmol/L) was observed in 5 patients; the lowest level observed was 3.3 mmol/L (n=3) in patients on Foradil Aerolizer. In terms of mean changes, the mean potassium level decreased in all active treatments groups in contrast by approximately 0.35 mmol/L. No clinically relevant changes in serum glucose were observed, and no clinically relevant changes in vital signs or ECGs were observed. Overally, the safety profile for the cumulative dosing of MF/F 100/5 and 200/5 was comparable to that of Foradil Aerolizer 12 mcg.

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 timepoints 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 urinanalysis: 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; 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). 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.

LABA
The safety and tolerability of cumulative doses of MF/F up to 1600/40 mcg were evaluated in the pivotal trial P05642 (Section 7.2.2). In addition, the pivotal trials incorporated monitoring for toxicities associated with LABAs, including screening for AEs such as tremor and headache and monitoring of laboratory, vital sign, and ECG parameters for adrenergic cardiac and metabolic effects.

7.3 Major Safety Results

7.3.1 Deaths

Three deaths were reported among patients who received MF/F. 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 P04334, a 53-year-old female (Patient 0012/Site 12) on MF/F 200/10 BID died from metastatic uterine leiomyosarcoma. Based on the nature and timing of these deaths, they do not appear to be related to MF/F. There were no asthma-related deaths reported in the clinical program.

7.3.2 Nonfatal Serious Adverse Events

Seven patients in the clinical program had serious asthma exacerbations resulting in hospitalization that were reported as SAEs. No intubations or deaths were reported. Of the 7, 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. The remaining 2 patients were on fluticasone propionate/salmeterol MDI and DPI, respectively. These patients are briefly summarized below:

- Patient 4195 (site 86): 52yo F with asthma exacerbation and upper respiratory infection 11 days after initiating treatment with F 10 BID. Discharged and recovery reported, discontinued from the trial.
- Patient 401 (site 191): 46yo F with asthma exacerbation and steroid-induced hyperglycemia 4 months after initiating treatment with MF/F 200/10 BID. AE resolved, discontinued from the trial.
- Patient 60 (site 21): 29yo F with asthma exacerbation and upper respiratory tract infection 7 months after initiating treatment with MF/F 200/10 BID. AE resolved, remained in trial.
- Patient 2194 (site 114): 55yo M with asthma exacerbation, chest pain, cardiac decompensation and supraventricular tachycardia 2 months after initiating treatment with MF/F 400/10 BID. AE resolved.
- Patient 3591 (site 69): 55yo F with asthma exacerbation 14 days after initating treatment with MF 200 BID. Discharged and recovery reported, discontinued from the trial.
- Patient 43 (site 20): 34yo F with asthma exacerbation, fever, dyspnea, and productive cough 6 months after initiating treatment with fluticasone/salmeterol 250/50 BID. AE resolved and patient remained in the trial.
- Patient 33 (site 24): 15yo F with asthma exacerbation and upper respiratory tract infection 10 months after initiating treatment with fluticasone propionate/salmeterol 250/50 BID. AE resolved, discontinued early due to ongoing treatment with oral corticosteroids.

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.

A wide range of non-asthma-related SAEs affecting various organ systems were also reported in the clinical program. These SAEs are described in Tables 34 to 36 of the Applicant's Summary of Clinical Safety, Module 2. Given the small numbers represented and the varying temporal relationship, a causal association cannot be made in the majority of cases. An exception may be ophthalmic lens disorders reported in 3 patients and ocular hypertension reported in 1 patient treated with MF/F 400/10 in the P04139. These are known adverse effects associated with inhaled corticosteroids. Ophthalmic AEs are discussed in further detail in Section 7.3.5.

7.3.3 Dropouts and/or Discontinuations

In the 3 pivotal safety and efficacy Phase 3 trials (b) (4) P04334, and P04431), 63 patients discontinued early due to adverse events. The number of patients discontinuing early was similarly distributed across the MF/F and MF treatment arms in the different trials, with a small excess of patients discontinuing early from the F 10 and placebo arms: (b) (4), 6 in the MF/F 200/10 group, 2 in the MF/F 400/10, 7 in the MF 200 group, 6 in the MF 100 group, 5 in the MF 400, 17 in the F 10 group, and 13 in the placebo group. 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 the long-term safety trial, 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

The safety of long-acting beta-adrenergic agents is an open question and the subject of current discussion within and outside the Agency. Sections 7.3.1 and 7.3.1 discuss serious asthma-related adverse events which occurred in the MF/F clinical program.

7.3.5 Submission Specific Primary Safety Concerns

There are several safety concerns associated with the approved mometasone and formoterol monotherapies. For formoterol, the major safety issues are related to acute effects (e.g. tremor, hypokalemia, hyperglycemia, adrenergic cardiac effects) and rare severe asthma-related outcomes (hospitalizations, intubations, and death), which have been associated with chronic use. These issues are discussed in further detail in Sections 7.2.2, 7.3.4, and 7.4. For mometasone, specific concerns include those that are regarded as class effects of ICS, namely HPA axis suppression and hypercorticism. These are discussed 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. In P03705, serial plasma cortisol levels were collected over a 24 hour period after 6 weeks of treatment using MF/F 200/10, 400/10, and F/SC 460/42 (Advair HFA 230/21

inhalation aerosol) compared to placebo. The mean AUC_{0-24h} was decreased from baseline by 16% for the higher dose of MF/F 400/10 (Table 40), indicative of mild cortisol suppression. This trial was limited by a small sample size and its open-label design; however, cross-study comparison to HPA assessments performed for the related mometasone product, Asmanex, suggests that the plasma cortisol measurements are comparable.

Table 40 Plasma cortisol parameters: P03705

Treatment	Day -1 Mean (%CV)		Day 42 Mean (%CV)	
	AUC0-24h (ng h/ml)	Ctrough (ng/ml)	AUC0-24h (ng h/ml)	Ctrough (ng/ml)
MF/F 200/10 BID N=15	1620 (19)	23.6 (40)	1670 (29)	24.1 (57)
MF/F 400/10 BID N=16	1570 (22)	20.3 (37)	1390 (49)	14.9 (50)
F/SC 460/41 BID N=16	1680 (31)	20.4 (44)	1240 (46)	16.4 (90)
Placebo N=17	1700 (38)	21.5 (61)	1830 (39)	22.9 (71)

Source: Module 5, study-report-p03705.pdf, Section 14.2.1.1

In P04139, 24-hour plasma cortisol levels were collected from a subset of 66 patients across the 4 treatment arms: MF/F 200/10, MF/F 400/10, F/SC 250/50, and F/SC 500/50. Decreases in plasma cortisol of 6% to 17% were observed for MF/F 200/10 and 31 to 34% for MF/F 400/10. No placebo group was included for comparison. These results are consistent with dose-related HPA axis suppression, which is a known adverse effect of inhaled corticosteroids. The correlation between plasma cortisol levels and clinical signs and symptoms of hypercorticism is not direct; however, these levels serve as an indicator of systemic exposure from the drug product and as indirect assessment of study medication compliance in the long-term safety trial.

Ocular disorders

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. 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 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.

Ophthalmologic exams including applanation tonometry and slit lamp exam with full dilation were performed for all patients in P04139 at Screening (Visit 1), Week 26 (Visit 9), and Week 52 (Visit 11). The LOCS III classification system was used for grading lens opacification. Ocular findings based on a change of ≥1 unit were reported in 5

patients (4%) on MF/F 200/10, 5 (4%) on MF/F 400/10, 4 (6%) on F/SC 250/50, and 1 (2%) on F/SC 500/50. Overall, the incidence of ocular findings was greater for MF/F compared to F/SC in the long-term trial.

The current approved package insert for mometasone DPI (Asmanex Twisthaler) 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. 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/F product are warranted.

Other ICS effects
Dysphonia was reported in 1.7% of the pooled Phase 3 database and 0.8% of all patients reported oral candidiasis ((b) (4) 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 Asmanex.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported AEs in the 2 pivotal, 12 week, placebo-controlled phase 3 trials were nasopharyngitis, upper respiratory tract infection, and headache. Observed AE event rates were similar across the treatment groups, including placebo.

Table 41 Common adverse events (>2%): Pooled placebo-controlled phase 3 trials

(b) (4)	MF/F 200/10 N=191	MF 100 N=188	MF 200 N=192	F 10 N=390	Placebo N=384
Any AE	97 (51)	86 (46)	88 (46)	165 (42)	148 (39)
Nasopharyngitis	12 (6)	13 (7)	15 (8)	20 (5)	12 (3)
Upper respiratory tract infection	11 (6)	17 (9)	18 (8)	32 (8)	29 (8)
Headache	9 (5)	11 (6)	10 (5)	15 (4)	14 (4)
Pharyngolaryngeal pain	-	4 (2)	-	5 (1)	4 (1)
Pharyngitis	8 (4)	2 (1)	6 (3)	6 (2)	12 (3)
Sinusitis	5 (3)	8 (4)	6 (3)	15 (4)	3 (1)
Pyrexia	6 (3)	3 (2)	5 (3)	6 (2)	3 (1)
Influenza	5 (3)	4 (2)	7 (4)	8 (2)	9 (2)
Cough	3 (2)	5 (3)	4 (2)	6 (2)	9 (2)
Oropharyngeal pain	6 (3)	-	4 (2)	3 (1)	7 (2)
Chest pain	2 (1)	4 (2)	1 (1)	1 (<1)	4 (2)
Bronchitis	5 (3)	5 (3)	3 (2)	8 (2)	9 (2)
Gastroenteritis	5 (3)	5 (3)	3 (2)	8 (2)	9 (2)
Rhinitis	5(3)	2 (1)	3 (2)	2 (1)	5 (1)
Viral infection	6 (3)	5 (3)	-	2	5 (1)
Dyspepsia	-	4 (2)	1 (1)	-	1 (<1)

Source: Module 5, integrated-summary-safety.pdf, Section 7.3.1.2

(b) (4) common adverse events from P04334, the pivotal, placebo controlled trial P04334, which evaluated MF/F 200/10, are provided in Table 42 for comparison. The nature and frequencies of the AEs are similar when the placebo-controlled Phase 3 trials are evaluated separately or in the pooled analysis shown in the table above.

Table 42 P04334: Common adverse events (>2%)

	MF/F 200/10 N=191	MF 200 N=192	F 10 N=202	Placebo N=196
Any AE	97 (51)	88 (46)	90 (45)	82 (42)
Nasopharyngitis	12 (6)	15 (8)	13 (6)	7 (4)
Upper respiratory tract infection	11 (6)	16 (8)	12 (6)	17 (9)
Headache	9 (5)	10 (5)	6 (3)	7 (4)
Oropharyngolaryngeal pain	6 (3)	4 (2)	3 (2)	7 (4)
Pharyngitis	8 (4)	6 (3)	3 (2)	6 (3)
Sinusitis	5 (3)	6 (3)	3 (2)	6 (3)
Pyrexia	6 (3)	5 (3)	2 (1	1 (1)
Influenza	5 (3)	7 (4)	5 (3)	5 (3)
Chest pain	2 (1)	1 (1)	1 (1)	4 (2)
Bronchitis	5 (3)	3 (2)	5 (3)	4 (2)
Cough	3 (2)	4 (2)	2 (1)	4 (2)
Gastroenteritis	1 (1)	4 (2)	2 (1)	-
Rhinitis	5(3)	3 (2)	1 (1)	4 (2)
Viral infection	6 (3)	-	1 (1)	1 (1)

Source: Module 5, study-report-p04334.pdf, Table 34

Trial P04431 was the 3rd 12 week pivotal efficacy and safety trial that evaluated MF 400, MF/F 200/10 and 400/10. Since this trial did not have placebo control, these results are presented separately below. However, the nature and number of AEs reported were similar to the pooled results of the 2 placebo-controlled trials, and there was no dose response in terms of AEs.

Table 43 Common adverse events (>2%): P04431

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

Source: Module 5, p04431-clin-study-report.pdf, Section 14.3.1.2

Trial P04139 was the 52 week long term safety trial that evaluated MF/F 200/10 and 400/10. F/SC 250/50 and 500/50 were included as active controls; no placebo group was included in this long term trial. The overall rate of AEs was higher, as might be expected with a trial of longer duration. The nature of AEs reported was similar to those observed in the 12-week efficacy trials, with headache, nasopharyngitis and pharyngitis, and bronchitis reported most commonly. AE rates across the treatment groups were similar. Common AEs (>5%) are displayed below in Table 44.

Table 44 Common adverse events (>5%): P04139, long-term safety trial

	MF/F 200/10 N=141	MF/F 400/10 N=130	F/SC 250/50 N=68	F/SC 500/50 N=65
Any AE	109 (77)	103 (79)	56 (82)	50 (77)
Headache	33 (23)	31 (24)	17 (25)	13 (20)
Nasopharyngitis	29 (21)	21 (16)	13 (19)	8 (12)
Bronchitis	17 (12)	20 (15)	14 (21)	7 (11)
Pharyngitis	15 (11)	11 (9)	9 (13)	9 (14)
Influenza	14 (10)	13 (10)	9 (13)	11 (17)
Rhinitis	7 (5)	7 (5)	8 (12)	1 (2)
Sinusitis	7 (5)	4 (3)	2 (3)	1 (2)
Upper respiratory tract infection	5 (4)	5 (4)	5 (7)	1 (2)
Viral upper respiratory tract infection	3 (2)	6 (5)	3 (4)	1 (2)
Rhinitis allergic	11 (8)	9 (7)	6 (9)	5 (8)
Pharyngolaryngeal pain	11 (8)	7 (5)	2 (3)	1 (2)
Dysphonia	7 (5)	5 (4)	5 (7)	2 (3)
Cough	8 (6)	2 (2)	4 (6)	2 (3)
Back pain	10 (7)	6 (5)	7 (10)	3 (5)
Arthralgia	7 (5)	4 (3)	3 (4)	3 (5)
Pyrexia	8 (6)	6 (5)	4 (6)	1 (2)
Abdominal pain	4 (3)	6 (5)	3 (4)	5 (8)
Abdominal pain upper	3 (2)	7 (5)	3 (4)	3 (5)
Aphthous stomatitis	3 (2)	3 (2)	4 (6)	-
Muscle spasms	2 (1)	3 (2)	2 (3)	4 (6)

Source: Module 5, p04139-clin-study-report.pdf, Section 14.3.1.2

Across all Phase 3 trials, the incidence of oral candidiasis was <2% for MF/F.

7.4.2 Laboratory Findings

In general, review of the laboratory test data did not identify any specific safety concerns. Given the negative findings and the heterogeneity of study designs and comparator arms, the application did not provide pooled analyses of these results but referred to the summary tables for the individual Phase 3 trials. For the purposes of this review, representative laboratory data from Trial P04334 for measures of central tendency and shifts from normal to abnormal are provided here. Only patients with a baseline value and at least one value during the treatment period were included. Results for individual marked outliers from any of the phase 3 trials are presented separately.

Hematology parameters

Analyses focused on measures of central tendency and shifts from normal to abnormal

No clinically relevant changes in median values for hematology parameters or differences among groups in terms of shifts from normal to abnormal were observed. Table 45 displays representative values from the pivotal efficacy and safety trial, P04334.

Table 45 Median hematology parameters: P04334

Parameter	MF/F 200/10 N=191	MF 200 N=192	F 10 N=202	Pbo N=196
HgB (g/L)				
Baseline	143	144	141	142
Post-baseline	140	143	141	140
Hct (v/v)				
Baseline	0.43	0.43	0.43	0.43
Post-baseline	0.42	0.43	0.42	0.42
RBC (10^{12}/L)				
Baseline	4.8	4.8	4.8	4.8
Post-baseline	4.7	4.8	4.8	4.8
WBC (10^9/L)				
Baseline	6.98	7.08	7.04	7.01
Post-baseline	6.90	6.85	7.07	6.73
Platelets (10^9/L)				
Baseline	263	263	280	266
Post-baseline	264	269	281	270
Neutrophils (10^9/L)				
Baseline	3.86	4.09	3.99	3.94
Post-baseline	4.05	3.81	4.01	3.77
Lymphocytes (10^9/L)				
Baseline	2.19	2.21	2.21	2.24
Post-baseline	2.08	2.10	2.18	2.15
Monocytes (10^9/L)				
Baseline	0.40	0.37	0.37	0.40
Post-baseline	0.39	0.18	0.40	0.37
Eosinophils (10^9/L)				
Baseline	0.19	0.19	0.19	0.23
Post-baseline	0.17	0.18	0.21	0.23
Basophils (109/L)				
Baseline	0.06	0.06	0.06	0.06
Post-baseline	0.05	0.05	0.06	0.05

Post-baseline at Week 26
Source: Module 5, study-report-p04334.pdf, Section 12.4.2.1

Outliers, marked outliers, and dropouts for laboratory abnormalities

In the Phase 3 program, 45 patients were noted to have laboratory values falling outside of the range of normal. The majority of these cases were small elevations in AST/ALT that were not clinically meaningful and were equally distributed across different treatment groups. The second most common abnormality was a lower hemoglobin value. No patients were discontinued from the trials secondary to these abnormalities.

In terms of marked outliers, the following patients were noted to have the following marked shifts from normal to abnormal during the treatment period:

- Patient P04431/125/000609 on MF 400 at Visit 7: platelet count 40 x10^9/L /L (130 x10^9/L to 394x10^9/L):
- Patient P04139/21/000358 on MF/F 400/10 at Visit 11: hemoglobin 65 g/L (116 to 164 g/L), platelet count 13 x10^9/L /L (140 x10^9/L to 400x10^9/L):

Chemistry parameters

Analyses focused on measures of central tendency and shifts from normal to abnormal

No clinically relevant changes in median values for chemistry parameters or differences among groups in terms of shifts from normal to abnormal were observed. Table 46 displays representative values from the pivotal efficacy and safety trial, P04334.

Table 46 Median chemistry parameters: P04334

Parameter	MF/F 200/10 N=191	MF 200 N=192	F 10 N=202	Pbo N=196
Sodium (mmol/L)				
Baseline	141	141	141	141
Post-baseline	141	141	141	141
Potassium (mmol/L)				
Baseline	4.3	4.3	4.2	4.3
Post-baseline	4.3	4.2	4.2	4.1
Chlorine (mmol/L)				
Baseline	103	104	104	104
Post-baseline	104	104	104	104
BUN (mmol/L)				
Baseline	4.6	4.9	4.6	4.6
Post-baseline	5.0	4.9	4.8	4.5
Creatinine (µmol/L)				
Baseline	76	71	71	73
Post-baseline	72	71	71	71
Calcium (mmol/L)				
Baseline	2.4	2.4	2.4	2.4
Post-baseline	2.4	2.4	2.4	2.4
Phosphorus (mmol/L)				
Baseline	1.1	1.1	1.1	1.1
Post-baseline	1.2	1.2	1.2	1.2
AST (U/L)				
Baseline	22	20	21	20
Post-baseline	21	20	20	19
ALT (U/L)				
Baseline	22	20	20	19
Post-baseline	20	20	20	18
Total bilirubin (µmol/L)				
Baseline	8.0	7.0	7.0	7.0
Post-baseline	8.0	7.0	7/0	7.0
Total protein (g/L)				
Baseline	73	74	73	74
Post-baseline	72	72	73	73
Albumin (g/L)				
Baseline	42	42	42	42
Post-baseline	41	41	41	41
LDH (U/L)				
Baseline	172	165	169	168
Post-baseline	171	167	167	168

Post baseline was intended as Week 26.
Source: Module 5, study-report-p04334.pdf, Section 12.4.2.1

Outliers, marked outliers, and dropouts for laboratory abnormalities

In the Phase 3 program, 45 patients were noted to have laboratory values falling outside of the range of normal. The majority of these cases were small elevations in AST/ALT that were not clinically meaningful and were equally distributed across different treatment groups. No patients were discontinued from the trials secondary to these abnormalities.

In terms of marked outliers, the following patients in the pivotal efficacy and safety trials were noted to have the following marked shifts from normal to abnormal during the treatment period:

- Patient P04334/169/04390 on F 10 at Visit 10: Total bilirubin 152 μmol/L (range 3 to 21 μmol/L)
- Patient P04431/125/000520 on MF/F 200/10 at Visit 7: Creatine kinase 771 U/L (range 0 to 190), GGT 132 U/L (range 0-49), triglycerides 9.89 mmol/L (0.65 to 3.29)

7.4.3 Vital Signs

Analyses focused on measures of central tendency and shifts from normal to abnormal

In general, review of the vital signs data did not identify any specific safety concerns. Given the negative findings and the heterogeneity of study designs and comparator arms, the application did not provide pooled analyses of these results but referred to the summary tables for the individual Phase 3 trials. For the purposes of this review, representative vital signs data from Trial P04334 for measures of central tendency and shifts from normal to abnormal are provided here. Only patients with a baseline value and at least one value during the treatment period were included. Results for individual marked outliers from any of the phase 3 trials are also presented.

Table 47 Median vital signs parameters: P04334

Parameter	MF/F 200/10 N=191	MF 200 N=192	F 10 N=202	Pbo N=196
Systolic BP (mmHg)				
Baseline	120	120	120	120
Post-baseline	120	120	120	120
Diastolic BP (mmHg)				
Baseline	78	75	78	75
Post-baseline	75	77	78	78
Respiratory rate (/min)				
Baseline	17	17	16	17
Post-baseline	17	17	17	17

Post baseline was intended as Week 26.
Source: Module 5, study-report-p04334.pdf, Section 12.5.1

Outliers, marked outliers, and dropouts for vital signs abnormalities

No patients on MF/F discontinued early due to vital signs abnormalities. Transient changes from normal to abnormal were observed for a few patients in all treatment arms, but the changes were not documented to be persistent or clinically relevant.

7.4.4 Electrocardiograms (ECGs)

No designated QT study was conducted for the MF/F program. A standard 12-lead ECG was obtained at Screening (Visit 1) and at the end of study for the pivotal Phase 3 efficacy trials (b) (4) P04334, and P04431) and the long-term safety trial. The ECGs were evaluated by the investigator but were processed by a central reader only in the long-term safety trial, P04139. No clinically significant changes were observed between baseline and followup in ventricular rate, PR, QRS, QTc, and QT intervals. No differences were observed between treatment groups. A summary of change from baseline for calculated QTc based on the Frediricia formula for P04431 is presented below.

Table 48 QTc interval change from baseline: P04139

				Change from baseline (msec)			
Treatment	**Baseline evaluations**	**N**	**Missing**	**<0**	**0 to 30**	**31 to 60**	**61 or more**
MF/F 200/10	Missing	1	1	0	0	0	0
	Normal	135	7	60	61	7	0
	Borderline	5	0	4	1	0	0
	Prolonged	0	0	0	0	0	0
	Overall	141	8	64	62	7	0
MF/F 400/10	Normal	128	6	57	62	3	0
	Borderline	2	0	1	1	0	0
	Prolonged	0	0	0	0	0	0
	Overall	130	6	58	63	3	0
F/SC 250/50	Normal	68	5	24	36	3	0
	Borderline	0	0	0	0	0	0
	Prolonged	0	0	0	0	0	0
	Overall	68	5	24	36	3	0
F/SC 500/50	Normal	63	1	29	32	1	0
	Borderline	1	0	1	0	0	0
	Prolonged	1	0	1	0	0	0
	Overall	65	1	31	32	1	0

Source: Module 5, study-report-p04139.pdf, Section 14.3.7.5

7.4.5 Special Safety Studies/Clinical Trials

P4703 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. Dose counter reliability poses a safety issue in the event of undercounting, which could lead to missed doses. 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.

7.4.6 Immunogenicity

Immunogenicity was not specifically assessed in the development program. Both mometasone and formoterol are small molecular entities which are 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 2 pivotal efficacy trials, do not indicate any apparent drug-disease interactions.

7.5.5 Drug-Drug Interactions

Study P03658 was an open-label, single-dose, crossover trial in 26 healthy subjects that assessed potential pharmacokinetic interactions between the MF and F components in combination. No significant drug interactions were observed, and systemic exposure to MF and F was similar when administered in combination as MF/F and when administered separately. This trial is reviewed in further detail in the Dr. Ying Fan's clinical pharmacology review. No other formal drug interaction studies with MF/F have been performed.

An earlier drug interaction study, I98-216-01, demonstrated that ketoconazole 200 mcg BID raised plasma concentrations of MF 400 DPI and decreased plasma cortisol levels, indicating that caution should be used when coadministering ketoconazole with mometasone.

In addition, the current approved package insert for Foradil Aerolizer notes that caution should be used when coadministering formoterol with quinidine, disopyramide, procainamide, phenothiazines, anithistamines, monoamine oxidase inhibitors, and tricyclic antidepressants or any drugs known the prolong the QTc interval, given the action of adrenergic agonists on the cardiovascular system. Also, concurrent administration of xanthine derivatives, steroids, or diuretics may potentiate the possible hypokalemic effects of formoterol. Similar caution is warranted with use of MF/F.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Specific evaluations for carcinogenicity were not conducted for this application. Mometasone and formoterol are both well known chemical entities which are not known to be carcinogenic.

7.6.2 Human Reproduction and Pregnancy Data

Specific evaluations of MF/F on reproduction and pregnancy have not been conducted. A total of 13 patients became pregnant while exposed to study treatment. The following updates were available.

- 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/F in pregnancy or lactation in humans is available. Information on the active mono-ingredients is available in the current Foradil and Asmanex product labels. The Foradil label notes that beta-agonists may potentially interfere with uterine contractility and should be used with caution in pregnancy. The Asmanex label notes that hypoadrenalism may occur in infants of mothers treated with systemic steroids during pregnancy. It is not known whether MF or F is excreted in human milk, although it has been established that other corticosteroids are excreted in human milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

In total, the full Phase 3 program and the 12-week dose-ranging trials enrolled 485 patients aged 12 to <18 years, of whom 186 had exposure to MF/F and which is comparable to the pediatric representation that has been seen in other ICS/LABA development programs (Table 49). Additional safety information was obtained from the patients treated with the MF and F monocomponents. The number of adolescent patients provides an adequate assessment of safety for this age subgroup, despite the lack of PK data.

Table 49 Patients 12 to <18 years of age in the Phase 3 and pivotal dose-ranging trials

	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	Pbo	Active control
Total	**63**	**89**	**34**	**16**	**37**	**34**	**41**	**9**	**2**	**40**	**61**	**59**
Phase 3												
(b) (4)												
P04334		19				10	22			18	16	
P04431		18	23									21
P04139		30	11									
P4703	35											
P4705		22										18
Phase 2 trials												
C97208				8		10	11	9			10	5
C97225				8		6					4	7
I97200					7	8	7					8
C97224							1		2		1	

Source: Collated from the respective CSRs in Module 5

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, but reduction in growth velocity is considered a potential adverse effect for all orally inhaled corticosteroids. The Asmanex package insert includes effect on growth in Section 5.7 Warnings and Precautions and recommends titration to the lowest effective dose. A similar recommendation for MF/F 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/F, MF, and F, although the limited sample size does not permit the exclusion of the risk of these events, which have been associated with chronic use of other LABA products.

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. Excessive beta adrenergic stimulation from the F component may result in angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia, as described in the current package insert for Foradil Aerolizer. In certain situations, treatment with a cardioselective beta-receptor antagonist may be warranted.

Given the mode of administration, the low systemic bioavailability, and the nature of the drug components, 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/F may theoretically precipitate an adrenal crisis.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 4-month safety update on September 22, 2009. The update contained safety information as of August 1, 2009, including follow-up on the outcome of one pregnancy reported during Trial P04334 which had previously been lost to follow-up. This information is described in Section 7.6.2. The safety update also referred to ongoing, blinded 52-week trials with MF/F in COPD and provided a list of SAEs reported in these trials. The nature of these SAEs was largely consistent with those expected in an older COPD population with chronic comorbidities and did not raise any new safety concerns for the use of MF/F in the proposed asthma population.

8 Postmarket Experience

MF/F is not approved for use in any country and no post-marketing experience is available. Post-marketing information is available for Asmanex and Foradil up to August 1, 2009. The application estimates worldwide patient exposure for Asmanex as 233,041,502 patient treatment days. The most frequently reported AES include: dyspnea, asthma, headache, cough, malaise, dysphonia, condition aggravated, rash, candidiasis, and pharyngolaryngeal pain. The list of AEs is generally consistent with the known safety profile for Asmanex described in the package insert.

For Foradil, the estimated patient exposure is 3.05 million treatment years. In asthma patients, AE reports have included viral infection, bronchitis, chest infection, dyspnea, chest pain, tremor, and dizziness. The list of AEs is generally consistent with the known safety profile for Foradil described in the package insert. The safety of LABAs in asthma remains the subject of ongoing discussion at the time of this review. Serious asthma-related outcomes (exacerbations requiring hospitalization, intubations, and death) have been suggested in large post-marketing trials, as discussed in Section 7.

9 Appendices

9.1 Literature Review/References

The application included a list of 12 clinical references. To supplement this list, the clinical review conducted a PubMed literature search [search terms: ("mometasone furoate asthma") and ("formoterol asthma safety"); limits: "English," "human"] which yielded 97 and 107 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 August 12, 2009. The Applicant seeks an indication for the (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older. The proposed PI contains a boxed warning regarding the risk of asthma-related death which has been associated with LABAs and notes that Dulera should only be used in patients who are not adequately controlled on other controller medications and whose disease severity warranted treatment with 2 maintenance therapies.

While a general indication for the treatment of asthma is supported for the MF/F 200/10 and 400/10 dose levels, the (b) (4) treatment of asthma is questionable given the concerns with the use of LABAs as a (b) (4) and the risk of serious asthma-related adverse events. As the appropriateness of LABAs as a (b) (4) is the subject of ongoing discussion in the Agency, the clinical review believes that the approval of an ICS/LABA combination for (b) (4) (b) (4) may be potentially problematic. For this reason, a more general asthma treatment indication is recommended.

(b) (4)

The PI also contains Warning and Precautions statements which are consistent with other ICS/LABA combinations: localized infections, immunosuppression, hypercorticism and adrenal suppression, paradoxical bronchospasm, decrease in bone mineral density, glaucoma and cataracts, effects on growth, caution due to beta-adrenergic stimulation, and hypokalemia and hyperglycemia. While these are

appropriate with class labeling, the clinical review also notes that eosinophilic disorders, i.e. Churg-Strauss syndrome has also been included on other ICS labels and would be an appropriate addition to the PI.

The following comments are in reference to specific sections of the PI:

- Section 6.1, Adverse Reactions, Clinical Trials Experience presents data for the 3 pivotal trials pooled together. (b) (4)
- Section 14.1, Clinical Studies, Study 1 (P04334)
  - (b) (4)
  - (b) (4) .
- (b) (4)
- Section 14.1, Clinical Studies, Study 3 (P04431)
  (b) (4)

9.3 Advisory Committee Meeting

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

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