NDA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	NDAs 22518/S-026 (Dulera) & 205641/S-010 Asmanex HFA
Priority or Standard	Priority
Submit Date(s)	February 12, 2019
Received Date(s)	February 12, 2019
PDUFA Goal Date	August 12, 2019
Division/Office	DPARP/ODE II
Review Completion Date	August 9, 2019
Established/Proper Name	mometasone furoate (MF); mometasone furoate + formoterol fumarate (MF/F)
(Proposed) Trade Name	Asmanex HFA®; Dulera®
Pharmacologic Class	Inhaled corticosteroid (ICS); ICS + long-acting β2-adrenergic agonist (LABA)
Applicant	Merck
Dosage form	Oral Inhalation
Applicant proposed Dosing Regimen	Asmanex: 50 mcg; 2 puffs twice daily (100 mcg twice daily) Dulera: 50 mcg/5 mcg; 2 puffs twice daily (100 mcg/10 mcg twice daily)
Applicant Proposed Indication(s)/Population(s)	Asmanex: Maintenance treatment of asthma as prophylactic therapy for patients 5 years of age and older Dulera: Treatment of asthma in patients aged 5 years of age and older.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Same as proposed
Recommended Dosing Regimen	Same as proposed

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jessica Lee, PharmD
Nonclinical Reviewer and Team Leader	Timothy Robison, PhD
Office of Clinical Pharmacology Reviewer(s)	Jing Niu, MD MS
Office of Clinical Pharmacology Team Leader(s)	Bavna Saluja, PhD
Clinical Reviewer	Natalie Pica, MD PhD
Clinical Team Leader	Miya Paterniti, MD
Statistical Reviewer	Jade Wang, PhD
Statistical Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Miya Paterniti, MD
Division Director	Sally Seymour, MD

Additional Reviewers of Application

OPQ	Chong Ho Kim
OPDP	Taylor Burnett/Kathleen Klemm
DMPP	Kelly Jackson/Marcia Williams/LaShawn Griffiths
OSE/DMEPA	Lissa Owens/Idalia Rychlik

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer and Supervisor	Timothy W. Robinson, PhD	ODEII/DPARP	Section: 5	**Select one:** _X_ Authored _X_ Approved
	Signature: Timothy W. Robison -S Digitally signed by Timothy W. Robison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300110610, cn=Timothy W. Robison -S Date: 2019.08.12 12:25:24 -04'00'			
Clinical Pharmacology Reviewer	Jing Niu, MD MS	OCP/DCPII	Section: 6	**Select one:** _X_ Authored _X_ Approved
	Signature: Jing Niu -S Digitally signed by Jing Niu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jing Niu -S, 0.9.2342.19200300.100.1.1=2002193111 Date: 2019.08.12 11:42:20 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Bavna Saluja, PhD	OCP/DCP2	Section: 6	**Select one:** ___ Authored _X_ Approved
	Signature: Bhawana Saluja -S Digitally signed by Bhawana Saluja -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bhawana Saluja -S, 0.9.2342.19200300.100.1.1=2000559312 Date: 2019.08.12 11:50:02 -04'00'			
Clinical Reviewer	Natalie Pica, MD, PhD	OND/DPARP	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 15	**Select one:** _X_ Authored _X_ Approved
	Signature: Natalie M. Pica -S Digitally signed by Natalie M. Pica -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002566393, cn=Natalie M. Pica -S Date: 2019.08.12 10:54:22 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Miya Paterniti, MD	OND/DPARP	Sections: 1-15	**Select one:** ___ Authored _X_ Approved
	Signature: Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour -S Date: 2019.08.12 13:41:13 -04'00' on behalf of Miya Paterniti			
Division Director (Clinical)	Sally Seymour, MD	OND/DPARP	Sections: 1-15	**Select one:** ___ Authored _X_ Approved
	Signature: Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour -S Date: 2019.08.12 13:42:53 -04'00'			
Statistical Reviewer	Jade Wang, PhD	OB/DBII	Sections: 8	**Select one:** _X_ Authored _X_ Approved
	Signature: Yu Wang -S Digitally signed by Yu Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yu Wang -S, 0.9.2342.19200300.100.1.1=2001185097 Date: 2019.08.12 10:57:27 -04'00'			
Statistical Team Leader	Yongman Kim, PhD	OB/DBII	Sections: 8	**Select one:** ___ Authored _X_ Approved
	Signature: Yongman Kim -S Digitally signed by Yongman Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yongman Kim -S, 0.9.2342.19200300.100.1.1=1300218531 Date: 2019.08.12 12:16:33 -04'00'			

Glossary

AE	adverse event
AUC	area under the curve
BID	twice a day
CSR	clinical study report
DPI	dry powdered inhaler
F	formoterol fumarate
FAS	Full Analysis Set
FDA	Food and Drug Administration
HFA	hydrofluoroalkane
HPA	hypothalamic-pituitary-adrenal axis
ICS	inhaled corticosteroid
IND	Investigational New Drug
ISR	incurred sample reanalysis
LABA	long acting beta$_2$-adrenergic agonist
LS	least squares
MDI	metered-dose inhaler
MF	mometasone furoate
MF/F	mometasone furoate + formoterol fumarate
NDA	new drug application
PAQLQ[S]	Pediatric Asthma Quality of Life Questionnaire with standardized activities
PK	pharmacokinetics
PMR	postmarketing requirement
PP	per protocol
SABA	short acting beta agonist
SAE	serious adverse event
sNDA	supplemental new drug application
TEAE	treatment emergent adverse event

1 Executive Summary

1.1 Product Introduction

Asmanex HFA metered dose inhaler (MDI) is an inhaled corticosteroid (ICS) inhalation product approved for the treatment of asthma. It is available in two dose strengths, 100 mcg and 200 mcg of mometasone furoate per actuation. The approved dosage is two actuations twice daily.

Dulera is an ICS/long acting beta$_2$-adrenergic agonist (LABA) inhalation product containing mometasone furoate and formoterol fumarate dihydrate. It is available in two dose strengths, 100 mcg and 200 mcg of mometasone furoate (MF) with 5 mcg of formoterol fumarate (F) per actuation. The approved dosage is two actuations twice daily.

Both Asmanex and Dulera are approved for the treatment of asthma in patients 12 years of age or older. The Applicant has submitted prior approval supplements for the use of these two products in pediatric patients aged 5 to 11 years of age. The Applicant proposes a new dose strength of 50 mcg per actuation, with a dosage of two inhalations twice daily.

While the Applicant submitted two separate efficacy supplements (supplement 10 to NDA 205641 for Asmanex and supplement 26 to NDA 22518 for Dulera), this document will serve as a combined review of the submitted materials, given that both products share the same ICS component and were evaluated for efficacy and safety together in a 24-week, phase 3 clinical trial.

For the remainder of this review, Asmanex HFA MDI will be referred to as MF and Dulera MDI as MF/F. When discussing dose, the total amount given at the time of administration will be specified (i.e. two actuations of 50mg MF twice daily will be referred to as 100 mg MF BID).

1.2 Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action from a clinical and statistical perspective is approval of the supplemental NDAs 205641 and 22518. This approval expands the indication of both MF and MF/F to include treatment of patients age 5 to 11. To support the expanded indication, the Applicant submitted efficacy data from Trials P086 and P087. Trial P086 was a 12-week, randomized, double-blind, placebo-controlled, dose-ranging study of MF MDI that randomized 583 children ages 5 to 11 with persistent asthma. Treatment with MF 100 mcg twice daily resulted in a statistically significant change from baseline in percent predicted FEV1 at week 12 compared to placebo. Trial P087 was a 24-week, randomized, double-blind, active-controlled, parallel-group study that demonstrated improvement in FEV1 (area under the curve (AUC) 0 to 60 minutes) through week 12 in pediatric patients aged 5-11 treated with MF and MF/F, with additional benefit seen with the ICS/LABA combination compared to the ICS alone.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

MF, an inhaled corticosteroid (ICS), and MF/F, an ICS and long-acting beta-agonist (LABA) combination product, are approved for the treatment of asthma in patients 12 years and older. The Applicant submitted efficacy supplements for both products to expand the indication to include treatment of patients 5 to 11 years of age. The Applicant is proposing a new dose of 100 mcg of MF and 10 mcg of F (administered as two actuations of a 50 mcg of MF or 50 mcg/5 mcg of MF/F metered-dose inhaler (MDI)) in patients aged 5 to 11 years.

The Applicant is providing data from four clinical trials to support this new pediatric indication. Trials P06476, P086 and P087 support efficacy and safety; Trial C96-361 provides additional safety data. Trial C96-361 was originally conducted to provide support for approval of MF DPI (Asmanex Twisthaler, NDA 21067) and includes data regarding the systemic effects of MF on the HPA axis in children. Trial P06476 was a randomized, evaluator-blind, single-dose, placebo-controlled, crossover study used to confirm the F dose in 92 children ages 5-11 years old. Trials P086 and P087 were conducted as pivotal safety and efficacy studies. Trial P086 was a phase 2, 12-week, randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study of MF MDI that randomized 583 children ages 5 to 11 with persistent asthma. Data from Trial P086 supported the proposed dose of MF 100 mcg twice daily by demonstrating a statistically significant change from baseline in percent predicted FEV1 at week 12 compared to placebo. Trial P087 was a multi-center, randomized, double-blind, active-controlled, parallel-group study in 181 children ages 5-11 years who were already receiving ICS/LABA therapy. Data from Trial P087 demonstrated a statistically significant change in FEV1 (area under the curve (AUC) 0 to 60 minutes) through week 12 compared to MF, which supported the additional benefit of the LABA over the ICS alone. The type and frequencies of common adverse events were similar to what is reported for adolescents and adults and was consistent with the known safety profile of other ICS and ICS/LABA products.

Overall, the data submitted by the Applicant supports a favorable benefit-risk assessment for the new pediatric indication of MF 100 mcg twice daily and MF/F 100/10 mcg twice daily in 5-11 year olds.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. Episodic increases in symptoms are referred to as asthma exacerbations. The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma, especially in the context of poorly controlled asthma. Severe exacerbations require emergency medical care and may even lead to hospitalization or death.	Asthma is a common condition. Patients can experience symptoms that are severe and life-threatening. Exacerbations can also impact patient's quality of life. Symptomatic control is important to protect against morbidity and mortality.
Current Treatment Options	Current treatment strategies aim to control symptoms, reduce impairment, and prevent exacerbations. There are several approved ICS and ICS/LABA products, though many are approved only for adults and adolescents.	Current treatment strategies aim to control symptoms, reduce impairment, and prevent exacerbations. ICS and ICS/LABA therapies are known to be effective treatment options for maintenance therapy.
Benefit	The effectiveness of MF 100 mcg twice daily and MF/F 100 mcg/10 mcg twice daily in patients 5 to 11 years old has been demonstrated in clinical trials, showing a change from baseline in percent predicted FEV1 through 12 weeks. The endpoints used were appropriate and clinically relevant.	The evidence submitted by the Applicant to support pediatric approval has met the statutory evidentiary standard for providing substantial evidence of effectiveness for the proposed age group of 5 to 11 years old.
Risk and Risk Management	No new safety concerns were identified. Safety issues identified *a priori* include known drug safety concerns for ICS and ICS/LABA products. Headache, oral/oropharyngeal candidiasis, and bronchospasm were seen in subjects using MF or MF/F MDI in Trial P086 and P087, though at low incidence.	A comprehensive review of safety data did not reveal new safety concerns. The risk of oral/oropharyngeal candidiasis can be mitigated through labeling and patient education.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		Section 8.2.6
		x	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify): Pediatric		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1 Analysis of Condition

Asthma is a chronic respiratory disease that affects over 26 million Americans, including over six million children [1]. Asthma is associated with airflow obstruction as well as symptoms of cough, shortness of breath, wheezing, and chest tightness that is caused by airway inflammation [2, 3]. Bronchoconstriction, as well as airway hyperresponsiveness and edema, are also seen [4]. Current treatment strategies aim to control symptoms, reduce impairment, and prevent exacerbations.

2.2 Analysis of Current Treatment Options

Asthma treatment focuses on a step-wise approach to achieve symptom control. There are six approved classes of asthma maintenance therapies (Table 1). Several ICS and ICS/LABA combination medications are approved for use in children younger than 12 years of age. Of note, mometasone furoate formulated as a dry powdered inhaler (DPI) is approved for the treatment of asthma in patients 4 years of age and older as the Asmanex Twisthaler (NDA 021067). It will be referred to as MF DPI for the remainder of the review.

Table 1: Maintenance Asthma Treatment Armamentarium

Class	Generic Name	Brand Name	Approved Age*
ICS	Flunisolide	Aerospan HFA	≥ 6 years old
	Ciclesonide	Alvesco HFA	≥ 12 years old
	Fluticasone furoate inhalation powder	Arnuity Ellipta	≥ 5 years old
	Mometasone	Asmanex HFA	≥ 12 years old
	Mometasone inhalation powder	Asmanex Twisthaler	≥ 4 years old
	Fluticasone propionate inhalation powder	Flovent Diskus	≥ 4 years old
	Fluticasone propionate	Flovent HFA	≥ 4 years old
	Budesonide inhalation powder	Pulmicort Flexhaler	≥ 6 years old
	Budesonide inhalation suspension	Pulmicort respules	12 months – 8 years
	Beclomethasone dipropionate	QVAR HFA	≥ 4 years old

Class	Generic Name	Brand Name	Approved Age*
ICS/LABA	Fluticasone propionate/salmeterol inhalation powder	Advair Diskus	≥ 4 years old
	Fluticasone propionate/salmeterol HFA	Advair HFA	≥ 12 years old
	Fluticasone propionate/salmeterol	AirDuo RespiClick	≥ 12 years old
	Fluticasone furoate/vilanterol inhalation powder	Breo Ellipta	≥ 18 years old
	Mometasone/formoterol HFA	Dulera	≥ 12 years old
	Budesonide/formoterol fumarate	Symbicort HFA	≥ 6 years old
Immunomodulators	Benralizumab (anti-IL5)	Fasenra	≥ 12 years old
	Reslizumab (anti-IL5)	Cinqair	≥ 18 years old
	Dupilumab (anti-IL4 receptor antagonist)	Dupixent	≥ 12 years old
	Mepolizumab (anti-IL5)	Nucala	≥ 12 years old
	Omalizumab (anti-IgE)	Xolair	≥ 6 years old
LAMA	Tiotropium bromide inhalation powder	Spiriva Respimat	≥ 6 years old
Leukotriene modifiers	Montelukast	Singulair	≥ 12 months old
	Zafirlukast	Accolate	≥ 5 years old
	Zileuton	Zyflo	≥ 12 months old
Xanthines	Theophylline	Multiple including Theo-24, Theochron, Elixophyllin	children and adults

Abbreviations: DPI: Dry powder inhaler; HFA: hydrofluroalkane
*Approved age for asthma indication.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

MF and MF/F are currently approved for asthma maintenance therapy in patients over 12 years of age. MF was developed under IND 52214 and approved on April 25, 2014, under NDA 205641. MF/F was developed under IND 70283 and approved on June 22, 2010, under NDA 22518.

3.2 Presubmission/Submission Regulatory Activity

Following approval of MF and MF/F, postmarketing requirements (PMRs) were issued for children 5 to 11 years of age. The requirement of studies in ages 0 to 4 years were waived as use is limited and likely not beneficial in this age group.

3.2.1 Correspondence Related to PMRs

The PMRs issued at the time of each approval are summarized below:

PMRs for MF:

- 2149-1: A 12-week, randomized, placebo-controlled, dose-ranging efficacy and safety study of MF metered dose inhaler (MDI) in the treatment of children ages 5 to 11 years with persistent asthma.
- 2149-2: A 12-week, double-blind, active-controlled, efficacy and safety study of two doses of MF/F combination MDI compared with the corresponding doses of MF monotherapy MDI in the treatment of children ages 5 to 11 with persistent asthma.
- 2149-3: A 6-month safety study, with a 6-month extension of two doses of MF/F MDI compared to fluticasone/salmeterol combination DPI in children 5 to 11 years of age with persistent asthma.

PMRs for MF/F:

- 1658-1: Compare the pharmacodynamics of MF/F with and without a spacer in children 5 to 11 years of age.
- 1658-2: Compare the pharmacokinetics of MF/F with and without a spacer in children 5 to 11 years of age.
- 1658-3: Evaluate the effects of MF/F on the hypothalamic-pituitary-adrenal (HPA) axis in children 5 to 11 years of age. In lieu of an HPA axis study, robust data to demonstrate that the systemic exposure of MF from MF/F is comparable or lower than that from the MF DPI may be provided.
- 1658-4: Evaluate the safety and efficacy of multiple doses of MF MDI in children 5 to 11 years of age with asthma.
- 1658-5: Evaluate the safety and efficacy of MF/F compared to MF MDI in children 5 to 11 years of age with asthma.

On March 1, 2012, the Applicant submitted a revised pediatric plan and requested to be released from PMR 1658-2. Because the Agency did not require formal studies involving the use of the spacer, the Applicant no longer wished to conduct these trials. The request was ultimately granted by the Agency on July 24, 2012. Following the submission of data from trial P06476, the FDA notified the Applicant that 1658-1 had been fulfilled.

At the time of issuance of 1658-3, the Division stated that data relating to the systemic exposure of MF DPI in children may be used in lieu of an additional HPA axis trial. Using data collected in support of MF DPI for pediatric use, it was reasoned that MF and MF/F MDI was unlikely to cause HPA axis suppression and that an additional HPA axis trial was not needed; therefore, on November 2, 2012, the Agency released PMR 1658-3.

With the intent to streamline the pediatric PMRs for the two related products, PMRs 2149-2, 2149-3, 1658-5, and 1658-6 were released and replaced with 2149-4 and 1658-7 on January 7, 2015 (listed below).

2149-4/1658-7	Conduct a study to evaluate the efficacy and long-term safety of mometasone furoate/formoterol fumarate combination MDI (Dulera) and mometasone furoate MDI (Asmanex) in children 5 to 11 year of age

On July 12, 2016, the Applicant was notified by the Agency that PMRs 2149-1 and 1658-4 had been fulfilled following their submission of an efficacy supplement containing study results from Trial P086.

Advice on pediatric programs relating to the completion of the outstanding PMRs with a single trial was communicated via Type C meetings in November 2014 and July 2015. The meeting minutes document the following:

- Evaluation of one dosage strength of MF/F in the pivotal phase 3 efficacy and safety study (P087) is reasonable with the dose chosen from the MF dose-ranging trial.
- The following specific parameters in P087 were found to be reasonable including:
    - Enrolling patients with persistent asthma adequately controlled on ICS/LABA
    - Randomizing 165 patients 5 to 11 years of age, of whom 20% will be age 5 to 7 years
    - FEV1 AUC (0 to 60 min) averaged across the 12-week treatment as the primary efficacy assessment. Serial FEV1 time curves beyond 60 minutes at baseline and at Week 12 were recommended to provide additional support
- The Applicant could consider conducting a shorter safety extension (total of 6 months of double-blinded, placebo-controlled data) given ongoing concerns regarding titration of asthma therapy and the available safety data.
- The Division concurred with the proposed study design including primary endpoint, and study length for P087 pending review of the data.
- Evaluation of the MF 100 mcg and MF/F 100 mcg/10 mcg formulation twice a day (BID) in P087 was reasonable based on the results of the MF dose ranging Trial P086.

Issues regarding content, format, and regulatory deliverables related to the submission of the supplemental NDA were communicated via a Type C meeting on June 27, 2018.

At the time of submission of the current pediatric efficacy supplements for MF and MF/F, there were two outstanding PMRs, 2149-4 and 1658-7. The Applicant has submitted results from P087 to fulfill the outstanding PMRs, which were ultimately fulfilled.

3.2.2 Correspondence Related to Pediatric Written Request

Following multiple interactions between the Agency and the Applicant, a Proposed Pediatric Study Request was submitted for Dulera on March 20, 2012, with a Written Request issued on July 23, 2012. The Applicant declined this Written Request on January 13, 2013, but submitted a proposal to amend the Written Request on March 30, 2017. The Agency then issued a Written Request on December 4, 2017, which was ultimately accepted by the Applicant on January 25, 2018.

The accepted Written Request is summarized below:

Description of clinical study: A randomized, double-blind, parallel-group, 12-week study with a 12-week safety extension evaluating the efficacy and safety of one dose of MF/F MDI compared to the corresponding dose of MF MDI in pediatric patients ages 5 to 11 years who are symptomatic on ICS

Objective of the study: To demonstrate the efficacy and safety

Age group: Children aged 5 to 11 years

Patients to be studied:

- The study will include a sufficient number of enrolled patients to produce a sample size adequately powered for detecting treatment differences between the two products based on estimates of the effect size of the primary efficacy endpoint.
- Approximately 20% or more of randomized patients should be children under the age of 8 years and approximately evenly distributed between the ages of 5 and 8.
- Patients should remain on their assigned, blinded treatment arms for the 24-week duration of the study.
- The study will include a sufficient number of patients to complete a safety database of at least 80 patients with exposure to Dulera and 80 to Asmanex for 24 weeks.
- The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.

- *Study endpoints:*
  - Change from baseline in AM post-dose percent predicted FEV1 (ppFEV1)

- Serial post-dose spirometric measures should also be evaluated and blood samples should be collected for measuring mometasone furoate plasma concentration in a subset of patients.

- *Safety monitoring:* Monitoring for known ICS and LABA safety concerns must be performed.

Following review by the Division and the Pediatric Exclusivity Board, it was determined that Trial P087 met all the requirements of the Written Request and Pediatric Exclusivity was granted. See Section 10 for more details.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations

Office of Scientific Investigations (OSI) inspections were not conducted for these supplements as OSI inspections are not routinely performed for pediatric supplements.

4.2 Product Quality

With this supplement, the Applicant introduced a new dosage strength of MF (50 mcg per actuation) and MF/F (50 mcg of MF and 5 mcg of F per actuation). Cross-reference is made for NDA 205641 to NDA 22518 for the MF and F chemistry, manufacturing, and control drug substance information as there are no changes to the drug substances with this application. The data provided in the supplement support the conclusion that the proposed control strategy for the new presentation combined with in process, release, and stability testing ensure process consistency and drug substance, (b) (4), and drug product with appropriate quality attributes. The Office of Pharmaceutical Quality recommends approval.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

There are complete nonclinical programs for MF and F. Nonclinical studies were also conducted with the combination of MF/F. These programs include inhalation toxicology studies in rats and dogs.

- Multiple target organs were observed in rats and dogs treated with mometasone furoate by the inhalation route. Findings included lymphoid depletion in bronchial-

associated lymphoid tissue and gut-associated lymphoid tissue, thymus, spleen, and lymph nodes (bronchial, mandibular, and mesenteric), and atrophy of the adrenal cortex.

- Increased heart rate was evident in dogs treated with F by the inhalation route. Increased heart rates were more pronounced at the beginning of the study. However, increases of heart rate were smaller as the study progressed, which was attributed to tachyphylaxis.
- In studies with the combination of MF/F, observed effects were generally consistent with the individual monoproducts. Most observed effects were attributed to MF.
- Rats and dogs were highly sensitive to the effects of MF and it was not possible to establish no-observed-adverse-effect-levels (NOAELs) in either species. Dogs were highly sensitive to the cardiac effects of F and NOAELs tended to be lower than proposed clinical doses. In general, the effects of MF and F were considered to be monitorable in the clinical setting.

The existing nonclinical programs with MF and F, as well as nonclinical studies with the combination of the two agents, were considered adequate to support clinical trials in pediatric patients aged 5 to 11 years. For inhalation drug products, inhalation toxicology studies with juvenile animals are not typically requested until the proposed patient population is less than 2 years of age. No additional nonclinical studies were requested.

6 Clinical Pharmacology

6.1 Executive Summary

The Applicant has submitted NDA 22518/S-026 and NDA 205641/S-010 seeking to extend the age of approval for MF and MF/F MDI for treatment of asthma from 12 years down to 5 years.

MF is approved at doses of 200 mcg and 400 mcg administered BID for the treatment of asthma in adults and adolescents aged 12 years and older. The proposed dose of Asmanex for the treatment of pediatric subjects with asthma aged 5 to 11 years of age, the proposed dosage is 100 mcg BID

MF/F is approved at doses of mometasone furoate/formoterol fumarate dihydrate 200/10 mcg and 400/10 mcg administered twice daily (BID) for the treatment of asthma in adults and adolescents aged 12 years and older. The proposed dose of MF/F for the treatment of pediatric subjects with asthma aged 5 to 11 years is 100/10 mcg BID.

The Clinical Pharmacology information of these supplemental NDAs contains pharmacokinetic (PK) data for MF from one phase 3 efficacy and safety trial in pediatric patients aged 5 to 11 years with persistent asthma (Trial P087). Due to failure of incurred sample reanalysis (ISR) for MF, the MF PK parameters (C_{max} and AUC) in patients aged 5 to 11 years old derived from the data collected from participants in the PK sub-trial cannot be included (b) (4) (b) (4).

6.2 Summary of Clinical Pharmacology Assessment

- The doses of MF and F in pediatric patients aged 5 to 11 years of age has been adequately explored. Prior to the confirmatory phase 3 trial (Trial P087), two dose finding trials (Trials P086 and P06476 for MF and F, respectively) were conducted in pediatric patients with asthma. Therefore, a dose of MF 100 mcg BID and F 10 mcg BID were selected for confirmation in the phase 3 program.
- Due to the ISR failure for the bioanalytical method used for determination of MF, the pharmacokinetic data (C_{max} and AUC) for MF from patients aged 5 to 11 years is not acceptable for inclusion (b) (4) (b) (4).

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Attributes of the Drug

MF is a corticosteroid having the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16 (alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) with the following chemical structure:

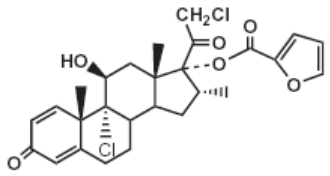


Figure 1: Molecular structure of mometasone furoate

Asmanex HFA 50 mcg, 100 mcg, and 200 mcg are each formulated as a hydrofluoroalkane (HFA-227: 1,1,1,2,3,3,3-heptafluoropropane) propelled pressurized metered dose inhaler containing sufficient amount of drug for 120 actuations. The 50 mcg strength is formulated for children 5 to 11 years of age.

MF/F is a fixed-dose combination product. MF is a corticosteroid demonstrating potent anti-inflammatory activity, and F is a long-acting selective beta2-adrenergic receptor agonist (beta2-agonist) having the chemical name of (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate with the following chemical structure:

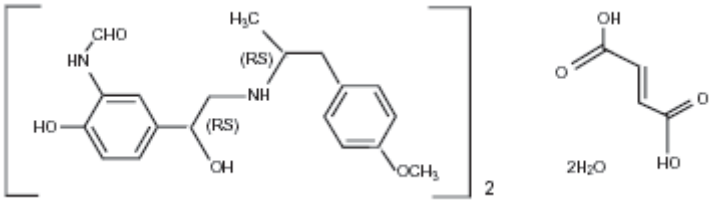


Figure 2: Molecular structure of formoterol fumarate

DULERA 50 mcg/5 mcg, 100 mcg/5 mcg, and 200 mcg/5 mcg are each formulated as a hydrofluoroalkane (HFA-227; 1, 1, 1, 2, 3, 3, 3-heptafluoropropane) propelled pressurized metered dose inhaler containing sufficient amount of drug for 60 or 120 inhalations. The 50 mcg/5 mcg strength is formulated for children 5 to 11 years.

6.3.2 Clinical Pharmacology Related Regulatory History

The Applicant was released from PMR 1658-3, a PMR requiring assessment of the effect of MF on the HPA axis in children 5 to 11 years of age because of the following:

- MF/F, up to a dose of 800 mcg twice daily in adults, consistently leads to lower systemic exposure of MF than the approved single component MF DPI product, Asmanex Twisthaler, at the same doses, in 3 different multiple-dose PK studies. The same trend can be expected in children dosed with either MF or MF/F MDI, at similar doses, as MF is primarily metabolized by CYP3A4 enzyme for which the expression is reported to be comparable between adults and children >4 years of age.
- Systemic exposure of MF from MF/F MDI 100/10 mcg BID in children 5 to 11 years is

expected to be much lower as compared to Asmanex Twisthaler 440 mcg BID, for which HPA axis data is already available.

Please refer to the Clinical Pharmacology review by Dr. Sheetal Agarwal for additional details (submitted to IND 70283 on October 18, 2012).

HPA axis labeling for children 5 to 11 years of age for MF and MF/F MDI will be based on HPA axis information included in the prescribing information for MF DPI product (Asmanex Twisthaler).

6.3.3 Clinical Pharmacology Questions

6.3.3.1 What are the clinical studies submitted to support this supplemental NDA?

Three clinical trials have been completed as part of the pediatric asthma clinical development program:

- **Trial P087:** A Phase 3, Randomized, Active-Controlled, Parallel-Group Clinical Trial to Study the Efficacy and Long-Term Safety of Mometasone Furoate / Formoterol Fumarate (MF/F, MK-0887A [SCH418131]), Compared with Mometasone Furoate (MF, MK-0887 [SCH032088]), in Children with Persistent Asthma
- **Trial P086:** A 12-Week, Randomized, Placebo-Controlled, Dose-Ranging, Efficacy and Safety Study of Mometasone Furoate Metered Dose Inhaler in the Treatment of Children Ages 5 to 11 Years with Persistent Asthma
- **Trial P06476:** A Randomized, Evaluator-Blind, Crossover, Single Dose Study of the Bronchodilator Effect of Formoterol Fumarate in Combination with Mometasone Furoate Metered Dose Inhaler Delivered with and Without a Spacer Versus Placebo and Foradil® Aerolizer® in Children Aged 5 to 11 Years with Persistent Asthma

6.3.3.2 What are the key features of the clinical studies used to support dosing of mometasone furoate and formoterol?

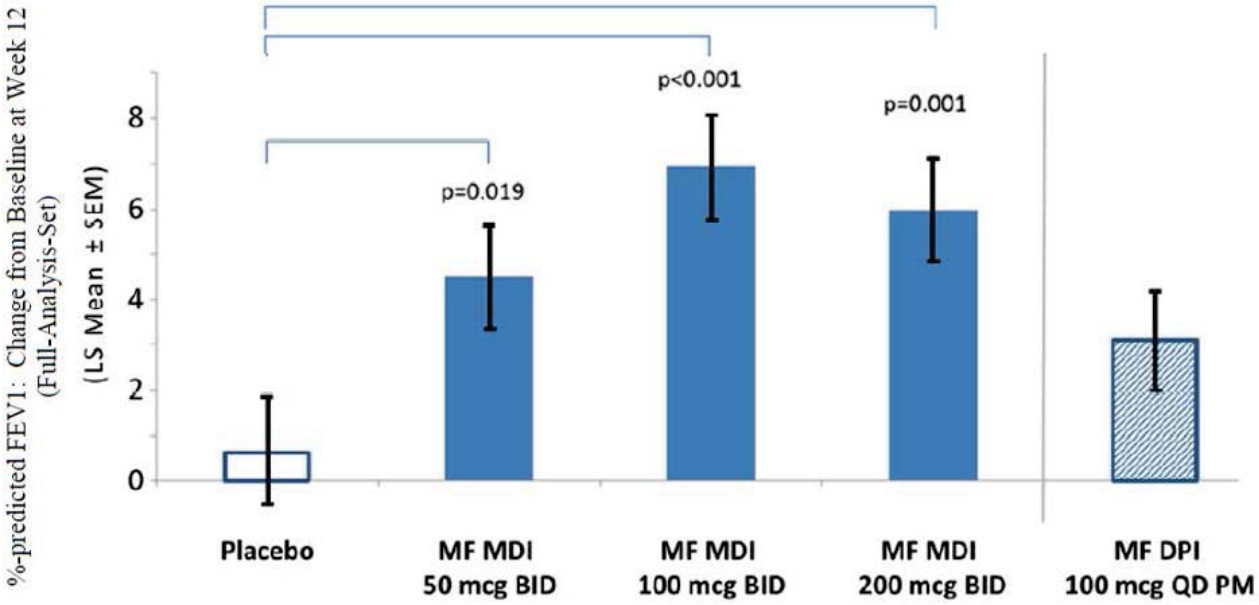
Trials P086 and P06476 were previously submitted by the Applicant to fulfill prior PMRs and are also being submitted to support dosing of MF and F in children 5 to 11 years, respectively.

Trial P086 was a phase 2, 12-week, randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study of MF MDI in children 5 to 11 years of age with persistent asthma. In Trial P086, MF 50 mcg BID, 100 mcg BID, and 200 mcg BID via MDI were compared with placebo and MF 100 mcg daily via DPI. The primary endpoint was the change in percent-predicted FEV1 from baseline at Week 12. All three MDI treatment arms (i.e., MF 50, 100 and 200 mcg BID) showed an increase with respect to the primary endpoint of percent-predicted FEV1 from baseline after 12 weeks of treatment compared to placebo. The 100 mcg BID dose provides a numerically superior benefit over the 50 mcg BID dose, with no additional benefit observed

with the higher 200 mcg BID dose (Figure 3). Additionally, all three MDI treatment arms demonstrated a greater numeric benefit compared to the approved MF DPI dose in children 5 to 11 years of age (MF DPI 100 mcg every evening). Therefore, the 100 mcg BID MF dose was carried forward into the phase 3 program.

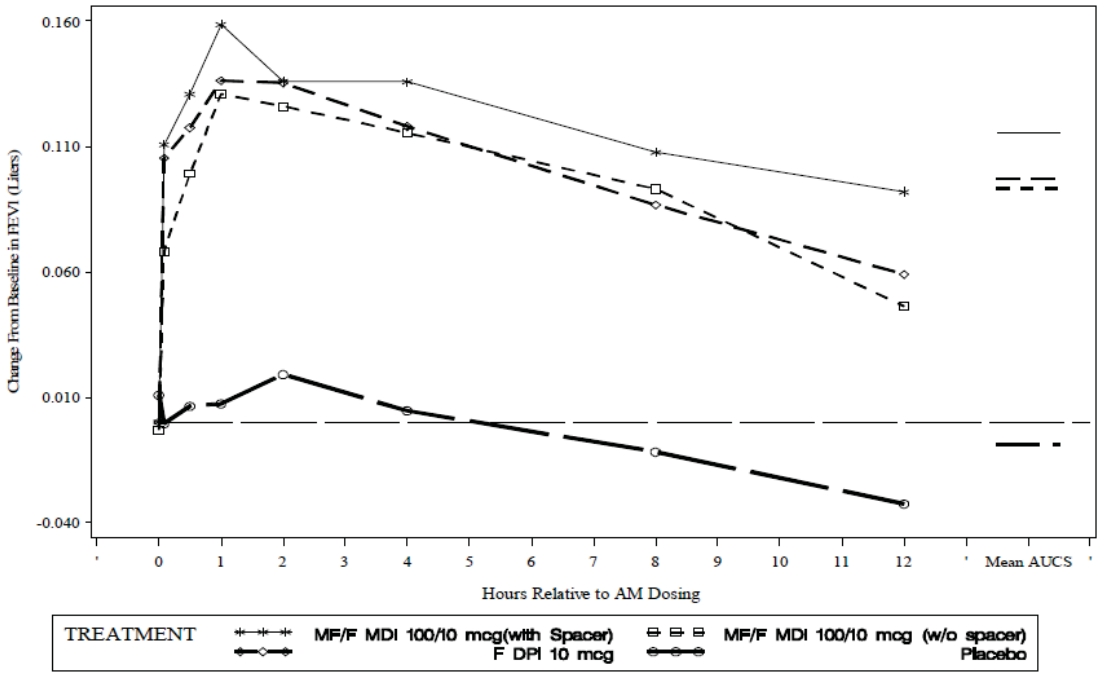
Trial P06476 was a randomized, evaluator-blind, single-dose, placebo-controlled, cross-over study used to confirm the formoterol dose in children 5-11 years of age. Participants received formoterol DPI 12 mcg (10 mcg delivered dose), MF/F MDI 100/10 mcg with and without a spacer, and placebo MDI with and without a spacer. The primary endpoint was the FEV1 $AUC_{(0\text{-}12\ hr)}$ following a single dose of study medication. Single dose of MF/F 100/10 mcg and F DPI demonstrated numerically better bronchodilation compared to placebo. No clinically meaningful differences in bronchodilator activity were observed between MF/F delivered with or without a spacer device. The MF/F MDI treatment arm also showed comparable bronchodilator activity compared to the F DPI 12 mcg (Figure 4).

Figure 3: Change from Baseline of ppFEV1 at Week 12, Trial P086 (Full Analysis Set)



Source: CSR for Trial P086, Figure 2-1, page 12

Figure 4: Serial Evaluations (0-12 hr) of FEV1 – Change from Baseline by Treatment, Trial P06476



Source: Figure 2 of CSR of P06476

6.3.3.3 What are the PK parameters of MF in pediatric patients aged 5 to 11 years?

The systemic exposure to MF in pediatric patients with asthma aged 5 to 11 years old was investigated in Trial P087.

Trial P087 was a phase 3, randomized, double-blind, active-controlled, parallel-group study to assess the efficacy and long-term safety of MF/F, compared with MF in pediatric patients. Pharmacokinetic data collected from participants in the PK sub-trial supported characterization of MF PK profiles and parameter values in children with persistent asthma.

Plasma PK profiles and PK parameters (eg, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}last}$, C_{max}, and T_{max}) for MF were characterized at steady state after multiple oral inhalations from MF/F MDI or MF MDI in children with persistent asthma. Based upon a pooled analysis of the treatments (MF/F and MF), the geometric mean $AUC_{0\text{-}12h}$, $AUC_{0\text{-}last}$ and C_{max} were 109 hr*pg/mL, 106 hr*pg/mL and 16 pg/mL, respectively, with moderate variability (GCV%) between approximately 54-68% (Table 2).

Due to the ISR failure (refer to section 6.4 for details), systemic exposure (C_{max} and AUC) for MF cannot be reliably estimated using PK data from Trial P087 (b) (4) (b) (4).

Despite the ISR failure, the reviewer considers that the original PK measurements may reflect the systemic MF plasma concentrations following oral inhalation of MF/F and MF MDI relative to the MF DPI (Asmanex Twisthaler). Across the 12-hour dosing interval, 89% of MF concentrations were less than 20 pg/mL and all MF concentrations across all PK sampling time points were less than 40 pg/mL, with the exception of a single concentration value (40.3 pg/mL). The observed MF concentrations were lower than those achieved with MF DPI (Asmanex Twisthaler) at similar doses; the C_{max} at steady state following multiple oral inhalations of 110 mcg BID dose from MF DPI in part of the study population was higher than 50 pg/mL (HPA axis Trial C96-361; cross study comparison). This observation is consistent with the findings in adults (Table 3); the systemic levels of MF from the MF/F MDI were consistently lower than the MF DPI (Asmanex Twisthaler) at the same nominal doses.

The Applicant conducted a dedicated HPA axis study (Study C96-361) which was reviewed previously by Dr. Wei Qui (submitted to NDA 21067 on December 5, 2007). Trial C96-361 was a 29 day, randomized, double-blind, placebo-controlled parallel-group clinical trial conducted in 50 children aged 6 to 11 years. HPA axis function was evaluated by 12-hour plasma cortisol $AUC_{0\text{-}12h}$ and 24-hour urinary free cortisol levels. Following 29 days of treatment, the mean difference from placebo in plasma cortisol $AUC_{0\text{-}12h}$ changes from baseline for the 110 mcg BID, 220 mcg BID and 440 mcg BID treatment groups were 3.4 mcg.hr/dL (95% CI: -14.0, 20.7), -16.0 mcg.hr/dL (95% CI: -33.9, 1.9), and -17.9 mcg.hr/dL (95% CI: -35.8, 0.0), respectively. The mean placebo corrected differences in change from baseline in 24-hour urinary free cortisol level for the 100 mcg BID, 200 mcg BID, and 400 mcg BID treatment groups were 3.1 mcg/day (95% CI: -3.3, 9.6), 3.3 mcg/day (95% CI: -3.0, 9.7), and -2.0 mcg/day (95% CI: -8.6, 4.6), respectively.

Table 2: Summary Statistics of Steady-State (Week 12) Plasma MF Pharmacokinetic Parameter Values Following BID Oral Inhalations of MF/F 100/10 mcg or MF 100 mcg to Pediatric Participants, Trial P087

PK Parameter	Mometasone Furoate/ Formoterol fumarate (MF/F) MDI 100/10 mcg BID	Mometasone Furoate (MF) MDI 100 mcg BID	Pooled MF/F MDI 100/10 mcg and MF MDI 100 mcg
AUC_{0-12} (hr·pg/mL)			
N	4	6**	10
Arithmetic Mean (SD)	148 (21.4)	103 (59.4)	121 (51.4)
Geometric Mean (GCV%)	146 (14.2)	89 (65.8)	109 (55.8)
Median (Min-Max)	144 (125- 177)	79 (36- 195)	134 (36- 195)
AUC_{0-last} (hr·pg/mL)			
N	4	7	11
Arithmetic Mean (SD)	148 (21.8)	101 (54.9)	118 (50.1)
Geometric Mean (GCV%)	147 (14.5)	89 (59.4)	106 (53.5)
Median (Min-Max)	144 (125- 177)	83 (36- 195)	125 (36- 195)
C_{max} (pg/ml)			
N	4	7	11
Arithmetic Mean (SD)	28 (8.6)	14 (8.6)	19 (10.6)
Geometric Mean (GCV%)	27 (28.3)	12 (62.8)	16 (68.2)
Median (Min-Max)	24.0 (22.0- 40.3)	10.0 (6.0- 30.0)	19.7 (6.0- 40.3)
T_{max} (hr)			
N	4	7	11
Median (Min-Max)	1.12 (0.67- 1.50)	1.48 (0.50- 12.00)	1.47 (0.50- 12.00)

N=Number of subjects with evaluable PK values, SD = Standard deviation, Min = Minimum, Max = Maximum, GCV = Geometric Coefficient of Variation a measure of between-subject variability is calculated in the natural log-scale with the equation:100 × sqrt(exp(s2)-1), where s2 is the observed variance on the natural log scale

* Evaluable population, **Parameter unable to be calculated for one subject due to inability to extrapolate terminal phase

Source: CSR for Trial P087, Table 11-11, page 108

Table 3: Day 5 Exposure of MF in Healthy Subjects and Patients with COPD after MF/F MDI or MF DPI administration

Study No./ Population (N)	Treatments	Parameter	Least-Squares Geometric Means[a]		GMR[b] (%)	90% CI (%)
			MF/F MDI	MF DPI		
P04275 Healthy (12)	MF/F MDI 800 mcg/20 mcg BID MF DPI 800 mcg BID	$AUC_{0\text{-}12\ hr}$ (pg·hr/mL	2197	2823	**75**	61–91
		Cmax (pg/mL)	241	383	61	49–75
P04689 COPD (14)	MF/F MDI 400 mcg/10 mcg BID MF DPI 400 mcg BID	$AUC_{0\text{-}12\ hr}$ (pg·hr/mL)	**431**	561	**77**	58–102
		Cmax (pg/mL)	44	77	56	41–**77**
P05527 Healthy (22-24)	MF/F MDI 100 mcg/10 mcg BID MF DPI 100 mcg BID	$AUC_{0\text{-}12\ hr}$ (pg·hr/mL)	150	247	**61**	46–80
		Cmax (pg/mL)	18.9	34.3	55	41–74

$AUC_{0\text{-}12\ hr}$=area under the concentration–time curve from 0 hr to 12 hr postdose, CI=confidence interval; Cmax=maximum plasma concentration; COPD=chronic obstructive pulmonary disease; CV=coefficient of variation; DPI=dry-powder inhaler; GMR=geometric means ratio; MDI=metered-dose inhaler; MF=mometasone furoate; MF/F=mometasone furoate/formoterol fumarate

a: Model-based (least squares) mean: ANOVA model extracting the effects due to treatment, sequence, period, and subject.

b: Treatment comparison: MF/F MDI vs. MF-DPI (MF-DPI as reference)

Source: Table 1 of the Clinical Pharmacology review by Dr. Sheetal Agarwal, page 8 (submitted to IND 70283 on October 18, 2012)

6.4 Analytical Section

6.4.1 What is the analytical method used to measure MF in Study P087?

The method for analysis of MF in plasma samples collected in Trial P087 was HPLC with MS/MS Detection ((b) (4) Method LCMSD 345.1 V 3). This method was similar to the bioanalytical method used in the original NDA with minor modifications. The calibration range was 0.25 – 25 pg/mL in human plasma. Accuracy of quality control samples ranged from -5.20 to 3.70% and precision ranged from 1.90 to 10.7%. A summary of the bioanalytical method was provided in Table 4.

To confirm assay reproducibility, 15 (10%) of 144 samples were selected for incurred sample reanalysis (referred to as ISR-1). The overall ISR-1 pass rate was 46.7%, which was below the acceptance criteria of 67%. A comprehensive investigation was undertaken to examine potential sources of the ISR-1 failure. The bioanalytical investigation did not identify any analytical or process concerns leading to the ISR-1 observations. However, the confirmed presence of MF on the outside of the sample tubes and the observations that MF concentrations increased with subsequent reanalysis on a subset of ISR-1 samples suggested the introduction of a contaminant (MF) from the exterior of the sample tube during reanalysis as the most plausible source for the ISR-1 results. A repeated ISR (referred to as ISR-2) was performed on a different subset of MF samples. None of the samples in ISR-2 were previously assessed in ISR-1. Additionally, efforts were made to mitigate any potential sources that led to failure of ISR-1 (e.g., replacement of caps on sample tubes, cleaning the exterior of each tube). Even though the Applicant made additional effort for ISR-2, it failed to meet the acceptance criteria with a pass rate of 33.3% using 27 samples.

Table 4. Summary of Analytical Method for analysis of MF in Study P087

Method Description	(b) (4) Method LCMSD 345.1 V 3
Analyte	Mometasone Furoate
Method Validation Report	(b) (4) Validation Report, Project KYZ2, Quantitation of Mometasone Furoate in Human Plasma via HPLC with MS/MS Detection
Reference Standards	Mometasone Furoate, I0L395 Mometasone Furoate $^{13}C,d_6$, BDG 12652
Matrix	Human Plasma
Anticoagulant	K_3 EDTA
Method of Detection	LC-MS/MS
Sample Aliquot Volume	1.00 mL
Calibration Range	0.250 to 25.0 pg/mL
Quality Control (QC) Concentrations	0.500, 1.00, 2.50, 6.00, and 19.0 pg/mL
Highest Dilution QC Concentration	80.0 pg/mL
Regression, Weighting	Linear, $1/conc.^2$
Demonstrated Storage Stability	1050 days at -20 °C
Maximum Sample Storage Duration From Collection to Analysis	533 days at -20 °C (within Stability Limits)
Analysis Start Date	04-DEC-2017
Analysis Completion Date	20-JUL-2018

Source: Section 1 of the bioanalytical report for Study P087

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Pediatric clinical data from four trials supports the use of MF and MF/F in the pediatric population (Table 5). Trial C96-361 was originally conducted to provide support for approval of Asmanex Twisthaler (MF DPI; NDA 21067) and includes data regarding the systemic effects of MF on the HPA axis in children. Trial P06476, a randomized, crossover, LABA dose finding study, was previously submitted to IND 70283 and is now cross referenced to NDAs 205641 and 22518. This trial fulfilled PMR 1658-1. Data from Trial P086 was previously submitted to IND 52214 and is now also cross referenced to NDAs 205641 and 22518. This trial fulfilled PMR 1658-4. Data from Trial P087, a phase 3, randomized, active-controlled, parallel-group clinical trial studying the efficacy and long-term safety of MF and MF/F is being submitted in support of the pediatric indication being proposed and to fulfill PMR 1658-7 and the Written Request (issued December 4, 2017; accepted January 25, 2018).

Table 5: Listing of Clinical Trials Relevant to This sNDA

Trial Date	Trial Design/ Duration	Regimen/ schedule/ route	N[x]	Population	Primary Endpoints	No. of Centers/ Countries
C96-361 Jun 1997- Sept 1997	R, DB, PC, PG 29 days	MF DPI 100 mcg BID MF DPI 200 mcg BID MD DPI 400 mcg BID Placebo	13 13 12 12	Children ages 6-11 w/ asthma diagnosis of at least 6 months, not on controller therapy	Plasma cortisol AUC (0-12 h) at Day 29	1 site-USA
P06476 Dec 2010 – Oct 2011	R, EB, SD, PC, 4-period cross over	F DPI 12 mcg BID (10 mcg delivered) MF/F MDI 100/10 mcg with spacer MF/F MDI 100/10 mcg without spacer Placebo MDI	90 88 91 90	Children ages 5-11 w/ asthma diagnosis of at least 6 months on ICS +/- LABA for at least 3 months	FEV1 AUC (0-12 hr)	24 sites-USA

Trial Date	Trial Design/ Duration	Regimen/ schedule/ route	N[x]	Population	Primary Endpoints	No. of Centers/ Countries
P086 Feb 2012 – Jan 2015	R, PC, DR 12 weeks	MF MDI 50 mcg BID MF MDI 100 mcg BID MF MDI 200 mcg BID MF DPI 100 mcg daily PM Placebo	120 113 108 125 112	Children ages 5-11 w/ asthma diagnosis + low to medium ICS for at least 3 months	Change in AM predose ppFEV1 from baseline to week 12	134 sites- Bulgaria, Colombia, Croatia, Estonia, Greece, Guatemala, Hungary, Latvia, Mexico, Poland, Puerto Rico, Romania, Russia, Serbia, S. Africa, Switzerland, Ukraine, and USA
P087 May 2016 – Dec 2017	R, AC, PG 12 week efficacy and safety 12 week safety extension 2 week safety follow-up	MF/F MDI 100/10 mcg BID MF MDI 100 mcg BID	91 90	Children ages 5-11 w/ asthma diagnosis of at least 6 months on ICS + LABA for at least 4 weeks	Change in baseline AM post-dose ppFEV1 AUC (0-60 min) through week 12	47 sites- Colombia, Guatemala, Hungary, Latvia, Mexico, Romania, Russia, South Africa, and the USA

Abbreviations: K: Randomized population; R: randomized; EB: evaluator-blind; DB: double-blind; SD: single dose; DR: dose-ranging; PC: placebo-controlled; AC: active controlled; PG: parallel group; ICS: inhaled corticosteroids; LABA: long-acting beta agonist; ppFEV1: percent predicted forced expiratory volume in one second; AUC: area under the curve; MF: mometasone furoate; F: formoterol fumarate; MDI: metered dose inhaler; DPI: dry powder inhaler
Source: Tabular Listing of All Clinical Studies

7.2 Review Strategy

The clinical review was conducted by one primary clinical reviewer and one statistical reviewer. Four studies are submitted as pertinent to the claimed pediatric indication (Table 5). Trials P06476, P086 and P087 support efficacy and safety; Trial C96-361 provides additional safety data. Trials C96-361, P06476, and P086 have been previously submitted and reviewed by the Division (see clinical reviews dated December 3, 2007, submitted to NDA 21067 for C96-361; July 26, 2012, submitted to IND 70283 for P06476; June 24, 2016, submitted to NDAs 205641 and 22518 for P086).

The key pivotal trials for efficacy are P086, which evaluated the efficacy of several doses of MF compared to placebo and P087, which evaluated the efficacy of MF/F compared to MF to demonstrate the additional benefit of F compared to MF. The results from Trial P086 (MF dose selection) had been previously reviewed by the Division for determination of PREA PMR fulfillment. Results from P086 were reviewed with this supplement for efficacy claims and labeling (Section 8 below).

Given that the Applicant is providing data from Trial P087 for this first time with this submission, it is reviewed extensively in this document. The trial design is discussed in Section 8.1.4, efficacy data in Section 8.1.5, safety data in Section 8.2 and labeling recommendations in Section 11. In order to provide a more robust assessment of safety, data from Trials P086 and P087 were pooled and discussed in Section 8.2.

Integrated Review of Efficacy was omitted as the efficacy of each trial was reviewed individually, either in this document or previously by the division.

8 Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Trial P06476

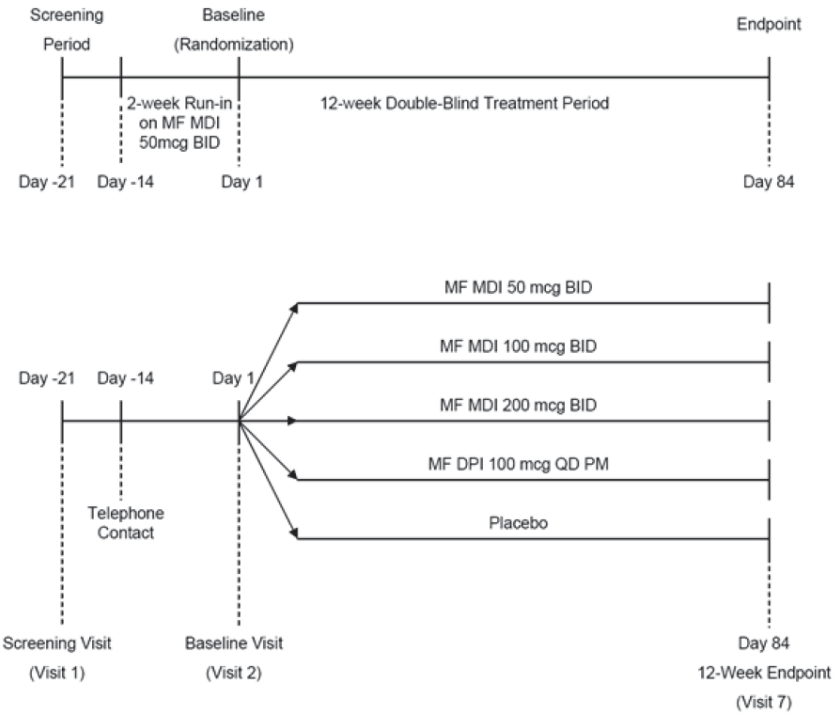
Trial P06476 was a randomized, evaluator-blind, single-dose, placebo-controlled, crossover study used to confirm the F dose in children ages 5-11 years old. This trial enrolled 92 children who had a diagnosis of asthma for at least 6 months and had been using ICS or ICS/LABA therapy for at least 3 months prior to trial entry. Participants received MF DPI 100 mcg daily for ~4 weeks and continued to use this dose during the treatment periods to standardize exposures. Participants received Foradil (F DPI) 12 mcg (10 mcg delivered dose), MF/F MDI 100/10 mcg with and without a spacer, and placebo MDI with and without a spacer. In this trial, the bronchodilatory effect of MF/F was comparable to F DPI and was shown to be superior

to placebo. Similar results were seen with and without the use of a spacer. Please see clinical review of Trial P06476 by Sofia Chaudhry dated July 26, 2012, submitted to IND 70283, for further trial details.

8.1.2 Trial P086

Trial P086 was a phase 2, 12-week, randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study of MF MDI in children ages 5 to 11 with persistent asthma and has been previously submitted by the Applicant to fulfill PMRs. It is also being submitted to this sNDA to support the use of MF and MF/F for ages 5 to 11. See the clinical review of trial P086 by Sofia Chaudhry dated June 24, 2016, submitted to NDAs 205641 and 22518, for details related to trial design and safety. The trial design is shown in Figure 5. A thorough review of efficacy is detailed below.

Figure 5: Trial P086 Design



Source: Trial P086 Protocol, Figure 1, page 8

8.1.2.1 Endpoints

The endpoints selected by the Applicant for Trial P086 are appropriate for the study of efficacy for MF. Each endpoint assessed the comparison of each MDI treatment arm (MF MDI 50 mcg BID, MF MDI 100 mcg BID, and MF MDI 200 mcg BID, MF DPI 100 mcg QD PM) versus placebo, unless otherwise stated. The endpoints are outlined below:

Primary Efficacy Endpoint

- Change in percent predicted FEV1 (ppFEV1) from baseline to Week 12 for the evaluation of dose-related efficacy of MF MDI BID

Secondary Efficacy Endpoints

- Change from baseline in AM peak expiratory flow at 12 weeks
- Change from baseline in the Pediatric Asthma Quality of Life Questionnaire with standardized activities (PAQLQ[S]) score at 12 weeks
- Efficacy of MF MDI 50 mcg BID compared with that of MF DPI 100 mcg daily PM in change in ppFEV1 from baseline to 12 weeks

8.1.2.2 Statistical Analysis Plan

Randomization and Sample Size

Approximately 1200 subjects were screened with the objective of randomizing 120 subjects into each of the five treatment groups (presumed screen failure rate = 50%). The sample size was chosen to detect a clinically meaningful difference between the treatment and placebo groups in the primary endpoint (mean change in ppFEV1 from baseline to week 12). Assuming an effect size of 5.3 percentage points in ppFEV1 at week 12, it was estimated that a power of 90% could be reached in tests with two-sided 5% level of significance.

Analysis Sets

Analysis of efficacy data was performed on the Full Analysis Set (FAS), which was defined as subjects who received randomized treatment assignment and had either a baseline measurement or at least one post-randomization measurement. However, the primary endpoint analysis was conducted on the per protocol (PP) population, which included all treated subjects that were determined to not have a significant protocol violation. It is of note that the current FDA review team does not agree with this approach. Unfortunately, FDA expectations on efficacy estimand and proper missing data handling were not conveyed to the applicant as Trial P086 was initially submitted at a time when efficacy was not thoroughly reviewed. Partially due to the level of statistical significance demonstrated from its pre-planned primary analysis, and partially due to the fact that Trial P086 is a legacy study, limitations in the statistical analysis plan were treated “as is” during this review of efficacy; deficiencies related to this will not be commented on further in this review.

The safety analysis population included all subjects who received at least one dose of randomized treatment and is designated as the All Treated Analysis Set.

Primary Analysis Model

Constrained longitudinal data analysis (cLDA) method was used to compare the change from baseline in ppFEV1 at Week 12 of all MF MDI doses compared to placebo (see description of the cLDA model in Section 8.1.4). Analyses adjusted for variations in treatment, time, treatment-by-time interaction, region (North America, Latin America, or European Union), and age stratum

(5-6 years or 7-11 years old.) The cLDA model provides valid statistical inference in the presence of possible missing data if the missing data mechanism is either missing at random or missing completely at random. These missingness assumptions could not be verified. In a confirmatory study, sensitivity analyses to missing data are necessary to evaluate how robust the primary analysis results were across varying missing data assumptions. Since this is a phase 2 trial to confirm efficacy and select doses for use in the phase 3 program, sensitivity analysis to missing data was not the primary focus in this review.

Multiplicity Control Procedure

A step-down approach was used for testing of MF MDI doses against placebo to control for multiplicity. Tests began at the highest dose of MF MDI. After success of MF MDI 200 mcg BID vs. placebo, the MF MDI 100 mcg BID and MF MDI 50 mcg BID were tested against placebo in sequential order. This controlled the overall two-sided alpha level of 5%. In addition, as the efficacy of the MF DPI formulation had already been established, the comparison of MF DPI 100 mcg daily and placebo for the primary efficacy endpoint was not examined using the p-value and the associated 95% confidence interval of the treatment difference was not adjusted for multiplicity. This examination was used in the interpretation of the effectiveness of MF MDI doses.

8.1.2.3 Protocol Amendments

A protocol amendment was finalized on August 26, 2013. The primary reason for the amendment was to clarify and align sections throughout the protocol and to remove an ANCOVA analysis originally proposed as a confirmatory analysis. Reasons for removal were to align the analysis with the upcoming phase 3 pediatric protocols and because the estimated treatment difference from the cLDA model would have been very close to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate.

8.1.3 Results for Trial P086

8.1.3.1 Analysis Datasets

Of the 1268 subjects screened, 685 were excluded during screening and not randomized. Of the 583 subjects randomized: 5 were randomized in error and 578 subjects received at least one dose of study medication; 6 did not have efficacy data and the resultant FAS population for trial P086 was 572 individuals. In addition to the 11 subjects excluded from the randomized population, five subjects were excluded due to violations in entry criteria and use of prohibited medications, resulting in a PP population of 567 subjects. The safety population is comprised of 578 subjects. Of note, a total of four subjects received incorrect study medication for 14 to 28 days during the randomized treatment period. Given the short duration of incorrect treatment during the 12-week trial, subjects were included in the FAS and All Treated Analysis Set populations and were analyzed according to assigned treatment group.

Table 6: Analysis Datasets, Trial P086

	Placebo	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID	MF DPI 100 mcg QD PM	Total
Screening population						1268
Screening failure						685
Randomized population	112	122	115	108	126	583
Full analysis set	111	118	112	108	123	572
Per-protocol population	111	117	109	107	123	567
Safety population	112	120	113	108	125	578

Source: FDA Reviewers

8.1.3.2 Disposition

Rates of discontinuation were high across treatment arms, with the highest rate of 46% seen in the placebo arm, followed by 33% for MF 50 mcg BID (Table 7). Across all treatment arms, the greatest reason for discontinuation was due to treatment failure/lack of efficacy, with the highest rate seen in the placebo arm (31%). These high rates of discontinuation are likely related to the discontinuation parameters outlined in Trial P086 protocol. Discontinuation was required if there was a "clinically judged deterioration of asthma", decrease in lung function below pre-specified stability limits, high SABA usage, or use of systemic corticosteroid. Higher rates of discontinuation in the placebo is suggestive of a positive treatment effect by the active treatment, including the MF 100 mcg BID dose group.

Table 7: Subject Disposition, Trial P086 (Full Analysis Set)

	Placebo N=111	MF MDI 50 mcg BID N=118	MF MDI 100 mcg BID N=112	MF MDI 200 mcg BID N=108	MF DPI 100 mcg QD PM N=123	Total N=572
Completed	60 (54.1%)	79 (66.9%)	81 (72.3%)	83 (76.9%)	88 (71.5%)	391 (68.4%)
Discontinuation	51 (45.9%)	39 (33.1%)	31 (27.7%)	25 (23.1%)	35 (28.5%)	181 (31.6%)
Disposition reason						
Treatment failure/Lack of efficacy*	34 (30.6%)	25 (21.2%)	22 (19.6%)	14 (13%)	20 (16.3%)	115 (20.1%)
Protocol violation	9 (8.1%)	9 (7.6%)	5 (4.5%)	6 (5.6%)	4 (3.3%)	33 (5.8%)
Adverse event[a]	3 (2.7%)	2 (1.7%)	1 (<1%)	0 (0%)	4 (3.3%)	10 (1.7%)
Technical problems	1 (<1%)	1 (<1%)	0 (0%)	2 (1.9%)	4 (3.3%)	8 (1.4%)
Withdrawal by subject	1 (<1%)	1 (<1%)	2 (1.8%)	1 (<1%)	1 (<1%)	6 (1.0%)
Non-compliance with study drug	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	2 (1.6%)	4 (<1%)
Excluded medication	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	3 (<1%)
Physician decision	1 (<1%)	1 (<1%)	0	0 (0%)	0 (0%)	2 (<1%)

Abbreviations: N: sample size in Full Analysis Set; n: sample size in corresponding category.
*Subjects who discontinued the trial for lack of efficacy and treatment failure were combined in this table, as the Applicant did not provide a clear definition of the difference between these two like terms.
[a]An asthma exacerbation was only considered an adverse event in Trial P086 if there was a clear temporal relationship to administration of study drug or if hospitalization or emergency treatment as a result of the exacerbation occurred.
Source: FDA Statistical Reviewer

8.1.3.3 Protocol Violations/Deviations

A protocol deviation was determined to be any change, divergence, or departure from the approved protocol. A major protocol violation was one that may significantly or adversely impact the completeness, accuracy, and/or reliability of the trial data or that may affect the safety or rights of the subject. Major protocol deviations were identified prior to unblinding.

8.1.3.4 Demographic Characteristics

Demographics for Trial P086 are summarized in Table 8. The majority of participants were male (60%) and 7-11 years old (87%). Participants mostly self-identified as white (70.5%) and as non-Hispanic or Latino (64.3%). Almost two-thirds of the participants were from the European Union. The average ppFEV1 at baseline was 78.6%. In general, demographic characteristics were balanced across treatment groups.

Table 8: Demographic Characteristics, Trial P087 (Full Analysis Set)

	MF MDI 50 mcg BID N=118	MF MDI 100 mcg BID N=112	MF MDI 200 mcg BID N=108	MF DPI 100 mcg daily PM N=123	Placebo N=111	Total N=572
Sex						
M	67 (56.8%)	68 (60.7%)	49 (45.4%)	75 (61.0%)	82 (73.9%)	341 (59.6%)
F	51 (43.2%)	44 (39.3%)	59 (54.6%)	48 (39.0%)	29 (26.1%)	231 (40.4%)
Age (Years)						
Mean (SD)	8.7 (1.7)	8.6 (1.9)	8.7 (1.7)	8.7 (1.7)	9.0 (1.7)	8.7 (1.8)
Age (Group)						
5 to 6	12 (10.2%)	22 (19.6%)	14 (13.0%)	15 (12.2%)	11 (9.9%)	74 (12.9%)
7 to 11	106 (89.8%)	90 (80.4%)	94 (87.0%)	108 (87.8%)	99 (89.2%)	497 (86.9%)
12[x]	0	0	0	0	1 (<1%)	1 (<1%)
Race						
White	82 (69.5%)	80 (71.4%)	72 (66.7%)	89 (72.4%)	80 (72.1%)	403 (70.5%)
Multi-racial	25 (21.2%)	26 (23.2%)	25 (23.1%)	24 (19.5%)	26 (23.4%)	126 (22.0%)
American Indian or Alaska native	4 (3.4%)	3 (2.7%)	8 (7.4%)	4 (3.3%)	3 (2.7%)	22 (3.8%)

	MF MDI 50 mcg BID N=118	MF MDI 100 mcg BID N=112	MF MDI 200 mcg BID N=108	MF DPI 100 mcg daily PM N=123	Placebo N=111	Total N=572
Black or African-American	7 (5.9%)	2 (1.8%)	3 (2.8%)	5 (4.1%)	2 (1.8%)	19 (3.3%)
Ethnicity						
Not Hispanic or Latino	77 (65.3%)	69 (61.6%)	66 (61.1%)	83 (67.5%)	73 (65.8%)	368 (64.3%)
Hispanic or Latino	38 (32.2%)	40 (35.7%)	38 (35.2%)	37 (30.1%)	36 (32.4%)	189 (33.0%)
Not reported	3 (2.5%)	3 (2.7%)	4 (3.7%)	3 (2.4%)	1 (<1%)	14 (2.4%)
Unknown	0	0	0	0	1 (<1%)	1 (<1%)
Location						
EU	69 (58.5%)	68 (60.7%)	64 (59.3%)	75 (61.0%)	67 (60.4%)	343 (60.0%)
Latin America	30 (25.4%)	27 (24.1%)	28 (25.9%)	27 (22.0%)	28 (25.2%)	140 (24.5%)
North America	19 (16.1%)	17 (15.2%)	16 (14.8%)	21 (17.1%)	16 (14.4%)	89 (15.6%)
ppFEV1 at Baseline†						
Subjects with data	116	108	102	125	110	561
Mean (SD)	79.4 (7.6)	78.8 (8.0)	78.8 (8.0)	78.3 (7.6)	77.8 (7.2)	78.6 (7.7)
Median (minimum, maximum)	80 (61, 97)	79 (57, 96)	79 (51, 105)	79 (54, 90)	78 (60, 95)	79 (51, 105)

Abbreviations: N: sample size in Full Analysis Set; n: sample size in corresponding category; SD: standard deviation; EU: European Union.
×One subject who was randomized at age 11 in the Integrated Voice Response System is reported to be age 12 due to a standard missing date imputation
†Baseline is the ppFEV1 (forced expiratory volume in 1 second) value on the day of treatment start date (Day 1).
Source: FDA Statistical Reviewer

8.1.3.5 Primary Endpoint

Compared to placebo, each of the MF treatment arms showed a statistically significant change from baseline in ppFEV1 at Week 12 (Figure 3, Table 9). Difference in LS means compared to placebo were 3.87 (p=0.019), 6.29 (p<0.001), and 5.34 (p=0.001) for 50 mcg, 100 mcg and 200 mcg MF mcg BID, respectively. Of note, the approved Asmanex Twisthaler pediatric dose (MF 100 mcg DPI daily) did not show a statistically significant effect compared to placebo (LS mean = 3.13, p=0.127). While each MF MDI strength tested showed superiority over placebo, the applicant determined that the 100 mcg BID dose provided additional benefit over the 50 mcg BID dose and there was no incremental benefit with the 200mcg BID dose. Thus, 100 mcg was selected as the optimal dose in the pediatric population. Analyses using the PP population yielded similar results.

Table 9: Analysis of Change from Baseline in Percent Predicted FEV1 (Liters) at Week 12, Trial P086 (Full Analysis Set)

	Placebo N=111	MF MDI 50 mcg BID N=118	MF MDI 100 mcg BID N=112	MF MDI 200 mcg BID N=108	MF DPI 100 mcg QD PM N=123
Number analyzed	111	114	109	105	122
ppFEV1 at baseline					
Observed mean (SD)	77.82 (7.21)	79.53 (7.47)	78.94 (7.85)	78.71 (7.96)	78.44 (7.57)
ppFEV1 at Week 12					
Observed mean (SD)	79.90 (11.55)	85.61 (12.43)	86.33 (13.09)	86.12 (11.69)	82.84 (10.14)
Change from baseline in ppFEV1 at Week 12					
Median	2.57	3.86	6.38	4.31	3.05
Observed mean (SD)	3.59 (11.65)	5.57 (11.71)	7.45 (11.32)	5.98 (8.38)	3.97 (9.06)
Model-based comparison: active vs. placebo					
Adjusted mean	0.66	4.52	6.95	6.00	3.13
Difference		3.87	6.29	5.34	2.47
95% CI		(0.64, 7.09)	(3.05, 9.53)	(2.07, 8.61)	(-0.70, 5.65)
p-value		0.019	<0.001	0.001	0.127

Abbreviations: N: sample size in Full Analysis Set; SD: standard deviation; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer; CSR for Trial P086, Table 11-1, page 75

8.1.4 Trial P087

8.1.4.1 Trial Design

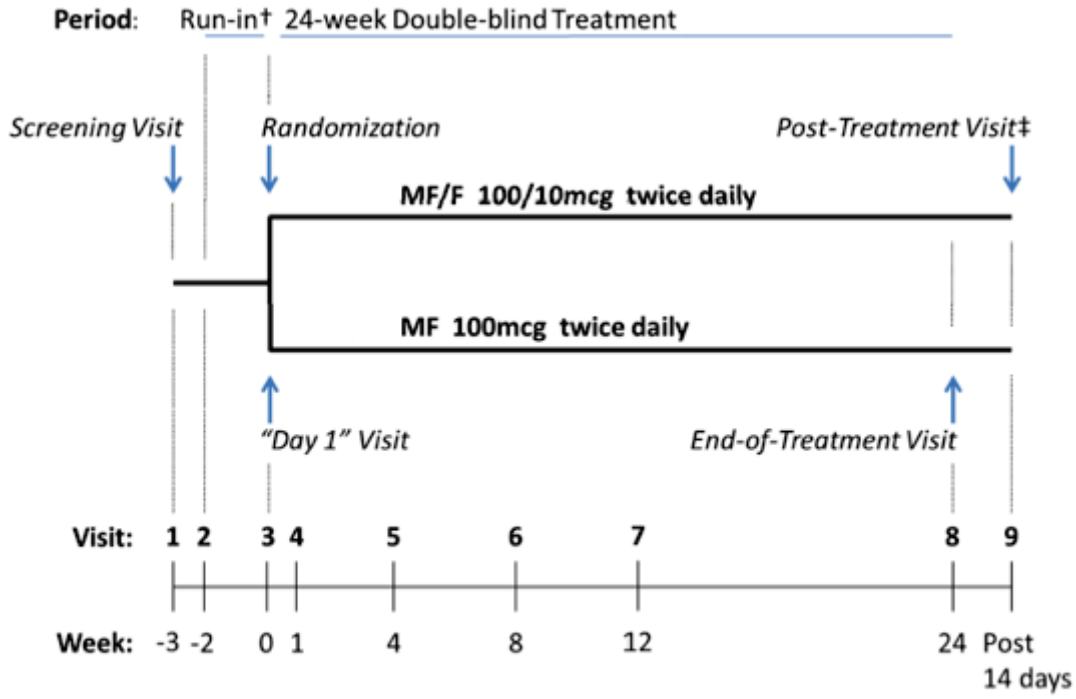
Trial P087 was a multi-center, randomized, double-blind, active-controlled, parallel-group study in children ages 5-11 years who were already receiving ICS/LABA therapy. Following screening and a run-in period where subjects were given MF 100 mcg for approximately 2 weeks, eligible subjects were randomized 1:1 to either MF 100 mcg or MF/F 100/10 mcg BID by MDI for a planned 24-week double-blind treatment period. Efficacy and safety data were collected for the first 12 weeks of double-blind treatment; safety data were collected for the last 12 weeks of double-blind treatment. After completion of the double-blind treatment period, each subject was followed for an additional 2 weeks for safety (Figure 6). This trial was initiated on May 20, 2016 and completed on December 4, 2017.

At the Screening Visit (Visit 1), patients and families provided consent. Appropriate MDI inhalation and peak expiratory flow meter techniques, as well as eDiary procedures, were

reviewed. Investigators provided rescue medication including short acting beta-agonist (SABA) and oral corticosteroids to families, as well as an asthma action plan for effective management of asthma symptoms based on clinical practice guidelines. Beginning at Visit 2, subjects transitioned from their prescribed ICS/LABA therapy to MF 100 mcg given by MDI BID for a 2-week, open-label run-in period. At Visit 3, eligible subjects were randomized to receive either MF 100 mcg of MF/F 100/10 mcg BID to begin the 24-week double-blind treatment period. Randomization was stratified by age group (5 to 7 or 8 to 11 years of age) using the Integrated Voice Response System, as well as by geographical region. This trial was conducted at 47 clinical sites across nine countries.

At each visit during the double-blind treatment period (Visits 3 through 7), blinded trial medication was administered as a witnessed dose, followed by one hour of serial spirometry measurements at 2-hour and 4-hour timepoints. At Visit 7, blood samples were collected from a subset of subjects for PK analyses. At the end of the treatment period (Visit 8), subjects were then followed for 2 additional weeks. The trial design is shown in Figure 6.

Figure 6: Trial P087 Design



†During Run-in (between Visits 2 and 3), all subjects receive open-label MF MDI 100mcg twice daily.
‡For the Post-Treatment Visit, only female subjects of child-bearing potential return to the clinic. All other subjects are contacted by telephone.

Source: Adapted from Figure 1 of P087 Protocol, Page 15

8.1.4.2 Study Population

Subjects ages 5 to 11 years with a diagnosis of persistent asthma on ICS/LABA combination therapy were enrolled in the trial.

Key Inclusion Criteria:

- Able to provide consent or assent
- Diagnosis of asthma per Global Initiative for Asthma Guidelines for at least 6 months prior to Visit 1
- Have asthma that is adequately controlled on a stable dose of ICS/LABA combination therapy for at least 4 weeks prior to Visit 1
- FEV1 >60 and ≤90% predicted when the following medications are restricted for the appropriate time intervals
    - Beta-adrenergic bronchodilators, sustained-release tablets; 48 hours
    - Beta-adrenergic bronchodilators, syrups and tablets; 24 hours
    - Ipratropium bromide, with or without albuterol/salbutamol; 12 hours
    - LABAs; 12 hours
    - SABAs; 6 hours
- An increase in absolute FEV1 of at least 12% within 30 minutes of albuterol/salbutamol
- Ability to use MDI correctly and follow all trial procedures

Key Exclusion Criteria:

- Subject requires the use of >8 inhalations per day of albuterol (100 mcg per actuation or equivalent doses), and/or >2 nebulized treatments per day of 2.5 mg albuterol (or its equivalent), on any 2 consecutive days between the Screening Visit (Visit 1) and the Randomization Visit (Visit 3); one nebulized treatment was considered equivalent to four inhalations by MDI
- Experiences a clinical worsening of asthma between the Screening Visit (Visit 1) and the Randomization Visit (Visit 3), that results in emergency room visit (for an asthma exacerbation), hospitalization due to asthma, or treatment with additional, excluded asthma medication (other than SABA)
- Recent upper or lower respiratory tract infection
- Demonstrates <80% compliance with use of trial medication during the 2-week Run-in Period
- Is considered to have unstable asthma at the end-of the Run-in Period
- Has had greater than four asthma exacerbations (defined as a worsening of asthma requiring systemic corticosteroid use and/or a 24-hour or longer stay in an emergency department, urgent care center, and/or hospital) within the 52 weeks prior to Visit 1
- Has had a history of life-threatening asthma, including an asthma episode that required intubation and/or was associated with hypercapnia requiring non-invasive ventilatory support.

- Has been taking restricted medications prior to the Screening Visit without meeting the required washout timeframes as listed below:
    - Investigational antibodies for asthma or rhinitis; 6 months
    - Monoclonal antibodies; 6 months
    - Methotrexate, cyclosporine, gold, and other cytotoxic agents; 3 months
    - Investigational drugs or vaccines; 1 month
    - Any systemic glucocorticosteroid; 3 months
    - Any oral glucocorticosteroid; 4 weeks
    - Glucocorticosteroids, high potency dermatologicals, plain and/or combination classifications of mid-strength, or potent or super potent by Stoughton-Cornell Scale; 4 weeks
    - Theophylline; 2 weeks
    - Cromolyn sodium, nedocromil (inhaled); 2 weeks
    - Leukotriene modifiers; 2 weeks
    - Beta-adrenergic bronchodilators, sustained-release tablets; 48 hours
    - Beta-adrenergic bronchodilators, syrups and tablets; 24 hours
    - Ipratropium bromide, with or without albuterol/salbutamol; 12 hours
    - SABAs; 6 hours
- Known hypersensitivity to any component of study medication

8.1.4.3 Dose Selection

Participants were randomized to MF 100 mcg BID or MF/F 100/10 mcg BID in Trial P087. The data from Trial P086 support the efficacy of MF 100 mcg BID. In Trial P06476, the bronchodilatory effect of MF/F 100/10 mcg BID was shown to be equivalent to F DPI 12 mcg and was selected as the LABA dose for Trial P087. Dose selection was therefore appropriate. For further details on dose selection, see Section 6 Clinical Pharmacology.

To assess the efficacy of MF and F in a combination product, MF monotherapy was used as a comparator treatment in Trial P087. Given that the safety and efficacy of MF monotherapy had been demonstrated in Trial P086, this design was to demonstrate the contributions of F to asthma maintenance therapy in children 5-11 years of age, as well as provide long term safety data for MF and MF/F.

8.1.4.4 Subject Completion, Discontinuation, and Withdrawal

Subjects were able to withdraw consent at any time and for any reason. Subjects who discontinued or withdrew from the trial prior to completion of the treatment regimen were continued to be monitored, unless consent was withdrawn.

8.1.4.5 Endpoints

The endpoints selected by the Applicant are appropriate for the study of efficacy for MF and MF/F. They are outlined below**:**

Primary Efficacy Endpoint

- Change from baseline in AM post-dose ppFEV1 AUC as measured across 0 to 60 minutes post-dose at 0, 5, 15, 30 and 60 minutes, averaged across Day 1, Week 1, Week 4, Week 8 and Week 12 of treatment

Secondary Efficacy Endpoints

- Key Secondary Endpoint: Change from baseline in AM post-dose ppFEV1 at 2 and 4 hours, as well as 5, 15, 30 and 60 minutes post-dose on Day 1 of treatment
- Change from baseline in AM post-dose ppFEV1 as measured across the 0 to 4 hour post-dose interval, at Day 1 and Week 12 of treatment
- Change from baseline AM pre-dose ppFEV1 averaged across Week 4, Week 8, and Week 12 of treatment
- Change from baseline in total daily SABA use across the first 12-weeks of treatment
- Characterize the plasma PK profile of MF

8.1.4.6 Statistical Analysis Plan

Randomization and Sample Size

Patients were randomized in Trial P087 in a 1:1 ratio to MF and MF/F. Randomization was stratified by age and region. The planned sample size was 160 subjects for the primary endpoint, assuming an underlying treatment difference between MF and MF/F would be at least 4.2 percentage-points. This would provide 77% to 82% power at an overall two-sided 5% alpha-level.

Analysis Sets

The FAS, which is defined as randomized subjects who received at least one dose of double-blind study medication and completed at least one primary efficacy evaluation following randomized treatment, was used as the primary population for all efficacy analyses.

Supportive efficacy analyses for the primary and key secondary endpoints were conducted using the PP population. This set excludes subjects who had deviations from the protocol that could potentially affect results of the trial. The criteria used to exclude individuals were finalized prior to database lock and were included in the supplemental statistical analysis plan.

All Subjects as Treated (ASaT) was designated as the population to be used for assessments of safety. This population consisted of all randomized subjects who received at least one dose of trial medication. For the discussion of safety, this will be referred to as the Safety Population.

Estimand

The primary analysis of the primary efficacy endpoint and the supporting sensitivity analyses targeted the *de facto* or treatment policy estimand, the treatment benefit in all subjects regardless of treatment adherence.

Primary Efficacy Endpoint

Analysis comparing the two treatment groups was performed using a constrained longitudinal data analysis (cLDA) method (Liang & Zeger, 1986). This model assumed a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. Time was treated as a categorical variable so that no restriction was imposed on the trajectory of the means over time. In this model, the response vector consisted of baseline and the values observed at each post-baseline time point. The analysis model adjusted for treatment, time, treatment-by-time interaction, age stratum (5 to 7 or 8 to 11 years of age, inclusive) and region. The treatment difference in terms of mean change from baseline to a given time point was estimated and tested from this model. An unstructured covariance matrix was used to model the correlation among repeated measurements. Although the baseline measurement was included in the response vector, it was independent of treatment, and hence, the baseline means were constrained to be the same for different treatment groups.

Missing Data Handling and Sensitivity Analyses

The primary analysis incorporated a control-based multiple imputation of missing data. Missing data for subjects who discontinued treatment early were estimated using the MF group; that is, the change from baseline AM post-dose ppFEV1 in patients who discontinued treatment and missed study visits was assumed to be similar to the change from baseline in patients who continued study visits through Week 12 in the MF treatment group. The dataset was first multiply imputed to have monotone missing patterns, then for each visit, a regression method was used to impute for missing data on both study drug arm and the control arm based on trend from the control arm. After applying the control-based multiple imputation, the cLDA analysis was performed. MF/F 100/10 mcg BID was considered superior to MF 100 mcg BID with a p-value ≤0.05.

While the control-based primary analysis represented reasonable missing data assumptions alternative to the assumption of missing-at-random, it did not comprehensively explore the plausible space of missing data assumptions. Therefore, the FDA review team recommended additional analyses to systematically and comprehensively explore the space of plausible missing data assumptions. In particular, the reviewers recommended the inclusion of tipping point analyses that vary assumptions about the missing outcomes in the two treatment arms relative to the analysis with missing at random assumption (carried out using the Mixed Effect Model Repeated Measurement approach) based on all observed data (including both on and off treatment data). The Agency recommended that the analyses be two-dimensional, i.e., should allow assumptions about the missing outcomes in the two arms to vary independently, and should include scenarios where dropouts on MF/F have worse slopes than dropouts on MF. The goal was to explore the plausibility of missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of treatment effect. The Applicant

complied with these recommendations and included all observed data, regardless of whether measurements were made on or off treatment.

Multiplicity Control Procedure
For the primary and key secondary endpoints, multiplicity was controlled by a sequential testing procedure. After success of the primary endpoint was met, the key secondary endpoints were evaluated sequentially, using the same analysis approach as described for the primary efficacy endpoint, at 4 hours, 2 hours, 60 minutes, 30 minutes, 15 minutes, and 5 minutes, and analyzed as the change from baseline (AM predose on Day 1).

Safety Analyses
The Applicant evaluated all AEs using a tiered approach (See Section 8.2.3 for more information). Tier 1 AEs were evaluated with p-values and 95% confidence intervals using the Miettinen and Nurminen method [5] to determine if differences existed between treatment groups. Tier 2 AEs were also evaluated with the Miettinen and Nurminen method using only 95% confidence intervals. Descriptive statistics were used for analysis of all three tiers.

8.1.4.7 Protocol Amendments

A protocol amendment was issued on October 4, 2016. The amendment modified the statistical analysis plan with regard to handling of missing data by reversing the roles of the primary analysis method using cLDA without explicit imputation, and the sensitivity analysis method using cLDA after a control-based imputation. Other changes included clarification and timing of trial procedures.

FDA review team accepted the change of primary analysis method and confirmed the applicant's findings based on the control-based analysis approach during this review.

8.1.5 Results for Trial P087

8.1.5.1 Compliance with Good Clinical Practice

The Applicant states that Trial P087 was conducted in accordance of generally accepted standards of good clinical practice as well as all applicable federal, state and local laws, rules and regulations.

8.1.5.2 Financial Disclosure

The Applicant adequately disclosed financial interests and arrangements with clinical investigators for Trial P087. There were no investigators with disclosable financial interest that may have impacted the trial conduct. Financial disclosure details are shown in Section 15.2.

8.1.5.3 Disposition

Approximately 160 subjects were planned to be randomized. Of 310 subjects screened, 129 failed screening and did not go on to receive randomized treatment (

Table 10). The most common reason for screening failure was FEV1 outside of the defined inclusion criteria. Eighteen subjects (5.8%) did not demonstrate an ability to follow trial procedures, which included using an MDI correctly. Of those that failed screening, 20 received open-label medication during the run-in. A total of 182 subjects were randomized, though one subject did not receive any double-blind treatment. Because all subjects took the treatments they were randomized to, and participated in one primary efficacy evaluation, the FAS, and safety populations are equivalent.

Table 10: Analysis Datasets, Trial P087

	MF MDI 100 mcg BID	MF/F MDI 100/10 mcg BID	Total
Screened population			310 (100%)
Screen failure			129* (41.3%)
Randomized population	91*	91	182* (58.7%)
Patients not treated	1*	0	1*
Patients treated	90	91	181
Full analysis set	90	91	181
Safety population	90	91	181

Source: FDA Statistical Reviewer
Note: * One subject (Subject ID = (b) (6)) was determined by the investigator as a screen failure. This subject was randomized in error but was not dispensed blinded treatment at Randomization (Visit 3).

The FAS for Trial P087 is comprised of 181 subjects; 90 subjects received MF and 91 received MF/F. Four subjects in each treatment arm discontinued blinded treatment early (Table 11). Of these eight subjects, four completed the trial (i.e., safety follow-up call was performed), for a total of 177 subjects (97.8%) completing the trial.

Table 11: Subject Disposition, Trial P087 (Full Analysis Set)

	MF MDI 100 mcg BID n=90	MF/F MDI 100/10 mcg BID n=91	Totals n=181
Trial disposition			
Completed	88 (97.8%)	89 (97.8%)	177 (97.8%)
Discontinued	2 (2.2%)	2 (2.2%)	4 (2.2%)
Lost to follow-up	0 (0.0%)	2 (2.2%)	2 (1.1%)
Withdrawal by parent/guardian	2 (2.2%)	0 (0.0%)	2 (1.1%)
Trial medication disposition			
Completed	86 (95.6%)	87 (95.6%)	173 (95.6%)
Discontinued	4 (4.4%)	4 (4.4%)	8 (4.4%)
Adverse event	3 (3.3%)	0 (0.0%)	3 (1.7%)
Lost to follow-up	0 (0.0%)	2 (2.2%)	2 (1.1%)
Non-compliance with study drug	1 (1.1%)	0 (0.0%)	1 (0.6%)
Withdrawal by subject*	0 (0.0%)	2 (2.2%)	2 (1.1%)

Source: Trial P087 CSR, Table 12-9, page 130
Study medication disposition data reflects reason for treatment discontinuation reported in Adverse Event eCRF Study Disposition of "Completed" indicates the protocol-specified safety follow-up call was performed.
*Reason reported for treatment discontinuation in the PMS1 eCRF = Subject moved; however, this was mapped to “withdrawal by subject” per SDTM convention.

8.1.5.4 Protocol Violations/Deviations

A protocol violation was defined as an event that may significantly impact the quality or integrity of key trial data or that may significantly affect a subject’s rights, safety or well-being. Of 69 subjects with important protocol deviations, 42 had deviations related to trial procedures (Table 12). The majority of trial-related deviations were failure to complete pulmonary function tests at scheduled visits.

Table 12: Important Protocol Deviations, Trial P087 (Full Analysis Set)

	MF MDI 100 mcg BID N=90 n (%)	MF/F MDI 100/10 mcg BID N=91 n (%)	Total N=181 n (%)
Per-Protocol Population			
No	10 (11.1%)	8 (8.8%)	18 (9.9%)
Yes	80 (88.9%)	83 (91.2%)	163 (90.1%)
Important Protocol Deviations			
	54	58	112
Subjects Meeting One or More Important Protocol Deviations			
No	55 (61.1%)	57 (62.6%)	112 (61.9%)
Yes	35 (38.9%)	34 (37.4%)	69 (38.1%)
Specific Important Protocol Deviation by Category and Description			
Trial Procedures	20 (22.2%)	22 (24.2%)	42 (23.2%)
Subject who did not perform specified or sufficient number of PFTs on a scheduled visit.	15 (16.7%)	15 (16.5%)	30 (16.6%)
Washout period not met	5 (5.6%)	5 (5.5%)	10 (5.5%)
Visit windows not met	1 (1.1%)	3 (3.3%)	4 (2.2%)
Repeated non-compliance with e-diary during the double-blind treatment period	1 (1.1%)	1 (1.1%)	2 (1.1%)
Continued use of study meds after completion of study	1 (1.1%)	0	1 (<1%)
Inclusion/ Exclusion Criteria	8 (8.9%)	4 (4.4%)	12 (6.6%)
Subject entered into the trial, i.e. progressed beyond screening, who did not meet key inclusion/exclusion criteria	8 (8.9%)	4 (4.4%)	12 (6.6%)
Safety Reporting	8 (8.9%)	4 (4.4%)	12 (6.6%)
Safety Events and/or Safety Event follow-up information not reported per protocol specified timelines	8 (8.9%)	4 (4.4%)	12 (6.6%)

	MF MDI 100 mcg BID N=90 n (%)	MF/F MDI 100/10 mcg BID N=91 n (%)	Total N=181 n (%)
Study Intervention	4 (4.4%)	5 (5.5%)	9 (5.0%)
Subject not re-dispensed SABA	1 (1.1%)	3 (3.3%)	4 (2.2%)
Non-compliance with study medication during double blind treatment period	1 (1.1%)	1 (1.1%)	2 (1.1%)
Accidental overdose without adverse effect	0	1 (1.1%)	1 (<1%)
Subject received incorrect study treatment and/or were administered improperly stored study treatment.	1 (1.1%)	0	1 (<1%)
Subjects with <= 50% study med compliance across the treatment period	1 (1.1%)	0	1 (<1%)
Prohibited Medications	2 (2.2%)	4 (4.4%)	6 (3.3%)
Disallowed concomitant medications	2 (2.2%)	4 (4.4%)	6 (3.3%)
Informed Consent Form	2 (2.2%)	0	2 (1.1%)
Incomplete ICF	2 (2.2%)	0	2 (1.1%)

Abbreviations: N: sample size in Full Analysis Set; n: number of patients who had one or more important protocol deviation in the corresponding category; PFTs: pulmonary function tests.
Source: FDA Statistical Reviewer; CSR for Trial P087, Table 10-1, page 56

Prior to database lock, all protocol deviations were reviewed against the criteria in the supplemental statistical analysis plan to select the subset of important protocol deviations that could substantially affect the results of the trial endpoints. Eighteen subjects were identified and excluded resulting in a PP population of 163 subjects.

The number of subjects with important deviations was generally low at each site except for site 265. Twenty-four protocol deviations related to 18 subjects were reported, with the majority related to trial procedures and safety reporting. The Applicant believes that the high number of deviations is likely related to the larger number of subjects at this site compared to other sites (24 total subjects). After review of the violations by the Applicant, only one subject was excluded from the PP analysis set due to a failure to report safety information per timelines specified in the trial protocol.

Overall, the incidence of protocol deviations was balanced between the two treatment arms. No subjects were excluded from the FAS analysis nor were any deviations considered to be good clinical practice compliance issues. In summary, it is unlikely that protocol deviations caused a meaningful impact on the conclusions of the trial.

8.1.5.5 Demographic Characteristics

Trial P087 enrolled 181 subjects (Table 13). The mean age of subjects was 9.1 and 22.1% of subjects were aged 5 to 7. More than half (53.6%) of the population was non-white, with 38.7% of the total population self-reporting at least two races (i.e., multiracial). Demographic characteristics were generally balanced between the treatment groups.

Table 13: Demographic Characteristics, Trial P087 (Full Analysis Set)

	MF MDI 100 mcg BID N=90 n (%)	MF/F MDI 100/10 mcg BID N=91 n (%)	Total N=181 n (%)
Age (Years)			
Mean (SD)	9.1 (1.7)	9.1 (1.7)	9.1 (1.7)
Median (Min, Max)	10 (5, 11)	10 (5, 11)	10 (5, 11)
Age Group (Years)			
5-7	19 (21.1%)	21 (23.1%)	40 (22.1%)
5	4 (4.4%)	3 (3.3%)	7 (3.9%)
6	4 (4.4%)	5 (5.5%)	9 (5.0%)
7	11 (12.2%)	13 (14.3%)	24 (13.3%)
8-11	71 (78.9%)	70 (76.9%)	141 (77.9%)
8	10 (11.1%)	9 (9.9%)	19 (10.5%)
9	14 (15.6%)	14 (15.4%)	28 (15.5%)
10	26 (28.9%)	25 (27.5%)	51 (28.2%)
11	21 (23.3%)	22 (24.2%)	43 (23.8%)
Sex			
Female	43 (47.8%)	46 (50.5%)	89 (49.2%)
Male	47 (52.2%)	45 (49.5%)	92 (50.8%)
Race*			
American Indian or Alaska Native	2 (2.2%)	5 (5.5%)	7 (3.9%)
Black or African American	10 (11.1%)	10 (11.0%)	20 (11.0%)
Multi-Racial	37 (41.1%)	33 (36.3%)	70 (38.7%)
White	41 (45.6%)	43 (47.3%)	84 (46.4%)
Ethnicity			
Hispanic or Latino	38 (42.2%)	40 (44.0%)	78 (43.1%)
Not Hispanic or Latino	52 (57.8%)	51 (56.0%)	103 (56.9%)
Region			
Outside of US	71 (78.9%)	72 (79.1%)	143 (79.0%)
US	19 (21.1%)	19 (20.9%)	38 (21.0%)

Abbreviations: N: sample size in Full Analysis Set; n: number of patients in the corresponding category;
*Race was self-reported
Source: FDA Statistical Reviewer; CSR for trial P087, Table 2-1, Page 7

8.1.5.6 Other Baseline Characteristics

Baseline asthma characteristics are summarized in Table 14. Two-thirds (66.3%) of the enrolled subjects had asthma exacerbations during the previous year. The average ppFEV1 at screening was 75.9. Asthma characteristics were generally balanced between the treatment groups.

Table 14: Baseline Asthma Characteristics, Trial P087 (Full Analysis Set)

Participant Characteristic	MF MDI 100 mcg BID n (%)	MF/F MDI 100/10 mcg BID n (%)	Total n (%)
Subjects in population	90	91	181
History of asthma exacerbation in the previous year			
Yes	61 (67.8%)	59 (64.8%)	120 (66.3%)
No	29 (32.2%)	32 (35.2%)	61 (33.7%)
Asthma duration (years)			
Mean (SD)	4.7 (4.0)	4.7 (4.3)	4.7 (4.1)
Screening lung function, mean (SD)			
ppFEV1	75.0 (8.5)	76.8 (8.7)	75.9 (8.6)
Baseline lung function, mean (SD)			
FEV1, L	1.6 (0.4)	1.6 (0.5)	1.6 (0.4)
ppFEV1	78.5 (12.7)	79.2 (11.4)	78.9 (12.1)
% FEV1 reversibility	23.7 (12.0)	23.2 (9.8)	23.4 (10.9)

Source: CSR for trial P087, Table 2-2, page 8, verified by FDA reviewers
[a]Based on first instance of pre- vs post-bronchodilator percent change of at least 12% between screening and baseline

8.1.5.7 Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance during the Double-Blind Treatment Period was high in both treatment arms overall (Table 15).

Overall treatment compliance was calculated as follows:
100 x (total number of puffs per dose counter during DBT/((Treatment end date – Treatment start date+1)*4)

One subject in the MF treatment group demonstrated ≤50% treatment compliance and was excluded from the PP analysis set.

Table 15: Treatment Compliance, Trial P087 (Full Analysis Set)

Participant Characteristic	MF MDI 100 mcg BID n (%)	MF/F MDI 100/10 mcg BID n (%)	Total n (%)
Subjects in population	90	91	181
Treatment compliance			
≤50%	1 (1.1%)	0 (0.0%)	1 (0.6%)
>50% to <80%	2 (2.2%)	5 (5.5%)	7 (3.9%)
≥80% to ≤120%	86 (95.6%)	84 (92.3%)	170 (93.9%)
>120%	1 (1.1%)	2 (2.2%)	3 (1.7%)
Summary statistics for treatment compliance			
Mean (SD)	98.22 (9.2)	97.6 (9.9)	97.9 (9.5)
Median	100	100	100
Range	44.2-121.5	58.9-129.7	44.2-129.7

Source: CSR for trial P087, Table 10-10; Verified by FDA reviewers

Rescue medications (SABA and oral corticosteroid) were provided to all subjects at the screening visit with instructions for use as rescue medications during an asthma exacerbation. SABA nebulization for treatment of asthma exacerbations was permitted as described above, though these were not provided to trial subjects by the Applicant.

8.1.5.8 Primary Endpoint

Primary Analysis Results

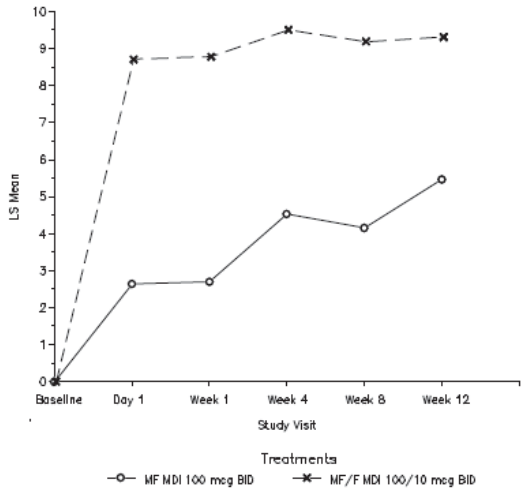
While both MF and MF/F were shown to produce a change from baseline, MF/F MDI 100/10 mcg BID was superior to MF MDI 100 mcg BID across 12 weeks based on AM post-dose 60-minute ppFEV1 AUC with a treatment advantage of 5.21 percentage points (p<0.001) (Table 16, Figure 7). The PP analysis of the primary efficacy endpoint yielded similar results, with an MF/F treatment advantage of 5.53 percentage points (p<0.001). These data demonstrate that both products improve ppFEV1 compared to baseline and that these effects persisted across 12 weeks.

Table 16: Analysis of Change from Baseline AM Postdose 60-minute AUC in Percent Predicted FEV1, Trial P087 (Full Analysis Set)

	MF MDI 100 mcg BID (N=90)	MF/F MDI 100/10 mcg BID (N=91)
Number analyzed	90	91
60-minute ppFEV1 AUC at baseline		
Observed mean (SD)	78.48 (12.79)	79.21 (11.44)
60-minute ppFEV1 AUC averaged across Day 1, Weeks 1, 4, 8, 12		
Observed mean (SD)	82.44 (11.67)	88.20 (11.42)
Change from baseline in 60-minute ppFEV1 AUC averaged across Day 1, Weeks 1, 4, 8, 12		
Median	4.07	8.48
Observed mean (SD)	3.96 (5.92)	8.99 (8.29)
Model based comparison: MF/F MDI 100/10 mcg BID vs. MF MDI 100 mcg BID		
Adjusted mean (SE)	3.90 (0.77)	9.11 (0.74)
Difference (SE)		5.21 (1.02)
95% CI		(3.22, 7.20)
p-value		<0.001

Abbreviations: N: sample size in Full Analysis Set; SD: standard deviation; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer; Trial P087 CSR, Table 11-1, page 83

Figure 7: Least Square Means of Percent Predicted FEV1 AUC, Change from Baseline AM Postdose Values, Trial P087 (Full Analysis Set)



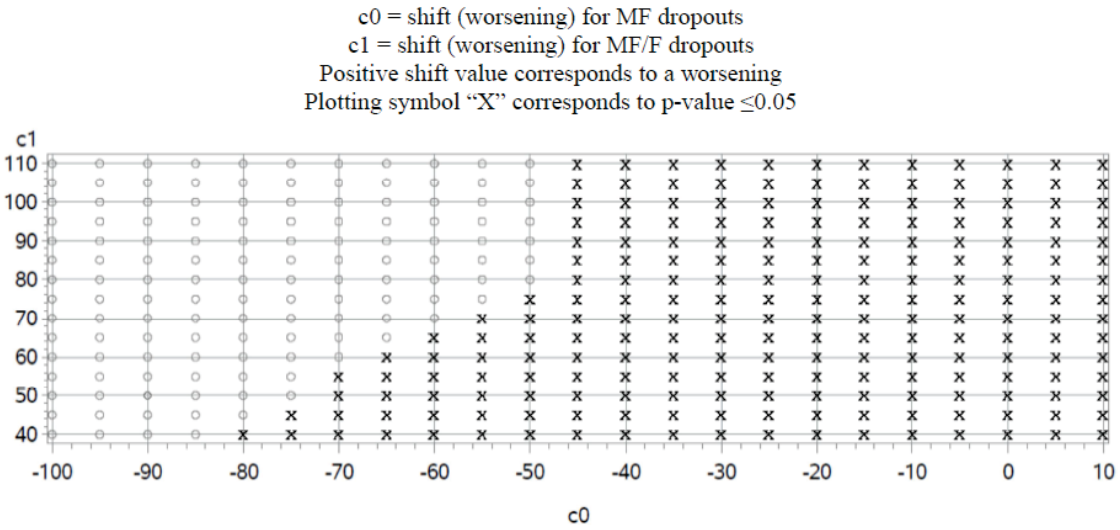
Source: Trial P087 CSR, Figure 11-1, page 84

Tipping Point Sensitivity Analysis Results

The primary analysis results, based on a control-based multiple imputation to missing values after dropout, showed strong statistical significance in treatment effect of MF/F relative to MF in AM post-dose 60-minute ppFEV1 AUC. The pattern mixture model approach represents a reasonable alternative assumption to the assumption of missing at random. A tipping point analysis was also performed to evaluate how robust the primary analysis results were across varying missing data assumptions, a more comprehensive range over scenarios assumed in the control-based primary analyses. The objective of this analysis was to more precisely identify the point at which the conclusion changes. In this analysis, missing data with monotone missingness patterns were first multiply imputed assuming that missingness was at random among those in the same treatment group, with the same region, age at baseline, and with comparable ppFEV1 values from baseline through discontinuation. Then for each treatment group, missing values were imputed in a stepwise fashion starting from the first postdose timepoint using a parametric regression model with all the covariates (excluding treatment) in the primary analysis model. These imputed values were then shifted by the shift parameter (c) corresponding to the patient's treatment arm. The results over a relatively comprehensive range of by-arm shift parameter (c) values are summarized in Figure 8. The column in the figure corresponding to c0 (shift in MF) equals to 0, can be read as a reference line: the analyses on this line assumes missing-at-random mechanism was employed and no shift (shift parameter = 0) was applied to the MF arm; the result along this line to a shift as large as 110 (c1=110) penalizing to the MF/F arm still maintained statistical significance in comparison. Across the range of by-arm shifts explored by the Applicant, it required shifts of 120 to 130 in the MF/F group, relative to those applied to the MF group, to tip the conclusion. If these shifts and relative shifts are clinically implausible, then missing data would be considered to have only minimal impact on the conclusions of the trial. Of note, while the above discussion centered the

tipping point analysis around the MAR assumptions, analysis based on MAR is likely far from true. For future presentation of tipping point analysis, we recommend centering the tipping point analysis around the best analysis in handling missing data.

Figure 8: Trial P087 Tipping Point Analysis – Rejection Region for a Range of Shift Values



Source: CSR for Trial P087, Figure 14.2-2, page 252

Sensitivity Analysis to Important Protocol Deviations

In addition, to address the review concern associated with the relatively high number of important protocol deviations found in Site 265, we conducted an additional sensitivity analysis to test the robustness of the primary analysis results when Site 265 data were removed from the FAS dataset. The estimated treatment advantage of 6.10 percentage points ($p<0.001$) (Table 17) based on FAS excluding Site 265 data was consistent and numerically higher than the primary analysis result (5.21 percentage points) based on the FAS. This sensitivity analysis shows that the observed treatment effect of MF/F over MF from the primary analysis is unlikely to be positively affected by the inclusion of Site 265 data.

Table 17: Sensitivity Analysis of Primary Endpoint: Change from Baseline in AM Post-dose 60-Minute Percent Predicted FEV1 AUC, Trial P087 (Full Analysis Set, excluding Site 265 Data)

	MF MDI100 mcg BID (N=90)	MF/F MDI 100/10 mcg BID (N=91)
Number analyzed	75	82
Model based comparison: MF/F MDI 100/10 mcg BID vs. MF MDI 100 mcg BID		
Adjusted mean (SE)	3.50 (0.84)	9.60 (0.81)
Difference (SE)		6.10 (1.12)
95% CI		(3.90, 8.30)
p-value		<0.001

Abbreviations: N: sample size in Full Analysis Set; SD: standard deviation; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer

8.1.5.9 Secondary and other relevant endpoints

The secondary endpoints for Trial P087 are listed above in Endpoints.

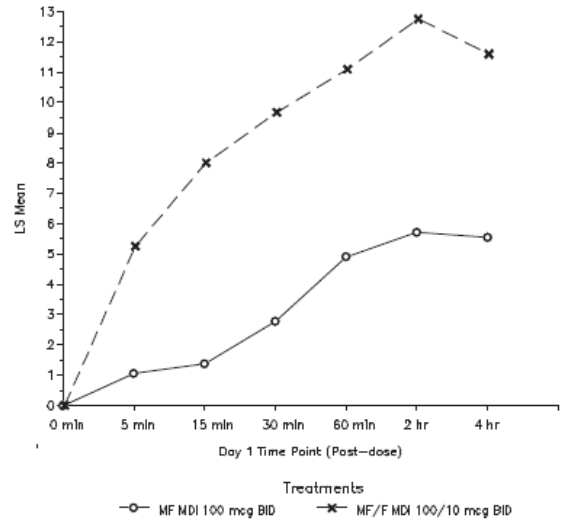
Significant improvement in the onset of action with MF/F relative to MF was achieved at 5 minutes and was sustained through 4 hours post-dose (p<0.001) (Table 18, Figure 9). PP and sensitivity analyses yielded similar results. It is likely that the addition of the LABA component to MF was responsible for the effect seen through 4 hours post-dose.

Table 18: Change From Baseline in AM Post-dose Percent Predicted FEV1 on Day 1, Trial P087 (Full Analysis Set)

	MF MDI100 mcg BID (N=90)	MF/F MDI 100/10 mcg BID (N=91)
Number analyzed	90	91
LS means at 5 minutes on Day 1	1.05	5.25
Difference in LS means (95% CI, p-value)		4.20 (2.50, 5.91) p<.001
LS means at 15 minutes on Day 1	1.37	8.01
Difference in LS means (95% CI, p-value)		6.64 (4.89, 8.39) p<.001
LS means at 30 minutes on Day 1	2.79	9.67
Difference in LS means (95% CI, p-value)		6.89 (5.10, 8.67) p<.001
LS means at 60 minutes on Day 1	4.90	11.09
Difference in LS means (95% CI, p-value)		6.19 (4.09, 8.28) p<.001
LS means at 2 hours on Day 1	5.71	12.75
Difference in LS means (95% CI, p-value)		7.04 (4.74, 9.35) p<.001
LS means at 4 hours on Day 1	5.55	11.59
Difference in LS means (95% CI, p-value)		6.05 (3.53, 8.56) p<.001

Abbreviations: N: sample size in Full Analysis Set; CI: confidence interval; LS: least square.
Source: FDA Statistical Reviewer; Trial P087 CSR, Table 11-5, page 95

Figure 9: Change From Baseline in AM Post-dose Percent Predicted FEV1 on Day 1, Trial P087 (Full Analysis Set)



Source: Trial P087 CSR, Figure 11-4, page 96

Significant improvements in the change from baseline AM post-dose ppFEV1 were also seen with MF/F relative to MF across the first 4 hours post dose at Week 12 (p=0.026) (Table 19).

Table 19: Change from Baseline in AM Post-dose 4-Hour Percent Predicted FEV1 AUC, Trial P087 (Full Analysis Set)

	Day 1		Week 12	
	MF MDI100 mcg BID (N=90)	**MF/F MDI 100/10 mcg BID (N=91)**	**MF MDI100 mcg BID (N=90)**	**MF/F MDI 100/10 mcg BID (N=91)**
Number analyzed	89	91	89	91
Baseline 4-hour ppFEV1 AUC				
Observed mean (SD)	78.48 (12.79)	79.21 (11.44)	78.48 (12.79)	79.21 (11.44)
Post baseline 4-hour ppFEV1 AUC				
Observed mean (SD)	84.43 (12.01)	90.31 (11.95)	86.07 (13.15)	90.20 (13.09)
Change from baseline in 4-hour ppFEV1 AUC				
Median	2.27	6.30		
Observed mean (SD)	2.70 (3.09)	7.17 (5.35)		
Model based comparison: MF/F MDI 100/10 mcg BID vs. MF MDI 100 mcg BID				
Adjusted mean	4.84	11.15	7.55	10.89
Difference (SE)		6.32		3.33
95% CI		4.36, 8.27		(0.41, 6.26)
p-value		<0.001		0.026

Abbreviations: N: sample size in Full Analysis Set; SD: standard deviation; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer; Trial P087 CSR, Table 11-6, page 98

While an improvement from baseline predose ppFEV1 averaged across Weeks 4, 8, and 12 of treatment was seen in both the MF and MF/F treatment groups, no statistical difference was seen between the groups (nominal p=0.197). Total daily SABA use was low at baseline and throughout the trial. As such, no difference in change of SABA usage was detected between the two treatment groups.

For a thorough discussion of the PK evaluation, see Section 6.

8.1.5.10 Durability of Response and Persistence of Effect

The effects of MF and MF/F on lung function were assessed through Week 12. Improvements from baseline in AM post-dose ppFEV1 were seen in both treatment groups.

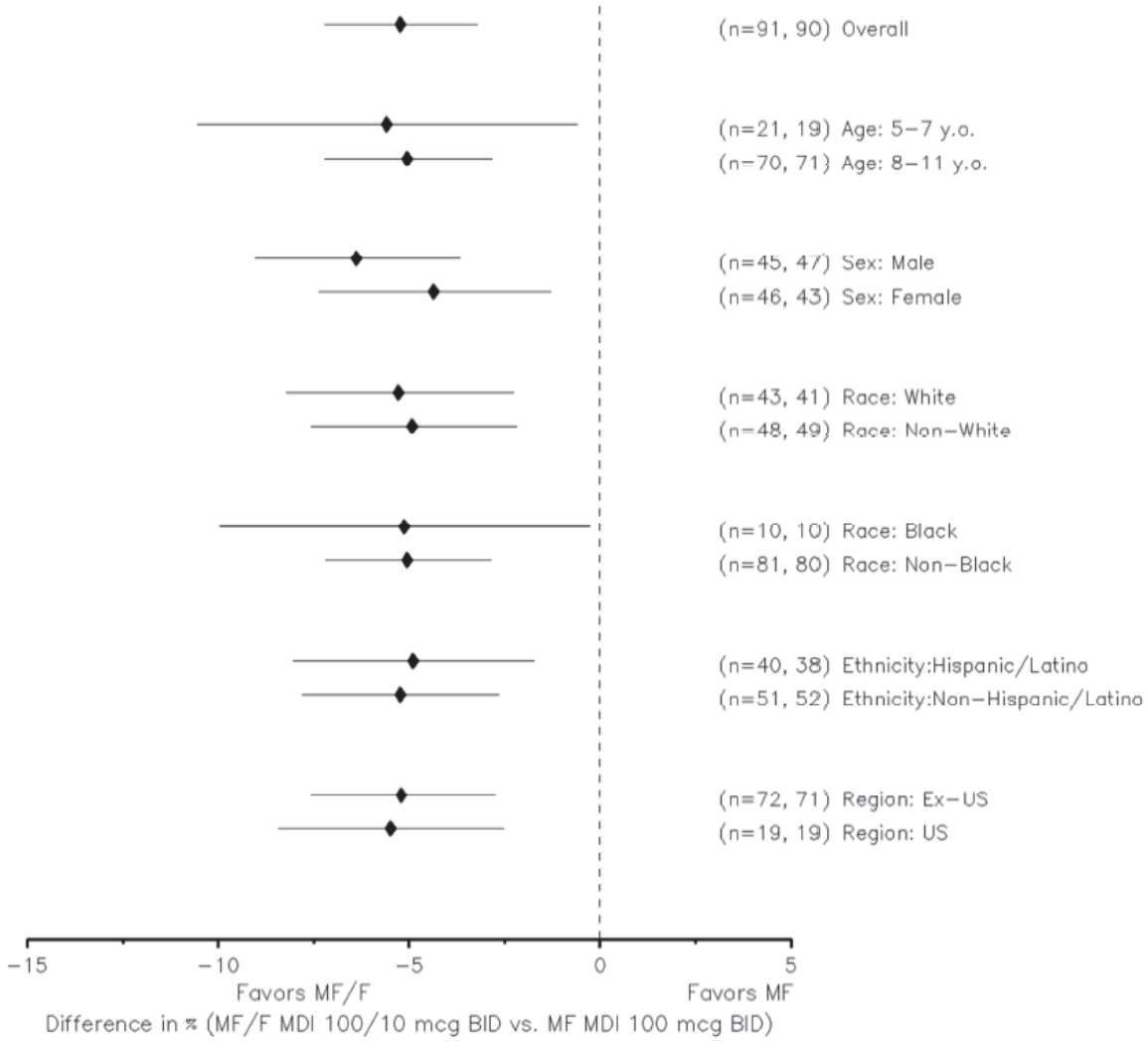
8.1.5.11 Subgroup analysis

The Applicant pre-planned subgroup analyses for the primary efficacy endpoint with subgroups based on age group (5 to 7 years or 8 to 11 years), sex (female, male), race (white, non-white), ethnicity, and region. No significant interaction was found between treatment and these subgroups at the 5% level of statistical significance.

This section provides the reviewer's subgroup analyses by age, sex, race, ethnicity, and region. For each subgroup factor, the model was adapted from the pre-specified primary efficacy analysis model. For the change from baseline in AM post-dose ppFEV1 endpoint, an interaction analysis was performed with the primary analysis cLDA model by including the subgroup variable, the subgroup variable-by-time interaction, and the subgroup variable-by-time-by-treatment interaction as covariates. By-subgroup mean change from baseline AM post-dose ppFEV1 were estimated to illustrate the treatment effects under each subgroup. Under each subgroup, the mean difference estimate between the MF/F group and the MF group together with associated CIs was presented using a forest plot.

The mean change from baseline in AM post-dose ppFEV1 by demographic subgroup is seen in Figure 10. Overall, the difference between the MF/F and MF groups was 5.21. Across the subgroup factors, there was no significant interaction between subgroups and treatment. The numbers are generally similar across subgroup categories. However, lack of a significant treatment-by-subgroup interaction could be due to small subgroup sample size and should not be interpreted as evidence that no interaction exists.

Figure 10: Change From Baseline in AM Post-dose 60-Minute Percent Predicted FEV1 AUC, by Subgroup, Trial P087 (Full Analysis Set)



Source: Applicant's CSR Figure 11-3.

Data Quality and Integrity

There were no data quality or integrity issues relative to the statistical analysis.

8.1.6 Assessment of Efficacy Across Trials

Due to the differences in trial design, an assessment of efficacy across trials was not performed.

8.2 Review of Safety

8.2.1 Safety Review Approach

The Applicant submitted safety data from Trials C96-361, P086 and P087 to support the use of MF and MF/F in pediatric patients. Trial P06476 is not included in the review of safety, as it was a single-dose, four-period cross-over study.

Trials C96-361 and P086 have been previously reviewed by the Division (see clinical reviews dated December 3, 2007, submitted to NDA 21067 for C96-361 and June 24, 2016, submitted to NDAs 205641 and 22518 for P086). Trial P087 is reviewed in this document as a stand-alone trial. The safety review focuses on all subjects as treated (equivalent to the Full Analysis Set), which includes all 181 randomized subjects who received at least one dose of blinded study medication.

Trials P086 and P087 were also reviewed as a pooled safety database to provide a more robust analysis of safety, consisting of 759 subjects. To avoid confounding due to differential treatment durations in the individual studies, the pooled data reflects exposure during the first 12 weeks of double-blind treatment, as well as events occurring 14 days after discontinuation of double-blind treatment.

The safety review includes an assessment of adverse events (AEs). In all AE tables, every subject is counted a single time for each applicable row. Safety issues identified a priori include known drug safety concerns for ICS and ICS/LABA products. AEs of “asthma” are not included in the pooled safety set due to differences in reporting of these events between the two trials. In P086, asthma exacerbations were defined as deterioration of asthma that results in hospitalization or emergency treatment with additional asthma treatment. Other asthma events not meeting these criteria were not reported as AEs unless there was temporal relationship to administration of study drug. Subjects who experienced asthma exacerbations were discontinued from the trial. In Trial P087, subjects were discontinued from treatment if they experienced more than one exacerbation, which was defined as worsening of asthma requiring systemic corticosteroid use and/or a 24-hour or longer stay in an emergency department, urgent care center, and/or hospital. All asthma events were reported as AEs in P087.

The review tools used to conduct independent reviewer analyses included use of JMP and JReview.

8.2.2 Review of the Safety Database

The safety database of pediatric patients is representative of 759 subjects, ages 5-11.

8.2.2.1 Overall Exposure

In P087, 181 children were exposed to MF or MF/MF during the 24-week trial. The majority of subjects were exposed for 24 weeks (Table 20).

Table 20: Number of Subjects by Duration of Exposure, Trial P087 (Safety Population)

Treatment	≥ 4 wks (≥28 days)	≥ 8 wks (≥56 days)	≥ 12 wks (≥ 84 days)	≥ 16 wks (≥ 112 days)	≥ 20 wks (≥ 140 days)	24 wks (168 days)	≥ 24 wks (≥ 169 days)	Total Subjects	Duration (Weeks)	
									Range	Mean (SD)
MF MDI 100 mcg BID	89 (98.9%)	89 (98.9%)	87 (96.7%)	87 (96.7%)	86 (95.6%)	53 (58.9%)	32 (35.6%)	90	1.4-29.2	23.4 (3.4)
MF/F MDI 100/10 mcg BID	89 (97.8%)	89 (97.8%)	88 (96.7%)	87 (95.6%)	87 (95.6%)	48 (52.7%)	33 (36.2%)	91	2-25.7	23.2 (3.7)

Source: Generated by reviewer

A total of 759 pediatric patients were exposed to MF or MF/F MDI during Trials P086 and P087 (Table 21). The analysis of AEs of this safety population focuses on the first 12 weeks of trial exposure to account for differences in design between the two trials. More than half of the safety population (58.6%) received treatment for ≥12 weeks, providing adequate exposure for interpretation of AEs.

Table 21: Number of Subjects by Duration Exposure, Trials P086 and P087 (Pooled Safety Population)

Treatment	≥ 4 wks (≥28 days)	≥ 8 wks (≥56 days)	≥ 12 wks (≥ 84 days)	≥ 16 wks (≥ 112 days)	≥ 20 wks (≥ 140 days)	24 wks (168 days)	≥ 24 wks (≥ 169 days)	Total Sub-jects	Duration (Weeks)	
									Range (weeks)	Mean (SD) (weeks)
Any treatment	660 (87%)	605 (79.7%)	445 (58.6%)	174 (22.9%)	173 (22.8%)	101 (13.3%)	65 (8.6%)	759	0.1-29.2	12.8 (7.1)
Placebo[a]	84 (75%)	70 (62.5%)	46 (41.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	112	0.3-14.4	8.5 (4.6)
MF MDI 50 mcg BID[a]	102 (85%)	89 (74.2%)	58 (48.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	120	0.1-12.7	9.6 (3.9)
MF MDI 100 mcg BID[b]	188 (92.6%)	178 (87.7%)	138 (68%)	87 (42.9%)	86 (42.4%)	53 (26.1%)	32 (15.8%)	203	0.1-29.3	16 (7.5)
MF MDI 200 mcg BID[a]	94 (87%)	86 (79.6%)	56 (51.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	108	0.4-13.6	10.1 (3.8)
MF DPI 100 mcg QD PM[a]	103 (82.4%)	93 (74.4%)	59 (47.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	125	0.7-13	9.6 (3.99)
MF/F MDI 100/10 mcg BID[c]	89 (97.8%)	89 (97.8%)	88 (96.7%)	87 (95.6%)	87 (95.6%)	48 (52.7%)	33 (36.2%)	91	2-25.7	23.2 (3.7)

Source: Generated by reviewer

[a]Trial P086 (~12-week treatment exposure); [b]pooled Trials P086, P087 (treatment exposure from ~12 weeks to ~24-weeks), [c]Trial P087 (~24-week treatment exposure)

8.2.2.2 Population Characteristics

Participant demographics and baseline asthma characteristics for subjects of Trials P086 and P087 is summarized below in Table 22. Most trial subjects (57.7%) were males. The average age of trial subjects in the two trials was 8.8 years, with 25% of subjects aged 5-7. While the majority of the subjects self-identified as white (65%), over 25% considered themselves multi-racial. Thirty-five percent of subjects identified themselves as Hispanic or Latino. Most subjects (83%) were enrolled in clinical trial sites outside of the United States. Almost half (48.9%) of the subjects had had a recent asthma exacerbation. The average ppFEV1 at screening was 76.7. Overall, baseline asthma characteristics were balanced across the various treatment arms.

Table 22: Demographics and Baseline Asthma Characteristics, Trials P086 and P087 (Pooled Safety Population)

Characteristic	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
Subjects in population	112	120	203	108	125	91	759
Gender							
Male	82 (73.2%)	69 (57.5%)	116 (57.1%)	49 (45.4%)	77 (61.6%)	45 (49.5%)	438 (57.7%)
Female	30 (26.8%)	51 (42.5%)	87 (42.9%)	59 (54.6%)	48 (38.4%)	46 (50.5%)	321 (42.3%)
Age (Years)							
Overall age, mean (SD)	9.0 (1.7)	8.71 (1.7)	8.84 (1.8)	8.69 (1.7)	8.74 (1.7)	9.1 (1.7)	8.83 (1.75)
5-7 stratum	26 (23.2%)	31 (25.8%)	51 (25.1%)	26 (24.1%)	35 (28%)	21 (23.1%)	190 (25%)
5	2 (1.8%)	4 (3.3%)	12 (5.9%)	6 (5.6%)	5 (4.0%)	3 (3.3%)	32 (2.0%)
6	9 (8.0%)	8 (6.7%)	18 (8.9%)	8 (7.4%)	10 (8.0%)	5 (5.5%)	58 (3.7%)
7	15 (13.4%)	19 (15.8%)	21 (10.3%)	12 (11.1%)	20 (16.0%)	13 (14.3%)	100 (6.3%)
8-11 stratum	86 (76.8%)	89 (74.2%)	152 (74.9%)	82 (75.9%)	90 (72%)	70 (76.9)	569 (75%)
8	16 (14.3%)	25 (20.8%)	26 (12.8%)	22 (20.4%)	15 (12.0%)	9 (9.9%)	113 (7.2%)
9	19 (17.0%)	19 (15.8%)	33 (16.3%)	19 (17.6%)	21 (16.8%)	14 (15.4%)	125 (7.9%)
10	24 (21.4%)	22 (18.3%)	48 (23.6%)	22 (20.4%)	36 (28.8%)	25 (27.5%)	177 (11.2%)
11	26 (23.2%)	23 (19.2%)	45 (22.2%)	19 (17.6%)	18 (14.4%)	22 (24.2%)	153 (9.7%)
12[x]	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Race							
American Indian or Alaska Native	3 (2.7%)	4 (3.3%)	5 (2.5%)	8 (7.4%)	4 (3.2%)	5 (5.5%)	29 (3.8%)
Asian	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	2 (0.3%)
Black or African American	2 (1.8%)	7 (5.8%)	12 (5.9%)	3 (2.8%)	5 (4.0%)	10 (11.0%)	39 (5.1%)
White	81 (72.3%)	84 (70.0%)	122 (60.1%)	72 (66.7%)	91 (72.8%)	43 (47.3%)	493 (65.0%)

Characteristic	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
Multi-Racial	26 (23.2%)	25 (20.8%)	63 (31.0%)	25 (23.1%)	24 (19.2%)	33 (36.3%)	196 (25.8%)
Ethnicity							
Hispanic or Latino	36 (32.1%)	39 (32.5%)	78 (38.4%)	38 (35.2%)	38 (30.4%)	40 (44.0%)	269 (35.4%)
Not Hispanic or Latino	74 (66.1%)	78 (65.0%)	122 (60.1%)	66 (61.1%)	84 (67.2%)	51 (56.0%)	475 (62.6%)
Not reported	1 (0.9%)	3 (2.5%)	3 (1.5%)	4 (3.7%)	3 (2.4%)	0 (0.0%)	14 (1.8%)
Unknown	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Region							
US	17 (15.2%)	20 (16.7%)	36 (17.7%)	16 (14.8%)	21 (16.8%)	19 (20.9%)	129 (17.0%)
Outside of US	94 (84.8%)	100 (83.3%)	167 (82.3%)	92 (85.2%)	104 (83.2)	72 (79.1%)	630 (83.0%)
History of Asthma Exacerbation*							
Yes	50 (44.6%)	57 (47.5%)	109 (53.7%)	47 (43.5%)	49 (39.2%)	59 (64.8%)	371 (48.9%)
No	62 (55.4%)	63 (52.5%)	94 (46.3%)	61 (56.5%)	76 (60.8%)	32 (35.2%)	388 (51.1%)
Asthma Duration (Years)							
Mean (SD)	5.5 (2.9)	5.0 (2.8)	4.7 (3.4)	4.6 (2.8)	4.9 (2.7)	4.7 (4.3)	4.9 (3.2)
ppFEV1 at Baseline†							
Subjects with Data	110	116	197	102	122	91	738
Mean (SD)	77.8 (7.2)	79.4 (7.6)	78.6 (10.4)	78.8 (8.0)	78.4 (7.6)	79.2 (11.4)	78.7 (8.9)

Source: Integrated Analysis of Safety, Table 5.3.5.3.3-asthmapeds:2 & Table 5.3.5.3.3-asthmapeds:3, Pages 8-14
[a]Trial P086; [b]pooled Trials P086, P087, [c]Trial P087
×One subject who was randomized at age 11 in the Integrated Voice Response System is reported to be age 12 due to a standard missing date imputation
*For P086, asthma exacerbation reported within 3 months of trial entry; for P087, reported within one year of trial entry.
†For P087 Baseline is the average of 30 min predose and 0 min ppFEV1 (forced expiratory volume in 1 second) value.
For P086 Baseline is the ppFEV1 (forced expiratory volume in 1 second) value on the day of treatment start date (Day 1).

8.2.2.3 Adequacy of the Safety Database

The safety database of 759 pediatric patients is of sufficient size and duration to assess the safety of the proposed doses of MF and MF/F for ages 5-11, given the overall safety profile of the ICS and ICS/LABA drug classes.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
No data quality issues as they relate to safety were identified in the review of this sNDA.

8.2.3.1 Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and serious AEs in the protocols. Adverse events were monitored throughout Trials P086 and P087, from signing of informed consent

until the time subjects completed or discontinued from the trial. The Applicant used a tiered approach to categorize AEs for both P086 and P087. Safety events of special interest were identified *a priori* and were characterized as Tier 1 safety endpoints. For both P087 and the pooled safety analysis, treatment-emergent AEs were defined as those that occurred while the subject was receiving double-blind treatment or within 14-days of treatment discontinuation.

The following tiered safety definitions were used:

For Trial P086:

- Tier 1: Treatment emergent AEs of interest: headache, oropharyngeal candidiasis, dysphonia, and post-dose bronchospasm
- Tier 2: Treatment-emergent AEs with at least 4 events in at least one treatment group
- Tier 3: Treatment-emergent AEs that do not occur with at least 4 events in at least one treatment group. Routine safety measures including vital signs are included in this tier

For Trial P087:

- Tier 1: Pre-specified safety events, which were oral/oropharyngeal candidiasis, headache, tremor, and tachycardia
- Tier 2: Asthma exacerbations, treatment emergent adverse events (TEAEs), serious adverse events (SAEs), drug-related AEs, serious and treatment-related AEs, treatment discontinuations due to AE, any specific AEs with incidence ≥4 subjects in one of the treatment groups, and asthma exacerbations requiring hospitalization, ER visit, or systemic corticosteroids use
- Tier 3: Any specific AE not pre-specified as either Tier 1 or Tier 2 endpoints that occurred in less than four subjects in both treatment groups and well as any vital sign changes from baseline

Tier 1 events will be termed AE of special interest (AESI) for the remainder of this review. All AEs were coded using MedDRa (version 17.1 for Trial P086 and version 20.1 for Trial P087). The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate.

Routine Clinical Tests
No post-screening laboratory safety tests were pre-specified in this protocol except for urine pregnancy tests for female subjects of childbearing potential. Vital signs were evaluated at each clinic visit. This approach is reasonable for evaluation of an approved product in a pediatric population.

8.2.4 Safety Results

8.2.4.1 Deaths

There were no deaths during the conduct of the pediatric clinical studies.

8.2.4.2 Serious Adverse Events

In Trial P086, 11 SAEs were reported. "Asthma" was the only event to occur in more than one subject, with events occurring in placebo (n=2) and the lower dose group (MF 50 mcg BID, n=2). No new safety concerns were identified (Please refer to clinical review by Sofia Chaudry submitted to NDAs 205641 and 022518 on June 24, 2016, for more information).

As shown in Table 23, the occurrence of SAEs was also low in P087. Three subjects reported a total of five events which included epididymitis, concussion, urticaria, and asthma. All events resolved.

Table 23: Serious Adverse Events, Trial P087 (Safety Population)

	MF MDI 100 mcg BID n=90	MF/F MDI 100/10 mcg BID n=90	Total n=180
Respiratory, thoracic and mediastinal disorders	1 (1.1%)	1 (1.1%)	2 (1.1%)
Asthma	1 (1.1%)	1 (1.1%)	2 (1.1%)
Infections and infestations	1 (1.1%)	0 (0.0%)	1 (0.6%)
Epididymitis	1 (1.1%)	0 (0.0%)	1 (0.6%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (1.1%)	1 (0.6%)
Urticaria	0 (0.0%)	1 (1.1%)	1 (0.6%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (1.1%)	1 (0.6%)
Concussion	0 (0.0%)	1 (1.1%)	1 (0.6%)

Source: Trial P087 CSR, Table 12-8, page 128

Review of SAEs in Trials P086 and P087 (Table 24) did not raise any new safety concerns for these products. The reported SAEs were singular events, with the exception of asthma, which was not greater than placebo.

Table 24: Serious Adverse Events, Trials P086 and P087 (Pooled Safety Population)

	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
Gastrointestinal disorders	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	2 (0.3%)
Dyspepsia	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Enteritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.1%)
Infections and infestations	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.6%)	0 (0.0%)	3 (0.4%)
Appendicitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.1%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.1%)
Otitis media	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Nervous system	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.1%)

	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
disorders							
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	2 (1.8%)	2 (1.7%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	6 (0.8%)
Asthma	2 (1.8%)	2 (1.7%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	6 (0.8%)

Source: Table 3 in Response to FDA on queries dated 03May2019
[a]Trial P086; [b]pooled Trials P086, P087, [c]Trial P087
Serious adverse event of 'asthma' (MedDRA preferred Term) corresponds to AE verbatim term of 'Asthma Exacerbation.' Asthma definition differed between trials.

8.2.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

Thirteen subjects discontinued treatment due to AEs during Trials P086 and P087 (n=10 in P086 and n=3 in P087) (Table 25). This represents a small proportion of subjects in both trials.

Of the 10 subjects who discontinued related to an AE in P086, only one subject was receiving the proposed pediatric dose for MF (100 mcg BID). This individual experienced respiratory viral infection that was determined to be severe. Other subjects who discontinued treatment received either placebo, MF 50 mcg MDI, or MF 100 mcg DPI, and reported asthma exacerbations, dyspnea, headache, pharyngeal inflammation, and respiratory tract infections.

The three subjects who discontinued study medication due to AEs in P087 were all receiving MF 100 mcg BID; they reported asthma exacerbations and exercise-induced bronchospasm. One subject went on to complete the trial; the other two subjects were withdrawn from the trial by their parent or guardian.

Review of these data does not raise any new safety concerns for the use of MF or MF/F in children ages 5-11.

Table 25: Disposition Related to Adverse Events, Trials P086 and P087 (Pooled Safety Population)

	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
Trial disposition							
Completed	60 (53.6%)	79 (65.8%)	169 (83.3%)	83 (76.9%)	88 (70.4%)	89 (97.8%)	568 (74.8%)
Discontinued	52 (46.4%)	41 (34.2%)	34 (16.7%)	25 (23.1%)	37 (29.6%)	2 (2.2%)	191 (25.2%)
Adverse event	3 (2.7%)	2 (1.7%)	1 (0.5%)	0 (0.0%)	4 (3.2%)	0 (0.0%)	10 (1.3%)
Infections and Infestations	1 (0.9%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.8%)	0 (0%)	3 (0.4%)

	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
Respiratory tract infection[a]	1 (0.9%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.8%)	0 (0%)	3 (0.4%)
Nervous system disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.1%)
Headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	2 (1.8%)	2 (1.7%)	0 (0%)	0 (0%)	2 (1.6%)	0 (0%)	6 (0.8%)
Asthma	2 (1.8%)	2 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.5%)
Dyspnea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.1%)
Pharyngeal Inflammation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.1%)
Study Medication Disposition							
Completed	60 (53.6%)	79 (65.8%)	167 (82.3%)	83 (76.9%)	88 (70.4%)	87 (95.6%)	564 (74.3%)
Discontinued	52 (46.4%)	41 (34.2%)	36 (17.7%)	25 (23.1%)	37 (29.6%)	4 (4.4%)	195 (25.7%)
Adverse event	3 (2.7%)	2 (1.7%)	4 (2.0%)	0 (0.0%)	4 (3.2%)	0 (0.0%)	13 (1.7%)
Infections and Infestations	1 (0.9%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.8%)	0 (0%)	3 (0.4%)
Respiratory tract infection	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	2 (0.3%)
Respiratory tract infection viral	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Nervous system disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.1%)
Headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	2 (1.8%)	2 (1.7%)	3 (1.5%)	0 (0%)	2 (1.6%)	0 (0%)	9 (1.2%)
Asthma	2 (1.8%)	2 (1.7%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	6 (0.8%)
Bronchospasm	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Dyspnea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Pharyngeal Inflammation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)

Source: FDA reviewer
[a]Trial P086; [b]pooled Trials P086, P087, [c]Trial P087

8.2.4.4 AESIs

Given known AEs associated with ICS and ICS/LABA drug classes, pre-specified AEs were designated as Tier 1 events in both Trials P086 and P087 (see Section 8.2.3). In P087, eight subjects reported an AESI (Table 26). Events of oral/oropharyngeal candidiasis were considered treatment-related by investigators, while the events of headache were thought to be treatment-independent. Tachycardia and tremor were not reported, nor were other signs and symptoms associated with known effects of adrenergic stimulation.

Table 26: Participants with Pre-Specified Tier 1 AE, Trial P087 (Safety Population)

	MF MDI 100 mcg BID n=90	MF/F MDI 100/10 mcg BID n=91	Totals n=181
Subjects with no pre-specified Tier 1 AE	86 (95.6%)	87 (95.6%)	173 (95.6%)
Subjects with one or more pre-specified Tier 1 AE	4 (4.4%)	4 (4.4%)	8 (4.4%)
Infections and infestations	3 (3.3%)	1 (1.1%)	4 (2.2%)
Oral candidiasis	2 (2.2%)	1 (1.1%)	3 (1.7%)
Oropharyngeal candidiasis	1 (1.1%)	0 (0.0%)	1 (0.6%)
Nervous system disorders	1 (1.1%)	3 (3.3%)	4 (4.4%)
Headache	1 (1.1%)	3 (3.3%)	4 (4.4%)

Source: Trial P087 CSR, page 123

The only pre-specified AESI reported in Trial P086 was headache, with nine subjects across the five treatments (Table 27). No events of oropharyngeal candidiasis, dysphonia, nor post-dose bronchospasm were reported in Trial P086. Review of these pooled data did not present any new safety concerns for MF and MF/F.

Table 27: Participants with Pre-Specified Tier 1 AE, Trials P086 and P087 (Pooled Safety Population)

	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
Infections and infestations	0 (0.0%)	0 (0.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	4 (0.5%)
Oral candidiasis	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	3 (0.4%)
Oropharyngeal candidiasis	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Nervous system disorders	2 (1.8%)	1 (0.8%)	3 (1.5%)	1 (0.9%)	3 (2.4%)	3 (3.3%)	13 (1.7%)
Headache	2 (1.8%)	1 (0.8%)	3 (1.5%)	1 (0.9%)	3 (2.4%)	3 (3.3%)	12 (1.6%)

[a]Trial P086; [b]pooled Trials P086, P087; [c]Trial P087
Excludes events of 'Asthma' due to pre-specified differences in adverse events (AE) reporting between P086 and P087.
Source: Trial P086 CSR, page 113; Trial P087 CSR, page 123, Response to FDA queries dated 03 MAY 2019

Overdoses were designated as events of clinical interest in both the P086 and P087 trials. During Trial P086, there were 61 subjects during the treatment period (10.6%) that reported one or more events of overdose, with a maximum dose of 700 mcg. Three events of overdose occurred in Trial P087 (1 in MF group, 2 in MF/F group); however the specific doses were not provided. No AEs were associated or reported with these events.

Asthma exacerbations were pre-specified events of clinical interest in Trial P087. A total of 18 subjects reported 19 asthma exacerbations across the two treatment arms. Two of the events

required hospitalization (Table 28). Given that asthma exacerbations were balanced across treatment groups, it is unlikely that F contributed to an any increases in asthma-related events.

Table 28: Asthma Exacerbation Events, Trial P087 (Safety Population)

	MF MDI 100 mcg BID n=90	MF/F MDI 100/10 mcg BID n=91	Totals n=181
Asthma exacerbation event of clinical interest	9 (9.9%)	9 (10.0%)	18 (9.9%)
Use of systemic corticosteroids[a]	9 (9.9%)	9 (10.0%)	18 (9.9%)
Emergency room visits[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hospitalization[c]	1 (1.1%)	1 (1.1%)	2 (1.1%)

Source: Trial P087 CSR, page 134
[a]refers to any systemic corticosteroid prescribed for asthma
[b]refers to a visit of <24 hour in an ER or other urgent care facility for asthma
[c]refers to ≥ 24 hour stay in a hospital or equivalent healthcare facility for asthma

Treatment Emergent Adverse Events and Adverse Reactions
Common AEs for Trial P086 have been reviewed by Sofia Chaudry in clinical review dated June 24, 2016.

Given absence of a placebo group in Trial P087, it is difficult to assess relatedness of events to medication use. Generally, events were mostly singular and balanced between treatment arms; therefore, a review of all AEs in Trial P087 did not reveal any new safety concerns. Common AEs (occurring in ≥3% of subjects in one or more treatment groups) reported in Trial P087 are summarized in Table 29. Of note, rhinitis was seen as a common AE in both Trials P086 and P087, however it was not considered common in the pooled safety population (Table 30). Influenza and upper respiratory tract infections were common AEs in analysis of Trial P087 and the pooled safety population, though this was mostly balanced between treatment and placebo arms. The occurrence of these events, though not commonly reported, may have clinical significance however, as viral infections can trigger asthma exacerbations. Overall, the safety profile for pediatric patients is similar to that observed in patients aged 12 years and older.

Table 29: Subjects with Adverse Events (Incidence ≥3% in One or More Treatment Groups), Trial P087 (Safety Population)

	MF MDI 100 mcg BID n=90	MF/F MDI 100/10 mcg BID n=91	Totals n=181
Infections and infestations	39 (43.3%)	25 (27.5%)	64 (35.4%)
Upper respiratory tract infection	3 (3.3%)	9 (9.9%)	12 (6.6%)
Nasopharyngitis	8 (8.9%)	2 (2.2%)	10 (5.5%)
Influenza	3 (3.3%)	5 (5.5%)	8 (4.4%)
Pharyngitis	6 (6.7%)	1 (1.1%)	7 (3.9%)
Respiratory tract infection	4 (4.4%)	2 (2.2%)	6 (3.3%)
Viral upper respiratory tract infection	3 (3.3%)	2 (2.2%)	5 (2.8%)
Rhinitis	5 (5.6%)	0 (0.0%)	5 (2.8%)
Viral infection	3 (3.3%)	1 (1.1%)	4 (2.2%)
Respiratory, thoracic and mediastinal disorders	19 (21.1%)	16 (17.6%)	35 (19.3%)
Asthma	15 (16.7%)	11 (12.1%)	26 (14.4%)
Cough	3 (3.3%)	3 (3.3%)	6 (3.3%)
Nervous system disorders	1 (1.1%)	3 (3.3%)	4 (2.2%)
Headache	1 (1.1%)	3 (3.3%)	4 (2.2%)

Source: FDA reviewer

Table 30: Subjects with Adverse Events (Incidence ≥3% in One or More Treatment Groups and Greater than Placebo), Trials P086 and P087 (Safety Population)

	Placebo[a] n=112	MF MDI 50 mcg BID[a] n=120	MF MDI 100 mcg BID[b] n=203	MF MDI 200 mcg BID[a] n=108	MF DPI 100 mcg QD PM[a] n=125	MF/F MDI 100/10 mcg BID[c] n=91	Totals n=759
Influenza	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	4 (2.0%)	3 (3.3%)	8 (1.1%)
Upper respiratory tract infection	4 (3.6%)	5 (4.0%)	2 (1.9%)	0 (0.0%)	6 (3.0%)	6 (6.6%)	23 (3.0%)

Source: FDA reviewer
[a]Trial P086; [b]Pooled Trials P086, P087, [c]Trial P087

Laboratory Findings

Treatment with ICS and ICS/LABA products has the potential to induce hyperglycemia and hypokalemia. The Applicant mentions that there were no reports of laboratory abnormalities in Trial P086 and P087, though upon review of the data and schedule of assessments, it doesn't appear that this was routinely measured. Given the relative low dose of the study drug, it is unlikely that this would be a significant safety concern.

Vital Signs

A review of the vital sign data does not reveal any safety concerns.

8.2.5 Analysis of Submission-Specific Safety Issues

Known AEs associated with ICS and ICS/LABA therapy include localized infection, post-dose bronchospasm, dysphonia, headache, tremor and tachycardia.

8.2.5.1 Oral/oropharyngeal candidiasis

While no events of oral/oropharyngeal candidiasis were seen in Trial P086, four subjects reported this AE during P087 (Table 26). These events were considered treatment-related by investigators. These infections were considered mild or moderate and all resolved. None of these events resulted in treatment discontinuation.

8.2.5.2 Headache

Headache was reported in both P086 and P087; four events in P087 and nine events in P086. In P086, one event (for subject receiving MF DPI 100 mg qPM) was considered serious. A subject with moderate headache (also in MF DPI treatment group) discontinued treatment. All four events in P087 were considered mild and resolved within one week, with the exception of one subject in the MF group that reported intermittent headache for 4 months. The events of headache in P087 were not considered to be treatment-related by investigators and did not result in discontinuation.

8.2.5.3 Bronchospasm

Paradoxical bronchospasm is a known side effect with ICS and ICS/LABA therapy. No events were reported in P086. One subject treated with MF in P087 reported worsening of exercise-induced bronchospasm. This was classified as mild and resolved following treatment discontinuation.

8.2.5.4 Tremor

There were no reports of tremor in Trials P086 and P087.

8.2.5.5 Tachycardia

Paroxysmal tachycardia was reported in Trial P086 for a subject receiving MF DPI 100 mcg daily. This was considered mild and resolved without intervention.

8.2.5.6 Dysphonia

There were no reports of dysphonia in Trials P086 and P087.

8.2.6 Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The PAQLQ[S] was used in Trial P086. Change from baseline in PAQLQ[S] score at 12 weeks was a secondary endpoint. The PAQLQ[S] assessments only included subjects in countries where a

validated translated questionnaire was available. Among the MDI treatment groups, only MF MDI 200 mcg BID demonstrated a significant improvement compared to placebo.

8.2.7 Safety Analyses by Demographic Subgroups

For Trial P087, a safety analysis by demographic subgroup was conducted by assessing differences in AE incidence greater than 5% relative to the overall trial population background rate (49.2%). Subgroup analyses were conducted for age, sex, race, ethnicity, and region, though it should be noted that Trial P087 was not powered to detect differences by demographic subgroup.

Age
The AE profile was similar between 5-7 and 8-11 year-old subgroups. While a difference of greater than 5% compared to background was not seen, it is of note that the overall proportion of AEs in the younger group (42.5%) was lower than the older group (51.1%). This difference was predominantly driven by the Infection and Infestation SOC, where the proportion of subjects in the 8-11 group (32.5%) was approximately 8% higher than the 5-7 age group (36.2%).

Sex
The percentages of AEs by sex was similar across treatment groups, though the overall rate was lower in males (43.5%) compared to females (55.1%).

Race
The highest proportion of AEs was seen in subjects who identified themselves as white (56%). AEs were higher in MF MDI 10 mcg BID across race subgroups, with the exception of the American Indian or Alaska Native subgroups which saw equal rates of AEs in each treatment arm.

Ethnicity
Within treatment groups and across the overall population, the proportion of AEs in subjects of Hispanic or Latino ethnicity and Not Hispanic or Latino Ethnicity was comparable.

8.2.8 Specific Safety Studies/Clinical Trials

No additional studies were conducted to evaluate a specific safety concern.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Not applicable to this sNDA.

Human Reproduction and Pregnancy
Not applicable to this sNDA.

Pediatrics and Assessment of Effects on Growth
Growth retardation was not reported in Trials P086 nor P087.

Of note, growth effects were seen with MF DPI following a 52-week trial conducted in 4 to 9 year-olds. The mean growth rates, expressed as least-squares mean in cm per year for subjects using 110 mcg BID, 220 mcg daily, 110 mcg daily or placebo were 5.34, 5.93, 6.15, and 6.44, respectively. The differences from placebo and the corresponding 2-sided 95% confidence of growth rates for 110 mcg BID, 220 mcg daily, 110 mcg daily were -1.11 (95% CI: -2.34, 0.12), 0.51 (95% CI: -1.69, 0.67), and -0.30 (95% CI: -1.48, 0.89), respectively. These data are provided in the prescribing information for MF DPI (Asmanex Twisthaler). Because the systemic exposure of MF administered by MDI has been shown to be comparable or less than by DPI administration, systemic effects evaluated with MF DPI are considered applicable to both MF and MF/F MDI. As such, these data represent theoretical growth effects, especially with prolonged use.

While it was not specifically assessed in Trials P086 and P087, the Applicant has provided data regarding evaluation of systemic effects of MF on HPA axis function in children from Trial C96-361. Mean plasma cortisol and urinary-free cortisol was assessed on Day 29, with no evidence of HPA axis suppression in the 110 mcg BID DPI treatment group. While MF 220 mcg and 440 mcg BID DPI caused a decrease in serum cortisol AUC for the first 12 hours after administration relative to placebo, the degree of suppression was not considered to be clinically important since all except one subject in the high dose group had a normal response to cosyntropin stimulation testing. Given that the systemic exposure of MF via a DPI is higher than an MDI, and that there was no evidence of HPA axis suppression in the lowest dosing group (110 mcg BID DPI), it is unlikely that MF 100 mg BID or MF/F 100/10 mcg BID would cause HPA axis suppression.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Not applicable to this sNDA.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
There is ongoing review for the postmarketing data for both MF and MF/F. No new safety concerns have been identified from this review that directly impacts the pediatric development program for this product.

Expectations on Safety in the Postmarket Setting
There is an expectation that safety continues to be monitored in the postmarket setting.

8.2.11 Integrated Assessment of Safety

Safety analysis of MF and MF/F is primarily based on Trials P086 and P087, which yielded a

pooled safety database of 759 subjects. There were no deaths reported during the conduct of these two clinical trials. Adverse events, including serious adverse events, were limited in number, evenly distributed between treatment groups and were not dose dependent. While AEs associated with ICS and ICS/LABA drug classes, such as headache and oral/ oropharyngeal candidiasis, were seen, these occurrences were rare. Influenza and upper respiratory tract infections were identified as common adverse events in a combined analysis of Trials P086 and P087, though this is consistent with clinical trial data generated from patients over the age of 12. Overall, the safety issues identified through the pediatric clinical trial program are similar to those of adult and adolescent populations. Considering safety data from Trials P086 and P087, MF 100 mcg BID and MF/F 100/10 mcg BID in the pediatric population has a favorable risk-benefit profile.

8.3 Statistical Issues

There were no outstanding statistical issues related to the review of this application.

8.4 Conclusions and Recommendations

The Applicant submitted efficacy supplements to NDAs 205641 and 22518 in support of expanding the indication for MF and MF/F MDIs to include treatment of asthma for patients 5 years of age and older. The Applicant submitted data from the pivotal trials (see Section 7.1) P086 and P087 support efficacy and safety. Trial P086 was a 12-week, randomized, placebo-controlled, dose-ranging study of MF MDI for pediatric patients 5 to 11 years of age with persistent asthma. MF 100 mcg twice daily in 5-11 year-olds resulted in a statistically significant change from baseline in ppFEV1 at Week 12 compared to placebo, supporting the appropriateness of this dose in both MF and MF/F products. Trial P087, a phase 3, randomized, active-controlled, parallel-group study in children ages 5-11 years was designed to study the efficacy and long-term safety of MF/F and MF MDI in children with persistent asthma. In this trial, 181 subjects received MF 100 mcg or MF/F 100/10 mcg MDI for a 12-week efficacy evaluation followed by an additional 12-week safety extension and 2-week safety follow-up. Data from Trial P087 supports the contribution of F to MF/F by demonstrating a statistically significant change in FEV1 ($AUC_{0\text{-}60\ minutes}$) through Week 12 for MF/F 100/10 mcg BID compared to MF 100 mcg BID.

A review of the safety data revealed a safety profile similar to what is seen in adolescents and adults and did not identify any new safety concerns. Considering the demonstrated efficacy and safety, the risk-benefit assessment is favorable and supports expanding the indication of MF/F down from 12 years of age to 5 years of age.

The recommended action is Approval.

9 Advisory Committee Meeting and Other External Consultations

MF HFA and MF/F are well characterized products and MF DPI is approved for use in the age range evaluated in this pediatric program. As such, no advisory committee meeting was held to discuss the results of this pediatric program.

10 Pediatrics

The Applicant submitted data from Trial P087 to fulfill the requirements of the Written Request. At the Pediatric Exclusivity Board on June 19, 2019, it was determined that the Applicant fulfilled all requirements. Exclusivity was granted on June 24, 2019 (See Pediatric Exclusivity Determination Checklist submitted to NDA 22518 on June 24, 2019).

On July 17th, 2019, The Pediatric Review Committee (PeRC) reviewed Trial P087 and agreed that this clinical trial fulfilled the two outstanding PMRs, 2149-4 and 1658-7. Approval of the pediatric indication (extending age of use down to 5 years of age) was also endorsed.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Prescribing information

The Applicant provided an amended label for both Asmanex HFA and Dulera. These labels incorporate the pediatric information that pertains to children ages 5-11 years in Sections 2 DOSAGE AND ADMINISTRATION, 5 WARNINGS AND PRECAUTIONS, 6 ADVERSE REACTIONS, 10 OVERDOSAGE, 12 CLINICAL PHARMACOLOGY, and 14 CLINICAL STUDIES. The Division of Medication Error, Prevention, and Analysis (DMEPA) also reviewed the label and suggested changes to sections 2 DOSAGE AND ADMINISTRATION and 16 HOW SUPPLIED/STORAGE AND HANDLING. Recommendations from labeling consultants in DMPP, OPDP, Patient Labeling Team were also incorporated into final label. Changes are described in Tables 31 and 32 that are reflective of the Asmanex and Dulera labels received on August 9, 2019.

Table 31: ASMANEX HFA Prescribing Information

Section	Proposed Labeling	Approved Labeling	Rationale
Section 2.1 Administration Information	Administration information provided by the Applicant	Section relabeled "Administration Information." Passive voice updated to active voice.	Edited for consistency across labels and for clarity.
Section 2.2: Recommended Dosage	Information related to dosage. (b) (4) (b) (4)	(b) (4) (b) (4), was deleted as it was considered redundant. Following phrase added: "After asthma stability has been achieved, it may be desirable to titrate to the lowest effective dosage to reduce the possibility of side effects." (b) (4)	Section edited for clarity and to minimize redundancy. (b) (4)
Section 2.2: Recommended Dosage	Information for prescriber regarding oral corticosteroid therapy	Section simplified to state: "It is recommended that patients currently receiving chronic oral corticosteroid therapy (e.g., prednisone) begin with ASMANEX HFA 200 mcg (2 inhalations twice daily)."	Edited for clarity and simplicity.

Section	Proposed Labeling	Approved Labeling	Rationale
Section 6 ADVERSE REACTIONS	"The first trial was a placebo-controlled trial comparing ASMANEX HFA 50 mcg to 2 other dosage strengths of mometasone furoate MDI ((b) (4), each administered as two inhalations, twice daily) as well as mometasone furoate DPI 100 mcg, administered as one evening inhalation."	Statement changed to clarify dose (25 mcg or 100 mcg, each administered as two inhalations, twice daily)	Trial P086 treatment arms included use of MDIs that dispensed 25 mcg and 100 mcg per actuation, administered as two inhalations twice daily.
Section 6 ADVERSE REACTIONS	(b) (4)	Statements removed	Edited for clarity and simplicity
Sections 10 – 17	Various statements referring to human subject data	Qualified statements describing if data generated in adults, adolescents or young children	Because the label now includes information pertaining to children ages 5 to less than 12, it is important for prescribers to know if that information affects their patient population
Section 12.2 Pharmaco-dynamics	(b) (4)	Statements removed	Statements (b) (4) (b) (4) were removed (b) (4) (b) (4)
Section 12.2 Pharmaco-dynamics	(b) (4)	Statement removed	Safety information is included in Section 6

Section	Proposed Labeling	Approved Labeling	Rationale
Section 12.2 Pharmaco-dynamics	Section describing pediatric HPA axis data	Section updated to include trial description and quantitative statistics	Because these data were generated as part of the Asmanex DPI Twisthaler NDA, this section was edited to more closely reflect what is included in the Asmanex Twisthaler label
Section 12.3 Pharmaco-kinetics	(b) (4)	Section removed	(b) (4)
Section 14 CLINICAL STUDIES	Description of adult and pediatric clinical trials	NCT numbers included	Edited for clarity and transparency
Section 14 CLINICAL STUDIES	Description of pediatric clinical trial program, (b) (4)	Section simplified to only include information relating to Trial P086, without details of dose-ranging. (b) (4) (b) (4)	Changes made to this section highlight the main efficacy findings of the placebo-controlled trial (Trial P086). (b) (4)
Section 16 HOW SUPPLIED/ STORAGE AND HANDLING	Description of how Asmanex HFA is supplied, stored, and handled	Passive voice changed to active voice	Edited for clarity

Section	Proposed Labeling	Approved Labeling	Rationale
Section 17 PATIENT COUNSELING INFORMATION	Information for counseling patients	Passive voice changed to active voice	Edited for clarity

Table 32: DULERA Prescribing Information

Section	Proposed Labeling	Approved Labeling	Rationale
Section 2.1 Administration Information	Administration information provided by the Applicant	Passive voice updated to active voice	Edited for clarity
Section 2.1 Administration Information	Administration information provided by the Applicant	Section relabeled "Administration Information." Passive voice updated to active voice.	Edited for consistency across labels and for clarity.
Section 2.2 Recommended Dosage	Dosage information provided by the Applicant for "Adult and Adolescent Patients Aged 12 Years and Older"	Line added: "After asthma stability has been achieved, it may be desirable to titrate to the lowest effective dosage to reduce the possibility of side effects."	This line was added as it is standard labeling language for ICS-containing products. This addition also helps to provide consistency across products.
Section 6 ADVERSE REACTIONS	(b) (4)	Statements removed	Edited for clarity and simplicity
Sections 10 – 17	Various statements referring to human subject data	Qualified statements describing if data generated in adults, adolescents or young children.	Because the label now includes information pertaining to children ages 5-11, it is important for prescribers to know if that information affects their patient population
Section 12.2 Pharmaco-dynamics	(b) (4)	Statements removed	Statements (b) (4) (b) (4) were removed (b) (4) (b) (4)

Section	Proposed Labeling	Approved Labeling	Rationale
Section 12.2 Pharmaco-dynamics	(b) (4)	Statement removed	Safety data is reported in Section 6
Section 12.2 Pharmaco-dynamics	Section describing pediatric HPA axis data	Section updated to include trial description and quantitative statistics	Because these data were generated as part of the Asmanex DPI Twisthaler NDA, this section was edited to more closely reflect what is included in the Asmanex Twisthaler label
Section 12.3 Pharmaco-kinetics	(b) (4)	Section removed	(b) (4)
Section 14 CLINICAL STUDIES	Description of adult and pediatric clinical trials	NCT numbers included	Edited for clarity and transparency
Section 14 CLINICAL STUDIES	Description of pediatric clinical trial program, including statements and figures relating to (b) (4) (b) (4) P087. Figure 2 shows primary efficacy endpoint (b) (4) (b) (4)	Section simplified to only include description and results of Trial P087, (b) (4)	Changes made to this section highlight the pertinent phase 3 clinical trial data for Dulera. (b) (4) (b) (4)
Section 16 HOW SUPPLIED/ STORAGE AND HANDLING	Description of how Asmanex HFA is supplied, stored, and handled	Passive voice changed to active voice	Edited for clarity

Section	Proposed Labeling	Approved Labeling	Rationale
Section 17 PATIENT COUNSELING INFORMATION	Information for counseling patients	Passive voice changed to active voice	Edited for clarity

12 Risk Evaluation and Mitigation Strategies

Given the favorable safety profile of MF and MF/F, there are no additional risk management strategies required.

13 Postmarketing Requirements and Commitment

Data submitted for Trial P087 fulfills PMRs 1658-7 and 2149-4. All PMRs associated with NDAs 205641 and 22518 have been fulfilled.

14 Division Director Comments

MF and MF/F MDIs are currently approved for the maintenance treatment of asthma in patients 12 years of age and older. Two efficacy supplements (NDA 22518/S026 and NDA 205641/S010) were submitted to expand the indication for MF and MF/F MDIs to include treatment of asthma in patients 5 to 11 years of age. Submission of these supplements is also intended to satisfy outstanding PREA PMRs (listed below) and to satisfy a Written Request for MF/F that was issued on December 4, 2017.

2149-4/1658-7 Conduct a study to evaluate the efficacy and long-term safety of mometasone furoate/formoterol fumarate combination MDI (Dulera) and mometasone furoate MDI (Asmanex) in children 5 to 11 year of age

While the Applicant submitted a number of trials to support the expanded indication, there are two key pivotal trials that support the efficacy of MF and MF/F in children 5 to 11 years of age, Trial P086 and Trial P087.

Trial P086 was a 12-week, randomized, placebo-controlled, dose-ranging study of MF MDI in pediatric patients 5 to 11 years of age with persistent asthma. Three doses of MF were evaluated: 50mcg, 100mcg, and 200mcg (given twice daily). MF DPI 100mcg once daily was an active comparator. The primary efficacy endpoint was the change in percent predicted FEV1 (ppFEV1) from baseline to Week 12. While each MF MDI strength tested showed superiority

over placebo, the 100 mcg BID dose provided additional benefit over the 50 mcg BID dose and there was no incremental benefit with the 200 mcg dose. The Applicant has chosen MF 100mcg BID (to be delivered via two inhalations of an MDI with 50 mcg of MF per actuation, twice daily) to market in children 5 to 11 years of age. The review team and I agree with the dose selection. The known efficacy of MF from adequate and well-controlled studies in adults/adolescents and results from Trial P086 establish the efficacy of MF 100 mcg BID in children 5 to 11 years of age with asthma.

Trial P087 was a randomized, active-controlled, parallel-group study in children ages 5 to 11 years evaluating the efficacy and safety of MF/F and MF MDI in children with persistent asthma. Randomized patients received either MF 100 mcg or MF/F 100/10 mcg MDI twice daily. The primary efficacy evaluation was at Week 12, but patients were followed for an additional 12 weeks for safety. The primary endpoint was the change from baseline in AM post-dose ppFEV1 $AUC_{0\text{-}60min}$ averaged across Day 1, Week 1, Week 4, Week 8 and Week 12. This efficacy endpoint is an assessment of the bronchodilator effect of F. Results showed a significant difference in AM post-dose ppFEV1 $AUC_{0\text{-}60min}$, demonstrating the contribution/benefit of F in MF/F over MF alone. The known efficacy of MF/F from adequate and well-controlled studies in adults/adolescents and results from Trial P087 establish the efficacy of MF/F 100/10 mcg BID in children 5 to 11 years of age with asthma.

In terms of safety, the safety profile of ICS and ICS/LABA are well-characterized. MF is currently approved in children 4 to 11 years of age in a DPI formulation. The Applicant provided safety data from not only the two key pivotal trials, P086 and P087, but also additional safety data from supportive trials. The review team's assessment of the safety data shows that the safety of MF and MF/F in patients 5 to 11 years of age is consistent with the established safety profile of these products. No new safety issues were identified.

The review team recommends approval of these supplements and I agree. The regulatory action is Approval. Labeling has been agreed to between the Applicant and Division. With approval of these supplements, PREA PMRs 2149-4/1658-7 are fulfilled. The Written Request has been fulfilled and exclusivity was granted on June 24, 2019 and communicated to the Applicant.

15 Appendices

15.1 References

1. Centers for Disease Control and Prevention. *Most Recent Asthma Data*. Asthma 2018 [cited 2019 March 27th]; Available from: https://www.cdc.gov/asthma/most_recent_data.htm.
2. Fanta, C.H., *Asthma.* N Engl J Med, 2009. **360**(10): p. 1002-14.
3. Global Initiative for Asthma (GINA). *Global Strategy for Asthma* 2018; Available from: https://ginasthma.org/gina-reports/.
4. *Guidelines for the Diagnosis and Management of Asthma*, in *National Asthma Education and Prevention Program Expert Panel Report 3*, National Heart Lung and Blood Institute, Editor. 2007.
5. Miettinen, O. and M. Nurminen, *Comparative analysis of two rates.* Stat Med, 1985. **4**(2): p. 213-26.

15.2 Financial Disclosure

Please see clinical review of trial P086 by Sofia Chaudhry dated June 24, 2016, submitted to NDAs 205641 and 22518, for information regarding financial disclosures for trial P086.

Covered Clinical Study (Name and/or Number): Trial P087

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 159		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): n/a Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NATALIE M PICA
08/12/2019 02:44:01 PM

SALLY M SEYMOUR
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