

## CLINICAL REVIEW

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Division / Office	DPARP/ODE2
Reviewer Name(s)	Sofia Chaudhry, MD
Review Completion Date	June 24, 2016
Established Name	Mometasone furoate/formoterol fumarate
Trade Name	Dulera
Therapeutic Class	Inhaled corticosteroid (ICS) ICS/long-acting beta- adrenergic agonist
Applicant	Merck Sharp & Dohm Corp
Formulation(s)	Metered dose inhaler
Dosing Regimen	Twice daily
Indication(s)	No new indication – submission of PREA study report and PLLR labeling
Intended Population(s)	Asthmatics <span style="background-color: gray; color: gray;">(b) (4)</span>

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

[REDACTED] (b) (4)

This pediatric [REDACTED] (b) (4) supplement includes results from a dose-ranging study of mometasone furoate HFA in children 5 to 11 years of age with persistent asthma conducted to fulfill post-marketing requirements (PMRs) outlined in the approval letters for Asmanex HFA and Dulera (PMR 2149-1 and 1658-4 respectively). [REDACTED] (b) (4)

The data from this study are sufficient to recommend that PMR 2149-1 and 1658-4 be fulfilled [REDACTED] (b) (4)

[REDACTED] However, inclusion of the data into the product labels for each product is not necessary. No new claims or indications are sought based on the results of these data, [REDACTED] (b) (4)

### 1.2 Risk Benefit Assessment

[REDACTED] (b) (4)



### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Not applicable for this pediatric (b) (4) supplement.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

Not applicable for this pediatric (b) (4) supplement.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Asmanex HFA is an inhalation aerosol approved to treat asthma in patients 12 years of age and older. It is available in two dosage strengths, 100 mcg or 200 mcg of mometasone furoate per actuation, with an approved dosage of 2 actuations twice daily for the treatment of asthma in patients 12 years of age and older.

Dulera is an inhalation aerosol containing a combination of mometasone furoate (100 or 200 mcg) and formoterol fumarate dihydrate (5 mcg) per actuation. It is available in two dosage strengths: 100/5 and 200/5 per actuation, with an approved dosage of 2 actuations twice daily for the treatment of asthma in patients 12 years of age and older.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Class	Generic Name	Brand Name
Inhaled corticosteroids	Fluticasone furoate DPI	Arnuity Ellipta
	Beclomethasone dipropionate HFA	QVAR
	Budesonide DPI/Respules	Pulmicort
	Fluticasone propionate HFA, DPI	Flovent HFA Flovent Diskus
	Mometasone DPI/HFA	Asmanex
	Ciclesonide HFA	Alvesco
Combination inhaled corticosteroids/long-acting beta agonist (ICS/LABA)	Budesonide/Formoterol HFA	Symbicort
	Fluticasone propionate/Salmeterol HFA, Diskus	Advair
	Mometasone/Formoterol HFA	Dulera
	Fluticasone furoate/Vilanterol	Breo Ellipta
Anti-IgE	Omalizumab	Xolair
Anti-IL5	Mepolizumab	Nucala
	Reslizumab	Cinqair
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton	Zyflo
Xanthines	Theophylline	Multiple
Anticholinergics	Tiotropium bromide	Spiriva Respimat

## 2.3 Availability of Proposed Active Ingredient in the United States

There are three formulations of mometasone furoate currently approved and marketed in the United States. Mometasone HFA is approved for the treatment of asthma in patients 12 years of age and older. A combination product containing mometasone furoate and formoterol fumarate is approved for the treatment of asthma in patients 12 years of age and older (Dulera, NDA 22-518, approved June 22, 2010). Mometasone furoate formulated as a dry powder inhaler is approved for the treatment of asthma in patients 4 years of age and older (Asmanex Twisthaler; NDA 021067, initial approval March 30, 2005).

For the remainder of this review, Dulera will be referred to as MF/F, Asmanex HFA as MF HFA, and Asmanex DPI as MF DPI.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The safety issues related to the use of inhaled corticosteroids (ICS) and combination products containing inhaled corticosteroid products and long-acting beta agonists (ICS/LABA) are well-characterized in the clinical literature and in the prescribing information of FDA-approved products.

In patients with asthma, product labeling for ICS monotherapy outlines the following risks:

- Localized infections
- Immunosuppression
- Hypercorticism and adrenal suppression
- Paradoxical bronchospasm
- Decrease in bone mineral density
- Glaucoma and cataracts
- Decreases in bone mineral density
- Growth suppression
- Impaired adrenal function when transferring patients from oral corticosteroids
- Deterioration of asthma and acute episodes (not to be used for relief of acute symptoms)

In patients with asthma, LABA monotherapy has been associated with serious asthma-related adverse events, including an increased risk of hospitalization, intubation, and death. LABA-containing drug products carry a Boxed Warning for these events.

With respect to other safety issues, risks highlighted in current ICS/LABA product labeling include:

- Localized infections
- Immunosuppression
- Hypercorticism and adrenal suppression
- Increased systemic corticosteroid and cardiovascular effects with co-administration with strong cytochrome P450 3A4 inhibitors
- Decreases in bone mineral density
- Glaucoma and cataracts
- Cautious use in patients with cardiovascular or central nervous system disorders due to beta-adrenergic stimulation

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

MF HFA was approved with 3 pediatric PMRs and MF/F with 6 pediatric PMRs (Table 1). With the intent of harmonizing and streamlining the pediatric PMRs for the two related products, the sponsor was notified in a January 7, 2015 letter that the Agency

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Sofia Chaudhry, MD  
NDA 22-518  
Mometasone furoate/formoterol fumarate (Dulera)

had released PMR 2149-2 and 2149-3 for MF HFA and 1658-5 and 1658-6 for MF/F and replaced them with 2149-3/1658-7 (see Table 1). The completed study conducted to fulfill PMR 2149-1 and 1658-4 is the basis for this pediatric (b) (4) supplement.

Table 1: Pediatric PMRs: MF HFA and MF/F

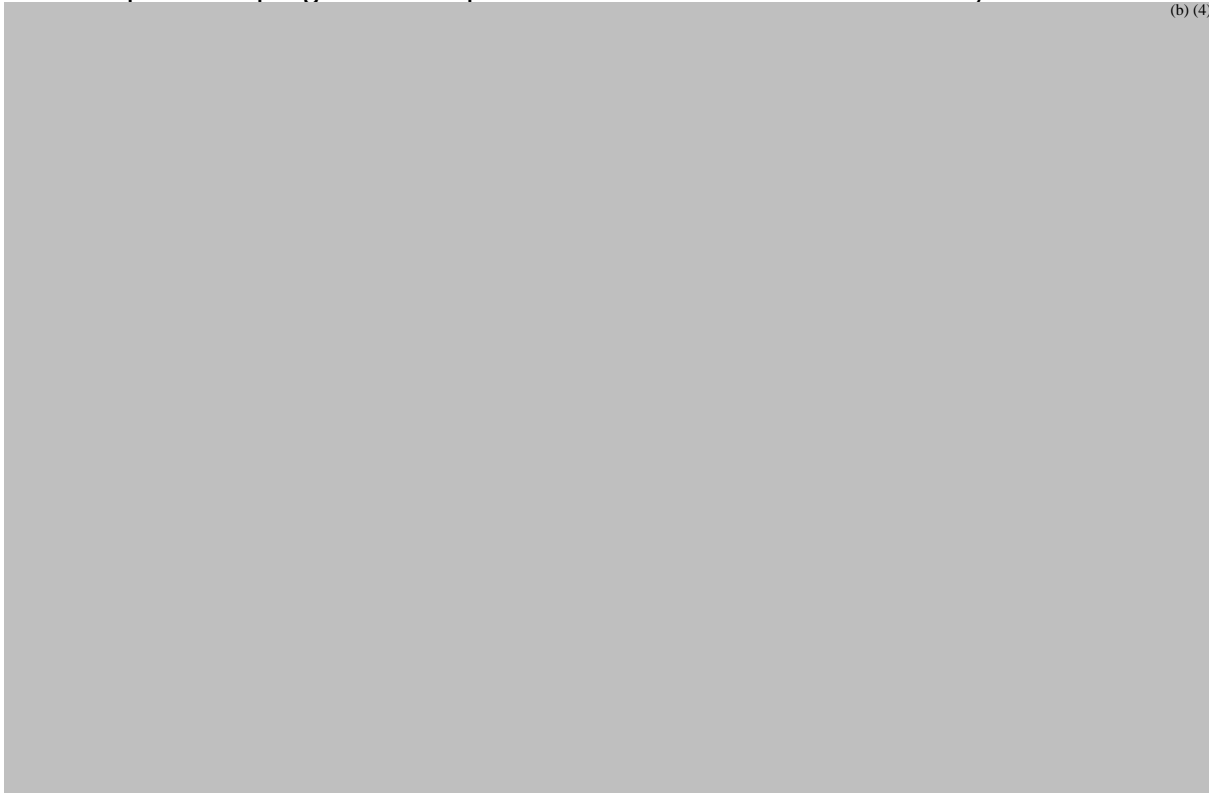
Number	Requirement	Status	Comment
<b>Asmanex HFA (MF HFA)</b>			
2149-1	12 week, randomized, placebo-controlled, safety and efficacy trial in children 5 – 11 years of age	Ongoing	Study complete  Basis for this supplement
2149-2	12-week double-blind, active-controlled, efficacy and safety trial of 2 doses of MF/F compared to corresponding doses of MF MDI in children 5-11 years of age	Released	See January 7, 2015 letter PMR 2149-4 issued
2149-3	6-month safety trial, with a 6 months extension of two doses of MF/F compared to FP/S in children 5 – 11 years of age	Released	See January 7, 2015 letter PMR 2149-4 issued
2149-4	Efficacy and long-term safety study of MF/F combination MDI (Dulera) and MF MDI (Asmanex HFA) in children 5 to 11 years of age	Pending  Protocol submitted 8/14/2015	See January 7, 2015 letter
<b>Dulera (MF/F)</b>			
1658-1	PD trial with and without a spacer in children 5-11 years of age	Fulfilled	
1658-2	PK trial with and without a spacer in children 5-11 years of age	Released	See letter dated July 24, 2012

Number	Requirement	Status	Comment
1658-3	Trial evaluating the HPA axis effects in children 5-11 years of age or to provide robust data demonstrating that the systemic exposure of MF in MF/F is comparable or lower than MF DPI	Released	See letter dated November 2, 2012.
1658-4	Safety and efficacy of multiple doses of MF HFA MDI in children 5-11 years of age (MF dose-ranging trial)	Ongoing	Study complete Basis for this supplement
1658-5	Safety and efficacy trial in children 5-11 years of age. Study will be 12-26 weeks in duration.	Released	See January 7, 2015 letter PMR 1658-7 issued
1658-6	Long-term safety in children 5 -11 years of age. Study will be 26 weeks duration with 6 month extension.	Released	See January 7, 2015 letter PMR 1658-7 issued
1658-7	Efficacy and long-term safety study of MF/F combination MDI (Dulera) and MF MDI (Asmanex HFA) in children 5 to 11 years of age	Pending  Protocol submitted 8/14/2015	See January 7, 2015 letter
1751-1	Randomized, double-blind, 26-week, active-controlled clinical trial comparing MF/F (Dulera) inhalation aerosol and mometasone furoate to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma	Ongoing	Large LABA safety trial

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Advice on the pediatric programs was provided in November 2014 and July 2015:

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## 2.6 Other Relevant Background Information

Not applicable.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

This pediatric (b) (4) supplement was submitted electronically and contained a clinical overview, proposed labeling, debarment certification, financial certification and disclosures and an environmental analysis. The complete study report for study P086 was submitted to IND 52,214.

Review of this application does not raise any data integrity concerns and no OSI audit is recommended.

### **3.2 Compliance with Good Clinical Practices**

The complete study report for P086 contains a statement of compliance with Good Clinical Practices.

### **3.3 Financial Disclosures**

See Appendix 9.4 for the Clinical Investigator Financial Disclosure Review Template.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

MF HFA and MF/F HFA are approved products. There are no proposed changes to the approved products in these supplements. An environmental analysis was submitted with this pediatric <sup>(b) (4)</sup> assessment.

### **4.2 Clinical Microbiology**

Not applicable.

### **4.3 Preclinical Pharmacology/Toxicology**

No new non-clinical information was submitted in this pediatric supplement. Details may be found in the current product labels,

### **4.4 Clinical Pharmacology**

#### **4.4.1 Mechanism of Action**

MF is an inhaled corticosteroid that acts as an anti-inflammatory agent. In asthma, MF is believed to inhibit multiple cell types in the lungs, including mast cells, eosinophils, neutrophils, macrophages, and lymphocytes, thereby inhibiting the release of inflammatory mediators from these cells.

F is a long-acting selective beta<sub>2</sub>-adrenergic receptor agonist. Inhaled F acts locally in the lung as a bronchodilator. The pharmacologic effects of beta<sub>2</sub>-adrenergic receptor agonists, including formoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine

triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells.

#### 4.4.2 Pharmacodynamics

No formal PD studies were conducted for this pediatric supplement.

#### 4.4.3 Pharmacokinetics

No formal PK studies were conducted for this pediatric supplement.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Study

Study	Design	Duration	Population	N	Treatment Arms (mcg)	Primary Efficacy Assessment	Study Sites (US subjects n, % of study population)
P086	R, PC, PG, DB, DD, dose-ranging efficacy and safety study	12 weeks	Asthmatics age 5 to 11 years	12 0 11 3 10 8 12 5 11 2	MF MDI 50* MF MDI 100* MF MDI 200* MF DPI QD† Placebo‡	Δ % predicted FEV <sub>1</sub> from baseline to Week 12	90 centers§ (US 91 subjects; 16%)



Study	Design	Duration	Population	N	Treatment Arms (mcg)	Primary Efficacy Assessment	Study Sites (US subjects n, % of study population)
<p>* BID + placebo DPI  † Q pm + placebo MDI  ‡ placebo MDI + placebo DPI  § Bulgaria (41 subjects), Croatia (5 subjects), Estonia (19 subjects), Greece (4 subjects), Hungary (8 71 subjects), Latvia (20 subjects) Poland (64 subjects), Romania (41 subjects), Serbia (1 subject), Switzerland (11 subjects), Russia (24 subjects), South Africa (14 subjects), Ukraine (32 subjects), Colombia (28 subjects), Guatemala (92 subjects), Mexico (20 subjects), Puerto Rico (5)</p> <p>MC = multi-center, R = randomized, PC = placebo-controlled, DD = double-dummy, PG = parallel-group, MDI = metered dose inhaler, DPI = dry powder inhaler</p>							

## 5.2 Review Strategy

This pediatric supplement contains data from one phase 2 dose-ranging trial for MF, P086 (see Table 2). The study design is discussed in Section 5.3, (b) (4) safety data in Section 7 and labeling recommendations in Section 9.2.

## 5.3 Discussion of Individual Studies/Clinical Trials

Study P086 was a phase 2, 12-week, randomized, placebo-controlled, double-blind, double-dummy, parallel-group, dose-ranging efficacy and safety study of MF HFA in children 5 to 11 years of age with persistent asthma.

Eligible subjects had to be age 5 to 11 years of age at Visit 1 or 2, carry a diagnosis of asthma for at least 6 months, have an FEV1 between 60% and 90-% predicted, be taking low to medium dose of ICS (either alone or in combination with a LABA) for at least 12 weeks, and have a positive reversibility test obtained within 12 months of study entry<sup>1</sup>. Subjects with a history of life threatening asthma, recent history of asthma exacerbation requiring ER or hospital management, uncontrolled asthma<sup>2</sup>, use of

<sup>1</sup> Positive reversibility defined by a  $\geq$  12% improvement in FEV1 within 30 minutes of albuterol/salbutamol treatment per standard office practice.

<sup>2</sup> Uncontrolled asthma defined by use of > 8 inhalations or 2 nebulizer treatments of short acting bronchodilator treatment, drop in PEF below run-in stability limits which were automatically calculated by the e-diary (average AM and PM PEF from the first 7 days after initiation of run-in open-label study drug

restricted medications within prohibited timeframes, or non-compliance or inability to comply with study medication or procedures were excluded from the study.

The study consisted of a 2 week run-in phase during which all subjects received open-label MF MDI and a 12-week, double-blind treatment phase. Subjects were equally randomized to one of three MF HFA doses (50 mcg, 100 mcg, and 200 mcg BID), placebo or MF DPI 100 every evening. The trial contained the lowest approved strength of MF HFA for patients 12 years of age and older (200 mcg BID) in addition to two lower dosage MF HFA strengths. Together, these three MF HFA dosage strengths provide a reasonable range of doses for evaluation in the younger pediatric population. The study also contained the approved formulation and dose of MF in children 5 to 11 years of age (MF DPI 100 mcg every evening) (b) (4)



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## 6.1 Indication

No indication is being sought based on the results of this study. The results of this study are being used (b) (4) to fulfill the MF dose-ranging PMRs outlined in the approval letters for each product.

### 6.1.1 Methods

This sNDA review evaluates the data from a single phase 2 dose-ranging efficacy and safety study. Study P086 was designed to fulfill PMR 2149-1 and 1658-4 for MF HFA and MF/F respectively. (b) (4)

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## 7 Review of Safety

### Safety Summary

The safety profile of orally inhaled steroids, including mometasone furoate, is well characterized. No new safety signals are seen from a review of the data from this phase 2 dose-ranging trial in asthmatic patients age 5 to 11.

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety assessment for this review relies on the data from the single phase 2 dose-ranging study submitted for this sNDA. The safety analysis for this study is based on the All Treated Analysis Set which contains data from individuals who received at least one dose of randomized treatment.

#### 7.1.2 Categorization of Adverse Events

All AEs were coded using MedDRA Version 17.1. The sponsor analyzed the AE data using a tiered approach. Safety parameters of special interest identified *a priori* constituted Tier 1 safety endpoints. Other AEs were classified as Tier 2 or Tier 3 depending on the number of events observed. For this study the following safety tiers were defined:

Tier 1:	Treatment emergent AE of interest: headache, oropharyngeal candidiasis, dysphonia, and post-dose bronchospasm
Tier 2:	Treatment-emergent AE with at least 4 events in at least one treatment group
Tier 3:	Treatment-emergent AE 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.

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

Not applicable to this review as only data from a single study were submitted.

## 7.2 Adequacy of Safety Assessments

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

The safety database is of adequate size and duration for review of this sNDA. A total of 578 randomized subjects received at least one dose of study medication and were included in the safety analysis. The majority of subjects were treated for 10 to 12 weeks in this 12 week trial.

Table 8: Extent of Exposure: All Treated Analysis Set

	≤ 2 weeks	2—4 weeks	4—6 weeks	6—8 weeks	8—10 weeks	10—12 weeks	> 12 weeks	Total
Any	67	34	30	22	20	263	142	578
Placebo	22	6	9	6	4	42	23	112
MF 50	14	7	5	6	7	50	31	120
MF 100	8	6	6	4	4	54	31	113
MF 200	12	3	5	2	1	57	28	108
MF 100 qpm	11	12	5	4	4	60	29	125

Source: P086 CSR Table 12-1

### 7.2.2 Explorations for Dose Response

This phase 2 dose-ranging study evaluated three doses of MF MDI. The safety analysis by dose is incorporated throughout this review. Of note, the study also included the current approved dose/formulation in this age group of inhaled mometasone furoate as an active comparator arm.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable

### 7.2.4 Routine Clinical Testing

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.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

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

This study monitored for toxicities associated with ICS use through adverse event monitoring. The following events were defined as events of special interest: headache, oropharyngeal candidiasis, dysphonia, and post-dose bronchospasm.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There are no deaths reported in this study.

### 7.3.2 Nonfatal Serious Adverse Events

There are a total of 11 serious adverse events (SAEs) reported during this trial. Review of these data does not reveal any new safety concerns for the use of this product in this age group.

The preferred term Asthma is the only event to occur in more than one subject in a treatment group which is not unexpected given the study population (2 each in placebo or MF 50 BID groups). <sup>(b) (4)</sup>


 data are limited given the infrequent occurrence of exacerbations in this study.

Table 9: Serious Adverse Events: All Treated Analysis Set

Treatment	MF 50 BID N = 120	MF 100 BID N = 113	MF 200 BID N = 108	MF DPI 100 qpm N = 125	Placebo N = 112
Dyspepsia	0	1 (1)	0	0	0
Enteritis	0	0	0	1 (1)	0

Treatment	MF 50 BID N = 120	MF 100 BID N = 113	MF 200 BID N = 108	MF DPI 100 qpm N = 125	Placebo N = 112
Appendicitis	0	0	0	1 (1)	0
Gastroenteritis	0	0	0	1 (1)	0
Otitis Media	0	0	1 (1)	0	0
Headache	0	0	0	1 (1)	0
Suicide Attempt	0	0	1 (1)	0	0
Asthma	2 (2)	0	0	0	2 (2)

Source: P086 CSR Table 12-6

### 7.3.3 Dropouts and/or Discontinuations

A total of 10 subjects discontinued this study due to an Adverse Event (see Table 10). Review of these data does not raise any new safety concerns for the use of this product in this age group.

Table 10: Adverse events leading to discontinuation

Treatment Group	AE	Severity
MF 50 MDI	Asthma	Severe
MF 50 MDI	Asthma	Severe
MF 100 MDI	Respiratory tract infection viral	Severe
MF 100 DPI	Headache	moderate
MF 100 DPI	Pharyngeal inflammation	Moderate
MF 100 DPI	Respiratory tract infection	Mild
MF 100 DPI	Dyspnea	Moderate
Placebo	Asthma	Moderate
Placebo	Asthma	Severe
Placebo	Respiratory tract infection	Mild

Source: P086 CSR Table 12-11

### 7.3.4 Significant Adverse Events

A total of 4 subjects had AEs determined by investigators to be related to double-blind study treatment (see Table 11). Review of these data does not reveal any new safety concerns.



Table 11: Drug-related adverse events as determined by investigator

Treatment Group	Comment
MF 50 MDI	Dysgeusia (no action taken with study drug)
MF 100 MDI	Accidental overdose (no additional associated AEs)
MF 200	Headache (no action taken with study drug)
Placebo	Asthma (SAE)

### 7.3.5 Submission Specific Primary Safety Concerns

In this study, Tier 1 Adverse Events (adverse events of special interest) included: headache, oropharyngeal candidiasis, dysphonia, and post-dose bronchospasm. The only Tier 1 event observed in the study is headache (9 subjects: placebo: 2[2%]; MF 50 MDI: 1[1%]; MF 100 MDI: 2[2%]; MF 200 MDI: 1[1%]; MF 100 DPI 3[2%]).

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The only AE observed in at least 5% of all treated subjects are: 'nasopharyngitis' and 'accidental overdose'. Nasopharyngitis is a labeled event in the product labels for MF/F and MF HFA. The events of accidental overdose are balanced between active treatment arms (placebo 13[11%], MF 50 MDI: 13[11%]; MF 100 MDI 13[12%]; MF MDI 200 11[12%]; MF 100 DPI 10[8%]). The sponsor states that the majority of these cases were caused by children handling the device and causing the dose-counter to advance without any additional associated adverse events.

A review of an incidence table reporting any adverse event occurring > 0% in any treatment arm does not reveal any new safety concerns beyond what is known and characterized. Events that occurred in more than one individual are few, balanced between active treatment arms and placebo, or generally minor events that occur frequently in the general population making assessment of causality to study drug difficult.

### 7.4.2 Laboratory Findings

Not applicable, see Section 7.2.4. There we no pregnancy AEs in this study.

### 7.4.3 Vital Signs

A review of the vital sign data from this completed study does not reveal any new safety concerns.

### 7.4.4 Electrocardiograms (ECGs)

Not applicable to this sNDA.

### 7.4.5 Special Safety Studies/Clinical Trials

Not applicable to this sNDA.


### 7.4.6 Immunogenicity

Not applicable to this sNDA.

## 7.5 Other Safety Explorations


### 7.5.1 Dose Dependency for Adverse Events

There are an insufficient number of AEs in this trial to draw any firm conclusions about a dose dependency for safety events. In general, no evaluated dose demonstrated significant toxicities in this clinical trial. (b) (4)



### 7.5.2 Time Dependency for Adverse Events

The data from this trial are insufficient to make any determinations regarding time dependency for adverse events. (b) (4)



### 7.5.3 Drug-Demographic Interactions

The data from this trial are insufficient to make any determinations regarding drug-demographic interactions for adverse events.

#### 7.5.4 Drug-Disease Interactions

Not applicable to this sNDA.

#### 7.5.5 Drug-Drug Interactions

Not applicable to this sNDA.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

Not applicable to this sNDA

#### 7.6.2 Human Reproduction and Pregnancy Data

Not applicable to this sNDA

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

The growth effects of MF DPI have been characterized and the results of a 52 week growth study can be found in the current MF DPI prescribing information (Asmanex Twisthaler; NDA 021-067). Given the availability of this information and an adequate PK link between MF HFA and MF DPI, an additional pediatric growth study is not necessary.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable to this sNDA

### 7.7 Additional Submissions / Safety Issues

## 8 Postmarket Experience

There is ongoing review of 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.

## 9 Appendices

### 9.1 Literature Review/References

Not applicable.

### 9.2 Labeling Recommendations

No changes to Section 8.4 are necessary based on the results of this dose-ranging study. (b) (4)

This sNDA also include an update to reflect the new PLLR formatting. Review of these changes remains ongoing at the time of this review.

### 9.3 Advisory Committee Meeting

(b) (4)  
As such, no advisory committee meeting was held to discuss the results of this pediatric dose-ranging trial.

### 9.4 Financial Disclosure Review Template

#### Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 205-641/22-518

Submission Date(s): November 24, 2015

Applicant: Merck

Product: Asmanex HFA and Dulera

Reviewer: Sofia Chaudhry, MD

Date of Review: October 26, 2015

Covered Clinical Study (Name and/or Number): P086

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
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Total number of investigators identified: 249 P086		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0 (listed as not applicable by applicant)</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0 (listed as not applicable by applicant)</u>		
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)): 0  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 sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

There were no investigators with disclosable financial interest that may have impacted the study conduct.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOFIA S CHAUDHRY  
06/24/2016

SALLY M SEYMOUR  
06/24/2016