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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 4, 2014
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205641
Applicant	Merck, Sharpe, and Dohme
Date of Submission	June 27, 2013
PDUFA Goal Date	April 27, 2014
Proprietary Name / Established (USAN) names	Asmanex HFA/mometasone furoate inhalation aerosol (metered dose inhaler)
Dosage forms / Strength	100 and 200 mcg mometasone furoate/actuation, Dose: 2 actuations twice daily
Proposed Indication(s)	"… indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older
Recommended:	Approval

1. Introduction

This is a 505(b)(1) New Drug Application for mometasone furoate (MF) oral inhalation aerosol (trade name Asmanex HFA) two inhalations administered twice daily indicated for the maintenance treatment of asthma as prophylactic therapy in adults and children 12 years of age and older. The metered dose inhaler (MDI) inhalation aerosol will be available in two dosage strengths, 100 and 200 mcg per actuation with the dose/strength used dependent on asthma severity. The application is notable in that the efficacy and safety of the Asmanex HFA MDI product are based on data from clinical studies conducted to support the efficacy and safety of the approved related mometasone furoate/formoterol fumarate (MF/FF) combination inhalation aerosol product (Dulera, NDA 22-518). This review will provide an overview of the application with a focus on the determination of efficacy based primarily on the trough FEV1 pulmonary function endpoint that is the generally recognized pulmonary function endpoint for inhaled corticosteroid products for asthma such as Asmanex HFA.

2. Background

As noted above, the support for the efficacy and safety for the Asmanex HFA MF monoproduct is primarily derived from the clinical data previously submitted to support the MF/FF combination product, Dulera that was approved in the US for the treatment of patients with asthma ≥12 years of age on June 22, 2010. Additional support is provided by the clinical program for another approved MF dry powder inhaler (DPI) product, Asmanex Twisthaler (NDA21-067) and additional studies conducted for the Applicant's previous MF MDI development program that has similarities to the currently proposed Asmanex HFA MDI.

During the Division's review of the Dulera MF/FF combination product application, the Division noted that commercial availability of the MF monotherapy MDI comparator used in the Dulera program would facilitate step-down to ICS alone for patients no longer in need of continuous LABA treatment and suggested the Applicant consider marketing the MF MDI monoproduct.

The Applicant ultimately agreed to bring forward the MF MDI monotherapy product and the current NDA is a response to that agreement. The Division and Applicant had previously agreed that no additional clinical trials would be necessary for approval of the MF MDI monoproduct in that the approval of the MF/FF combination inherently confirms that each of the monotherapies is efficacious.

According to NHLBI and GINA guidelines, ICS products like Asmanex HFA are first-line anti-inflammatory therapies for persistent asthma. There are several ICS-containing products currently approved for treatment of patients with asthma including Alvesco (ciclesonide), Flovent (fluticasone), Pulmicort (budesonide), and QVAR (beclomethasone diproprionate). Combination ICS plus LABA products to treat patients with more severe asthma include Advair MDI and DPI (fluticasone/salmeterol), Dulera MDI (mometasone furoate/ formoterol fumarate), and Symbicort MDI (budesonide/ formoterol fumarate). Other non-steroid classes of drug used in the treatment of asthma include beta-2 agonists, leukotriene inhibitors,

nonspecific phosphodiesterase inhibitors such as theophylline, and anti-IgE therapy (omalizumab).

3. Chemistry, Manufacture, and Controls

The drug substance is mometasone furoate, a well described glucocorticoid used in many pharmaceutical products. Information for mometasone has been provided by the Applicant by cross-reference to their approved NDAs 22518 (Dulera) and 21067 (Asmanex Twisthaler), both of which are also formulated for the oral inhalation route of administration. The MF pressurized metered dose inhaler (MDI) drug product is essentially the same MDI formulation and product as the Dulera product that is referenced minus the very small amount of the additional formoterol fumarate component in Dulera and a different color for the mouthpiece. The Asmanex HFA drug product is formulated with two strengths of MF (100 and 200 mcg/actuation ex-actuator). It also contains (b) (4) ethanol (b) (4) (b) (4) oleic acid, and (b) (4) HFA 227. The dose is obtained from two single actuations of the drug products. The container closure system for the drug products consists of a 16 mL aluminum canister (b) (4) closed with a (b) (4) valve. A (b) (4) press and breathe actuator with the mouthpiece cap and dose counter is attached to the pressurized canister to deliver a dose to the patient. For further CMC information, see the primary CMC review by Dr. Shen.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data were required or submitted with this NDA as the necessary pharmacology/toxicology data were submitted under NDA 22518 for the related Dulera product (see the pharmacology/toxicology reviews for NDA 22518). Following is a brief summary of the pharmacology/toxicology findings.

Studies in rats and dogs treated with MF by the oral route revealed multiple target organs typically associated with those attributed to the pharmacological action of corticosteroid products such as lymphoid depletion and atrophy of the adrenal cortex.

Regarding genetic toxicity, MF increased chromosomal aberrations in an in vitro Chinese hamster ovary cell assay, but did not have this effect in an in vitro Chinese hamster lung cell assay. It was also not mutagenic in the Ames test or mouse lymphoma assay.

In 2-year and 19 month carcinogenicity studies in Sprague Dawley rats and Swiss mice, respectively, MF by inhalation was not carcinogenic.

Reproductive studies in rats demonstrated no impairment of fertility produced by subcutaneous doses up to 15 mcg/kg (approximately 8 times the MRHD on an AUC basis), however, in mice, MF caused cleft palate at subcutaneous doses of 60 mcg/kg and above and fetal survival was reduced at 180 mcg/kg. No toxicity was observed at 20 mcg/kg. When rats received subcutaneous doses of MF throughout pregnancy or during the later stages of pregnancy, doses of 15 mcg/kg caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Other toxicology studies in rabbits also demonstrated fetal

effects that can be observed for corticosteroids such as cleft palate, umbilical hernia, and hydrocephaly.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology studies were conducted to support this application. Instead, the Applicant is supporting this application by making reference to clinical pharmacology studies conducted for the Dulera combination MDI product. Because the original Dulera program relied, in part, on safety and efficacy of the approved Asmanex Twisthaler program, the clinical pharmacology trials in the Dulera submission also provided a link between the Asmanex Twisthaler and Dulera. The studies conducted demonstrated several important concepts that ultimately allowed the Asmanex HFA program to fully rely on the clinical pharmacology data obtained for the Dulera and Asmanex Twisthaler programs. These include a lack of pharmacokinetic interaction between MF and F when co-formulated in an MDI and a lack of a lack of pharmaceutical interaction on MF when MF and F are formulated together. Additionally, since it was also determined that systemic exposure of MF is lower following MDI (Asmanex HFA) administration compared to DPI (Asmanex Twisthaler) administration, studies used to support the systemic safety of MF from the Asmanex Twisthaler program, i.e.,. HPA axis and growth studies could be referenced for the Asmanex HFA program. As a result, the clinical pharmacology support for this application is the same as that for the MF component of Dulera that can be found in the approved Dulera product label. For further specific details see the Clinical Pharmacology review by Dr. Dinko Rekic.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Overview of the Clinical Program

As noted above, the determination of efficacy for Asmanex HFA can be made from the clinical studies conducted for the Dulera MF/FF combination product program. Table 1 describes the relevant studies used to support the efficacy of Asmanex HFA.

Table 1: Relevant Clinical Studies which Form the Basis for Regulatory Decision Making

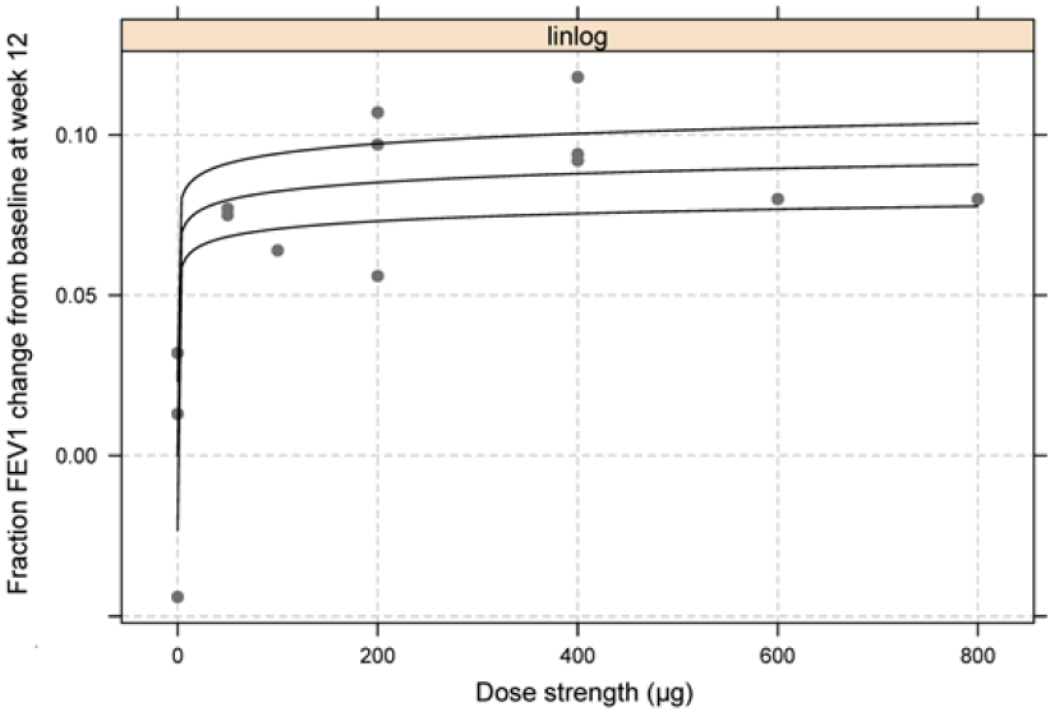
Study/ Year Initiated	Study Design	Study Duration	Age	Baseline FEV1	N	Treatments	Primary Endpoint
Primary Efficacy and Safety							
P04334 US, Canada, EU, Asia, South America *2008*	R, DB, PC Safety Efficacy	26 week	12-76	60-90% predicted	781	MF/F 200/10 BID MF 200 BID F10 BID Placebo	Post-dose FEV1
P04431 US, Europe, South America *2008*	R, DB Safety Efficacy	12 week	12-84	50-85% predicted	728	MF/F 200/10 BID MF/F 400/10 BID MF 400 BID	Post-dose FEV1
Dose Selection							
C97-208 US *1998*	PC, AC, Dose-range	12 week	12-81	60-90% predicted	435	MF-MDI 50 BID MF-MDI 200 BID MF-MDI 400 BID MF-MDI 600 BID BDP 168 BID Placebo	1-4 hr post-dose FEV1
C97-225 US *1998*	PC Efficacy, Safety	12 week	12-72	60-90% predicted	232	MF-MDI 50 BID MF-MDI 200 BID BDP 168 BID Placebo	1-4 hr post-dose FEV1
I97-200 EU, South America, South Africa *1998*	AC Efficacy, Safety	12 week	12-76	55-90% predicted	715	MF-MDI 100 BID MF-MDI 200 BID MF-MDI 400 BID FP MDI 250 BID-CFC	1-4 hr. post-dose FEV1
Long Term Safety							
C97-222 US *1999*	R, AC, OL	52 week	12-70	60-90% predicted	308	MF MDI 200 BID MF MDI 600 BID BDP 168 BID	Safety
P04139	R, OL, AC HPA axis	52 weeks	12-75	60-90% predicted	404	MF/F 200/10 BID MF/F 400/10 BID F/SC 250/50 BID F/SC 500/50 BID	Safety

MF=mometasone furoate; F=formoterol fumarate; MF/F=mometasone + formoterol; BDP= beclomethasone diproprionate; F/SC= fluticasone + salmeterol; FP= fluticasone propionate; R=randomized; DB=double blind; OL=open label; AC=active control

Dose Selection

Support for the 200 and 400 mcg twice daily doses of Asmanex HFA (2 actuations of the 100 and 200 mcg/actuation presentations twice daily) is derived from clinical studies conducted by the Applicant for a closely related older MF MDI for asthma program (studies C79-208, C97-225, and I97-200 listed in Table 1) and the Phase 3 trials conducted for the Dulera MF/FF MDI combination product (P04334 and P04431). Data from the earlier studies demonstrated that over a 12 week treatment period all doses of MF assessed improved FEV1 in patients with moderate asthma with doses from 200-800 mcg residing on the flat part of the dose response curve (Figure 1).

Figure 1. Estimated Dose Response Relationship based on Clinical Pharmacology Modeling*.



*Model based on meta-analysis of mean changes in FEV1 reported at week 12 from studies C97-208, C97-225, C97-224, and I97-200. Gray circles represent the mean change from baseline for a dose group at week 12 of the study. Lines represent the mean predicted response with confidence interval (CI: 90%). Adapted from Figure 2 found in the primary clinical pharmacology review by Dr. Dinko Redic.

Doses of 200 and 400 mcg twice daily were also evaluated in the factorial design Phase 3 studies used to support the approval of the MF/FF MDI combination product, Dulera. In those studies, a MF dose of 200 mcg by oral inhalation twice daily (delivered as 2 actuations of 100 mcg/actuation drug product) to patients with moderate asthma demonstrated a significant improvement in trough FEV1 compared to placebo. Additionally, a MF dose of 400 mcg twice daily (delivered as 2 actuations of 200 mcg/actuation drug product) to patients with more severe asthma (uncontrolled on high dose ICS at study entry) demonstrated a numerical (but not statistically significant) improvement in trough FEV_1 from baseline to week 12 than patients who received a 200 mcg twice daily MF dose (see below).

Phase 3 Clinical Program

The efficacy of Asmanex HFA was evaluated in two randomized, double-blind, placebo- or active-controlled multi-center clinical trials of 12 and 26 weeks duration, conducted as part of a MF/FF 100/5 mcg or 200/5mcg combination product (Dulera) development program in which a total of 1509 patients 12 years of age and older with persistent asthma (mean baseline FEV_1 of 66% to 73% predicted) were evaluated.

Study P04334: Clinical Trial to Support the 200 mcg Twice Daily Dose of Asmanex HFA

This 26-week, placebo-controlled trial evaluated 781 patients 12 years of age and older. Of these patients, 192 patients received Asmanex HFA 100 mcg and 196 patients received

placebo, each administered as 2 inhalations twice daily by metered dose inhalation aerosols. All other maintenance therapies were discontinued. The study included a 2- to 3-week run-in period with Asmanex HFA 100 mcg, 2 inhalations twice daily. Patients ranged from 12 to 76 years of age, 41% were male and 59% were female; 72% were Caucasian and 28% were non-Caucasian. Mean FEV_1 and mean percent predicted FEV_1 were similar among all treatment groups (2.33 L, 73%). Thirteen (7%) patients receiving Asmanex HFA 100 mcg and 46 (23%) patients receiving placebo discontinued the study early due to treatment failure.

The change in mean trough FEV_1 from baseline to week 12 compared to placebo was assessed to evaluate the efficacy of Asmanex HFA 100 mcg. The change from baseline to week 12 in the mean trough FEV1 was significantly greater among patients receiving Asmanex HFA 100 mcg 2 inhalations twice daily than among those receiving placebo with a treatment difference from placebo of 0.12L, 95% confidence interval (0.05, 0.20) Table 2.

Table 2: Study P04334, Change in Trough FEV1 from Baseline to Week 12

Treatment arm	N	Baseline (L)	Change from baseline at Week 12 (L)	Treatment difference from placebo (L)	P-value vs. placebo	P-value vs. formoterol
DULERA 100 mcg/5 mcg	167	2.33	0.13	0.18	<0.001	<0.001
Mometasone furoate 100 mcg	175	2.36	0.07	0.12	<0.001	0.058
Formoterol fumarate 5 mcg	141	2.29	0.00	0.05	0.170	
Placebo	145	2.30	-0.05			

LS means and p-values are from Week 12 estimates of a longitudinal analysis model.

Clinically judged deteriorations in asthma or reductions in lung function were also assessed to evaluate the efficacy of Asmanex HFA 100 mcg. Deteriorations in asthma were defined as any of the following: a 20% decrease in FEV_1; a 30% decrease in PEF on two or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol. Sixty-five (34%) patients who received Asmanex HFA 100 mcg reported an event compared to 109 (56%) patients who received placebo. The subjective impact of asthma on patients' health-related quality of life was evaluated by the Asthma Quality of Life Questionnaire Standardized (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). A change from baseline $\geq$0.5 points [the Minimal Important Difference (MID)] is considered a clinically meaningful improvement. The change from baseline AQLQ for ASMANEX HFA 100 mcg vs. placebo did not meet the MID of $\geq$0.5 points.

Study P04431: Clinical Trial to Support the 400 mcg Twice Daily Dose of Asmanex HFA
This 12-week randomized, double-blind, active controlled trial evaluated a total of 728 patients 12 years of age and older comparing Asmanex HFA 200 mcg (n=240 patients), MF/FF 200 mcg/5 mcg (n=255 patients), and MF/FF 100 mcg/5 mcg (n=233 patients), each administered as 2 inhalations twice daily by metered dose inhalation aerosols. All other maintenance therapies were discontinued. The trial included a 2- to 3-week run-in period with Asmanex HFA 200 mcg, 2 inhalations twice daily. Patients had persistent asthma and were uncontrolled on high-dose inhaled corticosteroids prior to study entry. Patients ranged from 12 to 84 years of age, 44% were male and 56% were female; 89% were Caucasian and 11% were non-Caucasian. Mean FEV_1 and mean percent predicted FEV_1 values were similar among all treatment groups (2.05 L, 66%). The number of patients who discontinued the trial early due to

treatment failure were 11 (5%) in the MF/FF 100 mcg/5 mcg group, 8 (3%) in the MF/FF 200 mcg/5 mcg group, and 13 (5%) in the Asmanex HFA 200 mcg group.

The primary efficacy endpoint for the combination product development program was the mean change in FEV_1 AUC (0-12 hr) from baseline to Week 12. However, in order to assess for added benefit of the 400 mcg twice daily dose of MF (200 mcg/actuation MF product) over the 200 mcg twice daily dose delivered from the 100 mcg/actuation product, trough FEV_1 at 12 weeks was compared between the MF/FF 200 mcg/5 mcg and 100 mcg/5 mcg treatment groups. Improvement in trough FEV_1 from baseline to week 12 in patients who received MF 200 mcg 2 puffs twice daily was numerically but not statistically significantly greater than among patients who received two inhalations twice daily of the 100 mcg/actuation product, both in the presence of two inhalations twice daily of 5 mcg/actuation FF; treatment difference 0.04 L, 95% confidence interval (-0.02, 0.10) Table 3.

Table 3: Study P04431, Change in Trough FEV1 from Baseline to Week 12

Treatment arm	N	Baseline (L)	Change from baseline at Week 12 (L)
DULERA 100 mcg/5 mcg	232	2.10	0.14
DULERA 200 mcg/5 mcg	255	2.05	0.19
Mometasone furoate 200 mcg	239	2.07	0.10

Efficacy Conclusion

The Applicant provides support for the efficacy of both the MF 200 and MF 400 doses from studies conducted for the MF/F combination product (Dulera) development program. Support for the efficacy of the MF 200 dose is provided in the factorial design trial, P04334, which included evaluation of MF 200 against placebo. For the MF 200 dose, the mean change in trough FEV1 compared to placebo was clinically and statistically significant (treatment difference from placebo = 0.12L; $p<0.001$). Additional support for efficacy was provided by demonstration of fewer/less asthma deteriorations, nocturnal awakenings, and SABA use as well as from supportive efficacy data obtained from a previous related MF MDI monoproduct development program.

Support for MF 400 mcg twice daily dose is derived mainly from the Phase 3 trial, P04431, which provided a direct comparison of MF/F 400mcg/10mcg and MF/F 200mcg/10mcg. This trial included MF 400 mcg as a third treatment arm, but did not include a placebo control, given the severity of the asthma population enrolled. A numerical separation between MF/FF 200mcg/10mcg and 400mcg/10mcg was demonstrated for the key secondary efficacy endpoint, trough FEV1 (treatment difference 0.04 L) which supports an added benefit for the 400 mcg MF dose over the 200 mcg dose in population of patients with more severe asthma. Additionally, the efficacy of MF 400 compared to placebo is supported by replicate, 12-week dose ranging trials (C97-208 and C97-224) from the related MF MDI monoproduct development product mentioned above. In summary, taken as a whole, the submitted data provide evidence of efficacy for both of the proposed MF 200 and MF 400 monotherapy doses.

8. Safety

Database

The clinical trial safety database is drawn primarily from that of the Dulera MF/FF combination product asthma development program which utilized the to-be-marketed formulations of MF 200 and MF 400 HFA and encompassed the studies listed in Table 1 above. Within those studies, at least 1781 patients received one dose or more doses of MF/F and at least 618 received at least one or more doses of MF monoproduct. Approximately 600 patients received doses of 200 or 400 mcg MF for at least six months and 252 for one year.

When data from an older MF asthma development program are considered, a total of about 4015 patients with asthma ≥12 years of age received MF at doses ranging from 50 to 100 mcg once daily to 800 mcg BID) for up to 52 weeks.

There were 3 deaths reported among patients who received MF in the Dulera program, all in patients who received 200mcg/10mcg MF/FF twice daily and all likely not related to study treatment; a 59 year-old male accidentally electrocuted at his place of employment, a 50-year old female who died of gastric cancer, and a 53-yearold woman who died from metastatic uterine leiomyosarcoma. In addition, there was a 26 year-old male subject receiving montelukast 10mg who died as the result of a homicide. Within the related, older MF MDI program, two patients with severe, oral steroid dependent asthma died, a 79-year-old who received MF 400mcg twice daily died from respiratory insufficiency and pneumonia, and a 60yo who received MF MDI variable dose died of myocardial infarction and septic shock. There were no deaths in pediatric patients < 16 years of age. There were no asthma-related deaths or intubations reported.

In the Dulera program Phase 3 trials (studies P04334 and P04431), 22 patients who received MF reported a total of 25 SAEs. Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in MF 200mcg and MF 400mcg treated patients included abdominal pain (2), chest pain (1), gastroenteritis (1), endometriosis (1), asthma (1), and hemoptysis (1); all at rates less than 1%. In terms of other serious asthma-related outcomes, 7 patients in the combination clinical program had asthma exacerbations resulting in hospitalization 3 who had received MF in combination with FF and one who received MF 200 mcg twice daily alone.

Adverse events of interest for ICS products include local adverse reactions such as dysphonia and oral candidiasis. As described for the Dulera product, dysphonia was reported in 1.7% patients in the pooled Phase 3 database while oral candidiasis was reported in 0.8% of patients. Overall, these frequencies are lower than those reported for the approved Asmanex DPI. Development of cataracts, particularly subcapsular cataracts, is another adverse event of interest for ICS products. No cases of posterior subcapsular cataracts were reported were reported in the safety database.

The most commonly reported AEs in the 2 pivotal trials (P04334 and P04431) were nasopharyngitis, upper respiratory tract infection, and headache. Observed AE event rates were similar across the treatment groups, including placebo. Tables 4 and 5 show AEs that occurred in ≥ 3% of patients for studies P04334 and P04431 through 26 and 12 weeks, respectively.

Table 4: Common Treatment-Related Adverse Reactions Occurring in ≥ 3% of Patients and Greater Than Placebo in Study P04334 (through 26 weeks)

	Placebo N=196 n (%)	Asmanex HFA 100mcg N=192 n (%)
Any AE	82 (42)	88 (46)
Nasopharyngitis	7 (4)	15 (8)
Headache	7 (4)	10 (5)
Influenza	5 (3)	7 (4)
Sinusitis	2 (1)	6 (3)

Table 5: Common Treatment-Related Adverse Reactions Occurring in ≥ 3% of Patients in any Treatment Group in Study P04431 (through 12 weeks)

	Asmanex HFA 200mcg N=240 n (%)	MF/F 100/5mcg N=233 n (%)	MF/F 200/5 mcg N=255 n (%)
Any AE	66 (28)	62 (27)	75 (29)
Nasopharyngitis	13 (5)	8 (3)	12 (5)
Headache	8 (3)	10 (4)	5 (2)
Bronchitis	6 (3)	2 (1)	7 (3)
Sinusitis	4 (2)	9 (4)	5 (2)

Safety Summary
Overall, the safety data for the Asmanex HFA program do not reveal any new ICS-related safety concerns. Adverse events were few and generally those observed with similar approved ICS products. There were no asthma related deaths and few SAEs or local ICS related AEs. In summary, the safety risks of ICS therapy for asthma continue to appear relatively small and are balanced by the efficacy of inhaled anti-inflammatory therapy with corticosteroids, including MF. The safety of both the 200mcg and 400 mcg twice daily doses by oral inhalation of MF is supported.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was not convened or required for this submission as the safety and efficacy of MF by inhalation as a maintenance treatment for patients with persistent asthma are well described. This finding was fully supported by the clinical trials used to support the efficacy and safety of Asmanex HFA.

10. Pediatrics

As a new dosage form, Asmanex HFA triggered PREA and subsequent need for a development plan for pediatric patients < 12 years of age. The Applicant petitioned for a partial waiver for development for children < 5 years of age as well as a deferral for pediatric patients 5-11 years of age. The pediatric plan was discussed at a PeRC meeting on January 15, 2014, at which time the PeRC agreed with the Division and Applicant to grant a partial waiver in patients less than five years of age because the product fails to offer a meaningful

therapeutic benefit and a deferral studies in patients 5 to 11 years because studies are underway as part of the pediatric development plan for the related MF/FF (Dulera) combination product.

11. Other Relevant Regulatory Issues

- Financial Disclosure: The financial disclosure information for the two Phase 3 trials used to support approval was already submitted as part of the review for the related Dulera combination product conducted under NDA 22-518. That review revealed three investigators with disclosable financial interests (honoraria) however it was felt payments would not generally affect an efficacy determination based on large, double-blind, multi-center clinical trials.

- DSI audits information: No additional DSI audits were conducted beyond those conducted for the related approved Dulera combination program NDA which revealed no substantial irregularities.

- Office of Compliance: The overall EES conclusion is Acceptable.

12. Labeling

The Applicant submitted a proposed label and Patient IFU for Asmanex HFA which contained elements from the labels of the related approved mometasone-containing asthma products, Asmanex Twisthaler and Dulera. The proposed label, carton and container labeling, and Patient IFU were reviewed by the appropriate disciplines within the Division as well as OPDP, DMPP, DRISK, DMEP, and SEALD who recommended various changes to correct formatting errors and to better describe the drug product and indicated population to healthcare providers. Labeling edits by the review team revolved around amending the submitted Asmanex HFA label to better describe the efficacy of Asmanex HFA (Section 14) and make the description of the safety of Asmanex HFA (Sections 5 and 6) consistent with the safety labeling of other ICS products indicated for the treatment of patients with asthma. The FDA-edited labeling was conveyed to the Applicant on March 27, 2014; final labeling language between the Applicant and the Division is still under discussion at the time of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for approval of Asmanex HFA, 100 and 200 mcg/actuation at the labeled dose of 2 actuations by inhalation twice daily in patients 12 years of age and older for maintenance treatment of asthma.

- Risk Benefit Assessment

The potential benefit of Asmanex HFA as an anti-inflammatory therapy in patients with asthma 12 years of age and older outweighs any unlikely potential risks such as immunosuppression, adrenal suppression, or effects on growth.

1. Recommendation for Post-marketing Risk Management Activities

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

2. Recommendation for other Post-marketing Study Commitments

No additional post-marketing commitments or required studies are recommended beyond the PREA requirements currently being fulfilled under the Dulera combination product pediatric development program.

3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

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/s/

ANTHONY G DURMOWICZ
04/04/2014