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RESEARCH**

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 22, 2010
From	Sally Seymour, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA# 22-518
Applicant	Schering Plough
Date of Submission	May 21, 2009
PDUFA Goal Date	June 22, 2010
Proprietary Name / Established (USAN) names	Dulera Inhalation Aerosol mometasone furoate and formoterol fumarate
Dosage forms / Strength	Metered dose inhaler (b) (4) 100/5 (mometasone furoate 100mcg and formoterol fumarate 5mcg) 200/5 (mometasone furoate 200mcg and formoterol fumarate 5mcg)
Proposed Indication(s)	(b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) (b) (4) in adults and children 12 years of age and older
Recommended:	Approval for Dulera 100/5 and 200/5 (b) (4)

1. Introduction

On May 21, 2009, Schering Plough submitted a 505(b)(1) New Drug Application (NDA) for the combination product, mometasone furoate (MF) and formoterol fumarate (FF) inhalation aerosol in an HFA 227 metered dose inhaler (MDI) formulation. The proposed indication is the (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) (b) (4), in adults and children 12 years of age and older. The proposed tradename is Dulera Inhalation Aerosol. The Applicant proposes (b) (4) dosage strengths (ex-actuator): (b) (4) 100 mcg mometasone furoate and 5mcg formoterol fumarate, and 200 mcg mometasone furoate and 5mcg formoterol fumarate. For simplicity, throughout this memo, the product will be referred to as MF/F.

To support this application, the Applicant submitted a clinical development program, including phase 3 clinical trials designed to establish the efficacy and safety of Dulera. In addition, a manufacturing, pharmacology/toxicology, and clinical pharmacology program were submitted. The original PDUFA date for this application was March 22, 2010. However, on February 16, 2010, the Applicant submitted a response to clinical issues in the 74 day letter, which included a new clinical study report to provide additional support for (b) (4) dose levels of Dulera. Because of the newly submitted clinical data, this submission was considered a major amendment and the PDUFA clock was extended. The new PDUFA date for this application is June 22, 2010. This memo will provide an overview of the application with a focus on issues that warrant further discussion, primarily the clinical efficacy and safety data. The memo will cover the entire review period and address the original primary review recommendations as well as the additional reviews from the extension period.

2. Background

Mometasone furoate (MF) and formoterol fumarate (FF) are currently approved active pharmaceutical ingredients in other inhalation products. Mometasone is a corticosteroid available in Asmanex Twisthaler for the treatment of asthma. Formoterol fumarate is a long acting beta agonist (LABA) available in Foradil Aerolizer, Foradil Certihaler, and in combination with budesonide as Symbicort Inhalation Aerosol. Inhaled corticosteroids (ICS) are one of the classes of medication used to treat asthma and are generally considered the most effective controller medication for asthma. LABA are another class of medications used for the maintenance treatment of bronchospasm in patients with asthma. LABA, including formoterol, have a known safety risk of asthma related death. Because of this risk, all LABA-containing products have a Boxed Warning and Medication Guide. The addition of a LABA to an ICS for the treatment of asthma is an accepted clinical practice and three ICS and LABA combination products are currently available: Advair Diskus, Advair HFA, and Symbicort Inhalation Aerosol.

There have been multiple interactions regarding the clinical development program. The following summarizes some pertinent regulatory history. During the November 3, 2004, Pre-IND meeting, the Agency noted that Asmanex and Foradil were not appropriate comparators for the factorial design clinical trials because of the pharmaceutical differences and the need to satisfy the Combination Rule. In a follow-up Pre-IND meeting on March 28, 2006, the use of a formoterol comparator HFA-134a formulation was noted. Because of the difference in formulation, the Agency noted that the Applicant would need to address the pharmaceutical comparability. The Agency also noted the need for dose ranging with the MDI formulations and that the “asthma worsening” endpoint was vague. The applicant submitted the phase 3 protocols without request for comments or questions. On February 22, 2007, the Agency issued written comments regarding the limitations of the (b) (4) asthma exacerbation definition.

A pre-NDA meeting was held on December 15, 2008. The Agency noted multiple issues, including the following: 1) provide replicate data to support the MF monotherapy against placebo at the lowest dose level because the MF monotherapy comparator needs to be fully developed; 2) provide dose ranging data and appropriate bridging between the Foradil Aerolizer and the 10 mcg formoterol HFA134a MDI monotherapy comparator; 3) address pharmaceutical performance of monoproducts in combination; 4) justify the (b) (4) dose levels: (b) (4) 100/5 and 200/5; 5) concerns with the asthma exacerbation endpoint; and 6) lack of PK data in adolescent patients.

3. CMC/Device

Mometasone furoate (MF)/formoterol fumarate (F) is a fixed dose combination metered dose inhaler. MF and F are the active pharmaceutical ingredients. The drug product also contains ethanol as a (b) (4) co-solvent, oleic acid as a surfactant, and hydrofluoroalkane (HFA) 227 as the propellant. There are (b) (4) proposed strengths for Dulera, based upon the ex-actuator dosages: (b) (4), 100/5 (100mcg mometasone furoate and 5mcg formoterol fumarate), and 200/5 (200mcg mometasone furoate and 5mcg formoterol fumarate). One therapeutic dose is obtained from

two single actuations, resulting in the following doses of MF/F: (b) (4) 200/10, and 400/10, respectively. The proposed dosing regimen is two actuations twice daily. Each canister provides 120 actuations (60 doses). The product includes a press and breathe actuator with an integrated dose counter. The dose counter was added to the actuator during phase 3. The CMC reviewer concluded that the addition of the dose counter did not affect the performance of the drug product. The proposed marketed product is not overwrapped. Despite issues with an (b) (4), stability data supports a 24 month expiry for MF/F stored at room temperature.

The drug substances are the same as in the approved NDAs (Foradil Aerolizer NDA, Asmanex Twisthaler). MF is a white (b) (4) powder that is manufactured and micronized by Schering Plough in Singapore and F is manufactured by Astellas Pharma Chemicals Co., in Japan with micronization by Novartis Pharma Stein AG in Switzerland. The drug product is manufactured by 3M Health Care Ltd in England.

Several issues were noted regarding the CMC aspect of the NDA: 1) F monotherapy comparator utilized different formulation than Dulera; 2) differences in APSD (b) (4) between F monotherapy component and Dulera; 3) lack of dose proportionality for Dulera dose strengths (b) (4) and 4) data integrity issues due to large number of corrections for CMC data as detailed in an amendment. These will be briefly addressed below.

The monotherapy comparator MDI products used for the clinical trials are not proposed for marketing. The MF comparator product is similar to the combination product without the FF active pharmaceutical ingredient. The F comparator product has some differences, including a difference in propellants - HFA 134a as the propellant instead of HFA 227, addition of lactose as an excipient, and a different valve. This difference in the F comparator product was known early in the development program. As stated above, in a Pre-IND meeting on March 28, 2006, the use of a formoterol comparator HFA-134a formulation was noted. Because of the difference in formulation, the Agency noted that the Applicant would need to address the pharmaceutical comparability.

The CMC reviewer noted that the monotherapy comparators were comparable to the combination product with regards to Dose Content Uniformity (DCU). The Aerodynamic Particle Size Distribution (APSD) for the MF comparator was similar to the combination product, but the APSD for the F comparator and combination product had some differences in the individual stage data (b) (4). This issue was discussed during the review period and was not determined to be a major issue because the DCU was similar and when the stage data was grouped, the differences were smaller.

In addition, the Dulera drug product is dose proportional for DCU but not dose proportional for APSD across the (b) (4) product strengths. This issue was discussed during the review period and was not determined to be a major issue because the DCU was dose proportional and when the (b) (4) data were grouped, APSD proportionality was demonstrated.

As stated above, the product includes an integrated dose counter. The CMC reviewer reviewed the dose counter information and noted that the Applicant has made some minor modifications/refinements of the dose counter to address issues of undercounting and failure to stop at zero in the patient use study. The Applicant has repeated in vitro analysis of the refined dose counter and the CMC reviewer noted the in vitro data demonstrated accuracy and reliability of the dose counter.

On October 29, 2009, the Applicant submitted an amendment to the NDA with a large number of corrections to the CMC section of the application. The discrepancies were noted by the Applicant upon preparation of submission of an application to other countries. Due to the number of corrections, data integrity concerns were raised and Compliance was notified of this issue. The CMC reviewed the corrections and noted the changes appeared to be minor. All facilities inspected by Compliance were acceptable.

The number of complaints regarding the functioning of the Dulera inhaler was 14 and per the Applicant is in the range of 0.02-0.13% of the total drug product units per trial. Although not all the complaint devices were returned, the Applicant did not identify any device specific problems and deemed the complaints as isolated incidents. Samples of normally functioning inhalers were returned from the clinical trials for analysis. The samples had DCU within range, but APSD did show a trend towards an (b) (4) in APSD.

According to the CMC reviewer, Alan Schroeder, the recommended regulatory action is approvable.

There are multiple CMC post-marketing agreements that the Applicant has agreed to as listed below:

- (b) (4) will be utilized as the different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier's certificate of analysis for HFA 227. (11/25/09 amendment)
- Re-evaluate the oleic acid individual fatty acid specifications within a period of two years after approval of the NDA, based on additional data. (11/25/09 amendment)
- Introduce methodology identical or equivalent/better than that contained within USP-NF General Chapter <401> for control of fatty acid composition in oleic acid. (1/14/2010 amendment)
- Re-evaluate the drug product specifications for APSD and the drug product specifications for degradation products "using the data from all available commercial stability batches once there are a minimum of 3 stability batches for each drug product strength where at least one batch has data through 24 months, the second batch has at least 12 months of stability data, and a third batch has at least 6 months of stability data." (11/25/09 amendment)
- Maintain specifications (i.e., a list of tests, the acceptance criteria and the test methods) in NDA 22-518 for each of the two drug substances. (1/14/10 amendment)
- Investigate the changes in particle size distribution of the emitted plume over the use life of the drug product and report the progress and submit results to the Agency within

6 months of the date of the information request. (February 19, 2010). (3/05/10 amendment)

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted a bridging toxicology program that included general toxicology studies of 13 weeks duration in rats and dogs with the MF and F combination to assess for potential additive or synergistic toxic effects. The toxicity profiles of formoterol and mometasone are well known; therefore, this nonclinical program evaluated potential interactions between mometasone and formoterol fumarate. The known target organs of toxicity are the immune and reproductive systems for mometasone and the heart and male reproductive system for formoterol. In the toxicology studies submitted, there was no evidence of additive or synergistic toxic effects with the combination mometasone and formoterol.

The pharmacology/toxicology review team concluded that the Applicant has an adequate bridging nonclinical pharmacology/toxicology program for Dulera. The recommendation is for approval.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted a clinical pharmacology program that evaluated the pharmacokinetic profile of Dulera and an HPA axis study. The results of the PK studies are described in Dr. Ying Fan's review. Dr. Fan's review of the clinical pharmacology program, noted several issues that will be briefly addressed below: 1) lack of relative bioavailability data for MF comparing MF/F with Asmanex MF in asthma patients; 2) limitations with the HPA axis study; and 3) lack of PK data in adolescents 12 to 17 years of age. The clinical pharmacology team was able to address these issues and concluded that the submitted clinical pharmacology data are acceptable for approval of Dulera.

PK data in healthy volunteers showed the systemic exposure of MF from MF/F 800 µg/20 µg was 25% (AUC_{0-12}) to 40% (C_{max}) lower than the Asmanex product 800 µg. Similar results were noted in COPD patients administered MF/F 400 µg/10 µg and Asmanex 400 µg. Although the Applicant did not perform a relative bioavailability study in asthma patients, the clinical pharmacology team addressed this issue by performing cross study comparison of the PK profile of mometasone from the Asmanex program and the Dulera PK data in the HPA axis study. The cross study comparison suggested a 9% lower C_{max} and 47% lower AUC_{0-12} for mometasone from MF/F 400 µg/10 µg compared to Asmanex 400 µg. With regard to formoterol, the systemic exposure of formoterol from MF/F 400 µg/10 µg was similar to Foradil Aerolizer 12 µg (10 µg emitted dose) in patients with asthma.

The application did not include PK data in patients 12 to 17 years of age. For inhalation products, PK data is used for assessment of systemic safety. There were a total of 298 patients ages 12 to 17 years of age in the phase 3 program, of which 129 were treated with MF/F. Because mometasone and formoterol are previously approved in patients down to 5 years of age, the systemic exposure to MF and F from MF/F in adults is lower or comparable to the

reference products, and there were sufficient numbers of adolescents in the clinical program, systemic safety in patients 12 to 17 years of age is adequately assessed in this application.

The Applicant conducted a dedicated HPA axis study, but there were a couple of limitations noted. The HPA axis study was a 6 weeks, open-label, placebo-controlled, active comparator study in 66 patients (Study P03705). The limitations of the study were the number of patients (<20 per arm) and the open-label design. However, the clinical pharmacology team determined that the results for cortisol suppression were similar to the Asmanex reference product and the positive control utilized in the study (Advair) and thus, the study is acceptable and will be described in the label.

6. Clinical Microbiology

This section is not applicable as MF/F is not an antimicrobial.

7. Clinical/Statistical- Efficacy

A combination ICS/LABA product is considered a combination of convenience. The safety and efficacy of the individual components need to be established in the clinical program as well as the contribution of each component. Since neither mometasone nor formoterol are currently marketed in the proposed HFA formulation, adequate support for dose selection is also expected.

To support the safety and efficacy of MF/F for the proposed indication, the Applicant submitted a full clinical program including three phase 3 clinical trials evaluating the efficacy and safety of MF/F as well as one long term safety trial and an HPA axis study. In addition, there are several relevant phase two trials to support the doses of F and MF carried forward into phase 3. The focus in this section will be the phase 3 clinical trials and the pertinent phase 2 dose selection trials. The HPA axis trial was briefly addressed in Section 5. The long term safety trial will be discussed in Section 8. The pertinent clinical trials in the MF/F program are shown in the table below. A dose counter study was also performed and will be briefly discussed.

Table 1 Summary of Dulera Clinical Development Program in Patients with Asthma

Trial No.	Purpose	Subjects	Design	Treatment Groups ^{†*}	Duration	Endpoints
Phase 3 Efficacy						
P04073 US, India, EU, Russia, Canada, Southeast Asia, South America Nov 2006-Nov 2008	P3, Efficacy/Safety	746 patients with asthma	R, DB, PC	MF/F 50/5, 2 puffs BID MF 50, 2 puffs BID F MDI 5, 2 puffs BID Placebo, 2 puffs BID	26 weeks	Efficacy - exacerbations - post-dose FEV1 Safety
P04334 US, Canada, South America, EU, India, Russia, Southeast Asia Nov 2006-Oct 2008	P3, Efficacy/Safety	781 patients with asthma	R, DB, PC	MF/F 100/5, 2 puffs BID MF 100, 2 puffs BID F MDI 5, 2 puffs BID Placebo, 2 puffs BID	26 weeks	Efficacy - exacerbations - post-dose FEV1 Safety
P04431 North America, Latin America, Europe, Ukraine, Russia Jul 2006-Feb 2008	P3, Efficacy/Safety	728 patients with asthma	R, DB	MF/F 100/5, 2 puffs BID MF/F 200/5, 2 puffs BID MF 200, 2 puffs BID	12 weeks	Efficacy - FEV1 AUC
Supportive						
P-04139 South America June 2006- Mar 2008	P3, Long term safety	404 patients with asthma	OL	MF/F 100/5, 2 puffs BID MF/F 200/5, 2 puffs BID Advair 250/50, 2 puffs BID Advair 500/50, 2 puffs BID	52 weeks	Safety
P03705 US Feb 2007 – Mar 2008	HPA Axis	66 patients with asthma	R, OL, PC, AC	MF/F 100/5, 2 puffs BID MF/F 200/5, 2 puffs BID Placebo Advair 230/21, 2 puffs BID	6 weeks	HPA axis Safety
P06144 Netherlands Feb 2002 - Jul 2002	Formoterol Dose Ranging	26 patients with asthma	R, DB, DD, PC, XO	F MDI 6*, 1 single puff F MDI 12*, 2 puffs of F6 F MDI 24*, 4 puffs of F6 Foradil Aerolizer 12, 1 cap Foradil Aerolizer 24, 2 caps PBO	Single Dose	FEV1
C97-208 US Oct 1997-June 1998	Mometasone Dose Ranging	435 patients with asthma	R, DB, PC, AC	MF 25, 2 puffs BID MF 100, 2 puffs BID MF 200, 2 puffs BID MF 300, 2 puffs BID Beclomethasone 168mcg BID PBO, 2 puffs BID	12 weeks	Change from baseline FEV1
C97-225 US Dec 1997-Aug 1998	Mometasone Dose Ranging	232 patients with asthma	R, DB, PC	MF 25, 2 puffs BID MF, 100, 2 puffs BID Beclomethasone 168mcg BID PBO	12 weeks	Change from baseline FEV1
C97-224 US Nov 1997-June 1999	Mometasone Dose Ranging	123 patients with asthma (severe)	R, DB, PC	MF 200, 2 puffs BID MF, 400, 2 puffs BID PBO	12 weeks with 9 month OLE	-% change in daily OCS requirement - Change from baseline FEV1
197-200 South America, EU, South Africa Nov 1997-Nov 1998	Mometasone Dose Ranging	715 patients with asthma	R, AC	MF 50, 2 puffs BID MF 100, 2 puffs BID MF 200, 2 puffs BID FP 125, 2 puffs BID	12 weeks	Change from baseline FEV1
P04703 US Mar 2008-Nov 2008	Dose Counter Handling	343 patients with asthma or COPD	OL	MF/F 50/5, 2 puffs BID	30 days	Dose counter performance
P05122 US, Europe Mar 2008-June 2009	Exhaled NO Dose Response	93 patients with asthma	R, DB, PC	MF/F 50/5, 2 puffs BID MF/F 100/5, 2 puffs BID MF/F 200/5, 2 puffs BID MF 100, 2 puffs BID MF DPI 100mcg, 2 puffs BID PBO	2 weeks	Change from baseline eNO

[†] F comparator is 134HFA MDI

*All doses of F and MF written as ex-mouthpiece, except in Study P06144, the dose of F is written as ex-valve and the ex-mouthpiece dose is 5mcg

Dose Selection

The Applicant conducted one key phase two clinical trial to select the dose of F to carry forward into phase 3 and several phase two dose ranging clinical trials with MF to support the doses in phase 3. These clinical trials are briefly summarized here.

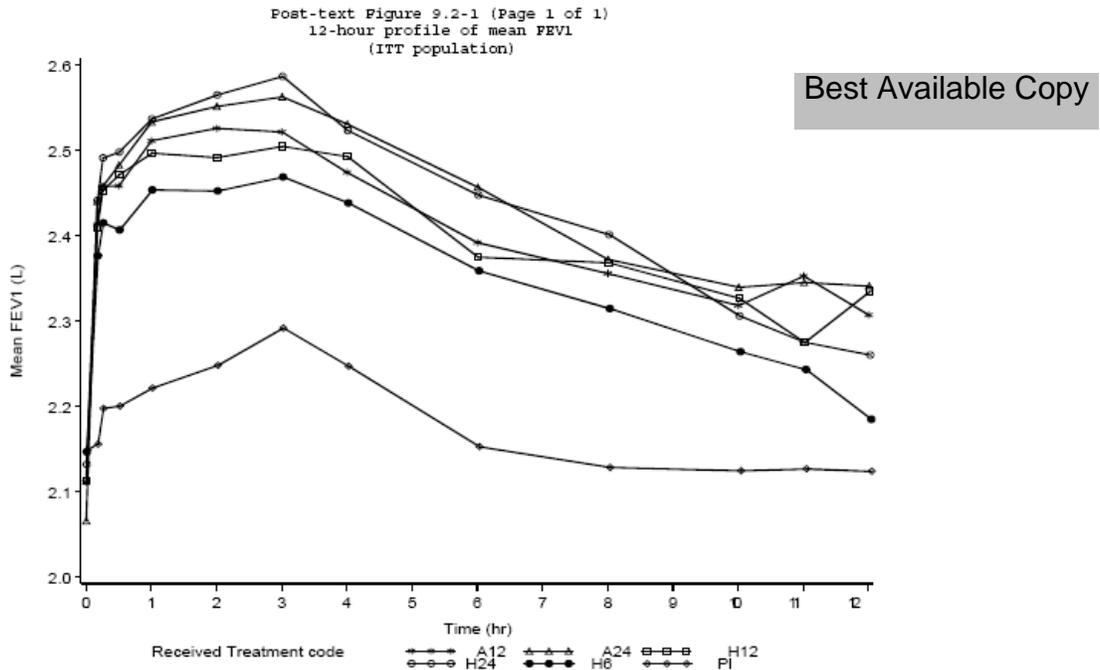
Formoterol (F) Dose Selection

The Applicant had a separate IND for development of the formoterol HFA134a MDI. Dose selection for the F MDI was based upon the results of Study P06144 from that program and the in vitro analysis of the ex-mouthpiece dose of Foradil Aerolizer 12mcg. Study P06144 was a single dose, dose ranging, cross-over study in 26 patients with asthma comparing 3 doses of F MDI HFA134a (6, 12, and 24mcg) to Foradil Aerolizer (12 and 24mcg) and placebo. The results are shown in the table and figure below.

Table 2 Study P06144 –Formoterol MDI Dose Ranging FEV₁ AUC Results			
Treatment	FEV₁ AUC (LS Mean in L)	Difference from Placebo	P value
F MDI HFA134a 6mcg* (one puff)	2.33	0.16	<0.0001
F MDI HFA134a 12mcg (two puffs 6mcg*)	2.41	0.24	<0.0001
F MDI HFA134a 24mcg (four puffs 6mcg*)	2.45	0.28	<0.0001
Foradil Aerolizer 12mcg (one capsule)	2.41	0.24	<0.0001
Foradil Aerolizer 24mcg (two 12mcg capsules)	2.46	0.29	<0.0001
Placebo	2.17		

* ex-valve dose, ex-mouthpiece dose of 5mcg; Ref: Study Report P06144.pdf, Table 9-2

Figure 1 Study P06144 – 12 hr FEV₁ Profile



The results of Study P06144 show that the F MDI 12mcg dose was similar to the Foradil Aerolizer 12mcg dose with regards to the AUC and the 12 hour FEV₁ profile. The 6mcg dose did not have as robust a response and the 24mcg dose did not offer significant benefit over the 12mcg dose. Based upon these results, the F MDI 12mcg dose (two puffs of 6mcg) was selected for further development. It is important to note that the doses of the F MDI in Study P01644 are expressed as ex-valve doses. An ex-valve dose of F MDI 6mcg corresponds to an ex-actuator dose of 5mcg, with two puffs providing an ex-actuator dose of 10mcg. The ex-mouthpiece dose of Foradil Aerolizer 12mcg is 10mcg. Thus, the ex-mouthpiece dose of F MDI selected to move forward into phase 3 and the approved Foradil Aerolizer dose are the same.

The Division typically recommends that the formulation and device for the monotherapy comparators be the same as the combination product in the phase 3 program. The Division noted the use of a formoterol comparator HFA-134a formulation early in the program and asked that the Applicant would need to address the pharmaceutical comparability of the MF/F product and the F comparator. As discussed in Section 3, the pharmaceutical comparability was considered acceptable. Given the results described above, there is sufficient support for the dose of F MDI selected for the phase 3 program.

Mometasone Dose Selection

According to the Applicant, the MF dose for the MF/F combination was determined based upon previous clinical trials with MF in different formulations, including a clinical program with a similar HFA-227 MDI formulation. The design and results of the pertinent clinical trials are shown below.

There are four pertinent clinical trials with regards to MF dose ranging (C97-208, C97-225, C97-224, and I97-200), which were randomized, placebo and/or active - controlled, 12 weeks in duration in patients with asthma. The treatment groups are outlined in Table 3. These trials were conducted a decade ago.

The primary efficacy endpoint was the change in FEV₁ from baseline to the last study visit (Study C97-225 and C97-208) and this was a secondary endpoint in Study C97-224. The FEV₁ was not a trough measurement, which is what is typically used to assess the efficacy of ICS. Dr. Limb discussed this issue in her review. She noted that study sites were encouraged to schedule spirometry at the same time of day throughout the trial to reduce diurnal variation, but specific timing of PFTs in relation to dosing was not prescribed. According to the Applicant, the majority of assessments were performed within 1 to 4 hours after the AM dose. As the ICS is not expected to have an acute effect, the Applicant suggested that these values would be comparable to trough values. While the use of trough FEV₁ and FEV₁ measurements obtained at a specified time are preferable, the results of these trials should provide some support for dose selection. The results are shown in the table below.

Table 3 Mometasone MDI Dose Ranging Change in FEV1 (L) at Endpoint (12 weeks)					
Treatment BID	N	Baseline	Change from Baseline	Difference from PBO	P value
Study C97-208					
MF 50 mcg	71	2.49	0.12	0.31	<0.01
MF 200 mcg	73	2.51	0.14	0.33	<0.01
MF 400 mcg	74	2.61	0.12	0.31	<0.01
MF 600 mcg	73	2.51	0.13	0.32	<0.01
Beclomethasone 168 mcg	72	2.57	0.02	0.21	<0.01
PBO	72	2.38	-0.19		
Study C97-225					
MF 50 mcg	58	2.49	0.13	0.31	<0.01
MF 200 mcg	57	2.66	0.16	0.34	<0.01
Beclomethasone 186 mcg	58	2.73	0.18	0.36	<0.01
Placebo	59	2.53	-0.18		
C97-224					
MF 400 mcg	42	1.79	0.08	0.25	<0.01
MF 800 mcg	43	1.71	0.08	0.25	<0.01
Placebo	38	1.71	-0.17		
Study 197-200					
MF 100 mcg	176	2.45	0.10		
MF 200 mcg	182	2.41	0.19	0.09*	<0.01
MF 400 mcg	176	2.49	0.18	0.08*	<0.01
Fluticasone 250 mcg	176	2.49	0.21	0.11*	<0.01

* difference from MF100

Overall, the results of the above trials show a significant difference in change from baseline FEV1 compared to placebo for doses of MF from 50mcg to 800mcg. There is replication of the finding for the 200 and 400mcg dose. Within each individual trial there is not a clear dose separation, which can be difficult to demonstrate for ICS. In Study C97-225, the 50mcg dose had a somewhat smaller effect. The Applicant chose to move forward with 100 and 200mcg dose and 400mcg for the more severe asthma population. The Applicant noted that the selected doses were similar for the MF MDI and the approved Asmanex Twisthaler. Dr. Limb noted that while the 200mcg and 400mcg doses seem reasonable and there is replication of the results compared to placebo, there is no placebo controlled trial with the 100mcg dose, and therefore, there is insufficient support for the 100mcg dose. In addition, given the current labeling recommendations for LABA products, addition of a LABA to a low dose ICS is not recommended. I agree with Dr. Limb's conclusion.

It is worth noting that the MF product used in the dose ranging trials differed somewhat from the MF and MF/F products used in the phase 3 program. While the excipients were the same, the valve and levels of excipients differed and thus some of the performance characteristics differed. Given the flat dose response from 200-600mcg of MF, the differences in the products are not expected to have a significant effect on the program and the doses chosen to move forward were further evaluated in the phase 3 program.

Phase 3 Study Design

The three phase 3 clinical trials shown in Table 1 will be discussed together in this section. The phase 3 clinical trials were randomized, double-blind, placebo-controlled (P04073 &

P04334), parallel group, efficacy and safety trials in patients 12 years of age and older with varying severities of asthma. Studies P04073 and P04334 were 26 weeks duration and Study P04431 was 12 weeks duration. Differences between the clinical trials included the treatment groups, which are listed in Table 1 and the patient population and baseline ICS requirement. All study treatments were administered twice daily.

Enrolled patients had to be 12 years of age and older, have a documented history of asthma for ≥ 12 months and demonstrate response to bronchodilator (reversibility with a $\geq 12\%$ increase in FEV₁ following albuterol administration or PEF variability $>20\%$ or PEF diurnal variations $>20\%$). The required FEV₁ percent predicted varied depending upon the asthma severity ($>60\%$ or $>50\%$). Baseline use of ICS was required. Patients with ≥ 10 pack year smoking history or current smokers were excluded.

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

In Studies P04073 & P04334, there were co-primary efficacy endpoints shown below.

- AUC_{0-12hr} of the change from baseline to week 12 in FEV₁
 - MF/F 100/10 vs. MF 100 to determine the F contribution
- time to first severe asthma exacerbation
 - MF/F 100/10 vs. MF 100 to determine the MF contribution
 - based upon any one of the following criteria
 - emergency treatment, hospitalization, or treatment with additional excluded asthma medications (e.g. OCS)
 - decrease in FEV₁ below treatment period stability
 - decrease in AM or PM PEF below treatment period stability on 2 consecutive days

In Study P04431, because there is no F or PBO group, the FEV₁ AUC_{0-12hr} is the only primary endpoint. With regards to the asthma exacerbation endpoint, there is no standardized definition of asthma exacerbation thus the definition is worth discussion. While the criteria proposed by the Applicant are useful criteria to evaluate the efficacy of asthma therapy, the Division raised concerns regarding the definition of asthma exacerbation when the phase 3 protocols were submitted. The Division noted that correlation with symptoms was not included and duration of symptoms was not specified. The Division also raised the concern with the asthma exacerbation definition in the 74 day letter. Because of concerns with the definition, the Division noted that for the contribution of the MF, the secondary endpoint, trough FEV₁, would be closely reviewed. In addition to trough FEV₁, other pertinent secondary efficacy variables included: AQLQ, ACQ, PEF, symptom scores, and nocturnal awakenings.

Safety monitoring included adverse events, physical examinations, laboratory parameters, vital signs, ECGs, and CXR.

Issues with the Phase 3 Program

Before discussing the results of the phase 3 program, it is important to highlight any issues with the phase 3 program. Going into the phase 3 program, there is reasonable support for the MF dose of 200 and 400mcg, but limited support for the MF 100mcg dose. There are differences in devices/formulations between the MF/F product and the F 134HFA MDI comparator product, but based upon CMC in vitro data, the pharmaceutical comparability is acceptable. In addition, concerns with the asthma exacerbation definition were conveyed to the Applicant.

Efficacy Results from Phase 3 Trials

Patients enrolled in the phase 3 trials were generally matched between treatment groups. In the 26 week trials (P040703, P04334), the patient population had more females (51-59%) and was primarily caucasian (70-78%) with a mean age of 37-43 years. There were 173 patients (11%) who were 12 to <18 years of age. In study P04431, the patient population was 90% caucasian and was slightly older with a mean age of 48-49 years. There were 63 patients (9%) who were 12 to <18 years of age. In the 26 week placebo controlled trials, more patients discontinued from the placebo group than other treatment groups. The primary reason for discontinuation in the placebo group was lack of efficacy.

The primary efficacy variables were described above and the results are shown in the table below.

Table 4 – Efficacy Results from Phase 3 Program[†]			
(All Randomized Patients)			
	Mean FEV1 AUC_{0-12hr} LS Mean change from baseline to Week 12 (Lxh)	Trough FEV₁ LS Mean change from baseline at Week 12 (L)	Time to 1st severe exacerbation*
P04334			
MF 200/10 vs. MF 200	1.81 (p<0.001)		
MF 200/10 vs. F 10		0.13 (p<0.001)	p<0.001
MF 200/10 vs. PBO	2.54 (p<0.001)	0.18 (p<0.001)	p<0.001
MF 200 vs. PBO		0.12 (p<0.001)	
F 10 vs. PBO	1.36 (p=0.009)		
P04431			
MF 400/10 vs. MF 400	2.15 (p<0.001)	0.09 (p=0.006)	
MF 400/10 vs. MF 200/10	0.60 (p=0.096)	0.05 (p=0.145)	
*refer to discussion for issues with definition			
[†] Results per the Applicant’s CSRs, which differ slightly from Dr. Abugov’s statistical review, but the interpretation is not affected.			

(b) (4)

The efficacy results can also be displayed graphically as shown in the following figures, which show the post-dose serial FEV1 in Study P04334 and P04431. A figure similar to one of these is planned for the product label.

Best Available Copy

Figure 2 Serial FEV1 in Study P040703 and P04431

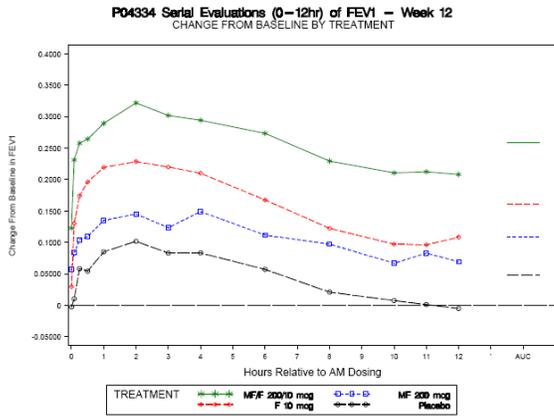
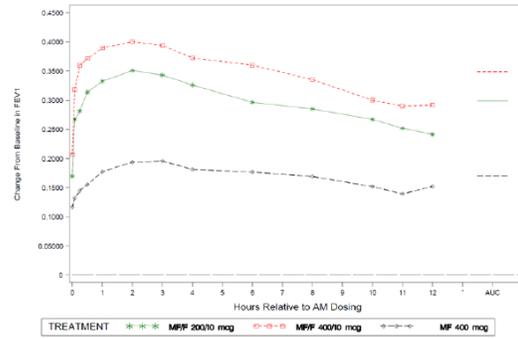


Figure 10 P04431: 12-hour serial evaluations of FEV1 at Week 12



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

As shown in Table 4, the results from the phase 3 program were generally statistically significant for the pre-specified primary endpoints and the important secondary endpoint, trough FEV1. There is replication of the efficacy of F 10 compared to placebo based upon FEV AUC_{0-12hr}. (b) (4)

. As discussed in the section on dose selection for MF, there was replication of efficacy of MF 200 and MF 400 compared to placebo. (b) (4)

In terms of the MF 200/10 dose, there is reasonable support for the MF 200 dose and Study P04334 establishes the contribution of F and the contribution of MF to the combination. Study P04331 included a comparison of MF 200/10 and MF 400/10. There was a numerical benefit of MF 400/10 over the lower dose.

(b) (4)

Table 5 Number and percentage of patients with deterioration in asthma

	N	Overall	↓ FEV1*	↓ PEFR**	Emergency Treatment	Hospitalization	Excluded meds†
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Study P04073

(b) (4)

Study P04334

MF/F 200/10	191	58 (30%)	18 (9%)	37 (19%)	0	1 (1%)	2 (1%)
MF 200	192	65 (34%)	19 (10%)	41 (21%)	1 (1%)	0	4 (2%)
F 10	202	109 (54%)	31 (15%)	62 (31%)	4 (2%)	0	17 (8%)
Placebo	196	109 (56%)	41 (21%)	61 (31%)	1 (1%)	0	8 (4%)

Study P04431

MF/F 200/10	233	29 (12%)	23 (10%)	2 (1%)	3 (1.3%)	0	5 (2%)
MF/F 400/10	255	31 (12%)	17 (7%)	4 (2%)	1 (<1%)	1 (0.4%)	8 (3%)
MF 400	240	44 (18%)	33 (14%)	3 (1%)	1 (< 1%)	0	12 (5%)

*Decrease in absolute FEV1 below the treatment period stability limit (defined as 80% of the average of the two predose FEV1 measurements taken 30 minutes and immediately prior to the first dose of randomized trial medication)

**Decrease in AM or PM peak expiratory flow (PEF) below the treatment period stability limit (defined as 80% of the AM or PM PEF obtained over the last 7 days of the run-in period)

†Patients received systemic steroids except 1 patient in Study P04334 in the F 10 arm who received formoterol DPI and 1 patient in Study P04431 in the MF/F 400/10 arm who received albuterol

Dr. Limb reviewed the key secondary efficacy variables and noted that they were generally supportive of the results for the primary efficacy variables. While the results for the AQLQ were numerically supportive of the efficacy of MF/F, the results did not consistently show a change from baseline of ≥ 0.5 and did not consistently show a treatment group difference for MF/F – placebo of ≥ 0.5 , which is considered the MID. The observed results differed somewhat from the analysis using data imputation (LOCF and average) (b) (4)

Regardless of the analysis, the confidence intervals clearly show that the treatment difference includes values below 0.5 as shown in the table below.

Table 6 AQLQ – Change from Baseline

(b) (4)

Study P04334						
	MF/F 200/10	MF 200	F 10	Placebo	Treatment Diff (MF/F – Placebo)	95% CI
Baseline	5.38	5.40	5.51	5.56		
Change from Baseline*						
Week 26	0.61	0.50	0.31	0.36	0.25	0.08, 0.43
Endpoint (LOCF)	0.49	0.37	0.05	-0.01	0.50	0.32, 0.68
Average [†]	0.48	0.31	0.11	0.07	0.41	0.28, 0.60

*Mean based upon ANCOVA model with treatment, site, and Baseline as covariate
[†]Longitudinal average across scheduled visits from mixed model with treatment and subject as fixed effects, treatment day by treatment interaction as random effects and baseline spirometry as covariate

The phase 3 clinical program included approximately 10% patients between the ages of 12 and < 18. Dr. Limb noted that there were similar patterns of efficacy regardless of age sub-categories.

Dose Counter

The product includes a press and breathe actuator with an integrated dose counter. The dose counter was added to the actuator during phase 3. The Applicant conducted an open-label patient handling study (P04703) to assess the dose counter. Patients received MF/F with a dose counter and results were compared to a Counterstrip, in which patients were instructed to scratch off a number for every actuation. Dr. Limb reviewed the study and noted an overall discrepancy rate of 0.14 discrepancies per 100 actuations. There were 14 reports of under-counting and the applicant has stated its plan to adjust the Count Point-Fire-Point relationship. In addition to the dose counter study, the in vitro performance of the dose counter is weighed heavily, which supported the reliability and accuracy of the dose counter (Section 3). Based upon questionnaires, patients generally noted the dose counter was easy to use. There were a number of comments about readability concerns b/c of small digits contrast, but despite these comments, the Applicant noted that patients generally correctly entered the counter value into the e-diary.

Exhaled NO

In the 74 day letter, the Division raised concerns regarding support for the (b) (4)

On February 16, 2010, the Applicant submitted the results of Study P05122 to provide additional support for the 3 dose levels of MF/F. Study P05122 compared three doses of MF/F in patients with asthma and evaluated the effect on exhaled nitric oxide (eNO). The PDUFA clock was extended because of this submission. Dr. Limb reviewed this clinical trial in a review dated May 19, 2010, and noted that there was a numerical separation of the three MF/F doses with regards to percent change from baseline eNO as shown in the table below. However, because eNO is not an

established biomarker for efficacy and has not been used for making regulatory decisions, the results of Study P05122 do not provide adequate justification for the 3 dose levels of MF/F. I concur.

Table 7 Percent Change from Baseline eNO (Study P05122)						
(All Randomized Patients)						
	(b) (4)	MF/F 200/10 N=16	MF/F 400/10 N=12	MF DPI 200 N=14	MF 200 N=15	Placebo N=13
Baseline (ppb)		70	77	103	66	80
Change at Day 14 (ppb)		-32	-49	-66	-33	-11
% change at Day 14		-45	-61	-51	-46	0.1

In summary, Dr. Limb has concluded that there is adequate support for the efficacy of MF 200/10 and 400/10, (b) (4) Dr. Robert Abugov, the Agency’s statistical reviewer also made the same conclusion. I concur with Drs. Abugov and Limb. (b) (4)

8. Safety

The primary support for the safety of MF/F comes from the phase 3 trials and the long-term safety trial. In the full phase 3 program submitted by the Applicant (6 trials), 1781 patients received at least one dose of MF/F: 464 received MF/F 100/10, 932 received MF/F 200/10, and 385 received MF/F 400/10. Approximately 10% of the population was 12 to < 18 years of age. In the 52 week safety study, there were 231 patients treated for a year or longer. The overall size of the safety database is considered acceptable. Safety assessments in the phase 3 clinical trials included adverse events (AEs), physical examinations, vital signs, electrocardiograms, laboratories.

There were three deaths in the clinical program, but no safety signal was suggested. Causes of death were: electrocution, gastric cancer, and metastatic uterine leiomyosarcoma. Serious adverse events (SAE) were reviewed by Dr. Limb and she did not note a new safety signal, except potentially ophthalmologic adverse reactions (lens disorders and ocular hypertension), which are known potential reactions with ICS. Of particular interest are asthma-related SAEs. No asthma related deaths or intubations were reported. Dr. Limb noted 7 asthma related hospitalizations in the clinical program, but these were balanced across treatment groups, including the active comparators.

AEs were more common in the MF/F group than in the placebo group, but were reported with similar frequency as in the MF and F treatment groups. Common AEs included headache, nasopharyngitis, upper respiratory tract infection, and pharyngolaryngeal pain. These types of AEs are common in asthma clinical development programs. There did not appear to be a dose-related effect with regards to AEs. In terms of the laboratory, physical exam, vital sign, and ECG data, Dr. Limb reviewed the data, and there were generally no safety signals suggested.

The long term safety trial was an open-label trial in patients 12 years of age and older with asthma. Entry criteria were similar to the other phase 3 clinical trials. The screening period was followed by a 12 month open-label treatment period. Patients received either MF/F

200/10, MF/F 400/10 BID, Advair 250/50, or Advair 500/50. Review of results of the long term safety trial did not suggest a new safety signal.

Formoterol is a long-acting beta agonist, which has a known safety signal of asthma related death. A joint Pulmonary-Allergy Drugs (PADAC), Drug Safety and Risk Management, and Pediatric Advisory Committee meeting was held on December 10-11, 2008, to discuss the safety of long acting beta agonists. Another PADAC meeting was held on March 10-11, 2010 to discuss the design of large safety trials to evaluate the risk of serious asthma exacerbations, including hospitalizations, intubation, and death when LABAs are added to an ICS. For this formoterol containing product, the large safety trial can be performed post-marketing and will be a post-marketing requirement. At the time of finalization of this review, the Agency is actively discussing the design of these safety trials and the details are to be determined.

9. Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee was not held to discuss this application. Mometasone and formoterol are both established active pharmaceutical ingredients for the treatment of asthma; therefore, discussion at an advisory committee was not warranted.

10. Pediatrics

The Applicant proposed the asthma indication in patients 12 years of age and older. The Applicant requested deferral of clinical trials in patients 5 to 11 years of age with asthma and a waiver in patients from 0 to 4 years of age. This proposal is acceptable. Deferral of trials in patients 5 to 11 years of age is reasonable because development of a lower strength formulation is necessary for evaluation in pediatric patients. The Applicant referred to discussions in 2008 regarding the proposed pediatric program. A phase 2 trial is ongoing and phase 3 trials are scheduled to begin in 2010. A waiver in children less than 5 years of age is reasonable as the use of a combination ICS/LABA product in patients younger than 4 to 5 years of age is generally not warranted. The deferral and waiver were discussed at PeRC on March 3, 2010. The following plan is based upon the Applicant's proposed pediatric plan dated June 11, 2010, and updated dates submitted on June 15, 2010. The submitted proposal is reasonable for this stage of development. The Division will have opportunity to provide comments on the protocols once submitted for review. Issues such as use of spacer will be addressed at that time.



11. Other Relevant Regulatory Issues

The Applicant conducted the clinical trials using Good Clinical Practices and the Applicant provided the required financial disclosure information for investigators. The financial disclosure information did not suggest a conflict with the investigators. The Applicant certified that no financial arrangements were made with clinical investigators. A DSI audit was requested of two clinical sites in the US that were high enrollers: Dr. Nayak Anjali in Normal, Illinois and Dr. Kerwin Edward in Medford, Oregon. The statistical reviewer did not note any center effects, so the high enrollers were chosen. The DSI inspected the two clinical sites above as well as the Applicant. In a report dated January 27, 2010, the DSI noted the adherence to GCP. Minor, isolated, regulatory violations were noted, which were unlikely to impact data integrity. The conclusion of the DSI was that the data appear to be reliable.

On February 16, 2010, the Applicant submitted a response to the 74-day letter. The submission included the following: a) study report from a new study with multiple doses of ICS and its effects on exhaled nitric oxide to support (b) (4) dose levels of MF/F and b) arguments to support asthma exacerbation definition and contribution of MF.

(b) (4)

12. Labeling

This section provides a high level overview of labeling issues. The proposed tradename is Dulera Inhalation Aerosol, which has been found acceptable from DMEPA. Consults from DDMAC were received and included in the labeling process. Because Dulera contains a long acting beta agonist (LABA), which has a safety risk of serious asthma outcomes (asthma death, asthma intubation, and asthma hospitalization) a Medication Guide is required. DRISK provided recommendations for the Medication Guide. Carton and container labeling were reviewed and comments regarding removal of a graphic and making the tradename more prominent were conveyed to the Applicant.

Regarding the package insert, the following are high level revisions that were made to the product label:

- removal of the (b) (4) indication as discussed in Section 6
- removal of the reference to the (b) (4) because of insufficient data to support approval
- removal of the (b) (4) and (b) (4) references from the indication because of the new LABA labeling
- Boxed Warning made consistent with current labeling for LABA products

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The recommended regulatory action is Approval for the 100/5 and 200/5 dosage forms of Dulera. The Applicant has provided substantial evidence of efficacy and safety for two of the (b) (4) dosages Dulera 100/5 (200/10 therapeutic dose) and Dulera 200/5 (400/10 therapeutic dose). The submitted clinical trials establish the contribution of MF and F to the combination product and the additional benefit of the higher dose.

(b) (4)

- Risk Benefit Assessment

Dulera is a combination of an ICS (mometasone) and a LABA (formoterol) for the treatment of asthma. ICS and LABA are established pharmacological classes for the treatment of asthma and both components are currently available as orally inhaled products for use in patients with asthma. There are 3 ICS/LABA combination products available on the market. The submitted clinical program demonstrates the efficacy of Dulera 100/5 and 200/5 on FEV1 in patients with asthma. Other efficacy variables are also supportive, including “asthma exacerbations”, AQLQ, nighttime awakenings, and rescue medication use. ICS have known risks of infection, adrenal suppression, and glaucoma. LABA have known risk of serious asthma outcomes (asthma related deaths, intubations, and hospitalizations). The submitted program did not identify any new safety signals with Dulera that are not already known for ICS and LABA products. The benefit/risk assessment of Dulera 100/5 and 200/5 is considered favorable; however, a Risk Evaluation and Mitigation Strategy is required to help ensure the safe use of Dulera. (b) (4)

- Recommendation for Postmarketing Risk Management Activities

A Risk Evaluation and Mitigation Strategy (REMS) is required to manage the risk of serious asthma outcomes with LABA and help ensure the safe use of Dulera. The REMS includes a Medication Guide and Communication Plan, which is consistent with the REMS for other LABA products. The Communication Plan includes a Dear Healthcare Provider letter and educational materials for professional societies and web/print based material. The REMS was reviewed by the Division and DRISK and found to be acceptable.

- Recommendation for other Postmarketing Study Commitments

During the review period, multiple post-marketing commitments and requirements were discussed with the Applicant. The post-marketing requirements are to address the safety of Dulera on serious asthma outcomes (asthma deaths, inbutations, and exacerbations). All Applicants of LABA products for asthma are required to conduct post-marketing large safety trial to assess the risk of serious asthma outcomes. Because Dulera contains formoterol, which is currently marketed, this safety study may be conducted post-marketing. Additional

requirements included pediatric trials in patients 5 years and older as discussed in Section 10. The following are post-marketing requirements:

FDAAA Post-marketing Requirement

- *Conduct one or more postmarketing clinical trials with DULERA compared to inhaled corticosteroids in adults and adolescent patients with asthma to evaluate the risk of serious asthma outcomes (asthma related death, intubations, and hospitalizations).*

Note that the protocol is under active discussion in the Agency and a timeline for protocol submission, start date, and final report submission is not available at this time.

PREA Post-marketing Requirements

- *Deferred pediatric trial under PREA to compare the pharmacodynamics of DULERA with and without a spacer in children 5 to 11 years of age*
 - *Protocol Submission: October 2010*
 - *Study Completion: February 2012*
 - *Final Report Submission: July 2012*
- *Deferred pediatric trial under PREA to compare the pharmacokinetics of DULERA with and without a spacer in children 5 to 11 years of age*
 - *Protocol Submission: July 2012*
 - *Study Completion: June 2014*
 - *Final Report Submission: November 2014*
- *Deferred pediatric trial under PREA to evaluate the effects of DULERA on the HPA axis in children 5 to 11 years of age. In lieu of an HPA axis study, you may provide robust data to demonstrate that the systemic exposure of mometasone from DULERA is comparable or lower than that from the mometasone dry powder inhaler.*
 - *Protocol Submission: May 2012*
 - *Study Completion: October 2013*
 - *Final Report Submission: March 2014*
- *Deferred pediatric trial under PREA to evaluate the safety and efficacy of multiple doses of mometasone MDI in children 5 to 11 years of age with asthma.*
 - *Protocol Submission: April 2012*
 - *Study Completion: March 2014*
 - *Final Report Submission: August 2014*
- *Deferred pediatric trial under PREA to evaluate the safety and efficacy of DULERA compared to mometasone MDI in children 5 to 11 years of age with asthma. This study will be 12- 26 weeks duration.*
 - *Protocol Submission: May 2014*

- *Study Completion:* August 2016
- *Final Report Submission:* January 2017

- *Deferred pediatric trial under PREA to evaluate the long-term safety of DULERA in children 5 to 11 years of age with asthma. This study will be 26 weeks duration with a 6 month extension*
 - *Protocol Submission:* July 2014
 - *Study Completion:* October 2016
 - *Final Report Submission:* March 2017

- Recommended Comments to Applicant

For the Approval letter for Dulera 100/5 and 200/5 there are no comments.

(b) (4)



Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

MOMETASONE
FUROATE/FORMOTEROL
FUMARATE

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/s/

SALLY M SEYMOUR

06/22/2010