U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA / Serial Number:	NDA 022-518 / 0000
Drug Name:	Dulera® (mometasone furoate / formoterol fumarate) inhalation aerosol
Proposed Indication(s):	(b) (4) treatment of asthma in patients 12 years of age and older
Applicant:	Schering-Plough
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Keywords: NDA review, clinical Studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Schering-Plough Corporation has proposed Dulera, a combination of mometasone furoate (M) and formoterol fumarate (F) administered via an HFA-227 pressurized metered dose inhaler, for 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 components of Dulera have been previously approved for separate administration via dry powder inhaler.

Effectiveness and safety of (b) (4) different dosages ex-mouthpiece were examined; (b) (4) (b) (4) M 200 µg plus F 10 µg (M/F 200/10), and M 400 µg plus F 10 µg (M/F 400/10). Proposed dosing is twice daily, with each dosage requiring two inhaler actuations.

Mometasone and formoterol in Dulera M/F 400/10 and 200/10 provided separate and distinct contributions to overall effectiveness for all major endpoints examined. In support of mometasone's contribution, after 12 weeks of treatment, patients assigned to receive M/F 200/10 or M/F 400/10 consistently showed statistically greater improvement in trough FEV_1 than patients assigned to receive F. In support of formeterol's contribution, after 12 weeks of treatment, patients assigned to receive M/F consistently showed statistically greater increases post-dose FEV_1 and FEV_1 $AUC_{0\text{-}12hr}$ over baseline FEV_1 than patients assigned to receive M.

(b) (4)

(b) (4), the definition of exacerbation employed to demonstrate superiority of (b) (4) over placebo was not considered as acceptable for regulatory purposes.

This submission supports effectiveness of M/F 200/10 and M/F 400/10 for treatment of asthma. (b) (4)

1.2. Brief Overview of Clinical Studies

(b) (4) double blind, parallel group, multicenter phase 3 efficacy studies were conducted on patients with persistent asthma to demonstrate that each active component of Dulera makes a distinct contribution to effectiveness. Studies (b) (4) P04334, and P04431 recruited patients previously treated with low, medium, and high doses of steroids respectively, and assessed effectiveness of (b) (4) M/F 200/10, and M/F 400/10 bid respectively. In addition, P04431 compared effectiveness of M/F 400/10 with M/F 200/10.

(b) (4)

Study P04334 randomized 781 patients with persistent asthma previously treated with medium doses of steroid among four treatment arms; M/F 200/10 (N=191), M 200 (N=192), F 10 (N=202), and placebo (N=196). After 12 weeks of treatment, patients assigned to receive M/F 200/10 showed (i) statistically greater improvement in trough FEV_1 than patients assigned to receive F 10 monotherapy, and (ii) statistically greater increases in post-dose FEV_1 and FEV_1 $AUC_{0\text{-}12hr}$ over baseline than patients assigned to receive M 200 monotherapy. After 26 weeks of treatment, patients assigned to receive M/F 200/10 showed a lower cumulative incidence of asthma exacerbations than patients assigned to receive F 10 monotherapy, indicating a separate contribution to effectiveness of mometasone in the Dulera combination. In addition, patients receiving M 200 and F 10 monotherapies showed statistically significantly greater improvement in trough FEV_1 and post-dose FEV_1 respectively than patients assigned to receive placebo.

Study P04431 randomized 728 patients with persistent asthma previously treated with high doses of steroid among three treatment arms; M/F 400/10 (N=233), M/F 200/10 (N=255), and M 400 (N=240). After 12 weeks of treatment, patients assigned to receive M/F 400/10 showed statistically greater increases in post-dose FEV_1 and FEV_1 $AUC_{0\text{-}12hr}$ over baseline than patients assigned to receive M 400 monotherapy. No difference in trough FEV_1 was seen between patients treated with M/F 400/10 and patients treated with M/F 200/10.

The foregoing results indicate that mometasone and formoterol provide separate contributions to the effectiveness of Dulera which correspond to their effects in monotherapy. Whether in the M/F combination or in monotherapy, mometasone reduces inflammation, as evidenced by the fact that patients receiving M/F rather than F alone (b) (4) P04334, P04431) or M rather than placebo (b) (4), P04334) show improvements in post-dose FEV_1 and exacerbation rate. Similarly, whether in the M/F combination or in monotherapy, formoterol is an effective bronchodilator, as evidenced by the fact that patients receiving M/F rather than M alone ((b) (4) P04334, P04431) or F rather than placebo (b) (4), P04334) show improvements in post-dose FEV_1 and FEV_1 $AUC_{0\text{-}12hr}$.

That study P04431 showed no significant difference in trough FEV_1 between patients treated with M/F 400/10 and patients treated with M/F 200/10 suggests an effectiveness plateau for mometasone at or less than 200 µg.

1.3 Statistical Issues

1.3.a Contribution of mometasone to effectiveness

<u>Potential Confounding of Formulation with Effects of Mometasone</u>

Because of manufacturing problems, the propellant HFA-227 in the M/F combination could not be used to formulate the F monotherapy comparator. The formoterol monotherapy comparator arm was instead formulated using HFA-134, (b) (4) (b) (4). Evaluations concerning the contribution to efficacy of mometasone in Dulera, conducted by evaluating differences between M/F and F, may therefore have been confounded with effect of formulation and, from a purely statistical point of view, it is unclear what the impact of the formulation differences would be for assessing steroid contribution to M/F. However, concerns around formulation effects are lessened by Pk trial P05643, which showed that change in FEV_1 $AUC_{0\text{-}12hr}$ from baseline of the F 10 monotherapy is essentially the same as that for M/F 400/10 and (b) (4) Consequently the Medical Reviewer, Dr. Susan Limb, has stated that the impact of formulation differences are likely to be minimal..

Pivotal endpoint

Because there is no clear consensus concerning the definition of 'asthma exacerbation,' use of time to first asthma exacerbation may not be an acceptable endpoint. As patients may experience multiple events, the effect might be more comprehensively assessed when all events are considered. Other than asthma exacerbation, to evaluate the contribution of mometasone, I therefore included analyses based on the key secondary endpoint, 12-week change from baseline of trough FEV_1, to compare the M/F and F treatment arms.

1.3.b Contribution of formoterol to effectiveness

To calculate FEV_1 $AUC_{0\text{-}12hr}$ within visits, the applicant imputed missing data using a combination of LOCF and linear interpolation. For the purposes of calculating area under a curve, LOCF should be used only if the response variable does not change over time, and should therefore not be used to estimate a post-dose FEV_1 profile. Also, when interpolating missing data for calculating area under curve, adequate precautions should be taken to ensure that linear interpolation does cut across peaks, precautions not taken by the applicant. To evaluate this submission, the analyses presented in the current review use only observed rather than imputed data.

The applicant's pivotal analyses examined treatment effects on change in FEV_1 $AUC_{0\text{-}12\ hr}$ at week 12 using ANCOVA with fixed effects treatment and study site. The applicant's secondary analyses for change in FEV_1 $AUC_{0\text{-}12\ hr}$ used repeated measures, looking at treatment effects overall rather than at the specified twelve week endpoint. Because changes in FEV_1 $AUC_{0\text{-}12\ hr}$ were measured at multiple timepoints for each individual, it makes more sense in a pivotal analysis to examine the data using a repeated measures analysis to address change from baseline specifically at 12 weeks. This is the approach taken in this review. In addition, use of random country and country--by treatment interactions were attempted, but were ultimately not used because models employing these terms failed to converge.

1.3.c Times for evaluation of efficacy

Although efficacy endpoints were nominally measured 12 or 26 weeks after commencement of treatment, patients sometimes arrived earlier or later, potentially obscuring secular trends. In this review, obscuration of secular trends from this mechanism should be minimal because, unless specified otherwise, actual measurements will consistently be within two weeks of nominal.

1.4 Data Sources

Datasets and documentation for this review were provided in EDR in the original submission and in folder 008 provided in response to the FDA 72 day filing review letter.

2. STATISTICAL EVALUATION

2.1 Study Design

2.1.a Objectives

Dulera, a combination of mometasone furoate (M) and formoterol fumarate (F) is proposed for 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 components of Dulera have been previously approved for separate administration via dry powder inhaler.

Primary efficacy endpoints were designed to assess whether each active component of Dulera makes a distinct contribution to effectiveness, as required by 21CFR§300.50. The long-acting β_2-agonist contribution of formoterol in Dulera was assessed by comparing between M/F and M the change in FEV_1 $AUC_{0\text{-}12\ hr}$ after 12 weeks of treatment. The anti-inflammatory contribution of mometasone in Dulera was assessed by comparing M/F to F alone for change in trough FEV_1, and as well as time to first severe asthma exacerbation.

Because Dulera includes novel excipients, propellant, manufacturer, and inhaler, the associated M and F monotherapies were both compared to placebo. M was compared to placebo for cumulative incidence of individuals experiencing at least one severe asthma exacerbation, F was compared to placebo for change in FEV_1 $AUC_{0\text{-}12\ hr}$ from baseline to week 12.

Dose ranging for mometasone was provided in a single phase 3 study, P04431, for the M/F combinations M/F 400/10 and M/F 200/10. After twelve weeks of treatment, no difference in trough FEV_1 was seen between patients treated with M/F 400/10 and patients treated with M/F 200/10.

2.1.b Experimental design

Effectiveness of doses (b) (4) M/F 200/10, and M/F 400/10 bid ex-mouthpiece was examined in three efficacy studies.

(b) (4)

Study P04334, conducted from 17 November 2006 to 10 October 2008, randomized patients with persistent asthma previously treated with medium doses of steroid among four parallel treatment arms; M/F 200/10, M 200, F 10, and placebo. Treatment continued for 26 weeks.

Study P04431, conducted from 17 November 2006 to 10 October 2008, randomized patients with persistent asthma previously treated with high doses of steroid among three parallel treatment arms; M/F 400/10, M/F 200/10, and M 400. Treatment continued for 12 weeks.

In the efficacy studies, serial pulmonary function tests (PFTs) were performed for each patient during clinical visits at baseline, week 1, and week 12 (final week) beginning 30 minutes and immediately before (0 hour) the subject's morning dose of study medication, and then at 5 minutes, 15 minutes, 30 minutes, and 1, 2, 3, 4, 6, 8, 10, 11, and 12 hours post-dose. PFTs were to be performed in the morning, prior to the morning dose of study medication, and at least 12 hours after the previous evening's dose. For clinical visits at baseline, week 4, and week 8, FEV_1, forced expiratory flow rate between 25% and 75% of forced vital capacity (FEFR), and FVC were measured. Subjects were also instructed to perform triplicate peak expiratory flow (PEF) measurements twice daily before administration of the study medication. Subjects also recorded, in daily diaries, short term beta-2 agonist (SABA) and oral prednisone use, number of nocturnal awakenings requiring SABA use, AM and PM asthma symptom scores, and scores for the asthma symptoms diary scale after daytime and overnight.

(b) (4)

2.1.c Efficacy endpoints

The applicant planned to conclude that Dulera is effective if it exhibits:

1. increased time-to-first asthma exacerbation over the 26-week treatment period compared to F alone (studies (b) (4) and P04334).

and

2. increased FEV_1 $AUC_{0\text{-}12\ hr}$ after 12 weeks of treatment compared to M alone (studies (b) (4) P04431, and P04334).

Exacerbation for primary endpoint 1 above was defined as

1.a. A decrease in FEV1 (absolute value) below the Treatment Period stability limit at any visit during the Treatment Period, defined as 80% of the average of the two predose FEV1 measurements 0 and 30 minutes prior to the first dose of randomized study medication.

or

1.b. A decrease in AM or PM peak flow below the Treatment Period stability limits on any 2 consecutive days during the Treatment Period, defined as 70% of the respective mean AM or PM PEF obtained over the last 7 days immediately prior to receiving the first dose of randomized study medication.

or

1.c. Any clinical deterioration of asthma resulting in emergency treatment, hospitalization due to asthma, or treatment with additional, excluded asthma medication (other than SABA) as judged by the clinical investigator.

Secondary endpoints examined included:

1. Change from baseline in AM FEV_1 pre-dose assessment, or trough FEV_1, at each visit and at study endpoint.
2. Change from baseline to final week in AQLQ(S) total score.
3. Change from baseline to final week in the ACQ total score.
4. Change from baseline in proportion of nights across the treatment period with nocturnal awakenings due to asthma which require use of SABA.
5. Daytime and nighttime SABA usage, including time to first SABA usage.
6. Proportion of subjects with 2 consecutive nights with nocturnal awakenings due to asthma which require use of SABA rescue medication during the treatment period.

7. Proportion of subjects with at least 2 consecutive days of more than eight inhalations of SABA or two or more nebulized treatments, during the treatment period..
8. Change from baseline in pulmonary function tests (FEF 25% to 75%, FVC, and % predicted FEV1) at each visit and endpoint.
9. Change from baseline in AM and PM PEF, AM and PM symptom scores, and daytime and nocturnal assessments from e-diaries at each week and endpoint (last week of diary data for each subject).
10. Change from baseline in proportion of days with no symptoms of asthma during the treatment period.
11. Change from baseline to endpoint (last week for each subject) in mean number of nocturnal awakenings due to asthma which required use of SABA.

2.1.d Analysis populations

Two analysis populations were defined: safety and efficacy. The safety population included all randomized patients who received double-blind study medication during the trial and/or open label mometasone during the run-in period. The efficacy population included all individuals in the safety population managed per protocol. The sponsor's use of 'safety' and 'efficacy' for these populations may be considered misnomers because, in accordance with intention to treat, primary safety and efficacy statistical analyses were conducted only on the safety population.

2.1.f Statistical methods and handling of missing data

To calculate FEV_1 $AUC_{0\text{-}12\ hr}$ for each visit, the applicant imputed missing FEV_1 data within visits using LOCF for patients terminating FEV_1 measurements two or more hours post-dose during a visit. No FEV_1 $AUC_{0\text{-}12\ hr}$ was recorded for visits in which patients missed more than three consecutive evaluation times or terminated measurement prior to two hours post-dose. The applicant replaced missing FEV_1 values using linear interpolation of measurements prior to and following the missing data if patients missed at most three consecutive evaluation times. Objections to this imputation approach for within visit FEV_1 are discussed above in Section 1.3.b, and the analyses presented in this review do not impute within visit FEV_1.

The applicant examined treatment effects on change in FEV_1 $AUC_{0\text{-}12\ hr}$ using ANCOVA with fixed effects treatment and study site.

The applicant analyzed treatment effects on time to first severe asthma exacerbation using the log-rank test.

2.2 Study Results

All of the efficacy studies were structured in similar designs. Therefore I group the results by topic to facilitate collective evaluation of results across studies.

2.2.a Patient disposition

Number of patients randomized to treatment, managed per protocol, and completing the study, are provided by treatment arm in Table 1. Table 1 suggests that withdrawal rates were higher among patients randomized to placebo or formoterol than patients assigned to formulations containing mometasone.

Table 1. Number of phase 3 enrollees in as randomized intent to treat (R), per protocol (P), and completed final visit (C) data sets, by treatment group. Blank cells indicate treatments not conducted for a given study.

Study	**Status**	**Treatment**						
		M/F			M		F	Placebo
		(b) (4) 200/10	400/10	100	200	400	10	(b) (4)
P04334	R	191			192		202	196
	P	123			126		131	126
	C	156			159		117	119
P04431	R	233	255			240		
	P	194	209			202		
	C	208	228			207		

2.2.b Demographic and baseline information

Table 2 provides an overview of the study populations in this submission, including number of adolescents, race, and asthma severity.

Table 2. Overview of populations randomized to treatment, by study.

	[redacted] (b) (4)	Study	
		P04334	P04431
Demographic Characteristics			
Mean age, years		42.4	47.9
12-17 years age n, (%)		63 (8.1)	63 (8.7)
Race: Caucasian n, (%)		718 (91.9)	665 (91.3)
Race: Black n, (%)		30 (3.8)	10 (1.4)
Asthma Characteristics			
Mean FEV_1 at baseline (L)		2.3	2.0
Mean FEV_1 % predicted at baseline		73	66.3
Mean reversibility at screening (%)		16.9	20.1

Additional data tables provided by the applicant show no obvious imbalances in baseline characteristics between treatments.

2.2.c Contribution of mometasone

Table 3 shows that inclusion of mometasone in Dulera reduces cumulative incidence of asthma exacerbation. The cumulative incidence of patients experiencing at least one asthma exacerbation on or before week 26 (week 1 = week of first treatment administration) was lower among M/F treated patients than among F treated patients. The log-rank p-values show that cumulative exacerbation incidence was significantly lower among M/F treated patients than among F treated patients.

Table 3. Kaplan−Meier cumulative incidence of patients experiencing at least one asthma exacerbation on or before Week 26. P-values are calculated using log-rank test on time to first asthma exacerbation. For any given study, dosage of M corresponds to that in M/F.

Study	**Treatment**				**P-Value**
	M/F	M		F	Placebo	M/F vs F
	[redacted] (b) (4) 200/10	100	200			
[redacted] (b) (4)						
P04334	.40		.39	.79	.60	<.001

Because the appropriate definition of asthma exacerbation is arguable, I further assess the contribution to efficacy of the mometasone component in Dulera using change in trough FEV_1, measured at each visit as the average of FEV_1 measured 30 minutes and just prior to the administration of the study drug.

Analysis of change from baseline of trough FEV_1 shows that mometasone contributed significant anti-inflammatory capabilities to M/F combination. The multicenter, randomized, double blind, phase-3 studies summarized in Table 4 provide (b) (4) (b) (4) one M/F 200/10 vs. F 10 µg contrast. M/F 200/10 showed a statistically significant 114 ml advantage for M/F 200/10 over F 10 monotherapy at 12-week. (b) (4) . The repeated measures statistical model used to calculate Table 4 included treatment, baseline pre-dose FEV_1, site, week, and week by treatment interaction as fixed effects, and site by treatment interaction as a random effect.

Table 4. Contribution of mometasone to effectiveness of Dulera. Least square means of twelve week change in pre-dose FEV_1, with calculated differences (Diff) and p-values. Sample sizes are within parentheses. Measurements are in milliliters.

Study	**12-Week Change Trough FEV1**							**M/F x/10 – F 10**	
	M/F			M		F	Placebo	Diff	P-Value
(b) (4)	200/10	400/10	100	200	400	10			
(b) (4)									
P04334	100 (167)			57 (175)		-35 (141)	-73 (145)	135	<0.001
P04431	143 (212)	185 (230)			92 (210)				

(b) (4)

2.2.d Contribution of formoterol

FEV_1 AUC Analysis

Formoterol contributes significant bronchodilatory capabilities to Dulera. The multicenter, randomized, double blind, phase-3 studies summarized in Table 5 provided one contrast (b) (4) of M/F 200/10 vs. M 200, and one of M/F 400/10 vs. M 400 in twelve week change in FEV_1 $AUC_{0\text{-}12\ hr}$; all showed a statistically significant advantage for the M/F combination over M monotherapy. The repeated measures statistical model used to calculate Table 5 included treatment, baseline pre-dose FEV_1, site, week, and week by treatment interaction as fixed effects, using the week by treatment interaction term to calculate least square means at week 12.

For the analyses, I used only values of FEV_1 $AUC_{0\text{-}12}$ calculated without any missing FEV_1 data. Problems with the sponsor's approach, which imputed missing data, are discussed in section 1.3.b.

Table 5. Contribution of formoterol to effectiveness of Dulera. Least square means of twelve week change in FEV_1 $AUC_{0\text{-}12}$, with calculated differences (Diff) and p-values. Sample sizes are within parentheses. Measurements are in liter-hours.

Study	**12-Week Change 12-Hour FEV1 AUC**							**M/F x/10 – M x**	
	M/F			M		F	Placebo	Diff	P-Value
(b) (4)	200/10	400/10	100	200	400	10			
(b) (4)									
P04334	3.25 (160)			1.71 (165)		2.23 (133)	0.88 (135)	1.54	<0.001
P04431	3.64 (207)	4.18 (232)			1.91 (211)			2.27	<0.001

Post-dose FEV_1 Analysis

Formoterol contributed to improvement by M/F compared to M of FEV_1 two hours after dosing. This is shown in Table 6, which compares twelve week observed change in two hour post-dose FEV_1 between M/F and M, using a repeated measures statistical model which included treatment, baseline pre-dose FEV_1, site, week, and week by treatment interaction as fixed effects and with site by treatment interaction as a random effect.

Table 6. Contribution of formoterol to effectiveness of Dulera. Mixed effect repeated measures least square means of difference between post-dose FEV_1 before commencement of treatment and two hour post-dose FEV1 twelve weeks after commencement of treatment. Sample sizes enclosed within parentheses. Measurements in milliliters.

Study	**12-Week Change 2-Hour Post-Dose FEV1**							**M/F x/10 – M x**	
	M/F			M		F	Placebo	Diff	P-Value
(b) (4)	200/10	400/10	100	200	400	10			
(b) (4)									
P04334	315 (166)			168 (171)		237 (138)	94 (137)	148	<0.001
P04431	353 (207)	395 (235)			187 (214)			208	<0.001

2.2.e Dulera and monotherapies compared to placebo

Compared to placebo, the M/F combination and component monotherapies showed effects on pre-dose FEV_1, exacerbation rate, and FEV_1 AUC_{0-12} consistent with effectiveness (Table 7). Treatments containing mometasone consistently increased trough FEV_1 after 12 weeks of treatment and consistently reduced the cumulative incidence of patients experiencing exacerbations after 26 weeks of treatment, while treatments containing formoterol consistently increased FEV_1 AUC_{0-12}.

Table 7. Effects of Dulera and component monotherapies compared to placebo. 'Diff' indicates the difference between treatment 1 and treatment 2 (Trt1 - Trt2). All differences are significant at the 0.01 level.

Study	Variable	Units	Trt1	Trt2	Diff	p-value
[redacted] (b) (4)						
P04334	Exacerbations	cumulative incidence	M 200 MF	Placebo	-0.20	<0.001
			200/10	Placebo	-0.19	<0.001
	FEV1 AUC 0-12	liters	F 10	Placebo	1.35	0.002
			M/F 200/10	Placebo	2.37	<0.001
	Pre-Dose FEV1	milliliters	M 200	Placebo	119	0.002
			M/F 200/10	Placebo	177	<0.001

2.2.f Dose ranging

In study P04431, there was no evidence that patients assigned to receive treatment M/F 400/10 experienced larger increases in trough FEV_1 than patients assigned to receive M/F 200/10 (Table 8), suggesting that effectiveness of mometasone in M/F plateaus at or below 200 micrograms of mometasone.

Table 8. Trough FEV_1 change from baseline after twelve weeks of therapy, comparing M/F 400/10 to M/F 200/10. Least square means of twelve week change in pre-dose FEV_1. Sample size within parentheses. Measurements in milliliters.

Study	**Treatment**			**M/F 400/10 – M/F 200/10**	
	M/F 400/10	M/F 200/10	M 400	Diff	P-Value
P04431	185 (230)	143 (212)	92 (210)	42	0.13

2.2.g Secondary endpoints

With the single exception of forced vital capacity (FVC) in study [redacted] (b) (4), improvements in asthma control questionnaire (ACQ), asthma symptom score (ASM), morning forced expiratory flow rate (FEF), forced vital capacity, and peak expiratory flow rate (PEFR) were greatest among patients receiving the M/F combination therapy (Table 9). The least square means in Table 15 were calculated using analysis of covariance with independent variables treatment, site, and baseline.

Table 9. Least square mean changes in secondary variables 12 weeks from baseline, calculated from ANCOVA. Sample sizes are within parentheses.

Variable	**12-Week Change From Baseline**						
Study	M/F			M		F	Placebo
(b) (4)	200/10	400/10	100	200	400	10	
ACQ							
(b) (4)							
P04334	-0.45 (161)			-0.22 (170)		-0.12 (138)	-0.04 (139)
P04431	-0.58 (189)	-0.59 (202)			-0.40 (182)		
ASM							
(b) (4)							
P04334	-0.48 (166)			-0.29 (175)		-0.27 (141)	-0.06 (146)
P04431	-0.57 (212)	-0.68 (227)			-0.43 (204)		
FEFR (ml/s)							
(b) (4)							
P04334	83 (159)			101 (163)		41 (134)	-78 (137)
P04431	126 (212)	201 (230)			56 (210)		
FVC (ml)							
(b) (4)							
P04334	162 (161)			46 (165)		59 (136)	26 (139)
P04431	153 (212)	155 (230)			118 (210)		
PEFR (l/m)							
(b) (4)							
P04334	27.87 (163)			6.16 (173)		-2.56 (139)	-16.16 (145)
P04431	33.66 (209)	37.94 (229)			18.76 (204)		

3. FINDINGS IN SPECIAL SUBGROUP POPULATIONS

The dependence of treatment effect on subgroups was analyzed for 12 week change in pre- and post-dose FEV_1 using analysis of covariance (ANCOVA), with fixed effects baseline, subgroup, treatment, site, and subgroup by treatment interaction. To further characterize the clinical patterns underlying significant ($p<0.001$) interactions, differences in least square means between subgroups were examined for each treatment.

Subgroup dependence of treatment effect on 26 week cumulative incidence of exacerbation 26 was signaled by significant ($p < 0.001$) treatment by subgroup interactions after fitting a type 1 extreme value distribution for time to first exacerbation in the context of a censored model, with fixed effects subgroup, treatment, and subgroup by treatment interaction. incidence of exacerbation in pre- and post-dose FEV_1. To further characterize the clinical patterns underlying significant ($p<0.001$) interactions, differences between subgroups in 26-week cumulative incidence of exacerbation were examined for each treatment.

Relatively strict criteria for significance ($p < 0.001$) were used to avoid false positives, improving the signal to noise ratio of these exploratory multiple outcome tests.

3.1 Age

3.1.a Trough FEV_1

No significant age by treatment interactions for post-dose FEV_1 were observed in studies (b) (4) P04431, or P04334.

3.1.b Post-Dose FEV_1

No significant age by treatment interactions for post-dose FEV_1 were observed in studies P04334 (p=.014), P04431 (p=.073), or (b) (4). .

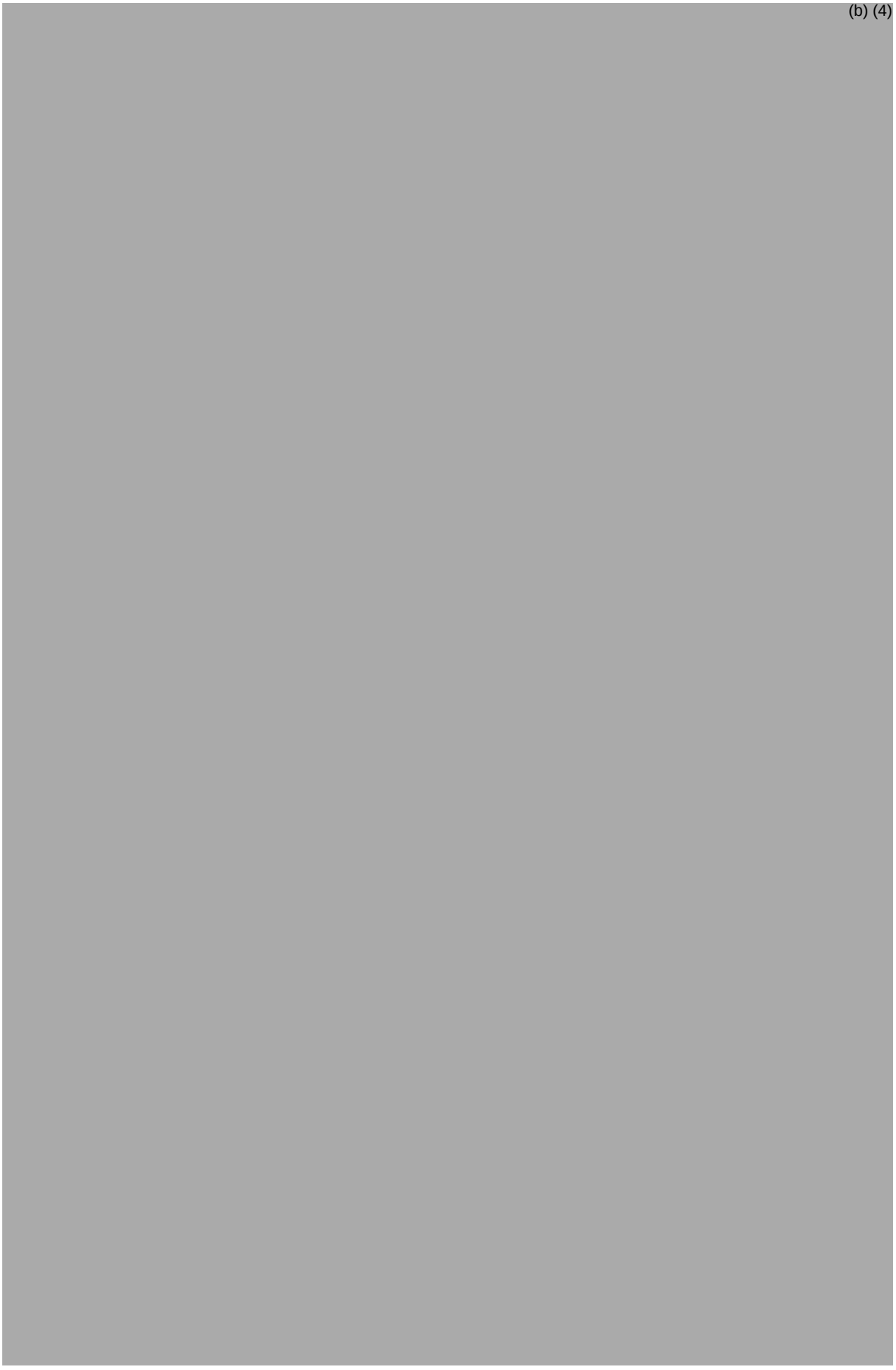
3.1.c Cumulative Incidence of Exacerbation

A nearly significant treatment by age interaction was found in study (b) (4) but not in study P04334 (p=0.853). (b) (4)

(b) (4)

While examining least squares means correctly predicts variability between subgroups of contrast *magnitudes*, it is also medically important to examine the variability between subgroups of contrast *signs*. For example, potential harm in older individuals would need to be considered if the contrast in exacerbation rate between Placebo and (b) (4) was positive for 18 to 64 year olds but negative for patients greater than 64 years of age.

(b) (4)


(b) (4)

3.2 Gender

3.2.a Trough FEV_1

Gender by treatment interaction was nearly significant in study (b) (4)) but not in studies P04431 (p=0.480) and P04334 (p=0.189). Table 12 suggests that, in study (b) (4), males receiving formoterol showed greater increases in pre-dose FEV_1 than females. From this we would predict that contrasts involving F 10 would be prone to differ by gender, a prediction borne out in Table 13, which shows differences within contrasts between genders are largest for contrasts involving treatments with F 10.

Although gender by treatment interaction was not significant in study P04334, it may be of interest to note that, (b) (4), males administered F 10 experienced higher changes from baseline of trough FEV_1 (163 ml) than females administered F 10 (-42 ml).

Table 12. Gender dependent treatment effects on twelve week change from baseline of trough FEV_1. Diff denotes least square mean difference in change from baseline for (Gender1 - Gender 2). N1 and N2 denote sample sizes at twelve weeks for Gender1 and Gender 2 respectively.

Table 13. Gender specific contrasts in trough FEV_1. The largest magnitude differences between genders were seen for contrasts which involved F 10.

(b) (4)

Table 14. Gender specific trough FEV_1 least square means for F 10, M 100, (b) (4) (b) (4) P04334 both suggest that F10 improves trough FEV_1 among males but not among females.

Study	Treatment	Gender	Estimate	N
(b) (4)				
P04334	F 10	F	-42	98
	F 10	M	163	43
	M 200	F	30	102
	M 200	M	107	73
	M/F 200/10	F	92	82
	M/F 200/10	M	151	85
	Placebo	F	-108	87
	Placebo	M	88	58

3.2.b Post-Dose FEV_1

Gender by treatment interaction was significant in study (b) (4) but not in studies P04431 (p=0.076) and P04334 (p=0.096). Table 15 suggests that, in study (b) (4) males receiving formoterol showed greater increases in pre-dose FEV_1 than females. From this we would predict that contrasts involving F 10 would be prone to differ by gender, a prediction borne out in Table 16, which shows differences within contrasts between genders are largest for contrasts involving treatments with F 10.

Although gender by treatment interaction was not significant in study P04334, it may be of interest to note that, as in study (b) (4) males administered F 10 experienced higher changes from baseline of trough FEV_1 (396 ml) than females administered F 10 (146 ml).

Table 15. Gender dependent treatment effects on twelve week change from baseline of two hour post-dose FEV_1. Diff denotes least square mean difference in change from baseline for (Gender1 - Gender 2). N1 and N2 denote sample sizes at twelve weeks for Gender1 and Gender 2 respectively.

(b) (4)

Table 16 indicates that gender dependent differences in contrast signs may exist, with F 10 depressing post-dose FEV_1 relative to (b) (4) among females but not among males. Table 17 provides the raw least square means which underlie these contrasts, suggesting that F 10 improves post-dose FEV_1 more among males than among females.

Table 16. Gender specific contrasts in trough FEV_1. The largest magnitude differences between genders were seen for contrasts which involved F 10.

(b) (4)

Table 17. Gender specific post-dose FEV_1 least square means for F 10 and [redacted] as well as other M/F combinations. Studies [redacted] and P04334 both suggest that F10 improves post-dose FEV_1 more among males than among females.

Study	Treatment	Gender	Estimate	N
[redacted]				
P04431	F 10	F	146	95
	F 10	M	396	43
	M/F 200/10	F	268	82
	M/F 200/10	M	376	84
P04334	M/F 200/10	F	317	120
	M/F 200/10	M	392	87
	M/F 400/10	F	336	129
	M/F 400/10	M	474	106

3.2.c Cumulative Incidence of Exacerbation

No significant treatment by gender interaction was found in study [redacted] or study P04334.

3.3 Country

I analyzed the dependence of treatment effect on country (USA versus non-USA) for twelve week change in pre- and post-dose FEV_1 using ANCOVA with fixed effects baseline, treatment, country, country by treatment, and site nested within country. Examination of differences in treatment effect between USA and non-USA countries were planned for studies in which there was a significant ($p<0.001$) treatment by country interaction.

The dependence of treatment effect on country was analyzed for time and incidence of exacerbation until 26 weeks after commencement of treatment, with analyses performed by looking for significant ($p < 0.001$) treatment by country interactions fitting a type 1 extreme value distribution for cumulative incidence of exacerbation in the context of a censored model, with fixed effects country, treatment, and country by treatment interaction. Examination of differences between subgroups in 26-week incidence of exacerbation were planned for studies in which there was a significant ($p < 0.001$) treatment by country interaction.

No significant treatment by country interactions were found for pre- or post-dose FEV_1 in studies [redacted] P04334, or P04431. No significant treatment by country interactions were found in studies [redacted] or P04334.

3.4 Race

No significant treatment by race interactions were found for trough or post-dose FEV_1 in studies [redacted] P04334, or P04431. No significant treatment by race interactions were found in studies [redacted] or P04334.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

With two reservations, the collective evidence in this submission demonstrates a positive contribution by each active component in M/F 200/10, and M/F 400/10 for the [redacted] twice daily [redacted] treatment of asthma, [redacted], in adults and children 12 years of age and older. Reservations are that (i) no definition of exacerbation currently exists for regulatory purposes, and (ii) the F 10 monotherapy arm, unlike the M/F combination drug, contained HFA-134, [redacted] - evaluation of the mometasone contribution for improvement of trough FEV_1 therefore depended upon similarity of effect on trough FEV_1 of the F 10 monotherapy arm with M/F missing mometasone.

Dose ranging for the mometasone component was provided in only a single study, P04431. Patients in that study assigned to receive M/F 400/10 experienced increases in trough FEV_1 similar to patients assigned to receive M/F 200/10. [redacted]

4.2 Conclusions and Recommendations

4.2.1 Submission

The phase 3 trials reviewed support effectiveness of M/F 200/10 and M/F 400/10 for treatment of asthma. In support of mometasone's distinct contribution, after 12 weeks of treatment, patients assigned to receive M/F 200/10 or M/F 400/10 consistently showed statistically greater improvement of trough FEV_1 than patients assigned to receive F 10, and, in support of formeterol's contribution, after 12 weeks of treatment, patients assigned to receive M/F 200/10 or M/F 400/10 consistently showed statistically greater increases in post-dose FEV_1 and FEV_1 $AUC_{0\text{-}12hr}$ over baseline FEV_1 than patients assigned to receive M 200 or M 400.

(b) (4)

(b) (4) I therefore recommend consideration of M/F 200/10 and M/F 400/10, (b) (4) for treatment of asthma.

4.2.2 Biometrics

(b) (4)

Examination of significant subgroup effects is facilitated by comparing subgroups within contrasts for differences in magnitude and sign. Where subgroups within contrasts differ in sign, subgroup least square means within treatments should be compared.

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

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/s/

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