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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review

CLINICAL STUDY

NDA / Sequence Number:	NDA 205641 / Seq 0000
Drug Name:	Asmanex® HFA (mometasone furoate dihydride)
Proposed Indication:	Asthma
Applicant:	Merck
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1 EXECUTIVE SUMMARY

Merck proposes Asmanex HFA metered dose inhaler, mometasone furoate 100 mcg (M100) or 200 mcg (M200) two actuations per twice daily dosing (bid), for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. Efficacy and safety of this inhaled corticosteroid (ICS) were examined in three phase 3 clinical trials.

The submission provides one adequately controlled phase 3 trial to evaluate the efficacy of M100 in asthma patients. That study shows statistically significant differences between M100 and placebo for change from baseline to week 26 incidence of exacerbations. Further exploratory analyses also show nominally significant differences between M100 and placebo for Δ trough FEV1, ΔAQLQ (S), ΔACQ, ΔAM PEFR and Δ proportion of nights awakened requiring use of short-acting beta agonists (SABA).

The submission also provides a study purporting to demonstrate efficacy of M200. However that study was conducted without a control arm to distinguish between treatment effects and placebo effects. An assessment of M200 relative to M100 in the presence of F5 suggested a numerical difference between the M200/5 and M100/5 groups which was not statistically significant.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Asmanex is an inhaled corticosteroid proposed for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

2.1.2 History of Drug Development

Asmanex is the mometasone furoate component of Dulera®, a combination product approved June 22, 2010 for the treatment of asthma in patients 12 years of age and older. Dulera is comprised of mometasone furoate 100 mcg plus formoterol fumarate dihydrate 5 mcg (M100/F5) or mometasone furoate 200 mcg plus formoterol fumarate dihydrate 5 mcg (M200/F5), administered by pressurized metered dose inhaler using a hydrofluoroalkane (HFA-227) propellent. At the labeling meeting on June 4, 2010, FDA recommended development of a corresponding mometasone monotherapy, presumably using the same HFA-227 propellant and metered dose inhaler, for patients at risk for complications associated with the LABA component formoterol. On June 11, 2010, the sponsor confirmed plans to develop such a monotherapy.

In a preliminary written response on September 9, 2011 to a briefing package submitted by the sponsor under PIND 112669 as background for a planned Type C meeting, the Agency agreed that studies completed under the Dulera program and an earlier mometasone monotherapy program would adequately characterize efficacy and safety for a mometasone monotherapy NDA. However the Agency anticipated difficulty in describing efficacy on the label because none of the trials compared mometasone 200 mcg (M200) to placebo (P).

In a written response, requested by the sponsor after cancelling the planned September 2011 Type C meeting, the Agency confirmed on September 14, 2011 (b) (4)

2.1.3 Current Submission

To support indications for M100 and M200 monotherapies, the submission included two phase 3, parallel arm, double-blind trials, P04334 and P04331, hereafter referred to as studies 34 and 31 (Table 1). Study 34 randomized 781 patients 1:1:1:1 to M100/F5 or M100 using an HFA-227 propellant, formoterol fumarate dihydrate 5 mcg using HFA 134 as a propellant (F5), or placebo (P), and study 31 randomized 728 patients 1:1:1:1 to M200/F5, M100/F5, or M200 using HFA-227 as a propellant. Designs for these studies are further discussed in section 3.2.1 below.

Study P04334 was conducted from 17 November 2006 to 10 October 2008, and study P04431 was conducted from 17 November 2006 to 10 October 2008.

Table 1. Phase 3 Studies in Current Submission.

Study[1]	Design	Population	Supplemental Claims
P04334 (Trial 1)	M100/F5 M100 F5 P Parallel arm DB P to W26	Adults and adolescents (≥ 12 yr) Persistent asthma (≥ 1 yr) On medium dose ICS Trough FEV1 at baseline (≥60%, ≤85% predicted) N=781 1:1:1:1	Incidence exacerbations W26 ΔTrough FEV1 W12 Nocturnal awakenings to W26 ΔAQLQ(S) W26 AM peak expiratory flow W26
P04431 (Trial 2)	M200/F5 M100/F5 M200 Parallel arm DB To W12	Adults and adolescents (≥ 12 yr) Persistent asthma (≥ 1 yr) On high dose ICS Trough FEV1 at baseline (≥50%, ≤85% predicted) At least one exacerbation 2 to 12 months prior to screening N=728 1:1:1	ΔTrough FEV1 W12 Nocturnal awakenings to W12 AM peak expiratory flow W12 ΔAQLQ(S) W12

1, Designation in parentheses corresponds to trial number on proposed label.
DB double blind

2.2 Data Sources

Data for both studies was provided by the sponsor in the original Dulera submission and is currently located at:

\\Cdsesub1\evsprod\NDA022518\0000\m5\datasets .

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data analysis and quality was adequate in the original Dulera submission. For further details, see the Biometrics review submitted to DARRTS on May 19, 2010.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Analyzed data was from two double blind, parallel group, multicenter phase 3 efficacy studies (Table 1) which were conducted on patients with persistent asthma to demonstrate effectiveness of Dulera, a combination drug containing mometasone and formoterol. Study 34 randomized 781 patients with persistent asthma previously treated with medium doses of ICS among four treatment arms; M100/F5 (N=191), M 100 (N=192), F 5 (N=202), and placebo (N=196). Treatment continued for 26 weeks. Study 31 randomized 728 patients with persistent asthma previously treated with high doses of ICS among three treatment arms; M200/F5 (N=233), M100/F5 (N=255), and M 200 (N=240). Treatment continued for 12 weeks.

Serial pulmonary function tests (PFTs) were performed for each patient during clinical visits at baseline, week 1, and the final visit (week 26 of study 31, week 12 of study 34) 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 at all visits were to be performed 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, FEV1, 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.

In the original Dulera submission, the sponsor planned to conclude efficacy in study 34 according to the following co-primary efficacy endpoints :

1. time-to-first asthma exacerbation over the 26-week treatment period

and

2. FEV_1 $AUC_{0\text{-}12\ hr}$ after 12 weeks of treatment compared to mometasone alone.

For primary endpoint 1 above, an exacerbation was defined as

1.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. 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.

The primary endpoint in study 31 was change from baseline FEV_1 $AUC_{0\text{-}12\ hr}$ after 12 weeks of treatment.

In both studies, key secondary endpoints were change from baseline to week 26 in AQLQ(S), change from baseline to week 26 ACQ total score, and change from baseline proportion of nights across the treatment period without awakenings due to asthma that required use of short-acting beta 2-agonists (SABA).

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For studies 31 and 34, other secondary endpoints included:

1. Change from baseline in AM FEV1 pre-dose assessment, or trough FEV1, at each visit and at study endpoint,
2. Daytime and nighttime SABA usage, including time to first SABA usage,
3. Proportion of subjects with 2 consecutive nights with nocturnal awakenings due to asthma which require use of SABA rescue medication during the treatment period,
4. 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,
5, Change from baseline in pulmonary function tests (FEF 25% to 75%, FVC, and % predicted FEV1) at each visit and endpoint,
6. 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),
7. Change from baseline in proportion of days with no symptoms of asthma during the treatment period, and
8. Change from baseline to endpoint (last week for each subject) in mean number of nocturnal awakenings due to asthma which required use of SABA.

3.2.2 Statistical Methodologies

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, a population often referred to as the modified intent-to-treat (mITT) population in other programs. 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 the primary efficacy statistical analyses were conducted on the safety population.

For studies 31 and 34, primary analyses for FEV1 and other continuous endpoints were conducted using analyses of covariance (ANCOVA) with independent factors treatment, study site, and baseline. For trough FEV1 in study 34, an amendment was implemented prior to unblinding which specified the primary analysis as a mixed effect repeated measures model (MMRM) to guage treatment effect at week 12, with fixed effects treatment, time, baseline, and visit by treatment interaction, and with random effect subject.

Proportions in both studies were analyzed using Cochran-Mantel-Haenzel (CMH) tests of proportions controlled for study site.

Time to first asthma exacerbation in study 34 was analyzed using the log-rank test.

Results from all analyses were evaluated at the 0.05 level of significance.

No new protocols were developed for the study of Asmanex. Therefore, control of type 1 in the submitted protocols followed that for Dulera.

In study 34, to control overall type 1 error, analyses were conducted in the following hierarchical order:

1. Week 12 ΔFEV1 $AUC_{0\text{-}12hr}$
    a. M100/F5 vs M100
    b. F5 vs P

2. Time to first asthma exacerbation over 26 weeks
    a. MF 100/5 vs F5
    b. M 100 vs P

If all four of the above co-primary endpoint comparisons were significant at the 0.05 level, then the following four endpoints were to be tested in the following sequense.

3. Week 12 trough ΔFEV1
    a. MF 100/5 vs F5 and MF 100/5 vs P ('simultaneously')

4. ΔAQLQ(S) Week 26
    a. MF 100/5 vs P

5. ΔACQ Week 26
    a. MF 100/5 vs P

6. ΔProportion of nights awakened requiring use of SABA
    a. MF 100/5 vs P

Other study 34 endpoints were not controlled for multiplicity, and should therefore be considered exploratory, including comparisons proposed for the Asmanex label between M100 and P for Δtrough FEV1, Δproportion of night awakenings requiring use of SABA, ΔAQLQ(S), proportion of patients with AQLQ(S) response, and ΔPEFR

In study 31, to control overall type 1 error, analyses were conducted in the following hierarchical order:

1. MF 200/5 vs M 200
    a. Week 12 ΔFEV1 $AUC_{0\text{-}12hr}$
    b. ΔACQ Week 12
    c. ΔAQLQ(S) Week 12
    d. ΔProportion of nights awakened requiring use of SABA

Other study 31 endpoints were not controlled for multiplicity, and should be considered exploratory, including all comparisons of M200/5 and M100/5 proposed for description of efficacy of the M200 mono-component in the Asmanex label.

In both studies 31 and 34, the sponsor imputed missing FEV_1 $AUC_{0\text{-}12\ hr}$ data within visits using last observation carried forward (LOCF) for patients terminating FEV1 measurements two or more hours post-dose during a visit. No FEV1 $AUC_{0\text{-}12\ hr}$ was recorded for visits in which patients missed more than three consecutive evaluation times or terminated measurement prior to two hours post-dose. The sponsor replaced missing FEV1 values using linear interpolation of measurements prior to and following the missing data if patients missed at most three consecutive evaluation times.

Pulmonary function test results for missing visits was imputed using LOCF.

Baseline for pulmonary function tests were defined as the average of the two pre-dose values 0 and 30 minutes prior to initial dosing. Baseline ACQ and AQLQ were obtained from a single measurement prior to initial dosing. For proportion of nightime awakenings requiring use of SABA, asthma symptoms, and PEF, baseline was derived from diary data during the 7 days prior to initial dosing.

To summarize, except for time to first exacerbation in study 34, all endpoints proposed for inclusion on the Asmanex product label are exploratory as studies 34 and 31 were designed to assess the efficacy of the combination product rather than the mometasone furoate component alone. Significance levels for these comparisons should therefore be considered nominal, with p-values underestimating the true type 1 error. Further, study 31 did not include a placebo control arm; a true treatment effect of M200 monotherapy therefore cannot be distinguished from a placebo effect.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The earlier review for Dulera NDA established that there were no obvious differences between treatment groups in demographic baseline characteristics in these studies. In both studies, approximately 80% of patients in the mometasone arm and 60% of the patients in the placebo arm completed treatment to week 26 (Table 2). Patterns of treatment discontinuation in study 34 were consistent with efficacy, with 23% of patients in the placebo arm and 7% of the patients in the mometasone arm discontinuing due to treatment failure.

Table 2. Disposition of Randomized Subjects for Treatments (b) (4)

Disposition	Study 34		Study 31
	M100	P	M200
Randomized	192 (100)	196 (100)	240 (100)
Discontinued	33 (17)	77 (39)	33 (14)
Adverse event	6 (3)	7 (4)	5 (2)
Treatment failure	13 (7)	46 (23)	13 (5)
Lost to followup	0 (0)	2 (1)	1 (<1)
Withdrew, reasons unrelated	3 (2)	8 (4)	4 (2)
Withdrew, reasonss related	1 (1)	5 (3)	1 (<1)
Noncompliance	5 (3)	6 (2)	3 (1)
Did not meet protocol eligibility	4 (2)	3 (2)	5 (2)
Administrative	1 (1)	0 (0)	1 (<1)
Completed treatment period	159 (83)	119 (61)	207 (86)

Source: Table 3 in clinical study reports

3.2.4 Results and Conclusions

Sponsor calculations were generally confirmed in this review and in the earlier review for the Dulera combination product.

For both studies, all comparisons of treatment arms involved post-hoc exploratory analyses, and the calculated p-values therefore underestimated true type I error rates. As a consequence, results from all statistical tests should be viewed with skepticism because they were conducted at a significance level larger than the standard value of 0.05.

Study 31 purported to demonstrate effect of M200 monotherapy by showing that patients treated with M200 improved from baseline after 12 weeks of treatment. However, because no control arm was included, the study could not clarify whether observed improvements from baseline were the result of treatment with M200 rather than the placebo effect. An assessment of M200 relative to M100, only in the presence of F5, is possible in that study because it includes the M200/F5 and M100/F5 treatment arms.

3.2.4.1 Study 34: M100 versus Placebo

3.2.4.1.1 Primary Endpoint in Original Study: ΔFEV1 AUC_{0-12hr} at Week 12

The difference between M100 and P for change from baseline FEV1 AUC_{0-12hr} at Week 12 was not statistically significant in in study 34 (Table 3). This endpoint was included in the Dulera submission to evaluate the efficacy of the formoterol component in the combination product by comparing M/F to M alone.

Table 3. ΔFEV1 AUC_{0-12hr} (liter - hours), M100 versus Placebo, at Week 12

Study	FEV1 AUC_{0-12hr}		Difference	
	M100	P	M(x) - P	P-Value
34	1.30 (169)	0.57 (128)	0.73	0.140

Source: auc.sas, see also Table 7, clinical study report

3.2.4.1.2 Primary Endpoint in Original Study: Exacerbation Incidence to Week 26

In study 34, the incidence of exacerbations at week 26 differed significantly between mometasone and placebo (Table 4).

Table 4. Kaplan Meier Incidence of Exacerbations, M100 versus Placebo, Week 26

Study	Incidence of Exacerbations		Difference	
	M100	P	M100 – P	P-Value
34	0.65	0.41	0.23	<.0001

Source: main.sas

The difference between mometasone and placebo for incidence of 'clinically treated exacerbations' at week 26, exacerbations involving emergency room treatment, hospitalization, or use of prohibited medications, did not differ significantly between placebo and mometasone (Table 5). The low rate of such exacerbations may explain the lack of statistical significance.

Table 5. Kaplan Meier Incidence of Clinically Treated Exacerbations, M100 versus Placebo, Week 26

Study	Incidence of Exacerbations		Difference	
	M100	P	M100 – P	P-Value
34	0.96	0.94	0.02	0.2144

Source: main.sas

The proportion of patients with exacerbations, broken out by cause, is given in (Table 6).

Table 6. First Exacerbations, Study 34, by Cause

Cause	N (%)	
	M100	P
All Exacerbations	65 (34)	109 (56)
FEV1	19 (10)	39 (20)
NONE	127 (66)	87 (44)
PEFR	41 (21)	59 (30)
Prohibited Meds	5 (3)	7 (4)
Hospitalization	0 (0)	0 (0)
Multiple Causes	0 (0)	4 (2)

source: main.sas

3.2.4.1.3 Exploratory Analyses of Secondary Endpoints

Because the protocol did not predefine comparisons between M100 and P, the following analyses of secondary endpoints, many of which are proposed for inclusion in the label, are only exploratory. While the measures of statistical significance are therefore only nominal, with p-values underestimating true probabilities of type 1 error, each of the p-values associated with these endpoints are highly significant, making it unlikely that there is no true treatment effect.

Differences between M100 and placebo were nominally significant for change from baseline in trough FEV1 at week 12 (Table 7), and for changes at study endpoint from baseline of AQLQ(S) AQC, proportion of of nights with nocturnal awakening requiring SABA, and PEFR. Proportion AQLQ (S) response, defined by the sponsor as ΔAQLQ (S) $\geq$ 0.5, was also greater among patients randomized to M100 than among patients randomized to placebo.

Table 7. Other Secondary Endpoints, Study 34

Week	Var	M100	P	Diff	P-Value
12	Δ Trough FEV1 (mL)	71 (190)	-52 (192)	123	0.001
26	ΔAQLQ (S)	0.37 (189)	-0.01 (189)	0.38	<.0001
26	ΔACQ	-0.23 (186)	0.14 (187)	-0.37	<.001
26	ΔProportion Noct Awakening	-0.05 (191)	0.00 (194)	-0.05	0.003
26	ΔPEFR (L/sec)	1.75 (188)	-28.44 (193)	30.18	<.001
26	ΔAQLQ (S) Response	0.42 (189)	0.23 (189)	0.19	<.001

source main.sas, aq.sas,, propn.sas
AQLQ higher values correspond to improvement, ACQ lower values correspond to improvement

3.2.4.2 Study 31: M200

Study 31 purported to demonstrate effect of M200 monotherapy by showing that patients treated with M200 improved from baseline after 12 weeks of treatment. However, because no control arm was included, it remains unclear whether such improvements were the result of treatment with M200 rather than the placebo effect.

If and only if there is clinical information that the effect of mometasone is independent of coadministered formoterol, efficacy of M200 may be estimated by showing superiority of M200/F5 over M100/F5, and therefore this comparison is provided herein for trough FEV1 at week 12. There was no statistically significant difference between M200/F5 and M100/F5 for change from baseline in trough FEV1 at week 12 (Table 8). Similarly, no statistically significant differences between M200/F5 and M100/F5 were seen for week 12 ΔFEV1 $AUC_{0\text{-}12hr}$, ΔAQLQ(S), ΔAQC, or Δproportion of nights with awakenings requiring SABA (data not shown).

Table 8. Change from Baseline Trough FEV1 at Week 12, Study 31

Var	M200/F5	M100/F5	Diff	P-Value (95% CI)
ΔTrough FEV1 (mL)	178 (255)	139 (232)	39	0.182 (-18, 97)

Source: Main study 31.sas

3.3 Evaluation of Safety

Safety evaluations for this submission were conducted by the Medical Reviewer, Kimberly Witzmann, M.D. and are provided in her review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Effects of gender, age, and geographic region on treatment efficacy were discussed in the statistical review of Dulera. Statistical tests involving all treatments revealed no significant interactions between these subgroups and treatment with mometasone.

For this submission, additional subgroup analyses were conducted for statistically significant results from study 34 by adding subgroup, treatment by subgroup interaction, and treatment by subgroup by study week interaction terms to the original MMRM for ΔFEV1 using data from only the placebo and M100 arms. While gender and age were not seen to affect treatment differences, there was a nominally significant interaction between treatment, week, and region (p=0.0057), with point estimates of differences between M100 and P for ΔFEV1 at week 12 equal to 222 mL in the USA and 80 mL outside of the USA.

For study 31, similar analyses were conducted with only M200/F5 and M100/F5 data, replacing site with site nested within country, and with subgroup and subgroup by treatment interactions. While region and race were not seen to affect treatment differences, there was a nominally significant (p=0.028) interaction between treatment and age category (≤17 yr, >17 yr and <64, >64 yr). Point estimates for ΔFEV1 at study endpoint were, for MF 100/5, -26, 125, and 242 mL respectively for the ≤17 yr, >17 yr and <64, >64 yr age categories, and for MF 200/5 were 254, 158, and 140 mL respectively for the ≤17 yr, >17 yr and <64, >64 yr age categories.

Overall then, results from the subgroup analyses are not consistent between studies, and any nominally significant interactions may represent type 1 error associated the large number of comparisons made. The interaction with the smallest nominal p-value, for country by treatment at week 12 in study 34 for ΔFEV1, was not qualitatively important because numerical improvements were seen regardless of region.

4.2 Other Special/Subgroup Populations

No other subgroup populations were analyzed for this submission.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

In study 34, except for incidence of exacerbations, comparisons between M100 and P were not preplanned. Therefore, while tests for statistical significance were only nominal, with the p-values underestimating true probabilities of type 1 error, each of the p-values associated with these endpoints was highly significant, making it unlikely that there is no true treatment effect.

Study 31 purported to demonstrate effect of M200 monotherapy by showing that patients treated with M200 improved from baseline after 12 weeks of treatment. However, because no control arm was included, it remains unclear whether observed improvements resulted from treatment with M200 or instead stemmed from the placebo effect. An assessment of M200 relative to M100, only in the presence of F5, is possible using data from Study 31; however, no significant difference between M200/F5 and M100/F5 were observed.

5.2 Collective evidence

The collective evidence suggests that, compared to placebo, M100 does provide some improvement for asthma patients. However the evidence is somewhat undermined by lack of control for type 1 error in the face of multiple unplanned endpoints.

The submission also included a study purporting to directly demonstrate efficacy of M200. However that study was conducted without a control arm to distinguish between treatment effects and placebo effects. An assessment of M200 relative to M100 in the presence of F5 suggested a numerical differences between the MF 200/5 and MF 100/5 groups which was not statistically significant.

5.3 Conclusions and Recommendations

The submission provides one adequately controlled phase 3 trial to evaluate the efficacy of M100 in asthma patients. That study shows statistically significant differences between M100 and placebo for change from baseline to week 26 incidence of exacerbations. Further exploratory analyses also show nominally significant differences between M100 and placebo for Δ trough FEV1, ΔAQLQ (S), ΔACQ, ΔAM PEFR and Δ proportion of nights awakened requiring use of short-acting beta agonists (SABA).

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