Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Asmanex Twisthaler 200 micrograms Inhalation Powder
Asmanex Twisthaler 400 micrograms Inhalation Powder

(mometasone furoate)

UK/W/0064/pdWS/004

Marketing Authorisation Holder: Merck Sharp & Dohme Limited

Rapporteur:	United Kingdom
Finalisation procedure (day 120):	02.03.2017

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Asmanex Twisthaler 200 micrograms Inhalation Powder Asmanex Twisthaler 400 micrograms Inhalation Powder
INN (or common name) of the active substance(s):	Mometasone furoate
MAH:	Merck Sharp & Dohme Limited
Currently approved Indication(s)	Indicated in adults and adolescents 12 years of age and older for regular treatment to control persistent asthma.
Pharmaco-therapeutic group (ATC Code):	Other Antiasthmatics, Inhalants, - Glucocorticoids R03B A07
Pharmaceutical form(s) and strength(s):	Inhalation Powder

ABBREVIATION LIST

ACQ-IA Interviewer-Administered Asthma Control Questionnaire	ACQ-IA Interviewer-Administered Asthma Control Questionnaire
AE(s) Adverse event(s)	AE(s) Adverse event(s)
AM Ante meridiem (refers to morning in this study)	AM Ante meridiem (refers to morning in this study)
ANCOVA Analysis of Covariance	ANCOVA Analysis of Covariance
BID Twice a day	BID Twice a day
cLDA Constrained longitudinal data analysis	cLDA Constrained longitudinal data analysis
CSR Clinical study report	CSR Clinical study report
DPI	Dry powder inhaler
FVC	Forced vital capacity
GCP	Good clinical practice
ICS	Inhaled corticosteroids
IVRS	Interactive voice response system
LABA	Long-acting beta-2 agonist
LOCF	Last observation carried forward
MDI	Metered dose inhaler
MF	Mometasone furoate
PAQLQ(s)	Paediatric Asthma Quality of Life Questionnaire With Standardised Activities
PEF	Peak expiratory flow
PFT	Pulmonary function test
PP	Per Protocol
SAE	Serious adverse event

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

No further action required.

III. INTRODUCTION

On 12 January 2016 the MAH submitted a completed paediatric study for Asmanex Twisthaler 200 micrograms Inhalation Powder and Asmanex Twisthaler 400 micrograms Inhalation Powder, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The only approved inhaled products containing mometasone are Asmanex Twisthaler 200 micrograms Inhalation Powder and Asmanex Twisthaler 400 micrograms Inhalation Powder. The SmPCs of these products state that safety and efficacy in children less than 12 years of age have not been established. No data are available.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Asmanex Twisthaler 200 micrograms Inhalation Powder and Asmanex Twisthaler 400 micrograms Inhalation Powder and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

See section IV.2.2.

IV.2 Clinical aspects

IV.2.1. Introduction

The MAH submitted a final report for:

A 12-Week, Randomized, Placebo-Controlled, Dose- Ranging, Efficacy and Safety Study of Mometasone Furoate Metered Dose Inhaler in the Treatment of Children Ages 5 to 11 Years With Persistent Asthma (Study No. P04223aAM3; also referred to by the MAH as P086).

The purpose of this study was to determine which dose to assess in the phase 3 part of the paediatric MF/formoterol fixed dose combination program.

Mometasone is a synthetic glucocorticosteroid that binds to the glucocorticoid receptor with very high affinity. Mometasone has been shown to exhibit a glucocorticosteroid receptor binding affinity in humans that is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone.

Inhaled mometasone furoate (MF) is only approved in EU~~UK~~ as Asmanex Twisthaler 200 and 400 micrograms Inhalation Powder. These products are indicated for adults and adolescents 12 years of age and older for regular treatment to control persistent asthma. The recommended starting dose is 400 mcg once daily or in two divided doses for mild to moderate asthma. For severe asthma, the dose is 400 mcg twice daily. The starting doses can be titrated down to the lowest effective dose of 200 mcg once daily. No inhaled mometasone products, either metered dose inhaler (MDI) or dry powder inhaler (DPI), are approved in children less than 12 years of age.

IV.2.2. Clinical study

- **Description**

Study No. P04223aAM3 (P086) is a phase 2 dose finding study to determine the efficacy and safety of MF MDI 50, 100 and 200 mcg twice daily in comparison to placebo and MF dry powder inhaler (DPI) 100 mcg once daily. The study formulations are not currently approved. The MF DPI treatment arm was included as an active control to better characterize the treatment effect of the MDI formulation.

The first patient was enrolled on 03-Feb-2012 and the last patient completed on 29-Jan-2015. Subjects were enrolled at a total of 90 sites worldwide. Thirty four centres were in the United States and the remainder were in EU, South Africa, Russia, Ukraine, Colombia, Guatemala, Mexico, and Puerto Rico. The study was conducted at all sites with approval of an ethics committee and complied with national and international GCP principles. The sponsor followed company and departmental Standard Operating Procedures for Quality Control (QC) and Quality Assurance (QA) including independent audits.

A number of protocol amendments were made since 29 April 2011. Two amendments occurred before the initiation of the study (clarify text and to update protocol template, remove interviewer asthma control questionnaire and to clarify events of interest). The third amendment on 26/08/2013 occurred before database lock on 04 March 2015 (clarify and align sections throughout the protocol and to remove an ANCOVA analysis originally proposed as a confirmatory analysis). These amendments do not raise any concerns with regards to the assessment of efficacy or safety.

➢ Methods

Objectives

The primary objective:

To demonstrate the dose-related efficacy, by evaluating morning lung function at the end of the dosing interval (AM pre-dose percent predicted forced expiratory volume in one second [FEV1]) across 12 weeks of treatment, of three doses (50 mcg, 100 mcg, and 200 mcg) of MF metered dose inhaler (MDI) twice a day (BID) compared with placebo in children 5 to 11 years of age, inclusive, with persistent asthma.

Secondary objectives

- To demonstrate the dose-related efficacy of MF MDI BID in improving morning (AM) peak expiratory flow (PEF) when compared with placebo
- To assess the dose-related efficacy of MF MDI BID compared with placebo as measured by the Paediatric Asthma Quality of Life Questionnaire with standardised activities (PAQLQ[S]) score;
- To compare the efficacy of MF MDI 50 mcg BID with that of MF DPI 100 mcg once a day (QD) in the evening (PM).

There were several other exploratory objectives assessing the changes in asthma symptoms or physical functions including time to first exacerbation, time to first clinical deterioration, percent of subjects with first exacerbations or clinical deterioration, changes in baseline PEF, pulmonary function test (PFT), questionnaire scores and use of short-acting bronchodilators.

Safety objective

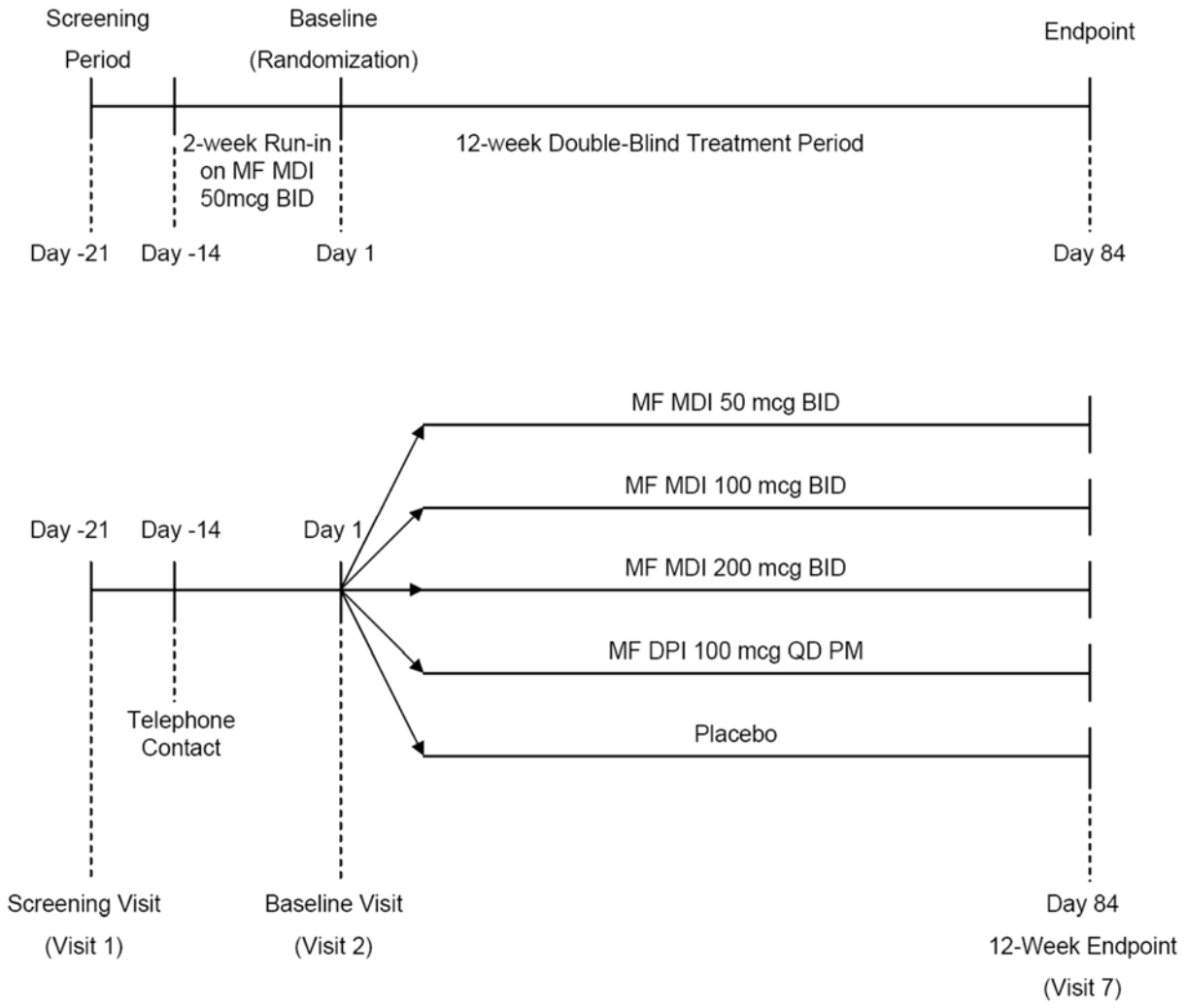
To observe the safety and tolerability of three doses of MF MDI and one dose of MF DPI.

The study objectives are acceptable.

Study design

This was a 12-week multicentre, randomized, placebo-controlled, parallel-group, double-blind, double-dummy dose-ranging efficacy and safety study. The study evaluated MF MDI 50, 100 and 200 mcg administered twice daily, and MF DPI 100 mcg once daily in the evening in children 5 to 11 years of age, inclusive, with persistent asthma.

Figure 1: study design



Study treatments

Subjects were randomly allocated to one of five treatment groups. Each patient used an MDI and DPI device (double-blind double-dummy design):

Table 1: Treatment regimens by treatment group

Treatment Group	Treatment Regimen	Morning Dose	Evening Dose	MF Total Daily Dose
A	MF MDI 50 mcg BID plus Placebo DPI	MF MDI 25 mcg X 2 inhalations	MF MDI 25 mcg X 2 inhalations plus Placebo DPI X 1 inhalation	100 mcg
B	MF MDI 100 mcg BID plus Placebo DPI	MF MDI 50 mcg X 2 inhalations	MF MDI 50 mcg X 2 inhalations plus Placebo DPI X 1 inhalation	200 mcg
C	MF MDI 200 mcg BID plus Placebo DPI	MF MDI 100 mcg X 2 inhalations	MF MDI 100 mcg X 2 inhalations plus Placebo DPI X 1 inhalation	400 mcg
D	MF DPI 100 mcg QD PM plus Placebo MDI	Placebo MDI X 2 inhalations	MF DPI 100 mcg X 1 inhalation plus Placebo MDI X 2 inhalations	100 mcg
E	Placebo (MDI and DPI)	Placebo MDI X 2 inhalations	Placebo MDI X 2 inhalations plus Placebo DPI X 1 inhalation	0

Abbreviations: BID= twice daily; DPI=dry powder inhaler; MF=mometasone Furoate.
QD=once daily.

The subjects were trained on the proper use of the inhalers using placebo training inhalers. Verbal and written instructions for proper use of the MDI and the DPI were also provided to the subjects.

At the Screening Visit, a short-acting β2 agonist (SABA) MDI and oral prednisone /prednisolone were provided to the subject as rescue medications. The subject was advised not to take the SABA or oral prednisone/prednisolone regularly or in anticipation of asthma symptoms. The use of prednisone/prednisolone during the study led to discontinuation of the subject. Nebulised treatment (albuterol/salbutamol) was also permitted.

The overall design is acceptable and is in line with the primary objective of the study which is to demonstrate dose-related efficacy of MF MDI vs placebo. The procedure for blinding the study treatments is acceptable.

Study population /Sample size

The study population included children 5 to 11 years of age, of either sex, with a diagnosis of asthma of at least 6 months duration. Other Inclusion criteria were as follows:

- FEV1 must be between 60% and 90% of predicted when all restricted medications were withheld for the appropriate intervals.
- Subjects were on low to medium daily dose of inhaled corticosteroid (ICS), either alone or in combination with a long-acting beta-agonist (LABA) for at least 12 weeks. No oral steroids were to be used for 12 weeks prior to screening. The subjects should have been on a stable dose of ICS for at least 2 weeks prior to screening.
- Documented positive (at least 12% increase in FEV1) reversibility test

Exclusion criteria

During the run-in period, subjects with a decrease in absolute FEV1 >20%, excessive use of short-acting bronchodilators, decrease in PEF on any two consecutive days, compliance <80% or clinical deterioration requiring oral steroids or hospitalisation, were excluded.

In accordance to CHMP guideline on orally inhaled products (Doc. Ref. CPMP/EWP/4151/00 Rev. 1, 2009), the following aspects of the study are acceptable:

- the population included children with persistent asthma who were responsive to inhaled steroids
- the recruited population is representative of the target population
- reversibility test showed at least 12% increase in FEV1

The study inclusion and exclusion criteria are acceptable.

Sample size

The sample size of 600 (120 in each treatment group) was chosen to detect a clinically meaningful difference in the percent predicted FEV_1 mean change from Baseline at Week 12 (the primary efficacy variable) between active treatment groups and placebo: 5.3%, with 90% power at the 5% significance level. Sample size was adjusted for dropout. Approximately 1200 subjects were planned for screening assuming a screen failure rate of 50%.

For the MDI vs. DPI comparison in percent-predicted FEV1, if the two devices provide the same efficacy (ie MDI - DPI = 0), the observed 95% confidence interval of the mean difference will be (-3.06%, 3.06%). Even though the study was not powered for equivalence, these confidence interval bounds of about 3% are well below 5%, which is considered clinically meaningful.

Of note, the study was powered in terms of pairwise comparisons and not in terms of dose-response modelling which would have been more efficient to address the study objective of demonstrating a dose-response related efficacy.

The MAH stated that the MF DPI arm was included in order to better characterise the treatment effect of the MDI formulation. Therefore results from comparisons between MF DPI and MF MDI will be considered exploratory.

Randomisation

Eligible subjects were randomized to 1 of 5 treatment groups (MF MDI 50 mcg BID, MF MDI 100 mcg BID, MF MDI 200 mcg BID, MF DPI 100 mcg QD PM, or placebo) in a 1:1:1:1:1 ratio. Randomisation was stratified by age (5 to 6 versus 7 to 11 years of age). Central randomisation was performed by means of an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) at each site according to the computer generated randomisation schedule. The IVRS/IWRS was used to monitor the simultaneous enrolment of both age groups.

The randomisation process is adequate. It should be noted however, that stratification is used to reduce the likelihood of imbalances between the treatment groups with respect to level of age categories and not to ensure adequate representation of younger subjects as stated by the MAH.

The primary analysis was adjusted for age, this adjustment is appropriate as age was used as a stratification factor in the randomisation. The primary analysis was also adjusted for region. The MAH explained that stratification by region was not employed as it was expected that adequate numbers of subjects would be randomised within each three regions with reasonable balance between the treatment groups. It can be agreed that the sample sizes were generally balanced across the treatment groups within each region.

Study/endpoints

The primary efficacy endpoint:

The change in percent-predicted FEV1 from Baseline to Week 12 for the evaluation of the dose-related efficacy of MF MDI BID, assessing the comparison of MF MDI 50 mcg BID vs. Placebo, MF MDI 100 mcg BID vs. Placebo, and MF MDI 200 mcg BID vs. Placebo.

Secondary efficacy endpoint

- Change from Baseline in AM (morning) PEF at 12 weeks (Week 12 of Diary Data) for the comparison of MF MDI 50 mcg BID versus placebo, MF MDI 100 mcg BID versus placebo, and MF MDI 200 mcg BID versus placebo.

- Change from Baseline in Paediatric Asthma Quality of Life Questionnaire with standardised activities (PAQLQ[S]) score at 12-weeks for the comparison of MF MDI 50 mcg BID versus Placebo, MF MDI 100 mcg BID versus Placebo, and MF MDI 200 mcg BID versus Placebo. The minimal clinically important difference is 0.42 for the overall score. The PAQLQ(S) will include only subjects in participating countries in which a validated translated questionnaire is available.

- Comparison of the efficacy of MF MDI 50 mcg BID with that of MF dry powder inhaler (DPI) 100 mcg once a day (QD) based on change in %-predicted FEV1 from baseline to 12-Weeks.

The chosen primary and secondary efficacy endpoints are acceptable.

Exploratory efficacy endpoints

These included SABA usage, proportion of symptom-free days and nights, nocturnal awakenings requiring SABA, % subjects with exacerbation of asthma, and time-to-first asthma exacerbation.

Safety endpoints

These included AEs, vital signs, and clinical laboratory tests. The effect on the hypothalamic pituitary adrenocortical (HPA) was not studied. This was justified by the MAH on the basis that the results of a previous HPA axis study (C96-361) can be extrapolated to MF MDI up to 400 mcg BID. This is acceptable.

Data collection

At Screening, each subject was given an e-diary to use for the duration of the study. The e-diary recorded PEF, asthma symptoms, use of rescue medication, events, and compliance. The primary and secondary endpoints excluding PAQLQ[S] were assessed at weeks 2, 4, 6, 8 and 12. Lung function was assessed using spirometry. The PAQLQ was assessed at weeks 2, 4, 8 and 12.

Protocol for physiological assessments

Pulmonary Function Test (PFT)

The subject was to refrain from using SABA 6 hours prior to PFT initiation unless the PEF fell below the stability limit. At all visits, PFTs were performed in the morning, prior to the AM dose of study medication. A standardized spirometer was provided to all sites. Spirometry was performed to measure FEV1, forced expiratory flow (FEF) between 25% and 75% of vital capacity (FEF25%-75%), and forced vital capacity (FVC). Polgar reference ranges were used to determine percent predicted.

Peak expiratory flow (PEF)

PEF measurements were conducted twice daily, prior to administration of study drug and/or SABA by the patient with the assistance of the parent/legal guardian. The best of three recorded PEF was documented.

The data collection methods for physiological measures followed standard practices which are acceptable.

The MAH has taken reasonable steps to comply with the data recording principles of GCP through the implementation for example of standardised spirometer, centralised reading of PFTs, independent audits and Clinical Quality Management group. The steps taken by the MAH to promote compliance with data collection are acknowledged.

Statistical methods

Handling of missing data

The morning pre-dose %-predicted FEV1 evaluations were scheduled at Weeks 2, 4, 6, 8, and 12. For the evaluations, a pre-specified window was assigned the scheduled evaluations to these visits. If two or more evaluations were performed within a visit window, the worst case was assigned to the visit (in this case the lowest value of the % predicted forced FEV1 evaluations within the visit window). If a subject discontinued early and the final visit evaluation was performed outside of a visit window, that evaluation was carried forward into the next scheduled visit window. The approach to assigning worst case to the visit where more than one evaluation was performed, for FEV1, could be acceptable depending on the distribution of subjects with more than one evaluation between the treatment groups. The concern is that if more such subjects are in the placebo group, considering the worst value could lead to bias in favour of the MF MDI treatments.

For diary data, interval averages were the mean of all non-missing values within that interval (e.g., Baseline and Week 12). For days where the am and pm diary data were to be averaged, if an am or a pm diary reading was missing on any given day, the average for that day equalled the non-missing value. An Endpoint Diary evaluation was derived for each diary variable at Week 12 by carrying forward the last week of non-missing diary data. The MAH has clarified that average was derived based on all available data with no minimum requirement for the number of non-missing observations. Therefore the average interval data should be interpreted with caution because of the varying available information at the individual level on which the average is computed; the interval average may represent a week worth of data or in some patients it may just the value for a single time-point.

Data quality

The sponsor ensured that their clinical quality management group implemented quality control plans to assess the state of compliance (real-time measurements) and to identify any potential process gaps (risk-based selection of processes). The goal is to identify any emerging risks/trends of non-compliance to support continuous process improvement as well as to prevent the recurrence of any identified quality issues.

Primary efficacy analysis

The primary efficacy analysis was the comparison of all MF MDI doses versus placebo using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger. This model assumes a common mean across treatment groups at Baseline and a different mean for each treatment at each of the post-Baseline time points. In this model, the response vector consists of Baseline and the values observed at each post-Baseline time point. The analysis model adjusts for treatment, time, treatment by time interaction, region (North America, Latin America, and the EU), and age strata (5 and 6 or 7 to 11 years of age, inclusive). The treatment difference in terms of mean change from Baseline to a given time point was estimated and tested from this model.

An unstructured covariance matrix was used to model the correlation among repeated measurements.

The use of cLDA model in the presence of missing data as the primary analysis is not supported. In a similar way to the MMRM model, cLDA assumes that data are missing at random (MAR). The major concern is the targeted estimand, since the cLDA assumes that subjects who drop out are similar to those subjects who remain in the trial and therefore it estimates what would have happened if everyone had stayed in the trial.

The cLDA method of analysis includes all subjects with at least one non-missing evaluation across the Baseline and post-Baseline visits. A constraint of a common baseline mean across treatment groups is imposed on the model as a result of randomisation in order to ensure that the baseline value is independent of treatment group. Intuitively, since the baseline mean is constrained to be equal across treatment groups, the inclusion of subjects with only a baseline value in the cLDA model does not contribute to the treatment differences at post-baseline time points. The inclusion of subjects with no baseline value but with at least one post-baseline value contain information about the treatment differences at post-baseline time points, hence the variances of estimated treatment differences at post-baseline time points for the cLDA model can be made arbitrarily small by including an increasing number of such subjects. The number of subjects with no baseline data was 3% (20 subjects).

The MAH performed a sensitivity analysis based on the cLDA primary analysis model with missing data imputed using BOCF, as requested.

The step-down approach was used for testing of MF MDI doses against placebo to control for multiplicity. Tests began at the highest dose of MF MDI. After success of MF MDI 200 mcg BID vs. placebo, the MF MDI 100 mcg BID and MF MDI 50 mcg BID was tested against placebo in sequential order. This controlled the overall two-sided alpha level of 5% for the primary endpoint. The step-down approach to control the Type I error as a result of multiple testing between the MF MDI doses and placebo is acceptable.

Subgroup analyses
The analyses by: geographic regions of the world, as well as the demographic variables of gender, age, and race as compared with the primary analysis were pre-specified. Analyses of change from baseline at Week 12 were descriptive. As requested, the MAH presented estimates of treatment effects in the pre-specified subgroups (age, race, region, and sex) estimated from a constrained longitudinal data analysis model.

Secondary efficacy analyses
Continuous diary and visit-based variables were analysed by means of the cLDA model as was used for the primary efficacy analysis, extracting sources of variation due to treatment, time, treatment by time interaction, region (North America, Latin America, and the EU), and age strata (5 and 6 or 7 to 11 years of age, inclusive).
Baseline for e-diary data is defined as the average of scores for Days -7 to 1 prior to first dose of study drug.

The proportion of subjects with 2 consecutive nights with nocturnal awakenings due to asthma and percentage of subjects with asthma exacerbation event over the 12-week Treatment Period were analysed using a Cochran-Mantel-Haenszel test correcting for age strata (5 and 6 or 7 to 11 years of age, inclusive). Time-to-first asthma exacerbation events were examined using logrank tests for equality of survival curves asthma exacerbation event criteria. Kaplan-Meier Survival curves were used to display treatment responses for time-to-first asthma exacerbation event.

The statistical methods for secondary and exploratory analyses are broadly supported. These are standard methods for the analysis of categorical and time to event data.

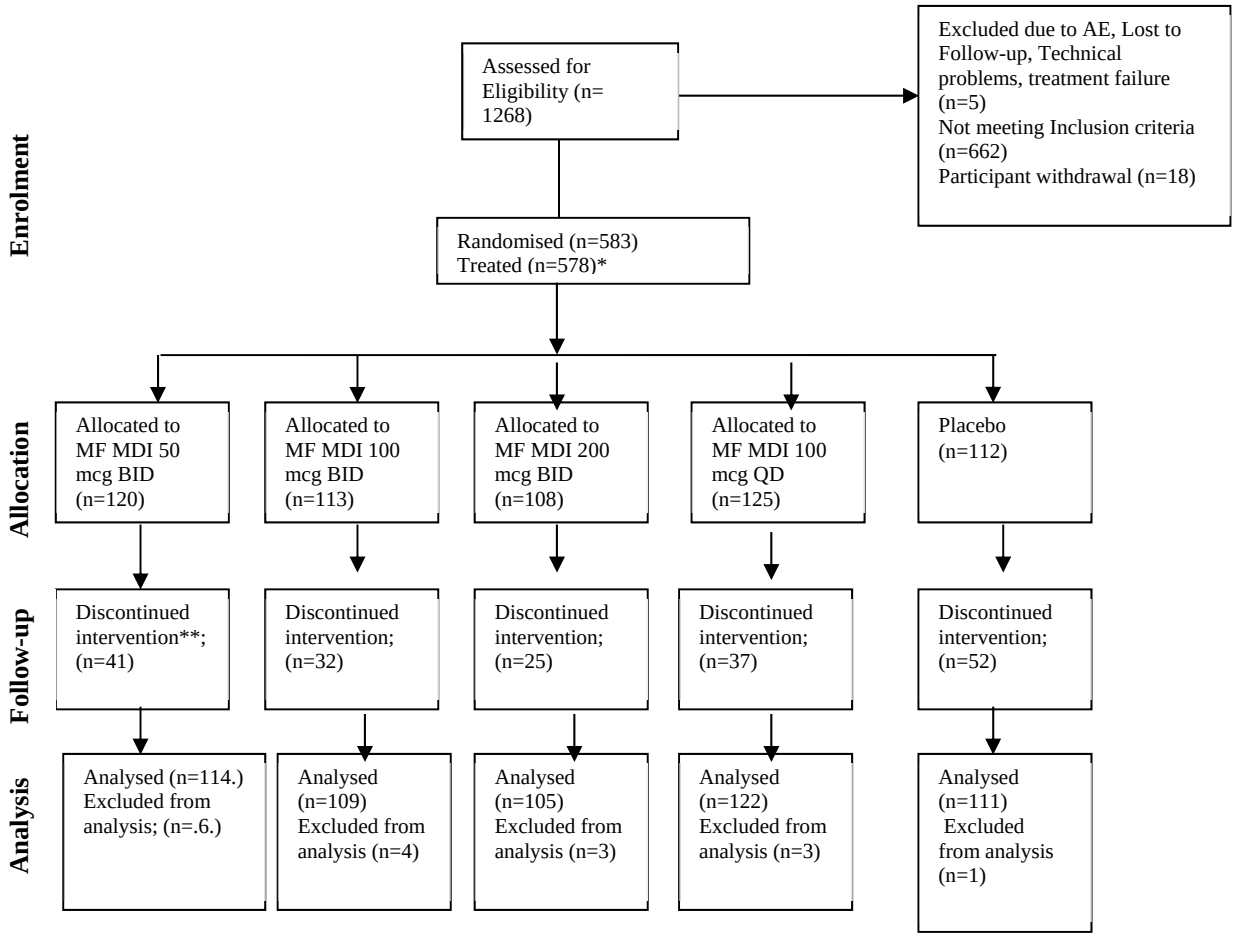
Analysis population
Full Analysis Set (FAS): The FAS included all subjects who received randomised treatment assignment and had either a baseline measurement or at least one post-randomisation measurement. The FAS was used for the primary efficacy analysis. The inclusion of only subjects who received randomised treatment in the FAS is acceptable. Whilst it is expected that not all subjects in the FAS would have a post-baseline measure, all subjects are expected to have a baseline measure of FEV1 since this was one of the inclusion criteria. Subjects without post-baseline measures should not be excluded from the FAS since the exclusion of such subjects could be related to treatment. With the current definition, it is likely that that these subjects are included on the basis of their baseline value.

A confirmatory analysis of the primary efficacy variable was performed on a Per Protocol (Efficacy Evaluable) set, which includes all treated subjects who meet key eligibility and evaluability criteria.

The All Treated Analysis Set (ATAS): The ATAS population consisted of all enrolled subjects who received at least one dose of randomised treatment.

- **Results**

Recruitment/ Number analysed
A total of 1268 subjects were screened; 685 subjects were excluded during screening. A total of 583 subjects were randomised into the trial; however, only 578 subjects received at least one dose of randomised study medication. Of the 578 randomised subjects in the All Treated Analysis Set, 391 (67.6%) completed the trial. Of the 187 subjects who discontinued treatment early, the majority ended participation due to Treatment Failure (103; 17.8%) and Protocol Violation (35; 6.1%).



*5 subjects were randomised in error and were not treated

** Reasons for discontinuation of treatment included: adverse events, excluded medications, lack of efficacy, non-compliance with study drug, physician decision, protocol violations, technical problems, treatment failure and withdrawal by subject.

Table 2: Number and percentage of patients completing the study and eligible for different efficacy analyses

	MF MDI 50 mcg	MF MDI 100 mcg	MF MDI 200 mcg	MF DPI 100 mcg	Placebo	Total
Randomised and treated*	**120**	**113**	**108**	**125**	**112**	**578**
Completed the study	79 (65.8%)	81 (71.7%)	83 (76.9%)	88 (70.4%)	60 (53.6%)	391 (67.6%)
Discontinuation rates**	**34.2%**	**28.3%**	**23.1%**	**29.6%**	**46.4%**	**32.4%**
Included in FAS +	114 (95%)	109 (96%)	105 (97%)	122 (98%)	111 (99%)	561 (97%)
Included in the PP	113	106	104	122	111	556 (96%)
Observed FEV_1data Baseline	116	108	102	122	110	558 (97%)
Observed FEV1 data Week 12 ++	80	79	77	92	67	395 (68%)
% missing FEV_1 at Week 12	**33%**	**30%**	**29%**	**26%**	**40%**	**32%**

+ All available data 567
++ Assessor's calculations derived from data presented in Table 14-12 and Table 14-13

The disposition has accounted for all patients screened and eligible for randomisation. Completion rates were generally comparable across the MF MDI 100 and 200 mcg but lower for the Placebo and MF MDI 50 mcg groups. The completion rates ranged from 53.6% (Placebo) to 76.9% (MF MDI 200 mcg). There were notably higher proportions of adverse events in the placebo group compare the MF MDI groups. However, this to be expected in asthma subjects who do not receive active treatment.

Protocol deviations

Deviations reported included 4 subjects receiving incorrect study medication for 14 - 28 days during the 12 week treatment period. Twenty patients did not have baseline FEV1 even though this was an inclusion criteria. The MAH explains that missing baseline FEV1 could be due to not performing spirometry at all or having spirometry data graded as unacceptable by an external spirometry central vendor. Patients who did not perform spirometry were categorised as protocol deviations whereas those with unacceptable FEV1 were treated as missing. In the primary analysis, the FAS included patients with baseline and or at least one post-baseline measure, therefore some of these subjects may have been included in the analysis if they have at least one post-baseline measure.

Baseline data

Table 3: Subject Characteristics (All Treated Analysis Set)

	MF MDI 50 mcg BID		MF MDI 100 mcg BID		MF MDI 200 mcg BID		MF DPI 100 mcg QD PM		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	120		113		108		125		112		578	
Gender												
Male	69	(57.5)	69	(61.1)	49	(45.4)	77	(61.6)	82	(73.2)	346	(59.9)
Female	51	(42.5)	44	(38.9)	59	(54.6)	48	(38.4)	30	(26.8)	232	(40.1)
Age (Years)												
5 to 6	13	(10.8)	22	(19.5)	14	(13.0)	14	(11.2)	11	(9.8)	74	(12.8)
7 to 11	107	(89.2)	91	(80.5)	94	(87.0)	111	(88.8)	101	(90.2)	504	(87.2)
Mean	8.7		8.6		8.7		8.7		9.0		8.8	
SD	1.7		1.9		1.7		1.7		1.7		1.8	
Median	9.0		9.0		9.0		9.0		9.0		9.0	
Range	5 to 11		5 to 11		5 to 11		5 to 11		5 to 12		5 to 12	
Race												
American Indian Or Alaska Native	4	(3.3)	3	(2.7)	8	(7.4)	4	(3.2)	3	(2.7)	22	(3.8)
Asian	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)	0	(0.0)	2	(0.3)
Black Or African American	7	(5.8)	2	(1.8)	3	(2.8)	5	(4.0)	2	(1.8)	19	(3.3)
Multi-Racial	25	(20.8)	26	(23.0)	25	(23.1)	24	(19.2)	26	(23.2)	126	(21.8)
White	84	(70.0)	81	(71.7)	72	(66.7)	91	(72.8)	81	(72.3)	409	(70.8)

	MF MDI 50 mcg BID		MF MDI 100 mcg BID		MF MDI 200 mcg BID		MF DPI 100 mcg QD PM		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ethnicity												
Hispanic Or Latino	39	(32.5)	40	(35.4)	38	(35.2)	38	(30.4)	36	(32.1)	191	(33.0)
Not Hispanic Or Latino	78	(65.0)	70	(61.9)	66	(61.1)	84	(67.2)	74	(66.1)	372	(64.4)
Not Reported	3	(2.5)	3	(2.7)	4	(3.7)	3	(2.4)	1	(0.9)	14	(2.4)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.2)
ALLERGY HISTORY												
No	36	(30.0)	34	(30.1)	33	(30.6)	40	(32.0)	35	(31.3)	178	(30.8)
Yes	84	(70.0)	79	(69.9)	75	(69.4)	85	(68.0)	77	(68.8)	400	(69.2)
ASTHMA HISTORY												
Yes	120	(100.0)	113	(100.0)	108	(100.0)	125	(100.0)	112	(100.0)	578	(100.0)
PRIOR ICS Treatment Taken												
Yes	119	(99.2)	112	(99.1)	108	(100.0)	124	(99.2)	112	(100.0)	575	(99.5)
No	1	(0.8)	1	(0.9)	0	(0.0)	1	(0.8)	0	(0.0)	3	(0.5)
Reversibility												
Historical reversibility	98	(81.7)	99	(87.6)	88	(81.5)	105	(84.0)	95	(84.8)	485	(83.9)

	MF MDI 50 mcg BID		MF MDI 100 mcg BID		MF MDI 200 mcg BID		MF DPI 100 mcg QD PM		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Reversibility												
Demonstrated reversibility at screening or prior to baseline	22	(18.3)	14	(12.4)	20	(18.5)	20	(16.0)	17	(15.2)	93	(16.1)
Weight (kg)												
Subjects with data	120		113		108		125		112		578	
Mean	35.4		34.0		34.5		35.8		35.3		35.0	
SD	11.4		10.8		10.5		13.5		12.4		11.8	
Median	33.3		32.0		33.0		33.6		34.0		33.0	
Range	15.0 to 69.0		16.0 to 68.0		16.0 to 71.9		18.0 to 89.0		15.0 to 91.0		15.0 to 91.0	
%Predicted FEV1												
Subjects with data	116		108		102		122		110		558	
Mean	79.4		78.8		78.8		78.4		77.8		78.7	
SD	7.6		8.0		8.0		7.6		7.2		7.7	
Median	79.6		79.1		79.3		79.3		77.5		79.2	
Range	61.1 to 97.0		56.5 to 95.6		50.7 to 104.8		53.9 to 90.3		59.7 to 95.3		50.7 to 104.8	

*The age strata is provided from the IVRS information. *Subject 102641, site: 2702 was randomized at age 11 in IVRS and derived age was 12 due to standard missing date imputation in database.

Data Source: [16.4]

Table 4: Summary of treatment compliance

	MF MDI 50 mcg BID		MF MDI 100 mcg BID		MF MDI 200 mcg BID		MF DPI 100 mcg QD PM		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	120		113		108		125		112		578	
Treatment compliance												
>20 to ≤40%	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
>40% to ≤60%	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
>60% to ≤80%	2	(1.7)	1	(0.9)	0	(0.0)	1	(0.8)	2	(1.8)	6	(1.0)
>80% to ≤120%	117	(97.5)	111	(98.2)	108	(100.0)	124	(99.2)	108	(96.4)	568	(98.3)
≥120%	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.8)	3	(0.5)
Summary statistics for treatment compliance (%)												
Mean	99.7		98.7		99.6		99.3		100.0		99.5	
SD	6.2		5.7		2.6		2.9		6.7		5.1	
Median	100.0		100.0		100.0		100.0		100.0		100.0	
Range	70.5 to 151.0		60.0 to 107.6		86.7 to 109.1		78.6 to 104.8		75.0 to 139.4		60.0 to 151.0	

Data Source: [16.4]

The demographic characteristics are similarly distributed across treatment groups. 87% of the participants recruited were in the age group 7-11 years. Treatment compliance was comparable across groups.

Efficacy results

A total of 583 subjects were randomised; 11 subjects were excluded from the full analysis set used for efficacy assessment. The subjects excluded meet the pre-defined exclusion criteria from the full analysis set.

Primary efficacy endpoint

The primary efficacy endpoint was the dose-related change in percent-predicted FEV1 from Baseline to Week 12 for the MF MDI BID, assessing the comparison of MF MDI 50 mcg BID vs. Placebo, MF MDI 100 mcg BID vs. Placebo, and MF MDI 200 mcg BID vs. Placebo.
The FAS analysis is presented in table 5 and Fig 2. Per protocol analysis is presented in table 6.

Additional analysis of change from baseline in percent predicated FEV1 (using cLDA model) at weeks 8, 6, 4 and 12, based on FAS using all available data are presented in Tables 14-18, 14-19, 14-20,and 14-21 respectively (refer to clinical study report).

Table 5: Analysis of Change from Baseline in % Predicted FEV1 (Liters) at Week 12 - Primary Analysis (Full-Analysis-Set)

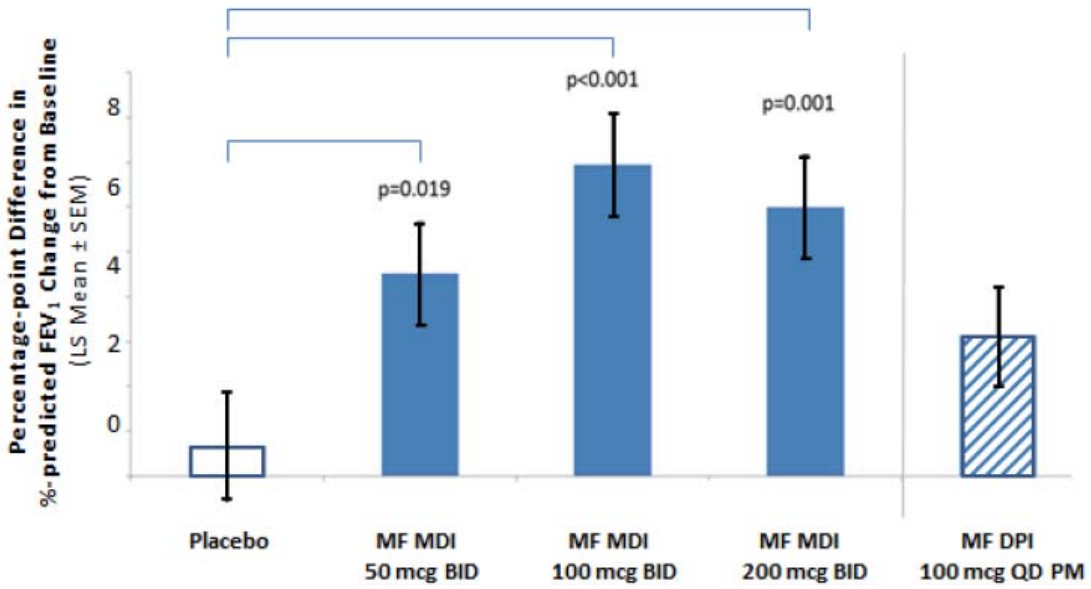
		Observed % Predicted FEV1 (Liters)				Change from Baseline in % Predicted FEV1 (Liters) at Week 12				
		Baseline		Week 12						
Treatment	N[1]	Mean	(SD)	Mean	(SD)	Median	Mean	(SD)	LS Mean	95% CI
Placebo	111	77.82	7.21	79.90	11.55	2.57	3.59	11.65	0.66	(-1.72, 3.03)
MF MDI 50 mcg BID	114	79.53	7.47	85.61	12.43	3.86	5.57	11.71	4.52	(2.32, 6.72)
MF MDI 100 mcg BID	109	78.94	7.85	86.33	13.09	6.38	7.45	11.32	6.95	(4.73, 9.16)
MF MDI 200 mcg BID	105	78.71	7.96	86.12	11.69	4.31	5.98	8.38	6.00	(3.74, 8.25)
MF DPI 100 mcg QD PM	122	78.44	7.57	82.84	10.14	3.05	3.97	9.06	3.13	(1.01, 5.25)

Estimated Differences with Placebo	Difference in LS Means*	95% CI	p-Value
MF MDI 50 mcg BID vs. Placebo at week 12	3.87	(0.64, 7.09)	0.019
MF MDI 100 mcg BID vs. Placebo at week 12	6.29	(3.05, 9.53)	<.001
MF MDI 200 mcg BID vs. Placebo at week 12	5.34	(2.07, 8.61)	0.001
MF DPI 100 mcg QD PM vs. Placebo at week 12	2.47	(-0.70, 5.65)	0.127
MF MDI 50 mcg BID vs. MF DPI 100 mcg QD PM at week 12	1.39	(-1.65, 4.44)	0.368

*Constrained longitudinal data analysis model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the EU).[1] Includes all subjects with at least one evaluation in the analysis (baseline and/or post-baseline).The primary analysis includes trough scores defined as those evaluations performed in the AM upon rising, and free of other medications, excludes post last dose evaluations, as well as those subjects documented to have not taken their drug as instructed the night prior to their FEV1 evaluation.
SD = Standard Deviation; CI = Confidence Interval.
Pooled SD = 10.80

Data Source: [16.4]

Figure 2: %-predicted FEV1: Change from Baseline at Week 12 (Full-Analysis-Set)



P-values are for the treatment differences compared with Placebo
MF = mometasone furoate, MDI = metered-dose inhaler, mcg = microgram, BID = twice daily, DPI = dry-powder inhaler, QD PM = once daily in the evening, LS = least squares, SEM = standard error of the mean

Table 6: Analysis of Change from Baseline in % Predicted FEV1 (Liters) at Week 12 - Primary Analysis (PP)

Table 14-11
Analysis of Change from Baseline in Percent Predicted FEV_1 at Week 12 - Primary Analysis
(Per Protocol Population)

		Observed Percent Predicted FEV_1				Change from Baseline in Percent Predicted FEV_1 at Week 12				
		Baseline		Week 12						
Treatment	N[2]	Mean	(SD)	Mean	(SD)	Median	Mean	(SD)	LS Mean	95% CI
Placebo	111	77.82	7.21	79.90	11.55	2.57	3.59	11.65	0.67	(-1.70, 3.04)
MF MDI 50 mcg BID	113	79.44	7.45	85.61	12.43	3.86	5.57	11.71	4.70	(2.50, 6.90)
MF MDI 100 mcg BID	106	78.72	7.76	85.87	12.71	6.26	7.16	11.28	6.67	(4.44, 8.91)
MF MDI 200 mcg BID	104	78.64	7.97	86.09	11.76	4.37	6.03	8.43	6.07	(3.80, 8.33)
MF DPI 100 mcg QD PM	122	78.44	7.57	82.84	10.14	3.05	3.97	9.06	3.16	(1.05, 5.27)

Estimated Differences	Difference in LS Means*	95% CI	p-Value
MF MDI 50 mcg BID vs. Placebo at week 12	4.03	(0.81, 7.25)	0.014
MF MDI 100 mcg BID vs. Placebo at week 12	6.00	(2.76, 9.25)	<.001
MF MDI 200 mcg BID vs. Placebo at week 12	5.40	(2.13, 8.66)	0.001
MF DPI 100 mcg QD PM vs. Placebo at week 12	2.49	(-0.68, 5.65)	0.123
MF MDI 50 mcg BID vs. MF DPI 100 mcg QD PM at week 12	1.54	(-1.50, 4.58)	0.320

*Constrained longitudinal data analysis model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the EU).[2] Includes all subjects with at least one evaluation in the analysis (baseline and/or post-baseline).The primary analysis includes trough scores defined as those evaluations performed in the AM upon rising, and free of other medications, excludes post last dose evaluations, as well as those subjects documented to have not taken their drug as instructed the night prior to their FEV1 evaluation.
SD = Standard Deviation; CI = Confidence Interval.
Pooled SD = 10.76

Data Source: [16.4]

Estimates of treatment effects show a statistically significant increase in percent predicted FEV1 from baseline in all MF MDI doses especially the high doses of MF MDI (100 mcg and 200 mcg BID) when compared to placebo. Estimates of treatment effects based on the FAS and PP populations are consistent.

The MAH performed a sensitivity analysis based on the cLDA primary analysis model with missing data imputed using BOCF, as requested. The MF MDI versus placebo effect sizes were 2.23 (MF MDI 50 mcg BID), 3.44 (MF MDI 100 mcg BID), and 2.97 (MF MDI 200 mcg BID). These effects sizes are smaller but consistent with those obtained from the primary analysis model; showing a greater efficacy in the MF MDI 100 mcg BID group compared to the other two MF MDI groups (p=0.005).

The MAH has also presented estimates of treatment effects derived from an ANCOVA model adjusted for baseline FEV1, age, and region based on Week 12 data, as requested. The MF MDI versus placebo effect sizes were 3.36 (MF MDI 50 mcg BID), 4.66 (MF MDI 100 mcg BID), and 3.44 (MF MDI 200 mcg BID). The dose response pattern is consistent with the primary analysis showing a greater efficacy in the MF MDI 100 mcg BID group (p=0.005) compared to the other MF MDI groups.

The MAH has clarified the discrepancies between the means and the LS means in the placebo group for both FEV1 and PEF. Some patients had missing baseline values for FEV1, therefore as the constraint longitudinal data analysis model incorporates all of the baseline data across the five treatment arms, the means and the LS means of change from baseline will be different. It agreed that these differences will be more pronounced in the placebo group as this group had the lowest completion rate (53.6%). A total of 62 patients in the placebo group had data at baseline and at Week 12. The discrepancies between the means and the LS means of change from baseline in PEF are due to the missing data since only 61 patients in the placebo group had data for PEF at baseline and at Week 12.

The treatment effects estimated based on weekly data are generally slightly smaller than those observed at Week 12 but consistently indicating greater treatment effect associated with MF MDI 100 mcg BID compared to treatment effect for MF MDI 50 mcg BID and 200 mcg BID.

The primary objective for this trial was to demonstrate the dose-related (50 mcg BID, 100 mcg BID, and 200 mcg BID) efficacy by evaluating the change in morning lung function at the end of the dosing interval after 12 weeks of treatment as compared to placebo in children 5 to 11 years of age with persistent asthma. The MF MDI treatment groups were superior to placebo as observed from the mean change in FEV1 from baseline to end of 12 week. In view of the purpose of the study, to determine a suitable dose based on dose response, a trend towards increasing efficacy is observed from 50 mcg BID to 100 mcg BID. From 100 mcg BID to 200 mcg BID, a trend towards decreasing efficacy is observed. MF DPI 100 mcg QD appears to be inferior to MF MDI 50 mcg BID.

Subgroup efficacy analyses

Subgroup analyses for age, race and region are presented in clinical study report tables 14-12, 14-13, and 14-14 respectively. Estimates of treatment effects for the subgroup are descriptive. The method of estimation of change from baseline in % predicted FEV1 at Week 12 is not consistent with the primary analysis. Therefore, assessment of whether estimates of treatment effects in the subgroups are consistent with those in the overall population is not possible. As requested, the MAH has presented estimates of treatment effects in the pre-specified subgroups (age, race, region, and sex) estimated from a constrained longitudinal data analysis model. It is agreed that the results are generally consistent with the primary analysis model. These results support the selection of the MF MDI 100 mcg dose for the Phase III study.

Secondary efficacy endpoint

Table 7: Change from Baseline in AM PEF (L/min) at Week 12 (Full-Analysis-Set)

Treatment	N‡	Observed AM PEF at Week 12				Change from Baseline in AM PEF at Week 12				
		Baseline		Week 12						
		Mean	(SD)	Mean	(SD)	Median	Mean	(SD)	LS Mean	95% CI
Placebo	111	214.54	72.85	215.94	90.95	3.54	-8.18	65.10	-1.32	(-15.49, 12.85)
MF MDI 50 mcg BID	118	204.44	55.84	229.71	59.99	8.60	14.73	47.23	17.83	(5.35, 30.30)
MF MDI 100 mcg BID	112	201.15	59.23	227.96	60.74	18.48	25.50	54.33	26.03	(13.55, 38.51)
MF MDI 200 mcg BID	108	193.18	64.01	218.90	61.77	22.71	19.46	62.46	16.68	(4.50, 28.86)
MF DPI 100 mcg QD PM	123	207.94	65.38	209.94	77.66	2.86	-3.97	66.85	-0.92	(-12.82, 10.99)

Estimated Differences	Difference in LS Means*	95% CI	p-Value
MF MDI 50 mcg BID vs. Placebo at week 12	19.15	(0.43, 37.87)	0.045
MF MDI 100 mcg BID vs. Placebo at week 12	27.35	(8.63, 46.08)	0.004
MF MDI 200 mcg BID vs. Placebo at week 12	18.01	(-0.51, 36.53)	0.057
MF DPI 100 mcg QD PM vs. Placebo at week 12	0.41	(-17.94, 18.75)	0.965
MF MDI 50 mcg BID vs. MF DPI 100 mcg QD PM at week 12	18.74	(1.68, 35.81)	0.031

*Constrained longitudinal data analysis model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the EU). All available data includes all evaluations collected in the trial regardless of trough status. ‡ Includes all subjects with at least one evaluation in the analysis (baseline and/or post-baseline).
SD = Standard Deviation; CI = Confidence Interval.
Pooled SD = 55.70

Data Source: [16.4]

Regarding change from baseline in AM PEF at Week 12, the greatest improvement was observed for the 100 mcg dose, supporting the primary outcome (FEV1).

Table 8: Analysis of Asthma Quality of Life Questionnaire with Standardized Activities-PAQLQ(S), Overall Score at Week 12 (Full-Analysis-Set)

Treatment	N‡	Observed PAQLQ(S) Overall Score				Change from Baseline in PAQLQ(S) Overall Score at Week 12				
		Baseline		Week 12						
		Mean	(SD)	Mean	(SD)	Median	Mean	(SD)	LS Mean	95% CI
Placebo	102	6.20	0.79	6.56	0.64	0.13	0.28	0.60	0.26	(0.12, 0.39)
MF MDI 50 mcg BID	111	6.16	0.75	6.58	0.58	0.26	0.36	0.50	0.35	(0.23, 0.48)
MF MDI 100 mcg BID	105	6.15	0.71	6.55	0.72	0.35	0.36	0.72	0.38	(0.25, 0.50)
MF MDI 200 mcg BID	101	6.03	0.93	6.58	0.60	0.37	0.52	0.88	0.44	(0.31, 0.56)
MF DPI 100 mcg QD PM	115	6.07	0.81	6.61	0.52	0.39	0.51	0.61	0.47	(0.35, 0.59)

Estimated Differences	Difference in LS Means*	95% CI	p-Value
MF MDI 50 mcg BID vs. Placebo at week 12	0.10	(-0.08, 0.27)	0.280
MF MDI 100 mcg BID vs. Placebo at week 12	0.12	(-0.06, 0.30)	0.178
MF MDI 200 mcg BID vs. Placebo at week 12	0.18	(0.00, 0.36)	0.045
MF DPI 100 mcg QD PM vs. Placebo at week 12	0.22	(0.04, 0.39)	0.014
MF MDI 50 mcg BID vs. MF DPI 100 mcg QD PM at week 12	-0.12	(-0.28, 0.04)	0.147

*Constrained longitudinal data analysis model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the EU). ‡ Includes all subjects with at least one evaluation in the analysis (baseline and/or post-baseline). Impairment score range from 1 (greatest impairment) through 7 (least impairment).
SD = Standard Deviation; CI = Confidence Interval.
Pooled SD = 0.55

Data Source: [16.4]

According to the MAH, the MCID is 0.42 for the overall score. The differences in LS means between treatment groups are less than the MCID.

Exploratory endpoints

SABA use

The MAH identified one patient amongst the 79 observed cases who reported 20 nebulizer uses while the remaining 78 patients did not report any nebuliser use. The MAH has presented an analysis excluding this patient's nebulizer use from the Week 12 analysis. This approach is

agreed. When this patient is excluded, there is a trend towards reduction in SABA use compared to baseline in all treatment groups. The MAH conducted a sensitivity analysis including FEV1 evaluations within 6 hours of SABA use. The results are supportive of the primary analysis, and the decision to select MF MDI 100 mcg BID for further evaluation in Phase 3.

Other endpoints

- There was an increase in the mean proportion of days and nights with a total symptom score of zero relative to baseline for the active treatment groups compared to placebo, but no clear dose-related trend.
- A decrease in nocturnal awakenings requiring use of SABA were observed with all active treatments, compared to an increase for placebo, but with no clear dose-related trend.
- The highest proportion of subjects with asthma exacerbation event was observed for the placebo group (31%) compared to MF MDI 50 mcg BID (22%), MF MDI 100 mcg BID (20%), MF MDI 200 mcg BID (13%) and MF PDI 100 mcg QD (15%). A dose-related trend is evident.
- Regarding time-to-first asthma exacerbation, MF MDI 100 mcg BID and MF MDI 200 mcg BID demonstrated significant improvement compared to placebo.

The exploratory endpoints related to nocturnal awakening, symptom scores and asthma exacerbation events were supportive of the primary outcome.

Safety results

The MAH has analysed the clinical safety of MF MDI 50 mcg BID, 100 mcg BID, 200 mcg BID and MF DPI 100 mcg QD, for up to 12 weeks, in children aged 5-11 years of age. The total daily dose exposure of MF in this study ranged from 100 mcg to 400 mcg. The licensed MF product in EU~~UK~~ is not approved for this age group. Therefore safety results have been reviewed against those reported in the Asmanex 200 mcg and 400 mcg DPI SmPC for adults and adolescents where the total daily exposure of MF varies from 200 mcg to 800 mcg.

Table 9: Adverse drug reactions in section 4.8 of Asmanex SmPC for MF 200 mcg once daily dosing

System Organ Class	Frequencies
Infections and infestations Candidiasis	common
Immune system disorders Hypersensitivity reactions including rash, pruritus, angioedema and anaphylactic reaction	not known
Psychiatric disorders Psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression	not known
Respiratory, thoracic and mediastinal disorders Pharyngitis Dysphonia Asthma aggravation including cough, dyspnea, wheezing and bronchospasm	 common uncommon not known

General disorders and administration site conditions Headache	common

Section 4.8 of Asmanex SmPC also states:
Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, and decrease in bone mineral density. As with other inhaled corticosteroids, rare cases of glaucoma, increased intraocular pressure and/or cataracts have been reported. As with other glucocorticoid products, the potential for hypersensitivity reactions including rashes, urticaria, pruritus and erythema and oedema of the eyes, face, lips and throat should be considered.

Exposure

All 578 randomized subjects were exposed to at least one dose of study medication. All of these subjects were included in the safety analysis (All treated analysis set).

Table 10: Summary of extent of exposure

Treatment	≤ 2 wks	> 2 wks to 4 wks	> 4 wks to 6 wks	> 6 wks to 8 wks	> 8 wks to 10 wks	> 10 wks to 12 wks	> 12 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	67	34	30	22	20	263	142	578	1 to 101 days	66.9 days
Placebo	22	6	9	6	4	42	23	112	2 to 101 days	59.2 days
MF MDI 50 mcg BID	14	7	5	6	7	50	31	120	1 to 89 days	67.1 days
MF MDI 100 mcg BID	8	6	6	4	4	54	31	113	1 to 91 days	70.1 days
MF MDI 200 mcg BID	12	3	5	2	1	57	28	108	3 to 95 days	70.9 days
MF DPI 100 mcg QD PM	11	12	5	4	4	60	29	125	5 to 91 days	67.4 days

Each subject is counted once on each applicable dosage category row.
Duration of exposure was calculated assuming one day of dosing = 1 day of exposure.
Duration was based on treatment begin date and treatment end date and did not take into account of possible dosing interruption and subject non-compliance.

Data Source: [16.4]

Exposure over three months period was adequate to allow a meaningful comparison of safety between placebo and MF treatment groups with a total daily exposure of 100 mcg, 200 mcg or 400 mcg. However, long terms effects of MF such as adrenal suppression, growth retardation and decrease in bone mineral density cannot be determined from this study due to the short duration of exposure.

Adverse events

Table 11: Summary of adverse events reported in randomised subjects

	MF MDI 50 mcg BID		MF MDI 100 mcg BID		MF MDI 200 mcg BID		MF DPI 100 mcg QD PM		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	120		113		108		125		112		578	
with one or more adverse events	39	(32.5)	50	(44.2)	35	(32.4)	49	(39.2)	43	(38.4)	216	(37.4)
with no adverse event	81	(67.5)	63	(55.8)	73	(67.6)	76	(60.8)	69	(61.6)	362	(62.6)
with drug-related† adverse events	1	(0.8)	1	(0.9)	1	(0.9)	0	(0.0)	1	(0.9)	4	(0.7)
with serious adverse events	2	(1.7)	1	(0.9)	2	(1.9)	4	(3.2)	2	(1.8)	11	(1.9)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.2)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	2	(1.7)	1	(0.9)	0	(0.0)	4	(3.2)	3	(2.7)	10	(1.7)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.2)
discontinued due to a serious adverse event	2	(1.7)	0	(0.0)	0	(0.0)	1	(0.8)	2	(1.8)	5	(0.9)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.2)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Data Source: [16.4]

Table 12: Subjects with adverse events (incidence ≥ 2%) - overall and drug-related

	MF MDI 50 mcg BID				MF MDI 100 mcg BID				MF MDI 200 mcg BID			
	Overall		Drug Related†		Overall		Drug Related†		Overall		Drug Related†	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	120		120		113		113		108		108	
with one or more adverse events	39	(32.5)	1	(0.8)	50	(44.2)	1	(0.9)	35	(32.4)	1	(0.9)
with no adverse events	81	(67.5)	119	(99.2)	63	(55.8)	112	(99.1)	73	(67.6)	107	(99.1)
Gastrointestinal disorders	**4**	**(3.3)**	**0**	**(0.0)**	**3**	**(2.7)**	**0**	**(0.0)**	**4**	**(3.7)**	**0**	**(0.0)**
Diarrhoea	1	(0.8)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.9)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**2**	**(1.7)**	**0**	**(0.0)**	**4**	**(3.5)**	**0**	**(0.0)**	**1**	**(0.9)**	**0**	**(0.0)**
Pyrexia	2	(1.7)	0	(0.0)	4	(3.5)	0	(0.0)	1	(0.9)	0	(0.0)
Infections and infestations	**22**	**(18.3)**	**0**	**(0.0)**	**31**	**(27.4)**	**0**	**(0.0)**	**19**	**(17.6)**	**0**	**(0.0)**
Conjunctivitis	3	(2.5)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.9)	0	(0.0)
Nasopharyngitis	8	(6.7)	0	(0.0)	5	(4.4)	0	(0.0)	7	(6.5)	0	(0.0)
Pharyngitis	2	(1.7)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory tract infection	1	(0.8)	0	(0.0)	3	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis	4	(3.3)	0	(0.0)	3	(2.7)	0	(0.0)	1	(0.9)	0	(0.0)
Upper respiratory tract infection	1	(0.8)	0	(0.0)	4	(3.5)	0	(0.0)	2	(1.9)	0	(0.0)

	MF MDI 50 mcg BID				MF MDI 100 mcg BID				MF MDI 200 mcg BID			
	Overall		Drug Related†		Overall		Drug Related†		Overall		Drug Related†	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**13**	**(10.8)**	**0**	**(0.0)**	**17**	**(15.0)**	**1**	**(0.9)**	**13**	**(12.0)**	**0**	**(0.0)**
Accidental overdose	13	(10.8)	0	(0.0)	13	(11.5)	1	(0.9)	12	(11.1)	0	(0.0)
Nervous system disorders	**2**	**(1.7)**	**1**	**(0.8)**	**2**	**(1.8)**	**0**	**(0.0)**	**1**	**(0.9)**	**1**	**(0.9)**
Headache	1	(0.8)	0	(0.0)	2	(1.8)	0	(0.0)	1	(0.9)	1	(0.9)
Respiratory, thoracic and mediastinal disorders	**4**	**(3.3)**	**0**	**(0.0)**	**3**	**(2.7)**	**0**	**(0.0)**	**2**	**(1.9)**	**0**	**(0.0)**

	MF DPI 100 mcg QD PM				Placebo				Total			
	Overall		Drug Related†		Overall		Drug Related†		Overall		Drug Related†	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	125		125		112		112		578		578	
with one or more adverse events	49	(39.2)	0	(0.0)	43	(38.4)	1	(0.9)	216	(37.4)	4	(0.7)
with no adverse events	76	(60.8)	125	(100.0)	69	(61.6)	111	(99.1)	362	(62.6)	574	(99.3)
Gastrointestinal disorders	**7**	**(5.6)**	**0**	**(0.0)**	**8**	**(7.1)**	**0**	**(0.0)**	**26**	**(4.5)**	**0**	**(0.0)**
Diarrhoea	3	(2.4)	0	(0.0)	1	(0.9)	0	(0.0)	7	(1.2)	0	(0.0)
Vomiting	1	(0.8)	0	(0.0)	5	(4.5)	0	(0.0)	6	(1.0)	0	(0.0)
General disorders and administration site conditions	**1**	**(0.8)**	**0**	**(0.0)**	**2**	**(1.8)**	**0**	**(0.0)**	**10**	**(1.7)**	**0**	**(0.0)**
Pyrexia	0	(0.0)	0	(0.0)	2	(1.8)	0	(0.0)	9	(1.6)	0	(0.0)
Infections and infestations	**30**	**(24.0)**	**0**	**(0.0)**	**22**	**(19.6)**	**0**	**(0.0)**	**124**	**(21.5)**	**0**	**(0.0)**
Conjunctivitis	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	6	(1.0)	0	(0.0)
Nasopharyngitis	8	(6.4)	0	(0.0)	8	(7.1)	0	(0.0)	36	(6.2)	0	(0.0)
Pharyngitis	2	(1.6)	0	(0.0)	4	(3.6)	0	(0.0)	9	(1.6)	0	(0.0)
Respiratory tract infection	2	(1.6)	0	(0.0)	2	(1.8)	0	(0.0)	8	(1.4)	0	(0.0)
Rhinitis	3	(2.4)	0	(0.0)	1	(0.9)	0	(0.0)	12	(2.1)	0	(0.0)
Upper respiratory tract infection	5	(4.0)	0	(0.0)	4	(3.6)	0	(0.0)	16	(2.8)	0	(0.0)
Injury, poisoning and procedural complications	**12**	**(9.6)**	**0**	**(0.0)**	**15**	**(13.4)**	**0**	**(0.0)**	**70**	**(12.1)**	**1**	**(0.2)**
Accidental overdose	10	(8.0)	0	(0.0)	13	(11.6)	0	(0.0)	61	(10.6)	1	(0.2)
Nervous system disorders	**3**	**(2.4)**	**0**	**(0.0)**	**3**	**(2.7)**	**0**	**(0.0)**	**11**	**(1.9)**	**2**	**(0.3)**
Headache	3	(2.4)	0	(0.0)	2	(1.8)	0	(0.0)	9	(1.6)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	**7**	**(5.6)**	**0**	**(0.0)**	**5**	**(4.5)**	**1**	**(0.9)**	**21**	**(3.6)**	**1**	**(0.2)**

†Determined by the investigator to be related to the drug.
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the "Overall" columns meets the incidence criterion in the report title, after rounding.

Data Source: [16.4]

The majority of AEs were reported in the *Infections and infestations* SOC, particularly upper respiratory tract infections, as would be expected for a paediatric population. Although nasopharyngitis is a common ADR of Asmanex, the incidence is comparable in the placebo arm. The MAH documented accidental overdose. However, it was found that the accidental overdose was due to improper use of the integrated dose-counter without an associated AE in all treatment groups.

Deaths and SAEs

Table 13: Subjects with serious adverse events

	MF MDI 50 mcg BID		MF MDI 100 mcg BID		MF MDI 200 mcg BID		MF DPI 100 mcg QD PM		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	120		113		108		125		112		578	
with one or more adverse events	2	(1.7)	1	(0.9)	2	(1.9)	4	(3.2)	2	(1.8)	11	(1.9)
with no adverse events	118	(98.3)	112	(99.1)	106	(98.1)	121	(96.8)	110	(98.2)	567	(98.1)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.9)**	**0**	**(0.0)**	**1**	**(0.8)**	**0**	**(0.0)**	**2**	**(0.3)**
Dyspepsia	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Enteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.2)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.9)**	**2**	**(1.6)**	**0**	**(0.0)**	**3**	**(0.5)**
Appendicitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.2)
Gastroenteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.2)
Otitis media	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.2)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.8)**	**0**	**(0.0)**	**1**	**(0.2)**
Headache	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.2)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Suicide attempt	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	**2**	**(1.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(1.8)**	**4**	**(0.7)**
Asthma	2	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.8)	4	(0.7)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Data Source: [16.4]

Asthma was the only SAE that led to discontinuation from the study. Four out of eleven SAEs were due to asthma, two of these patients were in MF MDI 50 mcg treatment group and 2 were in the placebo group. This supports the efficacy results. The other reported SAEs include common health issues in children aged 5-11 years, and do not raise any major concerns. No deaths were reported

Laboratory and other vital signs

No laboratory abnormalities were reported. There were no clinically meaningful differences in the changes from baseline in vital signs between treatment groups across the 12 week treatment period that would suggest a safety issue.

Safety conclusions

A total of 578 paediatric subjects were exposed to at least one dose of study medication. The daily dose ranged from 100 mcg to 400 mcg for a maximum of 3 months. Nasopharyngitis was the commonest AE. There were no unexpected AEs in comparison with the known safety profile of Asmanex 200 mcg Inhaler. Reported SAEs included 4 cases of asthma, two from the MF MDI 50 mcg group and 2 from the placebo group, likely due to lack of efficacy.

Overall, MF MDI 50-200 mcg BID, as well as MF DPI 100 mcg QD, appear to be safe and well tolerated when administered to children aged 5-11 years with persistent asthma for up to 3 months. The duration of exposure is insufficient to characterise longer-term effects.

IV.2.3. Assessment of responses to request for supplementary information

Question 1

Provide a summary on the approach used to choose the investigator sites for an audit.

Summary of MAH's response

The objective of the audit is to provide a systematic, quantitative assessment of the effectiveness of the Quality Control function (QC) of Merck monitored sites. This process audit was conducted on a statistically-defined sample of all clinical study sites monitored by Merck across all therapeutic areas and phases. The five sites audited in protocol MK-0887-086 were selected randomly.

Assessment of MAH's response

The MAH has clarified that the audited sites were selected randomly. This approach is acceptable.

Conclusion

Point resolved

Question 2

Provide clinically meaningful difference to detect improvement with the PAQLQ(s) questionnaire.

Summary of MAH's response

The Paediatric Asthma Quality of Life Questionnaire is a validated tool that contains 23 items across three domains that children with asthma have identified as troublesome in their daily lives. Minimal important differences between treatment groups in change from baseline scores tend to converge at 0.50 for other QLQ evaluations with similar scales. The PAQLQ(s) is consistent with this trend. According to Juniper and colleagues, the minimal important difference in quality of life in children 7-17 years of age was demonstrated to be 0.42 with fairly similar values for the symptom (0.54) and activity (0.70) domains but a somewhat lower value for the emotional function domain (0.28). For further information, please review the attached reference: [Ref. 5.4: 03P3RP].

Assessment of MAH's response

The MAH has discussed the minimal clinically important difference (MCID) for the individual domains and the overall score of the PAQLQ, based on evidence from the literature. PAQLQ items are equally weighted and results are expressed as the mean score per item for each domain as well as for overall quality of life. The domain and overall scores range from 1 to 7. The MCID is 0.42 for the overall score.

For study P04223aAM3, the subject of this article 46 procedure, the PAQLQ overall scores are summarised in table 8. The mean difference in LS means from placebo for changes from baseline in overall score at week 12 were 0.10, 0.12, 0.18, 0.22 and -0.12 for the MF MDI 50 mcg BID, MF MDI 100 mcg BID, MF MDI 200 mcg BID and MF DPI 100 mcg QD treatment groups. These treatment differences compared to placebo are not likely to be clinically important based on the reported MCID.

Conclusion

Point resolved

Question 3

Justify as to why HPA axis safety assessment was not considered.

Summary of MAH's response

The Sponsor has previously evaluated the systemic safety of mometasone furoate in children as part of the development of mometasone furoate inhalation powder (MF DPI; ASMANEX® TWISTHALER®). A summary of the hypothalamic pituitary adrenal (HPA) axis study and 3 relevant pharmacokinetic studies bridging MF DPI and MF MDI are provided. Additional information can be found in the investigator brochure [Ref. 5.3.5.4: 04FYX2].

In support of the clinical development in the paediatric population of children 4 to 11 years of age, the Sponsor conducted an HPA axis study (C96-361) to evaluate systemic safety. In that study, a 100 mcg BID dose of MF DPI showed no evidence of HPA axis suppression relative to placebo, based on mean plasma cortisol AUC and response to cosyntropin stimulation.

Moreover, in the same study, although doses of MF DPI 200 mcg and 400 mcg BID caused a significant decrease in plasma cortisol AUC relative to placebo, the degree of suppression was not considered to be clinically important since all but one patient (in the 400 mcg BID group) had a normal response to the cosyntropin stimulation test.

Additionally, the Sponsor has also conducted three multiple-dose pharmacokinetic (PK) studies evaluating the systemic exposure of MF administered from an MF MDI relative to the dose of MF administered from the dry powder inhaler (MF DPI). The Sponsor initially conducted two PK bridging studies, one in healthy subjects (P04275) at twice the maximum recommended adult dose and the second in patients with COPD at the maximum recommended adult dose (P04689), the primary objective of which was to evaluate the systemic exposure of MF following administration from an MDI relative to the marketed DPI (ASMANEX® TWISTHALER®) for which there is extensive safety experience. The PK data from these two studies showed a modestly lower systemic availability from the MDI compared to the DPI (25% and 23% lower, respectively, based on AUC) after multiple dosing to steady state (5 days). These two comparative studies were conducted using the highest dosage strength MF/F MDI formulation (200 mcg/5 mcg). Subsequently, the Sponsor conducted a third relative bioavailability study (P05527) using the lowest dosage strength MF/F MDI formulation (50 mcg/5 mcg). The results of this study (are consistent with the two previous studies (P04275 and P04689) in showing lower mean systemic bioavailability of MF from the MDI relative to the DPI, although with a larger difference (39%).

The results of all three studies, two in healthy volunteers and one in patients with COPD and across a dose range of MF/F MDI 100 mcg/10 mcg to 800 mcg/20 mcg BID, consistently show that the systemic exposure to MF is lower (mean 23-39% lower based on AUC) after

administration via an MDI versus the same dose administered via DPI. Consequently, these data demonstrate that the relevant data generated in Protocol MK-0887-C96-361, the paediatric HPA axis study, can be bridged to MF/F formulations.

Based on the aforementioned data, the Sponsor concluded that the MF/F MDI dose(s) used in the PN087 Phase III efficacy and safety study would not require further HPA axis evaluation since the same doses of MF administered via DPI (i.e., 100 mcg or 200 mcg BID; C96-361) were shown to have no HPA axis effect based on comparable changes on serum cortisol AUC to placebo and/or a normal response to cosyntropin stimulation.

Assessment of MAH's response

The assessment of the systemic effects of inhaled corticosteroids should include an appropriate sensitive measure of hypothalamic pituitary adrenocortical (HPA) axis function, in line with the *Guideline on the clinical investigation of medicinal products for the treatment of asthma* (CHMP/EWP/2922/01 Rev.1). Based on three PK studies in adults, the MAH concludes that the systemic bioavailability of MF from MDI is lower than that from an equivalent dose administered by DPI, across a relevant dose range. Therefore the results of the HPA axis study (C96-361), a Phase 1 study in children, can be extrapolated to an MF MDI dose up to 400 mcg BID. The justification for not conducting a separate study using MF MDI is acceptable. It appears that MF DPI 100 mcg BID has less effect on the HPA axis than 200 mcg BID and 400 mcg BID, as would be expected.

Conclusion

Point resolved

Question 4

Present the number of missing data at each assessment visit. Reasons for missing should be provided too.

Summary of MAH's response

The number and percent of subjects with missing percent predicted FEV1 evaluations (which were used to construct the primary endpoint), are provided for each analysis timepoint by treatment group. In addition, missing data are further categorized by reasons for being missing. The percentage of subjects with at least one missing evaluation ranged from 38.0% in the MF MDI 200 mcg BID group to 51.4% in the placebo group. The majority of these missing evaluations were in later timepoints driven by subjects who discontinued early. Throughout the 12 week evaluation period, additional missing data was observed due to excluding FEV1 measurements obtained after the use of short-acting betaagonist (SABA) and/or other prohibited medications, as well as missing data due to missed scheduled visits and/or not performing the procedures at a given visit.

Assessment of MAH's response

The MAH has presented the number and percent of missing data for predicted FEV1 at each assessment visit, by treatment group (FAS). The number and percent of missing were presented overall and by reason of missing (discontinuation, missing schedule visit, and or not performing procedures, missing due to SABA and/or other prohibited medication). The proportions of patients with missing data were higher in the placebo (51.4%) and MF MDI 100 mcg (46.4%) groups compared to the other groups. The proportions of patients with missing data generally increased with time in all groups, irrespective of the reasons for missing data. Discontinuation was the main reason for missing data. At all visits, the proportions of patients who discontinued from the study were higher in the Placebo group compared to the MF MDI and MF DPI groups. The proportions of patients with missing data due to missing visits and / or not performing procedures was generally higher in the MF MDI 50 mcg group compared to all other groups. The proportions of patients with missing data due to SABA and/or other medication use were variable depending on the visit.

Also see response to Question 11 re patients without baseline values for FEV1.

Conclusion

Point resolved.

Question 5

Provide summary of FEV1 at each assessment based on observed data.

Summary of MAH's response

A summary of observed percent predicted FEV1 at each analysis timepoint is provided. For completeness, a summary of observed FEV1 in liters (L) is also provided.

Assessment of MAH's response

The MAH has provided a summary of percent predicted FEV1 and observed FEV1 at each assessment visit based on all available data. The mean change in percent predicted FEV1 from baseline ranged from: 2.56 (MF MDI 50 mcg) to 6.99 (MF MDI 100 mcg) in the MF MDI groups, -0.09 to 4.13 in the Placebo group, and 2.60 to 3.71 in the MF DPI 100 mcg group. The results are consistent with the primary analysis where the mean change in %predicted FEV1 at Week 12 ranged from 5.57 (MF MDI 50 mcg) to 7.45 (MF MDI 100 mcg) in the MF MDI groups. The mean change in %predicted FEV1 was 3.59 in the Placebo and 3.97 in the MF DPI 100 mcg. These results demonstrate that patients who received MF MDI 100 mcg derived the greatest benefit in term of change from baseline in % predictive FEV1.

Conclusion

Point resolved.

Question 6

Clarify why there are discrepancies between the means and the LS means in the placebo group for both FEV1 and PEF.

Summary of MAH's response

Descriptive means, which are based on subjects with both Baseline and Week 12 data, are likely to deviate from LS means estimated from the constrained longitudinal data analysis (cLDA) model, since the cLDA model incorporates all of the Baseline data across the five treatment arms to calculate the LS means of change from baseline scores. Differences between Week 12 descriptive means and LS means of the change from baseline measurement are expected to be most pronounced in the placebo group given that the lowest completion rate of 53.6% was observed in this group compared to other treatments.

Percent Predicted FEV1 at Week 12

Baseline Percent Predicted FEV1 is reported as 77.82 among 110 placebo group subjects. However, the mean change of 3.59 is based on the 62 placebo group subjects with both Baseline and Week 12 data. For these 62 subjects, the mean Baseline of 76.13 was subtracted from their Week 12 score of 79.73 for a change of 3.59. In the constrained longitudinal analysis (cLDA), Baseline scores across all 552 subjects with a Baseline in the analysis dataset are used, where the LS mean Baseline score of 78.72 was subtracted from a Week 12 LS mean score of 79.39 for a change of 0.66. These results are provided in Table 11-1 of the clinical study report. Therefore, the difference in descriptive means and LS means can be attributed to the difference of 2.59 between the mean and LS mean at Baseline in addition to the adjustments of other model terms.

AM Peak Flow Rate at Week 12

Baseline AM Peak Flow is reported as 214.54 among the 110 placebo group subjects. However, the descriptive mean change of -8.18 is based on the 61 placebo group subjects with both Baseline and Week 12 data. For these 61 subjects, the mean Baseline of 224.12 is subtracted from their Week 12 score of 215.94 for a change of -8.18. In the cLDA model, Baseline scores across all 571 subjects with a Baseline in the analysis dataset are used, where the LS mean Baseline score of 204.67 was subtracted from a Week 12 LS mean score of 203.35 for a change of -1.32. These results are provided in Table 11-2 of the clinical study report. Therefore, the difference in descriptive means and LS means can be attributed to the difference of 19.45 between the descriptive mean and LS mean at Baseline in addition to the adjustments of the other model terms.

Assessment of MAH's response

The MAH has clarified the discrepancies between the means and the LS means in the placebo group for both FEV1 and PEF and the response is considered satisfactory. Some patients had missing baseline values for FEV1 (see also response to Question 4), therefore as the constraint longitudinal data analysis model incorporates all of the baseline data across the five treatment arms, the means and the LS means of change from baseline will be different. It agreed that

these differences will be more pronounced in the Placebo group as this group had the lowest completion rate (53.6%). A total of 62 patients in the placebo group had data at baseline and at Week 12. The discrepancies between the means and the LS means of change from baseline in PEF are due to the missing data since only 61 patients in the placebo group had data for PEF at baseline and at Week 12.

Conclusion

Point resolved.

Question 7

Provide estimates of treatment effects derived from the primary cLDA model using BOCF to impute missing data. Other methods for imputing missing data that penalises subjects after drop-out could also be considered.

Summary of MAH's response

Post-hoc analysis on the primary endpoint based on the cLDA model using the baseline observation carried forward (BOCF) imputation was performed. For the BOCF imputation, only missing values at analysis timepoints (e.g., Week 8, Week 12) after discontinuation were imputed using the baseline value within individual subject.

In the primary analysis, the MF MDI versus placebo Percent Predicted FEV1 effect sizes were 3.87, 6.29, and 5.34 percentage points across the 50 mcg BID, 100 mcg BID, and 200 mcg BID doses, respectively (P≤0.019), as provided in Table 11-1 of the clinical study report. When applying BOCF , the MF MDI versus placebo effect sizes were reduced to 2.23, 3.44, and 2.97 percentage points for the 50 mcg BID, 100 mcg BID, and 200 mcg BID doses, respectively. Statistical significance was not maintained for the lowest dose (P=0.065) but was maintained for other MF MDI doses. Given that the statistical significance was maintained for the 100 and 200 mcg BID doses (P≤0.017), coupled with a similar overall dose response pattern (the peak of the dose response curve begins at the 100 mcg BID dose), the decision to select MF MDI 100 mcg BID for Phase III is robust under the baseline imputation penalty for subjects after drop-out.

Assessment of MAH's response

The MAH performed a sensitivity analysis based on the cLDA primary analysis model with missing data imputed using BOCF, as requested. The MF MDI versus placebo effect sizes were 2.23 (MF MDI 50 mcg), 3.44 (MF MDI 100 mcg), and 2.97 (MF MDI 200). These effects sizes are smaller but consistent with those obtained from the primary analysis model; showing a greater efficacy in the MF MDI 100 mcg group compared to the other two MF MDI groups (p=0.005).

Conclusion

Point resolved.

Question 8

Present estimates of treatment effects derived from an ANCOVA model adjusted for baseline FEV1, age, and region based on Week 12 data.

Summary of MAH's response

Post-hoc analysis on the primary endpoint based on an ANCOVA model adjusted for baseline percent predicted FEV1, age and region was performed and the results are summarized . Using observed data only from Week 12, the MF MDI versus placebo effect sizes were 3.36, 4.66, and 3.44 percentage points for the 50 mcg BID, 100 mcg BID, and 200 mcg BID doses, respectively. Given that statistical significance was maintained for all MF MDI doses (P≤0.044), coupled with a similar overall dose response pattern as the primary analysis (the peak of the dose response curve begins at the 100 mcg BID dose), the decision to select MF MDI 100 mcg BID for Phase III is robust under the ANCOVA method of analysis.

Assessment of MAH's response

The MAH has presented estimates of treatment effects derived from an ANCOVA model adjusted for baseline FEV1, age, and region, based on Week 12 data as requested. The MF MDI versus placebo effect sizes were 3.36 (MF MDI 50 mcg), 4.66 (MF MDI 100 mcg), and 3.44 (MF MDI 200). The dose response pattern is consistent with the primary analysis showing a greater efficacy in the MF MDI 100 mcg group (p=0.005) compared to the other MF MDI groups

Conclusion

Point resolved.

Question 9

Present estimates of treatment effects in the pre-specified subgroups based on a model consistent with the primary analysis.

Summary of MAH's response

Post-hoc analysis was performed for each pre-specified subgroup using the cLDA model applied to the primary analysis. Tables are presented below in the order provided in the clinical study report where subgroups were presented using summary statistics: Age, race , region , and sex . Consistent with what was reported in the clinical study report, results across pre-specified subgroups were generally similar to that of the primary analysis. However, caution must be applied to subgroups with low numbers of subjects due to the inherent variability associated with

small sample sizes.

Assessment of MAH's response

The MAH has presented estimates of treatment effects in the pre-specified subgroups (age, race, region, and sex) estimated from a constrained longitudinal data analysis model. It is agreed that the results are generally consistent with the primary analysis model. These results support the selection of the MF MDI 100 mcg dose for the Phase III study.

Conclusion

Point resolved.

Question 10

Explore the dose-response relationship using a model based approach rather than pairwise comparisons.

Summary of MAH's response

The MCP-MOD (Multiple Comparison Procedures-Modeling) method was applied to the primary endpoint of change in percent predicted FEV1 from baseline to Week 12 as an exploratory analysis. The MCP-MOD [Ref. 5.4: 04H7QP] is a hybrid method to explore dose-response (DR) by combining multiple comparison procedures with a modelling approach. Four candidate DR models including linear, Emax, sigmoid Emax, and quadratic model were evaluated based on results of the primary analysis from four treatment groups: MF MDI 50 mcg BID, MF MDI 100 mcg BID, MF MDI 200 mcg BID, and placebo. The minimum effective dose (ED) was defined as the dose which gives 90% of the maximum effective dose within the dose range from 0 mcg BID to 200 mcg BID, using the model selected. While there is no general consensus on the cutoff of 90%, this choice is based on a suggestion from the PhRMA white paper [Ref. 5.4: 04H7Q3] and the upper limit of the 'dose range' definition introduced by MacDougall [Ref. 5.4: 04H8DC].

The MCP-MOD analysis was implemented by the "DoseFinding" package in software R. The Emax model was selected as the best model based on the Akaike information criterion, with an estimated ED of 102.9 mcg BID for the MF MDI. Therefore, the closest available manufactured dose of MF MDI 100 mcg BID is supported with this model-based approach. The output from the MCPMod() function of "DoseFinding" package is summarized in Table 10 below.

Table 10

MCP-MOD Output from DoseFinding Package in Software R Based on Change in % Predicted FEV_1 at Week 12 (Full-Analysis-Set)

Multiple Contrast Test			Model Selection Criteria (AIC)	Estimated Minimum Effective Dose
Model	t-Stat	Adjusted p-value		
sigEmax	3.884	<0.001	8.352552	n/a
emax	3.865	<0.001	7.243798	102.8937
linear	3.007	0.0040	11.489097	n/a
quadratic	2.235	0.0331	n/a	n/a

Assessment of MAH's response

The MAH used the MCP-MOD method to explore the dose-response relationship. The approach was recently qualified by the EMA as an efficient statistical methodology for model-based design and analysis of Phase II dose-finding studies. The MAH defined the minimum effective dose as the dose which gives 90% of the maximum effective dose within the dose range from 0 mcg BID to 200 mcg BID. Model selection was based on the Akaike information criterion (AIC), were low AIC indicates a better fit. This is an acceptable strategy for model selection.

The choice of the 90% cut-off point to determine the minimum effective dose was based on suggestion from PhRMA white paper and the upper limit of `dose range' definition introduced by MacDougall. The minimum effective dose was estimated to be 102.9 mcg BID for MF MDI. This dose is very close to the proposed to the manufactured MF MDI 100 mcg BID dose selected for the Phase III study.

Conclusion

Point resolved

Question 11

Clarify why 20 subjects did not have baseline FEV1 considering that FEV1 was used to assess eligibility criteria (criteria # 3).

Summary of MAH's response

The sponsor recognizes that there are 20 treated subjects without baseline % predicted FEV1. Nineteen subjects had data on pulmonary function test in the clinical database, and 1 subject was treated but with no data available.

Screening FEV1 data was collected at visit 1 and baseline FEV1 data was collected at visit 2 in this trial. For patients with missing baseline FEV1 data, this could be due to not performing spirometry at all or having their spriometry data graded as unacceptable. The patients who did not perform spirometry were categorized as protocol deviations. The remaining patients did perform spirometry at visit 2. However, subsequently these data were graded as unacceptable by an external spirometry central vendor and are therefore missing from the analysis database.

Even though these subjects did not have a baseline evaluation, those qualifying for the full-analysis-set (i.e., with at least one post-randomization measurement) were included in the primary analysis in alignment with the statistical analysis plan.

Assessment of MAH's response

The MAH explains that missing baseline FEV1 could be due to not performing spirometry at all or having spirometry data graded as unacceptable by an external spirometry central vendor. Patients who did not perform spirometry were categorised as protocol deviations whereas those with unacceptable FEV1 were treated as missing. In the primary analysis, the FAS included patients with baseline and or at least one post-baseline measure, therefore some of these subjects may have been included in the analysis if they have at least one post-baseline measure. Results from the primary analysis based on the per-protocol population, in which patients with missing FEV1 due to not performing spirometry are excluded from the analysis, were consistent with the primary analysis.

Conclusion

Point resolved.

Question 12

Indicate the number of subjects with baseline observations only.

Summary of MAH's response

The last FEV1 measurement after randomization from subjects who received at least one dose of randomized treatment with baseline observations only and no post-baseline FEV1 observations are listed. For each of the four active treatment groups, three subjects reported baseline observations only, and 8 subjects reported baseline observations only in the placebo group. The higher number of placebo group subjects reporting baseline observations only is consistent with the pattern of early discontinuations, since the rate of early discontinuations was highest in the placebo group.

Assessment of MAH's response

The MAH has provided a listing of patients who received at least one dose of study medication with baseline information only by treatment group. There were 6 such patients in the Placebo group and 3 patients in each of the active groups.

Conclusion

Point resolved.

Question 13

List the variables that were evaluated using interval average and those that were evaluated using data at Week 12 from diary data.

Summary of MAH's response

All diary data were collected daily. This includes variables as outlined in Table 12 below. For Week 12, all variables were evaluated using the interval average across days 79 through 85.

Table 12

Derived Diary Variables

Variable	*Label*
WHEZ	Wheezing *(Baseline, Change, Percent Change)*
BRTH	Difficulty Breathing *(Baseline, Change, Percent Change)*
COGH	Cough *(Baseline, Change, Percent Change)*
ASM	Total Asthma Symptom Score *(Baseline, Change, Percent Change)*
RESC	Amount of Rescue Medication Taken *(Baseline, Change, Percent Change)*
NEB	Number of Nebulized Treatments *(Baseline, Change, Percent Change)*
PKFLRT	PEFR Peak Flow Rate *(Baseline, Change, Percent Change)*
AWAKE	Number of Awakenings *(Baseline, Change, Percent Change)*
TRESC	Total Rescue Medication Taken *(Baseline, Change, Percent Change)*

Assessment of MAH's response

The MAH has indicated that all diary data were evaluated using interval average across days 79 through 85 (see response to Questions 14 and 15) and has listed these variables.

Conclusion

Point resolved.

Question 14

Present the number of observations with missing interval data by treatment group for all interval averages for diary data.

Summary of MAH's response

For analysis purpose, diary data were averaged over pre-specified time windows to obtain weekly values that were used as the actual response variable. Missing daytime and night time diary data are provided under the full analysis set for each analysis week of diary, as well as those with at least one missing analysis week (Any). The percentage of subjects with at least one week of missing daytime diary data was lowest among the MD MDI 200 mcg BID dose group (24.1%), with similar percentages across the lower doses of MF MDI and DPI 100 mcg BID (30.1% to 33.9%), and the highest percentage in the placebo group (45.0%). Night-time diary data reported similar percentages with the lowest and highest percentage of missing data in the MF MDI 200 mcg BID and placebo groups, respectively.

Assessment of MAH's response

The MAH has presented the number of patients with missing diary data by treatment groups. The proportions of patients with missing data were higher in the Placebo group compared to the active groups in both daytime and night-time diary data. The proportions of patients with missing data were generally comparable across the MF MDI groups. In all groups the proportions of missing data increased over time.

Conclusion

Point resolved.

Question 15

Clarify the minimum number of observations that was required to derive average interval data, if such requirement was applied.

Summary of MAH's response

The minimum number of observations required to derive an average for a given interval was one observation. Therefore, intervals were set to missing only if there were no data in that interval.

Assessment of MAH's response

The MAH has clarified that average was derived based on all available data with no minimum requirement for the number of non-missing observations. Therefore the average interval data should be interpreted with caution because of the varying available information at the individual level on which the average is computed; the interval average may represent a week worth of

data or in some patients it may just the value for a single time-point.

Conclusion

Point resolved.

Question 16

Present the number of observation with missing Week 12 data for diary data. Summaries should be presented based on observed data.

Summary of MAH's response

The number of subjects with missing Week 12 diary data was provided in Table 13 and Table 14 for the daytime and night-time diary data, respectively. Percentages of missing Week 12 daytime diary data were as follows: MF MDI 50 mcg BID (33.1%); MF MDI 100 mcg BID (29.5%); MF MDI 20 mcg BID (23.1%); MF DPI 100 mcg BID (29.3%), and placebo (44.1%). The same percentages were reported in the night-time diary for MF MDI 50 mcg BID, MF MDI 100 mcg BID, MF MDI 20 mcg BID, and MF DPI 100 mcg BID with the exception of placebo (45.0%). Given Week 12 is the final week of diary evaluation, the percentage of missing data was driven primarily by subjects who discontinued prior to the Week 12 evaluation interval.

Assessment of MAH's response

The MAH has presented the requested information.

(See answer to Question 15)

Conclusion

Point resolved.

Question 17

Discuss the increase in SABA usages in the MF MDI groups in particular in the 100 and 200 mcg MP MDI doses. The Applicant is requested to indicate if there are any subjects who used SABA outside the acceptable time frame of 6 hours before the first am evaluation of FEV1 and how their data were handled in the efficacy assessment. The impact of the use of SABA, outside the allowable window, on estimates of treatment effects should be evaluated through sensitivity analyses excluding these subjects from the primary analysis.

Summary of MAH's response

SABA Usage in MF MDI 100 and 200 MF MDI mcg BID

Upon review of the Week 12 rescue PM medication usage, LS mean changes in total SABA use (TRESC) were less than zero for all treatment groups with the exception of the MF MDI 100 mcg BID dose (an increase of 0.17 puff use units). No increase use trend was observed in the MF MDI 200 mcg BID treatment group. For the MF MDI 100 mcg BID dose, when examining the hand-held SABA device (RESC) and the nebulized treatments (NEB) separately, the increase in total SABA use was attributed to the nebulizer treatment, as the LS mean change from baseline for the hand-held and nebulized treatments were -0.08 puff use units and +0.17 nebulized uses, respectively. When combining hand-held and nebulized treatments for total SABA use, one nebulized treatment is calculated as 6 units and added to the number of hand-help puff units. Specifically, a hand calculation of -0.08 + 6 x 0.17 = 0.94 puff units, confirming the LS mean increase of 0.96 puff units at the Week 12 PM evaluation.

Review of the individual subject responses at Week 12 for PM nebulizer use revealed one outlier subject driving the increase. Among the 79 observed cases at Week 12 for MF MDI 100 mcg BID, Subject 103532 reported 20 nebulizer uses, while the other 78 subjects reported no nebulizer use at this time-point. Since subject 103532 did not report nebulizer use at Baseline, , excluding this subject's nebulizer use from the Week 12 analysis would result in a decrease in total SABA rescue use of -0.08 (matching the hand-held SABA device estimate) given there would be no contribution of nebulized treatments to the Week 12 estimate. Since the patient had no nebulizer treatments at baseline and there are no other adverse event data to corroborate such a dramatic clinical worsening of asthma, it is possible this entry represents a reporting error.

The Impact of SABA Use on Estimates of Treatment Effects

The primary analysis is based on FEV1 evaluations performed in the AM upon rising and free of other medications including SABA use. Therefore, subjects' FEV1 evaluations within 6 hours of SABA use were excluded from the primary analysis, provided below in Table 15 for quick reference. As provided 1 to address COMMENT 4 on reasons for missing data, the number of observations excluded from the Week 12 primary time-point due to SABA use and/or other prohibited medications was low, ranging from 3 subjects each in the MF MDI 50 and 100 mcg BID treatment groups (2.5% and 2.7% of the FAS, respectively), to 5 subjects each in the MF DPI 100 mcg QD and placebo treatment groups (4.1% and 4.5% of the FAS, respectively). To assess the potential impact of SABA use and/or other prohibited medications within 6 hours of FEV1 evaluation, an "All Available Data" analysis was performed on the FAS, provided below in Table 16, which also includes FEV1 evaluations performed within 6 hours of SABA use and/or other prohibited medications. In the primary analysis, the MF MDI versus placebo Percent Predicted FEV1 effect sizes were 3.87, 6.29, and 5.34 percentage points across the 50 mcg BID, 100 mcg BID, and 200 mcg BID doses, respectively ($P \leq 0.019$). When including all evaluations with SABA use and other medications within 6 hours for the all available data analysis, the MF MDI versus placebo effect sizes were reduced to 3.60, 5.48, and 5.00 percentage points the 50 mcg BID, 100 mcg BID, and 200 mcg BID doses, respectively ($P \leq 0.029$). Even though the inclusion of SABA and prohibited medication use FEV1 evaluations reduced the effect sizes by 0.27 to 0.81 percentage points due to the dilution created by adding these post-medication-use evaluations, the overall dose response profile did not change. Therefore, the decision to move forward with the MF MDI 100 mcg BID to Phase III was robust under consideration of the all available data sensitivity analysis.

Assessment of MAH's response

The MAH identified one patient amongst the 79 patients observed cases who reported 20 nebulizer uses while the remaining78 patients did not report any uses. The MAH has presented an analysis excluding this patient's nebulizer use from the Week 12 analysis. This approach is endorsed. When this patient is excluded, there is a trend towards reduction in SABA use compared to baseline in all treatment groups.

The MAH conducted a sensitivity analysis including FEV1 evaluations within 6 hours of SABA use. The results are supportive of the primary analysis, and the decision to select MF MDI 100 mcg BID for further evaluation in Phase 3.

Conclusion

Point resolved

Question 18

Present proportions of patients with more than one evaluation per visit in each treatment group.

Summary of MAH's response

The number and percent of subjects with more than one evaluation within an analysis time-point is provided for each treatment group. The number of such cases was low. Among the six time-points evaluated across each of the five treatment arms, half (15) reported no cases of more than one evaluation. The highest proportion was observed at Week 8 for MF MDI 100 mcg BID (5 cases for 4.5%). At the Week 12 primary analysis time-point, only one case of more than one evaluation per analysis time-point was observed, in the MF MDI 50 mcg BID treatment group (0.8%).

Assessment of MAH's response

The MAH has presented the proportions of patients with more than one evaluation per visit, as requested. The number of patients with more than one evaluation is very low. The highest proportion was observed at Week 8 for the MF MDI 100 mcg group (4.5%) and only 1 case (MF MDI 50 mcg) was observed at Week 12.

Conclusion

Point resolved.

Question 19

Justify the use of LOCF to impute missing Week 12 diary data.

Summary of MAH's response

The Sponsor wants to clarify that no LOCF algorithm was applied to derive the diary endpoints at Week 12, the weekly diary evaluations were prepared for analysis using only the observed data at the appropriate days of blinded treatment. Specifically, the Week 12 evaluation consists of an interval average across days 79 through 85 of blinded treatment.

Table 18 below is extracted from the derived database specifications which outline a complete set of intervals across Baseline and each of 12 Weeks across the blinded treatment period. Note each weekly interval only includes evaluations collected within the respective days of that week. For Week 12, no previous Weeks' data were included in that interval.

In the analysis, the weekly intervals were considered repeated measures in a single model used to extract least square means for each interval. Therefore, the sample sizes provided in the Week 12 table included any subject with at least one evaluation across Baseline through Week 12, even though not all subjects in the sample size column reported Week 12 evaluations.

In summary, LOCF was not applied to imputation of missing Week 12 diary data in the analysis.

Assessment of MAH's response

The MAH clarified that no LOCF algorithm was applied to diary data at Week 12. The weekly data was prepared using only observed data (days 79 through 85). The MAH has presented the range of days over which the average was computed corresponding to each week. (See response to Question 15).

Conclusion

Point resolved.

Question 20

Indicate in which countries the quality of life questionnaire (PAQLQ[S]) was administered.

Summary of MAH's response

The PAQLQ[S] was administered to 541 of the 583 subjects randomized in the trial. The following countries provided PAQLQ[S] data: Bulgaria, Columbia, Croatia, Estonia, Greece, Guatemala, Hungary, Latvia, Poland, Romania, Russian federation, Serbia, South Africa, Switzerland, Ukraine, and the United States. Missing evaluations occurred in Guatemala (9/93 subjects) and the United States (13/93 subjects). Mexico, with 20 randomized subjects, was the

only country in the trial that did not provide PAQLQ[S] data.

Assessment of MAH's response

According to the clinical study report, the PAQLQ was only administered when a validated translated questionnaire was available. In fact the majority of subjects provided data for this endpoint, and therefore the data is relatively robust.

Conclusion

Point resolved

Question 21

The MAH should clarify whether the current study results will be used to support an indication for Asmanex Twisthaler 200 micrograms Inhalation Powder in children aged 6-12 years as a potential type II variation (Refer to Annexure I for further details).

Summary of MAH's response

The Sponsor submitted the phase 2 clinical study data (PN086) to comply with the Article 46 requirements. As described in previous documents, PN086 was a dose ranging study that included a DPI arm for reference. The Sponsor will consider the Agency's suggestion to submit a type II variation for Asmanex Twisthaler 200 micrograms Inhalation Powder in children aged 6-12 years.

Assessment of MAH's response

This question was added to the RSI as a result of the day 85 comment by SE.

The MAH would need to consider the following before submitting a type II variation of Asmanex Twisthaler 200 micrograms Inhalation Powder to add an indication in children aged 6-12 years:

1. Asmanex is a 200 mcg strength MF DPI whereas study PN086 studied several strengths of MF MDI in addition to a 100 mcg strength MF DPI. Based on the results of this study, the 100 mcg MDI formulation dosed BID appears to be optimal in the 6-12 years age group.

2. According to the *Guideline on the clinical investigation of medicinal products for the treatment of asthma* (CHMP/EWP/2922/01 Rev.1), long-term safety assessment of at least one year duration is required in children.

Therefore, based on the available evidence, a posology for the 6-12 year age group is not recommended for Asmanex Twisthaler 200 micrograms Inhalation Powder or Asmanex Twisthaler 400 micrograms Inhalation Powder.

Conclusion

Point resolved

Supplemental Questions - Additional LoQ's in the Article 46 Document not Assigned an Agency Comment Number

Question

The Applicant is requested to justify why randomisation was not stratified by centre/region, in line with the recommendations in the ICH E9 (Statistical Principles in Clinical Trials) that apply to multicentre trials.

Summary of MAH's response

A considerable effort was applied to ensure an adequate number of younger subjects were included in the enrolment, and stratified randomization was performed to ensure balance across treatments for these younger subjects. Given the expectation adequate numbers of subjects would be randomized within each of three regions with reasonable balance between treatment groups, further stratification was not applied for region.

Even though a formal stratification for region was not applied, a review of the treatment by region sample sizes support balance across treatment within region. In summaries of adverse events by region, North America reports 16 to 21 subjects across the five treatment regimens; Latin America reports 27 to 30 subjects; and the EU reports 64 to 77 subjects (64 to 70 subjects when excluding the MF DPI 100 mcg QD PM active control arm). Relative to the total of 112 to 125 subjects across the five treatment regimens, subjects are well balanced across treatment group within each region despite not stratifying by region.

Assessment of MAH's response

The MAH explained that it was expected that stratification by region was not employed as it was expected that adequate numbers of subjects would be randomised within each three regions with reasonable balance between the treatment groups. It can be agreed that the sample sizes were generally balanced across the treatment groups within each region.

Conclusion

Point resolved.

Question

The Applicant is requested to present the discontinuation rates at each assessment visit by treatment groups.

Summary of MAH's response

The cumulative discontinuation rate across different timepoints during the study is provided for the Full-Analysis-Set population used in the efficacy analysis. As expected, the pattern of discontinuation across visits is highest in the placebo group, accumulating to 45.9% at the end of the trial (i.e. Week 12). A monotone decrease in cumulative discontinuation rate is observed across the three MF MDI doses, ranging from 23.1% in the MF MDI 200 mcg BID treatment group to 33.1% in the MF MDI 50 mcg BID treatment group.

Assessment of MAH's response

The discontinuation rates at the end of the trial were higher in the Placebo group (45.9%) compared to the active groups at all time (range: 23% to 33.1%). Discontinuation rates increased in all groups over time, with the Placebo discontinuation rates consistently higher than the active groups.

Conclusion

Point resolved.

IV.2.4. Discussion on clinical aspects

The MAH submitted the final clinical study report of a phase 2 dose-finding study of mometasone furoate metered dose inhaler (MF MDI 50 mcg BID, MF MDI 100 mcg BID, and MF MDI 200 mcg BID) in the treatment of children aged 5 to 11 years with persistent asthma. The purpose of this study was to determine which dose to assess in the phase 3 part of the paediatric mometasone furoate and formoterol (MF/F) fixed dose combination program.

Design and conduct
This was a 12-week, multicentre, randomized, double-blind, double-dummy, placebo-controlled efficacy and safety study. The primary objective of this study was to assess dose-response related efficacy based on the change from baseline at Week 12 in % predicted FEV_1 in children aged 5 to 11 years. The secondary objectives included dose-related efficacy in PEF and PAQLQ[S] score when compared to placebo and efficacy of MF MDI 50 mcg BID vs MF DPI 100 mcg once a day. Following the assessment of the MAH's responses to the request for supplementary information, there are no outstanding concerns regarding the study design or conduct.

A total of 583 subjects were randomised. Children aged 7-11 accounted for the majority of the subjects included in the study. The completion rates ranged from 53.6% (Placebo) to 76.9% (MF MDI 200 mcg BID). Treatment failures and non-compliance accounted for the majority of discontinuations. The majority of subjects had treatment compliance of at least 80%.

Efficacy data and additional analyses
The primary analysis was based on the FAS which included all treated subjects with either a baseline or post-baseline measure. The study met its primary objective which is to show that at

least one of the doses of MF MDI is superior to placebo. The estimates of the differences in mean changes (95% CI) from baseline for the % predicted FEV_1 were: 3.87 (0.64, 7.09), 6.29 (3.05, 953), and 5.34 (2.07, 8.61) for the MF MDI 50 mcg BID (p=0.019), 100 mcg BID (p<0.001) and 200 mcg BID (p=0.001) groups respectively. Results based on the PP population were consistent with those based on the FAS. The results of sensitivity analyses to account for missing values were also supportive of the primary outcome.

Results in the secondary core outcomes (symptoms, exacerbation, and lung function) are generally supportive. The mean differences in change from baseline in AM PEF (L/min) were: 19.5 (0.43, 37.87), 27.35 (8.63, 46.08), and 18.01 (-0.51, 36.53) for 50 mcg BID, 100 mcg BID and 200 mcg BID MF MDI respectively. There was a significant increase in the proportion of subjects with zero total symptom score over 12 weeks in all MF MDI groups but not placebo. The percentage of subjects with asthma exacerbation over 12 weeks was lower in the MF MDI groups compared to placebo with clear dose-response effect. PAQLQ(S) was an exploratory outcome as validated questionnaires were not available for use in all countries. There was no clinically relevant treatment difference in quality of life as measured by PAQLQ(S).

In view of the purpose of the study, to determine a suitable dose based on dose response, a trend towards increasing efficacy is observed from 50 mcg BID to 100 mcg BID. From 100 mcg BID to 200 mcg BID, a trend towards decreasing efficacy is observed. MF DPI 100 mcg QD appears to be inferior to MF MDI 50 mcg BID.

Safety results

Safety of total daily dose exposure from 100 mcg to 400 mcg of MF in this study over 3 months did not raise any concerns. There was a higher number of AEs in the MF MDI 100 mcg group due to higher incidence of upper respiratory tract infections. Nasopharyngitis was the most common AE. Reported SAEs included 4 cases of asthma, two from the MF MDI 50 mcg group and 2 from the placebo group, likely due to lack of efficacy. The safety profile does not raise any major concerns based on short term exposure. However, long-term exposure effects are yet to be determined.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submitted study did not investigate the approved 200 mcg or 400 mcg strengths of MF DPI (Asmanex). A 100 mcg strength MF DPI formulation was studied. However the optimum formulation in the 5-11 years age group was MF MDI 100 mcg BID, based on the efficacy and safety results.

According to the *Guideline on the clinical investigation of medicinal products for the treatment of asthma* (CHMP/EWP/2922/01 Rev.1), long-term safety assessment of at least one year duration is required in children.

Therefore, based on the available evidence, a posology for the 6-12 year age group is not recommended for Asmanex Twisthaler 200 micrograms Inhalation Powder or Asmanex Twisthaler 400 micrograms Inhalation Powder.

There are no new safety concerns.

- **Recommendation**

No further action required