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

NASONEX 50 micrograms/actuation Nasal Spray Suspension
Asmanex Twisthaler 400/200 micrograms Inhalation Powder

Mometasone furoate

UK/W/0064/pdWS/003

Marketing Authorisation Holder: MSD

Rapporteur:	UK
Finalisation procedure (Day 120):	22 October 2014
Date of finalisation of PAR:	19 November 2014

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	NASONEX 50 micrograms/actuation Nasal Spray Suspension Asmanex Twisthaler 400/200 micrograms Inhalation Powder
INN (or common name) of the active substance(s):	Mometasone furoate
MAH:	MSD
Currently approved Indication(s)	<u>NASONEX:</u> Adults and children over 12 years: treatment of symptoms of seasonal allergic or perennial rhinitis. children 6-11 years: Treatment of symptoms of seasonal allergic or perennial allergic rhinitis Adults over 18 years: Treatment of nasal polyps Prophylactic treatment of seasonal allergic rhinitis, may be initiated up to four weeks prior to the anticipated start of the pollen season. <u>Asmanex Twisthaler:</u> Regular treatment to control persistent asthma in adults and adolescents 12 years of age and older
Pharmaceutical form(s) and strength(s):	Nasal Spray Suspension Inhalation Powder

I. EXECUTIVE SUMMARY

The MAH has submitted completed paediatric studies for Mometasone furoate (nasal spray suspension and inhalation powder), in accordance with Article 46.

The rapporteur considers that the overall benefit:risk of Mometasone remains unchanged.

The SmPC of Nasonex contains the following information: "There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with NASONEX Nasal Spray." However it is considered that study P06333 shows that mometasone may cause HPA axis depression. Therefore it is recommended that this sentence should be removed from section 4.4. The CMDh supported the rapporteur's overall conclusion and recommendation.

The MAH and MSs should be aware that there is a separate ongoing Article 30 referral for Nasonex due for finalisation shortly. Further changes in the SmPC might be warranted after the conclusion of the referral procedure, however these do not influence the implementation of the outcome of this European Paediatric work-sharing procedure under Article 46. The MAH may implement the proposed deletion as a part of a group variation together with any changes to implement the outcome of the Article 30 referral.

Summary of outcome

☐ No change

☒ Change

- ☐ New study data: <section(s) xxxx, xxxx>
- ☐ New safety information: <section(s) xxxx, xxxx>
- ☒ Paediatric information clarified: sections 4.4 SmPC
- ☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

Based the final conclusion, the below deletion is recommended from section 4.4 of the SmPC of Nasonex:

~~*There is no evidence of hypothalamic pituitary adrenal (HPA) axis suppression following prolonged treatment with NASONEX Nasal Spray*~~

III. INTRODUCTION

On 19 Feb 2014, the MAH submitted completed paediatric study(ies) for Mometasone furoate (MF), 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 MAH stated that the submitted paediatric studies do not influence the benefit risk for Mometasone furoate and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

Mometasone furoate monohydrate (MF; SCH 032088/MK-0887) is a synthetic, 17-heterocyclic corticosteroid with anti-inflammatory activity and with less potential to cause systemic side effects often associated with the use of corticosteroids (e.g., hypothalamic-pituitary-adrenal [HPA]-axis suppression).

Two different formulations are approved and for ease of understanding these are considered separately below.

A. <u>NASONEX® Nasal Spray</u>

The approved indications of NASONEX® Nasal Spray, per the European Union (EU) Summary of Product Characteristics (SmPC) are:

Children 6 to 11 years of age

Indicated for the treatment of symptoms of seasonal allergic or perennial allergic rhinitis. In patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis (SAR), prophylactic treatment with Nasonex® Nasal Spray may be initiated up to four weeks prior to the anticipated start of the pollen season.

The usual recommended dose is one spray (50 μg /spray) in each nostril once daily (QD) (total daily dose of 100 μg).

Nasonex® Nasal Spray demonstrated a clinically significant onset of action within 12 hours after the first dose in some patients with SAR; however, full benefit of treatment may not be achieved in the first 48 hours. Therefore, the patient should continue regular use to achieve full therapeutic benefit.

Adults and children 12 years of age and older

Indicated for the treatment of symptoms of seasonal allergic or perennial rhinitis.

In patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis (SAR), prophylactic treatment with Nasonex® Nasal Spray may be initiated up to four weeks prior to the anticipated start of the pollen season.

The usual recommended dose is two sprays (50 μg /spray) in each nostril QD (total daily dose of 200 μg). Once symptoms are controlled, dose reduction to one spray daily in each nostril (total dose of 100 μg) may be effective for maintenance. If symptoms are inadequately controlled, the dose may be increased to a maximum daily dose of four sprays in each nostril QD (total daily dose of 400 μg). Dose reduction is recommended following control of symptoms.

Adults 18 years of age and older

Indicated for the treatment of nasal polyps.

The usual recommended starting dose for polyposis is two sprays (50 μg/spray) in each nostril QD (total daily dose of 200 μg). If after 5 to 6 weeks symptoms are inadequately controlled, the dose may be increased to a daily dose of two sprays in each nostril twice daily (BID) (total daily dose of 400 μg). The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. If no improvement in symptoms is seen after 5 to 6 weeks of BID administration, alternative therapies should be considered.

IV.2 Clinical aspects

1. Introduction

This submission contains the results of an MAH search for studies conducted since 2007 involving any Nasonex® exposure in subjects <18 years of age with an outstanding Article 46 reporting requirement.

This submission contains results of 11 clinical studies conducted with MF, the active ingredient in Nasonex®, in which patients at least 2 years of age were enrolled. A total of 3386 patients aged 2 to >65 years were included in these studies of which 804 patients were < 18 years of age.

Of the 11 studies, 4 were conducted in paediatric population (2 to 15 years) and 7 in paediatric and older population (12 years of age and older).

2. Clinical studies

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.

A brief description of these studies is given below:

Paediatric population 2-15 years (4 studies)

Protocol Number 04367

A Phase 4 open label pilot trial, evaluating the role of Nasonex® 100 µg QD in the management of nasal obstruction secondary to adenoid hypertrophy (AH) in children 2 to 11 years of age. This study was conducted in Lebanon.

This study included a total of 34 patients. The total duration of therapy was 3 months.

The primary objective was to document the long-term effect of treatment with Nasonex® in moderate to severe AH which caused >50% obstruction of the posterior choanae as reflected by the need for adenoidectomy within one year of the treatment regimen.

Study Design

The study design included:
- Screening Visit:
- Baseline Visit and Randomized Period:

Patients were randomized to MFNS, or placebo nasal spray in a 1:1 ratio in every group Visit 1 (6 weeks), Visit 2 (3 months), Contact 1 (6 months), Contact 2 (9 months), Contact 3 (15 months).

Study Treatment Including Formulation

Mometasone furoate nasal spray; One spray (50 µg per spray) in each nostril QD (100 µg daily) for 3 months.

Baseline Patient Characteristics

The study initially included 34 patients (19 males and 15 females) with mean age of 4.84 years, range 0.5 – 9.25 years, median 4.73 years. Included patients had average weight & height of 18.48 kgs (range 11.5 – 32 kgs) & 102.15 cms (range 82 – 129 cms) respectively and so the mean body mass index was 17.72 kg/m2 (range 12.74 – 23.06 kg/m2). Fifteen patients were later on discontinued (13 lost to follow-up, 2 preferred surgery) leaving only 19 patients under study where inclusion criteria included children aged between 2 and 11 years of both genders. (8 female, 11 male; mean age of 4.24 years, range 2.25 – 8.50 years, median 4.00 years).
Efficacy Results

MFNS appeared to be an effective treatment for patients with adenoids obstructing more than 50% of their posterior choanae, as assessed by endoscopy. The effect seemed to be independent of the presence of allergic rhinitis and was not influenced by the age or degree of symptoms of the patient. Girls seemed to respond better clinically but the margin of difference with boys was narrow. There was a 58% reduction in clinical score between V0 (baseline) and V1 (6 weeks from baseline) ($P < 0.05$). However, no further significant decrease in the score was noticed

between V1 (6 weeks from baseline) and V2 (12 weeks from baseline). The total reduction in the score over the treatment period was 68%. The estimated severity of nasal obstruction decreased 56% between V0 (baseline) and V1 (6 weeks from baseline) ($P < 0.05$). Again, there was no further significant reduction in severity of nasal obstruction between V1 (6 weeks from baseline) and V2 (12 weeks from baseline). The total reduction in severity over the treatment period was 67%. On endoscopic assessment, there was a significant decrease in the degree of obstruction as reflected by a decrease in the percentage of obstruction and thus the endoscopic grade ($P < 0.05$).

Safety Results

No AEs were reported. MFNS was considered safe and well tolerated.

Protocol Number 05155

A Phase 3 double-blind placebo controlled, randomized, parallel-group, multicenter clinical trial to evaluate efficacy and safety of MFNS 100 µg BID in children with AH 2 to 11 years of age. This study was conducted in Mexico and Venezuela.

This study included a total of 132 patients of which there were 66 patients on MFNS in the intent-to-treat (ITT) population and 49 patients in the per-protocol (PP) population. The total duration of therapy was 24 weeks (6 months).

The primary objective was size reduction of the adenoids from the baseline, evaluated by nasopharyngoscopic evaluation (Adenoid/Choana A/C Index).

Study Design

The study design included:
- Screening/Run-in Period (Day -15 to -1) (Visit 1)
- Double blind randomized period (Visit 2 and Visit 3)
Patients were randomized to MFNS or placebo group nasal spray in a 1:1 ratio.
- Blinded Follow-up (Visit 4)
- Blinded extension (Visit 5 and Visit 6) to complete 6 months (24 weeks) of follow-up by nasopharyngoscopic evaluation every 2 months

Study Treatment Including Formulation

Mometasone furoate nasal spray; One spray (50 µg per spray) in each nostril BID (200 µg daily) for 8 weeks.

Baseline Patient Characteristics

Of the 132 patients in the ITT population, 55 (41.7%) were females and 77 (58.3%) were males. Mean± standard deviation (SD) age of the patients was 5.46±2.38 years (median: 5 years, range: 2-11 years). Overall, mean±SD time of exposure was 59.8±5.4 days (median: 58 days, range 53-97 days). There were no relevant differences between the treatment groups with regard to demographic and baseline characteristics and exposure data.

Efficacy Results

This study did not demonstrate significant reduction in adenoid size or significant improvement of symptoms and quality of life in patients who used MFNS 100 μg BID over 8 weeks.

Safety Results

Thirty patients in the MFNS group and 28 patients in the placebo group experienced AEs. Of the 30 patients, 2 patients in the PP population had serious adverse experiences (SAEs) of appendicitis and upper airway infection which were considered not related to study medication. No new safety signals of concern were identified in this study. MFNS was considered safe and well tolerated.

Protocol Number 06332

A Phase 3 multicenter, double-blind, randomized, placebo-controlled study of MFNS in paediatric patients (100 μg QD for 5-11 years of age and 200 μg QD for 12-15 years of age) with perennial allergic rhinitis (PAR) 5 to 15 years of age. This study was conducted in Japan.

This study included a total of 333 patients of which 220 were in the MF group. The total duration of therapy was 2 weeks.

The study was conducted to assess the efficacy of MFNS in paediatric patients with PAR based on the primary endpoint, i.e., the change from baseline in the total score of 4 nasal symptoms (sneezing, rhinorrhea, nasal congestion and nasal itching symptom score) after 2 weeks (or at discontinuation) of treatment.

Study Design

The study design included:
- Pretreatment observation period (at least 7 days) (Visit 1)
- Double blind randomized period
- Blinded Follow-up

Study Treatment Including Formulation

Mometasone furoate nasal spray (50 μg per spray)
- For children 5 to 11 years of age: 1 spray in each nostril QD (100 μg/day) in the morning for 2 weeks.
- For children 12 to 15 years of age: 2 sprays in each nostril QD (200 μg/day) in the morning for 2 weeks.

Baseline Patient Characteristics

Of the 333 patients, 128 (38.4%) were females and 205 (61.6%) were males. Mean± SD age of the patients was 9.8±2.9 years (median: 10 years, range: 5-15 years).

Efficacy Results

The once daily administration of MF nasal spray (100 µg/day for children 5-11 years of age, and 200 µg/day for children 12-15 years of age) was demonstrated to be superior to placebo; therefore, MF nasal spray was confirmed to be effective against PAR in children.

Table 1 Change from baseline in the total score of 4 nasal symptoms at 2 weeks of treatment or at discontinuation

Treatment	Visit	LS Mean	SE	DF	t-value	p-value	95% Confidence Intervals	
							lower	upper
MF	week 1	2.4686	0.1441	328	17.14	<0.0001	2.1852	2.7520
	week 2 or discontinuation	3.9850	0.1633	329	24.40	<0.0001	3.6638	4.3063
Placebo	week 1	1.1651	0.1967	328	5.92	<0.0001	0.7781	1.5521
	week 2 or discontinuation	1.9081	0.2233	329	8.54	<0.0001	1.4688	2.3475

Safety Results

This study included a total of 333 patients of which 220 were in the MF group. Sixty-seven patients in the MFNS group experienced AEs and 4 patients experienced Adverse Drug Reactions (ADRs) which were AEs that were considered drug-related. All the ADRs were considered of mild severity. The incidence of AEs and Adverse Drug Reactions were comparable between MF and placebo groups. One patient in the MFNS group was discontinued from study therapy due to status asthmaticus, pharyngoconjunctival fever of children and bronchitis. None of these events were considered related to the study medication. No SAEs were reported in this study. MFNS was considered safe and well tolerated.

Protocol Number 06333

A Phase 3, long-term (12-24 weeks) study of MFNS in paediatric patients (100 µg QD for 3-11 years of age and 200 µg QD for 12-15 years of age) with PAR 3 to 15 years of age. This study was conducted in Japan.

This study included a total of 80 patients. The total duration of therapy was 24 weeks.

The study was conducted to assess the safety of long-term (12 weeks to up to 24 weeks) treatment with MFNS in paediatric patients with PAR.

Study Design

The study design included:
- Pretreatment observation period (at least 7 days) (Visit 1)
- First treatment phase (Visit 3-Visit 6)
- Extended treatment phase (Visit 7-Visit 9)

- Follow-up observation period (Visit 10)
- Presence or absence of AEs check period (30 days)

Study Treatment Including Formulation

MFNS 50 μg device was to be used:
3 to 11 years: one spray per nostril QD (100 μg /day) in the morning.
12 to 15 years: 2 sprays per nostril QD (200 μg /day) in the morning.

Baseline Patient Characteristics

Of the 80 patients, 26 (32.5%) were females and 54 (67.5%) were males. Mean± SD age of the patients was 9.2±3.4 years (median: 9 years, range: 3-15 years).

Efficacy Results

The reduction from baseline in the total nasal symptoms score practically reached a maximum at Week 8, and the treatment efficacy sustained for up to Week 24 (4.8+/-0.3) without attenuation. Reduction in the individual nasal symptom scores reached a maximum at Week 8. In the follow-up observation, improvement (close to 1 point) compared with baseline was maintained for the scores of all the nasal symptoms; thus, the efficacy equivalent to that at Week 2 or 4 was kept. There was consistent change, around 0.8, after Week 8 in the interference with performance of daily activities score through Week 12. This tendency was also consistently observed after Week 13 through Week 24 (or at discontinuation) in the subjects who entered the continued treatment period.

The global improvement rates of improvement (percentage of subjects with moderate and remarkable improvement) were 73.8% at Week 2, 84.8% at Week 4, 88.6% at Week 8 and 88.3% at Week 12, and thereafter an improvement rate of as high as ≥90% was maintained for up to Week 24. Based on time-course changes in the improvement rate, the treatment efficacy had reached a maximum at Week 8.

The long-term treatment with MFNS demonstrated sustained efficacy without attenuation during the 24-week treatment.

Safety Results

Seventy-six patients in the MFNS group experienced 76 AEs and 18 patients experienced ADRs (AEs that were considered drug-related). The most frequent ADRs were of decreased blood cortisol and were considered to be clinically insignificant. One patient reported an SAE of left inguinal hernia which was considered not related to the study medication. No serious ADRs were reported. Two patients were discontinued from the study due to AEs of allergic conjunctivitis which was considered not related to the study medication and decreased blood cortisol which was considered related to the study medication and was of mild severity. The incidence of both AEs and ADRs were similar between the younger and the older age groups. No severe AEs were reported; the intensity of AEs was similar between younger and older age groups. Long-term (12-24 weeks) administration of MFNS was considered safe and well tolerated.

Paediatric and older population >12 years (7 studies)

Protocol Number 04500

A Phase 2 efficacy and safety study of concurrent administration of MFNS and oxymetazoline nasal spray (OXY) QD (either as 2:1 sprays/nostril [50 µg/spray of MFNS and OXY 0.05%] or as 2:3 sprays/nostril [50 µg/spray of MFNS and OXY 0.05%]) vs. OXY (0.05%) (2 sprays/nostril) BID, MFNS 50 µg/spray (2 sprays/nostril) QD, matching placebo spray to MFNS administered intranasally to patients with SAR 12 years of age or older.

This study was conducted in the USA. This study included a total of 707 patients. Of the 139 patients in the MFNS group, 5 patients were 12-17 years of age. The total duration of therapy was 15 days.

The study was conducted to assess the efficacy of the combination of MFNS and OXY given concomitantly QD compared to OXY BID, MFNS QD, and placebo in patients with SAR in relieving nasal symptoms including nasal congestion. The primary endpoints of this study to address this objective were based on the change from Baseline in AM/PM NOW (instantaneous) TNSS averaged over Days 1 to 15 and the standardized area under the curve from zero to 4 hours (AUC [0-4 hr]) of the change from baseline in nasal congestion score on Day 1.

Study Design

The study design included:
- Screening Period (Days -14 to -3) (Visit 1)
- Treatment Period:
This was a 2-week (15 days) treatment period and consisted of Visit 2, Visit 3, and Visit 4.
Visit 2: Baseline Visit (Day 1)

Following completion of the screening period and performance of all baseline procedures at Baseline Visit/Visit 2 (Day 1), patients who continued to qualify for the study were to be randomized at this visit to receive one of the following five treatment arms:
Group 1: MFNS and OXY given concomitantly QD (1-spray OXY combination)
Group 2: MFNS and OXY given concomitantly QD (3-spray OXY combination)
Group 3: MFNS QD
Group 4: OXY BID
Group 5: Placebo
This was done in a 1:1:1:1:1 ratio and stratified by dosing sequence.

Visit 3: Day 8 Interim Visit (Days 4 to 12)
Visit 4: Day 15 End of Treatment or Early Termination (ET) Visit (Days 13 to 18)
- One Week (7 Days) Post-Treatment Follow-up Period (Visit 5)
This consisted of Day 22 Post-Treatment Follow-up Visit/Visit 5 (Days 18 to 29)
Study Treatment Including Formulation

Test Product, Dose, Mode of Administration:
- 1-spray combo: MFNS (50 µg/spray) 2 sprays/nostril and OXY (0.05%) 1 spray/nostril concurrently administered QD in AM.
- 3-spray combo: MFNS (50 µg/spray) 2 sprays/nostril and OXY (0.05%) 3 sprays/nostril

concurrently administered QD in AM.

Reference Therapy, Dose, Mode of Administration:
MFNS (50 µg/spray) 2 sprays/nostril administered QD in AM OXY nasal spray (0.05%) 2 sprays/nostril administered BID Matching placebo spray to MFNS administered intranasally.

Baseline Patient Characteristics

In the ITT population, the five treatment groups were well matched with regard to Baseline demographics. Approximately two-thirds of patients in each treatment group were females. The mean age across the five treatment groups was 38.0 to 40.2 years, with similar proportions of patients in each treatment group distributed among the three age groups (ages 2 to 17 years comprised 3.6%-8.6% of patients in each treatment group, ages 18 to 64 years comprised 89.2%-95% of patients in each treatment group, and ages 65 years or greater comprised 1.4%-2.9% of patients in each treatment group). The study population comprised primarily White patients (74.8%-82.4% across the five groups) and patients who were non- Hispanic or Latino (78.2%-85.5% across the five groups). Mean Baseline height and weight were also similar across the five treatment groups.

Efficacy Results

The combination of MFNS+OXY (1 spray and 3 spray) was an effective treatment for adult and adolescent patients 12 years of age or older with SAR. Each component (MFNS and OXY) contributes to the combination of MFNS+OXY. Onset of action of MFNS+OXY combinations was faster than that of MFNS. MFNS+OXY has a once-daily activity. There was no evidence for a dose-response between the MFNS+OXY combinations. There was some evidence of tachyphylaxis with OXY BID but not with the MFNS+OXY combinations or MFNS QD.

Safety Results

This study included a total of 707 patients. Of the 139 patients in the MFNS group, 5 patients were 12-17 years of age.Two patients in the paediatric population of the MFNS group reported one AE each (headache and nasopharyngitis) which were considered not related to study medication. No SAEs were reported in the paediatric population. The combination of MFNS+OXY was considered safe and well tolerated.

Protocol Number 04824

A Phase 3 efficacy and safety study of 200 µg BID MFNS vs. placebo as adjunctive treatment to antibiotics (Amoxicillin 1 gm/clavulanic acid 62.5 mg: two tablets BID for 16 year of age and older population. Amoxicillin 875 mg/clavulanic acid 125 mg: one tablets BID for 12-15 years of age population) in relief of symptoms of acute bacterial sinusitis in patients 12 years of age or older.

This study was conducted in the USA. This study included a total of 237 patients. Of the 114 patients in the MFNS group, 5 patients were 12-17 years of age. The total duration of therapy was 29 days.

The primary objective of this study was to evaluate the efficacy of intranasal MFNS as an adjunctive treatment to antibiotic therapy in acute episodes of bacterial sinusitis. Efficacy was to be determined by the change from Baseline in AM/PM PRIOR (reflective over the previous 12 hours) major symptom score (MSS) minus sinus headache averaged over Days 1 to 29, and the change in percentage of opacification of one maxillary sinus (the one with the highest percentage of opacification) as compared to antibiotic treatment alone.

Study Design

The study design included:
- Screening Period (Day -7 to -2) (Visit 1):
- Double-Blind Treatment Period:
This was a 29-day treatment period and consisted of Visit 2, Visit 3, and Visit 4.
Visit 2: Baseline Visit (Day 1)
Patients were randomized to receive MFNS 200 μg BID or placebo in a 1:1 ratio
Visit 3: Day 15 Visit (Days 12 to 17)
Visit 4: Day 29 Last Treatment Visit (Days 24 to 32)
- Two Weeks (14 Days) Post-Treatment Follow-up Period (Visit 5):
This consisted of Day 43 Follow-up Last Study Visit/Visit 5 (Days 37 to 50)

Study Treatment Including Formulation

Test Product, Dose, Mode of Administration:
MFNS 50 μg/spray, two sprays in each nostril BID.

Reference Therapy, Dose, Mode of Administration:
MFNS placebo administered intranasally
Amoxicillin 1 gm/clavulanic acid 62.5 mg: two tablets BID for patients 16 years or age and older
Amoxicillin 875 mg/clavulanic acid 125 mg: one tablet BID for patients 12-15 years of age

Baseline Patient Characteristics

The two treatment groups were generally well matched with regard to Baseline demographics. The majority of patients in both groups were female, with a greater percentage of females in the MFNS treatment group (70%) versus the placebo group (59%). The mean age across the treatment groups was 39.2 years, with similar proportions of patients in each treatment group distributed among the age groups. In both treatment groups, ages 12 to less than 18 years comprised 4% to 5% of patients; ages 18 to less than 65 years comprised 87% to 93% of patients. There were, however, more patients aged 65 years or greater in the placebo group (10 patients, 8%) than in the MFNS group (3 patients, 3%). The study population was comprised primarily of Caucasian (86%) patients. Mean Baseline height and weight were also similar in both treatment groups.

Efficacy Results

The study was terminated before reaching the planned enrollment of 600 patients when only 237 patients were enrolled. Reasons for termination were business priorities within the Sponsor

company and slower than anticipated enrollment of patients. As a result, no inferential statistical analysis was performed on the data, no hypothesis was tested, and the protocol-specified objectives could not be achieved.

Safety Results

This study included a total of 237 patients. Of the 114 patients in the MFNS group, 5 patients were 12-17 years of age. One patient in the paediatric population of the MFNS group reported an AE of haryngolaryngeal pain which was considered not related to study medication. No SAEs were reported in the paediatric population.

No safety issues were raised in this study which was terminated prematurely due to business priorities within the Sponsor company and slower than anticipated enrollment of patients.

Protocol Number 05067

A Phase 3 placebo-controlled study of MFNS 200 µg QD in the treatment of SAR in patients 12 years of age or older. This study was conducted in the USA. This study included a total of 426 patients. Of the 211 patients in the MFNS group, 18 patients were 12-17 years of age. The total duration of therapy was 15 days.

The primary objective of this study was to assess the efficacy of MFNS QD compared with placebo in patients with SAR in reducing the TNSS and the TOSS.

Study Design

The study design included:
- Screening Period (Day -14 to -3) (Visit 1)
- Double-blind treatment period:
This was a 15-day treatment period and consisted of Visit 2, Visit 3, and Visit 4.
Visit 2: Baseline Visit (Day 1):
Patients who qualified at the Baseline Visit were to be randomized to receive either 200 µg MFNS QD or placebo for 15 days in a 1:1 ratio
Visit 3: Day 8 Visit (Days 5 to 11)
Visit 4: Day 15 Visit (Days 12 to 18)

Study Treatment Including Formulation

Test Product, Dose, Mode of Administration:
MFNS 50 µg/spray, two sprays in each nostril QD

Reference Therapy, Dose, Mode of Administration:
MFNS matching placebo.

Baseline Patient Characteristics

The two treatment groups were well balanced with regard to baseline demographics. Approximately two-thirds of patients in each treatment group were female. The mean age of patients was 37.8 years in the MFNS 200 µg QD group and 35.6 years in the placebo group, with similar proportions of patients in each treatment group distributed between the three age subgroups (ages 12 to less than 18 years comprised 9% to 14% of patients in each treatment group, ages 18 to less than 65 years comprised 84% to 89% of patients in each treatment group, and ages 65 years or greater comprised 2% of patients in each treatment group). Caucasian patients comprised the majority of the study population: 80% of patients treated with MFNS 200 µg QD and 75% of patients treated with placebo. Mean baseline height, weight, and Body Mass Index (BMI) were also similar between the two treatment groups.

Efficacy Results

Since only one of the two co-primary endpoints was met, the primary objective of the study was not achieved. This study showed that, compared to placebo, MFNS 200 µg QD was effective in reducing TNSS but not TOSS. MFNS 200 µg QD was also effective in improving the nasal congestion score.

Safety Results

This study included a total of 426 patients. Of the 211 patients in the MFNS group, 18 patients were 12-17 years of age. Two patients in the paediatric population of the MFNS group reported one AE each. The AEs of headache and joint sprain were both considered not related to study medication. No SAEs were reported in the study. MFNS was considered safe and well tolerated.

Protocol Number 05106

A Phase 3 placebo-controlled study of MFNS 200 µg QD in the treatment of SAR in patients 12 years of age or older. This study was conducted in the USA. This study included a total of 429 patients. Of the 220 patients in the MFNS group, 31 patients were 12-17 years of age. The total duration of therapy was 15 days.

The primary objective of this study was to assess the efficacy of MFNS QD compared with placebo in patients with SAR in reducing the TNSS and the TOSS.

Study Design

The study design included:
- Screening Period (Day -14 to -3) (Visit 1):
- Double blind randomized period:
This was a 15-day double-blind treatment period.
Visit 2: Baseline Visit (Day 1)
Patients who qualified at the Baseline Visit were randomized to receive either 200 µg MFNS QD or placebo for 15 days in a 1:1 ratio.
Visit 3: Day 8 Visit (Days 5 to 11)
Visit 4: Day 15 Visit (Days 12-18)

Study Treatment Including Formulation

Test Product, Dose, Mode of Administration:
MFNS 50 µg/spray, two sprays in each nostril QD

Reference Therapy, Dose, Mode of Administration:
MFNS matching placebo, two sprays in each nostril QD

Baseline Patient Characteristics

The two treatment groups were well balanced with regard to baseline demographics. Sixty percent of patients in each treatment group were female. The mean age of patients was 34.5 years in the MFNS 200 µg QD group and 36.8 years in the placebo group, with similar proportions of patients in each treatment group distributed between the three age subgroups (ages 12 to less than 18 years comprised 11% to 14% of patients in that treatment group, ages 18 to less than 65 years comprised 84% to 87% of patients in that treatment group, and ages 65 years or greater comprised 1% to 2% of patients in that treatment group). Caucasian patients comprised the majority of the study population: 75% of patients in each treatment group. Mean baseline height, weight, and BMI were also similar between the two treatment groups.

Efficacy Results

This study showed that, compared to placebo, MFNS 200 µg QD was effective in reducing both TNSS and TOSS; therefore, the primary objective of this study was met. In addition, MFNS was significantly more effective than placebo in improving the nasal congestion score as well as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.

Safety Results

This study included a total of 429 patients. Of the 220 patients in the MFNS group, 31patients were 12-17 years of age. Four patients in the paediatric population of the MFNS group reported 5 AEs. Three patients had one AE each i.e., hypersensitivity, streptococcal pharyngitis, and nasal discomfort while one patient had pyrexia and pharyngolaryngeal pain. All AEs were considered not related to study medication. No SAEs were reported in the study. MFNS was considered safe and well tolerated.

Protocol Number 05528

A Phase 3 placebo-controlled study of MFNS 200 µg QD in the relief of nasal congestion associated with SAR in patients 12 years of age or older. This study was conducted in the USA. This study included a total of 324 patients. Of the 162 patients in the MFNS group, 7 patients were 12-17 years of age. The total duration of therapy was 15 days.

The primary objective of this study was to assess the efficacy in relieving the symptom of nasal congestion with MFNS 200 µg given QD compared to placebo in patients with symptomatic SAR.

Study Design

The study design included:
- Screening Period (Day -14 to -3) (Visit 1)
- Double blind randomized period:
This was a 15-day treatment period and consisted of Visit 2, Visit 3, and Visit 4.
Visit 2: Baseline Visit (Day 1):
Patients who qualified at Baseline Visit were randomized to either MFNS 200 µg QD or placebo QD for 15 days in a 1:1 ratio
Visit 3: Day 8 Visit (Days 5 to 11)
Visit 4: Day 15 Visit (Days 12 to 18)

Study Treatment Including Formulation

Test Product, Dose, Mode of Administration:
MFNS 50 µg /spray, two sprays in each nostril QD

Reference Therapy, Dose, Mode of Administration:
MFNS matching placebo, two sprays in each nostril QD

Baseline Patient Characteristics

The two treatment groups were well balanced with regard to baseline demographics. The majority of patients in each treatment group (70% to 72%) were female. The mean age of patients was 40.8 years in the MFNS group and 38.2 years in the placebo group, with similar proportions of patients in each treatment group distributed between the three age subgroups (ages 12 to less than 18 years comprised 4% to 5% of patients, ages 18 to less than 65 years comprised 91% to 95% of patients, and ages 65 years or greater comprised 4% of patients in the MFNS group). Caucasian patients comprised the majority of the study population: (76% to 77%). Mean baseline height and weight were also similar between the two treatment groups.

Efficacy Results

The primary objective of this study was not met. Of note, the Sponsor considers that this study should be considered invalid due to significant treatment-by-site interaction in the primary endpoint.

Safety Results

This study included a total of 324 patients. Of the 162 patients in the MFNS group, 7 patients were 12-17 years of age. One patient in the paediatric population of the MFNS group reported an AE of upper respiratory tract infection which was considered not related to study medication. No SAEs were reported in the study. MFNS was considered safe and well tolerated.

Protocol Number 05529

A Phase 3 placebo-controlled study of MFNS 200 µg QD in the relief of nasal congestion associated with SAR in patients 12 years of age or older. This study was conducted in the USA. This study included a total of 351 patients. Of the 176 patients in the MFNS group, 11 patients were 12-17 years of age. The total duration of therapy was 15 days.

The primary objective of this study was to assess the efficacy in relieving the symptom of nasal congestion with MFNS 200 µg given once daily compared to placebo in patients with symptomatic SAR.

Study Design

The study design included:
- Screening Period (Day -14 to -3) (Visit 1):
- Double blind randomized period:
This was a 15-day treatment period and consisted of Visit 2, Visit 3, and Visit 4.
Visit 2: Baseline Visit (Day 1):
Patients who qualified at Baseline Visit will be randomized to either MFNS 200 µg QD or placebo QD in a 1:1 ratio and treated with study medication for 15 days.
Visit 3: Day 8 Visit (Days 5 to 11)
Visit 4: Day 15 Visit (Days 12 to 18)

Study Treatment Including Formulation

Test Product, Dose, Mode of Administration:
MFNS 50 µg /spray, two sprays in each nostril QD

Reference Therapy, Dose, Mode of Administration:
MFNS matching placebo, two sprays in each nostril QD

Baseline Patient Characteristics

The two treatment groups were well balanced with regard to baseline demographics. The majority of patients in each treatment group (61% and 66%) were female. The mean age of patients was 37.9 years in the MFNS group and 38.6 years in the placebo group, with similar proportions of patients in each treatment group distributed between the three age subgroups (ages 12 to less than 18 years comprised 6% to 8% of patients, ages 18 to less than 65 years comprised 89% to 92% of patients, and ages 65 years or greater comprised 2% to 3% of patients). Caucasian patients comprised the majority of the study population: (78% to 79%). Mean baseline height and weight were also similar between the two treatment groups.
Efficacy Results

In summary, the results of this study demonstrated that compared with placebo, MFNS 200 µg QD was effective in reducing nasal congestion; therefore, the primary objective of this study was met. This effect was clinically meaningful, lasted for the whole dosing interval, and was comparable to what has been seen in previous Nasonex® trials with a similar design, as well as other approved decongestants such as pseudoephedrine. In addition, this study confirmed the superior efficacy of MFNS over placebo in improving the nasal symptoms of SAR.

Safety Results

This study included a total of 351 patients. Of the 176 patients in the MFNS group, 11patients were 12-17 years of age.No AEs were reported in the paediatric population of the MFNS group. MFNS was considered safe and well tolerated.

Protocol Number 05583

A Phase 3 placebo-controlled study of MFNS 200 µg QD in the relief of nasal congestion associated with SAR in patients 12 years of age or older. This study was conducted in the USA. This study included a total of 333 patients. Of the 168 patients in the MFNS group, 14 patients were 12-17 years of age. The total duration of therapy was 15 days.

The primary objective of this study was to assess the efficacy in relieving the symptom of nasal congestion with MFNS 200 µg given QD compared to placebo in patients with symptomatic SAR.

Study Design

The study design included:
- Screening Period (Day -14 to -3) (Visit 1):
Patients were to undergo a no-treatment Screening Period
- Double blind randomized period:
This was a 15-day treatment period and consisted of Visit 2, Visit 3, and Visit 4.
Visit 2: Baseline Visit (Day 1):
Patients who qualified at Baseline Visit will be randomized to either MFNS 200 µg QD or placebo QD in a 1:1 ratio and treated with study medication for 15 days
Visit 3: Day 8 Visit (Days 5 to 11)
Visit 4: Day 15 Visit (Days 12 to 18)

Study Treatment Including Formulation

Test Product, Dose, Mode of Administration:
MFNS 50 µg /spray, two sprays in each nostril QD

Reference Therapy, Dose, Mode of Administration:
MFNS matching placebo, two sprays in each nostril QD

Baseline Patient Characteristics

The two treatment groups were well balanced with regard to baseline demographics. The majority of patients in each treatment group (62% to 65%) were female. The mean age of patients was 38.6 years in the MFNS group and 39.0 years in the placebo group, with similar proportions of patients in each treatment group distributed between the three age subgroups (ages 12 to less than 18 years comprised 8% of patients in each treatment group, ages 18 to less than 65 years comprised 88% of patients in each treatment group, and ages 65 years or greater comprised 3% to

4% of patients). Caucasian patients comprised the majority of the study population (75% to 82%). Mean baseline height and weight were also similar between the two treatment groups.

Efficacy Results

The results of this study demonstrated that compared with placebo, MFNS 200 µg QD was effective in reducing nasal congestion; therefore, the primary objective of this study was met. This effect was clinically meaningful, lasted for the whole dosing interval, and was comparable to what has been seen in previous Nasonex® trials with a similar design, as well as other approved decongestants such as pseudoephedrine. In addition, this study confirmed the superior efficacy of MFNS over placebo in improving the nasal symptoms of SAR.

Safety Results

One AE of vomiting was reported in the paediatric population of the MFNS group. MFNS was considered safe and well tolerated.

3. Discussion on clinical aspects

For Nasonex, the MAH has provided 11 clinical studies involving paediatric patients, 4 were in paediatric age group only. These included phase 2, 3 and 4 studies ranging in duration from 2 to 24 weeks and were conducted in different regions of the world. The indications included adenoid hypertrophy, SAR and PAR, and acute bacterial sinusitis. Variable efficacy was observed in each. No new safety concerns were identified during the conduct of these studies.

One study, Protocol Number 04824 in ABS was terminated early due to slow recruitment and business reasons. Another study, Protocol Number 05528, in SAR was considered invalid due to large placebo effects in 3 of the 24 centres where the study was conducted.

B. Asmanex Twisthaler Inhalation Powder

As an inhaled corticosteroid, MF has been developed as a medicinal product globally as a monotherapy dry powder inhaler (DPI), monotherapy metered dose inhaler (MDI) and a combination MDI with formoterol fumarate by the sponsor.

For the monotherapy treatments, mometasone furoate dry powder inhaler (MF DPI) is currently available globally in multiple strengths, including 100 mcg, 200mcg & 400 mcg, and the mometasone furoate metered dose inhaler (MF MDI) is under regulatory review in one market for two strengths, 100 mcg & 200 mcg. Additionally, the fixed dose combination product of mometasone furoate + formoterol fumarate metered dose inhaler (MF/F MDI) is available in three strengths, 50/5 mcg, 100/5 mcg & 200/5 mcg. Within the European Union, MSD's only authorized dosage form is the MF DPI, presented in two strengths, 200 & 400 mcg, and the two other inhaled versions of MF are not registered.

Asmanex Twisthaler® was first approved for marketing in the EU by the UK in April 2001, and subsequently via the Mutual Recognition Procedure in 15 EU member states. The product is registered in 8 EU countries via the national procedure.

Asmanex Twisthaler® Inhalation Powder (200 mcg and 400 mcg per inhalation) is approved for the following indications in the EU MRP member states (for the other EU member states the indications can be slightly different).

Adults and adolescents >12 years
Asmanex® is indicated as prophylactic therapy in the management of all severities of asthmatic patients, including those who have been dependent upon either inhaled or systemically administered corticosteroids, and noncorticosteroid-dependent patients inadequately controlled on other drug regimens.

Approved dosing/posology in EU labeling:

Patients with persistent mild to moderate asthma: The recommended starting dose for most of these patients is 400 micrograms once daily. Data suggest that better asthma control is achieved if once daily dosing is administered in the evening. Some patients may be more adequately controlled on 400 micrograms daily, given in two divided doses (200 micrograms twice daily).

The dose of Asmanex Twisthaler® 200 micrograms Inhalation Powder should be individualized and titrated to the lowest dose at which effective control of asthma is maintained. Dose reduction to 200 micrograms once daily given in the evening may be an effective maintenance dose for some patients.

Patients with severe asthma: The recommended starting dose is 400 micrograms twice daily, which is the maximum recommended dose. When symptoms are controlled, titrate AsmanexTwisthaler® 200 micrograms Inhalation Powder to the lowest effective dose.

Clinical aspects

Since 2007, six clinical studies involving paediatric patients utilizing MF as an inhaled corticosteroid were undertaken by the sponsor and only one study was conducted with the EU-marketed MF DPI (P04879). An additional five studies (P04431, P04334, P04073, P04705, P06476) were conducted with mometasone furoate as an inhaled corticosteroid, either as a fixed dose combination (MF/F MDI) or as the fixed dose combination (MF/F MDI) versus monotherapy components of the combination (MF was utilized as MDI or DPI in these studies).

The MF/F clinical program for asthma included the above mentioned studies P04431, P04334, P04073, P04705, and P06476 and this program had an approved Modified Paediatric Investigation Plan and Partial Waivers (EMEA-000025-PIP01-07-M01 and P/4/2009).

Upon reviewing the results of these studies, the MAH supports that the risk/benefit profile of MF in paediatric subjects has not been altered; therefore, the SmPC for ASMANEX® Twisthaler® does not require revisions based on the Article 46 review.

A total of 415 subjects aged 5 to <18 years participated in the following six studies included in this submission.

P04879

Study Design

This was a phase 4, nonrandomized, and open-label, multicenter study in subjects with persistent mild and moderate asthma aged 12 and older with previous twice-daily Inhaled Corticosteroid (ICS) therapy. Total of 385 subjects were recruited and 281 subjects received MF-DPI (400 mcg once daily). The study included 5 visits: screening, ICS Dose Reduction (-28 to -1 days), day 1, week 4, week 8 & week 12. The study was conducted in Mexico.

• Primary Objective: To assess mean change in FEV1 from baseline to the endpoint of study. The objective was to demonstrate the long term efficacy of the MF-DPI in Mexican population.
• Formulation used: DPI
• Number of Paediatric subjects: 47

Baseline Subject Characteristics

A total of 281 subjects were enrolled in the study and screened for eligibility. 71.08% were female and 28.92% were men. The average age was 38.8 years with a standard deviation of 26.4 years. The maximum age recorded was 78 years old and the minimum was 12 years old.

Efficacy Results

The recorded data showed an increase in the mean FEV1 level of 19% and changes in score of Asthma quality of life and general quality questionnaires supports the objective that MF-DPI helps in improving health conditions. The reviewed variables support the hypothesis of an improvement of conditions in FEV1, PEFR and quality of life after 12 weeks of MF-DPI use.

Safety Results

There were 33 (11.74%) adverse events during and after the study from the 281 subjects. No serious adverse events were reported. Five adverse events were observed in the subjects aged 12 to <18 years. The most common adverse event in this age group was pharynx inflammation (n=3), the other two events were diarrhoea and the flu. None of the events were related to study therapy.

Conclusion

The study showed that MF DPI was safe and well tolerated in the Mexican population. With regard to paediatric data, the result of the study does not contribute significant new information to the known efficacy and safety profiles of MF in paediatric subjects. MF-DPI is shown to be safe in Mexican subjects aged from 12 to 65 years old with mild-to-moderate asthma.

P04431

Study Design

This was a Phase 3, randomized, multi-center, double-blind, parallel-group study in persistent asthmatics with a history of prior exacerbations, 12 years of age and older, and previously treated with high doses of ICS. After the 1-week Screening Period, all enrolled subjects underwent an approximately 2 to 3-week open-label Run-in Period with MF MDI 400 mcg BID, followed by a 12-week double- blind Treatment Period.

• Primary Objective: To evaluate the efficacy of mometasone furoate/formoterol fumarate (MF/F) Metered Dose Inhaler (MDI) 400/10 mcg twice daily (BID) compared with that of MF MDI 400 mcg BID as measured by the mean area under the curve (AUC) of the change from Baseline to Week 12 in forced expiratory volume (L) in one second (FEV1)
• Formulation used: MDI
• Number of Paediatric subjects: 63

Baseline Subject Characteristics

Overall, the median age was 52 years, 56% of subjects were female and 89% were white. A total of 643 (88%) subjects overall completed the protocol-specified, double-blind Treatment Period Demographic and Baseline characteristics were well matched between the treatment groups.

Efficacy Results

MF/F improved lung function more than MF alone. The contribution of F was demonstrated by the change from Baseline in 12-hour serial FEV1 at Week 12. Both MF/F treatment groups were statistically significantly superior to MF alone ($p<0.001$) in improvement FEV1 AUC. Both MF/F treatment groups were significantly superior to MF alone ($p\leq0.014$) in improving Asthma Control Questionnaire (ACQ) total scores at Week 12. A clinically important change in ACQ total score from Baseline to Endpoint was noted for both MF/F treatment groups only.

Safety Results

While 11 (17.5%) of the 63 subjects 12 - <18 years of age reported having non serious adverse events, there were no reports of Serious Adverse Events. During the Run-in period, all subjects received MF 400 mcg; this included 66 subjects <18 years of age. Only 2 AEs (1 headache and 1 chronic tonsillitis) were reported during the Run-in period. Of the 22 subjects randomized to the 400 mcg MF MDI treatment group, 3 adverse events were reported: nasopharyngitis, upper respiratory tract infection and dizziness. In the 18 – <65 years group, 29.8% of the subjects reported adverse events and in the >= 65 years group 23% reported adverse events.

Conclusion

The treatments were well tolerated. There were no notable differences in the occurrence or nature of adverse events reported compared to MF alone (400 mcg bid). The events reported were consistent with the known drug profile. Therefore, no new safety concerns were noted.

P04334

Study Design

This was a Phase-3 randomized, multi-center, double-blind, double-dummy, placebocontrolled, parallel-group study in persistent asthmatics 12 years of age and older previously treated with medium daily doses of ICS (either alone or in combination with a Long-Acting Beta-2 Agonist (LABA). Following a Screening Period that may have lasted several days, all enrolled subjects entered a 2- to 3-week (approximately) open-label Run-in Period with MF MDI 200 mcg BID, followed by a 26-week double- blind Treatment Period.

• Primary Objective: To determine the efficacy of mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) 200/10 mcg twice daily (BID) compared with MF MDI 200 mcg BID, in order to assess the added benefit of formoterol (F) MDI 10 mcg BID to the combination, and to determine the efficacy of MF/F MDI 200/10 mcg BID compared with F MDI 10 mcg BID, in order to assess the benefit of the steroid component (MF MDI 200 mcg BID) to the combination.
• Formulation used: MDI
• Number of Paediatric subjects: 63

Baseline Subject Characteristics

The four treatment groups were well balanced regarding the baseline characteristics. There was a higher proportion of female than male subjects in each treatment group, and ≥70% of subjects in each group were White with a median age of 45 years overall. Mean baseline heights and weights were similar across all treatment groups; and mean BMI ranged from 27.65 to 28.01 among treatment groups.

Efficacy Results

MF/F improved lung function more than MF alone ($p<0.001$) based on change from Baseline to Week 12 in FEV1 AUC (0-12 h r). The bronchodilator effect of F was also demonstrated: F alone was superior to placebo in FEV1 AUC ($p=0.009$). MF/F decreased the proportion of subjects who experienced a severe asthma exacerbation more than F alone ($p<0.001$). In addition, the MF

alone treatment group had fewer severe asthma exacerbations than subjects treated with F alone and placebo ($p<0.001$).

Safety Results

63 subjects aged <18 years were enrolled in the study. Adverse events were reported in 28 (44%) of these subjects. The most commonly reported adverse events in this group were pyrexia (6.3%), productive cough, bronchitis, pharyngitis, nasopharyngitis, otitis media, and eczema (3.2% for each event). Four SAEs were reported in those <18 years of age, including one which occurred during the open label period. In MF group there were no treatment related adverse events in subjects <18 years of age.

Conclusion

MF/F M D I 200/10 mcg BID was safe, and well tolerated. There were no notable differences in the occurrence or nature of AEs among the treatment groups and the placebo control group. The events reported were consistent with the known drug profile of MF. No new safety concerns were noted.

P04073

Study Design

This was a Phase 3, randomized, multi-center, double-blind, double-dummy, placebocontrolled, parallel-group study in persistent asthmatics 12 years of age and older previously treated with low daily doses of ICS (either alone or in combination with a LABA).Following a Screening Period that may have lasted several days, all enrolled subjects entered a 2- to 3-week (approximately) open-label Run-in Period with MF MDI 100 mcg BID, followed by a 26-week double-blind Treatment Period.

• Primary Objective: To determine the efficacy of mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) 100/10 mcg twice a day (BID) compared with MF MDI 100 mcg BID, in order to assess the added benefit of formoterol (F MDI 10 mcg BID) to the combination. And to determine the efficacy of MF/F MDI 100/10 mcg BID compared with F MDI 10 mcg BID, in order to assess the benefit of the steroid component (MF MDI 100 mcg BID) to the combination.
• Formulation used: MDI
• Number of Paediatric subjects: 110

Baseline Subject Characteristics

The four treatment groups were well balanced regarding the baseline characteristics. There was a higher proportion of female than male subjects in each treatment group, and ≥74% of subjects in each group were White with a median age of 39 years overall. Mean baseline heights and weights were similar across all treatment groups; and mean BMI ranged from 25.66 to 27.69 among treatment groups.

Efficacy Results

The AUCs corresponded to standardized increases from Baseline of 0.33 (13.8%), 0.21 (9.0%), 0.32 (12.3%), and 0.09 (4.1%) liters in FEV1, averaged across the 12-hour serial evaluation. The bronchodilator effect of F was also demonstrated: F alone was superior to placebo ($p<0.001$). The results of these two comparisons at Week 12 demonstrate the effectiveness of the F component, and confirm the superiority of the combination over the MF alone component. The bronchodilator effect of MF/F was maintained across the 12-hour evaluation period at Day 1 and at the end of treatment. MF/F decreased the proportion of subjects who experienced a severe asthma exacerbation more than F alone ($p<0.001$).

Safety Results

All three active treatments were well tolerated at the doses studied. During the Run-in period 139 subjects aged 12 - <18 years received 100 mcg MF BID, of which 10 subjects reported adverse events; the most common AE was headache (n=2). 110 subjects <18 years were enrolled in the study. Adverse events were reported in 48 (43.6%) of these subjects. The most common adverse events in the <18 years group were Nasopharyngitis (n=10), Upper Respiratory Infections (n=8), and Bronchitis (n=5); 4 of the 5 subjects reporting Bronchitis were from the placebo control group. 16 of the 30 subjects randomized to MF 100 mcg BID reported adverse events, the most commonly reported was nasopharyngitis (n=3), and upper respiratory infections (n=3). There was 1 SAE of hospitalization due to asthma which occurred in a 13 year old male. The investigator did not consider this event to be treatment related. Of those aged 18 – <65 years 40.5 % reported adverse events and 32.6% of those >= 65 years of age reported adverse events.

Conclusion

Treatment with MF/F MDI 100/10 mcg BID was well tolerated, and no new safety concerns were noted. The events reported were consistent with the known drug profile.

P04705

Study Design

This was a Phase 3, randomized, multi-center, open-label/evaluator-blind, activecontrolled, third-party dispenser, parallel-group efficacy and safety study in adult and adolescent subjects with persistent asthma who were previously treated with medium doses of ICS alone or in combination with a LABA.

The Screening Period was followed by a 2- to 4-week open-label Run-in Period with MF MDI 200 mcg BID, followed by an open-label, evaluator-blind, 12-week Treatment Period evaluating MF/F MDI 200/10 mcg BID and F/SC DPI 250/50 mcg BID. The protocol included a second 40-week phase, extending the blinded Treatment Period to a total of 52 weeks. However, the sponsor terminated the study early in response to changing competitive market conditions.

As a result of early closure of the study, 95% of randomized subjects (684 subjects) discontinued investigational treatment early (prior to Week 52), although some subjects did complete one full year of treatment before it was closed. The early closure had no impact on the evaluation of

results collected for the Phase 1 analysis; however, the complete 40-week Phase 2, as planned in the protocol, was not conducted.

• Primary Objective: Primary Objective: To demonstrate non-inferiority between mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) 200/10 mcg twice a day (BID) and fluticasone propionate/salmeterol (F/SC) dry powder inhaler (DPI) 250/50 mcg BID on the effect of lung function after 12 weeks of treatment, in subjects with persistent asthma requiring maintenance treatment on medium doses of inhaled glucocorticosteroids.
• Formulation used: MDI
• Number of Paediatric subjects: 40

Baseline Subject Characteristics

The two treatment groups were well-balanced regarding the Baseline characteristics. There was a higher proportion (approximately 2 to 1) of female than male subjects in each treatment group, and approximately 86% of subjects in each group were White with a median age of 46 years overall. Mean Baseline heights and weights were similar in both treatment groups; and mean BMI ranged from 15.6 to 56.4.

Efficacy Results (Primary and Secondary)

MF/F and F/SC were both effective in improving lung function. MF/F was non-inferior to F/SC in increasing the mean AUC (0-12 hr) of the change from Baseline to Week 12 Endpoint in FEV1and superior in onset-of-action to F/SC. MF/F was also non-inferior to F/SC at Day 1 and Week 12.

Safety Results

There were too few subjects less than 18 years of age (40 subjects, 5.5% overall) to provide meaningful analysis for this age group; however, there were no apparent differences in the pattern of AEs reported for the different age groups. Nonserious adverse events were reported in 6 (27.3%) of 40 subjects 12 - <18 years of age treated with MF/F, including fungal skin infection, influenza, pharyngitis, sinusitis, tonsillitis, viral infection, viral pharyngitis, neck pain, dysmenorrhea, oropharyngeal pain, wisdom teeth removal, and 9 (50%) of the subjects treated with F/SC. One treatment related AE of oropharyngeal candidiasis was reported for a 16 year old female subject treated with F/SC. One Serious AE (upper respiratory infection) was observed in a 14-year-old female subject treated with F/SC.

Conclusion

Review of the safety data indicated that treatment with MF/F 200/10 mcg BID was safe and well tolerated.

P06476

Study Design

This was a randomized, multi-center, evaluator-blind, single-dose, placebo-controlled, fourperiod crossover study in children with persistent asthma 5 to 11 years of age. Each subject was expected to make a minimum of five visits to the study center: Screening Visit (Visit 1) and four treatment visits, including the Baseline Visit (Visit 2), with additional optional visits [up to 3] during the Run-in Period to provide for additional delivery device [inhaler and spacer] and spirometry training and/or reversibility assessments. The Run-in Period was followed by four randomized treatment periods, each separated by 5 to 7 days Inter-Dose periods. Subjects received open-label MF 100 mcg QD during run-in period, Inter-dose as well as Treatment periods

• Primary Objective: To compare the bronchodilatory effect of a single dose of mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) 100/10 mcg delivered with the AeroChamber Plus® with Flow-Vu® Anti-Static Valved Holding Chamber (referred to as 'spacer') versus placebo MDI.
• Formulation used: MDI, DPI
• Number of Paediatric subjects: 92

Baseline Subject Characteristics

A total of 92 subjects between 5 to 11 years of age who met entry criteria were randomized into the study. There were 17 subjects (18%) who were between 5-7 years of age and 75 subjects (82%) between 8-11 years of age. Of these, 57 (62%) were male and 35 (38%) were female. The majority of subjects were white (59 subjects, 64%); while 33 subjects (36%) were non-white: 25 subjects (27%) were Black or African American, 6 subjects (7%) were multiracial, and 1 subject each (1%) was Asian and native Hawaiian or other Pacific Islander.

Efficacy Results

The FEV1 AUC (0-12 hr) analysis demonstrated a higher adjusted change from baseline mean values for MF/F MDI 100/10 mcg with a spacer (115 mL) when compared to the placebo group (-9 mL), resulting in a statistically significantly superior effect in bronchodilation as measured by an increase of 124mL (95% CI [94, 154], $p<0.001$) in FEV1 AUC (0-12 hr) when compared to placebo. The FEV1 AUC (0-12 hr) analysis demonstrated higher adjusted change from baseline mean values for MF/F MDI 100/10 mcg without a spacer (93 mL) when compared to the placebo group (-9 mL); for a treatment difference of 102 mL (95% CI [73, 131], $p<0.001$), resulting in a statistically significantly superior effect in improving FEV1 AUC (0-12 hr) when compared to placebo.

Safety Results

A total of 18 subjects (20%) reported adverse events during the study as summarized above. The most commonly reported AEs were pyrexia (3 subjects, 3%: 2 subjects in the placebo group and 1 subject in the F DPI 10 mcg group); ear infection (2 subjects, 2%: both subjects in the MF/F MDI 100/10 mcg without spacer group); viral respiratory tract infection (2 subjects, 2% in the F DPI 10 mcg group); with other reported AEs including eye swelling, vomiting, chills, rhinitis, neck pain, cough, headache and pruritus. None of the reported AEs were considered by the investigator as treatment-related.

Conclusion

MF/F MDI and MF DPI was well-tolerated in this study, there were no clinically important differences in the overall safety profiles of the MF/F treatment groups and no new safety signals were detected for both MF/F MDI and MF DPI.

Discussion on clinical aspects

For Asmanex, the MAH has provided 6 clinical studies involving paediatric patients, One study (P04879) is a local registration study and utilized the mometasone furoate (MF) dry powder inhaler product (DPI) as the main treatment. The other five studies were part of the development program for an MF/F MDI. MF DPI was used in the studies as comparator (P04431, P04334 and P04073), or run-in (P04705) or run-in and concomitant (background) treatment (P06476). Study P04705 was closed early for business reasons.

All studies were conducted for the treatment of asthma. Variable efficacy was observed in each study. No new safety concerns were identified during the conduct of these studies.

V. RAPPORTEUR'S PRELIMINARY CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submitted studies do not raise any new concerns regarding safety or efficacy for mometasone (nasal spray or DPI) in paediatric subjects. The MAH was asked to address the following point:

> In view of the reported vulnerability of children for inhaled mometasone containing drugs, in particular regarding hormonal development and growth, we identified a possible risk relating to aberrations of the serum cortisol level. This in view of potential long term use of the inhalation medication in case of symptom control. Although it is understood that this ADR was of mild severity we request additional information regarding the observed ADR of decreased blood cortisol in study P06333. As we did not receive the study data on the topic in the clinical package no definite conclusion on the reported phenomenon can be drawn at this moment.
> Apart from this obscurity regarding the safety of Nasonex with regard to the lowering of cortisol in patients, we endorse the opinion of the RMS.

VI. ASSESSMENT OF DAY 89 RESPONSES

The applicant provided the attached response:

COMPANY RESPONSE:

Study P06333 was a Phase III, multicenter, 24-week, open-label study conducted in Japan to evaluate the safety of nasally inhaled mometasone furoate (MF) in pediatric subjects with perennial allergic rhinitis; children 3 to 11 years of age used 100 µg/day and those 12 to 15 years of age used 200 µg/day. A total of 27 (33.8% of 80) subjects had an adverse event (AE) of decreased blood cortisol, all assessed as mild by the investigator; there were no AEs reported for a diagnosis of adrenal insufficiency/suppression. The use of adult normal ranges for evaluation of blood cortisol levels in this study and timing of sample collection may have contributed to the high percentage of subjects with an AE of decreased blood cortisol. As the central laboratory for this study did not have pediatric normal ranges for blood cortisol, the study used the central laboratory's adult normal range (4.5 - 21.1 µg/dL) to assess cortisol levels. If the study had used a pediatric normal range for blood cortisol (e.g., 2.51 - 22.9 µg/dL for 2 to 15 years old [Ref. 5.4: 03YK6H]), then only 6 of the 27 subjects with an AE of decreased blood cortisol had a level below the lower limit of the pediatric normal range (i.e., 2.51 µg/dL). As blood cortisol levels demonstrate diurnal variations, with peak levels in the morning hours (6 to 9 AM) and gradually decreasing throughout the day, the protocol specified sample collection to be between 8 and 10 AM, or at minimum at the same time of day. However, of the 27 subjects, 23 (including 5 of the 6 subjects with blood cortisol levels below the lower limit of the pediatric normal range) had blood cortisol measurements taken in the mid to late afternoon. Of the 27 subjects, 22 recovered while on study therapy or following completion of the study.

Of the 27 subjects with an AE of decreased blood cortisol in the study, 15 (18.8%) subjects had an AE of decreased blood cortisol assessed as drug related by the investigator. One of these subjects was discontinued from treatment due to the decreased blood cortisol (lowest value of 2.7 µg/dL was collected in the late afternoon and was within the pediatric normal

range of 2.51 - 22.9 µg/dL); as requested, additional information regarding this case is as follows:

An 8-year-old girl (Subject No. 0005-005503) with no medical history or complications being treated with MF 100 µg/day was discontinued on Day 123 due to an AE of blood cortisol decreased. Her blood cortisol levels were 9.9 µg/dL (at 17:30) at baseline, but decreased to 4.3 µg/dL (at 17:15) on Day 82 (Week 12). It was determined to be an AE at this point. Subsequently, they were 2.7 µg/dL (at 17:00) on Day 113 and 3.3 µg/dL (at 10:00) on Day 118. MF was discontinued on Day 123. Subsequent data showed improvements: 3.2 µg/dL (at 9:45) on Day 132 (10 days after discontinuation), and 3.9 µg/dL (at 9:40) on Day 181 (59 days after discontinuation). Other AEs included pharyngitis (occurring on Day 3), upper respiratory tract infection (Day 43), bronchitis (Day 77), pyrexia (Day 119), abdominal pain (Day 119), proteinuria (Day 27), and epistaxis (Day 118). The blood cortisol decrease was mild, and the outcome was "not resolved" although improvements were seen.

The above information is also included in the English translation [Ref. 5.3.5.4: 03YFR8], [Ref. 5.4: 03Y99S] of the original clinical study report (CSR) in local language (Japanese). An English translation of the CSR synopsis was previously submitted on 19Feb2014, in accordance with Article 46 of Regulation 1901/2006.

There were no AEs reported of decreased blood cortisol or adrenal insufficiency/suppression in the 16 other nasally or orally inhaled studies with mometasone furoate (up to 26 weeks of treatment) included in the Article 46 submissions of 19Feb2014. Of the 16 other studies, 2 with orally inhaled MF were of similar treatment duration (26 weeks) and used a similar dose (200 µg/day) or larger (400 µg/day) of MF (Studies P04073 and P04334) [Ref. 5.3.5.4: 00M5P7, 00KZ6W]; these were double-blind studies, unlike P06333 which was open-label in design. The overall results of these studies do not alter the risk/benefit profile of MF in pediatric patients.

Studies of both nasally and orally inhaled MF have been conducted to specifically assess the effect of MF on adrenal function. Three clinical pharmacology studies have been conducted in pediatric subjects (2 to 11 years of age) to assess the effect of nasally inhaled MF on adrenal function. In two of these studies, MF was administered to pediatric subjects (3 to 11 years of age) at daily doses of 50, 100, and 200 µg vs placebo for 7 or 14 days. MF, at all three doses, was not associated with a statistically significant decrease in mean plasma cortisol levels post-Cortrosyn® infusion compared to placebo; all subjects had a normal response to Cortrosyn® (Studies C95-136 and C94-140) [Ref. 5.3.5.4: 00KRDK, 00N030]. In the third study, pediatric subjects with allergic rhinitis (2 to <6 years of age) who were administered MF (100 µg daily) or placebo for up to 42 consecutive days demonstrated no statistical differences between the two groups in the 24-hour urinary free cortisol concentrations (corrected for creatinine) or serum cortisol $AUC_{0\text{-}24h}$ (Study P01225) [Ref. 5.3.5.4: 00VMS7].

In addition, a 4-month, placebo-controlled safety study assessed 24-hour urinary free cortisol levels (primary endpoint) in pediatric patients 6 to 17 years of age with nasal polyps treated with nasally inhaled MF (Study P04292). Doses of 100 µg once or twice daily were assessed

in children 6 to 11 years old, and 200 µg once or twice daily were assessed in those 12 to 17 years old. No clinically meaningful changes were noted in the 24-hour urinary free cortisol levels and 24-hour urinary free cortisol levels corrected for creatinine from baseline to Month 4 in any of the MF or placebo treatment groups. There was no statistical significance between the MF treatment groups and the pooled placebo treatment group in the 24-hour urinary free cortisol levels ($P \geq 0.194$) and the 24-hour urinary free cortisol levels corrected for creatinine ($P \geq 0.193$) [Ref. 5.3.5.4: 00LM75].

In a 29-day study of pediatric patients 6 to 11 years of age with asthma (Study C96-361), orally inhaled MF 100 µg twice daily, 200 µg twice daily, and 400 µg twice daily (2 to 8 times the highest pediatric recommended daily dose) were compared to placebo. Hypothalamic-pituitary-adrenal (HPA) axis function was assessed by 12-hour plasma cortisol AUC and 24-hour urinary-free cortisol concentrations. After 29 days of treatment, there was no evidence of HPA-axis suppression with the 100 µg twice daily dose based on plasma cortisol $AUC_{0\text{-}12h}$ and response to Cortrosyn®; plasma cortisol AUC results suggest a potential for systemic exposure in children given the higher doses of 200 µg twice daily and 400 µg twice daily (24% and 27% less than placebo mean AUC, respectively) [Ref. 5.3.5.1: 00H58G].

Two long-term studies (12 months duration) of orally inhaled MF (Study C97-384: double-blind, placebo-controlled with MF 100 µg daily, 100 µg twice daily, or 200 µg daily; Study C97-385: open-label, beclomethasone-controlled with MF 100 µg twice daily or 200 µg daily) in children (4 to 11 years) included assessment of plasma cortisol and 12-hour urinary concentrations. In both studies, results indicated no clinically significant difference among treatment groups in plasma or urinary cortisol data and supported the conclusion that MF, even when administered for up to 12 months, has little to no effect on the HPA axis [Ref. 5.3.5.1: 00H6BK, 00H6BS].

Studies of both nasally and orally inhaled MF have been conducted to specifically assess the effect of MF on growth in children. One study in children 3 to 9 years of age with allergic rhinitis (Study C96-094) found no statistically significant effect on growth velocity with nasally inhaled MF (100 µg/day) compared to placebo following one year of treatment; no evidence of clinically relevant HPA-axis suppression was observed following a 30-minute cosyntropin infusion [Ref. 5.3.5.4: 008H56]. Studies with orally inhaled MF in children showed minor effects on lower leg growth (as assessed by knemometry in children 6 to 12 years of age, Study P02236) and either no effect or no consistent effects on growth velocity in two 12-month studies in children 4 to 9 years of age (C97-384 and C98-477) [Ref. 5.3.5.1: 00H66D, 00H6BK], [Ref. 5.3.5.4: 002GQ9].

Adrenal suppression and effects on growth are known systemic effects with corticosteroid therapy. These potential systemic effects as well as the measures to minimize these effects have already been included in Section 4.4 (Special warnings and precautions for use) of both the NASONEX® (nasally inhaled MF) and ASMANEX® (orally inhaled MF) Summary of Product Characteristics (SmPCs).

Section 4.4 of the NASONEX® SmPC includes the following text with regards to adrenal suppression and growth effects:

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataracts, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroids if possible, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a paediatric specialist.

Treatment with higher than recommended doses may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Section 4.4 of the ASMANEX® SmPC includes the following text regards to adrenal suppression and growth effects:

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Possible systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataracts, glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Therefore, it is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

and

A reduction of growth velocity in children or adolescents may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians are advised to closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

If growth is slowed, review therapy with the aim of reducing the dose of inhaled corticosteroids if possible, to the lowest dose at which effective control of symptoms is achieved. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

When using inhaled corticosteroids, the possibility for clinically significant adrenal suppression may occur, especially after prolonged treatment with high doses and particularly with higher than recommended doses. This is to be considered during periods of stress or elective surgery, when additional systemic corticosteroids may be needed. However, during clinical trials there was no evidence of HPA axis suppression after prolonged treatment with inhaled mometasone furoate at doses of ≤ 800 micrograms per day.

Based on the available data in clinical trials for both nasally and orally inhaled MF in children and the current text in Section 4.4 (Special warnings and precautions for use) of the respective SmPCs, the MAH believes the current labelling adequately addresses the potential risk of systemic effects, including adrenal suppression and effects on growth in children.

Assessor's comments

The applicant has clarified that Study P06333 was a Phase III, multicenter, 24-week, open-label study conducted in Japan to evaluate the safety of nasally inhaled mometasone furoate (MF) in pediatric subjects with perennial allergic rhinitis; children 3 to 11 years of age used 100 µg/day and those 12 to 15 years of age used 200 µg/day. A total of 27 (33.8% of 80) subjects had an adverse event (AE) of decreased blood cortisol, all assessed as mild by the investigator; there were no AEs reported for a diagnosis of adrenal insufficiency/suppression. Of the 27 subjects with an AE of decreased blood cortisol in the study, 15 (18.8%) subjects had an AE of decreased blood cortisol assessed as drug related by the investigator. One of these subjects, an eight year old girl, was discontinued from treatment due to the decreased blood cortisol (lowest value of 2.7 µg/dL was collected in the late afternoon and was within the pediatric normal range).

The applicant states that this anamoly could have arisen due to adult reference ranges being applied to paediatric subjects. In addition, the sample timings were variable. The applicant has provided one reference in which the authors attempted to establish reference ranges for cortisol in paediatric subjects, specifically in Germany. However it is possible that these reference ranges may anyway not be applicable to the Japanese population. However the paper does demonstrate that the levels in different paediatric age groups can be different, and also different to that of adults and by sex. The derived reference ranges will also depend on the test methodology used.

The other studies mentioned by the applicant which include studies of both nasally and orally inhaled MF, have been conducted to specifically assess the effect of MF on adrenal function and growth. The studies cover the entire paediatric age group, a number of different indications and different doses. No safety concerns in relation to effects on cortisol level were reported in any study.

As adrenal suppression and effects on growth are known systemic effects with corticosteroid therapy, section 4.4 of the Nasonex and Asmanex SmPCs contain suitable wordings to make the healthcare professionals aware of this potential risk.

The SmPC contains the following information: "*There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with NASONEX Nasal Spray."* However it is considered that study P06333 shows that mometasone may cause HPA axis depression. Therefore it is recommended that this sentence should be removed from section 4.4.

The overall risk-benefit is still considered favourable.

VII. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

The rapporteur considers that the overall benefit:risk of Mometasone remains unchanged.

The SmPC of Nasonex contains the following information: "*There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with NASONEX Nasal Spray."* However it is considered that study P06333 shows that mometasone may cause HPA axis depression. Therefore it is recommended that this sentence should be removed from section 4.4. The CMDh supported the rapporteur's overall conclusion and recommendation.

VIII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Product name
MERCK SHARP & DOHME	Nasomet
MERCK SHARP & DOHME	Nasonex
MERCK SHARP & DOHME	NASONEX 50 micrograme/doză spray nazal suspensie
MERCK SHARP & DOHME	ASMANEX TM TWISTHALER TM
MERCK SHARP & DOHME	Asmanex TM Twisthaler TM 200 micrograms Inhalation Powder Asmanex TM Twisthaler TM 400 micrograms Inhalation Powder