EMA/25158/2011

WITHDRAWAL ASSESSMENT REPORT

FOR

Zenhale

International Non proprietary Name:

Mometasone Furoate / Formoterol Fumarate

Procedure No. EMEA/H/C/001217

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

TABLE OF CONTENTS

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP List of Questions on quality, safety and efficacy, the CHMP consider that the application for Zenhale in the maintenance treatment of asthma, including reduction of asthma exacerbations, in adults and adolescents 12 years of age and older.
Zenhale should be used for patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta2-agonist. Zenhale may also be used in patients already adequately controlled on both inhaled corticosteroid and long-acting beta2-agonist.
is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Inspection issues
A routine GCP inspection had been, requested by CHMP. This inspection focused on the conduct of the clinical study. No. P04334 at 3 study sites.
Whereas the inspection at one inspection site overall was satisfactory, a large number of critical and major findings were detected at the 2 other inspection sites. Due to the deficient monitoring and lack of adequate oversight the data reliability is questionable. In order to exclude that the problem is even more extensive the CHMP adopted at its April 2010 meeting that further inspections for study PO4073 at two different sites need to be performed.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The prevalence of atopy and asthma has increased steeply over the past few decades in Westernized countries and more recently in less-developed nations. Estimates suggest that as many as 300 million people are affected worldwide and that approximately 7% of Americans currently have asthma. In Europe, the prevalence of Clinical Asthma ranges between 18.4% in Scotland and 4.9% in Scandinavia and the Baltic States. In the United States, severe asthma exacerbations and asthma-related mortality rose sharply in the 1970s and 1980s. However, despite the high prevalence of disease, the most recently available data indicate improved outcomes, with fewer annual hospitalizations for asthmatic attacks and fewer asthma-related deaths. Possible explanations for these favourable trends include the more widespread use of inhaled corticosteroids (ICS) and the introduction of new, highly effective medications and improved medication formulations for the treatment of asthma over the past 10 to 15 years.
ICSs are currently the most effective anti-inflammatory medications for the treatment of asthma. LABAs are beta-agonist bronchodilator medications that improve pulmonary function and decrease the need for short-acting rescue bronchodilator use.
Mainly due to their superior efficacy, combinations of ICS and long-acting beta-2 agonists (LABA) have been at the core of the changes in asthma treatment and have largely replaced the regular use of short-acting beta-2 agonists (SABA) and the addition of theophylline to step-up asthma treatment.
Presently, the Global Initiative for Asthma (GINA) and in the US, the National Heart, Lung, and Blood Institute (NHLBI) recommend that for asthma patients 12 years and older who are not sufficiently controlled with low-dose ICS (Step 2), the step-up option of adding a LABA to the ICS is equivalent to the option of increasing the ICS dose (Step 3).
For subjects not controlled on medium-dose ICS, the preferred treatment (Step 4) is to combine a medium- or high-dose ICS with a LABA.
A fixed-dose combination (FDC) of an ICS with a LABA provides a very convenient way of providing incremental benefit of the combination over the individual components, as well as ensuring that a LABA is always used in conjunction with an ICS.

II.2 About the product

The mometasone furoate (MF) /formoterol fumarate (F) metered dose inhaler (MDI) (MF/F) is a novel FDC of MF and F that is being developed for the management of asthma patients not controlled on ICS alone.
MF is an ICS provided in a multi-dose dry powder inhaler (DPI). (Asmanex Twisthaler. It is currently approved for the maintenance treatment of asthma in adults and adolescents ≥ 12 years of age (in the United States of America [USA], the European Union [EU], and many other countries worldwide) and in children 4 to 11 years of age (in the USA).

Formoterol is a LABA provided in a single dose DPI (Foradil Aerolizer). It is currently approved for the maintenance treatment of asthma in adults and children 5 years of age or older in the USA, throughout Europe and South America, and in most other countries worldwide. In some regions, the Foradil Aerolizer is also indicated for the acute prevention of exercise-induced bronchospasm in adults and children 5 years of age or older, when administered on an occasional, as needed basis. In some countries, it is also approved in a pressurized MDI with a chlorofluorocarbon (CFC) propellant and more recently also in a hydrofluoroalkane (HFA) MDI with the HFA-134a propellant.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

This submission describes the core clinical trials that have explored the utility of MF/F for patients with persistent asthma. There are four key efficacy/safety studies, two of which compared the clinical benefit of MF/F to each of its components and to placebo, (P04073 and P04334), one compared the clinical benefit of MF/F to MF (P04431), and the fourth which compared the medium doses of MF/F and the approved FDC of fluticasone propionate/salmeterol (F/SC) (P04705).
To demonstrate that each component makes a contribution to the claimed effect of the combination without interference of device effects, it was decided to use MDIs as component comparator products rather than the approved MF and F DPIs.
While it was possible to keep the MF MDI component formulation almost identical to the MF/F MDI, developing an identical HFA-227 formulation for F was not possible due to the low fine particle content. Based on previous feasibility studies, it was decided to use an HFA-134a MDI formulation as the F comparator. However, these formulations are not approved products and therefore clinical studies P04073 and P04334 included placebo controls to demonstrate the efficacy of each component.
In relation to FDC products, the revised CPMP guidance (CPMP/EWP/4151/00 Rev.1) indicates that there is no approved FDC reference product, so studies should include an additional treatment group in which patients receive the ICS component alone. This has been addressed in the MF/F Phase 3 clinical development program.

Regarding article 7 of the Paediatric Regulation a positive opinion was issued by the PDCO for a Paediatric Investigation Plan (EMEA-000025-PIP01-07) on 25 October 2007 and on 12 December 2008 (request for modifications of an agreed PIP). A positive opinion for the compliance check was issued 24 July 2009.

II.4 General comments on compliance with GMP, GLP, GCP

The product is manufactured in accordance with cGMP

The pivotal toxicity studies were conducted in compliance with GLP.

The CHMP has requested a GCP triggered inspection of the clinical study P04334. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the List of Outstanding Issues.

II.5 Type of application and other comments on the submitted dossier

This application concerns the centralised procedure according to Regulation (EC) No 726/2004, article 3(2)(a) and is submitted in accordance with article 10b of Directive 2001/83/EC..
Accelerated procedure, conditional approval or approval under exceptional circumstances is not requested.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The product contains the known chemical entities mometasone furoate, anhydrous and formoterol fumarate, dihydrate as active substances. Both are monographed in the Ph.Eur.

Mometasone furoate is a crystalline powder with low water solubility and a solubility of 6.2 mg/ml in ethanol. It exists in the anhydrous form and displays optical rotation characteristics.

Formoterol furoate dihydrate is a crystalline powder with low water solubility and a solubility of 4.88 mg/ml in ethanol. It exists in the stable dihydrate form. Formoterol fumarate contains two asymmetric carbons and is an equal mixture of R,R and S,S configurations so no optical activity is observed.

For both syntheses, starting materials are well characterised and full details on suppliers are provided. The description of the manufacturing process, characterisation of the drug substance and impurities are in accordance with the EU guideline on *Chemistry of new active substances*. Specifications and testing procedures for starting materials are acceptable. Control of residual solvents is performed in line with CPMP/ICH/283/95-ICH Q3C (R3).

Control of heavy metals including catalysts (formoterol fumarate synthesis) is satisfactory. Both active substances are currently used on the EU market and are synthesised as described in this application. There are therefore no new or higher levels of genotoxic impurities introduced compared to the existing products.

Both drug substance specifications comply with the requirements in Q3A (R), Q3C and Q6A EU/ICH guidelines, with general Ph.Eur. requirements for substances for pharmaceutical use, and with their respective Ph.Eur. monographs The lack of microbiological testing in formoterol fumarate drug substance is fully explained on the basis of technical and safety reasons.

The analytical methods are validated in accordance with relevant EU/ICH guidelines and found to be acceptable. Reference materials are adequately characterised for both mometasone furoate and formoterol fumarate.

Packaging materials are suitable and are compliant with Ph.Eur. 3.1.3 for polyolefines and EU Directive 2002/72/EC relating to materials intended to come into contact with food stuff.

Satisfactory stability data is provided to support the proposed re-test period for both active sunstances.

Drug Product
The finished product is a homogeneous white suspension in a 16ml aluminium container fitted with a 50µl metering valve. A polypropylene press and breathe actuator is provided with the pressurized canister to deliver a dose to the patient. The pressurised metered dose suspension contains the active substances mometasone fumarate, anhydrous and formoterol fumarate, dihydrate and is to be marketed in three strengths containing mometasone fumarate anhydrous/formoterol fumarate dihydrate 50µg/5µg, 100µg/5µg and 200µg/5µg respectively per delivered (ex-actuator) dose. The metered doses (ex-valve) are 60µg/5.5µg, 115 µg/5.5µg and 225 µg/5.5µg respectively. The proposed market pack is 1 canister + 1 actuator. Each canister contains a nominal 120 doses, where one patient dose = two actuations.

The product composition consists of active substances mometasone furoate and formoterol fumarate suspended in propellant HFA227 with ethanol, anhydrous as co-solvent and oleic acid as surfactant. The excipients are those commonly used in manufacture of pressurised metered dose inhalation preparations. Target delivered dose of both APIs has been set based on clinical data using the proposed actuator and valve and full scale production batches of each product strength.

The development of the product has been satisfactorily performed and explained and is in accordance with EU guidelines on Development pharmaceutics and EMEA/CHMP/QWP/49313/2005 Corr. on the

Pharmaceutical Quality of Inhalation and Nasal Products. Patient handling instructions for priming/re-priming, handling after cold storage and cleaning procedures have all been satisfactorily addressed.

The packaging materials have shown suitable by acceptable product performance characteristics and stability studies.

The finished product specification is considered compliant with the general requirements of EU/ICH Q6A Guideline on Specifications, Ph.Eur. requirements for Preparations for Inhalation (monograph 671), and EMEA/CHMP/QWP/49313/2005 Corr. and includes relevant physicochemical, ID, assay, particle size analysis and purity tests. Limits have been justified and supported by clinical batch data.

Analytical procedures are properly described and validation provided in accordance with EU/ICH validation guidelines.

Satisfactory information has been provided on reference materials.

Canister, valve and actuator details are provided and compliance with Ph.Eur. and EU directive 2002/72/EC requirements is observed. Extractables and leachables from the container components have been addressed and no toxicological concerns arise.

A shelf-life of 24 months is proposed when stored below 30°C and protected from moisture and freezing. Stability studies have been performed in accordance with ICH Q1A and Q1B. The results point to a stable product and the proposed shelf-life may be accepted.

III.2 Non clinical aspects

Pharmacology
The non-clinical pharmacodynamic data indicate that the mometasone furoate in combination with formoterol fumarate could be beneficial for patients with reduced lung function and pulmonary inflammation such as in asthma. Results of in vitro and in vivo pharmacodynamic studies revealed both rapid onset and long duration of action, as well as at least equal or better potency and selectivity of mometasone furoate comparing to other approved inhaled glucocorticoids. Non-clinical data available on formoterol indicates that this compound also exhibits good efficacy profile with rapid onset and long duration of action. Furthermore, there is huge literature evidence, supported by clinical practice, that inhaled glucocorticoids in combination with inhaled long acting β_2 agonists represent the most important treatment option for asthma. Recently published review article of Chung, Caramori and Adcock perfectly define the place and role this dual therapy of asthma. The composition, pharmaceutical form and the route of Zenhale administration clearly indicate that it is a next fixed-dose combination belonging to this commonly accepted pharmacotherapeutic group with recognized safety and efficacy.

The lack of secondary pharmacodynamic, safety pharmacology and pharmacodynamic drug interaction is acceptable due to the extensive non-clinical and clinical data regarding the pharmacology of the individual compounds in addition to the clinical experience with formoterol marketed in combination with other glucocorticosteroids.

Pharmacokinetics
The pharmacokinetic profiles of both MF and F were adequately examined. The collected data are sufficient for the assessment of fixed-dose product planned for inhaled administration such as Zenhale. No significant changes in the pharmacokinetic parameters of either compound were observed in rats and dogs following co-administration of mometasone furoate with formoterol fumarate.
As no pharmacokinetic interactions were identified, further non-clinical pharmacokinetic testing is not deemed necessary in accordance with the guideline on fixed combinations (EMEA/CHMP/SWP/258498/2005).

Toxicology
The toxicological profile of mometasone furoate/formoterol combination consist of a 2- and 13- week inhalation toxicity studies of mometasone furoate/formoterol MDI in rats and dogs. The individual toxicological properties of mometasone furoate and formoterol are well known.
In the pivotal 13-week oral repeat dose toxicity study conducted in rats (30/3, 60/6, 120/12, 120/3, 120/0 and 0/12 µg/kg/day for mometasone furoate and formoterol fumarate), only known toxicity

relating to exaggerated pharmacological effect of mometasone furoate was observed. No formoterol fumarate-related effects were seen in this study.
Generally, effects consistent with known effects of mometasone furoate and formoterol fumarate were observed in the pivotal 13-week repeat dose toxicity study conducted in dogs (25/2.5, 50/5, 100/10, 100/2.5, 100/0, 0/10 µg/kg/day for mometasone fuorate and formoterol fumarate).
The exceptions were the observation of minimal epithelial vacuolization in the mammary gland and lymphoid depletion in the thymus observed in the formoterol fumarate alone group in dog study. Minimal epithelial vacuolization in the mammary gland was seen in 2/4 dogs in the formoterol fumarate alone group as compared to 2/2 dogs in the 100/2.5 ratio mometasone furoate/formoterol fumarate group and 1/4 in the mometasone furoate alone group. Five out of 8 dogs in the formoterol fumarate alone group had lymphoid depletion in the thymus. The findings were of either low severity and/or lower incidence than the mometasone furoate groups. These findings indicate that contamination of the fomoterol fumarate alone group may have had occurred as these toxicity findings may be related to mometasone furoate. It is acknowledged that no profound toxicity relating to monetasone furoate was observed in the formoterol fumarate alone group when compared to the toxicity observed in the mometasone furoate groups. Thus, the findings do not *per se* compromise the conclusions of the study.
The plasma exposures in the pivotal toxicity studies (99457 and 99458) were comparable or higher than that observed in humans following inhalation.
Some minor issues relating to cross-contamination have been identified in the non pivotal studies 95007 and 95008. However, none of the issues are likely to affect the conclusions of toxicity testing of mometasone fuorate/formoterol fumarate combination.
The lack of genotoxicity, carcinogenicity, reproductive and local tolerance studies with mometasone furoate/formoterol fumarate is acceptable due to the toxicity profile for the individual drugs is well defined.
The applicant has identified several impurities, degradation products and leachables in the drug product. The estimated daily intake of these compounds is below or close to the TTC level. In some cases, the applicant has conducted an analysis for structural alerts in relation to genotoxicity. Two of the leachables are known to be genotoxic and a weak tumour promoter, respectively. They are both controlled below the TTC level of 1.5 µg/day and are believed to act through different mechanism of actions. Thus, further actions are not deemed necessary from a non-clinical point of view.

Ecotoxicity/environmental risk assessment
The $PEC_{surface\ water}$ for mometasone and formoterol are below the trigger value of 0.01 µg/L. Thus, a Phase II ERA is not required. The applicant states that the log K_{ow} values for mometasone and formoterol are below the action limit of 4.5 indicating that a PBT analysis is not required. However, the submitted documents are not of acceptable quality. The applicant is asked to submit documentation in the form of published scientific literature or experimental study reports. The latter should be conducted in the compliance with GLP and OECD (i.e., OECD123 or 107).

III.3 Clinical aspects

- **Tabular overview of clinical studies**

Pharmacokinetics
The comparators used in the pivotal studies P04073, P04334 and P04431 (MF MDIs and F MDIs) are not authorized medicinal products. It is therefore considered crucial that sufficient bridging between the marketed DPIs and the MDIs used in the trials was provided.
The clinical PK studies submitted to support the application have concentrated on demonstration of comparable bioavailability and bioequvalence between mometasone and formoterol as single agents in a MDI formulation against the marketed DPI formulation and mometasone and formoterol as single agents in a MDI formulation against the combined MF/F MDI formulation. No studies on metabolism and excretion, interactions, distribution or studies in special populations were performed.

Study P04275 demonstrates significantly reduced bioavailability of **mometasone** from the developed MF/F MDI device compared to the marketed mometasone DPI device (steady state AUC exposure is reduced by 25% (90% CI 61 to 91)). Thus, an extrapolation from the dosage used in the marketed MF DPI to the MF/F MDI used in this clinical program cannot be performed. A direct comparison of mometasone (MDI) against mometasone DPI has not been performed and dose-finding studies have not either been performed. This is considered a major objection as a bridge to the marketed formulation (DPI) and the mometasone comparator (MDI) in the clinical study does not exist. The delivered doses via the DPI and MDI could affect the efficacy and disable interchangeability of the FDC

and dual therapy regimes with the same components.Data from COPD patients in study P04689 confirm the above data.

Based on PK data from studies P06144 and P05643 on urinary excretion, bioavailability of **formoterol** between the MDI and the DPI formulation appears similar. Plasma AUC data from P05643 appears to support similarity with respect to bioavailability as well. However, the applicant has apparently not performed a standard geometric mean ratio analysis. This should be supplied for urine data (both studies) and plasma AUC data (study P05643) to support comparable bioavailability of formoterol in the MDI against the DPI formulation.

Study P06144 demonstrates comparable efficacy, estimated as 12 hour FEV1 AUC of formoterol MDI at 12 and 24 mcg compared to formoterol DPI. 12 mcg was statistically superior to 6 mcg while no difference between 12 and 24 mcg could be demonstrated. The applicant selection of the 12 mcg for clinical studies appears reasonably justified.

Study P06143 demonstrates bioequivalence between formoterol (10 mcg) MDI and DPI as well as between formoterol MDI and formoterol MF/F MDI in terms of FEV1.

Dose-proportionality is reasonably convincingly demonstrated for formoterol in doses of 10, 20 and 40 mcg in combination with 400 mcg mometasone (M/F MDI). Systemic exposure to mometasone between the two combinations 400/20 and 400/40 mcg could not be demonstrated to be bioequivalent as mometasone AUC was about 12% (90% CI 6-335) higher for the 400/40 mcg combination. This is unlikely to be of clinical relevance.
There are no data allowing for an evaluation of mometasone dose-proportionality at the three different dosages suggested in the sought posology and suggested doses of mometasone i.e. between 200 and 800 mcg daily. Due to the lack of this information, the applicant is asked to justify why the comparative bioavailability between the MF/F MDI and the marketed MF DPI is not based on all three dose-strength

Mometasone MF/F MDI displays time-dependent pharmacokinetics as exposure increases following 42 days of treatment for both strengths of 200/10 mcg BID and 400/10 mcg BID. Cmax increases about 2 and 3 threefold, respectively while the accumulation ratio was 2.6 and 4.5, respectively. This is a relatively high degree of accumulation and the applicant has not provided a satisfactorily discussion on this.
A slight increase in exposure to formoterol was noticed for the 400/10 mcg MDI BID as Cmax increased about 2-fold, and the accumulation ratio was 1.7; this is less likely to be of clinical relevance.

After single-dose inhalation of MF/F in healthy volunteers, the intersubject CV across studies, dosage forms, and treatment groups ranged from 40% to 77% and 54% to 97% for Cmax and AUC, respectively. Following multiple dose administration to healthy and asthmatic subjects, the intersubject CV ranged from 36% to 72% and 35% to 70% for Cmax and AUC values, respectively.

Gender differences in PK of formoterol and mometasone does not appear to be an issue.

There are no PK or PD data presented for children aged 12 to < 18 years. In the light of the available safety data in this population (62 adolescents were included in the 52 weeks safety study P0139), the lack of paediatric PK data should not preclude a positive benefit risk assessment. However the applicant must provide these data as a post-marketing commitment. Generation of PK-data in the 5-11 years old to be used for interpolation of data between this sub-population and the adult population is also a key-binding element of the approved paediatric investigational plan (EMEA--0000025-PIP01-07).

An adequately designed and performed interaction study demonstrated no interaction between mometasone and formoterol when administered either separately as MDI or as the combined product MF/F MDI.

Pharmacodynamics
In terms of potential for suppression of the HPA axis, the MF/F product developed appeared comparable to, or slightly less, than fluticasone/salmetorol at clinical relevant doses.

Clinical efficacy

Dose-response studies

No clinical dose-finding studies were conducted for this fixed combination. The dose selection was based on previous studies with formoterol fumarate and mometasone furoate.
Currently marketed formoterol fumarate and mometasone furoate products are delivered via DPI (Asmanex® Twisthaler® and Foradil® Aerolizer®), whereas the mono-component MDIs used as comparators in the phase 3 clinical development program are non-approved products. Insufficient bridging studies were conducted (see Clinical Pharmacology). For MF in the FDC of this application Cmax and AUC on Day1 and Day5 were statistically significantly lower when compared to the marketed MF DPI device (Asmanex® Twisthaler®) in healthy volunteers (study P04725). Thus, a justification for the selected dosages of MF in the FDC is lacking. As regards the Formoterol part of the FDC bioequivalence has been established for FEV1 at 12h between F DPI, F MDI and MF/F MDI (study P05644); hence, no further dose-finding is deemed necessary. According to the applicant's reply to the D120 LoQ it was not intended to perform bridging as the applicant considers that a full clinical program was performed.
In the response to major objection 78 a new study P05122 (randomized, multi-center, double-blind, double-dummy parallel group, placebo-controlled, study in patients ≥ 12 years of age with persistent allergic asthma, documented reversibility and increased eNO levels) was submitted, investigating the efficacy of MF/F 100/10µg to 400/10 µg bid on exhaled nitric oxide (eNO) after 14 days of treatment. Exhaled nitric oxide is not a validated tool for assessment of airway inflammation and is currently used primarily for research purposes. Conflicting results have been obtained 1) as regards the ability of serial eNO monitoring to optimise ICS dosing and 2) on the estimated time needed for a measurable effects (ranging form 3 days to 8 weeks; Am J respir crit care Med, vol. 180; 59-99, 2009). Based on these considerations the obtained efficacy results (2 weeks washout too short; 2 weeks study duration too short; only the highest dose obtained the clinically meaningful twofold change) are considered insufficient to justify the selected dosages of MF in the FDC. Bridging to the marketed MF DPIs was not provided in the response to the D120 LoQs. This still poses a major objection

Main clinical studies
The phase III clinical efficacy program includes four pivotal efficacy and safety studies (table 2). Studies P04073 and P04334 of 26 weeks duration compared MF/F to its components and placebo. Studies P04431 and P04705 compared MF/F to MF alone and fluticasone propionate/salmeterol (F/SC) respectively.
Although being planned for 52 weeks, the active comparator study P04705 was terminated (not for safety reasons) after completion of phase 1 of the study, i.e. after 12 weeks. (It is mentioned that the study was closed in response to changing competitive market conditions. The sponsor felt that the exploratory and health-economic-based secondary endpoints after 52 weeks of treatment no longer addressed important clinical questions that needed to be examined with this clinical research trial.) Also study P04431 is a 12-week study only.
Asthma trials aimed at demonstrating the effect of controller medication should have a duration of at least 26 weeks. However, due to the fact that these trials involve known active substances the 12-week duration in two of the studies appears acceptable.

In addition the phase III program comprised one safety study (P04139 comparing MF/F to F/SC)) and one dose-counter functionality study (P04703).

Table 2 Relevant Efficacy Studies in the MF/F Clinical Program for Asthma

Study No.	Treatment Groups	Study Design / Duration of Active Treatment	No. of Subjects[a] Age Range	Subject Population	Primary endpoint
P04073	MF/F MDI 100/10 mcg BID MF MDI 100 mcg BID F MDI 10 mcg BID Placebo BID	Randomized, multicenter, double-blind, parallel-group 26 weeks of double-blind treatment	746 (182) 12-79	Adult and adolescent subjects with persistent asthma previously treated with low doses of ICS	Co-primary endpoints: AUC(0-12 hr) of the change from Baseline to Week 12 in FEV1 Time-to-first severe

Study No.	Treatment Groups	Study Design / Duration of Active Treatment	No. of Subjects[a] Age Range	Subject Population	Primary endpoint
					asthma exacerbation during the Treatment Period
P04334	MF/F MDI 200/10 mcg BID MF MDI 200 mcg BID F MDI 10 mcg BID Placebo BID	Randomized, multicenter, double-blind, parallel-group 26 weeks of double-blind treatment	781 (191) 12-76	Adult and adolescent subjects with persistent asthma previously treated with medium doses of ICS	Co-primary endpoints: AUC(0-12 hr) of the change from Baseline to Week 12 in FEV1 Time-to-first severe asthma exacerbation during the Treatment Period[b]
P04431	MF/F MDI 400/10 mcg BID MF/F MDI 200/10 mcg BID MF MDI 400 mcg BID	Randomized, multicenter, double-blind, parallel-group 12 weeks of double-blind treatment	728 (488) 12-84	Adult and adolescent subjects with persistent asthma previously treated with high doses of ICS	AUC(0-12 hr) of the change from Baseline to Week 12 in FEV1[a]
P04705	MF/F MDI 200/10 mcg BID Fluticasone propionate / Salmeterol DPI 250/50 mcg BID	Randomized, multicenter, evaluator-blind, parallel-group 12 weeks of open-label, evaluator-blind treatment and completion of the planned Phase 1[b]	722 (371) 12-82	Adult and adolescent subjects with persistent asthma previously treated with medium doses of ICS	AUC(0-12 hr) of the change from Baseline to Week 12 in FEV1[a]

Total Number of Subjects = 2977 (1232)

BID = twice daily; DPI = dry powder inhaler; F = formoterol fumarate;; ICS = inhaled corticosteroid; MDI = metered dose inhaler; MF = mometasone furoate; MF/F = mometasone furoate/formoterol fumarate combination.
a: Numbers in parentheses = the number of subjects treated with MF/F; **b:** Study P04705 was terminated early for reasons unrelated to any safety issue, prior to the planned 52-week duration. As specified in the protocol, the primary efficacy assessment was at Week 12, and the majority of subjects in this study had completed a minimum of 12 weeks of treatment when the study was terminated.

Studies P04073, P04334, P04431, and P04705 had similar inclusion criteria: Female and male subjects at least 12 years of age of any race, with a diagnosis of persistent asthma of at least 12 months' duration:

- The asthma diagnosis was assured by the demonstration of a subject's responsiveness to bronchodilators before randomization:
  - An increase in absolute FEV1 of at least 12% and a volume increase of at least 200 mL within approximately 15 to 20 minutes after administration of four inhalations of albuterol/salbutamol (total dose of 360 to 400 mcg), **or**

- A PEF variability of more than 20% expressed as a percentage of the mean highest and lowest morning pre-bronchodilator PEF over at least 1 week, **or**
- A diurnal variation in PEF of more than 20% based on the difference between the pre-bronchodilator (before taking albuterol/salbutamol) morning value and the post-bronchodilator value (after taking albuterol/salbutamol) from the evening before, expressed as a percentage of the mean daily PEF value.

▪ Subjects were not allowed to have used oral glucocorticosteroids within 30 days before Screening.

In addition study specific inclusion criteria were used to address a wide range of asthma severity based upon **1)** previous levels of ICS use (P04073: low dose; P04334: medium dose; P04431: high dose); **2)** FEV1 at screening (Studies P04073, P04334, and P04705: ≥60% and ≤90% predicted; Study P04331: ≥50% predicted); **3)** Baseline FEV1 (Studies P04073, P04334, and P04705: ≥60% and ≤85% predicted; study P04331: ≥60% and ≤90% predicted); **4)** Study P04331: At least one severe asthma exacerbation requiring a course of oral glucocorticosteroids 2 to 12 months before Screening; **5)** Study P04705 only: ≥2 asthma-related unscheduled visits either to a physician or to an emergency room within the past year OR ≥3 asthma-related unscheduled visits within the past 2 years and the use of 12 or more inhalations of SABA rescue medication during the last 10 days of run-in.

Exclusion criteria were acceptable and were primarily based upon exclusion of unstable patients with uncontrolled asthma or risk of uncontrolled asthma. In addition, current or previous smoking within the past 12 months or a cumulative smoking history > 10 years;

Spacers were not to be used with the study medication. Subjects requiring the use of a spacer with the MDI were not to be enrolled in the study. In the response to the D120 LoQs the applicant provided in-vitro data and in-vivo data obtained from COPD patients in order to support the use an AeroChamber Plus Valved Holding Chamber with the FDC inhaler. The Applicant's choice of the Aerochamber Plus device can be accepted on the basis of the performed in vitro analyses. However, the data set should be completed with raw data and statistical calculations for the in vitro APSD analysis - including influence of patient population dependent range of flow rates.

The studies were well balanced for demographic and baseline characteristics with the exception of quite large gender differences in study P04334 (female patients ranging from 51% to 64% in the different treatment groups).

Considering that this is an application for a fixed combination with 2 well-known substances, the number of adolescent patients between 12 and 18 years of age (represented by approx. 6-15% of patients) and the number of elderly patients ≥65 years of age (represented by 5-12% of patients) appears sufficient.

The majority of patients were white (range 70-90%) followed by multiracials, and with negligible numbers of subjects of different race (Blacks n=125, American Indians n=18, Asians n=221, Pacific Islanders n=3). This should be reflected in the SPC.

No considerable differences were noted for mean and median duration of asthma between the studies (mean duration ranged from 13.67 to 17.46 years). With increase in treatment steps as expressed by low, medium, or high dose of ICS (studies P04073, 4334, and 4431, respectively) baseline FEV1 lowered (P04073: 75.08%-; P04334 72.62%-; P04431 66.31% of predicted).

All pivotal studies were carried out in subjects showing clinically relevant reversibility of airway function (% beta-2 reversibility ranged from 17.25 to 24.44 % across all studies). The inclusion of less than optimally controlled asthma patients was reflected by the ACQ total scores across studies P04073 (1.31), P04334 (1.51) and P04431 (1.93). ACQ total score of 0 reflects good control and 6 reflects poor control, with a score ≥ 1.5 reflecting not well controlled asthma).

Methodology

All four pivotal studies were randomized, multicenter, parallel-group studies in which MF/F was compared to MF, F, placebo or the active comparator F/SC. The fixed combination guideline (CHMP/EWP/240795 Rev.1) requires a comparison of the fixed combination to its individual components as well as placebo whenever feasible. Nevertheless, although it was a requirement for inclusion that patients had to be on stable treatment with low and medium dose ICS, it is astonishing, that studies P04073 and P04334 were allowed to be performed with placebo arms. Furthermore, a monotherapy arm with formoterol was included in studies P04073 and P04334 despite the warnings of its use as monotherapy according to the GINA guideline (2008). It is understood that this treatment arm was introduced due to an FDA requirement however; it is surprising that these trials were permitted by Ethics Committees in Europe.

Studies P04073, P04334 and P04431 were double-blind studies whereas study P04705 was an evaluator blind study. Blinding was ascertained as follows: In studies P04073, P04334 and P04431 by use of double-dummy design (active MF/F, MF and placebo MF/F inhalers and active F and placebo F inhalers respectively, were identical in appearance. However, the two sets of inhalers were not

identical to each other); in study P04705 study drug was administered by a third-party dispenser, in an open-label, evaluator-blind manner as the MF/F MDI and F/SC DPI are different in appearance.

The primary objectives differed across the studies:
In studies P04073 and P04334 co-primary objectives were to assess the added benefit of F (10 mcg BID) and MF (100 and 200 mcg BID) respectively to the FCD of MF/F (100/10 mcg BID and 200/10 mcg BID) as regards efficacy on 1) change from baseline to week 12 in FEV1 AUC (0-12 hr) (superiority of MF/F vs. MF) and 2) time to first severe asthma exacerbation (superiority of MF/F vs. F). A severe asthma exacerbation was defined as a clinically judged deterioration of asthma or a meaningful reduction in lung function, based on any one of the following: 1) A decrease in FEV1 below 80% of Baseline; 2) A decrease in PEF below 70% of Baseline on 2 consecutive days; 3) Clinical Deterioration as judged by the clinical investigator requiring a course of action: emergency treatment, hospitalization or treatment with additional, excluded asthma medication (e.g. systemic corticosteroids).

In study P04431 the primary objective was to evaluate the benefit of MF/F (200/10 and 400/10 mcg BID) vs. MF (400 mcg BID) and in study P04705 the benefit of MF/F 200/10 mcg BID vs. F/SC 250/50 mcg respectively, as regards efficacy on change from baseline to week 12 in FEV1 AUC (0-12 hr); superiority for MF/F vs. MF and non-inferiority for MF/F vs. F/SC.
The spirometric endpoint FEV1 AUC (0-12hr) (common to all 4 studies) is a generally accepted endpoint for assessment of the LABA component. An endpoint measuring clinical function was chosen as co-primary endpoint in studies P04073 and 4334. "Time to first severe exacerbation" was chosen as the endpoint to assess the contribution of MF to the MF/F FDC. According to the CHMP guideline on asthma (CPMP/EWP/2922/01) FEV1 is considered the appropriate primary endpoint for assessing the effect of anti-asthma drugs, taking into account the relation to last dose as well as concomitant treatment. Trough FEV1 as endpoint for the efficacy of ICSs is a more sensitive (and easier) endpoint than "Time to first severe exacerbation".
According to the CHMP asthma guideline (CPMP/EWP/2922/01) "exacerbation rates" may be useful for assessing controller treatment in *more severe* asthma but not in mild to moderate asthma. The guideline further states that symptom scores and the use of reliever medication are acceptable symptom based endpoints.
Trough FEV1 was included as key secondary endpoint in Studies P04073 and P04334 only. Trough FEV1 and time to first (severe) asthma exacerbation were only "additional secondary endpoints" in study P04431 (which in addition was only of 12 weeks duration).
As stated above, "time to first severe exacerbation", would have been more suitable in a more severe asthma population observed for a longer period of time. Based on their previous use of ICS, patients included in P04073 and 4334 may at best have been judged to have asthma of moderate severity.. "Time to first severe exacerbation" was not properly evaluated in a more severe asthma population which becomes even more critical due to statistically significantly lower exposure to MF in the FDC as compared to the marketed MF DPI formulation.
According to "An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for clinical asthma trials and clinical practice (2009) a severe asthma exacerbation is defined as an event that requires urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma. However, there is no universally accepted and validated endpoint for severe asthma exacerbation. The applicant's proposed criteria for severe asthma exacerbations seem reasonable according to previous published literature. In addition, it is acknowledged that PEF was recorded in an electronic diary by the patients eliminating the risk of retrospectively completed entries. However, recent recommendations do not recommend percentage changes in PEF as a criterion for severe exacerbations (Reddel et al, Am J Respire Crit Care Vol 180 pp59-99, 2009 and An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations, 2009). According to the Task Force (referred to above) it is recommended that the definition should include at least 3 days´ use of systemic corticosteroids to avoid including inadvertent or inappropriate patient-initiated use. This 3-day criterion is clinically relevant, as a shorter duration of treatment is not recommended by guidelines. Further analyses including this criterion have been presented in the answer to the D120 LoQ.

The participant flow was as follows: In studies P04073 and P04334 the number of patients discontinuing treatment was quite high, roughly 20-40%. It was clearly highest in the placebo and formoterol groups and approximately comparable in the MF/F and MF groups. The majority of the discontinuations in the placebo and formoterol groups were not unexpectedly due to treatment failure (around 20%). In fact, the overall study drop-out in these treatment arms were approximately twice as high as presumed at the sample size calculations. Discontinuations due to AEs were similar across the treatment groups.

In study P04431 most discontinuations (14%) were noted in the MF group. Discontinuations in the MF/F 200/20 BID and 400/10 mcg BID groups were the same (10%). Similar rates for discontinuation for treatment failure and AEs were seen across the treatment groups.
In study P04705 study subject disposition was very similar for the 2 treatment arms.
The efficacy analyses were according to the statistical analysis plans to be carried out using an ITT population, principally consisting of all randomized subjects, and using an efficacy-evaluable-dataset defined as all randomized subjects who met key eligibility and evaluability criteria. The populations actually used for the efficacy analyses were not clearly defined but clarification has been provided by the applicant in the response to the D120 LoQs..
An analysis of covariance (ANCOVA), with treatment, study site, and Baseline as covariates was used to analyse responses for FEV1 AUC (0-12 hr). The log-rank test for equality of survival curves was used to analyse responses for time-to-first asthma exacerbation.

Efficacy results:

The results are presented in a uniform way that facilitates comparisons of results from the different endpoints and subgroups. Although the effect size in the pair wise comparison between the randomization groups can easily be computed by subtracting the relevant least square estimates, it would have been convenient that the pair wise comparison estimated effect sizes were also presented

Primary endpoints:

FEV1 AUC (1-12):
The primary efficacy variable to assess the contribution of formoterol to the efficacy of MF/F was the change from baseline to week 12 in FEV1 AUC (0-12 hr). This was the primary endpoint in the high dose ICS Study P04431 and study P04705 and co-primary endpoint in the low-dose and medium-dose ICS studies P0473 and P4334, respectively.
The primary treatment comparisons were as follows: In studies P04073 and P04334: MF/F vs. MF monotherapy (MF/F 100/10 mcg BID vs. MF 100mcg BID in P04073; MF/F 200/10mcg BID vs. MF 200mcg BID in study P04334); in study P04431: MF/F 400/10 mcg BID vs. MF 400 mcg BID; in study P04705: MF/F 200/10 mcg BID vs. F/SC 250/50 mcg BID.
In studies P04073, P04334 and P04431 at week 12 the fixed dose combinations of MF/F 100/10, 200/10 and 400/10 mcg BID induced a significant and clinical relevant increase from baseline in FEV1 AUC (0-12 h): 4.00 and 3.11 L x hr in studies P04073 and P04334 and 3.59 and 4.19 L x hr for the two doses in P04431 Tables 7A-C below). This data was supported by serial evaluations (0-12 h) of FEV1 for the 100/10 and 200/10 mcg dosages at week 12 amounting to >200 ml for all time points when compared to placebo in study P04073 and P04334 (data not shown in this document). No placebo group was included in the high dose study P04431 for ethical reasons.
Also at week 12 all three doses of MF/F were statistically significantly superior to MF alone in FEV1 AUC(0-12 h). These results were supported by analysis of the efficacy-evaluable subsets of subjects.

Table 7A (study P0473) FEV1 AUC(0-12 hour) (Liter x hour) - Change From Baseline Analysis of Covariance (All Randomized Subjects)

	MF/F MDI 100/10 mcg BID (A)		MF MDI 100 mcg BID (B)		F MDI 10 mcg BID (C)		Placebo (D)	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean
Change From Baseline[b]								
Day 1	178	3.94	184	1.85	187	4.09	187	1.64
Week 1	175	3.24	178	1.59	179	3.09	172	0.77
Week 12	**155**	**4.00**	**156**	**2.53**	**146**	**3.83**	**129**	**1.11**
Week 26	144	3.60	144	2.41	126	3.05	115	1.31
Endpoint[c]	181	3.43	185	2.10	188	2.59	188	0.63
Average[d]	181	4.08	185	2.50	188	3.63	188	1.44

		Model P-Values			Pairwise Comparisons P-Values					
	Pstd[a]	Trt	Site	Base	A-B	A-C	A-D	B-C	B-D	C-D
Change from Baseline										
Day 1	3.29	<.001	<.001	<.001	<.001	0.679	<.001	<.001	0.538	<.001
Week 1	3.85	<.001	<.001	<.001	<.001	0.717	<.001	<.001	0.052	<.001
Week 12	**3.71**	**<.001**	**<.001**	**<.001**	**0.001**	**0.711**	**<.001**	**0.004**	**0.002**	**<.001**
Week 26	4.23	<.001	<.001	<.001	0.027	0.325	<.001	0.242	0.053	0.003
Endpoint[c]	4.09	<.001	<.001	<.001	0.003	0.055	<.001	0.263	<.001	<.001
Average[d]	1.95	<.001		<.001	<.001	0.673	<.001	<.001	0.068	<.001

	95% Confidence Intervals					
	A-B	A-C	A-D	B-C	B-D	C-D
Change from Baseline						
Day 1	(1.39, 2.79)	(-0.84, 0.55)	(1.61, 3.00)	(-2.93, -1.55)	(-0.47, 0.90)	(1.77, 3.14)
Week 1	(0.82, 2.48)	(-0.68, 0.98)	(1.64, 3.31)	(-2.32, -0.67)	(-0.01, 1.65)	(1.49, 3.15)
Week 12	**(0.60, 2.35)**	**(-0.72, 1.06)**	**(1.98, 3.81)**	**(-2.19, -0.43)**	**(0.51, 2.33)**	**(1.81, 3.64)**
Week 26	(0.14, 2.25)	(-0.54, 1.63)	(1.17, 3.40)	(-1.73, 0.44)	(-0.01, 2.21)	(0.61, 2.87)
Endpoint[c]	(0.47, 2.20)	(-0.02, 1.71)	(1.95, 3.66)	(-1.34, 0.37)	(0.62, 2.33)	(1.11, 2.81)
Average[d]	(1.10, 2.58)	(-0.58, 0.89)	(1.78, 3.26)	(-2.41, -0.95)	(-0.05, 1.41)	(1.63, 3.09)

LS = least square. **a:** Post-Baseline LS Means and Pstd (pooled standard deviations) are obtained from the ANCOVA model with treatment (Trt), site effects, and the Baseline (Base) FEV1 (liters) as a covariate; **b:** Baseline is the mean of two pre-dose measurements (30 minutes prior to dosing, and 0 hour, immediately prior to dosing) on Day 1; **c:** Endpoint = the last post-Baseline non-missing FEV1 AUC(0-12 hr) result carried forward; **d:** Average = Longitudinal average across scheduled visits obtained from a mixed model with treatment and subject as fixed effects, treatment day and treatment day-by-treatment interaction as random effects, and Baseline FEV1 (liters) as a covariate.

Table 7B (study P04334) FEV1 AUC(0-12 hr) (Liter x hour) - Change From Baseline Analysis of Covariance (All Randomized Subjects)

	MF/F MDI 200/10 mcg BID (A)		MF MDI 200 mcg BID (B)		F MDI 10 mcg BID (C)		Placebo (D)	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean
Change From Baseline[b]								
Day 1	188	3.20	189	1.29	198	2.73	192	1.42
Week 1	179	2.82	184	1.41	189	2.19	177	0.36
Week 12	**166**	**3.11**	**169**	**1.30**	**135**	**1.93**	**128**	**0.57**
Week 26	152	3.33	153	1.48	118	2.56	114	0.60
Endpoint[c]	190	3.19	190	1.31	202	1.60	193	0.51
Average[d]	190	3.34	190	1.47	202	2.40	193	0.99

		Model P-Values			Pairwise Comparisons P-Values					
	Pstd[a]	Trt	Site	Base	A-B	A-C	A-D	B-C	B-D	C-D
Change from Baseline										
Day 1	2.96	<.001	<.001	<.001	<.001	0.124	<.001	<.001	0.687	<.001
Week 1	3.83	<.001	<.001	<.001	<.001	0.128	<.001	0.054	0.013	<.001
Week 12	**4.02**	**<.001**	**<.001**	**0.025**	**<.001**	**0.017**	**<.001**	**0.198**	**0.140**	**0.009**
Week 26	3.97	<.001	<.001	0.012	<.001	0.138	<.001	0.037	0.094	<.001
Endpoint[c]	3.98	<.001	<.001	0.002	<.001	<.001	<.001	0.491	0.055	0.008
Average[d]	2.03	<.001		<.001	<.001	0.090	<.001	<.001	0.310	<.001

	95% Confidence Intervals					
	A-B	A-C	A-D	B-C	B-D	C-D
Change from Baseline						
Day 1	(1.30, 2.53)	(-0.13, 1.08)	(1.17, 2.40)	(-2.04, -0.83)	(-0.74, 0.49)	(0.70, 1.91)
Week 1	(0.60, 2.23)	(-0.18, 1.44)	(1.64, 3.29)	(-1.59, 0.01)	(0.23, 1.87)	(1.02, 2.65)
Week 12	**(0.89, 2.71)**	**(0.21, 2.14)**	**(1.55, 3.51)**	**(-1.58, 0.33)**	**(-0.24, 1.70)**	**(0.34, 2.37)**
Week 26	(0.89, 2.81)	(-0.25, 1.78)	(1.70, 3.75)	(-2.10, -0.06)	(-0.15, 1.91)	(0.88, 3.03)
Endpoint[c]	(1.05, 2.70)	(0.78, 2.40)	(1.86, 3.50)	(-1.09, 0.53)	(-0.02, 1.63)	(0.28, 1.90)
Average[d]	(1.15, 2.48)	(-0.09, 1.22)	(1.49, 2.82)	(-1.90, -0.59)	(-0.32, 1.01)	(0.93, 2.24)

LS = least square. **a:** Post-Baseline LS Means and Pstd (pooled standard deviations) are obtained from the ANCOVA model with treatment (Trt), site effects, and the Baseline (Base) FEV1 (liters) as a covariate; **b**: Baseline is the mean of two pre-dose measurements (30 minutes prior to dosing, and 0 hour, immediately prior to dosing) on Day 1; **c:** Endpoint = the last post-baseline non-missing FEV1 AUC(0-12hr) result carried forward; **d:** Average = Longitudinal Average across scheduled visits obtained from a mixed model with treatment and subject as fixed effects, treatment day and treatment day-by-treatment interaction as random effects, and baseline FEV1 (liters) as a covariate

Table 7C (study P04431): FEV1 AUC(0-12 Hour) (Liter x Hour) - Change From Baseline Analysis of Covariance (All Randomized Subjects)

	MF/F MDI 200/10 mcg BID (A)		MF/F MDI 400/10 mcg BID (B)		MF MDI 400 mcg BID (C)			Model P-Values		
VISIT	N	LS Mean[a]	N	LS Mean[a]	N	LS Mean[a]	Pstd[a]	Treatment	Site	Base
Change From Baseline[b]										
Day 1	230	3.61	251	3.74	237	1.62	2.85	<.001	<.001	<.001
Week 1	229	3.61	247	3.75	229	2.03	3.28	<.001	<.001	<.001
Week 12	**204**	**3.59**	**231**	**4.19**	**211**	**2.04**	**3.63**	**<.001**	**<.001**	**<.001**
Endpoint[c]	232	3.53	255	3.99	240	1.90	3.59	<.001	<.001	<.001

	Pairwise Comparisons P-Values			95% Confidence Intervals		
VISIT	A-B	A-C	B-C	A-B	A-C	B-C
Change From Baseline						
Day 1	0.606	<.001	<.001	(-0.66, 0.38)	(1.46, 2.52)	(1.61, 2.65)
Week 1	0.639	<.001	<.001	(-0.75, 0.46)	(0.96, 2.20)	(1.12, 2.33)
Week 12	**0.096**	**<.001**	**<.001**	**(-1.30, 0.11)**	**(0.82, 2.27)**	**(1.44, 2.85)**
Endpoint[c]	0.163	<.001	<.001	(-1.12, 0.19)	(0.97, 2.29)	(1.45, 2.74)

LS = least square; **a:** LS Means and Pstd (pooled standard deviations) for post-baseline evaluations are obtained from the
ANCOVA model with treatment, site effects, and the baseline FEV1 (liters) as a covariate; **b:** Baseline is the mean of two pre-dose measurements (30 minutes before dosing and 0 hour, immediately before dosing) on Day 1; **c:** Endpoint = the last post-baseline non-missing FEV1 AUC(0-12 hr) result carried forward;

The differences in FEV1 AUC(0-12 h) for the MF/F 100/10 and 200/10 mcg dosages (study P04073 and P04334) vs. the respective MF alone dosages never reached the pre-defined level of 3.1 L x hrs (corresponding to an average FEV1 of 260 ml) used for sample size calculations and considered of clinical relevance by the applicant. Neither was the pre-specified difference of 2.5 L x hrs obtained in the high dose study P04431. However, the two lowest dosages of MF/F induced a brochodilatory effect which was similar and numerically higher than that induced by formoterol 10 mcg BID alone in study P04073 and P04334, respectively.
In study P04073 and P04334 according to the pre-specified statistical analysis plan the comparison of F alone vs. placebo in FEV1 AUC(0-12 hr) at week 12 should reach statistical significance before the two primary comparisons were to be conducted.
As regards Study P04705 non-inferiority of MF/F MDI 200/10 mcg BID vs. Fluticasone/Salmeterol DPI 250/50 mcg BID was proven at endpoint as the lower bound of the 95% confidence interval was above the pre-specified delta of -1.5L (corresponding to an average FEV1 of -125 ml).

Table 7D (study P04705): FEV1 AUC(0 - 12 hour) (Liter x hour) - Change from Baseline Analysis of Covariance (All Randomized Subjects)

	MF/F MDI 200/10 mcg BID		F/SC DPI 250/50 mcg BID		Analysis[a]				
VISIT	N	LS Mean	N	LS Mean	Pstd	Trt	Site	Base	95% CI
Change From Baseline[b]									
Day 1	362	3.66	343	3.29	3.12	0.132	<.001	<.001	(-0.11, 0.84)
Week 12	295	3.45	284	3.33	3.94	0.736	0.001	0.018	(-0.56, 0.79)
Endpoint[c]	**366**	**3.43**	**346**	**3.24**	**3.83**	**0.540**	**0.008**	**0.007**	**(-0.40, 0.76)**

a: Least squares (LS) means and Pstd (pooled standard deviations) are obtained from the ANCOVA model with treatment (Trt), site effects and the Baseline FEV1 (liters) as a covariate; **b:** Baseline is the mean of two pre-dose measurements (30 minutes prior to dosing, and 0 hour, immediately prior to dosing) on Day 1; **c:** Endpoint = the last Postbaseline non-missing FEV1 AUC(0-12hr) result carried forward. Note: 95% confidence interval (CI) is for the estimated difference of (MF/F - F/SC). Lower Bound of Non-Inferiority Claim is -1.5 Liter x hours

Time-to-first severe asthma exacerbation:
The primary comparison for this co-primary endpoint in studies P04073 and P04334 was MF/F vs. F.
Based on the pre-specified criteria MF/F 100/10 mcg BID and 200/10 mcg BID in studies P04073 and P04334 were proven superior to F 10 mcg BID in time-to-first severe asthma exacerbation over a 26 weeks period: 16.5% vs. 44.7% in study P04073 (p<0.001) and 30.4% vs. 54.0% in study P04334 (p<0.001) (tables 9A and B below).

Table 9A (study P04073): Number (%) of Subjects with at Least One Severe Asthma Exacerbation (All Randomized Subjects)

	Number (%) of Subjects			
	MF/F MDI 100/10 mcg BID (A)	MF MDI 100 mcg BID (B)	F MDI 10 mcg BID (C)	Placebo (D)
All First Severe Asthma Exacerbations	30 (16.5%)	53 (28.2%)	84 (44.7%)	86 (45.7%)
Severe Asthma Exacerbation Criteria				
FEV1[a]	5 (2.7%)	14 (7.4%)	25 (13.3%)	29 (15.4%)
PEF[b]	23 (12.6%)	35 (18.6%)	44 (23.4%)	42 (22.3%)
Clinical Deterioration[c]	1 (0.5%)	3 (1.6%)	10 (5.3%)	13 (6.9%)
Multiple Criteria				
PEF/Deterioration	0 (0.0%)	1 (0.5%)	2 (1.1%)	1 (0.5%)
FEV1/Deterioration	1 (0.5%)	0 (0.0%)	3 (1.6%)	1 (0.5%)

Time-to-First Severe Asthma Exacerbations: Pair-wise Comparisons p-values[d]

A-B	A-C	A-D	B-C	B-D	C-D
0.006	<0.001	<0.001	0.002	<0.001	0.467

a: A decrease in FEV1 below 80% of Baseline; **b:** A decrease in PEF below 70% of Baseline on 2 consecutive days; **c:** Clinical Deterioration as judged by the clinical investigator requiring a course of action; **d:** P-values are based on the Log-Rank test for equality of survival curves

Table 9B (study P04334): Number (%) of Subjects with at Least One Severe Asthma Exacerbation (All Randomized Subjects)

	Number (%) of Subjects			
	MF/F MDI 200/10 mcg BID (A)	MF MDI 200 mcg BID (B)	F MDI 10 mcg BID (C)	Placebo (D)
All First Severe Asthma Exacerbations	58 (30.4%)	65 (33.9%)	109 (54.0%)	109 (55.6%)
Severe Asthma Exacerbation Criteria				
FEV1[a]	18 (9.4%)	19 (9.9%)	29 (14.4%)	39 (19.9%)
PEF[b]	37 (19.4%)	41 (21.4%)	62 (30.7%)	59 (30.1%)
Clinical Deterioration[c]	3 (1.6%)	5 (2.6%)	16 (7.9%)	7 (3.6%)
Multiple Criteria				
FEV1/Deterioration	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (1.0%)
FEV1/PEFR	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)

Time-to-First Severe Asthma Exacerbations: Pair-wise Comparisons p-values[d]

A-B	A-C	A-D	B-C	B-D	C-D
0.565	<0.001	<0.001	<0.001	<0.001	0.967

a: A decrease in FEV1 below 80% of Baseline; **b:** A decrease in PEF below 70% of Baseline on 2 consecutive days; **c:** Clinical Deterioration as judged by the clinical investigator requiring a course of action; **d:** P-values are based on the Log-Rank test for equality of survival curves; Data Source

According to the "Time to First Severe Asthma Exacerbation" Kaplan-Meier Survival Curves, the curves for the MF/F 100/10 mcg and 200/10 mcg BID separated early and continued to be separated vs. F and placebo. A separation was also noted between MF/F 100/10 mcg BID vs. MF 100 mcg BID in study P04073 whereas, no difference was observed between MF/F 200/10 mcg and MF 200 mcg BID in study P04334.

50-75% of the severe exacerbations were based on the PEF criteria (A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment during the Treatment Period. The Treatment Period stability limit was defined as 70% of the respective mean AM or PM PEF obtained over the last 7 days immediately prior to receiving randomized study medication). Preferably, the criteria should have been based on a change from on-treatment PEF rather than baseline PEF, which would be in accordance with clinical practice ("An official American Thoracic Society/European respiratory Statement: Asthma control and Exacerbations – standardizing endpoints for clinical asthma trial and clinical practice (2008)").

It is acknowledged that also for the criterion "clinical deterioration" superiority of MF/F vs. F was proven. This was however, mainly based on use of systemic glucocorticoids as hardly any patients were hospitalised or had emergency treatment. The criteria for initiating the systemic glucocorticoid treatment seem not pre-defined thus, a standardised approach is lacking. A new analysis for clinical deteriorations requiring at least three days of systemic corticosteroid use, hospitalization, and ER Visits (instead of clinical deterioration judged by the investigator requiring a course of action) was presented in the response to the D120 LoQ for studies 4073 and 4334. The results, confirmed that the FDC of MF/F is significantly better than F and placebo.

The pre-specified primary analyses are however considered inappropriate for this application as standard therapy is ICS. It is recognised that study P04073 and P04334 were not powered for a comparison of MF/F vs. MF which again is a basic shortcoming in this application. MF/F 100/10 mcg was superior ot MF 100mcg whereas MF/f 200/10mcg vs. MF 200mcg was not. When applying the new criteria for clinical deterioration (requirement of at least three Days of Systemic corticosteroid Use, Hospitalization, and ER) neither of the MF/F dosages were superior to the MF monotherapy arms. Based on the provided data, it cannot be concluded that the FDC is better than standard therapy with MF. Thus, an advantage of MF/F vs. MF alone has not been demonstrated convincingly for asthma exacerbations for the low and medium doses. Neither has any convincing data been provided for the high dosage (study P04431); 12 weeks study duration is considered too short for proper assessment and no dose-relationship seems to exist between MF200/10µg and 400/10 µg.

The issues discussed above add on to the major drawback of this application: Bioequivalence was never proven for the MF-component in the MF/F MDI vs. the marketed MF DPI (please refer to the section on clinical pharmacology). The exposure to MF delivered by MF/F MDI was statistically significantly lower vs. the exposure to MF delivered by MF DPI (steady state AUC exposure reduced by

25% (90% CI 61 to 91)). The inconsistent effects of all dosages of MF/F on asthma control could reflect the lower exposure to MF. Therefore, based on the provided results an extrapolation from the dosage used in the marketed MF DPI to the MF/F MDI used in this clinical program cannot be performed. However, no dose-finding studies have been conducted. In response to the D120 LoQs the applicant refers to another MF MDI development program. Dose selection based on this program is however, not substantiated as no marketing authorisations exist for these MDIs.

As mentioned above a bridging study between the comparator MF MDI and the marketed MF DPI was not performed. According to the applicant a full clinical program was conducted and bridging was not foreseen.
In order to address the lack of bridging efficacy data and thus the interchangability of MF DPis and MF MDIs, the applicant provided data on AM PEF data across the run-in- and treatment periods in order to support the maintained efficacy of the MF MDIs
PEF is inferior to FEV1 as a clinic-measured parameter of airway obstruction as it confers no advantage in reproducibility, lacks accurate reference values for many populations and may underestimate airway obstruction in individuals with airway remodelling. No data on potential variability on PEF was provided for any of the different treatment arms. The crucial part is not considered to be the substantiation of a maintained efficacy of the MF MDIs but a substantiation of an equivalent efficacy of the MF MDIs vs. the marketed MF DPIs. Only PEF data for the run-in periods contained data on patients who were indeed previously treated with MF DPI. The run-in period reflects washout from previous bronchodilator treatment but not for steroid treatment which takes longer than 14 days. No data has been provided for these patients during the actual trial. However, the low number of patients (N=39 in P04073 and N=26 in P04334) would probably not allow conclusions to be drawn from such an evaluation. In addition in study P05122 (please refer to section on dose-finding studies) it is noted, that the MF DPI 200 µg seemed to have a stronger effect on eNO than observed for MF MDI 200µg and MF/F MDI 200/10 µg (-55.3% vs. -33.7% and -35.5%) substantiating the need for a bridging between the marketed MF DPI and the MF/F MDI. This difference may indeed reflect the lower systemic exposure to MF induced by MF/F MDI vs. the MF DPI.

The lack of bioequivalence between MF in the marketed DPI and in the FDC could in principle have been overcome by non-inferiority comparisons vs. the two marketed F and MF DPIs given concomitantly at relevant dosages. A non-inferiority comparison vs. another marketed FDC has been performed. However, the data obtained from study P04705 are only based on the use of one (medium) dose ICS, i.e. assay sensitivity has not been ascertained, exacerbations were not included as primary endpoint and the study was only of very short duration (12 weeks in total). The inclusion of placebo arms is also not considered sufficient to address the efficacy of MF in the FDC.
Based on the above reflections the MF/F FDC is not approvable for asthmatic patients not adequately controlled on low to high doses of ICS and as needed inhaled SABA as the effect on asthma control of MF in the three proposed dosages has not been substantiated.
For the same reasons we can not either support "reduction of asthma exacerbations" in the sought indication.
Finally the last part of the sought indication in patients "whose disease severity clearly warrants initiation of treatment with two maintenance therapies" is not in line with current asthma guidelines (e.g. GINA 2009). In the response to the D120 LoQs the applicant supports this notion.

Key secondary endpoints:
Superiority of MF/F compared to F in increasing the change from baseline to week 12 in **trough FEV1** was the first key secondary endpoint in studies P04073 and P04334.
In **study P04073** the mean change from baseline to week 12 in AM end-of-dosing interval trough FEV1 were as follows: MF/F 100/10 mcg BID: 160 ml; MF 100 mcg BID: 120 ml; F 10 mcg BID: 120 ml and placebo: 50 ml. MF/F was statistically significantly superior to placebo (p=0.002) whereas, no statistical significant difference was observed for the primary analysis vs. F (p=0.282). The same applies for the efficacy evaluable data-set (p=0.185)
According to the pre-specified hierarchical statistical test plan all remaining key secondary efficacy variables in study P04073 cannot be considered confirmatory as the overall two-sided alpha level of 5% is not preserved. Despite the exploratory nature of the additional key secondary endpoints (AQLQ, ACQ and "change from baseline in nights with nocturnal awakenings due to asthma that required the use of SABA"), the results could be considered supportive for the efficacy of MF/F, if convincing evidence was provided for the efficacy of MF/F 100/10µg vs. MF 100µg bid on asthma control (asthma

exacerbations (co-primary endpoint) and trough FEV1 (first key secondary endpoint). This is however not the case (please refer to discussion above)
In **study P04334** superiority of MF/F 200/10 mcg BID (120ml) vs. F 10 mcg BID (20ml) and MF/F 200/10 mcg BID vs. placebo (-30ml) on trough FEV1 was proven at week 12 ($p=0.014$ and $p<0.001$ respectively). The results were supported by the analysis of the efficacy-evaluable data-set.
As previously mentioned, trough FEV1 is considered a more sensitive endpoint for assessment of the efficacy of MF as "time to first severe asthma exacerbation". A comparison of MF/F vs. MF was not a planned part of the development. In studies P04073 and P04334 MF/F 100/10 and 200/10 mcg BID were not significantly superior to MF 100 and 200 mcg, respectively. In study P04431, where trough FEV1 was only an additional secondary endpoint, MF/F 400/10 was significantly superior to MF 400 mcg however, the difference was very small (Week 12: difference in LS mean change from baseline was 20 mL, $p=0.003$ (0.03, 0.16) and it is noted that in this analysis MF/F 200/10 mcg was also superior to MF/F 400/10 mcg; hence, this analysis is not considered supportive. These results stress the fact that MF/F has not been proven superior to MF as monotherapy.

Change in the **Asthma Quality of Life Questionaire (AQLQ) total score** was the second key secondary endpoint in studies P04073, P04334 (from baseline to week 26) and P04431 (from baseline to week 12). The AQLQ(S) consists of 32 questions each scaled from 1 (worst case) to 7 (best case).
For **studies P04073 and P04431** the overall alpha level of 5% was not preserved in this analysis. In study P04073 MF/F 100/10 mcg BID arms did not achieve superiority vs. formoterol for the first key secondary endpoint (trough FEV1 at week 12) and in study P04431 MF/F 400/10 mcg BID did not achieve superiority vs. MF 400 mcg BID for the first key secondary endpoint with a MID > 0.5 (ACQ at week 26:.Please refer to comments in the ACQ section below).
In **study P04334** MF/F 200/10 mcg BID was statistically superior to F 10 mcg BID and Pbo at all time points (Week 4, 12 and 26). The MID of >0.5 was only reached at endpoint (week 26 using LOCF: LS mean change from baseline scores of 0.49 and -0.01 respectively) and not at week 26 (LS mean change from Baseline scores of 0.61 and 0.36 with an observed effect size of 0.25 point).

Change in the **Asthma Control Questionnaire (ACQ) total score** was the third key secondary endpoint in studies P04073 and P04334 (from baseline to week 26) and the first key secondary endpoint in studies P04431 (from baseline to week 12) and P04705 (from baseline to week 12). The ACQ consists of seven questions each scaled from 0 (best case) to 6 (worst case). For the ACQ, the crossover point between well-controlled and not well-controlled is close to 1.00. This means that below 1.00 patients are more likely to have well-controlled asthma and above they are more likely to have not well-controlled asthma. A difference vs. placebo in mean total score of ≥ 0.5 is considered the MID.
For study **P04073** the overall alpha level of 5% was not preserved in this analysis of the third key secondary endpoint as MF/F 100/10 mcg BID arms did not achieved superiority vs. formoterol for the first key secondary endpoint (trough FEV1 at week 12)
In study **P04334** MF/F 200/10 mcg BID was statistically significantly superior to placebo with an LS mean change from Baseline scores of -0.40 vs. 0.14 for placebo at endpoint. A MID ≥ 0.5 was achieved as the effect size amounted to 0.54 points.
In study **P04431** MF/F 200/10 mcg BID (-0.59) and MF/F 400/10 mcg BID (-0.58) were statistically significantly superior to MF alone (-0.42) in improving the ACQ score, however none of them achieved the MID of ≥ 0.5. The MID of ≥ 0.5 was not either achieved at endpoint (effect sizes of -0.23 and -0.18 point respectively). Thus, the overall alpha level of 5% was not preserved in the analysis of the second (change in AQLQ total score, please refer to comments above) and the third key secondary endpoints (Change from Baseline in proportion of nights across the Treatment Period with nocturnal awakenings due to asthma that required the use of SABA).
In study **P04705** based on the pre-defined delta for non-inferiority of -0.25 point MF/F 200/10 mcg BID was proven non-inferior to F/SC 250/50 mcg BID at endpoint week 12 (LS mean change from baseline: MF/F 200/10 mcg BID=-0.65; F/SC 250/50 mcg BID=-0.65; $p<0.001$; 96.25% CI: -0.10, 0.10).

Change from Baseline in proportion of nights across the Treatment Period with nocturnal awakenings due to asthma that required the use of SABA was the fourth key secondary endpoint in studies P04073 and P04334 and the third in study P04431. However, in studies P04073 and P04331 the overall alpha level of 5% were not preserved as: 1) MF/F 100/10 mcg BID arms did not achieved superiority vs. formoterol for the first key secondary endpoint (trough FEV1 at week 12) in **study P04073**; 2) MF/F 400/10 mcg BID arms did not achieve the MID of ≥ 0.5 in AQLQ (the second key secondary endpoint) vs. MF 400 mcg BID at week 26 in **study P04431**.
In study **P04334** MF/F 200/10 mcg BID was statistically significantly superior to placebo (LS mean changes from baseline were -0.08 and 0.00 respectively; 95% CI: -0.12, -0.05; $p<0.001$)

The **proportion of days/nights combined across the Treatment Period with no asthma symptoms** (defined as a total asthma symptom score = 0) was a key secondary endpoint in **study P04705**. Mean proportions of symptom free days and nights (actual scores) were 0.42 and 0.43 for the MF/F 200/10 mcg BID and F/SC 250/50 mcg BID groups, respectively.. Based on the pre-specified delta for non-inferiority (the 20% magnitude of the F/SC proportion) MF/F MDI 200/10 mcg BID was proven non-inferior to F/SC DPI 250/50 mcg BID (LS mean change from baseline: MF/F 200710 mcg= -0.14; F/SC 250/50 mcg=-0.16; p<0.001; 95% CI -0.01, 0.04).
Onset of action at 5 minutes post dose on Day 1 (based on FEV1) was third key secondary endpoint in **study P04705**. The least-squares mean increases from Baseline FEV1 at 5 minutes post-dose on Day 1 were 0.20 (8.5%) and 0.09 (4.3%) litres for the MF/F 200/10 mcg BID and F/SC 250/50 mcg BID groups, respectively. The MF/F 200/10 mcg BID dosage had a clinically relevant onset of action 5 minutes post-dose amounting to 0.2 L. MF/F 200/10 mcg BID was statistically significantly superior to F/SC 250/50 mcg BID at this time point (p<0.001). A clinically relevant bronchodilatory effect of MF/F 200/10 mcg BID vs. baseline (> 200 ml) was maintained at all time points.

Subgroup analyses:
In each of the four efficacy studies, subgroup summaries by age, sex, race, allergic rhinitis (AR) status, and BMI were pre-specified for the primary and key secondary efficacy endpoints. Not surprisingly the youngest population (age 12- < 18 years) and the population belonging to the lowest BMI group (< 25) had the largest changes in FEV1 AUC (0-12 hr) from baseline irrespective of treatment.
No formal statistical comparisons have been provided in the study reports based on age (12-17, 18-64, 65 and over), sex, race (Caucacians vs. non-Caucacians) or +/- allergic rhinitis. However, the pattern of improvements in FEV1 (AUC 0-12hr) for all groups were similar to the overall efficacy results presented in the FEV1 AUC (0-12hr) section above.
As regards BMI the MF/F treatment arms were superior to placebo for all three BMI groups except for the 25 to < 30 group in study P04334. Further, in studies P04073 and P04334 only in the < 25 BMI group MF/F was proven superior to MF alone. In Study P04431 both dosages of MF/F were proven superior to MF 400 mcg alone except for the MF/F 200/10 mcg in the < 25 BMI group. As the number of patients in each BMI group was low (range 43-87), the results should be interpreted cautiously.
Sub-group analyses for the other co-primary endpoint as well as the key secondary endpoints have not been provided.

Clinical studies in special populations
No studies were performed in special populations

Supportive study(ies)
Study P04139 was a randomized, parallel-group, multi-center, open-label, evaluator-blind, 52-weeks safety study of medium and high doses of MF/F and medium and high doses of F/SC in persistent asthmatics previously treated with medium to high doses of ICSs.
The primary objective of this study was an evaluation of the safety profiles for MF/F 200/10 and 400/10 mcg BID compared to F/SC 250/50 mcg BID and 500/50 mcg BID in subjects with persistent asthma.

In the response to the D120 LoQ the applicant submitted a new clinical study, study P05122 evaluating the efficacy of different dosages of MF/F MDI (100/10 µg to 400/10 bid) and one dosage of MF DPI (200µg bid) and MF MDI (200 µg bid) on exhaled nitric oxide (eNO) . The study was a randomized, multi-center, double-blind, double-dummy parallel group, placebo-controlled, study in patients ≥ 12 years of age with persistent allergic asthma, documented reversibility and increased eNO levels (>30 ppb at a flow rate of 50 mL/second) and induced sputum eosinophil levels (>3% of total cell count). This study does not support the dose-responsiveness when compared to the different dosages of the marketed MF DPIs. Please refer to the section on dose-finding studies and the assessment of MO 78 for details.

Discussion on clinical efficacy
The primary efficacy variable to assess the contribution of formoterol to the efficacy of MF/F was the change from baseline to week 12 in FEV1 AUC(0-12 hr). This was the primary endpoint in the high dose Study P04431 and co-primary endpoint in the low-dose and medium-dose studies P0473 and P4334, respectively. At week 12 for all three studies the FDC of MF/F induced a significant and clinical relevant increase from baseline in FEV1 AUC (0-12 h). The response was statistically significantly superior to the MF monotherapy arms. The results were further supported by serial evaluations (0-12

h) of FEV1 at week 12 amounting to >200 ml for all time points when compared to placebo in the low- and medium dose studies (P04073 and P04334, respectively).
Time-to-first severe asthma exacerbation over a 26 weeks period was a co-primary endpoint in the low- and medium dose studies P04073 and P04334 but only an "additional endpoint" in the high dose study P04431. For the low- and medium dose studies the prespecified analyses were of MF/F vs. F in which superiority of MF/F vs. F was proven in both studies This was also the case when new analyses were performed using clinical deteriorations requiring at least three Days of Systemic corticosteroid Use, Hospitalization, and ER Visits (instead of clinical deterioration judged by the investigator requiring a course of action).
The pre-specified primary analyses are however considered inappropriate for this application as standard therapy is ICS. It is recognised that study P04073 and P04334 were not powered for a comparison of MF/F vs. MF. MF/F 100/10 mcg was superior to MF 100mcg whereas MF/F 200/10mcg vs. MF 200mcg was not. When applying the new criteria for clinical deterioration (requirement of at least three Days of Systemic corticosteroid Use, Hospitalization, and ER) neither of the MF/F dosages were superior to the MF monotherapy arms. In addition, inconsistent results were observed for the key secondary endpoints reflecting level of asthma control (trough FEV1, AQLQ, ACQ and Nocturnal awakenings).
Based on the provided data, it cannot be concluded that the FDC is better than standard therapy with MF. Thus, an advantage of MF/F vs. MF alone has not been demonstrated convincingly for asthma exacerbations for the low and medium doses. Neither has any convincing data been provided for the high dosage (study P04431); 12 weeks study duration is considered too short for proper assessment and no dose-relationship seem to exist between MF200/10µg and 400/10µg.

Bioequivalence was never proven for the MF-component in the MF/F MDI vs. the marketed MF DPI (please refer to the section on clinical pharmacology). The inconsistent effects of all dosages of MF/F on asthma control could reflect the lower exposure to MF when administered by the MF/F MDIs. Therefore, based on the provided results an extrapolation from the dosage used in the marketed MF DPI to the MF/F MDI used in this clinical program cannot be performed.

As a full clinical program was conducted according to the applicant, a bridging study between the comparator MF MDI and the marketed MF DPI was not foreseen.

In order to address the lack of bridging efficacy data and thus the interchangability of MF DPis and MF MDIs, the applicant provided data on AM PEF data across the run-in- and treatment periods in order to support the maintained efficacy of the MF MDIs. The crucial part is not considered to be the substantiation of a maintained efficacy of the MF MDIs but a substantiation of an equivalent efficacy of the MF MDIs vs. the marketed MF DPIs. In addition, no dose-finding studies have been conducted. A dose-response relationship for the low- to high dose MF/F MDIs by use of eNO measurements (study P05122) was not convincing and further substantiated the need for a bridging between MF DPI and MF/F MDI. Finally, a "full clinical program" with studies consisting of experimental arms only is not considered acceptable.

Conclusions on clinical efficacy
Bioequivalence was never proven for the MF-component in the MF/F MDI vs. the marketed MF DPI (please refer to the section on clinical pharmacology). The inconsistent effects of all dosages of MF/F on asthma control could reflect the lower exposure to MF when administered by the MF/F MDIs. Therefore, based on the provided results an extrapolation from the dosage used in the marketed MF DPI to the MF/F MDI used in this clinical program cannot be performed. As a full clinical program was conducted according to the applicant, a bridging study between the comparator MF MDI and the marketed MF DPI was not foreseen. However, no dose-finding studies have been conducted either.
In summary, the following short comings have been identified: 1) No bridging was performed between the marketed MF DPIs and the experimental MF MDIs; 2) As bridging was not foreseen and a full clinical program according to the applicant was provided, the use of unauthorised MF MDI comparators is not acceptable; 3) According to the GINA guideline ICS is standard therapy to control asthma. Therefore the appropriate comparison is MF/F vs. MF when assessing endpoints reflecting level of asthma control. This comparison was however not foreseen in the low- and medium dose studies and the post-hoc analyses of this comparison were inconsistent; 3) for the high dose study 12 weeks study duration is considered too short for proper assessment and no dose-relationship seems to exist between MF200/10µg and 400/10 µg; 4) The non-inferiority comparison of MF/F vs. the marketed F/SC in study P04705 could have overcome some of the above described issues, but the study lacks assay sensitivity.

Based on the above reflections the MF/F FDC is not approvable for asthmatic patients not adequately controlled on low to high doses of ICS and as needed inhaled SABA as the effect on asthma control of MF in the three proposed dosages has not been substantiated.
For the same reasons "reduction of asthma exacerbations" should be removed from the sought indication.
Finally the last part of the sought indication in patients "whose disease severity clearly warrants initiation of treatment with two maintenance therapies" is not in line with current asthma guidelines (e.g. GINA 2009). In the response to the D120 LoQs the applicant supports this notion.

Finally, based on the findings during a routine GCP inspection at 2 sites where a large number of critical findings were identified the overall data reliability is questionable. Further inspections are therefore requested in addition to re-calculation of the efficacy results.

Clinical safety

Table 2 Clinical Studies in the MF/F MDI Clinical Program in Adults with Asthma and COPD

Study No.	Objectives of the Study	Study Design	Treatment, Dosage Regimen	No. of Subjects[a] (Age Range)	Subject Population	Duration of Active Treatment
Clinical Pharmacology Studies						
P05644 (H2104)	PK and Safety	R, SD ,3-period crossover; PK, S/T MF/F MDI	MF/F MDI 400/10 mcg MF/F MDI 400/20 mcg MF/F MDI 400/40 mcg	24 (23 to 58 yr)	healthy volunteers	single dose
P03658	PK	R, OL, 4-period crossover; DDI, PK; MF MDI, F MDI	MF/F MDI 800/20 mcg MF MDI 800 mcg+F MDI 20 mcg MF MDI 800 mcg F MDI 20 mcg	26 (22 to 52 yr)	healthy volunteers	single dose
P04275	PK, Relative BA and Safety	R, OL, MD, 2-period crossover; PK, relative BA, S/T; MF DPI	MF/F MDI 800/20 mcg BID MF DPI 800 mcg BID	12 (18 to 57 yr)	healthy volunteers	4.5 days
P05643 (H2201)	PD, PK S/T	R, DB, DD, SD, 5-period crossover; single dose duration of action of F in MF/F MDI combination, PD, PK, S/T; F DPI, F MDI, placebo	MF/F MDI 100/10 mcg MF/F MDI 400/10 mcg F MDI 10 mcg F DPI 12 mcg[b] Placebo	25 (20 to 64 yr)	mild-to-moderate asthma	single dose
P05642 (H2101)	PD, PK, S/T	R, OL, cumulative dose, 3-period crossover; PD, PK, S/T; F DPI	MF/F MDI 100/5 device: 200/10 to 800/40 mcg ; MF/F MDI 200/5 device: 400/10 to 1600/40 mcg F DPI: 12 to 48 mcg cumulative doses 1 hr	18 (20 to 65 yr)	mild-to-moderate asthma	single dose

Study No.	Objectives of the Study	Study Design	Treatment, Dosage Regimen	No. of Subjects[a] (Age Range)	Subject Population	Duration of Active Treatment
			apart; 1 day			
P03705	PK	R, OL, MD, PC, PG active comparator, serum cortisol, PK, eNO, S/T, MF/F MDI; fluticasone/salmeterol MDI, placebo	MF/F MDI 200/10 mcg BID MF/F MDI 400/10 mcg BID F/SC 460/42 mcg BID Placebo	15 17 (18 to 64 yr)	mild-to-moderate asthma	42 days
P04689	PK, assess effect of spacer MF DPI	R, OL, MD, 3-period crossover; PK	MF/F MDI 400/10 mcg BID MF/F MDI 400/10 mcg BID with spacer MF DPI 400 mcg BID	14 (45 to 72 yr)	moderate-to-severe COPD	4.5 days
P06144 (I2201)	PD, PK, S/T	R, DB, DD, PC, CO	F MDI 6, 12, and 24 mcg (HFA) F 12 and 24 mcg DPI	26 (18 to 67 yr)	asthma	single dose
Phase 3 Studies						
Placebo-Controlled 26-Week Efficacy and Safety Studies						
P04073	Efficacy and Safety	R, MC, DB, DD, PC, PG	MF/F MDI 100/10 mcg BID MF MDI 100 mcg BID F 10 mcg BID Placebo	746 (182)[a] (12-79 yr)	moderate asthma previously treated with low-dose ICS	26 weeks
P04334	Efficacy and Safety	R, MC, DB, DD, PC, PG	MF/F MDI 200/10 mcg BID MF MDI 200 mcg BID F 10 mcg BID Placebo	781 (191)[a] (12-76 yr)	moderate asthma previously treated with medium-dose ICS	26 weeks
Non-Placebo-Controlled 12-Week Efficacy and Safety Studies						
P04431	Efficacy and Safety	R, MC, DB, PG	MF/F 400/10 mcg BID MF/F 200/10 mcg BID MF 400 mcg BID	728 (488) [a] (12-84 yr)	moderate-to-severe asthma previously treated with high-dose ICS	12 weeks
P04705[d]	Efficacy and Safety	R, MC, OL, PG, active-control	MF/F MDI 200/10 mcg BID F/SC DPI 250/50 mcg	722 (371) [a] (12-82 yr)	moderate asthma previously treated with	12 weeks

Study No.	Objectives of the Study	Study Design	Treatment, Dosage Regimen	No. of Subjects[a] (Age Range)	Subject Population	Duration of Active Treatment
			BID		medium-dose ICS	
Long-Term 52-Week Safety Study						
P04139	Long-Term Safety – HPA axis, Ophthalmologic Tests, AEs and Laboratory Parameters	R, MC , OL, EB, active-control, PG	MF/F MDI 200/10 mcg BID MF/F MDI 400/10 mcg BID F/SC MDI 250/50 mcg BID F/SC MDI 500/50 mcg BID	404 (271) [a] (12-75 yr)	Persistent asthma previously treated with medium or high-dose ICS dependent	52 weeks
Dose Counter Functionality Study						
P04703	Dose Counter Functionality Study	MC, OL, stratified by age	MF/F MDI 100/10 mcg BID	343 (12-92 yr)	Asthma or COPD for ≥6 months requiring ICS and LABA	4 weeks

Note:AE = adverse event(s); BA= bioavailability; BID= twice a day; CO= cross-over; COPD = chronic obstructive pulmonary disease; DB= double-blind; DD = double-dummy; DDI = drug-drug interaction; DP= dry powder; DPI = dry powder inhaler, EB = evaluator blind; eNO = exhaled nitrous oxide; F = formoterol fumarate, female; F/SC = fluticasone/salmeterol combination; HFA= hydrofluoroalkane ; HPA = hypothalamus-pituitary axis; ICS = inhaled glucocorticoids; LABA = long-acting beta agonists; MC = multi-center; MD = multiple-dose; MDI = metered-dose inhaler; MF = mometasone furoate; MF/F= mometasone furoate formoterol fumarate; OL = open-label; PC = placebo-controlled; PD = pharmacodynamics; PG = parallel-group; PK = pharmacokinetics; R = randomized; SD = single dose; S/T = safety and tolerability; yr=year.

a: Number of subjects randomized to MF/F MDI.

b: 12 mcg F is equivalent to 10 mcg ex-actuator

c: This study was not part of the MF/F Phase 1 clinical pharmacology program but is included as it supports the MF/F program by providing a PD bridge to F-MDI and the rationale for F dose selection.

d: P04705 study was closed early on 14 NOV 2008 at the completion of 12 weeks of treatment for non-safety reasons.

Patient exposure

A total of 3664 subjects in the Phase 3 studies and 150 subjects in the clinical pharmacology studies were included in the safety evaluation, 1961 of whom were treated with MF/F (includes 1901 asthma subjects and 60 healthy subjects).

A total of 380 subjects (10.2%) were between the ages of 12 and 18; 3012 subjects (82.4%) were between the ages of 18 and 64, and 271 subjects (7.4%) were 65 or older. Of the subjects randomized to MF/F, 193 (10.8%) were between the ages of 12 and 18; 1440 (81%) were between the ages of 18 and 64, and 152 (8.5%) were 65 years old or older.

In the six Phase 3 studies in this program, 1781 subjects received at least one dose of MF/F; 618 subjects received at least one dose of MF, 390 subjects received at least one dose of F, 133 subjects received at least one dose of F/SC MDI, 349 subjects received at least one dose of F/SC DPI, and 383 subjects received at least one dose of placebo. All subjects had asthma, except for the 60 subjects in Study P04703 who were diagnosed with COPD.

Table 1 Summary of Duration of Treatment – All Six Phase 3 Studies Pooled by Treatment Group

Number (%) of Subjects											
Duration (days)	MF/F 100/10 mcg BID (n=465)	MF/F 200/10 mcg BID (n=936)	MF/F 400/10 mcg BID (n=385)	MF 100 mcg BID (n=188)	MF 200 mcg BID (n=192)	MF 400 mcg BID (n=240)	F 10 mcg BID (n=390)	Placebo (n=384)	F/SC MDI 250/50 mcg BID (n=68)	F/SC MDI 500/50 mcg BID (n=65)	F/SC DPI 250/50 mcg BID (n=351)
Rec'd any treatment	464 (100)	932 (100)	385 (100)	186 (99)	192 (100)	240 (100)	390 (100)	383 (100)	68 (100)	65 (100)	349 (99)
≥15	411 (88)	904 (97)	381 (99)	183 (97)	190 (99)	233 (97)	375 (96)	362 (94)	67 (99)	64 (98)	335 (95)
≥30	391 (84)	880 (94)	372 (97)	174 (93)	187 (97)	227 (95)	348 (89)	336 (88)	67 (99)	62 (95)	328 (93)
≥60	165 (35)	841 (90)	355 (92)	168 (89)	180 (94)	211 (88)	304 (78)	293 (76)	66 (97)	61 (94)	311 (89)
≥90	159 (34)	538 (57)	138 (36)	160 (85)	175 (91)	11 (5)	285 (73)	277 (72)	66 (97)	60 (92)	220 (63)
≥120	154 (33)	499 (53)	118 (31)	154 (82)	168 (88)	0	271 (69)	260 (68)	65 (96)	59 (91)	196 (56)
≥178	138 (30)	383 (41)	115 (30)	131 (70)	142 (74)	0	223 (57)	218 (57)	64 (94)	58 (89)	95 (27)
≥267	0	160 (17)	109 (28)	0	0	0	0	0	60 (88)	57 (88)	25 (7)
≥356	0	144 (15)	108 (28)	0	0	0	0	0	58 (85)	57 (88)	17 (5)
≥363	0	131 (14)	96 (25)	0	0	0	0	0	52 (76)	48 (74)	11 (3)
≥371	0	27 (3)	13 (3)	0	0	0	0	0	8 (12)	8 (12)	2 (1)
≥386	0	3 (<1)	2 (1)	0	0	0	0	0	0	2 (3)	0
Randomized, not treated	1 (<1)	4 (<1)	0	2 (1)	0	0	0	1 (<1)	0	0	2 (1)
Statistics (Day)											
Median	43	136	86	182	182	85	180	181	365	365	127
Min	1	1	4	6	1	4	1	3	8	7	2
Max	211	389	394	217	212	94	195	197	382	393	373

Note: All treatments are MDI except for the last column.

Note: BID= twice a day; F= Formoterol, F/SC= fluticasone/salmeterol combination; mcg = micrograms; MF= mometasone furoate; MF/F= mometasone furoate/formoterol.

Data Source: Section 7.1.1.1, Module 5.3.5.3.

Sufficient numbers of patients have thus been treated with the MF/F combination (any dose) for approximately 6 and 12 months (636 subjects for ≥178 days, 227 patients for ≥356 days).

Adverse events

<u>All Phase 3 studies pooled (P04073, P04334, P04431, P04705, P04139 and P04703):</u>
The percentage of subjects reporting AEs in the Phase 3 studies were similar across the MF/F treatment groups and no dose-dependent effect emerged for the MF/F combinations 100/10, 200/10 and 400/10 mcg BID. The lowest percentage of AEs was noted in the MF/F 100/10 groups (28.6%) and the highest in the MF/F 200/10 groups (48.4%). The occurrence of AEs in the MF/F treatment groups was comparable to those in the placebo groups, and to those of the MF/F components.

The most frequent treatment emergent AEs in the phase 3 studies were headache (7.7%), nasopharyngitis (6.8%), and upper respiratory tract infections (5.3%). The most common treatment-related AEs were dysphonia, headache and oral candidacies. No dose dependency was observed.
On request the applicant provided an overview over AEs adjusted for exposure. There were no adverse events reported that were unexpected with either of the monocomponents or that would alter the safety profile for MF/F.
The frequency of subjects reporting treatment-emergent AEs and treatment- related AEs was higher in the 12 months safety study P04139 (MF/F 100/10 mcg: 77.3% and 28.4%; MF/F 400/10 mcg: 79.2% and 23.1%; Fluticasone/Salmeterol 250/50 mcg: 82.4% and 23.5% and Fluticasone/Salmeterol 500/50 mcg: 76.9% and 20.0%; Not shown above), however the pattern of AEs was similar compared to the overview of AEs for the six phase III studies. The most often reported treatment-emergent AEs for MF/F 200/10 and 400/10 mcg were headache (23.4-23.8%), nasopharyngitis (16.2-20.6%), bronchitis (12.1-15.4%) and pharyngitis (10.6-8.5%)), and likewise there was no clear dose-dependency. The pattern of treatment-related AEs is similar to the marketed Asmanex®.

Ophthalmologic events were evaluated in study P04139, the long term 52-week study.
It is well known that corticosteroids are cataractogenic. A dose response was not evident in this study but can hardly be expected considering the small number of events in the limited population. The information on cataract is adequately covered in the SPC.

There was no new safety signal in the evaluation of ocular AEs, hypersensitivity AEs, bronchospasm AEs or metabolic AEs.

Serious adverse events and deaths
Overall, 73 serious Adverse Events were reported. No unexpected SAEs were observed, neither was there a pattern for increased rates of any SAE for any of the doses of the MF/F FDC. In terms of rates (incidence /100 person-years) SAEs were reported with slightly increasing rates of 4.64, 5.60 and 6.39for MF/F 100/10, 200/10 and 400/10 mcg BID, respectively, as compared to 7.95 in F/SC MDI 250/50 mcg bid and 5.99 in F/SC DPI 250/50 mcg bid, respectively. Lower rates occurred in F MDI 10mcg, F/SC MDI 500/50 mcg bid and placebo.
Treatment with MF/F did not seem to be associated with Serious Asthma Exacerbations or Severe Asthma-Related Events.
Three subjects died during studies while receiving MF/F MDI. The deaths were not considered related to study drug (gastric cancer, electrocution, leiomyosarcoma with metastases).

Laboratory findings

Although there were sporadic clinical laboratory values that fell outside the normal reference ranges for the specific laboratory analysis, there was no pattern to indicate an effect of MF/F, or its components, or placebo on hematology, blood chemistry, or urinalysis.

Two studies investigated the effects of MF from the MF/F fixed combination on HPA axis function, the human pharmacology study P03705 and study P04139.
Study P03705 confirmed the effect on HPA axis of high doses of MF/F as well as F/SC: BID. Inhalations of MF/F 400 µg/10 µg or F/SC 460 µg/42 µg lowered mean cortisol AUC(0-24 hr) values from Baseline by 16% and 29%, respectively.

Study P04139 was a 1 -year safety study conducted in Middle and South America with the secondary objective of evaluating the safety effects of middle and high doses of MF and fluticasone, both in combination with a LABA, on 24-hour plasma cortisol AUC in a subset of patients. Both drugs (MF/F and F/SC) showed an apparently dose-dependent suppression of plasma cortisol 24-hour AUC, but no significant differences between treatment groups. There were, however, baseline imbalances and a placebo group was not included which limits the clinical relevance of this study.
The systemic effects of steroids on HPA axis are well-known and the goal is always to use the lowest effective dose as also indicated in the SPC.
As stated by the applicant there is no good correlation between ICS induced effect on the HPA axis effects and with other systemic effects of ICS (e.g. growth velocity in children or bone density in adults). The results from the analyses on the HPA-axis showed a clear suppression upon use of the high dosages of MF/F and F/SC, though the presented 1-year safety study P04139 was not fully conclusive on the extent of adrenal suppression.
A potential impact of systemic exposure to mometasone on growth and BMD in children and adolescents was intensively discussed by the PDCO during the PIP procedure for MF/F MDI. During the compliance check of the PIP prior to submission of this application, the applicant proposed an inclusion

of the following monitoring during daily pharmacovigilance activities which was agreed upon by the PDCO: Signalling procedures which involve periodic review of all new events by preferred term (bone density decreased, osteopenia, or osteoporotic fracture) and system organ class to highlight new events or changes in reporting will also address any association to children and adolescents as related to these events.

Safety in special populations
There are no studies in special population but AEs have been evaluated by age and race.
Very low numbers of patients in some of the treatment groups, especially in the adolescent and elderly age groups, makes an evaluation of AEs by age almost impossible. In the age group 18-<65 years, AEs were lowest in the placebo group in all but the MF/F 100/10mcg BID and the MF 400 mcg BID group. Apart from these aforementioned 2 treatment groups AEs seemed to be similar in the MF/F combination groups, the F group and MF groups, respectively, as well as the fluticasone/salmeterol 250/50 DPI mcg group. In contrast, AEs were approximately twice as high in the fluticasone/salmeterol 250/50 MDI mcg BID and 500/50 MDI mcg BID groups, however, the number of patients in these groups was limited.
The number of Whites (studies P04073, P04334, P04431, P04705, P04139, and P04703) was 2845 with AEs occurring in 40.7%, the number of Multiracials was 452, with AEs occurring in 61.5%. The number of subjects of different race was negligible (Blacks n=125, American Indians n=18, Asians n=221, pacific Islanders n=3); hence, no further conclusions can be drawn.. For the same reason an evaluation of AEs by race for the various treatment groups does not make sense. It should be reflected in the SPC that the evaluation was predominantly based on the white race.

No data exist on use of this fixed combination in patients with renal insufficiency and hepatic insufficiency.

Safety related to drug-drug interactions and other interactions
The applicant refers to the Clinical Pharmacology study P03658, an open-label, single-dose, crossover study in 26 healthy subjects which explored the potential for drug interaction as well as effects of combined administration on exposure. The pharmacokinetic parameters following 800 mcg MF alone, 20 mcg F alone, concurrent MF and F delivered separately, and MF and F delivered in a single device were compared. No significant PK drug interaction between MF and F was detected, and systemic exposures to MF and F were similar whether MF and F were administered from the FDC MDI device (MF/F MDI) or co-administered from single-ingredient MDI devices (MF MDI and F MDI).
Furthermore, the applicant refers to drug interaction study with ketoconazole. The information on the interaction with ketoconazole is already contained in the SmPCs for the MF DPI (Asmanex®) and is also contained in the proposed SPC for this FDC.

Discontinuation due to AEs
Discontinuations by treatment group (number and % of subjects) for the clinical studies are presented in the table below.

P04073					
Treatment (mcg)	MF/F (100/10)	MF (100)	F (10)	PBO	Total
Total Number subjects	182	188	188	188	746
Number subjects discontinued due to AE	7	6	9	6	28
% discontinued due to AE	3.8	3.2	5	3	3.8
P04334					
Treatment (mcg)	MF/F (200/10)	MF (200)	F (10)	PBO	Total
Total Number subjects	191	192	202	196	781
Number subjects discontinued due to AE	4	6	8	7	25
% discontinued due to AE	2.1	3.1	4	2	3.2
Placebo-controlled 26-week Efficacy and Safety Studies Combined					
Treatment Group	MF/F	MF	F	PBO	Total
Total Number subjects	373	380	390	384	1527

Number subjects discontinued due to AE	11	12	17	13	53
% discontinued due to AE	3	3	4.4	3.4	3.5

P04431				
Treatment (mcg)	MF/F (200/10)	MF/F (400/10)	MF (400)	Total
Total Number subjects	233	255	240	728
Number subjects discontinued due to AE	2	2	5	9
% discontinued due to AE	1	1	2	1.2

P04705			
Treatment (mcg)	MF/F (200/10)	F/SC DPI (250/50)	Total
Total Number subjects	371	351	722
Number subjects discontinued due to AE	9	6	15
% discontinued due to AE	2	2	2

Non-Placebo-Controlled 12 week Efficacy and Safety Studies Combined					
Treatment (mcg)	MF/F (200/10)	MF/F (400/10)	MF (400)	F/SC DPI (250/50)	Total
Total Number subjects	604	255	240	351	1450
Number subjects discontinued due to AE		2	5	6	24
% discontinued due to AE	1.8	0.8	2.1	1.8	1.7

P04139					
Treatment (mcg)	MF/F (200/10)	MF/F (400/10)	F/SC MDI (250/50)	F/SC MDI (500/50)	Total
Total Number subjects	141	130	68	65	404
Number subjects discontinued due to AE	5	6	2	0	13
% discontinued due to AE	4	5	3	0	3.2

Regarding discontinuations in the 52-week safety study it is noted that 3 patients in the MF/F 400/10mcg BID group and 1 patient in the fluticasone/salmeterol 250/50 mcg BID group discontinued due to lens disorders. This issue is appropriately addressed in the SmPC.

Discussion on clinical safety

A total of 3664 subjects in the Phase 3 studies and 150 subjects in the clinical pharmacology studies were included in the safety evaluation, 1961 of whom were treated with MF/F (includes 1901 asthma subjects and 60 healthy subjects).

In the Phase 3 studies included in this program, 1785 subjects with asthma were randomized to MF/F. Of these subjects, 193 (10.8%) were between the ages of 12 and 18; 1440 (81%) were between the ages of 18 and 64, and 152 (8.5%) were 65 years old or older.

The majority of patients included in the clinical studies were Whites.

The percentage of subjects reporting AEs in the Phase 3 studies were similar across the MF/F treatment groups and no dose-dependent effect emerged for the MF/F combinations 100/10, 200/10 and 400/10 mcg BID, also when analysed by exposure. The most frequent treatment emergent AEs in the phase 3 studies were headache (7.7%), nasopharyngitis (6.8%), and upper respiratory tract infections (5.3%).. The most common treatment-related AEs were dysphonia, headache and oral candidiasis. Ophthalmologic events were evaluated in study P04139, the long term 52-week study.

It is well known that corticosteroids are cataractogenic. A dose response was not evident in this study but can hardly be expected considering the small number of events in the limited population. The information on cataract is adequately covered in the SPC.

There was no new safety signal in the evaluation of ocular AEs, hypersensitivity AEs, broncospasm AEs or metabolic AEs.

Overall, 73 serious Adverse Events were reported. No unexpected SAEs were observed, neither was there a pattern for increased rates of any SAE for any of the doses of the MF/F FDC Three subjects died during studies while receiving MF/F MDI. The deaths were not considered related to study drug. (Gastric cancer, electrocution, leiomyosarcoma with metastases)

No data exist on use of this fixed combination in patients with renal insufficiency and hepatic insufficiency.This is reflected in the SPC.

Two studies investigated the effects of MF from the MF/F fixed combination on HPA axis function, the human pharmacology study P03705 and study P04139.
Study P03705 confirmed the effect on HPA axis of high doses of MF/F as well as flutic/salm: BID inhalations of MF/F 400 µg/10 µg or fluticasone propionate/salmeterol 460 µg/42 µg lowered mean cortisol AUC(0-24 hr) values from Baseline by 16% and 29%, respectively.
Study P04139 was a 1 -year safety study conducted in Middle and South America with the secondary objective of evaluating the safety effects of middle and high doses of MF and fluticasone, both in combination with a LABA, on 24-hour plasma cortisol area under the curve (AUC) in a subset of patients. Both drugs MF/F, and fluticasone/salmeterol showed an apparently dose-dependent suppression of plasma cortisol 24-hour AUC, but no significant differences between treatment groups. There were, however, baseline imbalances and a placebo group was not included which limits the clinical relevance of this study
The systemic effects of steroids on HPA axis are well-known and the goal is always to use the lowest effective dose as also indicated in the SPC.
As stated by the applicant there is no good correlation between HPA axis effects with other systemic effects of ICS (e.g. growth velocity in children or bone density in adults). The results of the above analyses on the HPA-axis showed a clear supression upon use of the high dosage, though the presented 1-year safety study P04139 was not fully conclusive on the extent of adrenal suppression.
A potential impact of systemic exposure to mometasone on growth and BMD in children and adolescents was intensively discussed by the PDCO during the PIP procedure. During the compliance check of the PIP prior to submission of this application the applicant proposed an inclusion of the following monitoring during daily pharmacovigilance activities which was agreed upon by the PDCO: Signalling procedures which involve periodic review of all new events by preferred term (bone density decreased, osteopenia, or osteoporotic fracture) and system organ class to highlight new events or changes in reporting will also address any association to children and adolescents as related to these events.

Conclusions on clinical safety
No new safety signal were identified for this fixed combination inhalational product

Pharmacovigilance system
A new description of the Pharmacovigilance system has been submitted..
The CHMP considers that the new Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management plan

A summary of the RMP is provided below:

Table 66 Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Asthma exacerbation	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Paradoxical bronchospasm	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Adrenergic cardiac effects	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Drug interactions information in Section 4.5 of the SPC • Communicated in the PIL
Hypokalemia	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Hyperglycemia	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Hypersensitivity	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Contraindication in Section 4.3 of the SPC • Communicated in the PIL
Oropharyngeal candidiasis	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Adrenal suppression	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Growth retardation	Routine PV: • Routine pharmacovigilance Signaling review will address any association to children and adolescents as related to this event.	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Cataracts	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Glaucoma	Routine PV: • Routine pharmacovigilance	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL
Bone density decreased	Routine PV: • Routine pharmacovigilance Signaling review will also address any association to children and adolescents as related to the events of bone density decreased, osteopenia, osteoporosis or osteoporotic fracture.	Routine Risk Minimization • Warning in Section 4.4 of the SPC • Communicated in the PIL

Note: SPC= Summary of Product Characteristcs; PIL= patient information leaflet; PV= pharmacovigilance

The updated RMP is well written and follows the current guidelines. The safety profile of the components of Zenhale is well known, and the experience with these components is extensive. The applicant suggests monitoring the safety concerns through routine pharmacovigilance. This is endorsed. Monitoring of the potential impact of systemic exposure to mometasone on growth and BMD in children and adolescents is now adequately described under the pharmacovigilance activities. Table 49 on known pharmacological class effects have also been updated adequately.
Risk minimisation activities will be handled through labelling - a decision that is endorsed by the assessor.
However, due to the potential off label use in COPD patients and in children < 12 years of age, a pharmacoepidemiological study one year after marketing should be carried out.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

Beneficial effects
This application concerns a fixed dose combination of two single components already marketed for the treatment of asthma: MF DPI (Asmanex® Twisthaler) and F DPI. (Foradil® Aerolizer®). The application is thus, based on well known efficacy and safety profiles of the single components.
The combination of the two single components is recommended in the current asthma treatment guideline (GINA 2008) when inhaled corticosteroids are not sufficient to control asthma symptoms.
All three proposed dosages of MF/F (100/10 mcg BID, 200/10 mcg BID and 400/10 mcg BID) were statistically superior to MF and placebo (placebo arms in studies P04073 and P04334) on FEV1 AUC (0-12 h). ; MF 100/10 mcg BID and 200/10 mcg BID were also statistically superior to F and placebo on Time-to-first severe asthma exacerbation.
Treatment compliance is expected to be better with a FDC compared to the single components due to a reduced number of puffs to be taken each day. Also from a safety perspective, an added benefit is expected as the FDCs may decrease the risk of erroneous use of formoterol as monotherapy.

Uncertainty in the knowledge about the beneficial effects
Bioequivalence was never proven for the MF-component in the MF/F MDI vs. the marketed MF DPI (please refer to the section on clinical pharmacology). The inconsistent effects of all dosages of MF/F on asthma control could reflect the lower exposure to MF when administered by the MF/F MDIs (compared to marketed MF DPI). Therefore, based on the provided results an extrapolation from the dosage used in the marketed MF DPI to the MF/F MDI used in this clinical program cannot be performed.
As a full clinical program was conducted according to the applicant, a bridging study between the comparator MF MDI and the marketed MF DPI was not foreseen. However, in this setting the efficacy results of the MF/F MDIs can not be appropriately assessed due to the use of unauthorised MF comparators. In addition, no dose-finding studies have been conducted
The non-inferiority study P04705 evaluating the efficacy of the medium dose MF/F MDI (200/10 mcg) with the authorised medium dose F/SC DPI (250/50 mcg) is acknowledged with respect to FEV1 (AUC0-12hrs) and ACQ however, as only one dose-level was applied assay sensitivity was not ascertained.

Based on the findings during a routine GCP inspection at two sites where a large number of critical findings were identified the overall data reliability is questionable. Further inspections are therefore requested in addition to re-calculation of the efficacy results.

A spacer device was not to be used with the study medication. Subjects requiring the use of a spacer with the MDI were not to be enrolled in the study. In the response to the D120 LoQs the applicant provided in-vitro data for the use of the AeroChamber Plus spacer device with the FDC inhaler. The Applicant's choice of the Aerochamber Plus device can be accepted on the basis of the performed in vitro analyses. However, the data set should be completed with raw data and statistical calculations for the in vitro APSD analysis - including influence of patient population dependent range of flow rates before final conclusions can be drawn on its use.

Risks

Unfavourable effects
The applicant has not been able to present appropriate data that demonstrate dose-proportionality of mometasone delivered by the MF/F MDI over the entire dosing range.

No new safety concerns emerged during the clinical development.

Uncertainty in the knowledge about the unfavourable effects
The lower exposure of MF when administered by the MF/F MDI, as described above, could theoretically imply that the underlying inflammation could be masked by the LABA component (which in turn had a trend to suprabioavailability) with its bronchodilating and symptom-relieving effects potentially resulting in increased bronchial hyper reactivity and more severe exacerbations .

As expected, when treating with the highest dosage of MF/F (400/10 mcg BID) a significant depression of the HPA axis seemed to occur. Despite methodological problems this depression seemed comparable to F/SC 500/50 mcg BID. The potential impact on bone mineral density (BMD) in the adolescent population is adequately addressed through pharmacovigilance activities.

No clinical data is available in patients with renal and hepatic impairment.

Importance of favourable and unfavourable effects

Benefit-risk balance
This fixed dose combination of MF/F MDI is based on the combination of the marketed F DPI and MF DPI mono-components both with a well known efficacy and safety profile. The combination may increase treatment compliance due to reduced daily number of puffs as well as it may reduce the risk of erroneous use of formoterol as monotherapy.. Data from the clinical phase III program demonstrated efficacy of MF/F on FEV1 AUC (0-12 hr).
Reservation of its use is the lack of proven bioequivalence between the systemic exposure to MF when delivered by the marketed MF DPI and the MF/F MDI.
The inconsistent effects of all dosages of MF/F on asthma control could reflect the lower exposure to MF when administered by the MF/F MDIs. Therefore, based on the provided results an extrapolation from the dosage used in the marketed MF DPI to the MF/F MDI used in this clinical program cannot be performed. As a full clinical program was conducted according to the applicant, a bridging study between the comparator MF MDI and the marketed MF DPI was not foreseen. However, no dose-finding studies have been conducted either.

Discussion on the benefit-risk assessment
When assessing this FDC it should be kept in mind that the mono-components of this FDC as well as other FDC of ICS and LABA are already authorised for the treatment of asthma. Thus there is no unmet medical need for this FDC.
Apart from the fact that dose proportionality of mometasone delivered by the MF/F MDI device could not be demonstrated, the following shortcomings have been identified on the clinical side:
1) No bridging was performed between the marketed MF DPIs and the experimental MF MDIs; **2)** As bridging was not foreseen and a full clinical program according to the applicant was provided, the use of unauthorised MF MDI comparators is not acceptable; **3)** According to the GINA guideline ICS is standard therapy to control asthma. Therefore the appropriate comparison is MF/F vs. MF when assessing endpoints reflecting level of asthma control. This comparison was however not foreseen in the low- and medium dose studies and the post-hoc analyses of this comparison were inconsistent; **4)** for the high dose study 12 weeks study duration is considered too short for proper assessment and no dose-relationship seems to exist between MF200/10µg and 400/10 µg; **5)** The non-inferiority comparison of MF/F vs. the marketed F/SC in study P04705 could have overcome some of the above described issues, but the study lacks assay sensitivity.

Finally, based on the findings during a routine GCP inspection at two sites where a large number of critical findings were identified the overall data reliability is questionable. Further inspections are therefore requested in addition to re-calculation of the efficacy results.

Based on the above reflections the MF/F FDC is not approvable.

V.1 Conclusions

The overall B/R of Zenhale is negative.