Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Flutiform 50 microgram/5 microgram per actuation pressurised inhalation, suspension

Flutiform 125 microgram/5 microgram per actuation pressurised inhalation, suspension

Flutiform 250 microgram/10microgram per actuation pressurised inhalation, suspension

(fluticasone propionate formoterol fumarate)

UK/H/2872/001-3/DC

UK authorisation nos: PL 16950/0167-9

Napp Pharmaceuticals Limited

Introductory Note to the Reader

This Public Assessment Report produced by the MHRA is written in the form of a date or time-based commentary on the assessment of the applications for Marketing Authorisations made by the Applicant. The document must therefore be read in its entirety in order to gain a complete and accurate understanding and awareness of the application made, the assessment procedure and outcomes, the resolutions of any issues and the conclusions reached.

LAY SUMMARY

On the 22 August 2012, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Napp Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Flutiform 50 microgram/5 micrograms, 125 microgram/5 micrograms and 250 micrograms/10 micrograms per actuation pressurised inhalation, suspension.

Flutiform is a fixed-dose combination containing the active substances fluticasone propionate and formoterol fumarate and administered via a pressurised metered dose inhaler (pMDI).

- Fluticasone propionate belongs to a group of medicines called steroids. Steroids help to reduce swelling and inflammation in the lungs.
- Formoterol fumarate dihydrate belongs to a group of medicines called long-acting β_2 agonists. Long-acting β_2 agonists are long-acting bronchodilators which help the airways in your lungs to stay open, making it easier for you to breathe

This medicine is used in the treatment of asthma and helps to stop you becoming breathless and wheezy.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Flutiform 50 microgram/5 micrograms, 125 microgram/5 micrograms and 250 micrograms/10 micrograms per actuation pressurised inhalation, suspension outweigh the risks; hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1

Product Name	Flutiform 50 microgram/5 microgram per actuation pressurised inhalation, suspension Flutiform 125microgram/5 microgram per actuation pressurised inhalation, suspension Flutiform 250 microgram/10 microgram per actuation pressurised inhalation, suspension
Type of Application	Fixed-dose combination, Article 10b
Active Substances	fluticasone propionate formoterol fumarate
Form	Pressurised inhalation, suspension
Strength	50 microgram/5 microgram 125microgram/5 microgram 250 microgram/10 microgram
Marketing Authorisation Holder in the Reference Member State	Napp Pharmaceuticals Limited Cambridge Science Park, Milton Road, Cambridge, CB4 0GW, England, UK.
Reference Member State (RMS)	UK
Concerned Member States (CMSs)	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Finland, France, Ireland, Iceland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia and Sweden
Procedure Number	UK/H/2872/001-3/DC
Day 205	14 October 2011
RMS CMD(h) Updated Assessment Report following receipt of Applicant's Response to final LoQ	28 November 2011
CMD(h) Arbitration	22 December 2011
CHMP arbitration started .	19 January 2012
Positive Opinion	19 April 2012

Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

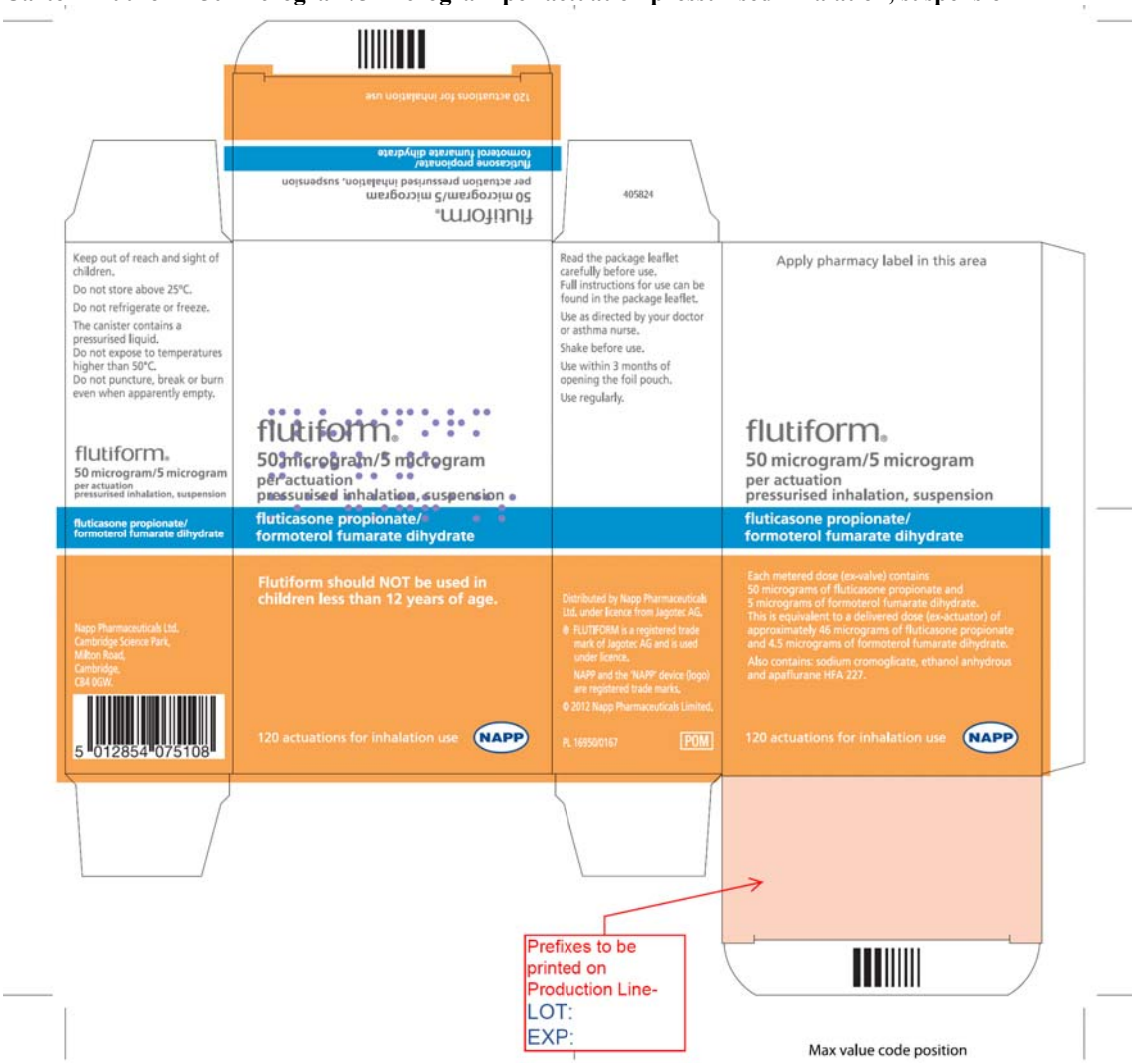
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a National level are available on the MHRA website.

Module 3
Product Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a National level are available on the MHRA website.

Module 4
Labelling

Carton-Flutiform 50 microgram/5 microgram per actuation pressurised inhalation, suspension



Cannister

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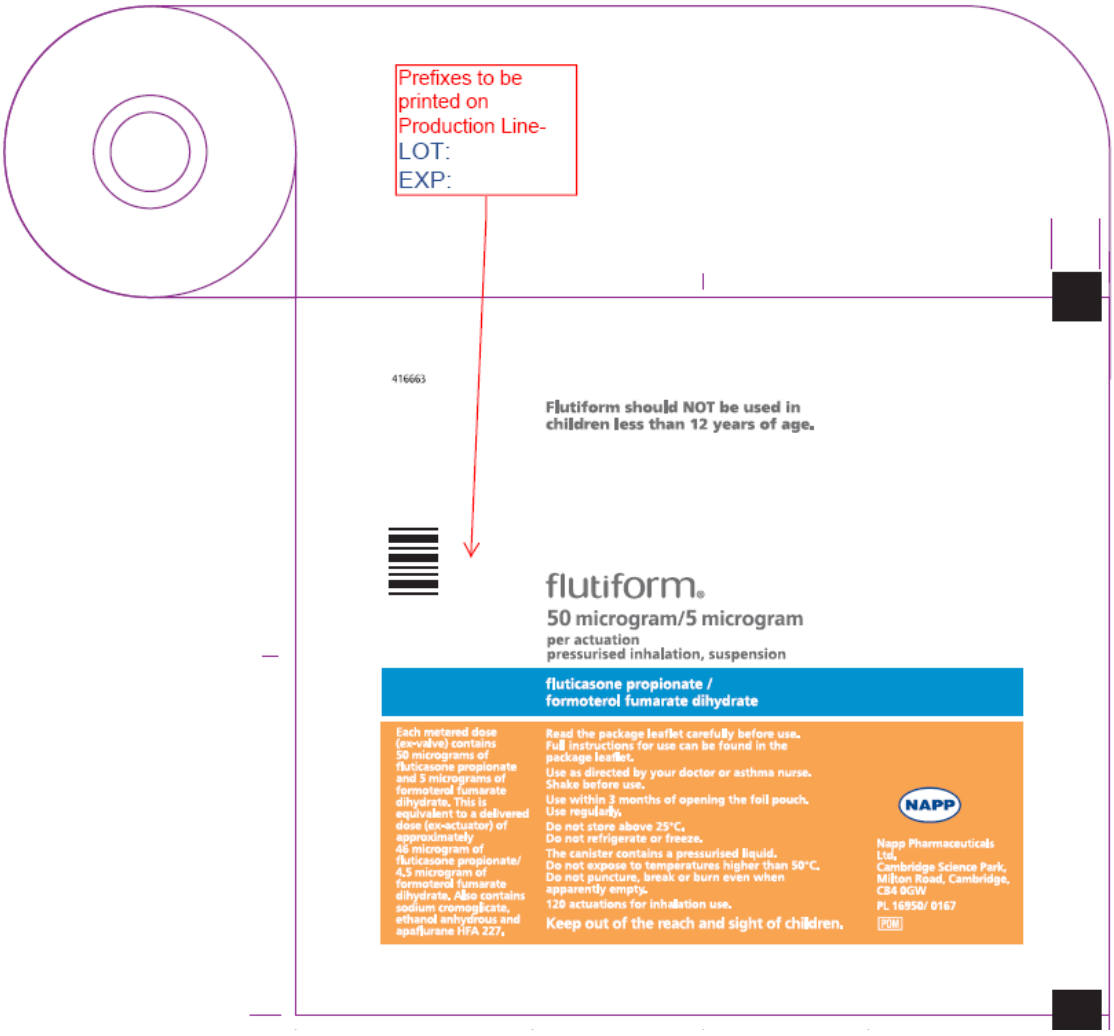
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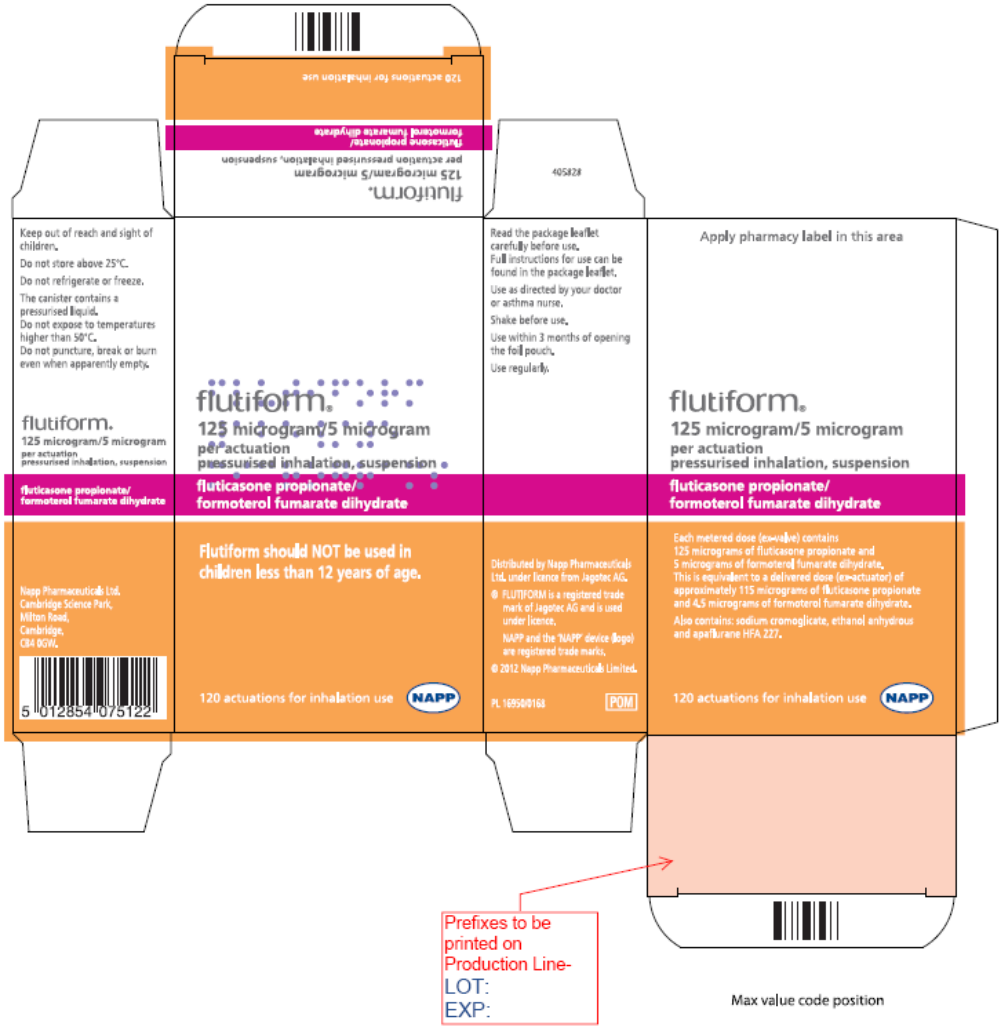
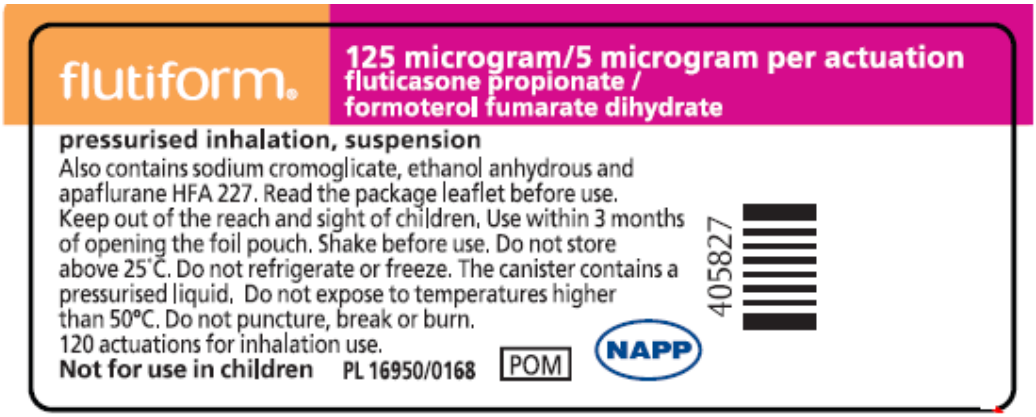
EXP:
416663
Flutiform should NOT be used in children less than 12 years of age.
flutiform
50 microgram/5 microgram
per actuation
pressurised inhalation, suspension
fluticasone propionate / formoterol fumarate dihydrate
Each metered dose (ex-valve) contains 50 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 46 microgram of fluticasone propionate/ 4.5 microgram of formoterol fumarate dihydrate. Also contains sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227.
Read the package leaflet carefully before use.
Full instructions for use can be found in the package leaflet.
Use as directed by your doctor or asthma nurse.
Shake before use.
Use within 3 months of opening the foil pouch.
Use regularly.
Do not store above 25°C.
Do not refrigerate or freeze.
The canister contains a pressurised liquid.
Do not expose to temperatures higher than 50°C.
Do not puncture, break or burn even when apparently empty.
120 actuations for inhalation use.
Keep out of the reach and sight of children.
NAPP
Napp Pharmaceuticals Ltd,
Cambridge Science Park,
Milton Road, Cambridge,
CB4 0GW
PL 16950/ 0167
PDN

Carton-Flutiform 125 microgram/5 microgram per actuation pressurised inhalation, suspension



Cannister



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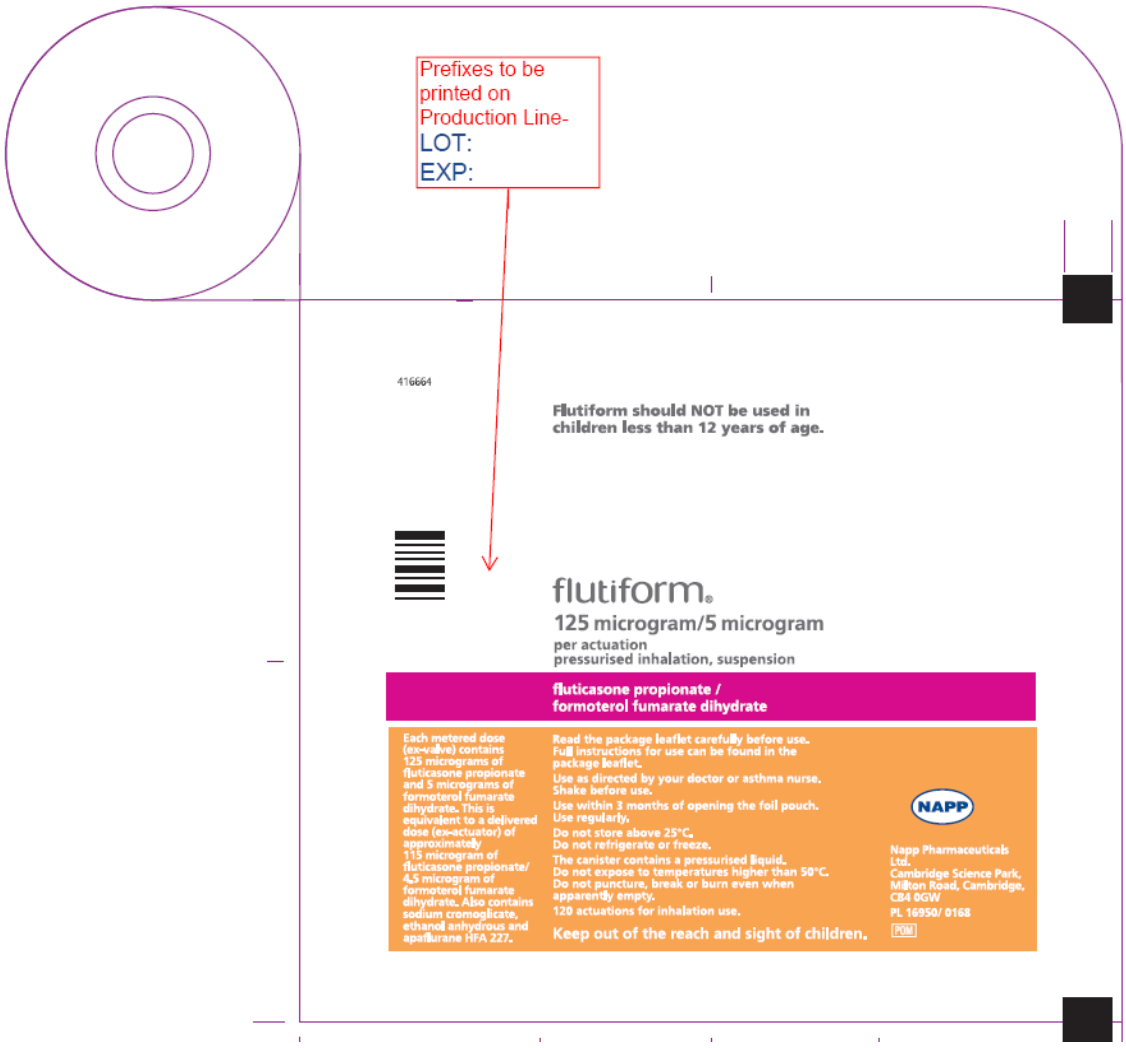
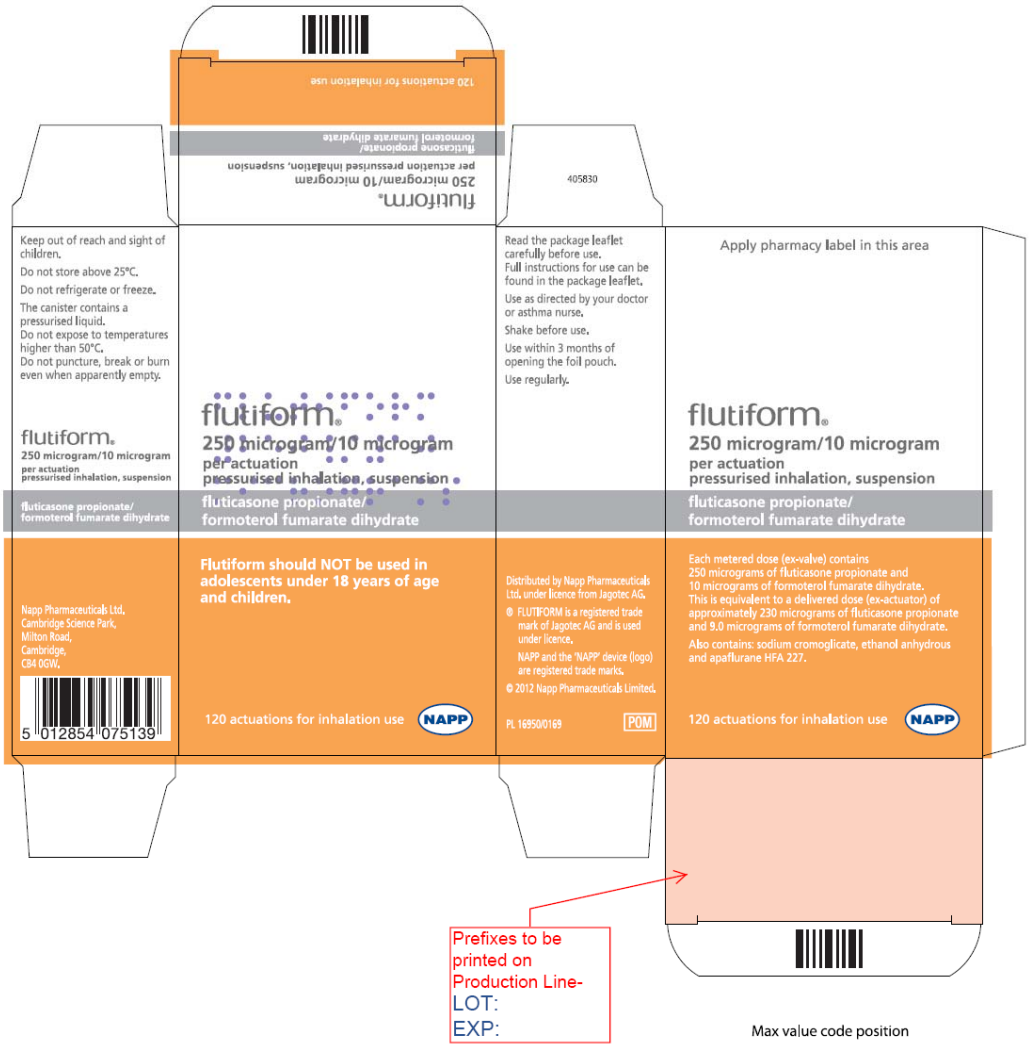
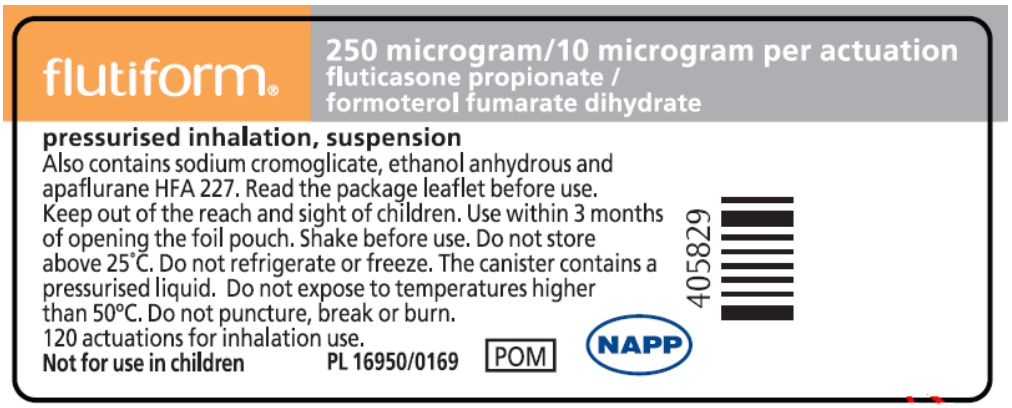

Prefixes to be printed on Production Line-
LOT:
EXP:
416664
Flutiform should NOT be used in children less than 12 years of age.
flutiform®
125 microgram/5 microgram
per actuation
pressurised inhalation, suspension
fluticasone propionate / formoterol fumarate dihydrate
Each metered dose (ex-valve) contains 125 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 113 microgram of fluticasone propionate/ 4,5 microgram of formoterol fumarate dihydrate. Also contains sodium cromoglicate, ethanol anhydrous and aparflurane HFA 227.
Read the package leaflet carefully before use.
Full instructions for use can be found in the package leaflet.
Use as directed by your doctor or asthma nurse.
Shake before use.
Use within 3 months of opening the foil pouch.
Use regularly.
Do not store above 25°C.
Do not refrigerate or freeze.
The canister contains a pressurised liquid.
Do not expose to temperatures higher than 50°C.
Do not puncture, break or burn even when apparently empty.
120 actuations for inhalation use.
Keep out of the reach and sight of children.
NAPP
Napp Pharmaceuticals Ltd.
Cambridge Science Park,
Milton Road, Cambridge,
CB4 0GW
PL 16950/ 0168
POM

Carton-Flutiform 250 microgram/10 microgram per actuation pressurised inhalation, suspension



Cannister



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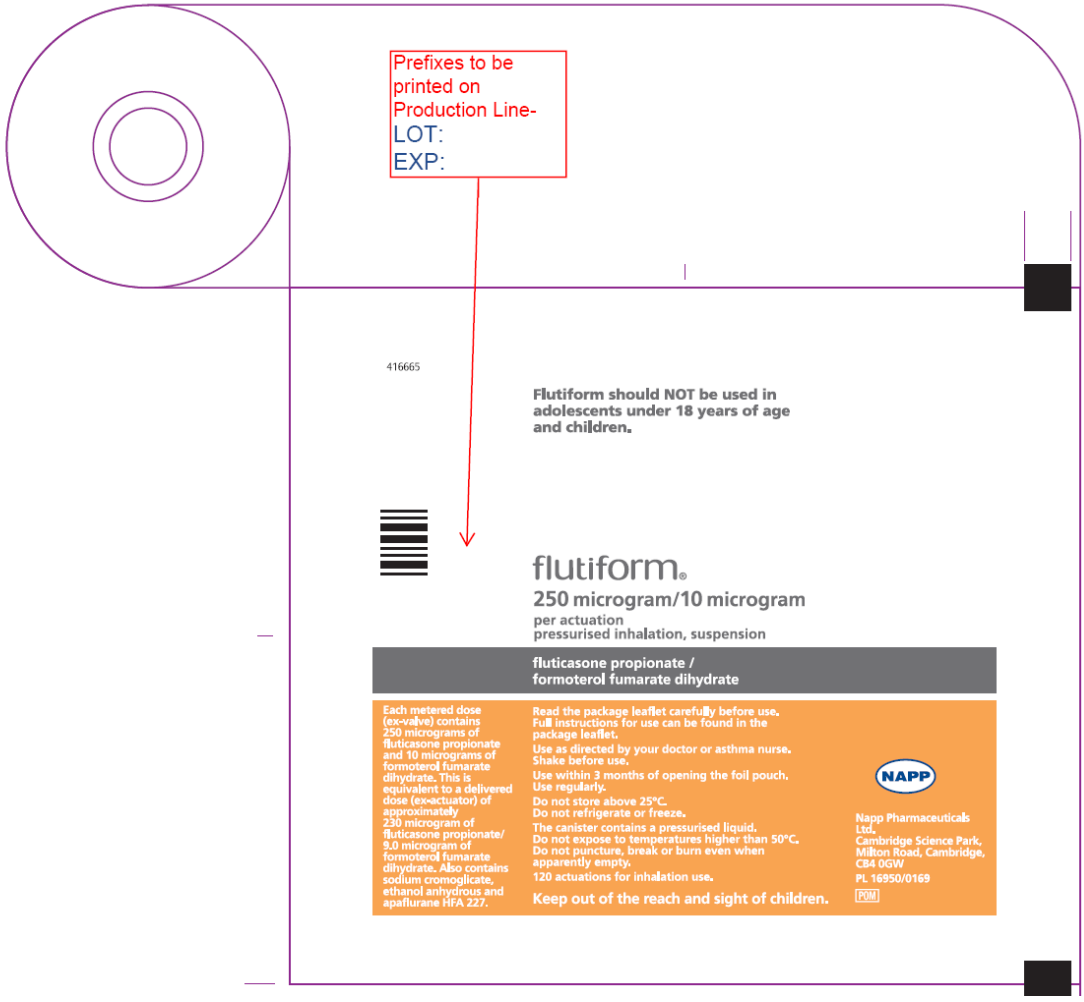
Prefixes to be printed on Production Line-
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EXP:
416665
Flutiform should NOT be used in adolescents under 18 years of age and children.
flutiform®
250 microgram/10 microgram
per actuation
pressurised inhalation, suspension
fluticasone propionate / formoterol fumarate dihydrate
Each metered dose (ex-valve) contains 250 micrograms of fluticasone propionate and 10 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 230 microgram of fluticasone propionate/ 9.0 microgram of formoterol fumarate dihydrate. Also contains sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227.
Read the package leaflet carefully before use. Full instructions for use can be found in the package leaflet.
Use as directed by your doctor or asthma nurse.
Shake before use.
Use within 3 months of opening the foil pouch.
Use regularly.
Do not store above 25°C.
Do not refrigerate or freeze.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.
120 actuations for inhalation use.
Keep out of the reach and sight of children.
NAPP
Napp Pharmaceuticals Ltd.
Cambridge Science Park,
Milton Road, Cambridge,
CB4 0GW
PL 16950/0169
POM

Module 5
Scientific discussion during initial procedure

NOTE: This assessment report has been updated to incorporate information provided by the Applicant in response to queries raised by the assessor and/or Committee for Medicinal Products for Human Use (CHMP) during the assessment process. Updates are generally not included at the point where queries are raised but in later appropriate sections. Therefore please read the entire document in order to obtain full information. However please note that all queries raised by the assessors, CMD(h) and CHMP were answered satisfactoriy by the Applicant, as presented in the section on Opinion of the Committee for Medicinal Products for Human Use.

I INTRODUCTION

On 19th April 2012, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Finland, France, Ireland, Iceland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Sweden and the UK agreed to grant Marketing Authorisations (MAs) to Napp Pharmaceuticals Limited for the medicinal products Flutiform 50 microgram/5 micrograms, 125 microgram/5 micrograms and 250 microgram/10 micrograms per actuation pressurised inhalation, suspension. The MAs were granted via a Decentralised Procedure (DCP), following referral at CHMP. The UK was the Reference Member State (RMS UK/H/2872/01-03/DC) in these procedures and after the national phase, MAs were granted in the UK on 22 August 2012 (PL 16950/0167-9). These products are prescription only medicines (POM).

These applications were made under Article 10b (fixed combination) of Directive 2001/83/EC for Flutiform 50 microgram/5 micrograms, 125 microgram/5 micrograms and 250 microgram/10 micrograms per actuation pressurised inhalation, suspension, containing the known active substances fluticasone propionate and formoterol fumarate. These fixed-dose combination products were not previously authorised in the Community.

Fluticasone propionate is an inhaled glucocortosteroid with high local anti-inflammatory activity and a lower incidence of adverse effects than is seen with oral corticosteroids. Fluticasone propionate has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyperreactive airways. Fluticasone propionate is a well established active substance and is recommended for use in the management of asthma in both adults and children.

Formoterol fumarate is a selective long-acting $ß_2$ adrenergic agonist and exerts a preferential effect on $ß_2$ adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Formoterol fumarate is used via the orally inhaled route in the management of patients with reversible airways obstruction. Following oral inhalation of formoterol the onset of bronchodilatation is rapid, within 1 - 3 minutes and bronchodilatation following a single dose lasts for 12 hours. Formoterol fumarate is particularly useful in patients with reversible airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airways obstruction and particularly asthma recommend the addition of a long-acting $ß_2$ agonist to the treatment regimen in these patients and studies have shown that the addition of a long-acting $ß_2$ agonist provides better control of asthma than increasing the dose of inhaled corticosteroid.

The products are orally inhaled products and this combination of an inhaled glucocorticosteroid and a selective long-acting $ß_2$ adrenergic agonist is a well established combination for use in the regular treatment of adults and children with asthma where the use of such a combination is deemed appropriate. However the specific combination of these two well known active substances, fluticasone propionate and formoterol fumarate, is new.

These new fixed-dose combination products are formulated as pressurised inhalation suspensions together with the hydrofluoroalkane (HFA) propellant, propellant HFA 227, a non-chlorofluorocarbon (non-CFC) alternative propellant. The Marketing Authorisations sought currently are not CFC-free replacement formulations developed to replace a pre-existing CFC-containing formulation of the same combination of active substances; the Applicant seeks authorisations for their first products containing these two active substances.

The Applicant has conducted 14-day and 13-week bridging toxicity studies in the rat and dog, embryofetal development studies in the rat and rabbit and a respiratory and cardiovascular safety pharmacology study in the dog to support these applications. In addition the Applicant has submitted a large and comprehensive clinical dossier comprising of nine completed Phase I and II studies, nine completed Phase III studies and two on-going Phase III studies in support of these applications. Over 1900 adult and adolescent subjects have been treated with at least one dose of FlutiForm.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH 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. The Marketing Authorisation Holder has provided a Risk Management Plan (RMP).

The Marketing Authorisation Holder has provided a satisfactory Environmental Risk Assessment (ERA).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State (RMS)	Flutiform 50 microgram/5 microgram per actuation pressurised inhalation, suspension Flutiform 125microgram/ 5 microgram per actuation pressurised inhalation, suspension Flutiform 250 microgram/10 microgram per actuation pressurised inhalation, suspension
Names of the active substances (INN)	fluticasone propionate formoterol fumarate
Pharmacotherapeutic classification (ATC code)	R03B A05-Fluticasone: Group: Glucocorticoids R03AK07- Fomoterol: Group: Adrenergics and other drugs for obstructive airway diseases
Pharmaceutical form and strengths	Pressurised inhalation suspension 50 microgram/5 microgram 125microgram/5 microgram 250 microgram/10 microgram
Reference numbers for the Decentralised Procedure	UK/H/2872/01-03/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Finland, France, Ireland, Iceland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia and Sweden
Marketing Authorisation Number(s)	PL 16950/0167-9
Name and address of the authorisation holder in the RMS	Napp Pharmaceuticals Limited Cambridge Science Park, Milton Road, Cambridge, CB4 0GW, England, UK.

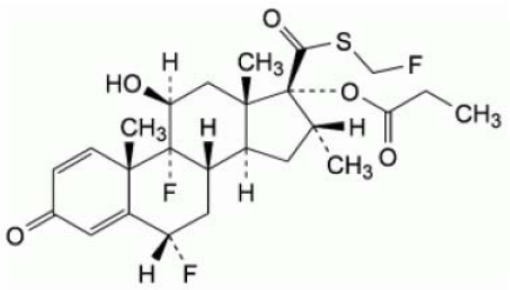
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE (1)

INN Fluticasone propionate

Chemical name: S-fluoromethyl 6α, 9α-difluoro-11β 17-dihydroxy-16α-methyl-3-oxoandrosta- 1,4-diene-17β-carbothioate, 17propionate.

Structure of Fluticasone Propionate



Molecular formula: $C_{25}H_{31}F_3O_5S$

Molecular weight: 500.6

General Properties

Fluticasone propionate is a white to almost white powder.

It is practically insoluble in water, sparingly soluble in dichloromethane and slightly soluble in ethanol.

The active substance, fluticasone propionate is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Manufacture

All aspects of the manufacture and control of the active substance fluticasone propionate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability and supplemented by additional in-house testing. The test methods used are based on general methods described in the European Pharmacopoeia and US Pharmacopoeia.

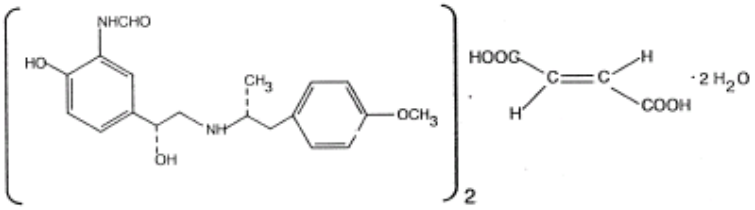
A re-test period has been included on the EDQM Certificate of Suitability.

ACTIVE SUBSTANCE (2)

INN Formoterol fumarate

Chemical name: N-[2-hydroxy-5-[1(RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (E)-butenedioate dihydrate

Structure



Molecular formula: $C_{42}H_{52}N_4O_{12}.2H_2O$
Molecular weight: 840.41

General Properties
Formoterol fumarate is a white to off white or slightly yellow powder.

It is soluble in methanol, slightly soluble in water and 2-propranol and practically insoluble in acetonitrile.

The active substance, formoterol fumarate is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Manufacture
All aspects of the manufacture and control of the active substance fluticasone propionate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability and supplemented by additional in-house testing. The test methods used are based on general methods described in the European Pharmacopoeia and US Pharmacopoeia.

A re-test period has been included on the EDQM Certificate of Suitability.

MEDICINAL PRODUCT
Description and Composition
The medicinal product is a liquid suspension; and contained in an aluminium canister which is in a white actuator with a grey integrated dose indicator and a light grey mouthpiece cover.

Flutiform® 50 microgram/5 microgram per actuation pressurised inhalation, suspension
Each metered dose (ex valve) contains:

50 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 46 microgram of fluticasone propionate/4.5 microgram of formoterol fumarate dihydrate.

Flutiform® 125 microgram/5 microgram per actuation pressurised inhalation, suspension.
Each metered dose (ex valve) contains:

125 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 115 microgram of fluticasone propionate/4.5 microgram of formoterol fumarate dihydrate.

Flutiform® 250 microgram/10 microgram per actuation pressurised inhalation, suspension.
Each metered dose (ex valve) contains:

250 micrograms of fluticasone propionate and 10 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 230 microgram of fluticasone propionate/9.0 microgram of formoterol fumarate dihydrate.

Other ingredients consist of pharmaceutical excipients, sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227. Appropriate justification for the inclusion of each excipient has been provided.

Ethanol anhydrous complies with its European Pharmacopeia monograph. Sodium cromoglicate and apaflurane (HFA 227) both comply with in-house specifications; which are satisfactory. Satisfactory Certificates of Analysis have been provided for all excipients. None of the excipients contain material from animal or human origin. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Pharmaceutical Development

The aim of the pharmaceutical development programme was to develop a consistent and reliable single pressurised metered dose inhaler (pMDI) delivery system for a medicinal product containing two well-established active substances, fluticasone propionate and formoterol fumarate, currently marketed as separate inhalation products, in the treatment of asthma.

The applicant has provided a suitable product development section.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on production-scale batches and are accepted. All validation data were within specification.

Finished Product Specification

Finished product specifications are provided for both release and shelf–life, and are satisfactory, providing an assurance of the quality and consistency of the finished product. Test methods have been described and adequately validated, as appropriate. Batch data are provided for the finished product and comply with the proposed release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in an aluminium pressurised canister crimped with a standard metering valve. This canister is inserted into a press and breathe actuator fitted with a mouthpiece cover (both made of polypropylene) and an integrated dose indicator which indicates the number of actuations (puffs) remaining. The actuator is white with a grey integrated dose indicator and a light grey mouthpiece cover. The assembled pMDI is pouched in an aluminium foil laminate and placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. Each container delivers 120 actuations.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and the results were within the proposed specification limits. Based on the results, a shelf-life of 2 years (unopened) and an in-use shelf-life of 3 months after opening the foil pouch has been set. Storage instructions are, ‘Do not store above 25°C”, “Do not refrigerate or freeze”, “If the inhaler is exposed to freezing conditions then the patient must be advised to allow the inhaler to warm at room temperature for 30 minutes then re-prime the inhaler (see section 4.2 of the SmPC)”, “The canister contains a pressurised liquid”, “Do not expose to temperatures higher than 50°C”and “Do not puncture, break or burn, even when apparently empty”.

Quality Overall Summary

A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided.

The Applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The results also show that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Forms

The MAA forms are pharmaceutically satisfactory.

ASSESSOR'S OVERALL CONCLUSION ON QUALITY

Further to the initial assessment there were pharmaceutical issues that required resolution prior to the granting of the Marketing Authorisations.

All issues were satisfactorily resolved and it is recommended that Marketing Authorisations are granted for these applications.

III.2 NON-CLINICAL ASPECTS

The pharmacology, pharmacokinetics and toxicology of fluticasone propionate and formoterol fumerate are well known, having been in clinical use as individual actives in inhalation products for many years. In addition, the combination of an inhaled glucocorticosteroid and a selective long-acting $ß_2$ adrenergic agonist is also well-established for use in the regular treatment of adults and children with asthma. The Applicant has conducted 14-day and 13-week bridging toxicity studies in the rat and dog, embryofetal development studies in the rat and rabbit and a respiratory and cardiovascular safety pharmacology study in the dog.

III.2.1 PHARMACOLOGY

III.2.1.1 Safety Pharmacology

The Applicant has submitted one new non-clinical cardiovascular and respiratory safety pharmacology study in dogs in support of this combination medicinal product.

Safety pharmacology

Effects on cardiovascular and respiratory function in the telemetered dog.

Flutiform® (formoterol fumarate (FF)/fluticasone propionate (FP)) was administered, via inhalation, to four male dogs at three doses. The responses obtained were compared with those following treatment with the control item (vehicle) - (FF in hydrofluoroalkane (HFA 227)-propelled pMDI).

The effects seen in the cardiovascular and respiratory safety pharmacology study in dogs were in line with those observed following FF alone. It is considered that no additional risk to the cardiovascular/respiratory system is expected through clinical use of the proposed combination product.

Overall Conclusions on pharmacology

The pharmacology of FF and FP alone are well-known following extensive clinical use. A brief review of pharmacology data for both actives in the literature has been presented in the non-clinical summary and the lack of non-clinical pharmacology studies is accepted.

Effects seen in a cardiovascular and respiratory safety pharmacology study were attributed to the FF component of Flutiform. No additional risk to the cardiovascular/respiratory system is expected through clinical use of the proposed combination product.

III.2.2 PHARMACOKINETICS

The pharmacokinetics of formoterol and fluticasone are well known as these two active substances have separately been in clinical use for many years. Exposure data obtained in the bridging toxicology studies are described below.

In summary, in toxicity studies of 14 and 91 days duration in rats and dog, plasma exposure to FF and FP increased with dose in a generally linear manner. In rat, both FF and FP plasma concentrations tended to increase throughout the course of the treatment duration. In dogs, plasma concentrations for FF and FP tended to be similar throughout the treatment period. In toxicity studies bridging to HFA 227 containing formulations, the plasma concentrations for both FF and FP were similar in rats and dogs regardless of formulation used.

Overall conclusions on pharmacokinetics

No pharmacokinetic studies were conducted in support of these applications which is acceptable given that the pharmacokinetics of FF and FP are well-known. Toxicokinetic analysis was included in the bridging toxicity studies.

III. 2.3 TOXICOLOGY

In support of the present Flutiform® formulation, the effects of Flutiform® and in some studies the individual components FF and FP were investigated in inhalation toxicity bridging studies in rats, dogs and rabbits. The main aims of the program were to demonstrate the safety of Flutiform® and to assess any possible interactions between the two active components of Flutiform®, FP and FF. All bridging studies were conducted by the inhalation route with the to-be-marketed formulation.

These studies showed only the well-characterized and known effects of the individual components, FP and FF. There was no indication of any interactions between the individual components.

III.2.3.1 Single dose toxicity

Single-dose toxicity studies are not required for these applications and none were provided by the applicant. The safety pharmacology study described above investigated some of the effects seen following single administration.

The proposed producs are intended for chronic use, therefore the results of repeat-dose toxicity studies are more relevant when considering the risk:benefit balance for the proposed combination products.

III.2.3.2 Repeat-dose toxicity

Flutiform®

Two 14-day (one rat and one dog) and three 13-week (one rat and two dog) bridging inhalation toxicity studies of Flutiform® were undertaken. Toxicokinetic evaluations were performed as part of these toxicology studies.

Conclusions

The repeated-dose toxicity studies were conducted in the rat and dog using Flutiform® and with FP and FF alone. The effects seen are in line with the known effects associated with administration of either FP or FF alone. No additional or synergistic toxicity is expected through clinical use of the proposed combination products.

Formoterol fumerate

In addition, a 14-day rat and two 13- week studies in the dog comparing FF administered via a

pMDI or a dry powder inhaler (DPI) were conducted. Toxicokinetic evaluations were performed as part of these toxicology studies.

Conclusions
The findings of the repeated-dose toxicity studies with FF (either formulated as a pMDI or a DPI) are largely attributed to known exaggerated pharmacological effects seen following administration of β_2 adrenergic receptor agonists. These findings are in line with published data and the combination of FF with HFA does not appear to be associated with any additional toxicity in comparison with dry powder formulations.

III.2.3.3 Genotoxicity
No genotoxicity studies were conducted with Flutiform®

Conclusion
This approach is acceptable as no additional genotoxic potential is expected on combination of FP and FF.

III.2.3.4 Carcinogenicity
No carcinogenicity studies have been conducted with Flutiform.

Conclusion
This approach is acceptable as no additional carcinogenic potential is expected on combination of FP and FF.

III.2.3.5 Reproductive and developmental toxicity
Two inhalation embryofetal development studies, one in the rat and one in the rabbit, (and associated dose range finding studies), were included in the Flutiform® nonclinical toxicology program. According to the applicant the effects of FF and FP on embryofetal development have not previously been investigated by the inhalation route and therefore the combination Flutiform® was tested in two species, the rat and rabbit.

III.2.3.5 (1) Fertility and early embryonic development
No fertility and early embryonic development studies were submitted.

This approach is in line with the CHMP Guideline on the Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005) and is acceptable for this type of product.

III.2.3.5.(2) Embryo-fœtal development
Embryofetal development studies in the rat and rabbit with Flutiform® confirmed the known reproductive toxicity effects of FF and FP and other actives in these pharmacological classes. No additional or new toxicity was observed.

III.2.3.5 (3) Prenatal and postnatal development, including maternal function
No prenatal and postnatal development studies were submitted.

This approach is in line with the CHMP Guideline on the Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005) and is acceptable for this type of product.

III.2.3.5.(4) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No juvenile animal studies submitted. The lack of these studies is acceptable for this type of product.

III.2.3.6 Local tolerance

No local tolerance studies submitted. The local tolerance of these products has been investigated in the repeated dose toxicity studies with the combination product. The combination of FF and FP is unlikely to result in additional toxicity in the lung.

III.2.3.7 Other aspects

Safety factors were calculated for a 60 kg human using exposure data from toxicology studies with Flutiform® in comparison with the worst case clinical exposure of 1000/40µg FP/FF derived from two doses of the 250/10 formulation taken twice daily (4 doses in total). The data demonstrate that the factors are not high and occasionally sub-therapeutic, but this is a common finding with inhaled corticosteroid formulations where animals tend to be more sensitive than humans. The prior clinical usage of the individual components of Flutiform® at these doses confirms the clinical safety.

Conclusion

The low margins of safety are acceptable for this type of product. Clinical experience with the proposed doses of the separate actives provides further reassurance of safety.

III.2.4 Excipients

Three excipients are included in the Flutiform® formulations: Propellant HFA 227, ethanol anhydrous and sodium cromoglicate.

HFA 227

HFA 227 is a well known propellant that has been subjected to extensive toxicological and pharmacological studies. It has been assessed by the Committee for Medicinal Products for Human Use (CPMP) and approved for use in pMDIs. HFA 227 is also used in previously approved products in Europe.

No adverse effects were attributed to the HFA 227 component of Flutiform® in the toxicity studies conducted in support of these applications. Indeed, no difference in the toxicity profile was seen following administration of the vehicle control (HFA 227 and sodium cromoglycate) compared with the air exposure control.

The non-clinical dossier contains a review of the available literature data on HFA 227 and concludes that no safety concerns are expected on incorporation of this excipient in the proposed product.

Ethanol

Ethanol is an excipient commonly used in pressurised metered dose inhalers and is listed in the European Pharmacopoeia (2008), Martindale (2008) and Rowe *et al* (2003) as an approved excipient. Additionally, its inclusion in the formulation has been qualified through the toxicity bridging studies.

Sodium cromoglicate (Ph.Eur.)

Sodium cromoglycate is contained in the Flutiform® formulations as an excipient to act as a suspension aid (bulking agent) and internal moisture scavenger. While the use of sodium cromoglicate as an excipient is novel, its clinical safety is well-established through use as an active substance in the treatment of asthma at considerably higher doses than those proposed here.

A review of the available non-clinical data on sodium cromoglycate has been presented in the applications which concluded that it is essentially non-toxic, not mutagenic, clastogenic or

carcinogenic, not a reproductive toxin, with very low acute and repeat dose inhalation toxicity. In addition, the 13-week bridging study in the dog also included a placebo Flutiform® exposed group compared with air exposure controls to determine if there was an effect of the components of the placebo formulation (i.e., HFA 227 and sodium cromoglicate). No evidence of an effect was observed.

Conclusions

The proposed excipients are commonly used in inhalation products and are considered to be acceptable. Further assurance of safety is provided through both the provision of toxicity bridging studies with this formulation and review of available literature data.

III.2.5 Impurities, Leachables and Extractables

Impurities

The impurities associated with the drug product appear to be well controlled and within ICH limits. No further toxicological qualification is considered necessary.

Leachables and extractables

A full assessment of the extractables and leachables for the Flutiform® formulations has been undertaken. Appropriate extractables studies have been performed to identify potential leachables. In addition, leachables levels were determined up to 24 months.

Conclusions

An appropriate risk assessment has been conducted for the identified leachables in the drug product using data from stability studies and literature. Additional reassurance is given through use of the proposed product in the bridging toxicity studies. No further toxicological qualification of the potential leachables is required.

III.2.6 Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) for Flutiform® has been submitted.

The logKow values of FP and FF are stated as 3.4 and 0.4 respectively. No additional investigation into persistence, bioaccumulation or toxicity is required in line with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

PECsurfacewater values of 5×10^{-6} mg/L and 2×10^{-7} mg/L have been calculated for FP and FF respectively using DOSEai values of 1.0 (FP) and 0.04 (FF) and the default values for Fpen, WasteWinhab and Dilution. No Phase II assessment is required in line with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

Conclusions

An acceptable ERA has been submitted for FP and FF. The $PEC_{surfacewater}$ values are below the threshold that triggers a Phase II assessment. No risk to the environment is expected on licensing of these products.

III.2.7 OVERALL CONCLUSIONS ON TOXICOLOGY

The toxicological profile for Flutiform® has been shown to be similar to that observed following administration of β_2 agonists and/or corticosteroids. The effects seen in the bridging studies have previously been reported for the individual active components of Flutiform®, FP and FF. No additional or unexpected toxicity was observed in the combination product and no interactions between the two components of Flutiform® were evident. Therefore, no safety concerns are raised on the combination of FP and FF in the proposed product formulations.

There are no objections to approval of Flutiform 50 microgram/5 micrograms; 125 microgram/5 micrograms and 250 microgram/10 micrograms per actuation pressurised inhalation, suspension from a non-clinical point of view.

III.3 CLINICAL ASPECTS

3.1 BACKGROUND

3.1.1 Therapeutic Class

Fluticasone propionate is an inhaled glucocortosteroid with high local anti-inflammatory activity and a lower incidence of adverse effects than is seen with oral corticosteroids. Fluticasone propionate has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyperreactive airways. Fluticasone propionate is a well established active substance and is recommended for use in the management of asthma in both adults and children.

Formoterol fumarate is a selective long-acting $ß_2$ adrenergic agonist and exerts a preferential effect on $ß_2$ adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Formoterol fumarate is used via the orally inhaled route in the management of patients with reversible airways obstruction. Following oral inhalation of formoterol the onset of bronchodilatation is rapid, within 1 - 3 minutes and bronchodilatation following a single dose lasts for 12 hours. Formoterol fumarate is particularly useful in patients with reversible airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airways obstruction and particularly asthma recommend the addition of a long-acting $ß_2$ agonist to the treatment regimen in these patients and studies have shown that the addition of a long-acting $ß_2$ agonist provides better control of asthma than increasing the dose of inhaled corticosteroid.

The mechanisms of action of the two drugs, fluticasone propionate and formoterol fumarate, are different but complementary.

3.1.2 Therapeutic Indications

The indications for ***Flutiform*** 50 microgram/5 microgram and 125 microgram/5 microgram and 250 microgram/10 microgram per actuation pressurised inhalation, suspension are as follows:

This fixed-dose combination of fluticasone propionate and formoterol fumarate (***Flutiform*** inhaler) is indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β_2 agonist) is appropriate:

- For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 agonist

  or

- For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist.

Please note:
Flutiform 50 microgram/5 microgram and 125 microgram/5 microgram inhaler are indicated **in adults and adolescents aged 12 years and above.**

Flutiform 250 microgram /10 microgram inhaler is indicated **in adults only.**

3.1.3 Posology and method of administration

For details of the posology and method of administration please refer to Section 4.2 of the SmPC.

3.1.4 Paediatric Development Plan

In the current submission the Applicant requests use of this combination pMDI in adults and adolescents 12 years of age and older only; use in children less than 12 years of age is not requested.

No pivotal clinical data in support of the use of these products in children less than 12 years of age have been submitted.

Article 7 of the Paediatric Regulation applies to these applications, these fixed-dose combination products are not previously authorised in the Community. These applications include a Paediatric Investigation Plan (PIP).

If these products are to be authorised for use in children less than 12 years of age clinical development in children will be required. Evidence of an appropriate benefit/risk balance must be demonstrated across the entire age range of intended use.

3.2 CLINICAL DEVELOPMENT PROGRAMME

The clinical development programme for Flutifom, a fixed combination inhalation suspension in three strengths, administered via a pressurised metered dose inhaler was set up to evaluate efficacy and safety in the intended patient population. The clinical development programme was designed to compare:

- The efficacy and safety of Flutiform with its individual components administered separately
- The efficacy and safety of Flutiform with other similar combination therapies –

  fluticasone propionate and formoterol fumarate administered concomitantly via separate inhalers

  and

  Seretide, a fixed-dose combination of fluticasone propionate and salmeterol xinafoate

and to confirm:

- The efficacy and safety of Flutiform administered either with or without a spacing device

and to investigate whether:

- The efficacy and safety of Flutiform were consistent across relevant subgroups.

The clinical development programme comprised nine completed Phase I and II studies, nine completed Phase III studies and two on-going Phase III studies.

3.3 CLINICAL PHARMACOLOGY

The clinical pharmacology programme comprised seven Phase I and two Phase II studies.

3.3.1 PHARMACOKINETICS

The Applicant presented seven studies to investigate the pharmacokinetics of this new fixed-dose combination pressurised metered inhaler containing fluticasone propionate and formoterol fumarate and compared the pharmacokinetics of this new combination with the pharmacokinetics of the two active substances administered together but via separate devices, one inhaled after the other. Four studies have been carried out in healthy volunteers and three in patients with mild to moderate asthma, and one of the patient studies, Study FLT2502, compared the pharmacokinetics of these two actives substances in adults (18 to 55 years) and adolescents (12 to 17 years). Two studies, one in healthy adult volunteers, Study FLT1501 and one in adults and adolescents with mild to moderate asthma, Study FLT2502, saw all study treatments administered via a pressurised metered dose

inhaler and the AeroChamber Plus spacing device. One further study conducted in healthy volunteers, Study FLT1503, was submitted during the Procedures.

Phase I Clinical Studies- Healthy Volunteers

3.3.1.1 Study AG20280-C101

A randomised, open-label, 4-way crossover, single-dose study to compare the pharmacokinetics of fluticasone propionate and formoterol fumarate combination (FlutiForm 250/10µg) via SkyePharma HFA MDI with fluticasone propionate HFA MDI (Flixotide Evohaler 250µg) and formoterol fumarate DPI (Foradil Aerolizer 12µg) administered concurrently or alone in healthy subjects (n=24)**.**

Note that the Flutiform formulation in this study was delivered via a Bespak actuator which is not the actuator used during the Phase III clinical development or in the marketed product

Study treatments – single dose treatments:

SKP FlutiForm HFA pMDI	2 actuations of 125/5µg/actuation (total dose: 250µg fluticasone propionate and 10µg formoterol fumarate)
Fluticasone propionate HFA pMDI	2 actuations of Flixotide Evohaler 125µg/actuation (total dose: 250µg fluticasone propionate)
Formoterol fumarate DPI	1 actuation of Foradil Aerolizer 12µg/actuation (total dose: 12µg formoterol fumarate)
Fluticasone propionate HFA pMDI and formoterol fumarate DPI administered concurrently	1 actuations of Flixotide Evohaler and 1 actuation of Foradil Aerolizer, administered concurrently (total dose: 250µg fluticasone propionate and 12µg formoterol fumarate)

To assess the potential for any drug-drug interaction of formoterol on fluticasone propionate, the pharmacokinetic parameters (C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$) for fluticasone propionate were log-transformed and fitted to an Analysis of Variance (ANOVA) model with effects for sequence, random subject within sequence, period and treatment.

Clinical Findings

Fluticasone Propionate

When FlutiForm was administered the geometric mean fluticasone propionate peak and total exposure were lower than were seen with the comparator treatments; the observed intersubject variability was also observed as being large

Fomoterol fumarate

In the early development of Flutiform, thre was no analytical method enabling deternmination of therapeutic concentrations of fomoterol in plasma. For this reason, most studies involved the determination of formoterol in urine only.

Only a small percentage of formoterol was excreted in urine following administration of formoterol alone (Foradil) or in combination with fluticasone propionate (SKP FlutiForm, Flixotide + Foradil).

The fractions of free and total formoterol excreted were comparable across treatment groups.

3.3.1.2 Study SKY2028-1-002

A randomised, open-label, parallel group, multiple-dose exposure study to compare the pharmacokinetics of fluticasone and formoterol combination (FlutiForm 100/10µg and 250/10µg) in a single inhaler (SkyePharma HFA pMDI) with the administration of Fluticasone (250µg) and Formoterol (10µg) concurrently or alone in healthy male and female subjects (n=50)***.***

Study treatments – administered twice daily for 7 days:

Treatment A	SKP FlutiForm 100/10µg pMDI: 2 actuations of 50/5µg/actuation twice daily
Treatment B	SKP FlutiForm 250/10 g pMDI: 2 actuations of 125/5µg/actuation twice daily
Treatment C	Fluticasone propionate 250µg pMDI and formoterol fumarate 10µg pMDI administered concurrently: 2 actuations of Flovent 125µg twice daily and 2 actuations of SKP Formoterol 5µg twice daily
Treatment D	Fluticasone propionate 250µg HFA pMDI: 2 actuations of Flovent 125µg/actuation twice daily
Treatment E	Formoterol fumarate 10µg pMDI: 2 actuations of SKP formoterol HFA pMDI 5µg/actuation twice daily

Clinical Findings

Fluticasone propionate
Fluticasone propionate reached peak mean concentrations in plasma within two hours on all study days.

On Day 1 the mean C_{max} and AUC_t for fluticasone propionate following a single dose appeared to be lower for FlutiForm 250/10µg compared with fluticasone propionate alone (Flovent 250µg) and fluticasone propionate (Flovent 250µg) with SKP Formoterol 10µg. However by Days 6 and 7, the mean C_{max} and AUC_t for fluticasone propionate at steady state were comparable for SKP FlutiForm 250/10µg and Fluticasone alone (Flovent 250µg) but both were lower when compared with fluticasone propionate (Flovent 250µg) administered with SKP Formoterol 10µg.

Systemic exposure to fluticasone propionate increased with increasing dose in healthy subjects receiving FlutiForm 100/10µg and 250/10µg. However the geometric mean C_{max} and AUC_t for fluticasone propionate between the two doses deviated from dose proportionality.

Formoterol fumarate
By Day 7 the differences in formoterol excretion were not as pronounced as seen on Day 1 with mean percentage figures of 6.61%, 5.14%, 4.12%, and 4.38% for FlutiForm100/10µg, FlutiForm 250/10µg, Flovent 250µg plus Formoterol 10µg, and Formoterol 10µg alone, respectively.

3.3.1.3 Study SKY2028-1-004

A randomised, open-label, parallel group, multiple-dose exposure study to compare the pharmacokinetics of fluticasone and formoterol combination (FlutiForm 250/10µg) in a single inhaler (SkyePharma HFA pMDI) with the administration of Fluticasone 250µg alone in healthy male and female subjects (n=36)***.***

Study treatments – administered twice daily for 7 days:

Treatment A	SKP FlutiForm 250/10µg pMDI: 2 actuations of 125/5µg/actuation twice daily
Treatment B	SKP Fluticasone 250µg pMDI: 2 actuations of 125µg/actuation twice daily

Clincal Findings
For both treatments fluticasone propionate reached peak mean concentrations in plasma within 1.5 hours on all study days.

On Day 1 the mean AUC_t and C_{max} associated with FlutiForm were slightly lower than those associated with SKP Fluticasone.

On Days 6 and 7 the corresponding values for AUC_t and C_{max} were slightly higher in the case of FlutiForm. On each study day the inter-subject variability was high. Overall no difference was noted between treatments.

Following multiple dosing for 7 days, the mean accumulation ratio for plasma fluticasone propionate was 2.20 for SKP FlutiForm and 1.56 for SKP Fluticasone alone. The median t_{max} and mean $t_{1/2}$ of fluticasone propionate for the two treatments appeared to be comparable.

3.3.1.4 Study FLT1501
An open-label, multiple dose, 2-treatment, randomised, parallel group study to assess the safety and pharmacokinetics of high dose FlutiForm pMDI 500/20µg twice daily and the individual components (fluticasone propionate pMDI 500µg and formoterol fumarate pMDI 24µg) in healthy subjects (n=48)**.**
.
Study treatments – administered twice daily for 28 days via a pressurised metered dose inhaler and the AeroChamber Plus spacing device:

Treatment A	SKP FlutiForm 500/20µg pMDI: 2 actuations of 250/10µg/actuation twice daily
Treatment B	Fluticasone 500µg (Flixotide Evohaler®): 2 actuations of 250µg/actuation twice daily and Formoterol 24µg (Foradil Spray): 2 actuations of 12µg/actuation twice daily

Clinical Findings

Fluticasone propionate
On Day 1 plasma fluticasone propionate concentrations were markedly lower from FlutiForm when compared with those seen following fluticasone propionate and formoterol administered together but from separate inhalers. The relative availability of fluticasone propionate from FlutiForm was in the region of 37%.

On Day 29 the availability of fluticasone propionate was higher than had been observed on Day 1 (for both study treatments), but the relative availability of fluticasone propionate from FlutiForm was still lower than that from the individual components and approximated 67%. This observation is in keeping with the pharmacodynamic findings. **(Please see section below on pharmacodynamics).**

Formoterol fumarate
On Day 1 plasma formoterol concentrations were markedly lower from FlutiForm when compared with those seen following fluticasone propionate and formoterol administered together but from separate inhalers. The relative availability of formoterol from FlutiForm, based on AUC_t values, was in the region of 17%.

On Day 29 the availability of formoterol was higher than had been observed on Day 1 (for both study treatments), but the relative availability of formoterol from FlutiForm was still lower than that from the individual components and approximated 75%.

Of note the pharmacokinetic findings for both active substances were not consistent with pharmacodynamic efficacy data from another study, FLT3503, which compared the same treatment arms, using the same strength products and same spacing device.

Phase I & II Clinical Studies in Patients with mild to moderate asthma

The following three studies are all single dose studies carried out in patients with mild to moderate asthma and are summarised below.

Study ID **Location**	**Objective** **Population** **Age**	**Design** **Control Type** **Duration of Treatment**	**Treatments**
Single Dose			
SKY2028-2-001 United Kingdom	Efficacy, safety and PK of FlutiForm compared with placebo or fluticasone and formoterol administered concurrently or alone. Mild to moderate asthma (steroid-requiring) 18-65 years	Phase II Clinical Study Randomised, double-blind, 6-way crossover, placebo- and active-controlled, single-dose	Inhaled, single dose without spacer: • FlutiForm 100/10 • FlutiForm 250/10 • Fluticasone 250[b]+ Formoterol 12[c] • Fluticasone 250 [b] • Formoterol 12 [c] • Placebo
FLT2502 South Africa	Systemic exposure of FlutiForm based on PK data. Mild to moderate asthma 12-17 years, 18-55 years	Phase I Clinical Study Open-label, parallel group, single-dose	Inhaled, single dose with spacer: • FlutiForm 250/10 adults vs adolescents
SKYE2201C/8722/01 United Kingdom	PK, safety and efficacy of formoterol in SkyePharma's HFA MDI compared with formoterol from Foradil DPI. Asthma 18-65 years	Phase I Clinical Study Randomised, double-blind, 5-way crossover, placebo-controlled, single-dose	Inhaled, single dose without spacer: • SKP Formoterol 12 • SKP Formoterol 24 • Formoterol 12 [c] • Formoterol 24 [c] • Placebo

3.3.1.5 Study SKY2028-2-001

A randomised, placebo-controlled, double-blind, incomplete block, 6-treatment, 4-way crossover, single-dose exposure study to compare the safety and efficacy of fluticasone and formoterol combination (FlutiForm 100/10µg and 250/10µg) in a single inhaler (SkyePharma HFA MDI) with the administration of Fluticasone (250µg) and Formoterol (12µg) concurrently or alone in subjects with asthma (n=64)**.**

Study treatments – single dose treatments

Treatment A	SKP FlutiForm 100/10µg HFA pMDI: 2 actuations of 50/5µg/actuation
Treatment B	SKP FlutiForm 250/10µg HFA pMDI: 2 actuations of 125/5µg/actuation
Treatment C	Fluticasone propionate 250µg HFA pMDI and formoterol fumarate 12µg DPI administered concurrently: 2 actuations of Flixotide Evohaler (125µg) and 1 actuation of Foradil Aerolizer (12 g)
Treatment D	Fluticasone propionate 250µg HFA pMDI: 2 actuations of Flixotide Evohaler 125µg/actuation
Treatment E	Formoterol fumarate 12µg DPI: 1 actuation of Foradil Aerolizer 12µg/actuation
Treatment F	Placebo

Note that the Flutiform formulation in this study was delivered via a Bespak actuator which is not the actuator used during Phase III clinical development or in the marketed product

Fluticasone propionate
Overall AUC_t and C_{max} of fluticasone propionate in plasma were highly variable for all treatments.

Based on the ratio of geometric means the AUC_t for fluticasone propionate from the SKP FlutiForm product increased dose proportionally from 100/10µg to 250/10µg. However, the ratio of geometric means for C_{max}/Dose for the SKP FlutiForm 100/10µg over SKP FlutiForm 250/10µg comparison suggested a less than proportional increase in the C_{max} for fluticasone propionate with dose though there was high intra-subject %CV observed for dose-adjusted AUC and C_{max}.

Formoterol fumarate
The mean fraction of formoterol excreted in urine over 24 hours was relatively low for all treatments; the maximum urinary excretion rate (R_{max}) and t_{max} were comparable across all treatments.

3.3.1.6 Study FLT2502

A Phase I open-label, single dose, parallel group study to determine the systemic exposure of FlutiForm pMDI 125/5µg (250/10µg total dose) in adult and adolescent subjects with mild to moderate asthma (n=65)**.**

It would be concluded that systemic exposure was no greater in adolescents than adults if the upper limit of the 90% confidence interval lay completely below 125% for the AUC_t, AUC_{inf} and C_{max} parameters.

Study treatments – single dose treatments – all patients received a single dose of SKP Flutiform 250/10µg (2 actuations of 125/5µg) administered via a pressurised metered dose inhaler and the AeroChamber Plus spacing device in a parallel group study comparing adults with adolescents:

Fluticasone propionate
On receipt of the final plasma fluticasone propionate concentration data it was seen that a significant number of subjects had quantifiable pre-dose fluticasone propionate concentrations (42/65 patients), findings which could not be explained.

In accordance with the EMEA Guideline on bioequivalence – CPMP/EWP/QWP/1401/98 Rev. 1 – the primary analysis excluded all subjects whose pre-dose fluticasone propionate concentration exceeded 5% of the C_{max} value for that subject; the secondary fluticasone propionate analysis included all subjects with valid plasma concentration data for fluticasone propionate.

The conclusions drawn from the secondary analysis were similar and the Applicant concludes that the quantifiable fluticasone propionate pre-dose concentrations did not (appear to) influence the outcome of the study.

The systemic availability and maximum observed plasma concentration for fluticasone propionate were higher in adolescents than in adults. Post-hoc exploratory analyses were performed to explore these differences, specifically AUC_t and C_{max}, by gender, age, weight, FEV_1% predicted, and race. The results from this analysis showed some interesting trends in the data indicating that higher systemic exposure levels seen with fluticasone propionate and formoterol in adolescents may partly be explained by demographic differences between adolescent and adult groups. However, these must be treated with caution due to their post-hoc nature, issues of multiple testing and small sample sizes within the subgroups.

Formoterol fumarate
The systemic availability of formoterol was slightly higher (10%) in adolescents compared with adults. The maximum observed plasma concentration for formoterol was also higher (31%) in adolescents compared with adults. These differences were less than those observed for fluticasone propionate.

In conclusion neither fluticasone propionate nor formoterol met the primary end points for equivalent systemic exposure in adolescents compared with adults in terms of AUC_t, AUC_{inf} or C_{max} – the upper limit of the 90% confidence interval must lie completely below 125% for the three parameters. The increased systemic exposure seen in adolescents is likely to be due to increased pulmonary deposition, together with a lower body weight and volume of distribution, compared with adults. No additional safety concerns relating to an increased exposure to fluticasone propionate and formoterol fumarate in adolescents compared with adults were found in the integrated safety analyses of the Phase III studies.

3.3.1.7 Study SKYE2201C/8722/01

A multicentre, randomised, double-blind, placebo-controlled, 5-way crossover study to compare the safety and efficacy of formoterol fumarate via SkyePharma HFA metered dose inhaler and conventional dry powder inhaler (Foradil) in subjects with asthma (n=45)**..**

Study treatments – single dose treatments

Treatment A	12µg SKP formoterol fumarate (2 inhalations of SKP formoterol fumarate 6µg)

Treatment B	24µg SKP formoterol fumarate (4 inhalations of SKP formoterol fumarate 6µg)
Treatment C	12µg formoterol fumarate (Foradil) (1 inhalation of Foradil DPI 12µg)
Treatment D	24µg formoterol fumarate (Foradil) (2 inhalations of Foradil DPI 12µg)
Treatment E	Placebo

At the 12µg dose level the mean cumulative amount of formoterol excreted was on average 24% higher after dosing with SKP Formoterol pMDI than after Foradil dry powder inhaler (DPI). At the 24µg dose level the mean cumulative amount of formoterol excreted was on average 39% higher after dosing with SKP Formoterol pMDI than after Foradil DPI.

3.3.1.8 Holding chambers and spacing devices

The Applicant has compared four different devices with regard to their suitability to deliver the fixed-dose combination of fluticasone propionate and formoterol fumarate (Flutiform) –

- The Trudell Medical International (TMI) Aerochamber® Plus
- The Trudell Medical International (TMI) Aerochamber® Hospital
- The Clement Clark International (CCI) Able Spacer Universal aerosol chamber

and

- The Pari Vortex® non electrostatic holding chamber

The Aerochamber® devices delivered a fine particle dose of fluticasone propionate and formoterol fumarate that was very similar to that delivered by the actuator alone and therefore the Aerochamber® spacers were identified as best suited for the delivery of FlutiForm. Of the two AeroChamber devices the Applicant has chosen the **TMI AeroChamber Plus spacing device** for use with Flutiform pMDI.

The initial pharmacokinetic studies were not designed to assess the pharamcokinetic parameters of fluticasone propionate and formoterol administered both with and without a spacing device.

However, cross study comparisons based on the initially available pharmacokinetic studies suggested that:

- The use of the Aerochamber® Plus spacing device increases the systemic exposure to fluticasone propionate (Flixotide) plus formoterol (Foradil) when administered via separate pMDIs

and

- The use of the Aerochamber® Plus spacing device increases systemic exposure to fluticasone propionate when FlutiForm is administered via the Aerochamber® Plus spacing device, but to a lesser extent than is seen with the comparator and already marketed product.

In view of the above the UK requested that the Applicant should conduct a pharmacokinetic study directly comparing the systemic exposure to fluticasone propionate and formoterol following administration of Flutiform both with and without a spacing device. Therefore a further pharmacokinetic study, FLT1503, was undertaken during the Decentralised Procedure. The study is briefly summarised below:

Study FLT 1503 – ***An open-label, single dose, randomised, 2-part crossover study to assess the systemic exposure of high dose Flutiform pMDI 250/10µg (500/20µg total dose) with and without a spacer (AeroChamber Plus) in healthy volunteers*** (n=30 randomised to study treatment).

Study treatments – single dose treatments

Treatment A (Test Treatment)

Study Drug	***Dosage Form***	***Unit Strength***	***Dosing Frequency***	***Total Daily Dose***	***Mode of Administration***
FlutiForm pMDI (Fluticasone/ Formoterol)	*2 puffs*	*250/10 µg*	*once (single dose)*	*500/20 µg*	*Inhaled with Spacer*

Treatment B (Reference Treatment)

Study Drug	***Dosage Form***	***Unit Strength***	***Dosing Frequency***	***Total Daily Dose***	***Mode of Administration***
FlutiForm pMDI (Fluticasone/ Formoterol)	*2 puffs*	*250/10 µg*	*once (single dose)*	*500/20 µg*	*Inhaled without Spacer*

The PK full analysis population included 29 of whom 26 (86.7%) completed the study.

Fluticasone propionate:

Summary Statistics for PK Parameters by Treatment – Fluticasone Propionate:
PK Full Analysis Population

Parameter	**Statistics**	**FlutiForm With Spacer**	**FlutiForm Without Spacer**	**Ratio (90% CIs)**
AUCt (pg.h/mL)	N	29	26	
	Geometric Mean	453.8	363.9	129.9
	(log SD)	(0.606)	(0.631)	(107.6, 156.8)
AUCINF (pg.h/mL)	N	27	26	
	Geometric Mean	536.9	417.1	134.8
	(log SD)	(0.557)	(0.604)	(113.5, 160.1)
Cmax (pg/mL)	N	29	26	
	Geometric Mean	29.8	24.6	125.0
	(log SD)	(0.399)	(0.441)	(110.7, 141.1)
tmax (h)	N	29	26	
	Mean (SD)	1.85 (1.027)	1.94 (1.181)	n/a
t1/2Z(h)	N	27	26	
	Mean (SD)	13.97 (3.718)	14.46 (3.088)	n/a
log: logarithm, n: Number of subjects with available data, h: hour, mL: millilitre, pg: picogram, PK: pharmacokinetic, SD: standard deviation				

The administration of FlutiForm via the AeroChamber Plus spacing device increased the mean bioavailability of fluticasone propionate by ~35%, based on AUC_{INF}, with a fluticasone propionate C_{max} 25% higher than that with the pMDI alone.

Approximately two-thirds of subjects demonstrated increased fluticasone propionate exposure with the AeroChamber Plus spacing device. Of the subjects showing increased exposure relative bioavailability ratios were considerably higher in some subjects than others, with 4 subjects showing between two- and four-fold increases based on AUC_{INF} values. In other subjects fluticasone propionate exposure was decreased with the AeroChamber Plus by up to 45%. Overall, individual relative bioavailabilities recorded in the study, based on AUC_{INF} value, ranged from 54% to 407%.

The bioequivalence ratios for the Completers population were all within 4% of those for the pharmacokinetic full analysis population and did not alter the conclusions drawn from the study.

Formoterol:

Summary Statistics for PK Parameters by Treatment – Formoterol Fumarate:
PK Full Analysis Population

Parameter	***Statistics***	***FlutiForm With Spacer***	***FlutiForm Without Spacer***	***Ratio (90% CIs)***
AUCt (pg.h/mL)	*N* *Geometric Mean* *(log SD)*	*29* *56.8* *(0.370)*	*26* *81.7* *(0.580)*	 *72.1* *63.6, 81.7*
AUCINF (pg.h/mL)	*N* *Geometric Mean* *(log SD)*	*25* *63.1* *(0.348)*	*25* *88.9* *(0.543)*	 *75.1* *(65.9, 85.6)*
Cmax (pg/mL)	*N* *Geometric Mean* *(log SD)*	*29* *15.6* *(0.447)*	*26* *15.6* *(0.525)*	 *103.0* *(88.4, 120.0)*
tmax (h)	*N* *Mean (SD)*	*29* *0.16 (0.259)*	*26* *0.61 (0.596)*	 *n/a*
t1/2Z(h)	*N* *Mean (SD)*	*25* *9.46 (2.538)*	*25* *10.23 (3.614)*	 *n/a*
log: logarithm, max: maximum, min: minimum, n: Number of subjects with available data, h: hour, mL: millilitre, pg: picogram, PK: pharmacokinetic, SD: standard deviation				

The administration of FlutiForm pMDI via the AeroChamber Plus spacing device decreased the mean bioavailability of formoterol by 25% based on AUC_{INF} values. The formoterol C_{max} values for the pMDI with AeroChamber Plus and pMDI alone were similar. The decrease in systemic bioavailability of formoterol maybe due to the elimination of gastrointenstinal absorption of formoterol following use of the spacing device which more than offsets a modest increase in pulmonary delivery of formoterol which may be seen with a spacing device.

The bioequivalence ratios for the Completers population were all within 2% of those for the pharmacokinetic full analysis population and did not alter the conclusions drawn from the study.

Approximately 50% of the plasma profiles for FlutiForm without spacing device demonstrated a pronounced secondary peak in exposure. In approximately 30% of the profiles the second peak provided the C_{max} for that profile.

The mean differences in the systemic availability of fluticasone propionate and formoterol when Flutiform is administered via a pMDI and a spacing device compared with administration via a pMDI alone are unlikely to have any clinically relevant impact.

The Applicant states that although large within-patient differences in systemic exposure were seen with and without a spacing device in some patients, these differences are unlikely to be product specific. Furthermore patients with particularly poor pMDI technique in whom such differences are likely to be most pronounced are unlikely to alternate between using and not using a spacing device.

3.3.1.9 Overall Conclusions on Pharmacokinetics

Fluticasone propionate
Across studies the level of systemic exposure to fluticasone propionate following administration of FlutiForm was generally less than that seen following administration of the comparator products, either administered alone or together with formoterol but via separate pMDIs, one inhaled after the other. The exception to this is the single dose study, Study SKY2028-2-001, where the mean C_{max} and AUC_t for fluticasone propionate from SKP FlutiForm 250/10µg were slightly higher than those observed when fluticasone propionate and formoterol (Flixotide 250µg + Foradil 12µg) were administered concurrently or fluticasone propionate (Flixotide 250µg) was administered alone (although the %CV was larger than the differences between the treatments).

Generally fluticasone propionate concentrations were numerically higher in healthy volunteers compared with patients with asthma. This difference is seen in the literature and is possibly due to reduced inspiratory flow and/or reduced airway calibre in the asthmatic patient compared with the healthy volunteer.

Compared with the first dose fluticasone propionate plasma concentrations were higher after 7 days of dosing. Whilst the accumulation ratio associated with FlutiForm was greater than that of the reference treatment in Study FLT1501, the level of systemic exposure to fluticasone propionate still remained lower following inhalation of FlutiForm compared with inhalation of the reference treatment at steady state.

Of note the pharmacokinetic data were not consistent with pharmacodynamic efficacy data which compared Flutiform with the marketed monoproducts. Therefore the pharmacokinetic data (only a surrogate for efficacy) do not appear to reflect comparative lung deposition.

Formoterol fumarate
The majority of the pharmacokinetic data collected in respect of the formoterol component of this fixed-dose combination product, Flutiform, have been generated from measurement of free and total formoterol in urine as the analytical method for measuring formoterol in plasma was not available at the commencement of the clinical pharmacology programme.

Across studies less than 11% per cent of the dose of free formoterol was recovered in the urine in both healthy volunteers and patients with asthma and urinary excretion of formoterol was higher following repeated dosing compared with a single dose.

Generally the level of systemic exposure to formoterol associated with FlutiForm was comparable with that associated with the comparator products, as assessed by urinary recoveries and the results from these studies are consistent with the literature.

Dose proportionality – Studies SKY2028-2-001 and SKY2028-1-002
The findings in two of the studies, Studies SKY2028-2-001 and SKY2028-1-002, question dose proportionality across the different strengths. In the single dose study, Study SKY2028-2-001, the ratio of geometric means for C_{max}/Dose for the comparison of SKP FlutiForm 100/10µg with SKP FlutiForm 250/10µg suggest a less than proportional increase in the C_{max} for fluticasone propionate with dose (although there was high intra-subject %CV observed for dose-adjusted AUC and C_{max}); in the multiple dose study in healthy subjects, Study SKY2028-1-002, systemic exposure to fluticasone propionate did increase with increasing dose, however the geometric mean C_{max} and AUC_t for fluticasone propionate between the two doses, Flutiform 100/10µg twice daily and Flutiform250/10µg twice daily, did not confirm dose proportionality. This is not surprising given the small sample size and high inter-individual variability observed. The CMC data which demonstrate linearity across doses support this view.

Pharmacokinetics in special populations
Eldery and Young children
The influence of age on FlutiForm pharmacokinetic parameters has not been investigated in young children and the elderly.

Adolescents – 12 to 17 years – Study FLT2502
The systemic exposure of FlutiForm was assessed for fluticasone propionate and formoterol fumarate in adult and adolescent patients with mild to moderate asthma in Study FLT2502. For both fluticasone propionate and formoterol greater availability and higher maximum plasma concentrations were observed in adolescents compared with adults, although the difference observed between adolescents and the adults was less for formoterol than for fluticasone propionate. These findings may be due to increased pulmonary deposition in the adolescent age group together with lower body weight and volume of distribution in the adolescent, compared with adults. No studies are referenced from the literature in which the pharmacokinetics of either fluticasone propionate or formoterol have been investigated and compared in adults and adolescents. Integrated safety analyses based on Phase III studies demonstrated no additional safety concerns relating to an increased exposure of fluticasone propionate and formoterol in adolescents compared with adults.

Patients with renal and hepatic impairment
The effect of renal and hepatic impairment on FlutiForm pharmacokinetic parameters has not been investigated.

Pregnant and breast-feeding women
No studies have been carried out in women who are either pregnant or breast-feeding.

Drug-drug interaction studies
Because of the volume of data available on the individual components, drug-drug interactions for FlutiForm have not been investigated.

Holding Chambers and spacing devices
The use of the Aerochamber® Plus spacing device increases the systemic bioavilability of the fluticasone propionate component of Flutiform by ~35% based on AUC_{INF} compared with delivery via the pMDI alone. Conversely the use of the Aerochamber® Plus spacing device decreases the systemic bioavilability of the formoterol component of Flutiform by ~25% based on AUC_{INF} compared with delivery via the pMDI alone. The decrease in systemic availability of formoterol maybe due to the elimination of gastrointenstinal absorption of formotero following use of the spacing device which more than offsets a modest increase in pulmonary delivery of formoterol which may be seen with a spacing device. This difference between the fluticasone propionate and formoterol data results from the known negligible oral bioavailability of fluticasone propionate compared with the known oral bioavailability of formoterol,.

3.3.2 PHARMACODYNAMICS

The Applicant presented three studies, Studies SKY2028-1-002, FLT 1501 and SKY2028-1-003, all multiple dose studies in adults, two of which were in healthy volunteers and one in patients with mild to moderate asthma (and corticosteroid-free). They compared the effects of fluticasone propionate on the HPA axis, administered as:

- Flutiform and as fluticasone propionate administered together with formoterol but via separate pMDIs, one drug inhaled after the other (Studies SKY2028-1-002 and FLT 1501)
- Flutiform but compared with the effects of oral prednisolone on the HPA axis. (Study SKY2028-1-003).

3.3.2.1 Study SKY2028-1-002

A randomised, open-label, parallel group, multiple-dose exposure study to compare the pharmacokinetics* (and systemic safety) *of fluticasone and formoterol combination (FlutiForm 100/10µg and 250/10µg) in a single inhaler (SkyePharma HFA pMDI) with the administration of Fluticasone (250µg) and Formoterol (10µg) concurrently or alone in healthy male and female subjects (n=50)**.**

Study treatments – administered twice daily for 7 days:

Treatment A	SKP FlutiForm 100/10µg pMDI: 2 actuations of 50/5µg/actuation twice daily
Treatment B	SKP FlutiForm 250/10 g pMDI: 2 actuations of 125/5µg/actuation twice daily
Treatment C	Fluticasone propionate 250µg pMDI and formoterol fumarate 10µg pMDI administered concurrently: 2 actuations of Flovent 125µg twice daily and 2 actuations of SKP Formoterol 5µg twice daily
Treatment D	Fluticasone propionate 250µg HFA pMDI: 2 actuations of Flovent 125µg/actuation twice daily
Treatment E	Formoterol fumarate 10µg pMDI: 2 actuations of SKP formoterol HFA pMDI 5µg/actuation twice daily

Twenty four-hour urine collections were made for measurement of urinary cortisol at screening, Day -1/1 (prior to first study drug administration) and on Day 8 (following inhalation of study treatments twice daily for 7 days).

Clinical Findings

No real differences were seen between treatment groups either at baseline or following 7 days of treatment; the two Flutiform study treatments showed similar 24-hour cortisol profiles to the comparator treatments. There did not appear to be any treatment-related trend regarding changes in cortisol parameters from baseline through the 7-day treatment period.

3.3.2.2 Study FLT1501

An open-label, multiple dose, 2-treatment, randomised, parallel group study to assess the safety and pharmacokinetics of high dose FlutiForm pMDI 500/20µg twice daily and the individual components (fluticasone propionate pMDI 500µg and formoterol fumarate pMDI 24µg) in healthy subjects (n=48)**.**

Study treatments – administered twice daily for 28 days via a pressurised metered dose inhaler and the AeroChamber Plus spacing device:

Treatment A	SKP FlutiForm 500/20µg pMDI: 2 actuations of 250/10µg/actuation twice daily

Treatment B	Fluticasone 500µg (Flixotide Evohaler®): 2 actuations of 250µg/actuation twice daily and Formoterol 24µg (Foradil Spray): 2 actuations of 12µg/actuation twice daily

Twenty four-hour urine collections were made for measurement of urinary free cortisol at screening, Days -2 to -1 (prior to first study drug administration) and on Days 27 to 28 (following inhalation of study treatments twice daily for 28 days). Basal morning serum cortisol measurements and an adrenocorticotrophic hormone (ACTH) stimulation test were carried out on Day 1(pre-study treatments) and on Day 29.

Clinical Findings

From this study it would appear that Flutiform produced slightly less HPA axis suppression than the individual components of this combination inhaler – fluticasone propionate (as Flixotide) and formoterol (as Foradil) administered together but from separate inhalers, one after the other – in respect of both 24-hour urinary free cortisol (corrected for creatinine) and serum cortisol after 28 days of study treatments.

The ratio (95% CI) of 24-hour urinary free cortisol at the end of the treatment period was 1.9 (1.5, 2.6) for Flutiform relative to fluticasone propionate plus formoterol.

There was no statistically significant difference in the peak cortisol response at 30 minutes following a 1µg injection of ACTH between the two treament groups on Day 1 or Day 28. The differences (95% CI) between the two treatment groups, Flutiform and fluticasone propionate plus formoteol administered from separate inhalers, in mean change in basal serum cortisol at 30 minutes following ACTH administration were -66.7nmol/L (-138.7, 5.3) and 15.7nmol/L (-30.8, 62.2) on Day 1 and Day 28, respectively.

3.3.2.3 Study SKY2028-1-003

A randomised, double blind, placebo- and active-controlled, parallel group, 6-week study to evaluate the effect of multiple doses of Flutiform 250/10µg HFA pMDI twice daily, Flutiform 100/10µg HFA pMDI twice daily, prednisolone and placebo on the hypothalamic pituitary adrenocortical axis in adult subjects with mild to moderate asthma (n=171)

Study treatments – administered twice daily for 6 weeks:

Treatment A	FlutiForm 100/10µg pMDI: 2 actuations of 50/5µg/actuation twice daily for 6 weeks
Treatment B	SKP FlutiForm 250/10 g pMDI: 2 actuations of 125/5µg/actuation twice daily for 6 weeks
Treatment C	Placebo prednisolone once daily for 5 weeks followed by prednisolone 10mg once daily for 7 days together with a placebo inhaler twice daily for 6 weeks
Treatment D	Placebo inhaler twice daily for 6 weeks

Twenty four-hour urine collections were made for measurement of urinary free cortisol at screening, Day -1 (prior to first study drug administration) and on Day 42 (following inhalation/ingestion of study treatments for 6 weeks).

Plasma concentration of fluticasone propionate was determined in the mornings on Days -1, 7, 14, 35 and 42 for assessment of dosing compliance.

Clinical Findings

The results suggest that 6 weeeks of treatment with either Flutiform 100/10µg or Flutiform

250/10µg twice daily did not affect HPA axis function in patients with mild to moderate asthma (as evaluated through the assessment of 24-hour urinary free cortisol).

At week 6 neither Flutiform treatment group differed statistically significantly from placebo. p=0.733 and p=0.510 for Flutiform 100/10µg and Flutiform 250/10µg, respectively.

This study had assay sensitivity as the prednisolone control arm showed statistically significant suppression of HPA axis function compared with placebo, p<0.001.

Studies FLT 3505 and FLT 3502
Two further studies, **Clinical Studies FLT 3505 and FLT 3502,** have assessed the effects of fluticasone propionate in Flutiform on the HPA axis. These two studies are discussed later in this Assessment Report alongside the assessment of the clinical safety of Flutiform – (see Clinical Safety Section).

3.3.2.4 Overall Conclusions on Pharmacodynamics
The findings from the three pharmacodynamic safety studies would suggest that fluticasone propionate in Flutiform exerts a lesser effect on the HPA axis at high dose than fluticasone propionate (as Flixotide) administered together with formoterol (as Foradil) but via separate inhalers, one after the other.

In the pharmacokinetic studies carried out with Flutiform (as discussed above) the level of systemic exposure to fluticasone propionate following administration of FlutiForm appears generally to be less than that seen following administration of the comparator products, fluticasone propionate (as Flixotide) administered alone or administered together with formoterol (as Foradil) but via separate inhalers, one after the other. This finding would suggest that the influence of FlutiForm on the HPA might be less than that of the comparator products and this does appear to be borne out in the pharamcodynamic studies presented. The findings in the pharmacodynamic studies are reassuring and do suggest that Flutiform may be a systemically safer alternative to fluticasone propionate administered either alone or in combination with formoterol but administered from separate inhalers (as in the reference products).

The pharmacokinetic and pharmacodynamic findings might suggest that this fixed-dose combination pMDI containing the two active drugs fluticasone propionate and formoterol fumarate might be a safer alternative treatment to some treatments available currently.

3.4 CLINICAL EFFICACY
The FlutiForm clinical development programme has been set up to evaluate the efficacy and safety of this new fixed-dose combination product containing fluticasone propionate and formoterol fumarate in three strengths and formulated as a pressurised inhalation, suspension in an excipient mix including the hydrofluoroalkane (HFA) propellant, propellant HFA 227 (1,1,1,2,3,3,3-heptafluoropropane), a non-chlorofluorocarbon (CFC) alternative propellant. This combination product is indicated for use in the regular treatment of asthma where use of a combination product (an inhaled corticosteroid and a long-acting β_2 agonist) is appropriate. Flutiform is intended for long-term maintenance treatment of asthma in adults and adolescents.

The clinical programme comprised two completed Phase II studies, nine completed Phase III studies and two on-going Phase III studies

The two Phase II studies were both single dose studies. In the Phase III clinical programme Flutiform was administered twice daily using dose regimens which were comparable to the dosing regimens already approved for the separate components of the combination product either when

administered alone as in the case of the corticosteroid component, fluticasone propionate, as in Flixotide, or when administered together but from separate pMDIs, one active inhaled after the other, fluticasone propionate as Flixotide and formoterol fumarate as Foradil. Dose regimens studied for Flutiform were also selected to be compatible with the dose regimens approved for the other fixed-dose combination products containing an inhaled corticosteroid and a long-acting inhaled β_2 adrenoceptor agonist, Seretide and Symbicort.

3.4.1 Phase II Studies

Both of the Phase II studies were multicentre, double blind, randomised, crossover, placebo-controlled single dose studies in adult patients, males and females with mild to moderate asthma and neither study used a spacing device for study drug delivery.

Summaries of these two studies in respect of study designs, treatment groups and study populations are presented below:

3.4.1.1 Study SKY2028-2-001

A randomised, placebo-controlled, double blind, six-way crossover, single dose exposure study to compare the safety and efficacy of Fluticasone and Formoterol Combination (Flutiform 100/10µg and 250/10µg) in a single inhaler (SkyePharma HFA MDI) with the administration of Fluticasone (250µg) and Formoterol (12µg) concurrently or alone in patients with asthma (n=64).

Study ID	**Design** **Control Type** **Duration of Treatment**	**Treatments**
SKY2028-2-001	Randomised, double-blind, 6-way crossover, placebo- and active-controlled, single-dose	Total Inhaled, single dose without spacer: • FlutiForm 100/10 • FlutiForm 250/10 • Fluticasone 250 + Formoterol DPI 12 • Fluticasone 250 • Formoterol DPI 12 • Placebo

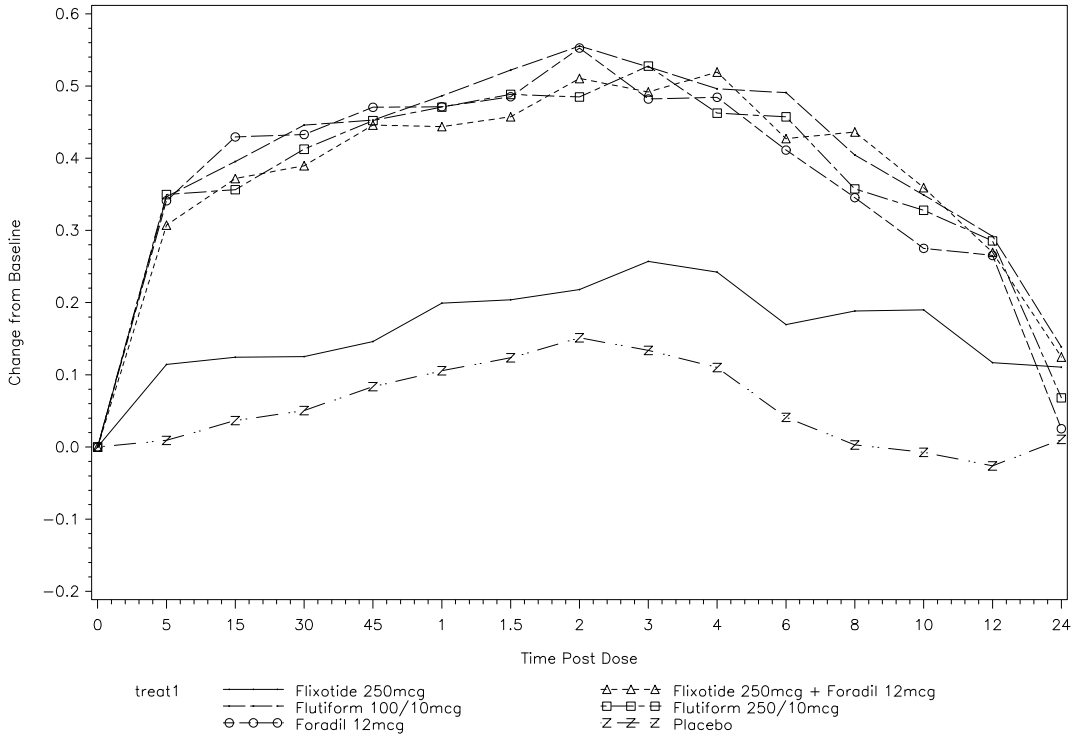
DPI = Dry Powder inhaler.

Note that the Flutiform formulation in this study was delivered via a Bespak actuator which is not the actuator used during Phase III clinical development or in the marketed product

The **primary objective** was to assess and compare the efficacy of the six treatments each administered as a single dose; the **secondary objectives** were to assess the safety profile of Flutiform and to compare the pharmacokinetics of fluticasone propionate and formoterol fumarate administered in combination as in Flutiform and administered both concurrently (the two active substances administered together but via separate inhaler devices, one inhaled after the other) and alone, in patients with asthma.

Clinical Findings

12-hour serial spirometry



In this single dose study the change from baseline to 12 hours post-dose in FEV_1 was similar in both Flutiform treatment groups and in the group where the single components were administered separately (in all treatment groups nominal formoterol doses of 10 -12 mcg were administered). Similar results were also seen in the group that received formoterol only. No dose response between the high and low dose Flutiform treatment groups was seen although this might be expected in a single dose study in patients with mild to moderate asthma.

Both Flutiform treatment groups were superior to placebo and to the group that received fluticasone propionate alone. These results provide good evidence to support the efficacy of the formoterol component of the combination.

3.4.1.2 Study SKY2028-2-002

A randomised, placebo-controlled, double blind, crossover, single dose exposure study to evaluate the early bronchodilating effect of Flutiform 100/10µg HFA pMDI and Flutiform 250/10µg, compared with placebo in adult subjects with mild to moderate asthma (n=42).

Study ID	Design Control Type Duration of Treatment	Treatments
SKY2028-2-002	Randomised, double-blind, 3-way crossover, placebo-controlled, single-dose	Total Inhaled, single dose without spacer: • FlutiForm 100/10 • FlutiForm 250/10 • Placebo

The **primary objective** was to evaluate the early bronchodilating effect of a single dose of Flutiform 100/10µg HFA pMDI and a single dose of Flutiform 250/10µg HFA pMDI compared with SKP placebo.

Clinical Findings

The findings of this study demonstrate superior early bronchodilatation of FlutiForm 250/10 and FlutiForm 100/10 compared with placebo, as early as 3 minutes post-dose and from 3 to 60 minutes following a single dose in adult subjects with mild to moderate asthma.

In this study similar results were seen in both Flutiform treatment groups. This is not surprising as the main analyses investigate efficacy up to 60 minutes post-dose. Therefore the changes in FEV_1 seen during this period are predominantly due to the effect of the formoterol component of the combination administered at the same dose of 10µg in both of the Flutiform treatment groups – Flutiform 250/10µg and Flutiform 100/10µg.

3.4.2 Phase III Studies

The nine Phase III clinical studies can be grouped as follows:

- **Studies SKY2028-3-001 (pivotal) and SKY2028-3-002 (pivotal)** – efficacy and safety in mild to moderate asthma
- **Studies FLT3501 and FLT3505** (supportive) – efficacy and safety in mild to moderate-severe asthma
- **Studies FLT3503 (pivotal), SKY2028-3-004 (pivotal) and SKY2028-3-005** (supportive) – efficacy and safety in moderate to severe asthma
- **Study SKY2028-3-003 (pivotal)** – long-term safety in mild to moderate-severe asthma
- **Study FLT3502** (supportive) – long-term safety extension in children with mild to moderate asthma

Of the nine Phase III studies four are described as the pivotal efficacy studies. Summaries of these four studies in respect of study designs and treatment groups are presented in the table below:

Study Designs and Treatment Groups: Pivotal Phase III Studies

Study ID	Design Control Type Duration of Treatment	Treatments
Pivotal study demonstrating Flutiform efficacy versus combination therapy		
FLT3503	Randomised, double-blind, parallel group, stratified, active-controlled, 8 weeks	Inhaled, BID with spacer: • FlutiForm 100/10 • FlutiForm 500/20[a] • Fluticasone 500 plus Formoterol 24 • Fluticasone 500
Pivotal studies demonstrating Flutiform efficacy versus individual components administrated seperately		
SKY2028-3-001	Randomised, double-blind, parallel group, stratified placebo- and active-controlled, 12 weeks	Inhaled, BID without spacer: • FlutiForm 100/10 • Fluticasone 100 • Formoterol 10 • Placebo
SKY2028-3-002	Randomised, double-blind, parallel group, stratified, active- controlled, 12 weeks	Inhaled, BID without spacer: • FlutiForm 100/10 • Fluticasone 100 • Formoterol 10
SKY2028-3-004	Randomised, double-blind, parallel group, stratified, placebo- and active-controlled, 12 weeks	Inhaled, BID without spacer: • FlutiForm 250/10 • FlutiForm 100/10[b] • Fluticasone 250 • Formoterol 10 • Placebo
SKY2028-3-005	Randomised, double-blind, parallel group, stratified, active-controlled, 12 weeks	Inhaled, BID without spacer: • FlutiForm 250/10 • Fluticasone 250 • SKP Fluticasone 250

BID = twice daily.
a The primary efficacy comparisons were based on FlutiForm 500/20 versus Fluticasone 500 plus Formoterol 24; the evaluation of dose-response involved both FlutiForm 500/20 and FlutiForm 100/10.
b The primary efficacy comparisons were based on FlutiForm 250/10. Dose response involved both FlutiForm 250/10 and FlutiForm 100/10.

The starting dose of study medication was based on the patient's asthma history and prior asthma medication. Subjects who required inhaled corticosteroids at a dose of 100-250 µg/day fluticasone propionate or equivalent received the lower dose and subjects who required >250-1000 µg/day received the higher dose.

The clinical efficacy of flutiform was assessed by

- comparing clinical efficacy of Flutiform with similar combinations of actives, either flutuicasone propionate and formoterol administered together but from separate inhalers (pivotal study, Study FLT3503) or fluticasone propionate and salmeterol administerd as the fixed-dose combination product, Seretide;
  or by
- comparing clinical efficacy of Flutiform with its individual components administered separately; Studies SKY2028-3-001, SKY2028-3-002 (pivotal for low dose), Study SKY2028-3-004 (pivotal for medium dose) and Study SKY2028-3-005 (supportive for medium dose)
  and by
- comparing clinical efficacy of Flutiform administered with and without a spacing device; Studies FLT3503, FLT3501 and FLT3505 (with spacer); SKY2028-3-001, SKY2028-3-002, SKY2028-3-004 and SKY2028-3-005 (without spacer).

The Applicant has taken due note of advice given in National Scientific Advice Meetings in a number of EU Member States and of CHMP guidance and referred to the following CHMP Guidelines:

- *CHMP Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in children and Adolescents CPMP/EWP/4151/00 Rev. 1 – January 2009*

  and

- *CHMP Guideline on Clinical Development of Fixed Combination Medicinal Products CHMP/EWP/240/95 Rev. 1*

General notes on study treatments
All studies included male and female patients with a known history of asthma for longer than six months and a documented reversibility of airway function of greater than or equal to 15.0% change in forced expiratory volume in one second (FEV_1) during the screening phase of ths study.

All pivotal Phase III studies included a run-in period prior to the treatment period. During the run-in period subjects received asthma therapy as listed in the Table below. The run-in periods provided an opportunity to assess persistence and severity of disease symptoms and compliance with study procedures. Also the run-in period allowed standardisation and provided harmonised inhaled corticosteroid (ICS) levels.

The run-in period:

Run-in Period: Duration and Treatment for Phase III Studies

Study	Steroid Use	Run-in Period Duration	Run-in Treatment (total daily dose)
SKY2028-3-001 and SKY2028-3-002	Steroid requiring	14 ± 3 days	• Fluticasone (Flovent) 100 • Rescue salbutamol/albuterol
	Steroid-free	14 to 28 days	• Rescue salbutamol/albuterol
SKY2028-3-004 and SKY2028-3-005	Steroid requiring only	14 ± 3 days	• Fluticasone (Flovent) 100 for subjects using ≤ 250 µg/day fluticasone propionate or equivalent ICS • Fluticasone (Flovent) 200 for subjects using >250 µg/day

			fluticasone propionate or equivalent ICS • Rescue salbutamol/albuterol
SKY2028-3-003	Steroid requiring only	14 ± 3 days	• Fluticasone (Flovent) 100 for subjects using ≤ 249 µg/day fluticasone propionate or equivalent ICS • Fluticasone (Flovent) 250 for subjects using > 249 µg/day fluticasone propionate or equivalent ICS • Rescue salbutamol/albuterol
FLT3503	Steroid requiring only	14 +/-3 days (may be extended to max 28 days)	• Fluticasone (Flixotide) 250 • Rescue salbutamol/albuterol

ICS – inhaled corticosteroid

(emboldened studies are pivotal)

Efficacy endpoints across studies included the following:

Pulmonary function tests (in the clinic) –

- FEV_1 – pre- and post-dose (co-primary endpoints)
- FVC – forced vital capacity
- PEFR – peak expiratory flow rate
- MEF_{25}, MEF_{50}, MEF_{75} – maximum expiratory flow at 25%, 50% and 75% of forced vital capacity
- FEV_1% of predicted normal – forced expiratory volume in 1 second reported as a percentage of the predicted normal FEV_1.
- Twelve hour FEV_1, area under the curve (AUC)

Discontinuation due to lack of efficacy/worsening asthma
Time to onset of action
Daily morning and evening PEFR (at home)
Symptom scores
Requirement for *rescue* medication
Asthma exacerbations – categorised as mild to moderate and severe
Asthma control days – defined as days with an asthma symptom score of 0, a sleep disturbance score of 0 and no requirement for *rescue* medication
Compliance with study medication
Asthma Quality of Life Questionnaire and patients' own assessment of study medication in some studies

3.4.2.1 Pivotal Efficacy Studies

Study FLT3503 – Pivotal Study to Demonstrate FlutiForm Efficacy versus Combination Therapy

A double blind, double dummy, randomised, multicentre, 4-arm parallel group study to assess the efficacy and safety of Flutiform pMDI 250/10µg (2 puffs bid) vs Fluticasone pMDI 250µg (2 puffs bid) plus Formoterol pMDI 12µg (2 puffs bid) administered concurrently in adult subjects with severe persistent, reversible asthma.

Study ID	Design Control Type Duration of Treatment	Treatments
Pivotal study demonstrating Flutiform efficacy verus combination therapy		
FLT3503	Randomised, double-blind, parallel group, stratified, active-controlled, 8 weeks	Inhaled, BID with spacer: • FlutiForm 100/10 • FlutiForm 500/20[a] • Fluticasone 500 plus Formoterol 24 • Fluticasone 500

BID – twice daily
a The primary efficacy comparisons were based on FlutiForm 500/20 versus Fluticasone 500 plus Formoterol 24; the evaluation of dose-response involved both FlutiForm 500/20 and FlutiForm 100/10.

A double-blind, double-dummy, 4-arm, parallel-group, multicentre Phase III study to designed to demonstrate the non-inferiority of FlutiForm 500/20 (high dose) versus fluticasone propionate 500 + formoterol 24 administered concurrently (from separate inhalers) in adult patients with moderate to severe persistent, reversible asthma, FEV_1% of predicted normal of >60% to ≤ 80% (moderate asthma) and ≥ 40% to ≤ 60% (severe asthma). The treatment period was for 8 weeks.

The study was stratified for baseline FEV_1% of predicted normal beween 40% to 60% and >60% to 80%.

All study treatments (test and reference) were inhaled via a pMDI used <u>with</u> an AeroChamber Plus spacing device.

The **primary objective of this study was to show non-inferiority** in respect of efficacy of FlutiForm 500/20 (high dose) compared with fluticasone propionate 500 + formoterol 24; the **secondary objectives of this study were to show superiority** in respect of efficacy of FlutiForm 500/20 (high dose) compared with fluticasone propionate alone (to demonstrate that the study design was sensitive enough to detect differences between treatments) **and to show superiority** in respect of efficacy of FlutiForm 500/20 (high dose) compared with FlutiForm 100/10 (low dose) (to demonstrate dose-response).

The primary efficacy endpoints of the non-inferiority study FLT 3503 are listed below:

- Primary endpoint - Change in FEV_1 from baseline (pre-dose Week 0) to pre-dose at Week 8 (end of study treatment period)
- Co-primary endpoint - Change in FEV_1 from baseline (pre-dose Week 0) to 2 hours post-dose at Week 8 (end of study treatment period)

The co-primary endpoint was to be analysed only if non-inferiority was demonstrated for the primary endpoint.

Treatment	Change		Difference[b]		
	LSMean[a]	95% CI	LSMean[a]	95% CI	p-value
Per protocol population					
FlutiForm high dose n=133	0.345	0.259, 0.430			
Fluticasone + Formoterol n=140	0.284	0.201, 0.368	0.060	-0.059, 0.180	<0.001[c]
FlutiForm low dose n=127	0.336	0.249, 0.424	0.008	-0.114, 0.131	
Fluticasone n=129	0.324	0.237, 0.411	0.020	-0.102, 0.142	
Intent to treat population[e]					
FlutiForm high dose n=154	0.346	0.267, 0.425			
Fluticasone + Formoterol n=156	0.267	0.189, 0.345	0.079	-0.032, 0.190	<0.001[c] 0.164[d]
FlutiForm low dose n=155	0.302	0.222, 0.381	0.044	-0.068, 0.156	0.437[d]
Fluticasone n=155	0.323	0.244, 0.401	0.023	-0.088, 0.135	0.681[d]

ANCOVA – analysis of covariance, CI – confidence interval, FEV1 – forced expiratory volume in one second, LS – least squares, n – number of subjects in treatment group, LOCF – last observation carried forward

[a] LSMean from ANCOVA with treatment as factor, pre-dose FEV_1 value on Day 0 and asthma severity as covariates, and centre as a random effect.

[b] Difference in LSMeans compared with FlutiForm high dose.

[c] P-value from ANCOVA F-test for treatment. Non-inferiority of FlutiForm high dose to Fluticasone + Formoterol is shown if the lower limit of the 95% CI from the ANCOVA is≥ -0.2 L.

[d] P-value from ANCOVA F-test for treatment (based on the null hypothesis of no treatment difference).

[e] Missing data imputed using the LOCF approach.

Change in FEV_1 [L] from Pre-morning Dose on Day 0 to 2 Hours Post-morning Dose on Day 56 in Study FLT3503

Treatment		Change		Difference[b]	
	LSMean[a]	95% CI	LSMean[a]	95% CI	p-value
Per protocol set					
FlutiForm high dose	0.518	0.435, 0.602			
n=133					
Fluticasone + Formoterol	0.500	0.419, 0.581	0.018	-0.098, 0.135	<0.001[c]
n=140					
FlutiForm low dose	0.545	0.459, 0.631	-0.027	-0.147, 0.093	
n=127					
Fluticasone	0.392	0.306, 0.477	0.126	0.007, 0.246	
n=129					
Intent to treat set[e]					
FlutiForm high dose	0.517	0.440, 0.594			
n=154					
Fluticasone + Formoterol	0.477	0.400, 0.554	0.040	-0.069, 0.149	<0.001[c]
n=156					0.471[d]
FlutiForm low dose	0.506	0.427, 0.584	0.011	-0.099, 0.122	0.840[d]
n=155					
Fluticasone	0.396	0.318, 0.474	0.120	0.011, 0.230	0.032[d]
n=155					

ANCOVA – analysis of covariance, CI – confidence interval, FEV_1 – forced expiratory volume in one second, LS – least squares, n – number of subjects in treatment group, LOCF – last observation carried forward

[a] LSMean from ANCOVA with treatment as factor, pre-dose FEV_1 value on Day 0 and asthma severity as covariates, and centre as a random effect.

[b] Difference in LSMeans compared with FlutiForm high dose.

[c] P-value from ANCOVA F-test for treatment. Non-inferiority of FlutiForm high dose to Fluticasone + Formoterol is shown if the lower limit of the 95% CI from the ANCOVA is ≥ -0.2 L.

[d] P-value from ANCOVA F-test for treatment (based on the null hypothesis of no treatment difference).

[e] Missing data imputed using the LOCF approach.

The primary and co-primary endpoints were chosen to allow the contribution to efficacy of both the long-acting β_2 agonist and inhaled corticosteroid components of Flutiform to be evaluated.

Serial spirometry (FEV_1 AUC_{0-12}) was assessed at Day 0 and Day 56 in a subgroup of patients. Effects on Day 0 with all combination therapies exceeded those with fluticasone propionate alone; on Day 56, differences between combination therapies and fluticasone propionate alone were less than those seen on Day 0. All between group comparisons were non-significant.

Discontinuations due to lack of efficacy in this European pivotal efficacy study are shown below:

Discontinuations due to Lack of Efficacy in Study FLT3503

Treatment		Yes[a]		No		Difference (% Yes)	
	N	n	(%)	n	(%)	Estimate	95% CI[b,c]
Per protocol set							
FlutiForm high dose	133	6	(4.5)	127	(95.5)		
Fluticasone + Formoterol	140	11	(7.9)	129	(92.1)	-3.3	-9.0, 2.3
FlutiForm low dose	127	11	(8.7)	116	(91.3)		
Fluticasone	129	13	(10.1)	116	(89.9)		
Intent to treat set							
FlutiForm high dose	154	6	(3.9)	148	(96.1)		
Fluticasone + Formoterol	156	12	(7.7)	144	(92.3)	-3.8	-9.0, 1.4
FlutiForm low dose	155	18	(11.6)	137	(88.4)	-7.7	-13.6, -1.8
Fluticasone	155	17	(11.0)	138	(89.0)	-7.1	-12.9, - 1.3

CI = confidence interval, N = number of subjects in treatment group, n = number of subjects with available data, SE = standard error, % = percentage based on N.

[a] Subjects who discontinued the study due to lack of efficacy.

[b] CI estimated using 100*[(p1-p2) ± 1.96SE(p1-p2)], where p1 and p2 are the proportions of subjects who discontinued.

[c] Non-inferiority of FlutiForm high dose to comparative treatment is shown if the upper limit of the 95% CI for the treatment difference is ≤ 10%.

Source: Study FLT3503 CSR Appendix B-1, Tables 10.1 and 10.2

In the FlutiForm low dose group patients started to discontinue soon after Day 14 suggesting that treatment was not optimal with FlutiForm low dose. In the fluticasone propionate alone treatment group patients did appear to continue in the study slightly longer than with FlutiForm low dose. Most discontinuations due to lack of efficacy in the FlutiForm low dose and fluticasone propionate alone treatment groups had occurred by approximately Day 42. FlutiForm high dose appeared superior to FlutiForm low dose and fluticasone propionate alone with regard to time to discontinuation due to lack of efficacy (hazard ratio for FlutiForm low dose versus FlutiForm high dose – 3.202, p = 0.0136; hazard ratio for fluticasone propionate alone versus FlutiForm high dose – 3.063; p = 0.0184 [ITT population].

Non-inferiority of FlutiForm 500/20 (high dose) compared with fluticasone propionate 500 + formoterol 24 was formally shown for the secondary endpoint of discontinuations due to lack of efficacy. In the PP population (4.5%) in the FlutiForm high dose group and (7.9%) in the fluticasone propionate + formoterol group discontinued the treatment phase due to lack of efficacy. The upper limit of the 95% CI for the difference was below the pre-defined non-inferiority limit of 10% (95%CI: -9.0 to 2.3). The supportive analysis of the ITT population confirmed this result (95%CI for the treatment difference: -9.0 to 1.4).

Treatment with FlutiForm high dose was also comparable with treatment with fluticasone propinate + formoterol for the remaining secondary efficacy endpoints based on pulmonary function.

No statistically significant difference between the 2 treatment groups (Flutiform high dose and fluticasone propionate + formoterol) was found for any of the secondary endpoints but with one exception – fewer subjects in the fluticasone propinate + formoterol group (57.7%) compared with the FlutiForm high dose group (72.7%) suffered from at least one mild or moderate asthma exacerbation (p = 0.006); severe asthma exacerbations were experienced by only 3 subjects (1.9%) in the FlutiForm high dose group and by no subject in the fluticasone propionate + formoterol group (p = 0.121).

Generally FlutiForm high dose provided better outcomes than fluticasone propionate alone for many clinically important endpoints.

Generally FlutiForm 500/20 (high dose) provided better outcomes than Flutiform 100/10 (low dose) for many clinically important symptom-based endpoints.

CONCLUSIONS ON STUDY FLT3503
Both primary endpoints provided clear evidence that the high dose Flutiform product was non-inferior to fluticasone propionate and formoterol administered together but from separate inhalers. Flutiform 500/20 was also superior to fluticasone propionate alone based on the mean change in FEV_1 from pre-morning dose on Day 0 to 2 hours post-morning dose on Day 56.

However in the comparison of the high and low dose Flutiform products the findings in respect of the change in pre-morning dose FEV_1 from Day 0 to Day 56 were very similar. In this analysis missing data were inputed using Last Observation Carried Forward (LOCF). In the ITT population the discontinuation rate was much higher (11.6%) in the low dose group than the high dose group (3.9%). Therefore imputing missing data using LOCF could explain why a statistically significant difference between the high and low dose Flutiform was not seen in the Day 56 analysis. A *post hoc* repeated measures ANCOVA without missing data imputation was conducted and this did show significant differences between the high and low dose Flutiform products at Days 14, 28 and 42.

So the main outstanding issue is the failure to demonstrate the superiority of high dose Flutiform over low dose Flutiform at the pre-specified timepoint. However clearly there is a differential rate of discontinuation due to lack of efficacy between the high and low dose Flutiform treatment groups. This is likely to bias the Day 56 analysis against showing a difference between the two treatments. Given that superiority is seen at other timepoints and consistent numerical differences in favour of high dose Flutiform are seen for a range of secondary endpoints, particularly symptom-based endpoints, it may be considered that sufficient evidence has been provided to conclude that high dose Flutiform is superior to low dose Flutiform.

To conclude, in Study FLT3503 it is accepted that there is some evidence of a dose response between Flutiform 250/10 (2 puffs bid) and Flutiform 50/5 (2 puffs bid). (In contrast no evidence of a dose response was seen between Flutiform 250/10 (2 puffs bid) and Flutiform 100/10 (2 puffs bid) in Study SKY2028-3-004. The flat dose response curve in terms of pulmonary function, particularly for fluticasone propionate, is well known).

Study SKY2028-3-001 – Pivotal Study to Demonstrate FlutiForm Efficacy versus Individual Components Administered Separately

A Randomised, Double blind, Placebo-controlled, Parallel Group, Stratified, Multicentre, 12-week Study Comparing the Safety and Efficacy of Fluticasone and Formoterol Combination (Flutiform 100/10µg twice daily) in a Single Inhaler (SkyePharma HFA pMDI) with the Administration of Placebo or Fluticasone (100µg twice daily) and Formoterol (10µg twice daily) Alone in Adolescent and Adult Patients with Mild to Moderate Asthma (n=475)

All study treatments (test and reference) were inhaled via a pMDI (used <u>without</u> a spacing device).

Both steroid requiring (requirement for inhaled steroids for at least four weeks prior to screening for entry into the study at a dose of fluticasone propionate or equivalent of not greater than 500µg per day) and non-steroid requiring (no use of steroids in the 12 weeks prior to screening for entry into the study) patients were recruited and the study was stratified for prior sterod use.

The **primary objective of this study was to demonstrate the efficacy** of (SkyePharma) FlutiForm 100/10 (low dose) compared with fluticasone propionate 100 alone, formoterol fumarate 10 alone and placebo, through the use of three co-primary endpoints each of which had to demonstrate statistical significance for the outcome of the study to be deemed positive; the **secondary objectives of this study were to demonstrate the efficacy** of (SkyePharma) FlutiForm 100/10 (low dose) using different endpoints of function and clinical endpoints, **to assess the safety profile** of (SkyePharma) FlutiForm 100/10 (low dose) and **to assess the 12-hour serial FEV_1 AUC in a subgroup of at least 160 patients.**

Co-primary efficacy endpoints:

- To demonstrate efficacy of the corticosteroid component – mean change in FEV_1 from morning pre-dose at baseline (Week 0) to pre-dose at Week 12
- To demonstrate efficacy of the long-acting β_2 agonist – mean change in FEV_1 from morning pre-dose at baseline (Week 0) to 2 hours post-dose at Week 12
- To demonstrate efficacy of Flutiform 100/10 compared with placebo – difference in the number of patients discontinuing the study due to lack of efficacy.

The primary analysis population for the analyses based on the three co-primary efficacy parameters was Full Analysis Set (FAS) Population; Last Observation Carried Forward (LOCF) was used to impute missing values.

FEV_1 (L): Mean Change from Pre-dose at Baseline to Pre-dose and 2 Hours Post-dose at Week 12 in Study SKY2028-3-001: FAS Using LOCF

		Treatment Group			
Change from Baseline Pre-dose FEV_1 to	**Statistic[a]**	**FlutiForm 100/10 N = 115**	**Fluticasone 100 N = 117**	**Formoterol 10 N = 116**	**Placebo N = 111**
Baseline	Mean (SD)	2.416 (0.5790)	2.425 (0.6625)	2.459 (0.6231)	2.352 (0.6114)
Contribution from fluticasone component					
Pre-dose FEV_1 at Week 12	LS Mean (SE)	0.195 (0.038)	0.092 (0.037)	0.094 (0.038)	0.047 (0.037)
Difference from FlutiForm 100/10					
	LS Mean (SE)		NA	0.101 (0.050)	NA
	95% CI		NA	0.002, 0.199	NA
	p-value		NA	0.045	NA
Contribution from formoterol component					
2 hours Post-dose FEV_1 at Week 12	LS Mean (SE)	0.392 (0.035)	0.191 (0.034)	0.330 (0.035)	0.124 (0.035)
Difference from FlutiForm 100/10					
	LS Mean (SE)		0.200 (0.047)	NA	NA
	95% CI		0.109, 0.292	NA	NA
	p-value		< 0.001	NA	NA

ANCOVA – analysis of covariance, CI – confidence interval, FEV_1 = forced expiratory volume in one second, LS – least squares, N – number of subjects in treatment group, NA – not applicable, S – standard deviation, SE – standard error.

[a] LS mean, SE, CI, and p-value are from ANCOVA with factors for treatment group, site, and prior steroid use, with Baseline FEV_1 value as a continuous covariate.

Superior efficacy of Flutiform 100/10 (low dose) was shown compared with the two components, fluticasone propionate and formoterol administered separately and placebo based on the co-primary pulmonary function variables.

FlutiForm 100/10 was shown to be superior to placebo for time to discontinuation due to lack of efficacy (third listed co-primary endpoint above). Discontinuations due to lack of efficacy were classified by the investigator as due to asthma exacerbation or due to loss of asthma control and were combined for analysis. The number of patients who discontinued due to lack of efficacy was 7 (6.1%) in the FlutiForm 100/10 treatment group, 9 (7.7%) in the fluticasone propionate 100 treatment group, 13 (11.2%) in the formoterol 10 treatment group and 18 (16.2%) in the placebo treatment group.

In respect of secondary endpoints, the mean 12-hour FEV_1 AUC for FlutiForm 100/10 was numerically greater than the mean 12-hour FEV_1 AUC for fluticasone propionate 100 and the mean changes in FEV_1 from pre-dose at baseline to pre-dose or 2 hours post-dose were generally numerically greater for FlutiForm 100/10 compared with its separate components and placebo beginning at Week 2 and were sustained throughout the 12-week treatment period.

Other secondary endpoints in this study further evaluated pulmonary function and also evaluated disease control and asthma symptoms. The findings supported the co-primary endpoints with demonstration of superior efficacy for FlutiForm 100/10 compared with its components, fluticasone propionate and formoterol and with placebo for pulmonary function measures (morning and evening PEFR) and requirement for *rescue* medication (statistical significance based on the sequential gatekeeping approach). Generally FlutiForm 100/10 showed numerically greater improvements compared with its two components administered separately and with placebo.

Conclusion: FlutiForm 100/10 provides greater efficacy compared with its components, fluticasone propionate and formoterol and with placebo in the management of patients with mild to moderate asthma.

Study SKY2028-3-002 – Pivotal Study to Demonstrate FlutiForm Efficacy versus Individual Components Administered Separately

A Randomised, Double blind, Active-controlled, Parallel Group, Stratified, Multicentre, 12-week Study Comparing the Safety and Efficacy of Fluticasone and Formoterol Combination (Flutiform 100/10µg twice daily) in a Single Inhaler (SkyePharma HFA pMDI) with the Administration of Fluticasone (100µg twice daily) and Formoterol (10µg twice daily) Alone in Adolescent and Adult Patients with Mild to Moderate Asthma (n=357)

All study treatments (test and reference) were inhaled via a pMDI (used <u>without</u> a spacing device).

Both steroid requiring (requirement for inhaled steroids for at least four weeks prior to screening for entry into the study at a dose of fluticasone propionate or equivalent of not greater than 500µg per day) and non-steroid requiring (no use of steroids in the 12 weeks prior to screening for entry into the study) patients were recruited and the study was stratified for prior sterod use.

The **primary objective of this study was to demonstrate the efficacy** of (SkyePharma) FlutiForm 100/10 (low dose) compared with fluticasone propionate 100 alone and formoterol fumarate 10 alone through the use of two co-primary endpoints each of which had to demonstrate statistical significance for the outcome of the study to be deemed positive; the **secondary objectives of this study were to demonstrate the efficacy** of (SkyePharma) FlutiForm 100/10 (low dose) using different endpoints of function and clinical endpoints including discontinuation due to lack of efficacy, and **to assess the safety profile** of (SkyePharma) FlutiForm 100/10 (low dose).

Co-primary efficacy endpoints:

- To demonstrate efficacy of the corticosteroid component – mean change in FEV_1 from morning pre-dose at baseline (Week 0) to pre-dose at Week 12
- To demonstrate efficacy of the long-acting β_2 agonist – mean change in FEV_1 from morning pre-dose at baseline (Week 0) to 2 hours post-dose at Week 12

The primary analysis population for the analyses based on the two co-primary efficacy parameters was the FAS Population; LOCF was used to impute missing values.

FEV_1 (L): Mean Change from Pre-dose at Baseline to Pre-dose and 2 Hours Post-dose at Week 12 in Study SKY2028-3-002: FAS Using LOCF

		Treatment Group		
Change from Baseline Pre-dose FEV1 to	Statistic[a]	FlutiForm 100/10 N = 118	Fluticasone 100 N = 116	Formoterol 10 N = 119
Baseline	Mean (SD)	2.476 (0.6012)	2.433 (0.5788)	2.404 (0.5795)
Contribution from fluticasone component				
Pre-dose FEV1 at Week 12	LS Mean (SE)	0.170 (0.031)	0.105 (0.032)	0.053 (0.031)
Difference from FlutiForm				
	LS Mean (SE)		NA	0.118 (0.042)
	95% CI		NA	0.034, 0.201
	p-value		NA	0.006
Contribution from formoterol component				
2 hours Post-dose FEV1 at Week 12	LS Mean (SE)	0.327 (0.030)	0.205 (0.031)	0.327 (0.030)
Difference from FlutiForm				
	LS Mean (SE)		0.122 (0.042)	NA
	95% CI		0.040, 0.204	NA
	p-value		0.004	NA

ANCOVA – analysis of covariance, CI – confidence interval, FEV_1 – forced expiratory volume in the one second, LS – least squares, NA – not applicable, SD – standard deviation, SE – standard error.

[a] LS mean, SE, CI, and p-value are from ANCOVA with factors for treatment group, site, and prior steroid use, with Baseline FEV_1 value as a continuous covariate.

FlutiForm 100/10 was shown to be superior to each of its components for the two co-primary endpoints based on change in FEV_1:

- the contribution from the fluticasone propionate component of FlutiForm 100/10 was demonstrated by the statistically significant difference (LS mean difference = 0.118L, 95% CI: 0.034 to 0.201, p = 0.006) between the FlutiForm 100/10 and formoterol 10 treatment groups for mean change from baseline pre-dose to pre-dose at Week 12 using LOCF imputation (first listed co-primary endpoint above);
- the contribution from the formoterol component of FlutiForm 100/10 was demonstrated by the statistically significant difference (LS mean difference = 0.122L; 95% CI: 0.040 to 0.204, $p < 0.004$) between the FlutiForm 100/10 and fluticasone propionate 100 treatment groups for mean change from baseline pre-dose to 2 hours post-dose at Week 12 using LOCF imputation (second listed co-primary endpoint above);

- Secondary efficacy endpoints of pulmonary function, asthma symptoms and disease control generally support the superior efficacy of FlutiForm 100/10 seen in the comparisons with the separate components of the combination through the co-primary endpoints;
  the mean change in FEV_1 from baseline over time to pre-dose and 2 hours post-dose at Weeks 2, 4, 8, and 12 was generally numerically greater in the FlutiForm 100/10 treatment group compared with the increase seen in the fluticasone propionate alone and formoterol alone treatment groups. The increase seen was sustained throughout the 12-week treatment period.

Conclusion: FlutiForm 100/10 provides greater efficacy compared with its components, fluticasone propionate and formoterol, in the management of patients with mild to moderate asthma.

Study SKY2028-3-004 - Pivotal Study to Demonstrate FlutiForm Efficacy versus Individual Components Administered Separately

A Randomised, Double blind, Placebo-controlled, Parallel Group, Stratified, Multicentre, 12-week Study Comparing the Safety and Efficacy of Fluticasone and Formoterol Combination (Flutiform 100/10µg or 250/10µg twice daily) in a Single Inhaler (SkyePharma HFA pMDI) with the Administration of Placebo or Fluticasone (250µg twice daily) and Formoterol (10µg twice daily) Alone in Adolescent and Adult Patients with Moderate to Severe Asthma (n=557).

[In this study: Moderate asthma – FEV_1% of predicted normal of >60% to ≤ 80%; severe asthma FEV_1% of predicted normal of ≥ 40% to ≤ 60%.]

All study treatments (test and reference) were inhaled via a pMDI (used <u>without</u> a spacing device).

Only steroid requiring patients (requirement for inhaled steroids for at least four weeks prior to screening for entry into the study at a dose of fluticasone propionate or equivalent of not greater than 500µg per day) were eligible for recruitment. Patients were stratified on entry to the study in respect of the severity of their asthma.

The **primary objective of this study was to demonstrate the efficacy** of (SkyePharma) FlutiForm 250/10 (high dose) compared with fluticasone propionate 250 alone, formoterol fumarate 10 alone and placebo **through the use of three co-primary endpoints each of which had to demonstrate statistical significance for the outcome of the study to be deemed positive.**

The **secondary objectives of this study were to demonstrate the efficacy** of (SkyePharma) FlutiForm 100/10 (low dose) using the same endpoints as for the primary objectives, **to demonstrate the efficacy** of (SkyePharma) FlutiForm 100/10 (low dose) and 250/10 (high dose) using different endpoints of function and clinical endpoints**, to assess the effects of (SkyePharma) FlutiForm 100/10 (low dose) and 250/10 (high dose) with respect to efficacy**, **to assess 12-hour serial FEV_1 AUC** in a sub-group population, and **to assess the safety profile** of (SkyePharma) FlutiForm 100/10 (low dose) and Flutiform 250/10 (high dose).

Co-primary efficacy endpoints:

- In order to demonstrate efficacy of the fluticasone propionate component, the primary endpoint was change in forced expiratory volume in 1 second (FEV_1) from morning predose at Baseline (Week 0) to predose at Week 12.
- In order to demonstrate efficacy of the formoterol fumarate component, the primary endpoint was change in FEV_1 from morning predose at Baseline (Week 0) to 2 hours postdose at Week 12.
- In order to demonstrate efficacy of SKP FlutiForm HFA pMDI in comparison with Placebo, the primary endpoint was the difference in discontinuations due to lack of efficacy.

The primary analysis population for the analyses based on the three co-primary efficacy parameters was the FAS Population; LOCF was used to impute missing values.

FEV1 (L): Mean Change from Pre-dose at Baseline to Pre-dose and 2 Hours Post-dose at Week 12 in Study SKY2028-3-004 – FAS Using LOCF

Change from Baseline Pre-dose FEV_1 to	Statistic[a]	Treatment Group: FlutiForm 250/10 N = 108	Fluticasone 250 N = 109	Formoterol 10 N = 110	Placebo N = 105
Baseline	Mean (SD)	2.085 (0.5509)	2.134 (0.5848)	2.143 (0.6237)	2.066 (0.5154)
Contribution from fluticasone component					
Pre-dose FEV_1 at Week 12	LS Mean (SE)	0.184 (0.043)	0.106 (0.041)	–0.004 (0.041)	–0.011 (0.043)
Difference from FlutiForm 250/10	LS Mean (SE)		NA	0.189 (0.056)	NA
	95% CI		NA	0.079, 0.298	NA
	p-value		NA	< 0.001	NA
Contribution from formoterol component					
2 hours Post-dose FEV_1 at Week 12	LS Mean (SE)	0.357 (0.040)	0.211 (0.039)	0.292 (0.039)	0.123 (0.040)
Difference from FlutiForm 250/10	LS Mean (SE)		0.146 (0.053)	NA	NA
	95% CI		0.042, 0.250	NA	NA
	p-value		0.006	NA	NA

ANCOVA – analysis of covariance, CI – confidence interval, FEV_1 = forced expiratory volume in one second, LS – least squares, N – number of subjects in treatment group, NA – not applicable, SD – standard deviation, SE – standard error.

[a] LS mean, SE, CI, and p-value are from ANCOVA with factors for treatment group, site, and Baseline FEV_1 % predicted category, with Baseline FEV_1 value as a continuous covariate.

FlutiForm 250/10 was demonstrated to be superior to each of its components for the 2 co-primary endpoints based on change in FEV_1:

- **The contribution from the fluticasone propionate component of FlutiForm 250/10** was demonstrated by the statistically significant difference (LS mean difference = 0.189L, 95% CI: 0.079 to 0.298, p<0.001) between the FlutiForm 250/10 and formoterol 10 treatment groups for mean change from baseline pre-dose to pre-dose at Week 12 using LOCF imputation (first listed co-primary endpoint above);
- **The contribution from the formoterol component of FlutiForm 250/10** was demonstrated by the statistically significant difference (LS mean difference = 0.146L; 95% CI: 0.042 to 0.250, p=0.006) between the FlutiForm 250/10 and fluticasone propionate 250 treatment groups for

mean change from baseline pre-dose to 2 hours post-dose at Week 12 using LOCF imputation (second listed co-primary endpoint above);

- **FlutiForm 250/10 was demonstrated to be superior to placebo** for time to discontinuation due to lack of efficacy (third listed co-primary endpoint above). Lack of efficacy leading to discontinuation was deemed to be caused by an acute exacerbation of asthma or loss of asthma control.
  The following patients discontinued due to lack of efficacy:
  - in the Flutiform 250/10 treatment group – 11 (10.2%) patients
  - in the fluticasone propionate 250 treatment group – 14 (12.8%) patients
  - in the formoterol 10 treatment group – 23 (20.9%) patients
  - in the placebo treatment group – 41 (39.0%) patients

The secondary endpoints in this study evaluated pulmonary function, disease control and asthma symptoms.

Generally FlutiForm 250/10 showed statistically significant improvement compared with placebo for all secondary endpoints (with the exception of *awakening-free nights*).

FEV_1 – Mean change from Baseline to Pre-dose and 2 hours Post-dose at Weeks 2, 4, 8 and 12 Using LOCF:
The mean changes from pre-dose at baseline over time (up to 12 weeks) demonstrated increased efficacy for FlutiForm 250/10 compared with the two active components, fluticasone propionate and formoterol fumarate and compared with placebo. Many of the treatment differences between FlutiForm 250/10 and the fluticasone propionate 250, formoterol 10 and placebo treatment groups at Weeks 2, 4, 8 and 12 were statistically significant, $p \leq 0.05$, supporting the sustained increased efficacy of FlutiForm 250/10 throughout the 12-week treatment period.

FEV_1 AUC_{0-12} was similar for Flutiform and formoterol fumarate on Day 0, but greater than for fluticasone propionate or placebo. At Week 12 effects with Flutiform exceeded those seen with the other study treatments.

In the further assessment of pulmonary function Flutiform 250/10 showed statistically significant (based on the sequential gatekeeping approach) increases in morning and evening PERF compared with the two active compoments administered separately and these findings are reflected in the use of *rescue* medication in the formoterol alone treatment group.

In the assessment of asthma symptoms and other measures of asthma control numerical improvements are seen in the treatment group receiving FlutiForm 250/10 compared with the two active components administered separately.

Comparison of the two stremgths of Flutiform – Flutiform 250/10µg versus Flutiform 100/10µg

Findings from the two treatment groups were summarised but not formally analysed.

Change in FEV_1
Flutiform 100/10 demomstrated numerical superiority when compared with the two active components fluticasone propionate and formoterol fumarate, and when compared with placebo for the first two co-primary endpoints (change in FEV_1); when compared with the higher strength of Flutiform, Flutiform 250/10 improvements were seen in both treatment groups for the first two co-primary endpoints, improvements which were comparable and not different clinically across the two treatment groups.

Discontinuation due to lack of efficacy
The percentage of subjects that discontinued due to lack of efficacy by the investigator was lower in the FlutiForm 100/10 group; the percentage of subjects who met the discontinuation criteria for lack

of efficacy (but who did not necessarily discontinue the study) was lower in the FlutiForm 250/10 group. The percentage of subjects who were discontinued for lack of efficacy by the investigator and/or met the discontinuation criteria for lack of efficacy was similar for both FlutiForm treatment groups.

FlutiForm 250/10 and FlutiForm 100/10
Discontinuations due to Lack of Efficacy in Study SKY2028-3-004

	Number (%) of Subjects	
	FlutiForm 250/10 N = 108	FlutiForm 100/10 N = 111
Number of subjects discontinued		
Lack of efficacy	11 (10.2)	8 (7.2)
Meeting discontinuation criteria for lack of efficacy	9 (8.3)	13 (11.7)
Lack of efficacy and/or meeting discontinuation criteria for lack of efficacy	14 (13.0)	14 (12.6)

Similarly for the secondary endpoints the findings from the two treatment groups were summarised but not formally analysed.

As for the co-primary endpoints the two Flutiform treatment groups both demonstrated improvements in the secondary endpoints and these were comparable and not clinically different across the two treatment groups.

However the findings in respect of asthma exacerbations did differ across the two strengths of Flutiform. There was a lower percentage of patients in the FlutiForm 100/10 group who experienced any asthma exacerbations at all and who experienced mild to moderate asthma exacerbations. However, severe asthma exacerbations were more frequent in this low strength FlutiForm treatment group compared with the high strength group,FlutiForm 250/10, and the mean percentage of days on which asthma exacerbations were reported (start time to stop time for an exacerbation) was also higher in the FlutiForm 100/10 group

This study demonstrates:

- **Co-primary endpoints**
  - superior efficacy of Flutiform 250/10 (high dose) compared with the two active components, fluticasone propionate and formoterol administered separately and compared with placebo.
- **Secondary endpoints assessing pulmonary function, asthma symptoms and disease control**
  - generally Flutiform 250/10 showed statistically significant improvements compared with placebo
  - support for the superior efficacy of FlutiForm 250/10 seen in the comparisons with the separate components of the combination
- **High and low dose Flutiform treatment groups**
  - FEV_1 data and secondary endpoints were comparable and not clinically different across the two treatment groups, but with the exception of the findings in respect of asthma exacerbations. Generally the findings are not unexpected based on the shallow dose-response for all classes of OIPs described in the literature.

In conclusion FlutiForm 250/10 provides greater efficacy when compared with its components, fluticasone propionate and formoterol and when compared with placebo, in the management of patients with moderate to severe asthma.

Supportive Efficacy Studies

Of the nine Phase III studies five are supportive efficacy studies described in the table below. The results of these studies have not been discussed in this report.

In the first three supportive studies listed below all study treatments (test and reference) were inhaled via a pMDI used with an AeroChamber Plus spacing device.

In the fourth and fifth supportive studies listed below study treatments (test and reference) were inhaled via a pMDI alone, spacing devices were not used.

Study ID Location	Objective Population Age	Design Control Type Duration of Treatment	Treatments
Supportive studies demonstrating Flutiform versus combination therapy			
FLT3501 Germany, Hungary, Poland, Romania, United Kingdom	Efficacy and safety of FlutiForm compared with Seretide. Mild to moderate-severe asthma. ≥18 years	Randomised, open-label, parallel group, active-controlled, 12 weeks	Inhaled, BID with spacer: • FlutiForm 100/10 • FlutiForm 250/10 • Seretide 100/50 • Seretide 250/50
FLT3505 Germany, Hungary, Poland, Romania, Netherlands	Efficacy and safety of FlutiForm compared with fluticasone plus formoterol Mild to moderate-severe asthma. ≥12 years	Randomised, open-label, parallel group, active-controlled, 12 weeks	Inhaled, BID with spacer: • FlutiForm 100/10 • FlutiForm 250/10 • Fluticasone 100[b] + Formoterol 12[e] • Fluticasone 250[b] + Formoterol 12 [e]
FLT3502 Czech Republic, Germany, France, Hungary, Poland, Romania	Efficacy and safety of FlutiForm compared with Seretide in paediatric subjects Mild to moderate asthma 4-12 years	Randomised, open-label, parallel group, active-controlled, 12-week core phase and an open-label 24-week extension phase	Inhaled, BID x 12 weeks (core phase) with spacer: • FlutiForm 100/10 • Seretide 100/50 Inhaled, BID:× 24 weeks (extension phase) with spacer: • FlutiForm 100/10
Other supportive study demonstrating FlutiForm versus fluticasone propionate			
SKY2028-3-005 Argentina, Chile, Mexico, Peru, Ukraine, Romania, United States	Efficacy and safety of FlutiForm compared with SKP fluticasone. Moderate to severe asthma (steroid-requiring) ≥12 years	Randomised, double-blind, parallel group, stratified, active- controlled, 12 weeks	Inhaled, BID without spacer: • FlutiForm 250/10 • SKP Fluticasone 250 • Flovent Fluticasone 250
Long term safety study			
SKY2028-3-003 Germany, Hungary, Poland, Romania, United Kingdom	Long-term safety and efficacy of FlutiForm. Mild to moderate-severe asthma (steroid-requiring) ≥12 years	Long-term, open-label, treatment assignment based on Baseline ICS dose, 6 or 12 months	Inhaled, BID without spacer: • FlutiForm 100/10 • FlutiForm 250/10

CONCLUSIONS ON CLINICAL EFFICACY

The Applicant has submitted a large and fairly comprehensive clinical dossier comprising nine completed Phase I and II studies, nine completed Phase III studies and two on-going Phase III studies. Over 1900 adult and adolescent subjects have been treated with at least one dose of FlutiForm.

At initial review by the RMS major clinical issues were highlighted which required resolution:

1. Dose proportionality

The findings in two of the clinical pharmacokinetic studies, Studies SKY2028-2-001 and SKY2028-1-002, question dose proportionality across the different strengths of Flutiform.

- In the single dose study in patients with asthma, Study SKY2028-2-001, the ratio of geometric means for C_{max}/Dose for the comparison of SKP FlutiForm 100/10µg with SKP FlutiForm 250/10µg suggest a less than proportional increase in the C_{max} for fluticasone propionate with dose (although there was high intra-subject %CV observed for dose-adjusted AUC and C_{max}).

- In the multiple dose study in healthy subjects, Study SKY2028-1-002, systemic exposure to fluticasone propionate did increase with increasing dose, however the geometric mean C_{max} and AUC_t for fluticasone propionate between the two doses, Flutiform 100/10µg twice daily and Flutiform250/10µg twice daily, did not confirm dose proportionality.

The two Phase III pivotal efficacy studies in which a high and a low dose of Flutiform are compared (Study FLT3503 and Study SKY2028-3-004) did not allay these concerns, although the lack of dose response in SKY2028-3-004 was unsurprising in view of the known shallow dose-response for OIPs. These two studies are described above.

Subsequently it was accepted that the pharmacokinetic studies which did not show proportionality were small, parallel group studies. Substantial inter-individual variability could confound between-dose group comparisons under these circumstances. The potential for inter-patient variability as a function of differences in head position, breath-hold-time, exhalation volume and inspiratory flow rate are reported in the literature. Furthermore Study SKY2028-2-001 was conducted with a Flutiform formulation administered via a Bespak actuator, which is not that used during subsequent product development or the actuator proposed for marketing. Finally the CMC data were accepted as confirming demonstrated linearity across doses.

2. Holding chambers and spacing devices

The pharmacokinetic studies were not designed to assess the pharamcokinetic parameters of fluticasone propionate and formoterol administered both with and without a spacing device. although two of the pharamcokinetic studies presented, Studies FLT1501 (a multiple dose study in healthy volunteers) and FLT2502 (a single dose study in adults and adolescents with mild to moderate asthma), did administer the study drugs via a pMDI with an AeroChamber Plus spacing device.

Therefore a pharmacokinetic study to compare the systemic load in respect of the two active components in Flutiform, when Flutiform is administered via a pressurised metered dose inhaler both with and without the AeroChamber Plus spacing device was requested.

The Applicant performed this additional study during the procedure. The results of the study, FLT1503, are summarised above. The study allowed differences in exposure to be quantified and appropriate statements to be made in the product literature.

CLINICAL SAFETY

The clinical programme submitted with these applications has been designed to demonstrate efficacy and safety of Flutiform, a fixed-dose combination of fluticasone propionate and formoterol fumarate, formulated as a pressurised inhalation suspension with the hydrofluoroalkane (HFA) propellant, propellant HFA 227 (Apaflurane), a non-chlorofluorocarbon (CFC) alternative propellant, in three strengths.

Out of the total figure of 1900 study subjects exposed to Flutiform, 337 were studied in Phase I and Phase II studies (a total of 500 were recruited into Phase I and Phase II). A total of 266 adolescent patients (aged 12 to 17 years) were recruited into the Phase III studies and of these 127 were exposed to FlutiForm. A total of 211 children (aged 4 to 12 years, mean age 8.6 years) were recruited into Study FLT3502 and of these 106 were exposed to FlutiForm. Pivotal clinical data in support of the use of these products in children less than 12 years of age have not been submitted.

Sub-groups of pooled analyses were also carried out to compare the findings across those studies in which study drugs were administerd via a pMDI with an attached spacing device and those studies in which study drugs were administerd via a pMDI alone – pooling of data across Studies FLT3501, FLT3503 and FLT3505, and Studies SKY2028-001, SKY2028-002, SKY2028-003 (enrolled into an open-label treatment period) and SKY2028-004, respectively.

ADVERSE EVENTS

There were no deaths or other serious adverse events (SAEs), or AEs resulting in discontinuation from a study reported for subjects in FlutiForm treatment groups in the **Phase I and Phase II studies**.

In Phase III studies the overall rates of AEs in the FlutiForm treatment groups were generally comparable with those in the active comparator and individual active component treatment groups. The rates of related AEs were higher in the placebo treatment groups than in the active treatment groups and more adverse events led to withdrawal from the placebo treatment groups; otherwise no real trends were seen. The AE profile seen was generally comparable across all treatment groups.

For **treatment-related AEs** in the pooled safety set, the only treatment-related AEs to occur in >1.0% of subjects per treatment group were asthma in the FlutiForm, fluticasone propionate, formoterol and placebo treatment groups, headache in the fluticasone propionate and placebo treatment groups, cough in the formoterol treatment group, dysphonia in the fluticasone propionate + formoterol treatment group, and bronchitis in the placebo treatment group.

Serious adverse events (SAEs) were reported by 42 of patients recruited into the Phase III studies. The vast majority of SAEs were assessed as not related to treatment with study medication. Two subjects experienced SAEs that were assessed as possibly related to study medication and seven subjects experienced SAEs that were deemed to be unlikely to be related to study treatments.

DEATHS

There was one unrelated death in the FlutiForm 100/10 treatment group in Study FLT3501.

Pharmacologically predictable adverse events

Hypothalamic Pituitary Adrenocortical axis (HPS Axis)

Phase II studies – Three pharmacodynamic studies, **Studies SKY2028-1-002, FLT 1501 and SKY2028-1-003,** all multiple dose studies in adults, two of which were in healthy volunteers and one in patients with mild to moderate asthma (and corticosteroid-free), have compared the effects of fluticasone propionate on the HPA axis, administered as Flutiform and as fluticasone propionate administered together with formoterol but via separate pMDIs (Studies SKY2028-1-002 and FLT 1501) and as Flutiform compared with the effects of oral prednisolone on the HPA axis (Study SKY2028-1-003). The details of these studies are available elsewhere in this assessment report. One further adolescent/adult study assessed HPA axis parameters and is described below:

Study FLT3505 ***An open, randomised, parallel group, multicentre study to compare the efficacy and safety of FlutiForm pMDI vs Fluticasone pMDI plus Formoterol DPI in adolescent and adult subjects with mild to moderate-severe persistent, reversible asthma*** (n=210)**.**

Study treatments – administered twice daily for 12 weeks via a pressurised metered dose inhaler and the AeroChamber Plus spacing device:

– FlutiForm 50/5µg pMDI: 2 actuations of 50/5µg/actuation twice daily

– FlutiForm 125/5µg pMDI: 2 actuations of 125/5µg/actuation twice daily

– Fluticasone 50µg (Flixotide Evohaler®): 2 actuations of 50µg/actuation twice daily and formoterol 12µg (Foradil Spray): 1 actuation of 12µg/actuation twice daily

– Fluticasone 125µg (Flixotide Evohaler®): 2 actuations of 125µg/actuation twice daily and formoterol 12µg (Foradil Spray): 1 actuation of 12µg/actuation twice daily

Following randomisation patients received a high (approximately 70% of the patient population in each study group) or a low dose of the randomised study treatments (see study treatments listed above) depending on asthma history and previous asthma medication. Patients starting the study on the low dose of study medication could be switched to the high dose if asthma was not controlled. Only one patient in each treatment group required a change from a low dose to a high dose.

Serum cortisol measurements were made at screening, at Week 6 and at Week 12 and 24-hour urinary cortisol collections were carried out in a sub-group (n=83) of patients on Day 0 and Week 12.

The findings were as follows:

Serum Cortisol [nmol/L]: Descriptive Statistics – Study FLT3505

Treatment	Study Day	n	Mean (SD)	Median	Min - Max
FlutiForm					
(N=105)	Screening	104	372.92 (120.97)	355.90	121.4 - 841.5
	Week 6	97	421.45 (134.73)	411.10	143.5 - 863.6
	Week 12	102	412.55 (142.03)	409.70	30.3 - 849.8
Fluticasone + Formoterol					
(N=105)	Screening	105	350.34 (158.62)	333.80	13.8 - 929.8
	Week 6	101	373.67 (141.60)	361.40	22.1 - 880.1
	Week 12	102	371.87 (160.39)	365.55	33.1 - 849.8

Max = maximum, Min = minimum, N = number of subjects in treatment group, n = number of subjects with data available, SD = standard deviation.
Source: Study FLT3505 CSR Table 25

Mean and median serum cortisols increased slightly from screening to Week 12 in both treatment groups, all patients receiving Flutiform and all patients receiving fluticasone propionate (Flixotide) and formoterol (Foradil). There were few shifts outside the nomal range for serum cortisol and only three patients showed a shift downwards below the lower limit of the normal range, two receiving Flutiform and one receiving Flixotide and Foradil.

Urine Free Cortisol Adjusted for Creatinine [nmol/mmol]: Descriptive Statistics – Study FLT3505

Treatment	Study Day	n	Mean (SD)	Median	Min - Max
FlutiForm					
(N=39)	Screening	27	5.1 (2.6)	5.0	1 - 11
	Week 12	27	6.0 (5.1)	5.0	1 - 25
Fluticasone + Formoterol					
(N=44)	Screening	34	6.2 (3.3)	5.0	3 - 16
	Week 12	34	8.1 (11.7)	4.5	1 - 69

Max = maximum, Min = minimum, N = number of subjects in specified treatment subgroup, n = number of subjects with data available, SD = standard deviation.
Source: Study FLT3505 CSR Table 26

A slight increase in mean urinary free cortisols was seen between Day 0 and Week 12 in both treatment groups. As with the serun cortisols There were few shifts outside the nomal range and only four patients showed a shift downwards below the lower limit of the normal range, two patients from each treatment group.

Study FLT3502 ***An open, randomised, parallel group, multicentre study to compare the efficacy and safety of FlutiForm pMDI vs Seretide pMDI in paediatric subjects with mild to moderate persistent, reversible asthma*** (n=211)**.**

This study in children aged between 4 and 12 years comprised a 12-week core treatment period followed by a 24-week extension phase to collect long-term safety data in children. As the Applicant is not seeking an indication for use of Flutiform in children 12 years of age and younger this study is discussed further.

CONCLUSIONS ON CLINICAL SAFETY

Over 1900 adult and adolescent subjects have been treated with at least one dose of FlutiForm and the long-term safety study, Study SKY2028-3-003 saw the recruitment of 472 patients, 224 of whom received Flutiform 100/10µg twice daily and 248 of whom received 250/10µg twice daily and of the 472 patients recruited, 256 were enrolled into a 6-month treatmenmt period and 216 were enrolled into a 12-month treatmenmt period. Of the 472 patients recruited 413 (87.5%) completed the study (59 patients discontinued), 435 (92.2%) remined in the study for at least 6 months and 175 completed 12 months in the study. The overall mean duration of exposure in this study was 25.9 weeks.

Generally, throughout the clinical pharmacology and clinical efficacy and safety study programmes Flutiform was deemed to be safe and well tolerated and no unusual or unexpected adverse events were reported. The adverse event profile seen was consistent with that which might be expected from the two well-known components of this fixed-dose combination and was consistent with that seen in the comparisons made with the reference products.

Conclusions on HPA axis function

Five studies have assessed the systemic effects of the fluticasone propionate component of Flutiform on the HPA axis over time/to steady state, three pharmacodynamic studies and two studies in the Phase III clinical programme. The findings from the three pharmacodynamic studies suggest that fluticasone propionate in Flutiform exerts a lesser effect on the HPA axis than high dose fluticasone propionate (as Flixotide) administered together with formoterol (as Foradil) and the Phase III studies

suggest that low and medium doses of Flutiform do not appear to have any significant impact on HPA axis function

These findings are in line with the findings in the pharmacokinetic studies carried out with Flutiform where the level of systemic exposure to fluticasone propionate following administration of FlutiForm appears generally to be less than that seen following administration of the comparator products, fluticasone propinate (as Flixotide) administered alone or administered together with formoterol (as Foradil). This finding would suggest that the influence of FlutiForm on the HPA axis might be less than that of the comparator products and this does appears to be borne out in the pharamcodynamic studies.

The findings in the pharmacodynamic and Phase III studies are reassuring and do suggest that Flutiform may be a systemically safer alternative to fluticasone propionate administered either alone or in combination with formoterol but administered from separate inhalers (as in the reference products).

Ideally in the pharmacodynamic/clinical assessment of systemic safety the maximun total daily dose should have been compared with a lower total daily dose, both doses administered to steady state, to ensure the sensitivity of the study. This study has not been included in the dossier. However in the light of the pharmacokinetic findings where the level of systemic exposure to fluticasone propionate following administration of FlutiForm appears generally to be less than that seen following administration of comparator products containing fluticasone propionate, the lack of such a pharmacodynamic comparison can be accepted.

Effects on serum potassium, glucose and heart rate
Across the Phase III clinical programme no clinically important trends were seen in mean changes over time in clinical chemistry variables, including serum potassium and blood glucose. There were no clinically important differences seen between FlutiForm and its two active components fluticasone propionate and formoterol, administered together but from separate inhalers or administered alone, between FlutiForm and Seretide (fluticasone propionate and salmeterol) or between FlutiForm and placebo. It should be noted that the protocols did not demand fasting blood samples for clinical chemistry assessments in any of the Phase III studies. A few patients did demonstrate elevated blood glucose during the course of the Phase III studies but overall these raised blood glucose levels were not considered to be significant.

As the systemic effects of long-acting β_2 agonists may include elevation of blood glucose and a fall in serum potassium, changes in these parameters were evaluated for the pooled safety set. No noticeable trends were observed in any of the treatment groups, dose groups or in the spacing device versus non-spacing device treatment groups. Changes in mean blood glucose and serum potassium over time were small and not clinically relevant.

No noticeable trends across treatment groups, dose groups or in the spacing device versus non-spacing device treatment groups in the Phase III studies and from the pooled safety set were seen in heart rate. Changes in mean heart rate over time were small and not felt to be clinically relevant.

Arrhythmias and cardiac ischaemia and the QTc interval
A review of adverse events related to arrhythmia and cardiac ischaemia identified only few events associated with the use of FlutiForm and did not suggest any unexpected findings. Flutiform did not appear to have any significant effect on the QTc interval.

Safety in Special Populations

Children 12 years of age and younger

Use in children less than 12 years of age is not requested. No pivotal clinical data in support of the use of these products in children less than 12 years of age have been submitted; the Applicant has agreed that a PIP will be completed by December 2013.

Adolescents 12 to 17 years of age

Safety in Adolescents – 12 to 17 years – Study FLT2502
The systemic exposure of FlutiForm was assessed for fluticasone propionate and formoterol fumarate in adult and adolescent patients with mild to moderate asthma in Study FLT2502. For both fluticasone propionate and formoterol greater availability and higher maximum plasma concentrations were observed in adolescents compared with adults, although the difference observed between adolescents and the adults was less for formoterol than for fluticasone propionate. These findings may be due to increased pulmonary deposition in the adolescent age group together with lower body weight and volume of distribution in the adolescent, compared with adults. No studies are referenced from the literature in which the pharmacokinetics of either fluticasone propionate or formoterol have been investigated and compared in adults and adolescents. Integrated safety analyses based on Phase 3 studies demonstrated no additional safety concerns relating to an increased exposure of fluticasone and formoterol in adolescents compared with adults.

The systemic effects of the glucocorticoid component of Flutiform on the HPA axis in the adolescent have been studied in Study FLT3505. The study was not stratified in respect of adults and adolescents but overall showed no evidence of HPA axis suppression.

It is felt that further clinical studies in the adolescent population are not required at this time.

Patients with renal and hepatic impairment.
Patients with renal and hepatic impairment have not been investigated.

Safety Related to Drug-Drug Interactions and Other Interactions
Interaction studies have not been performed.

Excipients
The excipients in these new fixed-dose combination pressurised metered dose inhalers containing fluticasone propionate and formoterol fumarate, formulated as pressurised inhalation suspensions, include alcohol (ethanol, anhydrous) as a wetting agent, sodium cromoglycate as a suspension aid and moisture scavenger and the non-CFC propellant, propellant HFA 227 (Apaflurane).

Preclinical testing of HFA 227 has been carried out through IPACT-II. In 1995 IPACT II applied for and gained approval from the then CPMP for the use of HFA 227 as an alternative propellant in metered dose inhalers.

Ethanol is a known excipient used previously in pressurised metered dose inhalers.

The safe use of sodium cromoglicate (at much higher doses) as Intal 1 & 5 mg per inhalation, for use in the management of asthma is well recognised; its use as an excipient is novel.

The presence of these excipients in the test product does not appear to adversely influence the performance of the product, aerosol particle behaviour or inhalation behaviour of the patient.

Post-Marketing Data
No post-marketing experience exists with these fixed-dose combination pressurised metered dose inhalers formulated as pressurised inhalation suspensions with the hydrofluoroalkane propellant, propellant HFA 227 (Apaflurane), a non-CFC alternative propellant. The applicant proposes to conduct an observational study and include study end-points such as cough, bronchospasm, worsening asthma as well as the safety concerns listed in the Risk Management Plan

CLINICAL EXPERT REPORT
A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

PRODUCT LITERATURE
Summary of Product Characteristics (SmPC)
The SmPC was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisations

Patient Information Leaflet (PIL)
The PIL was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisations

Labelling
The labeling was assessed and amended and found to be satisfactory at the time of the Marketing Authorisations.

CONCLUSIONS

The RMS considered that all points raised on these applications, potential serious risks to public health, points for clarification and points for consideration, had been resolved on Day 195 of these Procedures; however one CMS was of the opinion that Potential Serious Risks to Public Health remained unresolved at this time. The applications were referred to CMD(h) but Member States were still unable to reach agreement. Therefore the applications and reasons for disagreement were submitted to the European Medicines Agency on 22nd December 2011 for consideration by the Committee for Medicinal Products for Human Use (CHMP). The referral opinion is discussed in the next section of this report.

The referral procedure commenced on 19 January 2012.

OPINION OF THE COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

These applications were considered by the Committee for Medicinal Products for Human Use (CHMP). The grounds for referral were concerns raised by a Concerned Member State (CMS) over data showing that the levels of fluticasone propionate in the blood following dosing with Flutiform are lower than when fluticasone propionate is given alone, which may indicate a lower amount of fluticasone propionate being deposited in the lungs from Flutiform. In the light of this the long-term efficacy of this product in respect of asthma control was considered by the Committee.

CHMP considered the following issues:

Masking of lesser corticosteroid effect

There were concerns with the evidence of efficacy provided in the clinical programme in respect of the fluticasone proprionate component of this fixed-dose combination (particularly with regard to anti-inflammatory effects). The anti-inflammatory effects of fluticasone propionate could be masked by formoterol.

Conclusions

Of the five pivotal studies submitted with these Marketing Authorisation Applications three studies were designed such that they facilitate a rigorous, internally validated examination as to whether the long-acting β_2 agonist formoterol fumarate "masks" deficient corticosteroid effects of Flutiform upon pre-dose FEV_1. This endpoint (i.e. change in FEV_1 from pre-dose at baseline) was designated *a priori* as the primary endpoint to assess corticosteroid effect.

The CHMP supported the clinical study designs in the Phase III clinical development programme and the use of pre-dose FEV_1 as the primary endpoint for efficacy in respect of corticosteroid effect. The Committee was also of the opinion that the corticosteroid effects seen with Flutiform are no less than those seen with the GSK fluticasone propionate pressurised metered dose inhaler (pMDI) and that formoterol fumarate does not appreciably "mask" any lesser corticosteroid effect. The apparent lower systemic availability of fluticasone propionate in Flutiform compared with that from the GSK fluticasone propionate pMDI would not appear to result in a lesser clinical effect. The clinical findings suggest that fluticasone propionate in Flutiform is non-inferior in respect of clinical effects to already marketed fluticasone propionate preparations.

Asthma control and exacerbations

Asthma control is one of two principal treatment goals in asthma management (the other being the reduction of exacerbation risk). It is a multidimensional concept incorporating symptoms, night time awakenings, use of rescue medication, lung function and activity limitation. Several endpoints which reflect these different facets of asthma control are modulated by long-acting β_2 agonists.

Data submitted by the Applicant demonstrated that asthma control with Flutiform is superior to that with fluticasone propionate pMDI alone and that asthma control with Flutiform is similar to that with fluticasone propionate pMDI + formoterol fumarate pMDI. With regard to the duration of the pivotal studies (8-12 weeks), literature data support the view that treatment effects upon asthma control variables are maximal within 3 months and sustained thereafter. As such the Applicant claimed that the asthma control results from the pivotal studies should logically be extrapolated to the longer-term.

Substitution therapy for patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist
CHMP was of the view that the clinical effects of Flutiform in respect of asthma control and exacerbation risk are comparable with/similar to the clinical effects of fluticasone propionate and formoterol fumarate given concomitantly.

Step-up indication for patients not adequately controlled with inhaled corticosteroids and *as required* inhaled short-acting β_2 agonist
CHMP accepted the view that the clinical effects of Flutiform in respect of asthma control are superior to the clinical effects of fluticasone propionate administered alone. The data presented in respect of exacerbations demonstrate an increased protective benefit of Flutiform compared with fluticasone propionate administered alone – the odds of any exacerbation occurring were 33% higher and the annual exacerbation rate was 49% higher in patients receiving fluticasone propionate alone than in patients receiving Flutiform.

OVERALL OPINION

The Committee reviewed all available data submitted by the Applicant to address the potential serious risk to public health, in particular the efficacy data in respect of long-term asthma control.

The Committee considered that the overall safety and efficacy have been sufficiently proven by the studies presented.

On 19th April 2012 CHMP concluded that the benefit-risk balance of Flutiform in the applied indications is favourable.and recommended the granting of the marketing authorisations for Flutiform 50 microgram/5 micrograms, 125 microgram/5 micrograms and 250 microgram/ 10 micrograms per actuation pressurised inhalation, suspension.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Flutiform 50 microgram/5 micrograms, 125 microgram/5 micrograms and 250 microgram/10 micrograms per actuation pressurised inhalation suspension are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

The toxicological profile for Flutiform® has been shown to be similar to that observed following administration of β_2 agonists and/or corticosteroids. The effects seen in the bridging studies have previously been reported for the individual active components of Flutiform®– fluticasone propionate and formoterol fumarate. No additional or unexpected toxicity was observed in this fixed-dose combination product and no interactions between the two components of Flutiform® were evident. Therefore no safety concerns are raised on this fixed-dose combination of fluticasone propionate and formoterol fumarate in the proposed product formulation.

EFFICACY

Fluticasone propionate and formoterol fumarate are well established active drug substances and have been used to treat symptoms of asthma for many years. Any safety concerns arising from these applications have been fully resolved.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The Summaries of Product Characteristics (SmPCs) and Patient Information Leaflet (PIL) are acceptable and consistent with those of the reference products. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK BALANCE ASSESSMENT

The quality of the product is acceptable and any preclinical and clinical safety concerns are fully resolved. The risk benefit balance is therefore considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome