SCIENTIFIC DISCUSSION

1. Introduction

Allergic rhinitis (AR) in its seasonal and perennial form is a common allergic condition. It is clinically defined as a symptomatic disorder of the nose induced by IgE-mediated inflammation after allergen exposure to the mucous membranes of the nose. Symptoms of AR include rhinorrhoea, nasal obstruction, nasal itching and sneezing, accompanied frequently by eye symptoms.

Rhinopathies can be classified as being structural, infectious, allergic, or non-allergic. AR, an inflammatory condition of the nasal mucosa mediated by an IgE-associated response to indoor and outdoor environmental allergens, has traditionally been classified as being seasonal (SAR) or perennial (PAR), depending on whether an individual is sensitized to cyclic pollens or year round allergens, such as dust mites, pets, cockroaches, and moulds.

The diagnosis of AR can be made presumptively based on the types of symptoms and the history of allergen triggers. The diagnosis is further supported by documentation of specific IgE reactivity through determination of allergen sensitivity by using skin prick testing or in vitro specific IgE determination. These procedures can help detect specific allergic sensitivities and provide information for directing environmental control interventions.
According to data supplied from the applicant the prevalence of allergic rhinitis is 30% of US population and similar in Europe; 13-19% among adolescents (13-14 years olds) and 5-10% for children 6-7 years old. Higher figures have been reported in some countries, in which 40% of children were found to have symptoms compatible with allergic rhinitis.

The goal of allergic rhinitis therapy is to manage both the acute and chronic manifestations of the disease by minimizing the associated symptoms and improving quality of life. To achieve this, current treatment recommendations include allergen avoidance, immunotherapy and/or pharmacotherapy. Avoidance is difficult to achieve for the most common allergens (e.g., pollen, dust mites). Immunotherapy is an effective chronic therapy in some patients but it is time-consuming, inconvenient, and has potential serious adverse effects (such as large local reactions and anaphylaxis). Current pharmacotherapy options include intranasal corticosteroids, antihistamines, non-steroidal anti-inflammatory agents and decongestants. Local (intranasal) glucocorticoids are considered drugs of choice in symptomatic treatment of AR. Their well-known, class-typical anti-inflammatory properties enable efficacious control of symptoms of AR in the majority of patients treated.

Avamys nasal spray suspension (27.5 micrograms per spray) contains fluticasone furoate (FF) as active substance. Fluticasone furoate (GW685698X) is a new corticosteroid developed by GlaxoSmithKline (GSK) presented as an aqueous suspension in a novel side-actuated nasal spray delivery system claimed for once daily treatment for topical use in relieving symptoms of seasonal (SAR) and perennial (PAR) allergic rhinitis.

This application concerns a centralised procedure, according to Regulation (EC) No 726/2004, "optional scope" Article 3(2)(a) – new active substance. This application is submitted in accordance with the Article 8(3) in Directive 2001/83/EC – i.e. dossier with administrative, quality, preclinical and clinical data for a new active substance. The application is a full application.

2. Quality aspects

Introduction

Composition
Avamys is a multidose preserved aqueous nasal spray suspension. Each spray delivers 27.5microgram of the active substance fluticasone furoate to the patient (ex device).
Other ingredients include dispersible cellulose (as suspending agent), glucose (as a tonicity-adjusting agent), Polysorbate 80 (as a surfactant), benzalkonium chloride solution and disodium edetate (as preservatives) and purified water.
The suspension is contained in an amber glass bottle fitted with a metering atomising spray pump. The bottle is enclosed within an outer plastic device with a dose indicator window, a side-actuated lever and a nozzle, which is protected by a lid containing a stopper.
The product is provided in three pack sizes to deliver a minimum of 30, 60 or 120 sprays respectively.

Active Substance

Fluticasone furoate is a tetracyclic steroidal molecule. It contains 9 sterogenic centres and is the isomer with the 6S, 8S, 9R, 10S, 11S, 13S, 14S, 16R, 17R configuration. It is a neutral molecule and has no acidic or basic centres. It is non-hygroscopic, practically insoluble in water and slightly soluble in acetone, dimethylsulphoxide and ethanol. The proof of chemical structure was achieved by elemental, spectroscopic and X-Ray diffraction analysis. Fluticasone furoate exists in 3 polymorphic forms; Form 1 is thermodynamically stable at room temperature. It is a crystalline powder, which may exist in an acicular or tetragonal pyramid crystal form. The latter is preferred due to its enhanced flow properties.

- Manufacture

The active substance is synthesised with a six step synthetic process using flumethasone as the steroidal starting material followed by a particle size reduction step. The route of synthesis has four major stages, including preparation of a key intermediate from flumethasone, preparation of intermediate grade fluticasone furoate, preparation of non-micronised fluticasone furoate and finally micronisation of fluticasone furoate. The synthetic process for non-micronised fluticasone furoate delivers only Form 1 material with a tetragonal bipyramidal crystal form. This material has good flow properties and is readily micronised.
For the development and validation of the manufacturing process the principles described in the ICH Q8 and Q9 guidelines have been taken into account. Several studies have been performed to identify the critical quality attributes of the active substance that have the potential to affect the safety and efficacy of the finished product, to gain a better understanding of the process and develop a Design Space for the manufacturing process. In addition appropriate control strategies (including PAT) have been developed to monitor the critical process parameters.
The impurity profile of the active substance has been extensively investigated and meets the ICH requirements. All potential impurities have been identified and characterised. All solvents used in the manufacture of the active substance are controlled in compliance with ICH guidelines.

- Specification

The active substance specification includes tests for description, identification (IR), solid state form (IR), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (Karl Fischer), residue on ignition (IR) and particle size distribution (Laser Diffraction).
Batch analysis data have been provided from 3 production scale batches manufactured according to the synthetic process intended for marketing and 3 production scale batches manufactured according to a non-optimised process, which was used for stability studies. Batch analysis data are also presented for 15 batches used in non-clinical and clinical studies. The batch analysis data presented confirm that the proposed process can reproducibly produce a product that complies with the set specifications.

- Stability

Twenty-four months stability data at the long-term storage condition of 30°C/65% RH and 6 months data at the accelerated storage condition of 40°C/75% RH have been presented for three batches of micronised fluticasone furoate packaged in containers representing those proposed for use in routine production.
The parameters tested were the same as at release except for identification, residual solvents and residue on ignition. The analytical methods used were appropriately validated and have been shown to be stability indicating. The stability data demonstrate that the active substance has a very good stability profile. All results were within the predefined specifications.

Results from photostability studies performed in accordance with the ICH requirements show that the unprotected active substance is sensitive to light and therefore it is recommended that it should be protected from it.

Medicinal Product

- Pharmaceutical Development

The aim of the Pharmaceutical Development was to develop a product that would provide a consistent dose to the patient throughout its use and minimise the potential for inhalation to the lungs. A risk-based approach has been applied, where appropriate, throughout the development using the principles described in the ICH Q8 and Q9 guidelines. Methodologies such as Failure Mode and Effects Analysis (FMEA), Relationship Matrices and Design of Experiments have been employed to identify and manage the critical to quality attributes of the process and the product and to improve the overall product and process understanding.
The active substance has been formulated as an aqueous suspension, because the results of pharmacokinetic studies showed that a suspension formulation results in less systemic exposure than other formulations and was therefore appropriate for topical delivery to the nasal mucosa. The active substance is incorporated into the finished product in a micronised form. The formulation includes a suspending agent (dispersible cellulose) to ensure that the active substance remains homogeneously distributed and to prevent variation in the droplet size distribution of the finished product. A tonicity adjusting agent (glucose) and a broad spectrum preservative system (benzalkonium chloride disodium edetate) are also included. The use of benzalkonium chloride as a preservative has been fully justified on the basis that it is a broad spectrum antimicrobial agent and is further supported by its use in other commercially available nasal formulations. All excipients used in the product are of non-animal origin and comply with their corresponding European Pharmacopoeia monographs.
The container closure system comprises of an inner container within an outer device. The outer device is a side-actuated plastic delivery system with a lever, a dose indicator window and a lid containing a stopper. The bottle is not intended to be accessible to the patient from the assembled container closure system. Mechanically and ergonomically the device has been designed to facilitate treatment of patients 2 years and older, with self-administration from 7 years. The container closure system was designed to assure consistent dosing. The pump has been chosen so as to provide consistent and reliable spray weight delivery. The nozzle delivers a consistent droplet size distribution in the spray and the pack retains a primed state during extended periods of non-use. The same basic design has been used throughout clinical trials and stability testing.
Extensive pharmaceutical development studies have been conducted on the finished product in compliance with the "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products". These include priming and repriming tests, in use studies, effect of orientation during use, minimum fill justification, testing to exhaustion, temperature cycling and robustness.
All the plastic materials of the pump and nozzle comply with the European Directive, 2002/72/EC, on plastics for food contact and meet composition requirements of Ph.Eur. The extractable and leachable profile of the finished product has been satisfactorily investigated.

- Manufacture of the Product

The manufacturing process is a standard process for these kind of formulations and consists of the following steps: suspension manufacture, filling and assembly

All critical process parameters have been identified and controlled by appropriate in process controls. It has been demonstrated that the process is reproducible and provides a product that complies with the in-process and finished product specifications.

- Product Specification

The specification for the finished product at release and shelf life includes tests for description, identity (IR), assay (HPLC), preservative content (potentiometric titration, HPLC), pH, microbial limits, delivered dose uniformity (HPLC) , contents weight, number of sprays, droplet size distribution (laser diffraction) and impurities (HPLC).
The proposed specification encompasses the requirements of the "Guideline on the pharmaceutical quality of inhalation and nasal products" and the Ph. Eur. monograph for nasal products. All tests included in the specification have been satisfactorily described and validated.
Batch analysis data are presented for the primary stability and clinical batches. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

The stability studies have been performed in accordance with the ICH guidelines and the requirements of described in the "Guideline on the pharmaceutical quality of inhalation and nasal products". Stability data have been presented for 3 primary stability batches. The composition, size and volume of the container closure system were the same as that proposed for commercial production. Samples have been stored for up to 24 months at 30ºC/65%RH and for up to 6 months at 40ºC /75% RH.
The parameters tested were appearance, assay, impurities, benzalkonium chloride and EDTA content, preservative efficacy, microbial limit testing, leachables content, pH, uniformity of delivered dose and droplet size and weight loss. The analytical methods used in most cases were the same as those used for release testing and are stability indicating.
Data from stressed stability studies have also been presented for one batch each of the 30, 60 and 120 presentations, stored at 50°C/ambient RH for up to three months, up to 12 months at 5°C/ ambient humidity and seven days storage in a light cabinet. In addition, data are presented from one batch of each of the 120 and 30 spray packs stored under temperature cycling conditions (5ºC/40ºC) for up to one month. The results of stressed stability studies demonstrate the chemical and physical stability of the finished product in all storage conditions.
In all cases the stability results provided were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Avamys is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

The active substance is stable, well characterised and documented. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The applicant has performed extensive development studies both for the active substance and the finished product and has applied, where appropriate, the principles described in ICH Q8 and Q9 guidelines The device component of the finished product has been evaluated as an integral part of the medicinal product. The manufacture, analytical procedures and specifications set for the container closure system and have been adequately described. The manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

At the time of the CHMP opinion there were some outstanding minor quality issues, which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

3. Non-clinical aspects

Introduction

Safety pharmacology studies, a number of pharmacokinetic studies commissioned by GlaxoSmithKline at contract research organisations, and all pivotal toxicity studies (including the toxicokinetic arm of each study) were carried out in full compliance with Good Laboratory Practice (GLP) regulations. However for one toxicology study a GLP non-compliance was found (at the time of adoption of the Day 180 List of Outstanding Issues), following which the CHMP requested a GLP inspection. All other studies were conducted in line with the company's Standard Operating Procedures and Policies, and in general accordance with the principles of GLP.

Pharmacology

Topical glucocorticoids interact with many of the inflammatory pathways, and there is a large body of clinical evidence to support their use in rhinitis, asthma and chronic obstructive pulmonary disease.

Fluticasone furoate is a new glucocorticoid with potent anti-inflammatory activity. Fluticasone furoate is not a salt or prodrug; the entire molecule is required for pharmacological activity.
The 17-α furoate ester is metabolically stable. Fluticasone furoate is not metabolised to fluticasone, i.e. the furoate ester is an integral part of the respective medicinal entity and remains covalently bound to the fluticasone steroid backbone.

- Primary pharmacodynamics

In Vitro
In vitro assays (both human and rat cell lines) of glucocorticoid receptor-induced transrepression and transactivation and also assays of cytokine release, revealed that fluticasone furoate (FF) has a very high binding affinity equivalent to that observed with fluticasone propionate (FP) and greater than other inhaled corticosteroids. Fluticasone furoate is a very potent glucocorticoid agonist with comparable or superior activity to the clinical standards fluticasone propionate (FP) and mometasone furoate (Table 1). The affinity of FF, FP and mometasone for a number of associated receptors including androgen receptor (AR), oestrogen receptor, mineralocorticoid receptor (MR) and progesterone receptor (PR) were investigated and are outlined in Table 1. Fluticasone furoate (FF) has properties at the steroid nuclear receptors which are broadly similar to FP with high potency and intrinsic efficacy at the glucocorticoid receptor, low intrinsic efficacy on MR agonist activity, AR affinity, PR agonist activity but no activity at the oestrogen receptors.
Fluticasone furoate potently suppressed the activation of NFκB and AP-1 and activated glucocorticoid response element (GRE), which are associated with the agonism of glucocorticoid receptor. Furthermore, FF increased the transactivation of MMTV (murine-mammary-tumour virus) and GRE-mediated TAT (tyrosine aminotransferase) induction and inhibited the release of IL-8 from bronchial epithelial cells exposed to TNF-α. The NFκB pathway is known to play a key role in the synthesis of a wide number of inflammatory cytokines. Both FF and FP inhibit NFκB mediated IL-1β stimulated release of IL-6, IL-8 and GM-CSF, however FF continued to demonstrate a more potent inhibition over a prolonged period of time (16 hours) in comparison to FP. Furthermore, FF demonstrated significant suppression of TNF-α release to a greater degree than a number of other clinically used inhaled corticosteroids.
Both FF and FP exposure to bronchial epithelial cells resulted in the equivalent induced expression of SLPI (secretory leuko-proteinase inhibitor) and MKP-1 (mitogen-activated protein kinase phosphatase 1), with expression maintained for 16 hours following exposure to FF. The prolonged duration of action of FF coincided with the nuclear retention of glucocorticoid receptor (GR) for at least 24 hours following exposure. Together with the prolonged nuclear retention, FF also induced a faster and greater degree of nuclear translocation of the GR than fluticasone propionate and dexamethasone at concentrations close to the normal pharmacological range (10 nM). FF also showed significant selectivity with respect to a number of steroid hormone receptors (Table 1).

The primary metabolite GW694301X showed significantly less activity (6000-fold) in comparison to FF when tested in a number of GR dependent assays (including NFκB, AP-1 and GRE).
Glucocorticoids have previously demonstrated their ability to protect and improve barrier function and protect bronchial epithelial monolayers from protease damage and cell detachment which have been associated with lung inflammatory diseases such as asthma.
In assays of protease-induced cell damage and mechanically induced cell damage, FF demonstrated a similar protective effect to that of other glucocorticoids in protecting against neutrophil elastase damage, reduced the decrease in epithelial monolayer permeability and improved epithelial layer integrity following mechanical damage. The mechanism of these protective effects has as yet not fully been elucidated. The rank order of potency for FF and the other glucocorticoids studied, irrespective of the protective effect studied (elastase wounding, epithelial permeability or mechanical wound studies) was similar. FF always demonstrated a similar or greater degree of protection, FF >FP ≥MF >Budesonide >Dexamethasone >BMP.

Table 1 Comparison of the *In Vitro* Pharmacology of FF with other Clinically Used Steroids.

Assay System	GW685698X (FF)	FP	MF	BUD	CIC-AP	DEX	BMP
GR binding (RRA)	2989 ± 135	1775 ± 130	ND	ND	ND	100 ± 5	ND
NFκB	0.026 nM 0.032 nM	0.037 nM 0.04 nM	0.025 nM 0.025 nM	ND ND	ND 0.20 nM	1.25 nM ND	ND ND
AP1	0.10 nM	0.14 nM	0.15 nM	ND	ND	ND	ND
MMTV-GRE	0.12 nM	0.20 nM	0.080 nM	ND	0.63 nM	6.3 nM	ND
HSV-TK -GRE	0.06 nM	0.07 nM	0.1 nM	ND	ND	ND	ND
IL8	0.003 nM	0.007 nM	0.005 nM	0.048nM	ND	ND	ND
GM-CSF	0.01 pM	0.09 pM	ND	ND	ND	ND	ND
IL8	0.02 nM	0.04 nM	0.04 nM	ND	ND	2 nM	ND
TNF	0.12 nM	0.23 nM	ND	3.89nM	3.16 nM	ND	ND
Cellular protection – elastase damage	0.04 nM (TER_1) 0.1 nM (TER_2) 0.005 nM ($flux_1$) 0.005 nM ($flux_2$)	0.06 nM 0.3 nM 0.01 nM 0.015 nM	0.2 nM 0.55 nM ND ND	ND ND 0.9nM 0.35nM	ND ND ND ND	4 nM 5 nM 2.5 nM 1 nM	ND ND ND ND
Cellular protection – mechanical damage	0.025 nM (exp_1) 0.03 nM (exp_1) 0.025 nM (exp_2) 0.02 nM (exp_2)	0.15 nM ND 0.06 nM ND	ND 0.06 nM ND 0.09 nM	ND 0.15nM ND 0.55nM	ND ND ND ND	0.5 nM 0.4 nM 3.5 nM 3 nM	2.5 nM ND 7 nM
NFκB selectivity vs. MR	794-fold	631-fold	20-fold	ND	10-fold	ND	ND
NFκB selectivity vs. PR	32-fold	25-fold 62-fold	<1-8-fold	ND	20-fold	ND	ND
NFκB selectivity vs. ER	>100 000-fold	>100 000-fold	>100 000-fold	ND	> 10000 -fold	ND	ND
NFκB selectivity vs. AR	>10 000-fold	>10 000-fold	5011-fold	ND	3162-fold	ND	ND

Notes: Values are EC50s; ND=not determined. Drug name key: FP=fluticasone propionate; MF=mometasone furoate; BUD=budesonide; CIC_AP=ciclesonide active principle; BMP=beclomethasone monopropionate; DEX=dexamethasone. Receptor key: MR=mineralocorticoid receptor; PR=progesterone receptor; ER=oestrogen receptor; AR=androgen receptor. Assay key: MMTV-GRE=Mouse Mammary Tumour Virus promoter glucocorticoid response element assay; HSV-TK-GRE= herpes simplex virus thymidine kinase.

Investigation of tissue binding in an epithelial cell monolayer revealed that the association of FF was greater (approximately 2-fold) than for FP and the rate of flux from the apical to basolateral surface of cells was slower for FF than for FP. FF was also found to bind more avidly to a suspension of whole lung tissue. These results indicate that FF would be retained in the lungs and potentially nasal tissue for longer than FP and subsequently result in a longer duration of action.

In Vivo

The anti-inflammatory properties of FF were investigated in two unrelated animal models of inflammation with differing immunology. FF and FP administered intratracheally at doses <100µg, completely and dose dependently inhibited lung eosinophilia in the Brown Norway rat (model of

characteristic eosinophil inflammation of the lung). FF more potently inhibited lung eosinophilia than FP at the lowest doses (10µg and 30µg). FF and FP equally inhibited skin inflammation after topical administration of oxazolone in a Delayed Type Hypersensitivity model of ear inflammation in rats (SH 2002/00044/00). Oxazolone induced sensitization (ear swelling) in BALB/c mice was potently and dose dependently inhibited by the administration of FF to the treated ear, with slight systemic effects observed through reduced swelling observed in the untreated ear (SH2003/0031/00).

- Secondary pharmacodynamics

Secondary pharmacodynamics of FF assessed by using rat thymus involution model as an index of the systemic pharmacodynamic effects of glucocorticoids, showed that FF has glucocorticoid systemic activity. Three daily intratracheal doses of 100 µg FF induced significantly smaller reduction in thymus weight ($p = 0.004$) when compared to an equivalent dose of FP (67% of thymus weight with FF vs. 78% reduction with FP).

- Safety pharmacology programme

Table 2 Summary of safety pharmacology tests of FF (Source: study reports from Module 4)

<table>
<tr><th>Test type
(report number in CTD)</th><th>Dose/
Concentration
of FF
(route of
administration)</th><th>Results</th></tr>
<tr><td>Study on action potential duration in dog Purkinje fibre preparations (WD2001/01020/00)</td><td>0; 880; 2640; 8800 pg/ml in 0.1% DMSO in PSS buffer</td><td>No effect on any of the action potential parameters in fibres treated with FF at concentrations up to 2200 pg/ml (100 times the expected human unbound plasma level).
<u>Note:</u> concentration 2200 pg/ml is an equivalent of baseline concentration of 8800 pg/ml after taking into account an anticipated loss of test material in the perfusion apparatus of about 75%.</td></tr>
<tr><td>Investigation of single intravenous dose in the dog (FD2002/00019/00)</td><td>0; 0.1 mg/kg (i.v., 1 min. infusion)</td><td>Treatment with FF was associated with a transient decrease in blood pressure and a small transient increase in heart rate. These effects were similar to those seen following vehicle treatment. $AUC_{0-\infty}$: 49.3 h·ng/ml, C_{max}: 41.7 ng/ml</td></tr>
<tr><td>Single intravenous dose cardiovascular study in dogs (FD2002/00011/01)</td><td>0; 0.03; 0.1 mg/kg (i.v., 2 min. infusion)</td><td>No additional effects above those seen with vehicle treatment were observed following treatment wit FF.
<table>
<tr><td></td><td>$AUC_{0-\infty}$</td><td>C_{max}</td></tr>
<tr><td>0.03 mg/kg</td><td>16.8 h·ng/ml</td><td>14.0 ng/ml</td></tr>
<tr><td>0.1 mg/kg</td><td>61.6 h·ng/ml</td><td>39.1 ng/ml</td></tr>
</table>
</td></tr>
<tr><td>Single subcutaneous dose cardiovascular study in rats (FD2002/00033/00)</td><td>0; 4 mg/kg (s.c.)</td><td>The cardiovascular and pathological effects (mild, though sustained increase in blood pressure and an associated reduction in heart rate, body temperature and spontaneous locomotor activity, moderate reduction in body weight) observed following administration of FF at 4 mg/kg were known pharmacological actions in response to high concentrations of corticosteroids.</td></tr>
<tr><td>Evaluation of the effect on respiration in the unrestrained conscious rat following single subcutaneous administration (FD2001/00004/00)</td><td>0; 4; 10 mg/kg (s.c.)</td><td>No effect on respiratory function at dose at least 10 mg/kg.</td></tr>
<tr><td>Overt central and peripheral pharmacodynamic effects following acute subcutaneous administration in conscious Wistar Han rats (WD2001/00889/00)</td><td>0; 4; 10 mg/kg (s.c.)</td><td>No overt pharmacodynamic effects at the doses tested.</td></tr>
</table>

Overt central and peripheral pharmacodynamic effects following acute subcutaneous administration in the conscious dog (WD2002/00077/00)	0, 4, 10 mg/kg (s.c.)	No overt pharmacodynamic effects at the doses tested over the 48 hour monitoring period. Delayed adverse effects (muscle wasting and polyuria) were believed to be the result of prolonged release of FF from the subcutaneous depot into the systemic circulation.

There were no safety concerns based on safety pharmacology studies. Changes in cardiovascular parameters were associated with the vehicle or have previously been associated with this class of compound in the rat, and therefore there is no cause for concern.

- Pharmacodynamic drug interactions

The applicant did not perform pharmacodynamic drug interaction studies because there are no known additive pharmacological interactions of glucocorticoid agonists such as FF. The glucocorticoid antagonists, having a theoretical potential of reducing agonist activity of FF, are not in clinical use. The justification was acceptable to CHMP.

Pharmacokinetics

Since much of an intranasal dose is swallowed, the oral route of drug administration was used as a surrogate for this part of the dose during non-clinical pharmacokinetic studies. The intravenous route of drug administration was used as a surrogate for material reaching the systemic circulation following absorption from the nasal cavity.

- Methods of analysis

Seven validated analytical methods were used in determining the pharmacokinetics of FF. These methods utilized liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). Methods were developed and validated in mouse plasma, rat plasma, rabbit plasma and dog plasma. The lower limit of quantification was 10 pg/ml (rabbit) or 20 pg/ml (other species) with upper limit being 100- to 200-fold higher. Radiolabelled metabolite profiles from in vitro samples and from extracts of samples obtained from mice, rats, dogs and humans were studied using HPLC with either on-line or off-line radiochemical detection. Studies to identify the metabolites of these samples were performed using ^{1}H-NMR, LC-MS and LC-MS/MS. Radio-chromatographic profiles in selected extracts of human plasma samples were obtained using accelerator mass spectrometric technique (AMS) for radio-determination due to the low levels of radioactivity present in these samples.

- Absorption

Animal studies demonstrated rapid absorption with limited bioavailability following oral administration. After intravenous administration there was a high exposure to drug related material at the later time points, indicating a high systemic exposure to circulating metabolites. The oral bioavailability of FF was higher in the bile duct-cannulised rat and dog (30% and 19% respectively) based on the recovery of total drug-related material in bile and urine, indicating extensive first pass metabolism.

The pharmacokinetic parameters obtained in non-clinical studies of FF (single dose) are presented in the following tables (table 3a and 3b):

Table 3a Tabulated absorption data of FF after oral and intravenous administration to rat and rabbit (Source: Module 4.2.2.2, Report WD2001/00769/00 and WD2001/01091/00).

Study ID	Species	N	Dose (mg/kg)	Route	Analysis	C_{max} (ng/ml)	T_{max} (h)	AUC (h·ng/ml)
WD2001/00769/00	Wistar Han rat,	3, ♂	0.11	oral	LC/MS/MS	0.0686	0.25	0.21
WD2001/00769/00	Wistar Han rat,	3, ♀	0.11	oral	LC/MS/MS	0.0774	0.25	0.08
WD2001/01091/00	New Zealand White rabbit	4, ♀	0.919	oral	HPLC/MRM	0.30 ± 0.52	0.25	0.08 ± 0.13
	New Zealand White rabbit	3, ♀	0.11	i.v.	HPLC/MRM	-	-	26.9

Table 3b Tabulated absorption data of FF after oral administration to dogs (Source: Module 4.2.2.2, Report WD2001/00850/00).

Pharmacokinetic Parameters of Radioactive Drug Related Material following oral administration						
Sex	Dose (mg/kg)		AUC_t (h*pg-eq./mL)	C_{max} (pg-eq./mL)	T_{max} (h)	$t_{½}$ (h)
Male	0.10	Mean	431000	2480	24-32	136
		SD	67600	245	NC	13.7
Female	0.11	Mean	407000	3020	8-32	166
		SD	79200	366	NC	11.5

n = 3 males and 3 females
AUC_t Calculated to 336 hours
NC Not calculated

The pharmacokinetic profile of FF after single intravenous administration was similar in all species tested with a high plasma clearance and large volume of distribution (see Table 4).

Table 4 Tabulated pharmacokinetic data of FF after intravenous administration to rat, rabbit, dog and human (Source: Module 2.4).

	Rat	Rabbit	Dog	Human
Dose (mg/kg)	0.1	0.1	0.1	0.25 mg/subject
Plasma Clearance (mL/min/kg)	89	71	40	17
Volume of distribution at steady state (L/kg)	8.5	15.1	10.3	10
Terminal half-life (h)	2.9	4.6	11.1	13.6

Subcutaneous administration of FF to rat and dog showed significant prolongation of half-life (25 hours and 160 hours in rat and dog respectively), related to subcutaneous drug deposit.

Repeat dose pharmacokinetic data for FF were obtained from multiple dose studies performed in the mouse, rat, rabbit and dog after inhaled and intranasal administration. As the inhaled route of administration is less relevant to the proposed method of Avamys administration, these are considered as supportive data (showing low systemic absorption after inhaled administration. Multiple dose pharmacokinetics of FF using intranasal route of administration were obtained from a multiple dose (13 or 26 week, once or twice daily) toxicology study to assess nasal irritancy and systemic toxicity of FF in nasal suspension following administration to the dog. Results of the pharmacokinetic part of this study are presented in the table below:

Table 5 **Absorption data of FF after multiple intranasal administration to dogs** (Source: Module 4.2.3.2, Report WD2004/01625/00)

Dose	**Male**		**Female**	
(µg/animal)	1200 od	1200 bid	1200 od	1200 bid
$AUC_{(0-t)}$ (pg.h/mL)				
Week 4	49.3	353	182	603
Week 13	185	901	254	800
Week 26	289	1280	587	584
C_{max} (pg/mL)				
Week 4	30.4	93.9	103	151
Week 13	127	208	91.6	177
Week 26	62.0	270	151	135

The absorption phase of FF is documented sufficiently. The results of studies using the methods of administration close to the proposed mode of administration to humans (oral, inhaled, intranasal) indicate that FF has very low systemic bioavailability. The comparison of animal pharmacokinetic data obtained following administration of doses more than 10-fold higher than clinical with clinical pharmacokinetic data obtained after administration of FF as recommended for Avamys, suggests that the probability of occurrence of significant systemic absorption followed by systemic activity of intranasal FF at dosage of 110 µg/day is minimal.

- Distribution

FF was found to be highly protein bound in all species at > 98%, with no notable binding or retention in melanin containing tissues. Furthermore, FF has a high plasma clearance equivalent to or exceeding the hepatic blood flow in the species tested. This indicates, in conjunction with the high concentrations of circulating metabolites relative to parent compound, that FF is cleared extensively by metabolism, with a large volume of distribution and a high tissue uptake.
Data obtained from *in vivo* and *in vitro* distribution studies did not suggest any important risk connected with nasal use of FF related to its distribution characteristics.

- Metabolism

The overall metabolic profile of FF was considered essentially similar in all species tested. FF was determined to be primarily metabolised via the CYP3A4 enzyme. In all species tested the principal metabolism was the hydrolysis of the S-fluoromethyl carbothioate group to form GW694301X (M10). The metabolism of FF in human liver microsomes was almost completely inhibited by ketoconazole. Thus, a potent inhibitor of CYP3A4 such as ketoconazole could potentially increase the systemic exposure to FF. FF is not expected to interfere with the metabolism of other compounds via this route. FF was found to be a substrate of two membrane transporters including P-glycoprotein and OATP1B1, however it is not expected to interfere with transport of other compounds.

- Excretion

The rates and route of excretion of drug related material were similar in rats, dogs (and humans) following either intravenous or oral administration. Following i.v administration to male dogs (0.1mg/kg) and rats (1mg/kg), the primary route of excretion was via the faeces (81.1% (dog) and 86.4% (rat) of the dose). Urinary elimination was only a minor route of elimination (approx. 4% (dog) and 1.7% (rat)). Elimination was initially rapid with >85% recovered during the first 24 hours from the rat and 80% being recovered within the first 48 hours from the dog. Total radioactivity recovered was 86% (after 96 hours) and 91.2% (after 48 hours) of the administered dose from the dog and rat, respectively.

Studies in bile duct cannulated rats or dogs following single intravenous administration of FF indicated that the majority of the dose excreted in the faeces was secreted via the bile. In these animals, a small amount (< 5%) was excreted in the faeces indicating that there was some secretion directly into the gastro-intestinal tract (GIT).

Results following oral administration indicate that either FF was not absorbed from the GIT or absorbed and eliminated via the bile back into the GIT.

Following subcutaneous administration the majority was excreted within the first 72 hours post administration. This delay in excretion indicates formation of a depot with release of drug over a sustained period, which has been supported by pharmacokinetic data, where plasma levels are sustained over 168 hours. Furthermore, a considerable amount of drug related material was retained in the carcass (5-43%) up to 168 hours post-dose.

Irrespective of the route of administration there were no qualitative differences with respect to excretion between males and females, although there are possible slight quantitative differences.

Toxicology

A summary of the main toxicology studies is outlined in table 6; in addition, references were made to published literature.

Table 6 Overview of Toxicology studies

Study Type and Duration	Route of Administration	Species
Single	Oral, Intravenous and Inhalation	Mouse and Rat
Repeat Dose		
1 month	Inhalation	Rat and Dog
3 months	Inhalation	Mouse, rat and dog
6 months	Inhalation	Rat
9 months	Inhalation	Dog
2 weeks	Intranasal	Rat
1 month	Intranasal	Dog
6 months	intranasal	Dog
Genetic Testing	In Vitro	NA
	Intravenous	Rat
Carcinogenicity	Inhalation	Mouse and Rat
Reproductive		
Male fertility and early embryonic development	Inhalation	Rat
Female fertility and embryofoetal development	Inhalation	Rat
Embryofoetal development	Inhalation	Rat and Rabbit
Pre- Post-natal development	Inhalation	Rat
Local Tolerance		
Dermal irritancy	Topical	Rabbit
Ocular Irritancy	Topical	Rabbit
Other Toxicity		
Respiratory hypersensitivity	Inhalation	Guinea Pig

- Single dose toxicity

Single dose toxicity studies were performed in mice, rats and dogs. FF was administered by oral, intravenous and inhalation route.
The results of single dose studies in mice and rats (high doses of FF administered orally, intravenously or by inhalation, producing measurable systemic exposure) showed the effects typical for excess of glucocorticoids i.e. reduction of body weight and lymphoid depletion.

The table below shows a summary of single dose toxicity studies.

Table 7 Summary of single-dose toxicity studies

Study ID/GLP	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
WD2001/00582/00 GLP	Wistar Han rats (3/sex/group)	Dose Range Finding Study: 1000, 1500 and 2000 mg/kg (Gavage)		All doses: Body weight loss (Days 1 to 3); thereafter, body weight generally increased.
	Wistar Han rats (6/sex/group)	0, 2000 mg/kg (Gavage)	≥2000 mg/kg	A dose of 2000mg/kg was associated with body weight loss, changes in the stomach, glycogen vacuolation in the liver, apoptosis in the adrenals and lymphoid tissue (lymphoid depletion in the thymus, spleen and mesenteric lymph nodes). Full or partial recovery was seen in the stomach, liver and adrenals of animals killed on Day 15; however, there was only negligible or minimal resolution of the lymphoid changes.
WD2001/00583/00 GLP	Mouse (CD-1) (3/sex/group)	1000, 1500 and 2000 mg/kg (Gavage)		All doses: Body weight loss
	Mouse (CD-1) (3/sex/group)	0, 2000 mg/kg (Gavage)	≥2000 mg/kg	Lymphoid depletion in the thymus and spleen and a reduction in haematopoiesis in the spleen in animals killed on Day 3; these changes were not seen in animals killed on Day 15.
WD2001/00686/00 GLP	Mouse (CD-1) (3/sex/group)	0, 0, 30, 18 mg/kg (Intravenous)	18 mg/kg	Animals administered vehicle with or without GW685698X displayed irregular breathing, low posture, subdued behaviour and white areas around the injection site. On day 3 treatment related decreases in bodyweight were observed and remained until termination.
	Mouse (CD-1) (6-7/sex/group)	0, 18 mg/kg	Could not be determined as the results were considered to be influenced by the toxicity of the vehicle:10% (w/w) ethanol :90% (w/w) PEG400.	Irregular breathing, low posture, subdued behaviour, bruising and white areas. Treatment related decrease in bodyweight and weight gain. Treatment was associated with lymphoid depletion of the thymus (marked) and spleen in animals killed on Day 3; these changes were not observed in animals killed on Day 15. Administration was also associated with very slight adrenal cortical vacuolation and atrophy
WD2001/00936/00 GLP	Han Wistar Rat	Range Finding 0, 12, 18 mg/kg		Animals administered vehicle with or without GW685698X displayed jerky movements, low posture, rapid/irregular breathing and subdued behaviour. Decreased activity, loss of righting reflex and piloerection were also noted in animals receiving the highest dose of vehicle. Injection site reactions were also noted. Treatment related decreases in bodyweight and weight gain.

Table 7 Continued

Study ID/GLP	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
	Han Wistar Rat (6/group)	Males: 0, 12 mg/kg Females 0, 18 mg/kg	The determination of the MNLD may have been influenced by the toxicity of the vehicle	Treatment related decreases in body weight and weight gain was observed in all animals receiving GW685698X;. Lymphoid depletion (moderate/ very marked) was noted in the mesenteric lymph nodes, spleen and thymus of animals receiving GW685698X. in addition, minor treatment related changes were seen in the adrenals of both sexes (increased cortical vacuolation) and the liver of females (lipid vacuolation). Full or partial recovery was seen in animals killed on Day 15. Damage at the injection site, ranging up to moderate severity, was noted for animals receiving vehicle or GW685698X.. The vehicle used in this study (10% (w/w) ethanol : 90% (w/w) PEG400) resulted in very slight to moderate damage to the injection site in both treated and control animals and similar signs as observed in the range finding study.
WD2001/01017/00 GLP	CD-1 Mice (6/sex/group) Although particle size was larger than intended, systemic exposure to the test material was evident based on the observed findings.	Inhalation, nose only exposure. 0, 7.1 mg/kg	No deaths	Body weight losses were observed in both sexes, with slight body weight loss observed in treated males. Marked atrophy was observed in the thymus of all animals on day 3 and slight lymphoid atrophy of the spleen. Observed effects were reversible with only one animal showing slight signs of lymphoid atrophy in the spleen by day 15.
WD2001/01018/00 GLP	Han Wistar Rat (6/sex/group)	Inhalation, nose only exposure. 0, 4.4 mg/kg	No deaths	Marked transient weight loss from day1 -3 in all treated animals. Exposure to GW685698X caused a size reduction of the thymus with reddish discoloration of the thymus and the bronchial lymph nodes. Microscopic findings revealed atrophy and histocytosis of the thymus in all treated animals, as well as atrophy of the tracheobronchial lymph nodes. Findings in the lymph nodes were almost completely reversed by day 15.
WD2004/00866/00 GLP	Irritancy Study Sprague Dawley Rat	Oral: 0, 1.25 mg/kg: (vehicle) 100% propylene glycol		There were no signs of irritancy associated histopathological findings indicative of gastrointestinal tract irritation, approximately 48 hours after treatment.

- Repeat dose toxicity (with toxicokinetics)

In the repeat dose toxicity studies FF was administered by the inhaled route (mice, rats, dogs) and by the intranasal route (rats, dogs). The repeat dose studies are very important for the non-clinical safety assessment of intranasal FF taking into account its proposed long-term use.

The list of repeat dose studies performed with FF is given in tables below:

Table 8 Repeat dose toxicity studies of FF by the inhaled route (Source: Module 2.6.7.)

Species & Strain	Duration of Dosing	Doses (µg/kg)^{TD}	GLP	Report Number (Study Number)
Mouse (CD-1)	3 months	0, 7, 17, 70 [0, 7.3, 18.6, 76.9]^{AD}	Yes	WD2003/00100/00 (M23602)
Rat (Wistar Han)	4 Weeks	0, 6, 15, 64 [0, 6.9, 17.6, 71.7]^{AD}	Yes	WD2001/01019/00 (R23246)
Rat (Wistar Han)	1 month	0, 7.6, 19.2, 75.9 [0, 6.5, 19.5, 72.0]^{AD}	Yes	WD2002/00525/02 (R23525)
Rat (Wistar Han)	3 months	0, 3, 7, 17 [0, 4.3, 8.5, 24.3]^{AD}	Yes	WD2003/00099/00 (R23603)
Rat (Wistar Han)	6 months	0, 3, 7, 17 [0, 3.2, 8.3, 20.3]^{AD}	Yes	WD2003/01044/01 (R23653)*

Notes: AD = Estimated achieved dose
TD = Target dose

*: A GLP issue was reported on 21.05.2007 for study R23653

Table 9 Repeated dose toxicity studies of FF by the inhaled route (cont.) (Source: Module 2.6.7.)

Species & Strain	Method of Administration	Duration of Dosing	Doses (µg/kg)^{TD}	Report Number (Study Number)
Dog (Beagle)	Inhalation	1 month	0, 10, 30, 100 [0, 10.6, 30.6, 105]^{AD}	WD2001/01015/00 (D23245)
Dog (Beagle)	Inhalation	1 month	0, 10, 30, 100 [0, 9, 22, 74]^{AD}	WD2002/00981/00 (D23514)
Dog (Beagle)	Inhalation	3 months	0, 10, 30, 60 [0, 11.3, 33.0, 64.7]^{AD}	WD2003/00645/00 (D23588)
Dog (Beagle)	Inhalation	9 months	0, 10, 30, 60 [0, 13.3, 30.1, 59.6]^{AD}	WD2004/00523/01 (D24159)

Notes: AD = Estimated achieved dose
TD = Target dose

Table 10 **Repeated dose toxicity studies of FF after intranasal administration** (Source: Module 2.6.7.)

Species & Strain	Method of Administration	Duration of Dosing	Doses (µg/kg)[TD]	GLP Compliance	Testing Facility	Report Number (Study Number)	Location (Module)
Rat (Wistar Han)	Intranasal	2 Weeks	0, 80 µg once or twice daily	Yes	CTBR	WD2004/00128/01 (R24885)	m4.2.3.2
Dog (Beagle)	Intranasal	1 month	0, 400, 1200 µg/animal	Yes	COV	WD2002/01366/01 (D23901)	m4.2.3.2
Dog (Beagle)	Intranasal	6 months (3 month interim kill)	0, 1200, 2400 µg/animal	Yes	COV	WD2004/01625/00 (D25132)	m4.2.3.2

Further to the reporting by the applicant of a GLP non-compliance issue in study BVR157 (Toxicity study by inhalation administration to Wistar Han rats for 26 weeks – GSK report R23653) conducted at a contract research facility, a GLP inspection of the study facility was performed. The inspection focused on clinical chemistry data generated in the studies performed at this facility which had been submitted as part of the Avamys dossier. The inspection concluded that the corticosterone assays performed on week 26 samples from study R23653 were determined to be unreliable. An amended final report without these results was produced. All other specialised clinical chemistry assays performed within the 11 studies audited were considered reliable.

The battery of multiple dose inhalation and intranasal toxicological studies of FF administered to mice, rats and dogs revealed a range of findings class-specific to glucocorticoids. These findings were typically associated with systemic exposure to glucocorticoids and commonly reported for other marketed intranasal steroids.

Table 11 **Principal Toxicological Findings in Rats, Mice and Dogs following Inhalation Administration of Fluticasone Furoate**

Finding	Rat[a,b,c]		Mouse[b]		Dog[b,d]	
	Effect Dose	No Effect Dose	Effect Dose	No Effect Dose	Effect Dose	No Effect Dose
Reduced weight gain	3.2[c]	<3.2[c]	7.3	<7.3	13.3[d]	<13.3[d]
Increased weight gain	NE	20.3[c]	NE	76.9	30.3[d]	13.3[d]
Lymphocytopenia	3.2[c]	<3.2[c]	7.3	<7.3	13.3[d]	<13.3[d]
Reduced adrenal weight/cortical atrophy	<6.5[a]	<6.5[ae]	NE	76.9	13.3[d]	<13.3[d]
Decreased cellularity of lymphoid tissues	3.2[c]	<3.2[c]	7.3	<7.3	13.3[d]	<13.3[d]
Hypocellularity/prominent adipocytes in bone marrow	8.3[c]	3.2[c]	NE	76.9	13.3[d]	<13.3[d]
Reduced plasma cortisol	NM	NM	NM	NM	13.3[d]	<13.3[d]
Increased liver weight	NE	20.3[c]	18.6	7.3	11.3[b]	<11.3[b]
Increased hepatic glycogen	NE	20.3[c]	NE	76.9	13.3[d]	<13.3[d]

Key:
Doses in terms of µg/kg/day; NM = Not measured; NE = No effect
a = Based on 1 month studies b = Based on 3 month study c = Based on 6 month study
d = Based on 9 month study e = No effect at 20.3 µg/kg/day in the 6 month study.

Both local and systemic effects observed after intranasal administration were related to the estimated maximum nasal doses greatly exceeding the dose in humans occurring after intranasal dosage

proposed for Avamys. They were 28-, 10- and 20-fold higher in rats (one study) and in dogs (two studies) respectively. Local effects observed in the long-term intranasal studies (confined to minimal goblet cell hyperplasia and hypertrophy of the epithelium) indicate an acceptable level of safety.

Testicular findings in the dog (tubular vacuolation) observed following 28-day intranasal exposure were considered not to be significant in light of the lack of clear treatment related findings together wit negligible clinical exposure.

Toxicokinetic analysis of parameters obtained during toxicity studies suggests that the risk of the occurrence of significant systemic effects related to glucocorticosteroid activity of FF is unlikely because of negligible systemic exposure to FF after intranasal use in doses proposed for Avamys.

The lack of a comparative analysis of toxicological profiles of FF and FP was raised as a CHMP concern in the Day 120 List of Questions (LOQ). In their response the applicant submitted a general comparative review of toxicology findings observed in non-clinical studies of FP and FF, which indicated that both compounds have similar effects, typical of corticosteroids.

- Genotoxicity

The results of submitted *in vivo* and *in vitro* genotoxicity tests did not reveal any significant risk carried by FF. The lack of genotoxicity of FF was verified positively in carcinogenicity studies. Nevertheless, an additional micronucleus study was conducted at high intravenous doses (up to 40 mg/kg) on request of the FDA. The results of the study were submitted together with the Day121 responses "WD2006/02023/00. GW68569X: Additional Rat Bone Marrow Micronucleus Assay in Rats (GSK Study R26808)". At all doses tested a small reduction in group mean %PCE (polychromatic erythrocytes) was observed. As all values were within the historical control range it was not considered to be of any biological significance. FF did not induce micronuclei in rats in a valid in vivo bone marrow micronucleus assay, after two intravenous doses of 10, 20 or 40 mg/kg/day, given approximately 24 hours apart.
On the basis of the data submitted, there is no risk of genotoxicity/mutagenicity of FF even if administered at dosages producing very high systemic exposure, impossible to obtain in clinical practice after proposed intranasal administration.

- Carcinogenicity

Carcinogenicity was studied in mice and rats following intranasal administration for 2 years (Table 12). There was no evidence of treatment-related increases in tumour incidence following lifetime administration of FF by the inhalation route. Although the incidence of bronchioloalveolar tumours was increased in intermediate dose male mice, it was similar to the historical background incidence levels for CD-1 mice, and there was no increase at the highest dose administered.

Table 12 Carcinogenicity studies

Species & Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)[TD]	GLP Compliance	Report Number (Study Number)
Mouse	Inhalation	2 years	0, 2, 6, 18 [0, 2.2, 6.1, 18.8][AD]	Yes	WD2005/00894/01 (M24141)
Rat	Inhalation	2 years	0, 1, 3, 9 [0, 1.0, 3.2, 8.6][AD]	Yes	WD2005/00895/02 (R24142)

- Reproduction Toxicity

Reproduction and developmental toxicity studies showed no abnormalities in foetus and no hazard for pregnancy at lower doses. Typical class effects of corticosteroids were observed in juvenile dogs.

A list of FF reproduction studies (Source: Module 2.6.7) is given in the table below:

Table 13 Toxicology (Reproduction studies)

Type of Study	Species & Strain	Method of Administration	Duration of Dosing	Doses (µg/kg/day)[TD]	GLP Compliant	Report Number (Study Number)
Male fertility & early embryonic development	Rat (Wistar Han)	Inhalation	28 days prior to pairing, during pairing & until necropsy	0, 5, 12, 24 [0, 6.6, 12.9, 29.4][AD]	Yes	WD2003/01271/00 (R24208)
Fertility & Embryofoetal development	Rat (Wistar Han)	Inhalation	2 Weeks prior to mating & up to Day 17 of pregnancy	0, 6, 16, 64 [0, 11, 23, 91][AD]	Yes	WD2002/01055/00 (R23393)
Embryofoetal development	Rabbit (New Zealand White)	Inhalation	Day 8 to 20 post coitum	0, 10, 50, 100 [0, 9.7, 46.6, 85.1][AD]	No	WD2001/01016/00 (L23306)
Embryofoetal development	Rabbit (New Zealand White)	Inhalation	Day 8 to 20 post coitum	0, 1, 3, 10 [0, 1.8, 3.2, 8.1][AD]	Yes	WD2002/00882/00 (L23338)
Pre- & Post-natal development	Rat (Wistar Han)	Inhalation	Days 6 to 20 post coitum & Days 2 to 21 of post partum	0, 5, 12, 24 [0, 5.5, 15.7, 27.2][AD]	Yes	WD2003/01783/00 (R24209)

Notes: AD = Estimated achieved dose
TD = Target dose

- Local tolerance

A formulation irritancy study was performed in dogs (Beagle) in order to check irritancy potential of two different formulations (containing Triton X-100 (5% w/w) versus Tyloxapol (5% w/w)). The Triton X-100 formulation was not tolerated and caused nasal irritancy, whereas there were no treatment related findings with the Tyloxapol formulation. Neither formulation was selected for development.

Evaluation of local tolerance demonstrated practically no irritancy to the skin and eyes of rabbits.
A study in rabbit to evaluate the potential ocular irritancy of the intranasal clinical formulation of FF (0.05% w/w aqueous suspension) showed that there is a very low potential for ocular irritancy. A volume administered during the study was equivalent to double spray volume per actuation of the clinical dosage device.
Dermal irritancy was evaluated in 2 studies in rabbits. The substance was administered in solid form (0.5 mg for 4 hours) and as 2 µg/mL solution in ethanol (0.5 ml for16 hours). The observations were continued up to 72 hours after removal of the dressing. No erythema or oedema symptoms were noted.

- Immunotoxicity

Inhalation tolerability and immunological sensitisation was investigated in the guinea pig (5 daily doses followed by single inhalation challenge exposure 17 days later). No hypersensitivity reaction was noted.

Ecotoxicity/environmental risk assessment

The regulatory and scientific strategy of ERA chosen by the applicant is reasonable and the scope of studies (Phase I and Phase II, Tier 1) acceptable.

Discussion on the non-clinical aspects

The dossier submitted, containing applicant's data supported by literature references, indicates that the pharmacological profile of FF is well defined. Its mode of action is typical for corticosteroids.
The results of in vitro pharmacodynamic studies indicate that FF exhibits anti-inflammatory activity which is class specific for glucocorticoids used in anti-inflammatory therapy. The in vitro potency of FF in term of receptor affinity, receptor selectivity and anti-inflammatory activity is at least equal or higher than that of previously approved glucocorticoids in AR therapy, such as FP and MF. The activity of the primary metabolite of FF (GW694301X) is much lower than FF.
Results of in vitro onset and duration of action studies and in vitro tissue binding studies indicate that FF has clinical potential in respect of very rapid GR activation (maximum effect observed after 20 minutes) and long duration of action (until 30 hours). This characteristic has a positive impact on the reduction of systemic exposure to FF.
The in vivo studies support the opinion that the in vitro profile of FF is group-specific. These studies demonstrate that it is an effective, high affinity anti-inflammatory agent in a number of distinct animal models of inflammation.
CHMP considered the lack of comparative analysis with FP in the majority of in vitro pharmacology studies as a weak side of this part of the dossier. This concern was resolved by submission of additional (indirect) comparative review data with FP (as response to the Day 120 LOQ), showing similar toxicology profiles.

The results of safety pharmacology studies indicate no significant effects of FF other than corticosteroid-specific. These effects were observed only when the route of administration and dose administered produced systemic exposure definitely higher in comparison to exposure obtained after intranasal administration in humans as proposed for Avamys.

The pharmacokinetic profile of FF was adequately examined. Generally speaking, its pharmacokinetic profile is similar between animal species tested and humans. The dog is a species with the highest similarity to humans in term of FF pharmacokinetics.

The pharmacokinetic behaviour of FF absorbed systemically after intranasal administration is similar to oral and intravenous administration. The oral route of administration used in non-clinical studies may be acknowledged as partially simulating the intranasal route.
Subcutaneous administration of FF is connected with "depot effects" (subcutaneous depot of drug which is released gradually).
The most important pharmacokinetic data from studies performed in dogs following intranasal administration indicate that systemic bioavailability of FF after intranasal administration is minimal (less than 1%). In addition, there is the first pass effect accompanied by an effective biotransformation to inactive metabolite and rapid elimination.
There is no real risk of FF accumulation after intranasal administration at the dose as proposed for Avamys.

Based on the very small systemic availability of FF (administered intranasally) the risk related to its systemic toxicity in proposed clinical dosage is low. Thus, the burden of toxicological assessment concentrated mainly on the local toxicity to the tissues being in direct contact with the product at the site of administration.

The toxicology profile of the product is well documented. The comparative toxicokinetic data confirmed that intranasal administration of FF in doses proposed for Avamys produces no measurable systemic exposure to FF and that occurrence of systemic glucocorticoid activity after Avamys administration is unlikely.

4. Clinical aspects

Introduction

The clinical dossier includes 22 pharmacology and 12 phase II/III original studies. The applicant states that phase II/III clinical trials were designed in accordance with FDA draft guideline "Allergic rhinitis: Clinical Development Programs for Drug Products" (FDA- 2000) and the CHMP Guideline on the Clinical Development of Medicinal Products for the treatment of Allergic Rhinoconjunctivitis (CHMP 2004).
The Scientific Advice received from CHMP in July 2004 concerned the following issues:

- Duration of the SAR/PAR clinical development program in adult, adolescent and paediatric populations;
- Inclusion of active control arm in SAR/PAR studies in addition to vehicle placebo control;
- Total nasal symptoms score alone as an appropriate primary efficacy endpoint for the SAR/PAR populations;
- Adequacy of safety and efficacy data in the proposed clinical program for registration for the indications SAR and PAR in adults, adolescents and the paediatric population;
- Benzalkonium chloride - preservative in formulation.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.
The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

This product for intranasal topical use is intended for local delivery of fluticasone furoate. The main aim of PK studies is the extent of systemic absorption (as per the Note for Guidance on pharmacokinetics) in targeted populations for safety reasons.
The applicant presented 22 clinical pharmacology studies in support of the MAA (table 14). Eight of those were conducted with claimed formulation and route of administration (intranasal).

Table 14 Overview of Completed Clinical Pharmacology Studies by Route and population

	Route					Subjects	
Study	**IN**	**IH**	**O (S)**	**CS**	**IV**	**Type**	**Dosed/ Completed**
FFR10001	X					Healthy, dose escalation study 50,100,200,400,800mcg PK/PD	24 /21
FFR10002 [1]	X					Healthy dose escalation study 5,10,20,40,80mcg PK/PD	24 /23
FFR10003 [2]	X					Healthy, 7 days repeated doses 50,100,200,400,800mcg PK/PD	24 /22
FFR10005	X					Healthy Japanese, single and 7 days repeated doses 100,200,400mcg, PK	12 /11
FFR10006	X					Healthy, fluticasone furoate (400mcg) and propionate (400mg) effect on nuclear translocation of the glucocorticoid receptor using biopsy	20 /20
FFR10007	X					Allergic Rhinitis was discontinued for technical reasons	59 /55
FFR10008			X		X	Healthy	5 /5
FFR10010	X				X	Healthy, absolute bioavailability	16 /16
FFR10013	X					Healthy, effect of 110mcg dose /7days with ketoconazole on serum cortisol level	20 /20
FFA10001		X				Healthy	20 /19
FFA10002		X				Healthy	36 /35
FFA10003		X			X	Healthy	24 /23
FFA10004				X		Healthy	24 /24
FFA10007 [3, 4]		X				Asthmatic	6 /0
FFA10008 [3]		X			X	Healthy	15 /15
FFA10009		X				Healthy	24 /24
FFA10013		X				Moderate hepatic impairment & Healthy	10 /10 10 /10
FFA10022		X				Asthmatic	40 /38
FFA10026 [3]		X				Asthmatic	24 /18
FFA10027 [3]		X				Asthmatic	24 /18
FFA10028		X				Asthmatic	28 /27
FFA103096		X				Healthy	44 /40
Route: IN Intranasal (Nasally Inhaled) IH Orally Inhaled O (S) Oral (Swallowed) CS Cutaneous IV Intravenous All of the nasal inhalation studies used a suspension formulation except for 1. FFR10002 (solution) 2. FFR10003 (microfluidised suspension). 3. These studies did not provide relevant pharmacokinetic, pharmacodynamic or safety data for consideration of this intranasal product. 4. Study FFA10007 was discontinued for technical reasons.						Total	533 /494 (92.7%)

Additionally the sponsor presented PK data from the following studies:

Table 15 Additional PK studies

Study No.	Phase	Study Type	Doses	No. of Subjects[a]	Treatment Duration
Adult and Adolescent Studies					
FFR20001	2b	SAR Dose ranging	55mcg QD 110mcg QD 220mcg QD 440mcg QD Placebo	127 127 129 130 128	2 weeks
FFR102123	3	PAR – long term safety, PK	110mcg QD placebo	605 201	52 weeks
FFR 20002	3	PAR/HPA axis safety, PK	110mcg QD Placebo Placebo/prednisone	48 51 13	6 weeks
Paediatric studies					
FFR100012 paediatric subjects 2 to <12 years of age	3	PAR/HPA axis safety PK	110mcg QD placebo	57 55	6 weeks
FFR101747b paediatric 6-11 years of age	3	SAR and/ or PAR knemometry Safety,	110mcg QD placebo	58	2 weeks
FFR 30008 paediatric subjects 2-12 years of age	3	PAR PK	55mcg QD 110mcg QD placebo	185 185 188	12 weeks

The method used for analysis of plasma samples collected for pharmacokinetic profiling of fluticasone furoate during the clinical development programme involved solid phase extraction and high pressure liquid chromatography with tandem mass spectrometric detection (SPE- HPLC-MS/MS). The method has been validated and demonstrates reliable and reproducible quantisation of fluticasone furoate.

Pharmacokinetic data analysis was performed on the basis of all 22 phase I studies and additionally the phase IIb study and five phase III (2 adult and 3 children) studies providing pharmacokinetic data. The analysis could have been more transparent if the applicant had restricted to those studies involving the claimed formulation and route of administration.

The statistical methods were adequate.

- Absorption and distribution

– Bioavailability

Study FFR 10001 examined the pharmacokinetics, pharmacodynamics, and tolerability of single and multiple intranasal doses of FF. Twelve healthy male volunteers received single doses of 50, 100, 200 µg FF (cohort A) and twelve received doses of 200, 400, 800 µg FF (cohort B). The multiple dosing part of the study consisted of seven daily doses at the 200 µg and 800 µg level for cohorts A and B respectively.
FF levels were undetectable in most volunteers at most time points and only at the highest single dose was it possible to estimate Cmax. No other pharmacokinetic parameters could be established for any dose either single or multiple. The 24 hour time-course for serum cortisol for 7 day treatments for placebo, 200 µg, 800 µg were overlapping.

Table 16 Pharmacokinetics parameters of FF intranasal single & multiple dose (median and range)

	50 – 400 µg	800 µg
AUC (0→t) pg.h/ml	BLQ*	BLQ
Cmax pg/ml	BLQ	11.7 (BLQ, 26.2)

*BLQ: below limit of quantisation

Study FFR 10002 examined the pharmacokinetics, pharmacodynamics, and tolerability of single increasing intranasal doses of FF administered as a solution formulation. It was conducted at a single UK centre between August and October 2002. Twenty-four healthy male volunteers received single doses of 5, 10, 20, 40, 80 µg FF with a five-day washout between dose escalations. Many individuals and time points showed no quantifiable drug levels; derived pharmacokinetic data for the 80 µg dose are shown in Table 17. There was no dose response relationship with respect to plasma cortisol levels.

Table 17 Pharmacokinetic parameters of FF intranasal single dose 80 µg (median and range)

AUC (0→t) pg.h/ml	145 (6.8 – 403.5)
Cmax pg/ml	81.9 (22.8 – 285.0)

Upon request from CHMP (Day 120), the applicant provided clarification regarding the higher bioavailability observed in study FFR 10002 compared to FFR 10001; this was ascribed to use of an experimental solution formulation with poorly water soluble drug in FFR10002; no further development work was conducted with this formulation.

Study FFR10010 aimed to establish the absolute bioavailability of a single intranasal dose of FF. Sixteen healthy volunteers participated (8 male and 8 female). Subjects received intranasal FF 880 µg, 8-hourly for a total of 10 doses, and a single intravenous dose of FF 250 µg. The absolute bioavailability of FF was 0.50% (90% CI 0.34 – 0.74). The derived pharmacokinetic parameters are shown in Table 18.

Table 18 Pharmacokinetic parameters of FF. Data are geometric mean and 90% CI.

	880 µg intranasal	250 µg intravenous
AUC (0→t) pg.h/ml	74.9 (43.6 – 128.6)	3787 (3479– 4124)
Cmax pg/ml	20.5 (16.0 – 26.3)	6652 (5803 – 7625)
$t_{1/2}$ (h)	NA	10.6 (7.7 – 14.5)

– Bioequivalence

Although different formulations are mentioned in the data submitted, only one has persisted beyond very early clinical trials. All the development work has been done with the same formulation. Therefore, bioequivalence studies are not necessary.

- Elimination

– Excretion

Study FFR10008 was a mass balance evaluation of the elimination of FF. Five healthy male volunteers received single doses of 2,000 µg [^{14}C]-FF orally, and 250 µg [^{14}C]-FF intravenously, separated by a washout of 28 days. Blood, urine and faeces were collected for 168 hours or until 90% of the radioactivity had been recovered. Following oral administration 101% of radioactivity was recovered in faeces by 168 hours. Following intravenous administration 90% of radioactivity was recovered in faeces by 264 hours.

Urinary excretion accounted for approximately 1% and 2.6% of the administered dose following oral and i.v. administration respectively.

FF was quantifiable up to 48 hours post intravenous dosing; but only up to 9 hours post oral dosing. The metabolite GW694301X was quantifiable up to 3 hours following oral dosing and was not quantifiable after intravenous dosing.
The bioavailability of FF from the oral solution was 1.26% (95% CI 0.463 - 3.418).

Following i.v. dosing, the clearance of FF was 57.45 L/h (95% CI 45.51 - 72.52) which is similar to liver blood flow (49 L/h) and the volume of distribution was 608.4 L (95% CI 375.4 - 985.8).
The terminal phase elimination half-life of FF following intravenous dosing was 15.12 h (95% CI: 11.82 - 19.35h). *In vitro* plasma protein binding was >99%.

– Metabolism

Study report WD2005/01496/00 describes the characterisation of the major metabolites of FF following a single injection in healthy male volunteers (Study FFR10008). Due to the low levels of radioactive drug-related material in plasma and excreta accelerator mass spectrometry (AMS) was required as the detector to obtain metabolite profiles in plasma. Assignments of metabolites relied extensively on co-chromatography with reference standards.

Following intravenous administration to healthy male subjects, the principal radiolabelled component in plasma was unchanged FF. Following oral administration there were two notable radiolabelled components in plasma: the 17-β-carboxylic acid of FF (GW694301X also called M10) and parent compound. There was no other component representing more than 5% of total plasma radioactivity.

Elimination of FF was largely by metabolism via the faeces with hydrolysis of the thioester moiety to GW694301X (M10) as the predominant route. The only other route of metabolism involved defluorination and hydroxylation. Unchanged FF was a minor component in faecal samples from all subjects by either dosage route.

Following oral and intravenous dosing approximately 30% of the administered dose of drug related material was identified; the remainder was not identifiable due to low levels precluding useful mass spectrometric data. Urinary excretion of drug-related material was minor (<3%) and therefore was not investigated further.

- Dose proportionality and time dependencies

Given the very low plasma drug levels following intranasal administration it is difficult to reach any meaningful conclusion on dose proportionality. Following dosage by the inhalational route there is evidence of approximate dose proportionality.

- Special populations

– Hepatic impairment

Study FFA10013 was an evaluation of the pharmacokinetics and pharmacodynamics of FF in subjects with moderate hepatic impairment (Child-Pugh-B 7-9) (n = 10) and in healthy subjects (n = 10) following a single inhaled dose of 400 μg FF. Patients were matched with controls for gender, age, and lean body mass. The derived indices of absorption and excretion are in Table 19.

Table 19 Pharmacokinetics parameters of FF data are mean and 95% CI.

	Healthy	Hepatic impairment
AUC (0→∞) (pg.h/ml)	337 (84, 590)	1142 (473, 1811)
Cmax (pg/ml)	40.6 (28.5, 52.7)	61.9 (40.7, 83.1)
Tmax (h)	0.51 (0.27, 0.75)	4.4 (1.7, 7.1)
t1/2 (h)	11.5 (5.7, 17.3)	25.6 (10.1, 41.1)
CL/F (L/hr)	794 (416, 1172)	228 (80, 376)
Baseline mean cortisol (mg.dL)	9.07 (7.30, 10.83)	8.96 (6.43, 11.69)
Treatment mean cortisol (mg.dL)	8.30 (7.02, 9.58)	6.60 (4.36, 8.85)

No studies have been performed in patients with impaired renal function because there is negligible renal elimination of FF.

– Pharmacokinetics in target population

The pharmacokinetics in adults and adolescents is sufficiently documented in phase I studies. The analysis of PK data from paediatric studies is not clear. CHMP requested clarification from the applicant: presentation of PK data from paediatric studies in 2 groups, i.e. children between 12 and 6 years of age and children between 6 and 2 years of age. The applicant's response presented robust data for the population above 6 years; data for the 2 to 5 year olds are very limited.

- Pharmacokinetic interaction studies

In vitro

Report FD2003/00126/00 describes the effect of FF on the metabolism of specific substrates for cytochrome P450 (CYP450) enzymes in a pooled human hepatic microsome system. Positive controls were used for all tests. FF inhibited the activity of CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6, but not CYP1A2, CYP2A6 and CYP2E1. The most potent inhibition was observed on CYP2C8 and CYP3A4 (IC50 ≤ 0.8 μg/ml); for the other enzymes the IC50 was ≤ 5.4 μg/ml. There was no potential as a time and NADPH dependent inhibitor of any of the cytochrome P450 enzymes investigated.

Report WD2005/00543/00 describes the effects of the FF metabolite GW694301X on the CYP450 enzymes in a pooled human hepatic microsome system. There was no direct or metabolism-based inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4.

Report WD2005/00763/00 showed that FF and GW694301X inhibit the human organic ion transporter OATP1B1, heterogeneously expressed in the CHO cell line (Chinese Hamster Ovary), with calculated IC_{50} values of 0.11 μg/ml and 1.4 μg/ml respectively.

Report FD2005/00368/00 was an investigation of the effects of FF and GW694301X on the transport of digoxin by MDCKII cells which express the human efflux transporter P-glycoprotein. There was no inhibition of drug transport by FF or GW694301X up to concentrations of 30 μM and 100 μM respectively.

In vivo

Study FFR10013 was an evaluation of the potential for an interaction between the potent CYP3A4 inhibitor, ketoconazole, and FF. The study was a 7-day, double blind, placebo controlled, two-way crossover evaluation of the effect of co-administration of ketoconazole 200 mg daily and FF 110 μg daily administered by nasal spray. Twenty-four hour serum cortisol weighted mean on Day 7 was the variable of primary interest. Twenty healthy male volunteers completed the study.

For the majority of subjects drug levels of FF were below the limit of quantification at most time points. Drug levels were detectable in one subject on FF/placebo and in six subjects on FF/ketoconazole. Data for twenty-four hour serum cortisol weighted mean are shown in Table 20.

Table 20 Derived mean (s.d.) 24-hour serum cortisol (nmol/L)

	Baseline	Study end
FF + placebo	201.48 (43.04)	157.48 (38.17)
FF + ketoconazole	203.76 (37.59)	149.56 (32.26)

In the Day 120 LOQ, CHMP requested additional information from the applicant regarding the possible consequences of concomitant use of moderate and potent CYP3A4 inhibitors from a safety perspective, and asked the applicant to submit revised proposals for relevant parts of the SPC. In their response the applicant stated that although inhibition of the metabolism of FF by inhibitors of CYP3A4 increases systemic exposure, levels observed are unlikely to result in any adverse systemic effects and therefore proposed no change to SPC section 4.5. As CHMP maintained their concern, the applicant proposed to re-arrange the text in SPC section 4.5 and included additional text specifically highlighting to the prescriber to be aware of the potential for systemic effects to occur during concomitant administration with potent inhibitors of CYP3A4, thus conferring a greater prominence to this information.

Pharmacodynamics

- Mechanism of action

While the exact pharmacological mechanism of intranasal corticosteroids is not clear, these medications are known to reduce vascular permeability and oedema of the nasal mucosa through inhibitory effects on inflammatory cells and mediator activity. As steroids diffuse across the cell membrane they bind to specific intracellular receptors, forming a complex that is then transported into the nucleus, where it binds to glucocorticoid response elements. As a result transcription of glucocorticoid response element associated genes is either down-regulated or up-regulated. This leads to a reduction of the nasal mucosa inflammatory cells and their associated cytokines.

- Primary pharmacology

Report SH2005/00036/00 describes the *in vitro* binding of FF, fluticasone propionate (FP) and other commonly used corticosteroids to the human glucocorticoid receptor (GR) and inhibition of the NFκB pathway. The principal results are shown in Table 5.

Table 21 Principal pharmacodynamic results of Report SH2005/00036/00 (data are mean and s.d.)

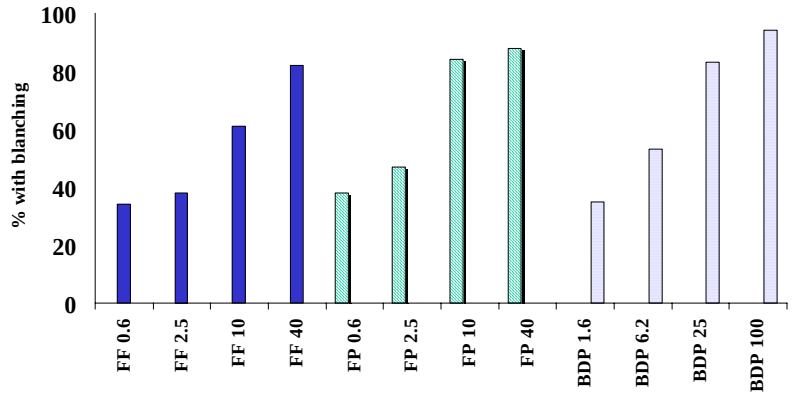
	FF	FP	MF	GW694301X (metabolite)	DEX
Relative GR receptor affinity compared to dexamethasone	2989 ± 135	1775 ± 130	NA	NA	100 ± 5
pEC50 NFκB inhibition	10.6 ±0.04	10.5 ±	10.6 ± 0.03	6.53 (n = 2)	
Drug association with 16HBE14 monolayer 2 – 4 hours	~ 28%	~ 15 %	NA	NA	NA
Drug association with lung homogenate 15 – 60 minutes (ng/mg)	~ 3	~ 3.5	NA	NA	NA

MF = mometasone furoate DEX = dexamethasone

Study FFA10004 examined the skin-blanching response of healthy volunteers (n = 24) to various steroids. Subjects received FF (0.6, 2.5, 10 and 40 ng), FP (0.6, 2.5, 10 and 40 ng), and beclomethasone diproprionate (BDP 1.6, 6.2, 25 and 100 ng) dissolved in ethanol applied to the skin of the forearm under an occlusive dressing and in double blind format. The primary endpoint was the

incidence of blanching (i.e., present or absent) at each dose level at 2 hours. The data for the primary variable are shown graphically in Figure 1.

Figure 1 Study 10004 proportion of subjects with skin blanching according to treatment. Numbers are the dose in ng. (



BDP = beclomethasone. (data from study report; rapporteurs` graphic)

Study FFR101816 was a double blind, placebo-controlled, single-dose, evaluation of the onset of action of FF 110 µg in adolescent and adult patients with seasonal allergic rhinitis and a history of ragweed pollen sensitivity. They received a single dose of placebo or FF 110 µg and had a twelve hour allergen exposure in an allergen chamber. The variables of interest were changing from baseline in total nasal symptom score (NTSS) and the speed of onset of action of FF. The study was powered on the assumption that the standard deviation in change from baseline of NTSS and the sample size 380 patients gave 90% power to detect a treatment difference of 0.75 NTSS with $\alpha = 0.05$. The result for the primary efficacy variable is shown in Table 22.

Table 22 Change in NTSS by time and treatment (treatment differences were not statistically different p ~ 0.4 at most time points)

	Placebo (n = 191)	FF 100 µg (n = 191)
Baseline	8.8 (0.11)	8.8 (0.11)
4 hours	5.7 (0.20)	5.5 (0.22)
12 hours	4.9 (0.23)	4.7 (0.22)

- Secondary pharmacology

Study FFA103096 was a 5-way crossover trial in 44 healthy men and women. Each treatment period consisted of eight days, during which the subjects received inhaled FF once daily, fluticasone propionate (FP) twice daily or placebo on Days 1–7, with a 24 h urine and serum cortisol profile on Day 7. The primary objective was to estimate the dose of FF that had an equivalent effect on twenty-four serum cortisol excretion as FP 1000 µg daily. Treatments consisted of placebo, FF 100, 200, 400, 800, 1600 µg, FP 250, 500, 1000 µg. All treatments were delivered by dry powder inhaler. A predicted dose of FF of approximately 650µg QD from the dry powder inhaler was found to be equivalent in effect on 0-24h serum cortisol to FP dry powder inhaler 500 µg twice daily.

Clinical efficacy

Details of studies on dose-ranging, clinical efficacy and safety are shown in the table below:

Table 23 Studies on clinical efficacy and safety

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
FFR20001	8 (USA) Texas	Double blind placebo controlled, parallel group	Placebo 55 mcg 110 mcg 220 mcg 440 mcg	Dose ranging, safety, efficacy	118 per arm 642 randomized 1 did not receive treatment	5 – 21 day screening period 2 week study	M – 421 F – 220 Age mean (SD) 39,3 (13,8) Range 12 - 80	Seasonal allergic rhinitis cedar mountain pollen	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS).
FFR30003	7 (USA) Texas	Double blind randomized Parallel group Placebo controlled	110 mcg placebo	Comparison of efficacy and safety	Total 303 randomized, 302 received treatment 152 active 150 placebo	5 – 21 day screening period 2 week study	M 111 F 191 Age mean (SD) 37,6 (13,74) range 12-75	Seasonal allergic rhinitis cedar mountain pollen	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS).
FFR103184	23 (Europe) EST (3) Latvia (4) Lithuania (4) NL (6) RUS (3) S (3)	Double blind randomized Parallel group Placebo controlled	110 mcg placebo	Comparison of efficacy and safety	285 randomized, Active 141, Placebo 144	2 week	M 151 F 134 Age mean (SD) 30,1 (11,32) range 12-65	Seasonal allergic rhinitis grass pollen	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS).
FFR104861	17 (USA)	Double blind randomized Parallel group Placebo controlled	110 mcg placebo	Comparison of efficacy and safety	299 randomized Active 151 placebo 148	5 – 21 day screening period 2 week study	M 119 F 180 Mean age (SD) 35,0 (13,95) Range 12-74	Seasonal allergic rhinitis Ragweed pollen	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS).

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
FFR30002	47 (USA 42), (Canada 5)	Double blind randomized Parallel group Placebo controlled	110 mcg placebo	Comparison of efficacy and safety	302 randomized 149 FF100 153 placebo	7 – 14 day screening period 4 week study	M 113 F 189 Mean age (SD) 36,7 (14,89) Range 12-76	Perennial allergic rhinitis animal dender, house dust mites, cockroach, mould	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS).
FFR102123	75 centres, Australia (5), Chile (2), Estonia (5), Germany (13), Italy (5), Latvia (5), Lithuania (5), Netherlands (7), New Zealand (3), Romania (4), Russia (10), Spain (7), Sweden (4)	Double blind randomized Parallel group Placebo controlled	110 mcg, placebo	Assessment of safety and tolerability	806 randomized, placebo 201, FF100 605	7 – 14 day screening period, 52 week study	M 393 F 413 Mean age (SD) 32,4 (14,38) Range 12-77	Perennial allergic rhinitis animal dender, house dust mites, cockroach, mould	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS). Safety endpoints
FFR20002	2 (USA 1) (Canada 1)	Randomized, double blind, parallel group, placebo and active controlled	110 mcg, placebo placebo/ prednisone	HPA axis safety	Placebo 51 Active 48 Placebo/ prednisone 13	7 – 14 day screening 6 week, 5 – 7 days post treatment	M 53 F 59 Mean age (SD) 36,3 (12,79) Range 12-62	PAR	Pharmaco-dynamic assessment from baseline in 24 hour serum cortisol weighted mean
FFR101816	1 (USA)	Randomized, double blind, parallel group, placebo	110 mcg placebo	Evaluation of action onset 100 mcg versus placebo in allergen challenge chamber exposition to Ragweed allergen	Randomized 382 Active 191 placebo 191	Single dose	M 115 F 267 Mean age (SD) 33,4 (12,5) Range 12-64	SAR Ragweed pollen	The primary efficacy endpoint was the mean change from baseline in subject rated iTNSS (instantaneous total nasal symptom scores) during 12 hour post dose exposure period in the allergen challenge chamber

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
FFR100010	57 (USA)	Randomized, double blind, parallel group, placebo	55 mcg 110 mcg placebo	Safety and efficacy	554 randomized FF50 184 FF100 184 placebo 186	2 week	M 323 F 231 Mean age (SD) 8,1 (2,5) Range 2-12	SAR Ragweed pollen	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS)
FFR30008	61 USA (39) Argentina (5), Italy (5), Slovakia (4), Mexico (3), Finland (3), Chile (2),	Randomized, double blind, parallel group, placebo	55 mcg 110 mcg placebo	Safety and efficacy	558 randomized FF50 185 FF100 185 placebo 188	12 weeks	M 310 F 248 Mean age (SD) 7,7 (2,52) Range 2-12	PAR	The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS)
FFR100012	10 (USA)	Randomized, double blind, parallel group, placebo	110 mcg placebo	HPA axis safety	112 randomized FF 100 57 Placebo 55	6 weeks	M 56 F 56 Mean age (SD) 6,3 (2,7) Range 2-11	PAR	Pharmaco-dynamic assessment from baseline in 24 hour serum cortisol weighted mean
FFR101747	1 Denmark	Randomized, double blind, two week crossover knenometry safety	110 mcg	Effect on lower leg growth rate	58 randomized	2 weeks	M 35 F 18 Mean age (SD) 9,0 (1,39) Range 6-11	SAR and or PAR	none

- Dose response studies

Study FFR20001 evaluated doses of FF 55, 110, 220, 440 µg once daily by aqueous nasal spray for fourteen days in adolescent and adult patients with seasonal allergic rhinitis due to Mountain Cedar pollen. The total nasal symptom score (TNSS) is the sum of four individual symptom scores for rhinorrhoea, nasal congestion, nasal itching and sneezing, where each symptom is scored 0 to 3 giving a maximum score of 12. Patients were predominantly (~ 90%) in the age group 18 – 65 years, with 7% below 18 years and less than 1% above 75 years; approximately two thirds were female. The principal outcomes are shown in Table 6. All efficacy differences from placebo are statistically significant ($p < 0.001$)

Table 24 Principal results of Study FFR20001 figures are mean (sd)

	Pbo n = 128	55 µg n = 127	110 µg n = 127	220 µg n = 129	440 µg n = 130
Completed	124	121	125	124	126
Baseline TNSS*	9.6 (0.15)	9.6 (0.13)	9.5 (0.13)	9.5 (0.14)	9.6 (0.15)
Change in TNSS	-1.7 (0.12)	-3.6 (0.25)	-3.9 (0.27)	-3.3 (0.25)	-4.1 (0.25)
Change from baseline urinary 24 hr cortisol mean µg/24 hrs	0.9 (19.9)	1.7 (26.1)	-0.6 (24.0)	-1.2 (19.4)	0.5 (17.7)

* TNSS: Total nasal symptoms score

- Main studies

Seasonal allergic rhinitis (SAR)

Study FFR103184 was a two week, double blind, placebo controlled, evaluation of the safety and efficacy of intranasal FF 110 µg once daily in adult and adolescent patients suffering from seasonal allergic rhinitis (SAR) triggered by grass pollen. The principal efficacy endpoint was the effect on change from baseline on total nasal symptom score (TNSS) during the full treatment period.

The study was powered on the basis that 288 subjects were required, based on results from the dose finding trial which suggested the standard deviation of mean change from baseline over the treatment period was 2.6. Using a two-sample t-test with a two sided significance level of 0.05, 288 patients should provide 90% power to detect a difference of 1.0 [in NTSS score] between active treatment and placebo.

The results for study completion and the primary efficacy variable are shown in Table 25.

Table 25 Main outcomes of Study FFR103184 data are mean (s.e.) except for age (s.d.)

	Placebo n = 144	110 µg n = 141	Placebo comparison
Age (mean and s.d.)	29.4 (10.9)	30.7 (11.7)	
Proportion female (%)	56	50	
Completed	128	138	
Baseline TNSS	8.4 (0.11)	8.3 (0.12)	
Change in TNSS week 1	-2.7 (0.20)	-4.3 (0.20)	
Change in TNSS week 2	-3.7 (0.24)	-5.4 (0.21)	$p < 0.001$ weeks 1 + 2

Study FFR30003 was a two week, double blind, placebo controlled, evaluation of the safety and efficacy of intranasal FF 110 µg once daily in adult and adolescent patients suffering from seasonal allergic rhinitis (SAR) triggered by Mountain Cedar pollen. The principal efficacy endpoint was the effect on change from baseline on total nasal symptom score (TNSS) during the full treatment period. The study power calculations were identical with those for FFR103184, described above. The efficacy results are shown in Table 26.

Table 26 Main outcomes Study FFR30003 data are mean (s.e.) except for age

	Placebo n = 150	110 µg n = 152	
Age (mean and s.d.)	38.1 (13.6)	37 (13.9)	
Proportion female (%)	66	61	
Completed	138	145	
Baseline TNSS	9.7 (0.11)	9.8 (0.11)	
Change in TNSS week 1	-2.3 (0.19)	-2.7 (0.20)	
Change in TNSS week 2	-2.4 (0.22)	-3.6 (0.22)	p = 0.003 weeks 1 + 2

Study FFR104861 was a two week, double blind, placebo controlled, evaluation of the safety and efficacy of intranasal FF 110 µg once daily in adult and adolescent patients suffering from seasonal allergic rhinitis (SAR) triggered by ragweed pollen. The principal efficacy endpoint was the effect on change from baseline on total nasal symptom score (TNSS) during the full treatment period. The sample size and power were as described for Study FFR103184 above. The efficacy results are shown in Table 27.

Table 27 Main outcomes Study FFR104861 data are mean (s.e.) except for age

	Placebo n = 148	110 µg n = 151	
Age (mean and s.d.)	34.5 (14.1)	35.4 (13.85)	
Proportion female (%)	57	64	
Completed	142	144	
Baseline TNSS	9.9 (0.11)	9.6 (0.13)	
Change in TNSS week 1	-1.9 (0.18)	-3.1 (0.22)	
Change in TNSS week 2	-2.3 (0.2)	-3.9 (0.24)	p < 0.001 weeks 1 + 2

Perennial allergic rhinitis (PAR)

Study FFR30002 was a four week, double blind, placebo controlled, evaluation of the safety and efficacy of intranasal FF 110 µg once daily in adult and adolescent patients suffering from perennial allergic rhinitis (PAR). Eligible patients were otherwise healthy male and female subjects, at least twelve years old with a history of PAR triggered by an appropriate allergen such as animal dander, house dust mite, etc. The principal efficacy endpoint was the effect on change from baseline in total nasal symptom score (TNSS) during the full treatment period. The sample size and power were as described for Study FFR103184 above. The main efficacy results are shown in Table 28.

Table 28 Main outcomes Study FFR30002 data are mean (s.e.) except for age

	Placebo n = 153	110 µg n = 149	
Completed	142 (93%)	137 (92%)	
	35.8 (14.8)	37.7 (14.9)	
Age (mean and s.d.)			
Proportion female (%)	55	70	
Baseline TNSS	8.7 (0.14)	8.6 (0.13)	
Change in TNSS week 1	-1.6 (0.17)	-2.1 (0.17)	
Change in TNSS week 2	-2.3 (0.20)	-3.0 (0.18)	
Change in TNSS week 3	-2.5 (0.21)	-3.5 (0.21)	
Change in TNSS week 4	-2.8 (0.23)	-3.6 (0.22)	p = 0.005 weeks 1 - 4

- Analysis performed across trials (pooled analyses and meta-analysis)

The applicant's review across studies shows that the studies are consistent. The magnitude of the benefit is variable but only in as much as expected. There are no evident outliers, and apart from one challenge study no negative studies.

- Clinical studies in special populations

Clinical studies in children

Study FFR30008 was a twelve week, double blind, placebo controlled, evaluation of the safety and efficacy of intranasal FF 55 µg and 110 µg once daily in paediatric patients aged 2 to 11 years suffering from perennial allergic rhinitis (PAR). It was anticipated that 25% and 75% of those enrolled would be 2 to <6 and 6 to <12 years of age, respectively. Due to the difficulty in assessing subjective symptoms in very young subjects, the 6 to <12 years population was selected as the primary population of interest for efficacy. Randomisation was stratified by age. Patients had at least a one year history of PAR (six-months for those aged less than four years) triggered by an appropriate allergen. The principal efficacy endpoint was the effect on change from baseline on total nasal symptom score (TNSS) during the first four study weeks of the FF 110 µg treatment arm compared to placebo.

The study was powered on the basis that 432 subjects were required based on results from the dose finding trial in seasonal allergic rhinitis. The principal outcome is shown in Table 29.

Table 29 Main outcomes Study FFR30008 data are mean (s.e.) except for age

	Placebo n = 188	55 µg n = 185	110 µg n = 185
n = aged 6 to less than 12 years (the efficacy population)	147	144	140
Total completed	161	163	168
Age (mean and s.d.) total population	7.9 (2.5)	7.7 (2.6)	7.4 (2.5)
Proportion female (%)	34	45	45
Baseline TNSS	8.5 (0.13)	8.5 (0.14)	8.6 (0.13)
Least squares mean change in TNSS Weeks 1 – 4	-3.4 (0.24)	-4.16 (0.21)	-3.86 (0.25)
	(efficacy population) p versus placebo = 0.003 for 55 µg and 0.073 for 110 µg		

Study FFR100010 evaluated doses of FF 55, 110 µg once daily for fourteen days in children at least two but less than twelve years old with seasonal allergic rhinitis. Patients were required to have a documented history of SAR and a positive skin test or positive *in vitro* tests for specific IgE to seasonal allergens prevalent within the geographic region. The primary efficacy endpoint was the change from baseline in daily, total nasal symptom score (TNSS) in patients 6 to < 12 years old. The principal outcomes are shown in Table 30.

Table 30 Main outcomes Study FFR100010 data are mean (s.e.) except for age

	Placebo n = 186	55 µg n = 184	110 µg n = 184	
Completed	180 (97%)	175 (95%)	181 (98%)	
Age (mean and s.d.)	8.0 (2.6)	8.2 (2.4)	8.0 (2.5)	
Proportion female (%)	42	42	40	
Baseline TNSS*	8.4 (0.14)	8.6 (0.15)	8.5 (0.14	
Change in TNSS week 1	-2.2 (0.19)	-2.3 (0.20)	-2.7 (0.18)	
Change in TNSS week 2	-2.8 (0.23)	-3.2 (0.24)	-3.7 (0.23)	p = 0.025 for 110 µg vs. placebo

(*age 6 to <12 population n ~ 150 treatment arm)

FFR101747 was a two-week, crossover, placebo-controlled study of 58 children aged 6 to 11 years with seasonal and/or perennial allergic rhinitis. The study evaluated the effect on short-term lower-leg growth of two weeks' treatment with FF nasal spray 110 µg daily using a knemometer. Eligible subjects were females 6 to <11 years of age or males 6 to <12 years of age, with a documented clinical history of SAR and/or PAR. The primary endpoint was the mean growth rate (mm/wk) in lower-leg length, with a margin of non-inferiority set at -0.20 mm/wk. The principal outcome of the study is shown in Table 31.

Table 31 Main outcome Study FFR101747

	Placebo	Active 110 µg
Completed	57	57
Age (years.)		9.1 range (6 – 11)
Proportion female (%)	53	51
Period 1 (mm/week)	0.45 (0.05)	0.44 (0.06)
Period 2 (mm/week)	0.40 (0.05)	0.39 (0.08)
	Treatment difference -0.016 (95% C.I -0.13, 0.10) p = 0.8	

Study FFR100012 was a six-week, double blind, placebo controlled evaluation of the effects of intranasal FF 110 µg once daily on the HPA axis in children aged at least two and younger then twelve years old. Subjects with a physician confirmed diagnosis of perennial allergic rhinitis were eligible. The primary comparison was FF non-inferiority to placebo of 24 hour serum cortisol, with a non-inferiority margin of the lower limit of the 95% confidence interval for the mean ratio being greater than 0.80. Randomisation was stratified by age by the following categories: 2 to <4 years old (20%), 4 to <6 years old (20%), and 6 to <12 years old (60%). The pharmacodynamic results for plasma and urinary cortisol are shown in Table 32.

Table 32 Serum and urinary cortisol results by treatment figures are geometric mean (95%C.I.)

	Weighted 24 hr. serum cortisol	
	PLACEBO	FF 110 µg
Baseline (nmol/L)	185 (171, 200)	190 (175, 206)
Week six (nmol/L)	182 (169, 196)	182 (167, 198)
Ratio from baseline	0.98 (0.91, 1.05)	0.94 (0.86, 1.02)
Treatment ratio	0.97 (0.88, 1.07)	
	24 hour urinary cortisol*	
Baseline (nmol/day)	22.35	**25.06**
Week six (nmol/day)	**28.20**	**24.43**
Ratio from baseline	**1.26**	**0.97**

* error estimates for geometric mean not provided in study report

- Supportive studies

Study FFR20002 was a six-week, double blind, placebo and active controlled evaluation of the effects of FF 110 µg once daily by nasal spray on the hypothalamic-pituitary-adrenocortical (HPA) axis. Subjects of 12 to 65 years of age with a physician confirmed diagnosis of perennial allergic rhinitis and a positive skin test to a relevant antigen. Patients were randomised 4:4:1 to FF 110 µg: placebo: oral prednisone 10 mg daily. The primary comparison was FF non-inferiority to placebo of 0-24h serum cortisol, with a non-inferiority margin of the lower limit of the 95% confidence interval for the mean ratio being greater than 0.80 the study has approximately 90% power to demonstrate non-inferiority if there is no true difference between groups. The pharmacodynamic results for plasma and urinary cortisol are shown in Tables 33 and 34 respectively.

Table 33 Weighted mean (0 – 24) plasma cortisol by treatment geometric mean and 95% CI

	Placebo (n = 44)	FF (n = 43)	Prednisone (n = 12)
Baseline	238 (221, 257)	249 (224, 277)	237 (213, 264)
Week 6	237 (214, 262)	236 (215, 259)	116 (97, 138)
Placebo ratio (95% CI)		0.98 (0.89, 1.07)	0.49 (0.43, 0.57)

Table 34 24 hour urinary cortisol excretion by treatment arithmetic mean and s.d.

	Placebo (n = 42)	FF (n = 43)
Baseline	67.4 (51.4)	106 (125)
Week 6	72.4 (46.7)	89.3 (76.9)
Change from baseline	5.03 (47.2)	-16.7 (116.4)

Discussion on clinical efficacy

The data submitted from concluded clinical studies demonstrated the efficacy of fluticasone furoate in the treatment of the symptoms of SAR. Fluticasone furoate nasal spray demonstrated statistically significant reductions from baseline compared with placebo for the primary endpoint daily rTNSS (reflective TNSS) over the entire treatment period in the SAR studies. The treatment differences were -2.012 (**FFR20001**), -1.757 (**FFR103184**), -1.473 (**FFR104861**) and -0.777 (**FFR30003**). These treatment differences were within the range observed with marketed products that are effective for allergic rhinitis. The results for the primary endpoint were supported by the key secondary efficacy endpoint AM pre-dose iTNSS (instantaneous TNSS); treatment effect ranged from -0.902 to -1.898, $p<0.001$ across the studies. This confirmed that once-daily administration of fluticasone furoate maintained the improvement in nasal symptoms of SAR until the end of the 24-hour dosing interval. Similar improvements were seen for AM and PM rTNSS suggesting consistent daytime and night time symptom relief. No individual nasal symptom disproportionately influenced the composite score for rTNSS and the resulting overall treatment difference over placebo.
The three Phase 3 studies also confirmed the efficacy on ocular symptoms demonstrated in the Phase 2b study. The treatment effect on rTOSS (reflective total ocular symptoms score) ranged from -0.546 to -0.741 ($p\leq0.008$) across the three studies, which is within the range expected with oral antihistamines used in clinical practice, such as desloratadine. These findings were generally supported by the mean change from baseline in AM pre-dose iTOSS, AM and PM rTOSS and by individual ocular symptom scores, where fluticasone furoate showed significantly greater improvements compared with placebo for most endpoints. Across the studies, scores for subjects treated with fluticasone furoate 110mcg were significantly better than placebo, with a large proportion reporting moderate to significant improvement in this group compared with placebo (integrated analysis results: 52% and 30%, respectively).

The overall findings from FFR30002 demonstrated that fluticasone furoate nasal spray 110mcg was effective in improving the nasal symptoms of PAR and confirm that the once daily administration of fluticasone furoate nasal spray adequately maintains the improvement in nasal symptoms of PAR until the end of the 24-hour dosing interval. The treatment effect for the primary efficacy endpoint (mean change from baseline in daily rTNSS) was statistically significant over placebo (-0.706, $p=0.005$). This was within the range expected for an intranasal corticosteroid currently used in clinical practice. The primary efficacy results were supported by the data from the key secondary endpoints. The mean change from baseline in AM pre-dose iTNSS was significantly greater for fluticasone furoate nasal spray than placebo with a treatment difference of -0.705 ($p=0.006$). The statistical analysis of overall response to therapy supported the results of the primary endpoint. More subjects treated with fluticasone furoate reported moderate to significant improvements compared with those on placebo (44% and 33%, respectively). Other secondary endpoints were also supportive of the primary endpoint. Similar improvements over placebo were seen with the AM and PM scores, suggesting consistent daytime and night time symptom relief. For individual nasal symptoms of rhinorrhoea, sneezing and nasal itching, significant improvements were seen with fluticasone furoate nasal spray

110mcg compared with placebo; these findings contributed equally to the overall rTNSS score reduction.

Of the clinical studies in children FFR100010 showed that fluticasone furoate 110mcg demonstrated a greater reduction from baseline in rTNSS compared with placebo over the 2-week treatment period (-0.616, p=0.025). The treatment difference was significant in favour of fluticasone furoate 110mcg for the key secondary and the other nasal symptom-related secondary endpoints. For fluticasone furoate 55mcg, there were no statistically significantly greater improvements in SAR symptoms compared with placebo for the primary (-0.161, p=0.553) or secondary endpoints. In the 12-week PAR study FFR30008, the efficacy results were somewhat discordant with the SAR study results for the two doses (110mcg and 55mcg). The mean change from baseline in daily rTNSS for fluticasone furoate 110mcg was numerically greater than placebo, although not statistically significant (-0.452, p=0.073). The 110mcg dose resulted in numerically greater changes than placebo for the key secondary and other secondary efficacy endpoints, which were statistically significant for some endpoints, including AM iTNSS (-0.651, p=0.009) and individual scores of nasal congestion, rhinorrhoea and sneezing. For fluticasone furoate 55mcg, the treatment effect over placebo was significant for daily rTNSS (-0.754, p=0.003) and for all key secondary and other secondary endpoints excluding AM reflective nasal itching.
A significant treatment effect was not achieved on the primary efficacy endpoint for the fluticasone furoate 110mcg treatment group over the first 4 weeks. However, FFR30008 was unusual in that compared with placebo, the response to the 110mcg dose increased with time in the FFR30008 study. A significantly greater reduction in daily rTNSS for the RITT population 6 to <12 years of age was observed over Weeks 1 to 6 (-0.584, p=0.018 for fluticasone furoate 110mcg; -0.862, p<0.001 for fluticasone furoate 55mcg) and Weeks 1 to 12 (-0.672, p=0.006 for fluticasone furoate 110mcg; -0.816, p<0.001 for fluticasone furoate 55mcg) compared with placebo for both the 110mcg and 55mcg doses; this was supported by the results in the entire RITT population.

As requested in the CHMP Day 120 LOQ, the applicant reported the results of PK/PD, efficacy and safety separately for the age group 2-5 and 6-12, as well as justification for the inclusion in the indication of children below 6 years of age .The CHMP view was that the number of patients from the subpopulation aged 2-5 years (176 patients exposed to FF in clinical trials) is very limited and does not allow to reach any safety or dosing conclusion.
The lower age limit for the indication, as well as the lack of a study with active comparator was further addressed during the Oral Explanation (please refer to Overall Conclusions).

Clinical safety

- Patient exposure

A total of 3954 adult, adolescent, and paediatric subjects participated in the Phase II/III studies, with approximately 60% of subjects (2359) treated with FF 110 µg (1990) or FF 55 µg (369). This does not include the 386 subjects in the dose ranging study (FFR20001) who were treated with the 55mcg, 220mcg, and 440mcg dosages of fluticasone furoate and the 58 subjects who were randomized in the knemometry study (FFR101747) that utilized a crossover design.

The majority of SAR and PAR studies were 2 - 12 weeks in treatment duration, and thus approximately 80% of the subject exposures were 12 weeks or less. In the safety database of 3954 subjects, 501 (25%) of the subjects (adults and adolescents) exposed to fluticasone furoate 110mcg once daily were exposed to treatment for a period of ≥6 months and 400 (20%) adult and adolescent subjects were exposed for ≥12 months.

More female subjects (1262 of the female subjects treated with the 110mcg or 55mcg dosages of fluticasone furoate) than male subjects (1097 of the male subjects treated with the 110mcg or 55mcg dosages of fluticasone furoate) were exposed to fluticasone furoate in the clinical development program.
The largest number of subjects exposed to fluticasone furoate 110mcg in the clinical development program was in the 18 to <65 year age group; 1333 of these subjects treated with the 110mcg dosage. In the adolescent population (aged 12 to <18 years), 198 subjects were exposed to fluticasone furoate 110mcg in the clinical studies.

In the paediatric, phase 3 placebo-controlled, parallel group clinical studies (subjects ≥2 to <12 years of age), 176 subjects 2 to <6 years of age were treated with the 110mcg or 55mcg dosages of fluticasone furoate and 618 paediatric subjects 6 to <12 years of age were treated with the 110mcg or 55mcg dosages; 54 of these subjects were ≥2 to <4 years of age and were treated with either a 55mcg or 110mcg dosage of fluticasone furoate nasal spray.

To assess for potential systemic corticosteroid effects, a 12-month adult and adolescent study FFR102123 and the 12-week paediatric study FFR30008 (described in the section on Efficacy) included ophthalmic examinations and outpatient collection of urine for 24-hour cortisol excretion.

Study FFR102123 was a one year, double blind, placebo controlled evaluation of the safety of FF 110 µg once daily. It was carried out at seventy-five centres internationally, from September 2004 to December 2005. Eligible subjects were at least 12 years of age with a diagnosis of perennial allergic rhinitis for at least two years and a positive skin test to a relevant antigen (animal dander, dust mite etc.) within the last year. They were required to have a TNSS of at least 4 during the screening week prior to randomisation. Randomisation was 3:1 to active and placebo treatments. Subjects with other significant systemic or nasal health problems were excluded. Use of local or systemic steroids or other allergy treatments was not allowed. No statistical assumptions were made so the study was not specifically powered to detect any defined event.

During the procedure the report of a perennial allergic rhinitis study, which was ongoing at the time of initial submission of the MAA, was submitted with the applicant's responses to the CHMP Day 120 List of Questions. **Study FFR 106080** was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of once-daily intranasal administration of GW685698X aqueous nasal spray 110mcg for 6 weeks in adult and adolescent subjects 12 years of age and older with perennial allergic rhinitis (PAR). A total of 302 subjects were randomised, 151 in each of the fluticasone furoate 110mcg and placebo groups.
Results of the study FFR 106080 are in line with those seen in the pivotal studies, in particular with the clinical efficacy and safety of the 110 mcg daily dose of FF.

- Adverse events

Standard safety evaluations (i.e., adverse events, laboratory evaluations, vital signs and ECG) and detailed nasal examinations were performed in all studies. In order to obtain an accurate assessment of adverse event frequencies the safety data obtained from the adult and adolescent studies with a treatment duration of six weeks or less were integrated (i.e., FFR20001, FFR30003, FFR103184, FFR104861, FFR30002 and FFR20002). For the paediatric studies, adverse event data from studies FFR100010, FFR30008 and FFR100012 were integrated.

Adverse events in adults and adolescent studies
Few subjects receiving fluticasone furoate in clinical trials reported moderate or significant worsening compared with those receiving placebo (integrated analysis results: 3% and 12%, respectively).

In 6 adult and adolescent studies (FFR20001, FFR20002, FFR30002, FFR30003, FFR103184, FFR104861), 29% of subjects in the fluticasone furoate nasal spray 110mcg group and 27% in the placebo group experienced at least one adverse event (AE) during the treatment period. All AEs that occurred at an incidence rate of ≥1% are summarized in table 35.
Adverse events that occurred more commonly in the fluticasone furoate 110mcg group than in the placebo group were headache, epistaxis, pharyngolaryngeal pain, nasal septum ulceration and back pain. The majority of adverse events noted were mild or moderate in intensity across both the fluticasone furoate and the placebo treatment groups. Overall, of the 209 subjects reporting an AE in the placebo group, 22 subjects (11% of subjects reporting any AE) had adverse events classified as severe. For the fluticasone furoate 110mcg group, of the 225 subjects reporting an AE, 11 subjects (5% of the subjects reporting any AE) had an adverse event classified as severe. Less than 1% of the subjects in the placebo and the fluticasone furoate 110mcg group reported severe headache. There were no reports of severe epistaxis in either treatment group.

Table 35 Summary of adverse events with an incidence greater than or equal to 1% during treatment (ITT population – FFR20001, FFR20002, FFR30002, FFR30003, FFR103184, FFR104861)

	Number (%) of subjects	
Adverse event	**Placebo N=774**	**FF 110mcg QD N=768**
Any event	209 (27)	225 (29)
Headache	50 (6)	64 (8)
Epistaxis	32 (4)	45 (6)
Pharyngolaryngeal pain	8 (1)	15 (2)
Nasal septum ulceration	2 (<1)	9 (1)
Nasopharyngitis	11 (1)	9 (1)
Sinusitis	13 (2)	6 (<1)
Back pain	7 (<1)	9 (1)
Ear pain	8 (1)	4 (<1)

Source: CTD - module 2.7.4 Summary of Clinical Safety

In the long-term safety study FFR102123, 464 subjects (77%) in the fluticasone furoate nasal spray 110mcg group and 142 subjects (71%) in the placebo nasal spray group experienced at least one AE during the 52-week treatment period. The ten most common AEs in each treatment group are summarized in the following table (table 36).

The most common AEs in both treatment groups were headache, nasopharyngitis, epistaxis, pharyngolaryngeal pain, back pain and upper respiratory tract infection. Epistaxis was more commonly reported with fluticasone furoate nasal spray 110mcg than with placebo nasal spray (fluticasone furoate nasal spray 20%, placebo 8%).

Most of the AEs reported during the long-term safety study (FFR102123) were mild or moderate in intensity. The maximum intensity of reported AEs was similar in the two treatment groups, except for epistaxis. In the fluticasone furoate nasal spray 110mcg group, 83 subjects (14%) reported epistaxis with a maximum intensity of mild, 39 subjects (6%) with a maximum intensity of moderate, and one subject reported 2 episodes considered to be severe. In the placebo nasal spray group, all episodes of epistaxis were of mild intensity.

Table 36 Summary of the 10 most common adverse events in each treatment group in the long-term safety study (ITT population – FFR102123)

	Number (%) of subjects	
Adverse event	**Placebo (N=201)**	**FF 110mcg (N=605)**
Subjects with any adverse event	**142 (71)**	**464 (77)**
Headache	69 (34)	186 (31)
Nasopharyngitis	51 (25)	157 (26)
Epistaxis	17 (8)	123 (20)
Pharyngolaryngeal pain	18 (9)	53 (9)
Back pain	12 (6)	39 (6)
Upper respiratory tract infection	16 (8)	37 (6)
Influenza	13 (6)	32 (5)
Cough	7 (3)	29 (5)
Abdominal pain upper	11 (5)	23 (4)
Toothache	5 (2)	29 (5)
Dysmenorrhoea	8 (4)	22 (4)
Pyrexia	9 (4)	21 (3)
Ear pain	8 (4)	10 (2)

Source: CTD - module 2.7.4 Summary of Clinical Safety

1. In this study, 106 females were randomized to the placebo group and 307 females were randomized to the fluticasone furoate 110mcg group. Thus, incidences for dysmenorrhoea were 8% (8/106) in the placebo group and 7% (22/307) in the fluticasone furoate 110mcg group based on the female enrolment.

In the adult and adolescent clinical studies (including the long-term safety study), adverse events considered by the investigators to be drug-related occurred at a very low incidence. The most common drug-related AEs which occurred in a higher proportion of subjects treated with fluticasone furoate nasal spray than with placebo were epistaxis, nasal ulceration, nasal dryness and headache. Most of the drug-related AEs reported in the adult and adolescent studies were mild or moderate in intensity. Three subjects in the fluticasone furoate 110mcg group reported drug-related AEs that were of severe intensity (epistaxis; anosmia and parosmia; herpes virus infection).

Adverse events in paediatric studies

In the 3 paediatric studies (FFR100010, FFR30008, FFR100012), 43% of subjects in the fluticasone furoate nasal spray 55mcg group, 41% in the fluticasone furoate 110mcg group and 37% in the placebo group experienced at least one AE during the treatment period. All adverse events that occurred at a ≥1% incidence in the integrated paediatric database are summarized in table 37. The majority of adverse events reported were mild or moderate in intensity across both the fluticasone furoate and the placebo treatment groups. The most common AEs were headache, nasopharyngitis, epistaxis, pyrexia, pharyngolaryngeal pain, cough and bronchitis. The incidences of all AEs in the paediatric population were similar across the two FF treatment groups and the placebo group, with the exception of pyrexia. Pyrexia was reported more frequently in the fluticasone furoate treatment groups (5% and 4% in the fluticasone furoate 55mcg and 110mcg groups, respectively) compared with 2% in the placebo group; pyrexia was commonly reported in the 2 to <6 year age group.
Less than 1% of the subjects in the placebo and the FF 55mcg group, and 1% of the subjects in the fluticasone furoate 110mcg treatment group reported a severe adverse event. There were no reports of severe epistaxis in either treatment group.
Adverse events considered by the investigators to be drug-related occurred at a low incidence in the paediatric studies. The most common drug-related AEs were epistaxis and headache (2% of the subjects in the FF 110mcg treatment group and 4% of the subjects in the FF 55mcg treatment group compared with 3% in the placebo group). Headache considered drug-related occurred at an incidence of <1%, 2% and 1% in the FF 110mcg, the FF 55mcg group and the placebo group respectively. All other drug-related AEs occurred at an incidence of <1% across the treatment groups.

Table 37 Summary of all adverse events with an incidence greater than or equal to 1% during treatment (ITT population – FFR100010, FFR30008, FFR100012)

	Number (%) of subjects		
Adverse event	**Placebo N=429**	**FF 55mcg QD N=369**	**FF 110mcg QD N=426**
Any event	157 (37)	158 (43)	174 (41)
Headache	30 (7)	28 (8)	32 (8)
Nasopharyngitis	21 (5)	20 (5)	21 (5)
Epistaxis	19 (4)	17 (5)	17 (4)
Pyrexia	7 (2)	17 (5)	19 (4)
Pharyngolaryngeal pain	14 (3)	16 (4)	12 (3)
Cough	12 (3)	12 (3)	16 (4)
Bronchitis	11 (3)	11 (3)	8 (2)
Asthma	10 (2)	9 (2)	2 (<1)
Upper Respiratory Tract Infection	6 (1)	6 (2)	7 (2)
Vomiting	3 (<1)	7 (2)	8 (2)
Abdominal pain upper	5 (1)	4 (1)	8 (2)
Sinusitis	5 (1)	7 (2)	4 (<1)
Pharyngitis	4 (<1)	4 (1)	7 (2)
Diarrhoea	5 (1)	5 (1)	4 (<1)

Tonsillitis	3 (<1)	5 (1)	4 (<1)
Pain in extremity	3 (<1)	6 (2)	2 (<1)
Ear pain	2 (<1)	3 (<1)	5 (1)
Ear infection	3 (<1)	5 (1)	2 (<1)
Arthralgia	3 (<1)	4 (1)	3 (<1)
Scab	2 (<1)	2 (<1)	5 (1)
Influenza	1 (<1)	2 (<1)	5 (1)
Arthropod bite	2 (<1)	4 (1)	1 (<1)
Excoriation	1 (<1)	4 (1)	1 (<1)
Contusion	1 (<1)	4 (1)	0

Source: CTD - module 2.7.4 Summary of Clinical Safety

Adverse events in clinical pharmacology studies

The most common adverse events following nasal inhalation of fluticasone furoate in the clinical pharmacology studies [FFR10001, FFR10003, FFR10005, FFR10006, FFR10007, FFR10010 (in this study subjects also received a single 250mcg intravenous infusion of fluticasone furoate)] were headache and upper respiratory tract symptoms. There was no clear differentiation between active and placebo administration in the incidence of AEs.

- Serious adverse event/deaths/other significant events

There were no deaths in the fluticasone furoate nasal spray clinical development program.

Overall, 29 subjects in the adult and adolescent clinical studies (including the long-term safety study) experienced a non-fatal serious adverse event.
Five subjects from the two adult and adolescent studies (FFR104861, FFR30002) experienced non-fatal serious adverse events (SAEs). In FFR104861, three subjects reported SAEs.; two SAEs during the screening period (severe diabetes mellitus, moderate gastroenteritis) and one SAE during the post-treatment period (severe cholelithiasis six days after the last dose fluticasone furoate 110mcg; this event was not considered to be related to study drug). In FFR30002, two subjects experienced SAEs. One subject reported breast cancer during the treatment period (not considered drug-related as the subject had a history of fibrocystic breast disease when enrolled into the study). One subject in the placebo group reported two SAEs during the treatment (severe abdominal pain) and nephrolithiasis in the post-treatment period; neither event was considered to be related to study drug as the subject had a prior history of renal calculi.
During the study period in the long-term safety study (FFR102123), 20 subjects (3%) in the fluticasone furoate nasal spray 110mcg group and four subjects (2%) in the placebo group experienced SAEs. No individual SAE was reported by more than one subject in either treatment group. None of the SAEs were considered by the investigator to be related to study treatment and all were resolved or resolving at the end of the study except for one SAE (breast cancer).
Four subjects, all treated with fluticasone furoate nasal spray 110mcg were withdrawn prematurely from the study due to SAEs (glandular polyp of the endometrium and uterine bleeding; worsening haemorrhoids; herpes zoster of the face and neck; cervical vertebral fracture).

Four subjects from the three integrated paediatric studies (FFR100010, FFR30008, FFR100012) experienced four non-fatal serious adverse events.
In FFR100010, one SAE was reported for one subject in the placebo group during the treatment period (insulin-dependent diabetes mellitus; not considered drug related). The subject was withdrawn from the study. In FFR30008, two subjects experienced SAEs. During the treatment period, SAEs were reported for one subject in the FF 55mcg group (peritonitis) and for one subject in the FF 110mcg group (appendicitis). Both subjects recovered without sequelae. In FFR100012, one subject in the placebo group experienced a fracture of the ulna and radius while roller-skating and was hospitalized. Treatment with investigational product was continued. Neither event was considered related to study drug.

- Laboratory findings

No safety issues were identified in the laboratory data collected in the integrated SAR/PAR studies in adult and adolescent subjects, and paediatric subjects, and in the long-term safety study (FFR102123). The majority of subjects in each treatment group had either no change in clinical chemistry and haematology parameters or a shift into the normal range during the study periods (over 80%). The percentage of subjects who shifted to above or to below the normal range was low. The number of subjects with non-serious laboratory abnormalities reported as adverse events in these studies was low across the programme.

Nasal examination

A nasal examination of the turbinates, mucosa, septum and secretions was performed during the clinical development program for intranasal fluticasone furoate (nasal patency, size of any polyps and ulcers, presence of oropharyngeal or nasal candidiasis). In the integrated adult and adolescent and paediatric studies and in the long-term safety study, no particular safety concerns were noted across the assessed parameters, with a high proportion of subjects showing no change or improvements in nasal examinations.

In adult and adolescent studies, presence of mucosal bleeding for all visits was similar between the fluticasone furoate (0 to 10%) and placebo (0 to 7%) groups, except for week 4 where mucosal bleeding was present in 10% of the subjects in the fluticasone furoate group and 3% of the subjects in the placebo group. In the long-term safety study FFR102123, mucosal crusting and mucosal bleeding were seen in a slightly higher proportion of subjects in the fluticasone furoate group than in the placebo group. The proportion of subjects with mucosal crusting and bleeding did not increase with longer term treatment. The incidence of ulcers on the turbinates or septum was higher in subjects treated with fluticasone furoate (ranging from 2% to 6% at each visit) compared with placebo (ranging from 0 to 3% at each visit).

In paediatric studies, presence of mucosal bleeding was similar between the fluticasone furoate 110mcg (<1 to 6%), fluticasone furoate 55mcg (0 to 5%), and placebo (1 to 8%) groups. No subjects in any of the treatment groups had findings of ulceration in the turbinates or septum at endpoint.

No instances of septal perforation were reported during the clinical development program for intranasal fluticasone furoate.

Ophthalmic examinations

Ophthalmic examinations were performed in the adult and adolescent long-term safety study (FFR102123; at baseline and week 12, week 24 and week 52) and in children with perennial allergic rhinitis in the 12-week efficacy and safety study (FFR30008; at baseline and week 12). In both studies, assessments included slit lamp and funduscopic examinations of the cornea, iris and lens; detection of subcapsular cataracts, retinal vascular abnormalities and glaucoma; measurements of intraocular pressure.

The results from both studies were similar; there was no evidence for adverse effects of treatment with intranasal fluticasone furoate on thorough ophthalmic examinations. Most subjects had normal ophthalmic examinations at baseline and throughout the treatment period. Mean changes in intraocular pressure and funduscopic cup to disc percentage were small and similar between the treatment groups. Increased intraocular pressure was reported as an AE for three subjects in study FFR102123 and for four subjects in study FFR30008; all were considered to be of mild intensity (except for a moderate intensity for one subject in placebo group in FFR30008). Glaucoma was not reported as an adverse event in either study.

HPA axis evaluation

HPA (hypothalamic-pituitary-adrenal) axis function was assessed in five clinical studies (FFR20002, FFR100012, FFR20001, FFR102123 and FFR30008). In two of these studies, FFR20002 (6-week HPA-axis study; adults and adolescents) and FFR100012 (6-week HPA-axis study; children 2 to <12 years of age), serial serum samples and urine were collected over 24 hours to determine 24-hour serum cortisol and 24-hour urine cortisol excretion. The primary objective of these two studies was to assess the effects of 6 weeks treatment with fluticasone furoate nasal spray 110mcg once daily on HPA-axis

function compared to vehicle placebo nasal spray in male and female subjects with perennial allergic rhinitis. In FFR20002, prednisone (10mg once daily) was included as an active control during the last 7 days of treatment to ensure the assay was sufficiently sensitive to detect a drug effect. This active control arm of prednisone was not included in study FFR100012 due to ethical concerns over the suppression of adrenal function in children. The conclusions from the two HPA-axis studies suggest there is a very low potential for adverse effects related to HPA axis function with intranasal fluticasone furoate. In study FFR20002, at week 6 geometric mean serum cortisol concentrations were similar for fluticasone furoate 110mcg once daily and placebo (236.26 and 236.85 nmol/l respectively). Geometric mean ratios from baseline at week 6 were similar for the fluticasone furoate and placebo treatment groups (0.99 for placebo, 0.97 for FF, 0.49 for prednisone group). In FFR20002, a summary of 24-hour urinary cortisol excretion showed similarities between the placebo and fluticasone furoate 110mcg once daily treatment groups. In study FFR100012, geometric mean ratios from baseline at week 6 were similar for both treatment groups (0.979 for placebo and 0.935 for FF).
Data from the three other clinical studies (FFR20001, FFR102123 and FFR30008), in which 24-hour urine collections to evaluate urinary cortisol excretion were completed, supported the results from the two HPA-axis studies; urine cortisol excretion was similar for subjects treated with intranasal fluticasone furoate and with placebo.
As expected for intranasal corticosteroids, the risk of adverse events related to the potential pharmacological systemic effect of intranasal fluticasone furoate nasal spray 110mcg once daily appears to be very low.

Growth assessment

Study FFR101747 (knemometry study) was conducted to assess any potential effect on lower-leg growth rate from treatment with intranasal fluticasone furoate 110mcg once daily compared with placebo in children ages 6 to 11 years with seasonal allergic rhinitis/perennial allergic rhinitis. The primary safety endpoint was the mean growth rate in lower leg length over a 2-week treatment period. The applicant's conclusion, that intranasal fluticasone furoate is unlikely to have a clinically relevant effect on lower-leg growth is accepted.
The following preautionary wording has been added to SPC section 4.4:
"Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a paediatric specialist (see section 5.1)."
The package leaflet has been adapted accordingly.

- Safety in special populations

AEs were assessed in subgroups of the overall intent-to-treat population (i.e., by age, race, sex, ethnicity and geographic region) in the adult and adolescent studies and in the paediatric studies. No clinically relevant differences were observed in any of the subgroups.

There are no data with intranasal fluticasone furoate in patients with hepatic impairment. A study of a single 400 microgram dose of orally inhaled fluticasone furoate in patients with moderate hepatic impairment resulted in increased Cmax (42 %) and AUC(0-∞) (172 %) and a modest (on average 23 %) decrease in cortisol levels in patients compared to healthy subjects. From this study the average predicted exposure of 110 micrograms of intranasal fluticasone furoate in patients with moderate hepatic impairment would not be expected to result in suppression of cortisol. Therefore moderate hepatic impairment is not predicted to result in a clinically relevant effect for the normal adult dose. There are no data in patients with severe hepatic impairment, therefore no dosage recommendation can be proposed in this patient population.

Other than the HPA/growth studies (described above) the applicant has not done special studies in special populations other than those with hepatic impairment. However, there is no particular issue which requires addressing.

- Safety related to drug-drug interactions and other interactions

There is potential for increased exposure to fluticasone furoate when co-administered with a CYP3A4 inhibitor, and hence increased potential for systemic side effects, such as cortisol suppression.

In study FFR10013, there was some evidence for an increase in systemic exposure on co-administration of fluticasone furoate 110mcg once daily with ketoconazole, compared to placebo, because fluticasone furoate was quantifiable in 6 out of 20 subjects after ketoconazole, compared with only 1 out of 20 subjects after placebo. However, the level of systemic exposure to fluticasone furoate in the ketoconazole group was below levels that would be expected to lead to suppression of cortisol secretion. There was no clear evidence in this study that healthy subjects tolerated the combination of nasal inhalation of fluticasone furoate and oral ketoconazole less than administration of fluticasone furoate alone.

Co-administration of fluticasone furoate and the highly potent CYP3A4 inhibitor ritonavir is not recommended based upon a multiple dose, crossover drug interaction study with fluticasone propionate (another intranasal corticosteroid, which is also a substrate of CYP3A4). In this study, co-administration of ritonavir with fluticasone propionate resulted in a significant increase in plasma fluticasone propionate exposure and a significant decrease in plasma cortisol area under the plasma concentration versus time curve (AUC). Therefore, there is potential for increased exposure to fluticasone furoate when co-administered with a CYP3A4 inhibitor, and hence increased potential for systemic side effects, such as cortisol suppression.

The applicant has agreed with the CHMP request for additional information in SPC section 4.4 (Special warnings and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction). As enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between fluticasone furoate and the cytochrome P450 mediated metabolism of other compounds at clinically relevant intranasal doses, no clinical studies have been conducted to investigate interactions of fluticasone furoate on other drugs.

- Discontinuation due to adverse events

The number of withdrawals due to adverse events was low during the clinical development program for intranasal fluticasone furoate.
Overall, 18 subjects (12 from the placebo group and 6 from the FF group) withdrew from six studies in the adult and adolescent integrated database due to adverse events. Six of the 12 subjects from the placebo group had adverse events of infections (viral gastroenteritis, nasopharyngitis, sinusitis (2), pharyngitis, upper respiratory tract infection); two subjects withdrawn had seasonal allergy, one subject had both abdominal pain and nephrolithiasis, one subject had tendon rupture, one subject had back pain, and one subject had epistaxis. In the FF group four of six subjects were withdrawn due to infections (viral gastroenteritis, nasopharyngitis, bronchitis, and viral infection); one subject had hypersensitivity to coconut and one 62-year old subject was withdrawn due to increased intraocular pressure diagnosed during a routine ophthalmic examination nine days after beginning treatment.

In the long-term safety study FFR102123, 38 subjects (6%) in the fluticasone furoate nasal spray 110mcg group and 7 subjects (3%) in the placebo group were withdrawn due to AEs (most frequently were reported epistaxis, asthma, headache, nasal septum ulceration and nausea). Epistaxis was the only AE that led to the discontinuation of more than 1% of subjects. This AE led to the withdrawal of 15 subjects (2%) in the fluticasone furoate 110mcg group and no subjects in the placebo group. The majority of discontinuations due to epistaxis (10/15) occurred within the first 12 weeks of treatment and only one subject was withdrawn after more than 6 months of treatment.

In the paediatric integrated studies, 28 subjects (2%) were withdrawn due to AEs: 13 subjects (3%) in the placebo group, 10 subjects (3%) in the fluticasone furoate 55mcg group and 5 subjects (1%) in the fluticasone furoate 110 mcg group (most frequently were reported asthma and epistaxis).

Twenty one subjects were withdrawn from 11 clinical pharmacology studies; the 5 withdrawals attributed to an AE were: sore throat, transient hypotensive episode, abnormal liver enzymes, dizziness, abdominal pain.

- Post marketing experience

Fluticasone furoate nasal spray is commercially available in the USA since May 2007.

Discussion on clinical safety

The most relevant clinical problem following intranasal administration of fluticasone furoate appears to be a low incidence of epistaxis and nasal ulceration; these are described in the SPC. To further complement the available data GSK has committed, as part of FUMs, to submit results (including biopsy data) from a study investigating the effects of one year of continuous treatment with FF nasal spray on the nasal mucosa of PAR subjects.
At the request of CHMP, the applicant has added a warning statement with respect to Benzalkonium chloride to the Product Information, in line with the Guideline on excipients in the label and package leaflet of medicinal products for human use.

In response to the Day 120 LOQ, the applicant submitted additional analyses of the safety database for FF nasal spray regarding the possible adverse event of pyrexia. These confirmed that the slight increase in the proportion of children on FF reporting pyrexia in the clinical programme is not associated with upper respiratory tract infections, and there is no evidence for a dose-response effect. Furthermore the clinical presentation of the pyrexia events is not consistent with the characteristics of a drug-induced fever. CHMP agreed to the proposal from the applicant that the inclusion of pyrexia in section 4.8 of the SPC is not warranted, based on their commitment to specifically monitor reports of pyrexia in the post-licensing period. CHMP will monitor this through PSURs and updates of the RMP.

The low systemic availability means that the general metabolic and other unwanted properties of corticosteroids are unlikely to be a problem with this formulation used at the recommended dose.

Fluticasone furoate undergoes extensive first-pass metabolism. Based on the data submitted, moderate hepatic impairment is not expected to result in a clinically relevant effect for the normal adult dose. There are no data in patients with severe hepatic impairment, therefore no dosage recommendation can be proposed in this patient population, and caution is advised when treating these patients (SPC section 4.4).

Caution is recommended when co-administering fluticasone furoate with potent CYP3A4 inhibitors, as an increase in systemic exposure cannot be ruled out. At the request of CHMP the applicant has modified the proposed wording in SPC sections 4.4 and 4.5. The final wording is as follows:
-SPC Section 4.4
"Ritonavir
Concomitant administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate (see section 4.5)."
-SPC Section 4.5
"Caution is recommended when co-administering fluticasone furoate with potent CYP3A4 inhibitors as an increase in systemic exposure cannot be ruled out. In a drug interaction study of intranasal fluticasone furoate with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable fluticasone furoate concentrations in the ketoconazole group (6 of the 20 subjects) compared to placebo (1 out of 20 subjects). This small increase in exposure did not result in a statistically significant difference in 24 hour serum cortisol levels between the two groups (see section 4.4)."

In the FF clinical development programme for FFNS, patients with asthma who required inhaled or oral corticosteroids were excluded. Nevertheless, further to published case reports of adults and children who developed signs of hypercortisonism after use of cumulative doses of other inhaled (intranasal and intrabronchial) steroid, this potentially important issue has been addressed in the SPC and PL.

The following wording was agreed for SPC section 4.4 :
"As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently. "

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which has been updated according to comments from the CHMP assessment.

Table Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Effects on nasal mucosa	Routine pharmacovigilance including targeted questionnaires 12-month biopsy study (currently ongoing)	SPC Section 4.8 (Undesirable effects) Very common: epistaxis Common: nasal ulceration
Concurrent use of CYP3A4 inhibitors	Routine pharmacovigilance	-SPC Section 4.4 "Ritonavir Concomitant administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate (see section 4.5)." -SPC Section 4.5 "Based on data with another glucocorticoid (fluticasone propionate), that is metabolised by CYP3A4, co-administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate. Caution is recommended when co-administering fluticasone furoate with potent CYP3A4 inhibitors as an increase in systemic exposure cannot be ruled out. In a drug interaction study of intranasal fluticasone furoate with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable fluticasone furoate concentrations in the ketoconazole group (6 of the 20 subjects) compared to placebo (1 out of 20 subjects). This small increase in exposure did not result in a statistically significant difference in 24 hour serum cortisol levels between the two groups (see section 4.4)."
Use in patients with hepatic impairment	Routine pharmacovigilance	SPC Section 4.2: Hepatic Impaired Patients: No dose adjustment is required in mild to moderate

		hepatic impairment. There are no data in patients with severe hepatic impairment (see section 4.4 and 5.2). SPC Section 4.4 Fluticasone furoate undergoes extensive first-pass metabolism, therefore the systemic exposure of intranasal fluticasone furoate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events (see section 4.2 and 5.2). Caution is advised when treating these patients." SPC Section 5.2 Hepatic Impairment: There are no data with intranasal fluticasone furoate in patients with hepatic impairment. A study of a single 400 microgram dose of orally inhaled fluticasone furoate in patients with moderate hepatic impairment resulted in increased Cmax (42 %) and AUC(0-□) (172 %) and a modest (on average 23 %) decrease in cortisol levels in patients compared to healthy subjects. From this study the average predicted exposure of 110 micrograms of intranasal fluticasone furoate in patients with moderate hepatic impairment would not be expected to result in suppression of cortisol. Therefore moderate hepatic impairment is not predicted to result in a clinically relevant effect for the normal adult dose. There are no data in patients with severe hepatic impairment. The exposure of fluticasone furoate is likely to be further increased in such patients.
Systemic corticosteroid effects	Routine pharmacovigilance including targeted questionnaire	Warning in SPC section 4.4 : "Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery. Fluticasone furoate 110 micrograms once daily was not associated with hypothalamic-pituitary-adrenal (HPA) axis suppression in adult, adolescent or paediatric subjects. However the dose of intranasal fluticasone furoate should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. **As with all intranasal corticosteroids,**

		the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently."
Potential cataract development	Routine pharmacovigilance including targeted questionnaire 24 month ocular study	
Limited long term clinical experience in children including a potential effect on long-term growth in children	-12 month stadiometry study - Routine pharmacovigilance	
Pyrexia	Routine Pharmacovigilance including evaluation of events across age groups	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The results of in vitro pharmacodynamic studies indicate that FF exhibits anti-inflammatory activity which is similar to that of other glucocorticoids used in anti-inflammatory therapy. The in vitro potency of FF in terms of receptor affinity, receptor selectivity and anti-inflammatory activity is at least equal or better than the potency of previously approved glucocorticoids in AR therapy, such as fluticasone propionate and mometasone furoate. Results of in vitro onset and duration of action studies, and in vitro tissue binding studies indicate that FF has promising clinical potential in respect of the very rapid glucocorticoid receptor activation (the maximum effect is observed after 20 minutes) and long duration of action (up to 30 hours). This characteristic has a positive impact on reduction of systemic exposure to FF. The in vivo studies support the opinion that the in vitro profile of FF is group-specific. These studies demonstrate that it is an effective, high affinity anti-inflammatory agent in a number of distinct animal models of inflammation. Results of safety pharmacology studies indicate no significant adverse effects of FF, other than corticosteroid-specific.

The pharmacokinetic profile of FF was adequately examined. The collected data are sufficient for the assessment of FF for intranasal administration. In general FF pharmacokinetics is similar between the animal species tested and humans. The pharmacokinetic behaviour of FF absorbed systemically after intranasal administration is similar to that following oral and intravenous administration. Studies performed in dogs following intranasal administration indicate that systemic bioavailability of FF after intranasal administration is minimal (less than 1%); additionally, it is supported by a first past effect accompanied by an effective biotransformation to an inactive metabolite and rapid elimination. There is no appreciable risk of FF accumulation after intranasal administration at the proposed therapeutic dose. The toxicology studies performed by the applicant covered single dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity, local tolerance and other toxicity studies.
Single dose toxicity studies were performed in mice, rats and dogs. FF was administered by oral, intravenous and inhalation routes. The results of single dose studies in mice and rats (high doses of FF administered orally, intravenously or by inhalation, producing measurable systemic exposure) showed the effects typical for excess of glucocorticoids i.e. reduction of body weight and lymphoid depletion. In the repeated dose toxicity studies FF was administered by the inhaled route (mice, rats, dogs) and by the intranasal route (rats, dogs). The battery of multiple dose inhalatory and intranasal toxicology studies of FF administered to mice, rats and dogs revealed a range of findings class-specific to glucocorticoids. These findings were typically associated with systemic exposure to glucocorticoids and commonly reported for other marketed intranasal steroids. Local effects observed in the long-term intranasal studies suggest acceptable level of safety. The safety profile of the product is well documented and supported by the series of properly planned and completed studies. Comparative toxicokinetic data obtained from animal and human studies showed that intranasal administration of FF at the proposed doses produces no measurable systemic exposure to FF and the occurrence of systemic glucocorticoids activity is unlikely.

Efficacy

The clinical development has demonstrated the efficacy of fluticasone furoate in the treatment of the symptoms of SAR and PAR.
In the SAR studies FF nasal spray demonstrated statistically significant reductions from baseline compared with placebo for the primary endpoint (daily rTNSS) over the entire treatment period. The results for the primary endpoint were supported by the key secondary efficacy endpoint AM pre-dose iTNSS. This confirmed that once-daily administration of fluticasone furoate maintained the improvement in nasal symptoms of SAR until the end of the 24-hour dosing interval. Similar improvements were seen for AM and PM rTNSS suggesting consistent daytime and night time symptom relief. No individual nasal symptom disproportionately influenced the composite score for rTNSS and the resulting overall treatment difference over placebo. Across the studies, scores for subjects treated with fluticasone furoate 110mcg were significantly better than placebo, with a large proportion reporting moderate to significant improvement in this group compared with placebo (integrated analysis results: 52% and 30%, respectively). Fewer subjects receiving fluticasone furoate reported moderate or significant worsening compared with those receiving placebo (integrated analysis results: 3% and 12%, respectively a significant positive effect on ocular symptoms was observed) in 4 out of 4 studies in SAR.

The overall findings from the PAR studies were that fluticasone furoate nasal spray 110mcg was effective in improving the nasal symptoms and that once daily administration of fluticasone furoate nasal spray adequately maintains the improvement in nasal symptoms of PAR until the end of the 24-hour dosing interval. The treatment effect for the primary efficacy endpoint was statistically significant over placebo. The primary efficacy results were supported by the data from the key secondary endpoints.

Safety

Safety data were collected from the six short-term adult and adolescent phase 3 studies. The majority of SAR and PAR studies were 2 - 12 weeks in treatment duration, and thus approximately 80% of the subject exposures were 12 weeks or less.

In the safety database of 3954 subjects, 501 (25%) of the subjects (adults and adolescents) exposed to fluticasone furoate 110mcg once daily were exposed to treatment for a period of ≥6 months and 400 (20%) adult and adolescent subjects were exposed for ≥12 months.
The largest number of subjects exposed to fluticasone furoate 110mcg in the clinical development program was in the 18 to <65 year age group; 1333 of these subjects were treated with the 110mcg dosage.
In the adolescent population (aged 12 to <18 years), 198 subjects were exposed to fluticasone furoate 110mcg in the clinical studies.
In the paediatric phase 3 placebo-controlled clinical studies (subjects ≥2 to <12 years of age), 176 subjects 2 to <6 years of age were treated with the 110mcg or 55mcg dosages of fluticasone furoate and 618 paediatric subjects 6 to <12 years of age were treated with the 110mcg or 55mcg dosages. 54 of these subjects were ≥2 to 4 years of age and were treated with either a 55mcg or 110mcg dosage of fluticasone furoate nasal spray.

The most relevant clinical problem following intranasal administration of fluticasone furoate is a low incidence of epistaxis and nasal ulceration; these are described in the SPC. To further complement the available data GSK has committed to submit results (including biopsy data) from a study investigating the effects of one year of continuous treatment with FF nasal spray on the nasal mucosa of PAR subjects (as listed in 2.7 FUMs following the Marketing Authorisation).

The low systemic availability means that the general metabolic and other unwanted properties of corticosteroids are unlikely to be a problem with this formulation used at the recommended dose.
Caution is recommended when co-administering fluticasone furoate with potent CYP3A4 inhibitors, as an increase in systemic exposure cannot be ruled out. At the request of CHMP the applicant has modified existing wording to SPC sections 4.4 and 4.5

Fluticasone furoate undergoes extensive first-pass metabolism. Based on the data submitted, moderate hepatic impairment is not expected to result in a clinically relevant effect for the normal adult dose. There are no data in patients with severe hepatic impairment, therefore no dosage recommendation can be proposed in this patient population, and caution is advised when treating these patients (SPC section 4.4).

In the FF clinical development programme for FFNS, patients with asthma who required inhaled or oral corticosteroids were excluded. Nevertheless, further to published case reports of adults and children who developed signs of hypercortisonism after use of cumulative doses of other inhaled (intranasal and intrabronchial) steroid, this potentially important issue has been addressed in the SPC and PL.
The following wording was agreed for SPC section 4.4 (Special warning s and precautions for use) :
“As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently.”

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant has provided the User testing of Avamys to demonstrate readability and usefulness of the patient information leaflet to patients. The results of the user consultation were satisfactory and no further re-testing was requested at the time of the CHMP Opinion.

Risk-benefit assessment

FF is a synthetic glucocorticoid with proposed use as a topical anti-inflammatory compound in allergic rhinitis (AR) therapy. The idea of FF use is consistent with extensive clinical experience with other approved glucocorticoids administered as nasal spray in local therapy of AR. The pharmacological profile of FF is well defined. Its mode of action is typical for corticosteroids. FF exhibits potent anti-inflammatory activity.

During the Oral Explanation held during the September CHMP meeting, the applicant addressed the outstanding issues, in particular the indicated age range for children, lack of clinical study with active comparator, SPC wording.

Based on the data provided on quality, efficacy and safety (as discussed above) and further to the oral explanation by the applicant (and clarifications after the oral explanation), the CHMP concluded that FF has a positive benefit risk ratio in adults, adolescents and children aged 6 years and over .
For the age group 2 up to 6 years, CHMP considered that the number of patients in this age group (176 exposed to FF) and the lack of a clear dose response relationship do not allow concluding that the efficacy and safety of this medicinal product in such a population has been sufficiently established.

Further to the applicant's presentation regarding feasibility and methodological limitations of active-comparator studies with other intranasal corticosteroids, and because the results provided from placebo-controlled studies were sufficiently convincing, CHMP did not pursue this point as a follow-up measure.

The applicant agreed with the CHMP request to simplify and shorten the indication wording, in line with the Guideline on SPC; the description of symptoms (including the effect on ocular symptoms) was moved to SPC section 5.1.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Avamys 27.5 micrograms nasal spray suspension in the treatment of "the symptoms of allergic rhinitis" was favourable in adults, adolescents (12 years and over) and children (6 – 11 years)" and therefore recommended the granting of the marketing authorisation.