Decentralised Procedure

Public Assessment Report

Kantos / Foster / Kantos Master / Inuvair 200 Mikrogramm/6 Mikrogramm pro Inhalation Druckgasinhalation, Lösung

Kantos / FOSTER / KANTOS MASTER / INUVAIR NEXThaler 200 Mikrogramm/6 Mikrogramm pro Inhalation Pulver zur Inhalation

Beclometasone dipropionate + Formoterol fumarate Dihydrate

DE/H/0871-874/003-004/DC

Applicant: Chiesi Farmaceutici S.p.A.

Reference Member State	DE

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Name of the drug substance (INN name):	Beclometasone dipropionate (Ph.Eur.) + Formoterol fumarate Dihydrate (Ph.Eur.)
Pharmaco-therapeutic group (ATC Code):	R03AK08
Pharmaceutical form(s) and strength(s):	Pressurised inhalation solution Inhalation powder
Reference Number(s) for the Decentralised Procedure	DE/H/0871-874/003-004/DC
Reference Member State:	DE
Concerned Member States:	**DE/H/0871/003/DC**: AT, CZ, EL, ES, FR, HU, IT, NL, PL, PT, SI, SK, UK **DE/H/0871/004/DC**: AT, EL, ES, FR, HU, IT, NL, PL, PT, SI, SK, UK **DE/H/0872/003-004/DC:** IT **DE/H/0873/003/DC:** BE, BG, CY, DK, EE, EL, ES, FI, FR, IT, LT, LU, LV, NO, RO, UK **DE/H/0873/004/DC:** BE, BG, CY, EE, EL, ES, FI, FR, IT, LT, LU, LV, NO, RO **DE/H/0874/003-004/DC:** IT
Applicant (name and address)	Chiesi Farmaceutici S.p.A. 26/a Via Palermo I-43122 Parma

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Foster 200/6*, *Kantos 200/6, Kantos Master 200/6, Inuvair 200/6* and *Foster NEXThaler 200/6, Kantos NEXThaler 200/6, Kantos Master NEXThaler 200/6, Inuvair NEXThaler 200/6*,

- in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta2-agonist) is appropriate:
    - patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta2-agonist or
    - patients already adequately controlled on both inhaled corticosteroids and long-acting beta2-agonists.

is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The present application is submitted according to Article 10b of Directive 2001/83/EC as amended (fixed combination application) and concerns a line extension of the licensed fixed combination of the two well known active substances, i.e. beclometasone diproprionate (BDP) and formoterol fumarate (FF) (DE/H/0871-0874/01/MR).

With Germany acting as the Reference Member State in this Decentralised Procedure, the applicant is applying for the Marketing Authorisations in

CHF 1535 200/6 µg pMDI
DE/H/0871/003/DC: AT, CZ, EL, ES, FR, HU, IT, NL, PL, PT, SI, SK, UK
DE/H/0872/003/DC: IT
DE/H/0873/003/DC: BE, BG, CY, EE, EL, ES, FI, FR, IT, LT, LU, LV, NO, RO, UK
DE/H/0874/003/DC: IT

CHF 1535 200/6 µg NEXThaler®
DE/H/0871/004/DC: AT, EL, ES, FR, HU, IT, NL, PL, PT, SI, SK, UK
DE/H/0872/004/DC: IT
DE/H/0873/004/DC: BE, BG, CY, EE, EL, ES, FI, FR, IT, LT, LU, LV, NO, RO
DE/H/0874/004/DC: IT

as Concerned Member States.

The active substances are not considered “new active substances”.

II.2 About the product

Chiesi CHF 1535 is an anti-asthmatic, fixed-dose combination (FDC) of the ICS beclometasone dipropionate (BDP) and the LABA formoterol fumarate (FF). The present application concerns two different formulations of CHF 1535

- as solution containing 200 µg BDP and 6 µg FF per inhalation, delivered using the pMDI device (DE/H/0871-874/003-004/DC), and
- as inhalation powder containing 200 µg BDP and 6 µg FF per inhalation, delivered through the multi-dose breath-actuated device (DE/H/0871-874/004/DC).

Beclometasone dipropionate (BDP) is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone-17-monopropionate (B17MP) which has a more potent topical anti-inflammatory activity compared with the pro-drug beclometasone dipropionate.

Formoterol fumarate (FF) is a selective beta$_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after dose administration.
The proposed indication is the following:

- Regular treatment of asthma in adults where use of a combination product (inhaled corticosteroid and long-acting β2-agonist) is appropriate:
    - patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2-agonist or
    - patients already adequately controlled on both inhaled corticosteroids and longacting β2-agonists

The proposed dose regimen is 2 inhalations twice daily. The product is indicated for adult patients only.

CHF 1535 100/6 µg pMDI

CHF 1535 was first developed by Chiesi as a solution delivered through a pressurised metered dose inhaler (pMDI) with hydrofluoroalkane (HFA)-134a as propellant (norflurane) and containing BDP 100 µg and FF 6 µg per actuation (CHF 1535 100/6 µg pMDI). CHF 1535 100/6 µg pMDI is currently licensed in almost all EU countries under various trade names e.g. Foster®, Fostair® and Inuvair® (MRP refs: DE/H/0871/001/MR, DE/H/0872/001/MR, DE/H/0873/001/MR, DE/H/0873/001/MR/E01 and DE/H/0874/001/MR).

CHF 1535 100/6µg pMDI is approved for the indication:

- Regular treatment of asthma in adults where use of a combination product (inhaled corticosteroid and long-acting β2-agonist) is appropriate:
    - patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2-agonist or
    - patients already adequately controlled on both inhaled corticosteroids and longacting β2-agonists

Recently, the use of CHF 1535 100/6 µg pMDI has also been extended to the following additional dose regimen/indication, by approval of two separate Type II variations:

- "Maintenance and reliever therapy (MART) taken as regular maintenance treatment and as needed in response to symptoms" (DE/H/0871/001/II/021, DE/H/0872/001/II/016, DE/H/0873/001/II/024, DE/H/0874/001/II/015).
- "Symptomatic treatment of patients with severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1 second [FEV1] <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators" (DE/H/0871/001/II/025, DE/H/0872/001/II/020, DE/H/0873/001/II/029, DE/H/0874/001/II/019).

CHF 1535 100/6 µg NEXThaler®

Furthermore, Chiesi has developed a inhalation powder containing 100 µg BDP and 6 µg FF per inhalation, delivered through a new multi-dose breath-actuated device (CHF 1535 100/6 µg NEXThaler®). CHF 1535 100/6 µg NEXThaler® is currently licensed in 23 EU countries under various trade names e.g. Kantos NEXThaler®, Foster NEXThaler® and Inuvair NEXThaler® (DE/H/0871-0874/002/DC, DE/H/0871-0873/002/E/001).

The dry powder inhaler CHF 1535 100/6 µg NEXThaler® has been developed in order to provide physicians and patients with an alternative delivery system, especially for patients experiencing poor coordination with pMDIs. Other FDCs of ICS + LABA, namely Symbicort® and Seretide®, are already present on the market as dry powder inhaler (DPI) formulations.

CHF 1535 100/6 µg NEXThaler® is approved for the indication:

Regular treatment of asthma in adults where use of a combination product (inhaled corticosteroid and long-acting β2-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2-agonist or

- patients already adequately controlled on both inhaled corticosteroids and longacting β2-agonists.

CHF 1535 100/6 µg NEXThaler® is currently not approved for MART and not approved for COPD. However, Chiesi plans to extend the use of CHF 1535 100/6 µg NEXThaler® to the COPD indication via a separate type II variation.

CHF 1535 200/6 µg pMDI and CHF 1535 200/6 µg NEXThaler®

As with the other licensed CHF 1535 formulations, CHF 1535 200/6 µg pMDI and CHF 1535 200/6 µg NEXThaler® were developed with a high "extra-fine" inhaled particle fraction (i.e. mass median aerodynamic diameter MMAD of 1.4 – 1.7 µm) for both active ingredients, enabling efficient lung distribution and deposition through the entire bronchial tree, while minimising systemic exposure through reduced gastrointestinal (GI) absorption.

This new dose strength 200/6 µg was developed in an effort to provide caregivers with flexibility to adapt treatments to specific patients' conditions. According to the 2012 update of the GINA guideline, treatment of asthma may involve a step-up and step-down of the current treatment including changing the steroid dose to reach and maintain asthma control. In this context, patients should be assessed and treatment adjusted periodically in a stepwise approach based on their asthma control status. The anticipated dosing schedule of CHF 1535 200/6 µg (2 actuations bid, i.e. BDP/FF 800/24 µg/day), is expected to be an adequate step-up in therapy for patients with severe persistent asthma who are not adequately controlled either on high doses of ICS monotherapy or on medium doses of ICS within a fixed combination ICS and LABA.

II.3 General comments on the submitted dossier

Paediatric Investigation Plan

An approved PIP in the asthma indication is in place for CHF 1535, covering both the pMDI and the DPI formulations. The PIP was approved in April 2010. All paediatric studies in the PIP are deferred but some of them are ongoing at the time of the present application. The PIP was agreed to be completed by October 2014.

Regulatory guidance and advice

Following guidelines are applicable:

- CHMP Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in children and Adolescents CPMP/EWP/4151/00 Rev. 1 – January 2009;
- CHMP Guideline on Clinical Development of Fixed Combination Medicinal Products CHMP/EWP/240/95 Rev. 1; and
- CHMP Guideline on Investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1.

The development plan was shared in scientific advice meetings with the BfArM and the MHRA.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

No GCP issues have been detected.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

CHF 1535 200/6 µg pMDI

BDP+ formoterol 200/6 µg Pressurised Inhalation Solution (referred to in this dossier also as CHF 1535 HFA 200/6) is a pressurised inhalation solution containing beclometasone dipropionate (BDP) 200 micrograms and formoterol fumarate (FF) 6 micrograms per metered dose, delivered via pressurised metered dose inhaler using a HFA-134a (non CFC) as propellant. Each can contains 120 or 180 doses.

CHF 1535 200/6 µg NEXThaler®

CHF 1535 NEXT DPI 200µg/6µg inhalation powder is an inhalation powder containing the fixed combination beclometasone dipropionate (BDP) 100 micrograms and formoterol fumarate (FF) 6 micrograms per metered dose, delivered via the novel NEXT DPI® dry powder inhaler. Each inhaler contains 120 doses.

Drug Substance

CHF 1535 200/6 µg pMDI, Drug Substance, part of the Pressurised Metered Solution for Inhalation

Beclometasone Dipropionate Anhydrous (BDP), non-micronized, from suppliers A and B have been used for the manufacture of the drug product. Both sources comply with the requirements of Ph. Eur. monograph current edition.

The manufacturers of drug substance from both sources have obtained the Ph. Eur. Certification of Suitability respectively.

A re-test period is not mentioned on the CEP for the BDP of supplier B. However, the re-test period of 5 years is considered acceptable.

Formoterol Fumarate Dihydrate sourced from suppliers C and A complies with the requirements of Ph. Eur. Monograph current edition. The manufacturers of drug substance from both sources have obtained the Ph. Eur. Certification of Suitability respectively.

A re-test period is not mentioned on the CEP for FF from supplier A. However the re-test period of 36 months is considered acceptable for FF by the data provided.

CHF 1535 200/6 µg NEXThaler, Drug Substance, part of the Dry Powder Formulation

For the micronized drug substance, BDP, the applicant has submitted a valid CEP. An additional test for residual solvent by GC and further physical tests (test of apparent volume, apparent density, tapped density and PSD) are required. In the CEP a re-test period of the drug substance (5 years if stored, protect from light in a double PE bag placed into an aluminium box) is displayed. The holder of the certificate declares the absence of the use of material of human or animal origin in the manufacture of the substance.

For the -micronized drug substance, FF, sourced from supplier C, the applicant has submitted a Certificate of Suitability. An additional test for residual solvent methanol by gas chromatography is required. An adequate description of the approved GC-method has been provided in the appendix of the CEP.

Primary packaging material and a re-test period have not been is displayed in the CEP.

The holder of the certificate declares the absence of the use of material of human or animal origin in the manufacture of the substance.

Drug Product

CHF 1535 200/6 µg pMDI, Pressurised Metered Solution for Inhalation

BDP+ formoterol 200/6 µg Pressurised Inhalation Solution is a pressurised inhalation solution containing beclometasone dipropionate (BDP) 200 micrograms and formoterol fumarate (FF) 6 micrograms per metered dose, delivered via pressurised metered dose inhaler using a HFA-134a (non CFC) as propellant. Each can contains 120 or 180 doses.

The manufacturing process is a non-standard process (content of BDP & FF < 2 % and the type of pharmaceutical form).

All provided IPCs established are justified. The manufacturing process and in-process controls together with intermediate testing correspond to the actual standards of pharmaceutical technology and are suitable to guarantee an appropriate quality of the finished product. The presented specification of the finished product complies with the Ph. Eur., the requirements of QWP Guideline CHMP/QWP/49313/2005 and relevant ICH Guidelines.
Impurities which can occur during manufacturing/ stability of the DP have been discussed. The specifications set for release and shelf-life have been acceptably justified.
Based on the stability data provided, a shelf-life of 15 months is accepted, when stored in a refrigerator, and as in use storage condition "Do not store above 25°C (for a maximum of 5 months)".

CHF 1535 200/6 µg NEXThaler, Dry Powder Inhalation Product
The applicant has developed a fixed combination of the inhaled corticosteroid BDP and the long-acting β_2-agonist FF as dry powder for inhalation to be administered through a novel inhaler named NEXT DPI. Development of formulation has been mostly acceptably described. The pharmaceutical development studies for the container closure system have been provided fully in accordance with QWP Guideline, CHMP/QWP/49313/2005. During the development studies suitability and robustness of the dry powder inhaler NEXT DPI and the drug product, CHF 1535 NEXT DPI as well as comparability of clinical and commercial batches has been demonstrated.

The manufacturing process is a non-standard process (content of BDP & FF < 2 % and the type of pharmaceutical form), which includes the Chiesi "Hard Pellets" technology which necessitates two types of lactose: a coarse fraction and a 'fine' one to prepare a pre-blend which is micronized. The "coarse lactose" and the "micronized pre-blend" are then blended together to produce the "carrier". The "carrier" and drug substances are mixed and blended to produce the final drug substance blend which is filled into the inhaler. Description of the manufacturing process is acceptable.
All provided IPCs established are justified. The manufacturing process and in-process controls together with intermediate testing correspond to the actual standards of pharmaceutical technology and are suitable to guarantee an appropriate quality of the finished product.

The presented specification of the finished product complies with the Ph. Eur., the requirements of QWP Guideline CHMP/QWP/49313/2005 and relevant ICH Guidelines.

Impurities which can occur during manufacturing/stability of the DP have been discussed. The specifications set for release and shelf-life have been acceptably justified. Based on the stability data provided, the shelf-life of 24 months is accepted including the in-use stability of six months. The precaution advice "do not store above 25 °C" for the un-pouched product is accepted.

III.2 Non-clinical aspects

General aspects with regard to nonclinical evaluation
The present application concerns two different formulations of CHF 1535:

- as solution containing 200 µg BDP and 6 µg FF per inhalation, delivered using the pMDI (pressurized metered dose inhaler) device (DE/H/0871-874/003/DC), and
- as inhalation powder containing 200 µg BDP and 6 µg FF per inhalation, delivered through the DPI dry powder inhaler) device (DE/H/0871-874/004/DC).

The present applications are submitted according to Article 10b of Directive 2001/83/EC as amended (fixed combination application) and represent line extensions of already approved fixed combination products providing 100 µg of beclomethasone diproprionate and 6 µg of formoterol fumarate per application, delivered via

- the pMDI device (DE/H/0871-874/001/MR)
- the DPI (DE/H/0871-0874/002/DC)

with the only relevant difference in pharmaceutical composition being a higher content of beclomethasone diproprionate (i.e. 200 µg versus 100 µg per application).

No additional studies were performed with the new strength. This is considered acceptable, since the new formulations contain the same excipients/propellant as the currently licensed ones with only minor quantitative difference and the active ingredients have similar particle size.

The main difference is the strength of BDP. However since previous studies tested the currently approved formulations of CHF 1535 (100 µg BDP/6 µg FF) at high doses and no increase in toxicity or synergism of the two components was found, the toxicological studies previously conducted are relevant also to the formulation (200 µg BDP/6 µg FF) subject of the present application.

A short summary of the nonclinical discussion/results previously provided for the CHF 1535 (100 µg BDP/6 µf FF) combination is presented below.

Pharmacology
BDP and FF are well known representatives of the glucocorticoid and long acting β_2-agonist (LABA) classes. Inhaled corticosteroids (ICS) like beclometasone exhibit local anti-inflammatory and immune suppressive effects via multiple mechanisms. They reduce the number and/or activity of inflammatory cells, inhibit the transcription of several cytokines that are over expressed in asthma, inhibit phospholipase A2 with consequent reduced formation of prostaglandins and leukotrienes in the airway, and inhibit plasma exudation. LABA like formoterol bind to the G-protein coupled β_2-adenoreceptor and induce a cAMP/protein kinase signalling cascade, which results in smooth muscle relaxation, and possible anti-inflammatory effects.

Several interactions between GCS and LABA, like increased receptor expression by enhanced gene transcription and synergistic suppression of inflammatory mediator release have been reported.

The pharmacological profile of the two active compounds as well as non-clinical and clinical data supporting the combined use of BDP and formoterol had been adequately reviewed in the nonclinical overview and relevant aspects are briefly described in the submitted SmPC.

Pharmacokinetics
BDP and formoterol are well known compounds with broad clinical use. Pharmacokinetic data of the two active compounds are described in detail in section 5.1 of the SmPC.

Toxicology
BDP and formoterol are well known representatives of the glucocorticoid and long acting β_2-agonist (LABA) classes, and the toxicological profile of the individual compounds have been extensively reviewed.

A toxicity program consisting of studies on single and repeated dose toxicity, genotoxic potential and reproductive toxicity has been performed for the fixed combination of BDP and /formoterol. Toxicity studies include repeat dose inhalation toxicity studies in rats and dogs (up to 13 weeks) with a DPI formulation similar to that intended for human treatment. Additionally, inhalation toxicity studies with the excipient magnesium stearate were performed in rats (up to 26 weeks) and dogs (up to 4 weeks), and also separate in vitro studies with this inactive compound to examine its solubility and potential cytotoxic potential.

The results of repeated dose inhalation studies in rats and dogs up to 13 weeks, carried out with a BDP/formoterol DPI formulation similar (with a content of magnesium stearate of 0.3% instead of 0.2 %) to that intended for human treatment, evidenced adequate safety margins. No significant signs of lung irritation were seen up to the highest dose (up to 214 and 27 times the maximum human dose of 400/24 µg as systemic exposure) administered to rats and dogs for 13 consecutive weeks. The main systemic alterations were related to the immuno-suppressive activity of BDP observed in both species and the cardiovascular effects seen mainly in dogs (tachycardia, myocardial fibrosis at high doses). The NOAELs of BDP/formoterol showed a systemic exposure 12 and 3 times (beclomethasone-17-

monophospat) and 1 (or more) and 6 times (formoterol) in rats and dogs of the respective exposure observed in humans after a inhalation dose of 400 µg BDP/24 µg FF per day. The NOAELs of the DPI formulation were superimposable to those of the corresponding pMDI formulations, showing an equivalent toxicity profile.

Inhalation toxicology studies with magnesium stearate in the dog up to 4 weeks and in the rat up to 26 weeks have shown no specific toxicity in either species. The rats exhibited on nasal cavities minor non-specific effects to the very high burden of magnesium stearate particles used in the 4-week study which was not observed in the dog and in subsequent 6-month study in rats. In particular, in the latter study no pathological findings or signs of accumulation of particles were seen at the histological examination of the lungs. The no effect levels in these studies were 332 and 19,000 µg/kg/day in the rat and dog respectively, indicating no risk for the human exposure to the BDP/formoterol DPI formulation with a maximum exposure to magnesium stearate of 80 µg/day (i.e. 20 µg/4 actuation/day).

Corresponding in vitro studies reveal an enhanced solubility of MgSt blended on lactose in BAL, and no relevant pro-inflammatory or unspecific cell damaging effect of MgSt up to a concentration well above the intended clinical use has been observed in human lung epithelial cells.

Studies on metabolic clearance in A549 cells suggest that MgSt uptake and metabolism in lung cells is similar to that reported for stearic acid. Following intratracheal administration of MgSt, no development of granulomas was noted, contrary to comparable silica treatment.

Overall, based on the provided extended data set on the excipient magnesium stearate, no safety concern due to the small quantities (0.2 % w/w) of MgSt as present in the DPI formulation was identified.

Environmental Risk Assessment
Since the present application concern line extensions of the licensed fixed combinations of two well-known active substances, i.e. BDP and FF, no phase I and II experimental studies on environmental risk assessment according to the EMEA/CHMP/SWP/4447/00 [1] are considered necessary. For the present application an increase in environmental risk is not foreseen since the clinical use of the new formulations is an alternative to that of other already marketed similar formulations.

III.3 Clinical aspects

CHF 1535 200/6 µg pMDI

The clinical development programme for CHF 1535 200/6 µg pMDI includes six studies: three PK single-dose studies, one PD multiple-dose study and two phase III pivotal clinical studies:

- Study CP01 (**PK, dose proportionality, without charcoal**): A phase I, monocentre, open, randomized, placebo-controlled, 4-way crossover study to evaluate the pharmacokinetics and pharmacodynamics of BDP/B17MP and formoterol with increasing dose strengths of the BDP/formoterol HFA134a pMDI combination (CHF 1535) (CCD-0813-CSRPR-0002, EUDRACT No.: 2008-000619-13).
- Study CP03 (**PK, dose proportionality, with charcoal**): A phase I, monocentre, open, randomized, 3-way cross-over clinical pharmacology study to evaluate the lung bioavailability of BDP/B17MP and formoterol across three different dose strengths of CHF 1535 pMDI (fixed combination of beclomethasone dipropionate plus formoterol fumarate 50/6 µg, 100/6 µg, 200/6 µg) administered with activated charcoal in healthy volunteers (CCD-1203-PR-0078, EUDRACT No.: 2012-000716-28).

A lower strengths (50/6 µg) was also used in studies CP01 and CP03 as this strengths is currently under development for use in children as part of an approved PIP in the asthma indication.

- Study CP02 (**PK, with and without spacer**): Open, randomised, 3-way cross-over, placebo controlled, single dose clinical pharmacology study in 24 healthy volunteers after inhalation of

BDP/formoterol (200+6 µg) HFA fixed combination using the standard actuator with or without Aerochamber Plus spacer (CCD-0811-CSR-0013, EUDRACT No.: 2008-006406-42).

- Study CP04 (**supportive**): Dose response evaluation of CHF 1535 HFA pMDI in asthmatic patients using lung function, adenosine monophosphate bronchial challenge and fractional exhaled nitric oxide (FE_{NO}). Randomized, double-blind, double-dummy, placebo controlled, multiple doses, 3-way cross-over design (CCD-0708-CSR-0006, EUDRACT No.: 2007-004345-14).
- Study CT01 **(phase III study)**: A 24-week, multicentre, multinational, randomized, double-blind, triple-dummy, 3-arm parallel group study comparing the efficacy and safety of CHF 1535 200/6 (beclomethasone dipropionate 200 µg plus formoterol 6 µg/actuation), 2 puffs b.i.d., versus beclomethasone dipropionate HFA (250 µg/actuation), 4 puffs b.i.d., versus Seretide® 500/50 (fluticasone 500 µg plus salmeterol 50 µg/actuation), 1 inhalation b.i.d., in patients with severe asthma (CCD-0605-PR-0021, EUDRACT No.: 2007-002587-99).
- Study CT02 **(phase III study)**: A 12-week, multinational, multicentre, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of CHF 1535 200/6 µg (fixed combination beclomethasone dipropionate/formoterol) versus beclomethasone dipropionate in adult asthmatic patients not adequately controlled on high doses of inhaled corticosteroids or on medium doses of inhaled corticosteroids plus long-acting β2-agonists (CCD-1005-CSR-0071, EUDRACT No.: 2010-020602-14).

Overall, more than 1100 asthmatic patients representing the target population were treated during the programme.

<u>CHF 1535 200/6 µg NEXThaler®</u>
The line extension application for CHF 1535 200/6 µg NEXThaler® includes one PK single-dose study and one PD single-dose study:

- Study CP01 200/6 DPI (**PK, dose proportionality, with and without charcoal**): A Phase II, monocentre, open, randomized, 6-way cross-over clinical pharmacology study to evaluate the lung bioavailability of BDP/B17MP and formoterol and the total systemic exposure across two different dose strengths of CHF 1535 NEXThaler® DPI (fixed combination of beclomethasone dipropionate plus formoterol fumarate 100/6 µg and 200/6 µg) administered with and without activated charcoal in adult asthmatic patients (CCD-1205-PR-0087, EUDRACT No.: 2012-002370-30).
- Study CT01 200/6 DPI (**PD study on FF efficacy**): A phase II, multicentre, double blind, randomized, 5-way cross-over study to test the non-inferiority of the bronchodilator effect of CHF 1535 200/6 DPI versus CHF 1535 100/6 DPI in partially controlled and uncontrolled adult asthmatic patients (CCD-01535BA1-01, EUDRACT No.: 2013-004826-27).

Clinical Pharmacokinetics
<u>CHF 1535 200/6 µg pMDI</u>
The PK programme includes two dose-proportionality studies (CP01 and CP03) and one study investigating the use of CHF 1535 200/6 µg coupled with a named spacer (CP02). A lower strengths (50/6 µg) was also used in studies CP01 and CP03 as this strengths is currently under development for use in children as part of an approved PIP in the asthma indication.

The main objectives of the pharmacokinetic studies were to investigate:

- the proportionality of BDP and B17MP (active BDP metabolite) total systemic exposure (AUC_{0-t} and C_{max}) across the three BDP dose strengths (50, 100, 200 µg);
- the proportionality of lung deposition of B17MP across the three BDP dose strengths (50, 100, 200 µg) through the use of activated charcoal block,
- the equivalence of formoterol lung deposition and total systemic exposure in the three formulations (50/6 µg, 100/6 µg, 200/6 µg); and
- the systemic exposure to B17MP and formoterol when CHF 1535 200/6 µg is used with a spacer device.

Studies CP01, CP02 and CP03 evaluated supra-therapeutic doses (4 inhalations of 50/6 µg, 4 inhalations of 100/6 µg and/or 4 inhalation of 200/6 µg). Nevertheless, starting from 1-2 h post dose (depending on the total dose), almost all subject had BDP plasma concentrations below LLOQ and most BDP PK parameters could not be reliably estimated. Thus - as pre-specified - in study CP02 and CP03 the pharmacokinetics of the metabolite B17MP were used as relevant metric.

Study CP01
B17MP

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	89.2 %	79.8 % – 99.7 %	18.7 %
Cmax	88.9 %	78.0 % - 101.2 %	21.8 %

[1] Calculated from a Residual Mean Square of 0.03450 for AUC_{0-t} and 0.04635 for C_{max}. These values take into consideration all treatments included in the Analysis of Variance.

Formoterol

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	102.2 %	90.4 % - 115.5 %	20.5 %
Cmax	97.2 %	81.8 % - 115.5 %	29.1 %

[1] Calculated from a Residual Mean Square of 0.04125 for AUC_{0-t} and 0.08152 for C_{max}. These values take into consideration all treatments included in the Analysis of Variance.

Results of study CP01 (safety study) show that there is no increased systemic exposure to B17MP and FF.

Study CP03
B17MP

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC^{2}_{(0-t)}$	91.63	83.79-100.20	18.6
Cmax	88.20	78.07-99.65	25.6

[1]Estimated from the Residual Mean Squares.

In the phase III study CT02 the applicant has successfully demonstrated that CHF 1535 200/6 (BDP/FF) has beneficial effects with respect to BDP alone in improving lung function in uncontrolled asthmatic patients. Thus, although the lower limit of the 90% CI for the dose-normalised B17MP Cmax in study CP03 (lung deposition study) was slightly below the acceptance interval (78.07%), this observed difference should not considered to be clinically relevant.

Formoterol

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC^{2}_{(0-t)}$	86.15	75.94-97.74	26.5
Cmax	89.30	81.86-97.42	18.1

[1]Estimated from the Residual Mean Squares.

The slightly lower bound of formoterol AUC0-t in the lung deposition data is expected not to have a relevant clinical impact on bronchodilation on the basis of the evidence provided by the peer-reviewed literature, by evidence from the 200/6 µg DPI program (see results of study CT01 200/6 DPI) and clinical data obtained in the pivotal phase III study CT02.

Study CP02
Study CP02, also performed in healthy subjects, compared CHF 1535 200/6 µg administered with standard actuator and with AeroChamber Plus® spacer (which is currently approved for CHF 1535 100/6 µg formulation). The study showed that the use of the spacer increased peak plasma concentration (C_{max}) of B17MP and formoterol. The increased areas under the curve in the first 30 minutes ($AUC_{0-30\ min}$) of formoterol reflects a higher lung deposition, but there was no increase in the total systemic exposure (AUC_{0-t}) to both B17MP and formoterol

The higher peak concentration and exposure over 30 min as well as the decrease in systemic exposure observed for B17MP and formoterol when using the AeroChamber Plus® spacer device has been previously recognised in the type II variation procedure (DE/H/0871/001/II/013, DE/H/0872/001/II/011, DE/H/0873/001/II/014, DE/H/0874/001/II/010).

CHF 1535 200/6 µg NEXThaler®
Whereas the line extension for CHF 1535 200/6 µg pMDI is based on a full clinical development plan, for CHF 1535 200/6 µg NEXThaler® one PK study was conducted to demonstrate the dose proportional delivery of BDP between the 100/6 and 200/6 strengths of CHF 1535 DPI as well as the consistency of Formoterol delivery between the two strengths.

Study CP01 200/6 DPI
In Study CP01 200/6 DPI asthmatic patients were supposed to receive either CHF 1535 NEXThaler® 100/6 µg or 200/6 µg with or without activated charcoal. Aim of the study was to determine the dose-proportionality of the ICS component and to determine bioequivalence of the LABA component. Similar to the PK studies conducted with the pMDI, study CP01 200/6 DPI evaluated supra-therapeutic doses (total dose of 400 µg BDP / 24 µg formoterol and 800 µg BDP / 24 µg formoterol, respectively).

B17MP:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref		Confidence Intervals		CV%[1]
	Test/Ref	Test/Ref+CB[2]	Test/Ref	Test/Ref+CB[2]	
$AUC_{(0-t)}$	85.28	89.86	80.61-90.21	85.03- 94.97	12.2
Cmax	80.95	87.53	76.12- 86.08	82.40-92.98	13.3

[1] Estimated from the Residual Mean Squares.
[2] CB = Charcoal Block

The results show that AUC_{0-t} and C_{max} of B17MP increased proportionally with the dose throughout the CHF 1535 dose range 100/6 µg and 200/6 µg, when administered with and without activated charcoal.

Formoterol:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref		Confidence Intervals		CV%[1]
	Test/Ref	Test/Ref+CB[2]	Test/Ref	Test/Ref+CB[2]	
$AUC_{(0-t)}$	85.99	78.23	78.35-94.37	70.72-86.55	22.4
Cmax	79.57	80.17	72.63- 87.18	73.29-87.69	19.9

[1] Estimated from the Residual Mean Squares.
[2] CB = Charcoal Block

The results show that CHF 1535 NEXThaler® 200/6 µg is

- non-inferior to CHF 1535 NEXThaler® 100/6 µg with regard to total systemic exposure (safety surrogate) for (the upper 90% confidence intervals [CIs] for the T/R ratios of Cmax and AUCt after study treatment administration without oral charcoal were below the limit of 1.25).

- not bioequivalent with CHF 1535 NEXThaler® 100/6 µg in pulmonary deposition (efficacy surrogate) (95% CIs for the T/R ratios of Cmax and AUCt after study treatment administration with oral charcoal were below bioequivalence limits of 0.80).

Since therapeutic equivalence in efficacy could not be shown by pharmacokinetics, a PD study on formoterol efficacy is needed to confirm therapeutic equivalence between the CHF 1535 NEXThaler® 200/6 µg and CHF 1535 NEXThaler® 100/6 µg.

Pharmacodynamics
BDP given by inhalation at recommended doses has a glucocorticoid antiinflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol is a selective beta2-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

No new data with regard to the pharmacodynamics of BDP and formoterol has been provided.

Clinical efficacy
Study CP04
The objective of this PD study was to evaluate the onset and the dose-response of the bronchoprotective and anti-inflammatory action of CHF 1535 100/6 pMDI at two dose levels (1 inhalation 100/6 µg BID and 4 inhalation 100/6 µg BID). The assessments were made in adult, steroid-naive, asthmatic patients following repeated administration of CHF 1535 over 3 days. Primary endpoints were FEV1 normalised by time (AUC0-4h) on Day 1 of each study period, FeNO levels at 4 hours after the morning dose on Day 3 of each study period immediately before the AMP challenge, and PC20 AMP immediately after the exhaled FENO measurement.

AUC0-4h FEV1 was significantly higher in both the high dose period (p=0.0001) and the low dose period (p=0.0001) compared to placebo. However, there was no significant difference between doses. PC_{20} AMP was statistically significantly higher in the high dose period (p<0.0001) and the low dose period (p<0.0001) compared to placebo. Also, PC_{20} AMP in the high dose period was also significantly higher than in the low dose period (p=0.0185). FE_{NO} at 4 hours was significantly lower in both the high dose (p<0.0001) and low dose periods (p=0.0043) compared to placebo. Also, Fe_{NO} in the high dose period was significantly lower than in the low dose period (p=0.0423).

In conclusion, there was a significant early bronchodilator effect following CHF 1535 pMDI treatment and dose response for the ICS was demonstrated on surrogate markers of inflammation PC_{20} AMP and Fe_{NO}.

<u>CHF 1535 200/6 µg pMDI</u>
The two phase III studies evaluated the clinical efficacy and safety of CHF 1535 200/6 µg in patients with not adequately controlled asthma:

- Study CT01 was a 24 week, randomised, double blind, parallel group, 3 arm study that investigated the superiority of CHF 1535 200/6 µg (2 puffs bid) vs. non extrafine BDP (Clenil®; 250 µg, 4 puffs bid) in terms of pulmonary function (change from baseline in pre-dose FEV1) and asthma control (percentage of complete days without asthma symptoms), and the non-inferiority of CHF 1535 200/6 µg vs. Seretide® (fluticasone 500 µg/salmeterol 50 µg, 1 puff bid) in terms of pulmonary function. Secondary objectives of the study were to evaluate the effect of treatments on additional lung function parameters (e.g. PEF) and clinical outcome measures (e.g. rescue use and symptoms scores), to assess the achievement of asthma control and the safety and tolerability (e.g. hypothalamic-pituitary-adrenal axis suppression) of CHF 1535 200/6.
- Study CT02 was a 12 week randomised, double blind, parallel group, 2 arm study comparing the efficacy and safety of CHF 1535 200/6 µg (2 puffs bid) vs. extrafine BDP

(Qvar®; 100 µg 4 puffs bid). In this study, the primary endpoint was the change in average pre-dose morning peak expiratory flow (PEF) from baseline to the end of treatment.

Study CT01
Initially, study CT01 was planned as pivotal study. However, the superiority of CHF 1535 vs. BDP for the change from baseline in pre-dose FEV1 and in percentage of complete days without asthma symptoms was not achieved.

Study CT02
A new pivotal study was planned with the aim to demonstrate the efficacy of CHF 1535 200/6 versus ICS monotherapy. The new study was designed taking into consideration the findings of study CT01 and the recommendations from regulatory authorities (with the MHRA on 17th February 2011 and with the BfArM on 8th August2011). In particular, the applicant was advised by the MHRA that it is not necessary to establish non-inferiority of the proposed new higher strengths to an existing marketed fixed-dose combination product. Also, pre-dose morning PEF was chosen as the primary endpoint and a BDP extrafine formulation (QVAR®) was used as comparator for the corticosteroid monotherapy.

Adult asthmatic patients who, despite previous treatment with high dose of ICS in monotherapy or medium dose of combination ICS/LABA, had a low FEV1 (<80 % predicted) were not fully controlled (based on GINA asthma control parameters and ACQ), were included in the study. According to the stepwise treatment approach outlined in the GINA guidelines, these patients can be assigned to treatment steps 3 and 4, which correspond to those who may benefit from switching to high dose of ICS+LABA.

A total of 542 patients were screened, of whom, 376 were randomised to receive CHF 1535 (N = 192) or BDP (N = 184). 7.3% patients in the CHF 1535 group and 10.9% patients in the BDP group discontinued the study with no relevant difference among groups in the reasons for discontinuation. The demographic characteristics were similar in the two treatment groups. At study entry, the majority of patients (about 90%) were treated with ICS/LABA.

At screening, mean FEV1% of predicted was 64% in both groups. Mean reversibility (%) was 27.7% in the CHF 1535 arm and 30. 2% in the BDP arm. At baseline, pre dose-morning PEF was similar in the two treatment groups (310 L/min and 313 L/min in the CHF 1535 and BDP group respectively). Baseline ACQ was similar in the two groups: 2.1, ranging from 0.86 to 4.14.

Results
The change from baseline to the entire treatment period increased in the CHF 1535 group compared to a slight decrease in the QVAR® group (18 L/min and -1 L/min, respectively). The difference in the adjusted mean change from baseline between the two treatment groups was statistically significant in favour of the CHF 1535 group (19 L/min, 95% CI: 10, 27, $p < 0.001$), indicating superiority of CHF 1535 versus QVAR®. Results in the PP population were similar to those in the ITT population: the difference in the adjusted mean change from baseline between the two treatment groups was statistically significant in favour of the CHF 1535 group (18 L/min, 95% CI: 10, 26, $p < 0.001$), confirming the superiority of CHF 1535 treatment versus QVAR®.

Overall, the mean difference versus QVAR® was 19 L/min. This difference is in line with the mean value of the difference between FDC and ICS monotherapy reported in the review of Li et al 2007 (17.86 L/min, 26) and in the Cochrane review (19.64 L/min, Ducharme et al. 2010). Also, the average minimal patient perceivable improvement which was reported by Santanello et al. 1999 in a similar asthma population was 18.79 L/min for morning PEF, thus consistent with results of study CT02.

Also, a series of secondary efficacy analyses confirmed the greater benefit of CHF 1535 as compared to BDP monotherapy. Specifically, compared to BDP, CHF 1535 resulted in a statistically significantly greater improvement of the following lung function parameters: pre-dose evening PEF, daily PEF variability and pre-dose FEV1.

Overall, results of study CT02 successfully demonstrated its primary objective i.e that CHF 1535 200/6 (BDP/FF) has beneficial effects with respect to BDP alone in improving lung function in uncontrolled asthmatic patients.

CHF 1535 200/6 µg NEXThaler®

Study CT01 200/6 DPI

The Applicant has conducted a PD study (CT01 200/6 DPI) aimed at evaluating the clinical efficacy of the two CHF 1535 DPI strengths in terms of bronchodilation associated with the LABA component.

The study was conducted according to a double blind, randomised, 5-way crossover, placebo controlled design. Two different single doses (1 or 4 inhalations) of CHF 1535 DPI (BDP/FF 100/6 µg and BDP/FF 200/6 µg) or placebo were administered to adult asthmatic patients who were partially controlled or uncontrolled as assessed by an Asthma Control Questionnaire (ACQ) score > 0.75. A pre-bronchodilator $FEV_1 \geq 60\%$ and $\leq 85\%$ of the predicted normal value, and a positive reversibility test ($FEV_1 \geq 12\%$ and ≥ 200 mL over baseline after 400 µg salbutamol pMDI) were required. The 60 randomized patients were mostly white (66.7%) with a balanced proportion between males (28 subjects, 46.7%) and females (32 subjects, 53.3%). At study entry patients had a median age (range) of 37 (19-64) years, with a mean (SD) baseline FEV_1 value of 2.52 (0.60) L, i.e. 74.17% (6.79) of the predicted normal value and a mean (SD) ACQ score of 1.65 (0.5).

The primary objective was to demonstrate the non-inferiority of a single dose of CHF 1535 200/6 DPI as compared to a single dose of CHF 1535 100/6 DPI at two FF dose levels (6 and 24 µg) in terms of bronchodilator effect. The primary variable was FEV_1 measured serially over 12 hours post-treatment (FEV_1 $AUC_{0\text{-}12h}$ normalised by time). Secondary endpoints included other pulmonary function parameters including peak FEV_1 and FEV_1 $AUC_{0\text{-}4h}$ normalised by time as well as safety in terms of AEs, and ADRs.

Results

FEV_1 $AUC_{0\text{-}12h}$ (L) standardized by time, Per Protocol population - Study CT01 200/6 DPI

	CHF 1535 DPI 100/6µg N=60	**CHF 1535 DPI 200/6µg N=57**	**CHF 1535 DPI 400/24µg N=58**	**CHF 1535 DPI 800/24µg N=59**	**Placebo N=60**
Adjusted Mean (95% CI)	2.754 (2.722, 2.786)	2.783 (2.749, 2.818)	2.870 (2.837, 2.903)	2.897 (2.863, 2.930)	2.477 (2.444, 2.510)
Difference vs reference treatment (95% CI)		0.029 (-0.018, 0.076)		0.027 (-0.020, 0.073)	
Difference vs Placebo (95% CI) p-value	0.277 (0.231, 0.324) p<0.001	0.306 (0.259, 0.354) p<0.001	0.393 (0.347, 0.439) p<0.001	0.420 (0.374, 0.466) p<0.001	
Differences higher dose vs lower dose (95% CI) p-value			0.116 (0.069, 0.162) p<0.001	0.113 (0.066, 0.161) p<0.001	

The primary endpoint analysis showed that the lower limits of the two-sided 95% CIs for the adjusted mean difference between treatments were well above the pre-specified non-inferiority limit (-0.12 L). The results were confirmed in the ITT population. Importantly to validate the study design, superiority of CHF 1535 DPI for both strengths versus placebo was demonstrated at each dose level, confirming assay sensitivity. Similar results were observed in the ITT population. The analysis of secondary endpoints (peak FEV1 and FEV1 AUC0-4h) supported the non-inferiority of CHF 1535 200/6 DPI compared to CHF 1535 100/6 DPI.

Overall, the results of study CT01 200/6 DPI demonstrate that the therapeutic effect of formoterol on lung function parameters is comparable between CHF 1535 DPI strengths and not affected by the different strengths of BDP. Therefore, this study excludes that the differences in formoterol pharmacokinetics observed in the CP01 200/6 DPI study may translate into clinically different effect.

Clinical safety
This application is a line extension to the currently approved products CHF 1535 100/6µg pMDI and CHF 1535 100/6µg DPI to add new CHF 1535 dose strengths containing a higher dose of BDP (i.e. 200 µg) combined with the same dose of FF (6 µg).

The clinical development program consists of two clinical studies in subjects with uncontrolled asthma (CT01 and CT02), four clinical pharmacology studies (CP01, CP02, CP03 and CP01 200/6 DPI) and one PD study (CT01 200/6 DPI) evaluating the clinical efficacy of the two CHF 1535 DPI strengths in terms of bronchodilation associated with the LABA component. A further supportive study (CP04) was provided within the MAA. However, this study was conducted with the already approved strength 100/6 µg pMDI.

In the PK studies CP01, CP02 and CP03 healthy subjects received a single dose of CHF 1535 pMDI (4 puffs) according to a cross over design (50/6 µg, 100/6 µg and 200/6 µg in Studies CP01 and CP03; 200/6 µg with standard actuator or with AeroChamber Plus® spacer in Study CP02). In the PK study CP01 200/6 DPI adult asthmatic patients received a single dose of CHF 1535 DPI (4 puffs) according to a cross over design (100/6 µg and 200/6 µg, with and without activated charcoal).

In the PD efficacy study CT01 200/6 DPI two different single doses (1 or 4 inhalations) of CHF 1535 DPI (BDP/FF 100/6 µg and BDP/FF 200/6 µg) or placebo were administered to adult asthmatic patients.

In the two clinical studies CT01 and CT02, patients were treated with CHF 1535 200/6 µg (2 puffs, twice daily) for 24 and 12 weeks, respectively. Comparators were:

- Study CT01: BDP Clenil® non extrafine 250 µg (4 puffs, twice daily) and Seretide® Accuhaler® 500/50 µg (1 puff, twice daily);
- Study CT02: BDP Qvar® extrafine 100 µg (4 puffs, twice daily).

Safety data were presented separately by each study. Additionally, an integrated post hoc analysis of TEAEs and ADRs was performed by pooling all the events regardless of the different duration of the studies CT01 and CT02 and of the different BDP formulation (Clenil® and Qvar®).

In study CT01 239 asthmatic patients were treated with CHF 1535 200/6 pMDI and in study CT02189 asthmatic patients were treated with CHF 1535 200/6 pMDI. Patients were treated for approximately 150 days in Study CT01 and for approximately 80 days in study CT02.

In addition, 66 healthy subjects were treated CHF 1535 200/6 pMDI in the three PK studies CP01, CP02 and CP03.

Also, 29 asthmatic patients received CHF 1535 200/6 µg DPI in the PK study CP01 200/6 DPI and 60 asthmatic patients received CHF 1535 200/6 µg DPI in the PD study CT01 200/6 DPI.

The analyses of Studies CT01 and CT02 showed that the safety profile of CHF 1535 200/6 µg was similar to that of BDP (Clenil® or Qvar®) in terms of TEAEs and ADRs. No particular issues were observed in terms of haematology and blood chemistry parameters. Also, the 12 week and 24 week exposure to CHF 1535 200/6 µg showed no clinically relevant effect on the HPA axis, while the same exposure to BDP resulted in reduced serum cortisol levels. In addition, ECG parameters were comparable among treatment groups with no clinically relevant changes in CHF 1535 or BDP group. The mean changes from baseline in RR, QT and QTc intervals were also not clinically significant confirming the safety of the formoterol component in the ICS/LABA combination.

Legal Status
POM

User Testing
For CHF 1535 200/6 pMDI, a new User Testing on the Patient Information Leaflet has been carried out. The PL text has been revised to increase clarity and readability in accordance with current Guidelines and QRD template. Overall, the test methodology follows the guidelines of the European Commission (*Guideline on the readability of the label and package leaflet of medicinal products for human use*, Revision January 2009; Update of Directive 2001/83/EC as amended by Directive 2004/27/EC / *Guidance concerning consultations with target patient groups for the packet leaflet*, May 2006). Both the first and the second test round met the success criteria of 90% of the subjects being able to locate the requested information, and of those, 90% being able to give the correct answer, to indicate that they understood the information presented. The general impression of the PL (Content, language and layout) was mostly positive.
Directive 2001/83/EC as amended require that consultation with target patient groups are carried out to demonstrate the readability and usefulness of the package leaflet to patients. The applicant has included the results of consultation with target patient group in Module 1.3.4 of the application. The result of the consultation with target patient groups is accepted.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS/Rapporteur considers the Summary acceptable.

Risk Management Plan

Important Identified risks:	- Hypokalaemia - Adrenal suppression - Hyperglycaemia - Asthmatic crisis/Paradoxical bronchospasm - ECG QTc prolongation, tachycardia, tachyarrhythmia - Glaucoma - Cataract - Atrial fibrillation - Granulocytopenia - Thrombocytopenia - Angina pectoris - Psychiatric disorders [Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)] - Bone density decreased - Cushing's syndrome - Angioedema - Foetal malformation, tocolytic effect - Tremor - Pneumonia
Important Potential risk:	- Growth retardation (in children and adolescents)
Potential risks:	- Increased frequency of ICS extradoses-related adverse events (MART regimen) - Pulmonary toxicity with chronic use due to magnesium stearate deposition in the lungs when the DPI formulation is used

Missing information:	- Effects in the breast-fed baby - Safety in children aged 5-11 and in adolescents aged 12-17 with asthma - Safety in long term use of CHF 1535 NEXThaler® - Use in hepatic/renal impaired patients

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV. BENEFIT RISK ASSESSMENT

The present application is submitted according to Article 10b of Directive 2001/83/EC as amended (fixed combination application) and concerns a line extension of the licensed fixed combination of the two well-known active substances, i.e. beclometasone diproprionate (BDP) and formoterol fumarate (FF) (DE/H/0871-0874/01/MR).

The present application concerns two different formulations of CHF 1535

- as solution containing 200 µg BDP and 6 µg FF per inhalation, delivered using the pMDI device (DE/H/0871-874/003/DC), and
- as inhalation powder containing 200 µg BDP and 6 µg FF per inhalation, delivered through the multi-dose breath-actuated device (DE/H/0871-874/004/DC).

For CHF 1535 200/6 µg pMDI the Applicant has submitted a dossier which includes three PK single-dose studies, one PD multiple-dose study and two phase III clinical studies. Overall, more than 1100 asthmatic patients representing the target population were treated during the programme. For CHF 1535 200/6 µg DPI the Applicant has submitted one PK single-dose study and PD efficacy study.

Overall, for both products the benefit-risk-balance is positive.
The application is approved.
For intermediate amendments see current product information.