22 April 2010
EMA/464905/2010

Evaluation of Medicines for Human Use

CHMP assessment report

Daxas

International Nonproprietary Name: roflumilast

Procedure No. EMEA/H/C/001179

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Nycomed GmbH submitted on 06 May 2009 an application for Marketing Authorisation to the European Medicines Agency for Daxas, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the Agency/CHMP on 22-25 September 2008.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

1.1.1. Information on paediatric requirements

Pursuant to Article 7, of Regulation (EC) No 1901/2006 the application included an Agency Decision P/21/2008 for the following condition: Chronic obstructive pulmonary disease (COPD) on the granting of a (product-specific) waiver.

1.1.2. Licensing status:

A new application was filed in the following countries: Australia, Brazil, Canada, Malaysia, New Zealand, Russia, South Africa, Turkey, USA, Venezuela.

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. Calvo Rojas Co-Rapporteur: Dr. Lyons

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 06 May 2009.
- The procedure started on 27 May 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2009 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2009.
- During the meeting on 21 to 24 September 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 September 2009.
- The summary report of the inspection carried out in South Africa, Poland and Germany was issued on 08 December 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 November 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 January 2010.
- During the CHMP meeting on 18 to 21 January 2010, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant. The List of Outstanding Issues was sent to the applicant on 21 January 2010.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 February 2010.
- During a meeting of an Expert group on 01 March 2010, experts were convened to address questions adopted by the CHMP at the February 2010 meeting.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 02 March 2010.
- During the CHMP meeting on 15 to 18 March 2010, outstanding issues were addressed by the applicant during an oral explanation before the CHMP. During the CHMP meeting on 18 March 2010, the CHMP agreed on a second List of Outstanding Issues to be sent to the applicant. The second List of Outstanding Issues was sent to the applicant on 18 March 2010.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 26 March 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 31 March 2010.
- During the meeting from 19 to 22 April 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Daxas on 22 April 2010. The applicant provided the Letter of Undertaking on the follow-up measures to be fulfilled post-authorisation on 22 April 2010.

2. Scientific discussion

2.1. Introduction

Chronic obstructive pulmonary disease is the fourth leading cause of death in Europe, and is a major public health problem. COPD is generally but not exclusively associated with tobacco smoking. Tobacco smoke is considered the most important risk factor for COPD worldwide.

COPD comprises pathological changes in four different compartments of the lungs (central airways, peripheral airways, lung parenchyma, pulmonary vasculature), which, in turn, give rise to the physiological abnormalities in COPD: mucous hypersecretion and cilliary dysfunction, airflow limitation and hyperinflation, gas exchange abnormalities, pulmonary hypertension, and systemic effects.

Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced.

The most widely accepted classification of the severity of COPD is according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD classification is based on the degree of impairment of lung function. Four categories are recognised: mild, moderate, severe, very severe (Stages I-IV).

The most important aspect of management of the condition is educational and social: the avoidance and cessation of tobacco smoking. The medications for COPD currently available can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. At present no treatment is shown to modify the rate of decline in lung function. Combining different agents produces a greater change in spirometry and symptoms than single agents alone.

Roflumilast is a selective phosphodiesterase type 4 (PDE4) inhibitor. PDE4 is an important regulator of cyclic AMP in most cell types involved in inflammatory processes. Inhibition of PDE4 reduces the breakdown of cAMP, which in turn down-regulates the inflammatory process.

A so-called full application for marketing authorisation has been submitted, i.e. a complete and independent/stand-alone Marketing Authorisation Application. The applicant submitted a request for an accelerated assessment. However, the CHMP did not conclude that the availability of roflumilast in the community would be of major interest from a public health perspective given that roflumilast does not seem to modify the long term decline of the lung function or to have a modifying effect on the disease. Hence, the criteria for accelerated assessment were not considered to be met.

Roflumilast was object of a previous registration procedure for the treatment of COPD and asthma which was withdrawn by the Applicant.

Roflumilast was also investigated in allergic rhinitis, osteoarthritis and rheumatoid arthritis but these indications have not been further investigated.

Formal Scientific Advice was given by CHMP on the questions of the primary and secondary endpoints, the statistical approach, the investigation of a PK/PD correlation. The Applicant did not fully adhere to the advice given with regards to the design of the pivotal trials.

The safety and efficacy of roflumilast in COPD have not been assessed in patients younger than 18 years of age due to the nature of the indication. A paediatric waiver has been granted by the EMA for roflumilast for the indication COPD as, according to GOLD, the condition should only be considered in an individual over the age of 40 with characteristic symptoms.

The therapeutic indication claimed in the present application is "the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations".

The approved indication is "Daxas is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment."

The medicinal product is a film-coated tablet containing 500 microgram roflumilast. The recommended dose is one 500 microgram tablet once daily.

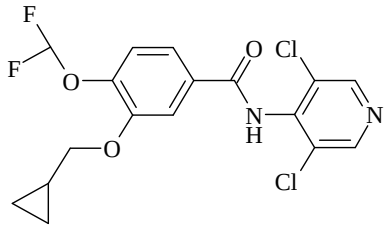
2.2. Quality aspects

2.2.1. Introduction

The medicinal product Daxas is presented as film-coated tablets (immediate release) containing 500 microgram of the active substance roflumilast. The tablets are D-shaped, coated with a yellow non-functional film coating and embossed with "D" on one side. The tablet core contains besides the active substance roflumilast the following excipients; lactose monohydrate, maize starch, povidone (K90), magnesium stearate. The tablet coating contains hypromellose 2910, macrogol 4000, titanium dioxide (E171) and iron oxide yellow (E172). The medicinal product is packed in PVC/PVDC aluminium blisters.

2.2.2. Active substance

Roflumilast is a novel phosphodiesterase 4 (PDE 4) -inhibitor with the chemical name: 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy) benzamide N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. The molecular formula is C17H14Cl2F2N2O3 and the molecular weight is 403.22 g/mol. The structural formula is shown below:



Roflumilast is a white to off-white powder. It is practically insoluble in water (0.52 – 0.56 mg/l at 22°C) and hexane, sparingly soluble in ethanol and freely soluble in acetone. Since it is a weak acid with a pKa of 8.74, the solubility in aqueous solvents increases from about 0.8 mg/l under neutral conditions to about 35.8 mg/l at pH 10. The pH of a saturated solution at 21 – 22°C is 6.35. The partition coefficient between 1-octanol and aqueous phosphate buffer at pH 7.4 is log P = 3.99. The melting point was determined at 159.7°C. Roflumilast contains no asymmetric centres and it is not hygroscopic. Based on the results of DSC and X-ray powder diffraction, it is concluded that there is no evidence of polymorphic forms. Due to its low solubility roflumilast is micronized. There is no PhEur monograph for roflumilast. Roflumilast is not known to have polymorphic forms. The chemical structure of roflumilast has been confirmed by elemental analysis, UV, IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and mass spectra and crystal X-ray analysis. All data are consistent with the proposed structure.

2.2.2.1. Manufacture

The manufacture of roflumilast consists of a four-step process. Detailed information on the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates, process development and process validation of the active substance have been provided by the applicant. All manufacturing steps are adequately described. Adequate in-process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterized. Potential impurities arising from the starting materials, reagents or the route of synthesis have been discussed. Five of these impurities are controlled in the active substance specifications. No single structurally known organic impurity is limited above the limit of max.0.15%, which would require specific toxicological qualification. Validation batches results confirm the reproducibility of the manufacturing process to produce the drug substance with the quality established. Roflumilast is supplied by two active substance manufacturers.

2.2.2.2. Specification

As no PhEur. monograph exists for roflumilast, in-house specifications have been set for the active substance, in accordance with the principles of the relevant ICH guidelines.

The active substance specifications include appropriate tests for appearance, identification (IR spectra and HPLC), assay of roflumilast (titration, HPLC) and related substances (HPLC), particle size (laser diffraction), residual solvents (GC), water content (Karl Fischer), heavy metals and sulphated ash.

The analytical test procedures have been satisfactorily described and validated in accordance with the ICH guidelines. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data been presented and all batches were in compliance with the predefined active substance specification.

2.2.2.3. Stability

Stability studies have been performed at long term (25 ± 2°C, 60 ± 5% RH), intermediate (30 ± 2°C, 65 ± 5% RH), and accelerated (40ºC ± 2°C / 75%RH ± 5% RH) conditions on at least five batches. These include batches from both active substance manufacturers. Up to 60 months of long term stability data has been provided, confirming the stability of roflumilast. All batches tested were produced using the current manufacturing procedure and subsequently micronized. The routine HPLC method has shown to separate and detect all degradation products and is therefore considered as stability indicating. The test parameters evaluated in these studies were appearance, assay by HPLC, related substances, water content and particle size.

Forced degradation studies have been performed on roflumilast to identify potential degradation products that might be formed in drug substance. When roflumilast (in solid state) is stored in a drying oven at 100 °C for up to 14 days, no change in content nor an increase in impurities could be observed.

Furthermore, photostability testing has been performed according to ICH Q1B. Roflumilast in solid state is not affected by exposure to light, however, solutions in acetonitrile of the drug substance are sensitive to light. At room temperature, solutions of roflumilast in 0.1 M hydrochloric acid, demineralised water and 0.1 M sodium hydroxide are stable within 24 hours.

In addition, three batches have been tested for microbiological purity, at the beginning and after 36 months of storage under different conditions. No trend for a change in the microbiological profile was found. The CHMP considers that the stability data provided justify the proposed retest period when the active substance is stored with no special storage conditions. In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

2.2.3.1. Pharmaceutical Development

The aim of the pharmaceutical development was to develop an immediate-release tablet that can be handled easily by the target patient population of elderly chronic obstructive pulmonary disease (COPD) patients.

Physicochemical and biological properties of the drug substance have been studied. The active substance can be classified as a Class II active substance (high permeability, low solubility) according to the Biopharmaceutics Classification System (BCS). This implies that particle size is expected to impact dissolution of the active substance and thus bioavailability. Therefore the active substance is micronized in order to improve its solubility.

Dissolution studies have been performed to support the specification of the particle size range for the active substance. Due to the low drug content (500 microgram) in the tablets, special focus was taken on blend and content uniformity during development, scale-up and validation, and that the homogeneous distribution of the drug substance and homogeneity of the granules is determined for each batch during release testing by content uniformity.

Different excipients were investigated by preparing binary combinations containing the drug substance and the excipient and stored in different ambient conditions. Only those excipients with a proven compatibility with roflumilast were selected for development. All excipients comply with the current versions of compendial monographs.

The development of the formulation has been adequately explained and justified. Different immediate-release tablet formulations were used throughout drug development and the amount of excipients was changed to increase the tablet weight and volume. This leads to improved patient handling of the dosage form. Finally a film-coated formulation was chosen for marketing authorisation. To allow easy tablet differentiation, the tablets were given a unique D-shaped form and it was decided to coat the tablets with a yellow (non functional) coating. A satisfactory dissolution method has been developed and the dissolution results provided indicate that the commercial formulation has a comparable in-vitro dissolution profile to that of the formulation used in clinical studies, and a bioequivalence study confirmed that the two formulations are bioequivalent.

A stability study with different packaging materials was performed to assess the suitability of different blisters materials. The different packaging materials were compared and drug product stability was evaluated. The proposed primary packaging materials are adequate for marketing.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.3.2. Adventitious agents

The only excipient of animal origin in the finished product is lactose monohydrate. It is derived from milk collected from healthy animals as used for human consumption. According to the Note for Guidance EMEA/410/01, milk and its derivatives are regarded as unlikely to present any risk of contamination in the light of the current scientific knowledge and irrespective of the geographical origin. Excipients of human origin are not contained.

2.2.3.3. Manufacture of the product

Daxas film-coated tablets are manufactured by a conventional wet granulation process with a final film-coating. The manufacturing process has been adequately described and validated. Taking into account the very small quantity of active substance in the finished product (< 2 %) this process is considered a non-standard process, as per Annex II to Note for Guidance on Process Validation (CPMP/QWP/2054/03). Therefore critical steps must be identified. All critical process parameters have been identified and are controlled by appropriate in-process controls. The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the in-process and finished product specifications.

2.2.3.4. Product specification

The medicinal product specifications for Daxas at batch release include the following tests: appearance, identity of roflumilast (UV and HPLC) and the colourant iron oxide (colour reaction), water content (PhEur), purity (HPLC), assay of roflumilast by UV or HPLC), content uniformity, dissolution and microbiological purity (all three according to PhEur). The product specification is standard for immediate-release tablets. The proposed test procedures and acceptance criteria follow the principles of the ICH Q6A guideline.

All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. All excipients used in the formulation comply with the requirements of the European Pharmacopoeia (PhEur) and/or the European Food Colors Directive. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Eight batches of the finished product proposed for marketing, manufactured on full scale have been analysed. Batch analysis results comply with the proposed specification and confirm consistency & uniformity of manufacture and indicate that the process is under control.

2.2.3.5. Stability of the product

Stability studies have been carried out under long term (25°C/60% RH), intermediate (30°C/75% RH) and accelerated (40°C/75% RH) conditions according to the ICH requirements for three production scale batches. The use of a higher humidity level at the intermediate storage condition (75% instead of 65%) is considered acceptable. Twenty-four months stability data have been provided under long term and intermediate conditions and six months under accelerated conditions. All batches placed on stability studies were manufactured at the proposed site of finished product manufacture, according to the proposed process and using active substance obtained from the proposed active substance manufacturer. All batches were packaged as proposed for marketing (transparent PVC/PVDC -Al blisters). The parameters tested and analytical methods used were identical to those used for the

release specifications. However, some release tests (such as identity and content uniformity) were not repeated at the end of shelf-life.

Furthermore, a photostability study was performed on one batch of the film-coated tablets in accordance with ICH Q1B. The tablets were exposed directly to light without packaging material. No changes in the specified test parameters were observed.

The stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC. In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on manufacture, control and stability of the active substance and medicinal product have been presented in a satisfactory manner. The excipients are commonly used in this type of formulation and comply with PhEur and/or the European Food Colors Directive. The packaging material is commonly used and well documented. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Batch analysis results indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. Stability tests performed under ICH conditions indicate that the product is chemically stable for the proposed shelf life.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Daxas is adequately established. Satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

The quality of this medicinal product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. At the time of the CHMP opinion there are no unresolved quality issues which have a negative impact on the benefit/risk balance of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant conducted a full non-clinical development program. This program is in general agreement with the applicable guidelines.

With the exception of safety pharmacology, for which the studies were performed prior to the implementation of the CPMP/ICH/539/00 Note for Guidance ICH S7A, the pivotal safety pharmacology and toxicity studies have been conducted in compliance with GLP.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

In vitro roflumilast, and its major metabolite roflumilast N-oxide, have been shown to be highly selective PDE4 antagonists. PDE4 is a major cyclic adenosine monophosphate (cAMP)-metabolizing enzyme found in inflammatory and immunomodulatory cells. Inhibition of PDE4 leads to elevated intracellular cAMP levels and mitigates COPD-related malfunctions of leukocytes, airway and pulmonary vascular smooth muscle cells, endothelial and airway epithelial cells and fibroblasts in experimental models. Upon in vitro stimulation of human neutrophils, monocytes, macrophages or lymphocytes, roflumilast and roflumilast N-oxide suppress the release of inflammatory mediators. In vitro roflumilast and roflumilast N-oxide has been shown to weakly inhibit serotonin or methacholine-induced airways contraction in different in vitro test systems. Roflumilast was demonstrated in vitro to stimulate the airway ciliary beat frequency in proximal and distal airways.

When administered orally following LPS-challenge to mice and rats, roflumilast and roflumilast N-oxide significantly reduced the circulating TNF-α, the TNF-α in BAL (pro-inflammatory mediator) and increased IL-10 (anti-inflammatory mediator). Increase in the incidence of chest infections and cancers was observed in COPD patients treated with TNF-α inhibitors.

In vivo studies showed that roflumilast prevented the cigarette-smoke induced pulmonary changes, reduced the experimentally induced goblet-cell hyperplasia and influenced the experimentally induced pulmonary remodelling and hypertension in mice and rats. In in vivo models, roflumilast and roflumilast N-oxide inhibited bronchoconstriction.

2.3.2.2. Secondary pharmacodynamic studies

Potential receptor interactions have been investigated *in vitro*. Roflumilast and roflumilast N-oxide did not interact with muscarinic, histaminergic, purinergic, and adrenergic receptors. Lowered binding affinity of rolipram and prazosin binding to rolipram R (PDE4 receptor) and α1A-receptors was observed. However no interactions are expected at those levels since the effect on rolipram binding was expectable, and antagonistic pharmacological profile of the functional α1-adrenoceptor population was demonstrated to be sensitive to the influence of the cellular environment.

2.3.2.3. Safety pharmacology programme

The Applicant conducted safety pharmacology studies to assess the effect of roflumilast on the central and autonomic nervous system, cardiovascular system and respiratory, renal, and gastrointestinal functions.

No concerns were raised from the safety pharmacology studies on central and autonomous nervous system since the first effects occur at doses higher than the clinical dose, and these effects have not been reported in humans.

Cardiovascular effects have been observed in dogs given roflumilast. The dog species was very sensitive to roflumilast effects. However, no cardiovascular risk for the use of roflumilast in humans is assumed in view of the dog-specificity of the cardiac lesions and the high safety margins in other species.

Effects of increased gastric acid secretion and delayed gastric emptying were observed during the safety pharmacology studies. These effects are possibly related to the class of compound. No concerns were raised from the findings on renal functional parameters in rats at high exposure since no renal findings were noted in standard toxicity studies.

2.3.2.4. Pharmacodynamic drug interactions

In in vitro studies, roflumilast did not potentiate the β1-mediated chronotropic or inotropic effect of isoprenaline. However, the combination of roflumilast N-oxide and isoprenaline resulted in a relaxation of the trachea via an additive synergistic effect on the β2-adrenoreceptors.

In vivo studies demonstrated that roflumilast had a synergistic anti-inflammatory effect with dexamethasone in a COPD model. Roflumilast showed a significant synergistic bronchodilatory effect when administered with formoterol or montelukast. In addition, roflumilast inhibitory effect on bronchoconstriction was potentiated when co-administered with cetirizine and muscarinic receptor antagonists (i.e. revatropate and tiotropium). None the above compounds showed this effect when administered alone.

2.3.3. Pharmacokinetics

The pharmacokinetic program mainly consisted of single-dose studies in mouse, rat, hamster, guinea pig, rabbit, minipig, dog and monkey. Roflumilast was administered per os or intravenously. Validation of bioanalytical methods for roflumilast and its metabolites (roflumilast N-oxide, ADCP and ADCP N-oxide) was performed. The routine quantification of roflumilast from serum and plasma was performed either by HPLC with fluorescence detection or by LC/MS/MS. The quantification limit ranged from 0.1 µg/L to 1 µg/L.

Absorption

Dose-linearity was established for the low-dose range; at high doses, non-linearity was often encountered. Low gastrointestinal absorption of oral roflumilast was apparent in several species, variation of which may account in part for the observed non-linearity. Moderate bioavailability suggested the presence of a first-pass effect.

Roflumilast is non-ionised at pH<8 and absorption occurs via non-ionic dissolution.

Distribution

Volumes of distribution were highest in the rat whereas in mice, dogs and monkeys a more limited distribution to organs and tissues was noted. Following multiple oral administrations in rats, plasma concentrations of ^{14}C-roflumilast attained a steady state after about 4 days with a slight accumulation of about 2-fold.

Roflumilast is highly bound to plasma/serum proteins with an unbound fraction being lowest in humans and minipigs (1.1%), and slightly higher in various animal species (1.6 to 4.8% in mouse, rat, hamster, guinea pig, rabbit, dog and monkey). The free fraction of the metabolite, roflumilast N-oxide was 3.4% in human plasma and clearly higher in the animal species evaluated (6.4 to 12.9%). In addition, roflumilast N-oxide showed a fewer binding to human albumin and α1-glicoprotein than roflumilast. The observed differences in unbound fraction of roflumilast and roflumilast N-oxide between humans and animals supports the comparison of drug levels across species based on the concentration of the free fraction.

Roflumilast has been demonstrated to cross the placenta in pregnant rats. In addition it is secreted into milk of breeding dams. This information is adequately reflected in the SPC.

Metabolism

The percentage of [^{14}C]-roflumilast N-oxide and its glucuronide decreased among animal species in the following order: monkey, rat, hamster, mouse, dog. Various products of O-dealkylation and oxidative

mono-dechlorination followed by conjugation were identified in animal plasma except in rat, monkey and human. ADCP and ADCP N-oxide were identified in rodent plasma as products of amide cleavage. The metabolite patterns in rat and monkey plasma were the closer to human. In some species, some metabolites were found in urine although they were not identified in plasma.

Excretion

Terminal half-lives were comparable in rat, rabbit, dog and monkey (6-8h), while roflumilast was eliminated much more rapidly from guinea pig and mouse plasma (2 h) and slowly from hamster, minipig and human plasma (12-14h).

The plasma/serum clearance ranged from 1.83 L/h/kg in mice to 3.9 L/h/kg in rats; while clearance in dogs, monkeys and cats was significantly lower (0.38 l/h/kg, 0.32 l/h/kg and 0.18 l/h/k, respectively).

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies have been performed in animals. Given the availability of human data on the pharmacokinetic drug interaction, this was considered acceptable to the CHMP.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

The single-dose toxicity of roflumilast and roflumilast N-oxide has been investigated in mice, rats, and dogs. Compound administration was followed by 14-days observation period. The results show a range of non-lethal doses of at least 100 mg/kg in rodents (10,000-times the human dose) after oral drug administration and of at least 20 mg/kg after intravenous administration. The causes of death after administration of lethal doses were not established. Target organs at necropsy were the forestomach (hyperplasia), glandular stomach (ulcer, hemorrhage), small intestine (thickening, submucosal cell infiltration, serositis), testes (atrophy), and olfactory epithelium (inflammation). In dogs, the highest dose of 18 mg/kg roflumilast or its N-oxide induced vomiting and tremor but caused no mortality.

2.3.4.2. Repeat dose toxicity (with toxicokinetics)

All pivotal repeat-dose toxicity studies of roflumilast (and in some instances of roflumilast N-oxide) were performed by oral route in five animal species (longest duration in parentheses): mouse (6 months), rat (6 months), hamster (3 months), dog (12 months) and monkey (42 weeks). Please refer to table 1 for a summary of the studies.

Table 1 - Repeat dose toxicity (with toxicokinetics)

Study ID	Species No/sex/group (+ recovery)	Duration (+ recov.) (months)	Doses a (mg/kg/day)	NOAEL (mg/kg/day)
216/98; 262/97; 20/2001	Mouse, B6C3F1 10	3	0, 6, 12, 18 R	6
33/2002; 197/2001	Mouse, B6C3F1 20 (+ 8)	6 (+1)	0. 4, 12, 36 R	4
54/2002; 52/2002	Mouse, B6C3F1 20 (+ 8)	6 (+1)	0. 4, 10, 25 R-NO	4
81/95; 20/2001; 31/2001; 44/2001; 42/2002	Rat, Wistar 10 (+ 8)	1 (+1)	0, 0.5, 2, 8 R	0.5
116/99; 20/2001; 27/2001	Rat, Wistar 10 (+ 8)	1 (+1)	0, 0.4, 1.2, 3.6 R-NO	1.2
38/98; 20/2001	Rat, Wistar 8 (+ 8)	1+3 (+2)	0, 0.02, 0.2, 2 R	0.2

Study ID	Species No/sex/group (+ recovery)	Duration (+ recov.) (months)	Doses a (mg/kg/day)	NOAEL (mg/kg/day)
14/96; 20/2001; 97/96 191/2000;	Rat, Wistar 20 (+ 8)	6 (+1)	0, 0.5, (0.8), 1.5, 2.5 R	0.8
252/98; 20/2001; 147/99	Hamster, Syrian Golden 10	3	0, 4, 8, 16 R	4
68/95; 20/2001; 157/95; 12/98	Dog, Beagle 3 (+ 2)	1 (+ 1)	0, 2, 6, 18 R	2
33/99; 20/2001; 5/2001	Dog, Beagle 3 (+ 2)	1 (+ 1)	0, 0.6, 1.2, 2.4 R-NO	1.2
94/96; 147/97; 20/2001; 22/2001; 34/2002; 35/2002	Dog, Beagle 5 (+ 2)	6 (+ 1)	0, 0.2, 1, 4 R	0.2
132/2000; 20/2001; 4/2001	Dog, Beagle 5 (+ 2)	12 (+ 1)	0, 0.2, 0.6, 2.0 R	0.6
162/2001; 160/2001; 22/2001; 34/2002; 35/2002	Dog, Beagle 5 (+ 2)	12 (+ 1)	0, 0.1, 0.4, 0.8, 1.2 R-NO	1.2
232/2001; 242/2001; 108/2002	Monkey, Cynom. 3 4 (+ 2)	1 9 (+ 2)	0, 0.1, 0.25, 0.5 R	0.25 R

Olfactory mucosa toxicity

Olfactory mucosa lesions were seen in mouse, rat and hamster, all rodent species, but in none of the non-rodent species tested in the repeat-dose toxicity program. Dose-related changes in rodent olfactory mucosa consisted of disorganization, degeneration/necrosis accompanied by basal cell hyperplasia and inflammatory changes of Bowman's gland and submucosa. The rat was the most sensitive species (NOAEL 0.8 mg/kg/day), while mice and hamsters were less sensitive (NOAELs 4 mg/kg/day). Olfactory toxicity was shown by mechanistic studies to be rodent specific. The dog and monkey did not demonstrate this effect, even at higher levels of roflumilast than what rodents were exposed to. All this data support the lack of risk of this effect in humans.

Gastrointestinal toxicity

In dogs, vomiting was induced by roflumilast and roflumilast N-oxide in a dose-dependent manner. This finding can be attributed to the high inhibition potency of roflumilast and roflumilast N-oxide on PDE4D, which theoretically accounts for gastrointestinal effects as nausea and vomiting. Hypersalivation was seen in animals administered roflumilast N-oxide. No morphological lesions of the gastrointestinal tract were seen in mice, hamsters or dogs. Morphologic changes in the gastrointestinal tract (i.e. erosion, ulceration and/or inflammation) were seen both in rats and monkeys. Considering that the safety margins in the sensitive species for gastrointestinal findings are between 3.7 and 15-fold higher than the expected exposure in humans and clinical dose, morphologic changes in the gastrointestinal tract are not expected at therapeutic dose in humans.

Cardiac toxicity

Cardiac lesions such as focal hemorrhages, hemosiderin deposits and lympho-histiocytic cell infiltration in the right atria/auricles were found in repeat-dose toxicity studies with roflumilast and roflumilast N-oxide in dogs. No other species suffered any cardiac affection, even at higher roflumilast exposures than dogs. PDE inhibitors are well known for dog-specific cardiac toxicity. In addition, considering there

are safety margins, wider for roflumilast (21-fold) than for its main metabolite roflumilast N-oxide (4.4-fold), cardiotoxic effects would not be expected in humans at roflumilast therapeutic dose.

Male reproductive organ toxicity

Testicular tubular dilation in some cases associated with tubular degeneration and epididymal sperm granulomas were found in rats. No toxic effect was noted on male reproductive organs in any of the other species tested. The safety margin for roflumilast and roflumilast N-oxide exposure levels in relation with these effects were quite narrow, 1.7 and 6 respectively. However, considering safety margins in other species were at least 20-fold higher than clinical human exposure, and no effect was observed in healthy volunteers, there is no further concern regarding potential toxicity of roflumilast on male reproductive organs.

Female reproductive organ toxicity

Prolongation of oestrus cycle length was observed in monkeys despite of the absence of alterations in reproductive hormones. The oestrus cycle prolongation observed in these studies is likely to be related to general stress patterns in the animal given high dose roflumilast. In specific fertility studies in rats, there were no effects on reproductive function. Also, the AUC exposure multiples in monkeys are sufficiently high for this not to warrant concern at the therapeutic dose level in humans.

2.3.4.3. Genotoxicity

Summary of genotoxicity tests with roflumilast and roflumilast N oxide is provided in table 2:

Table 2 - Summary of genotoxicity tests with roflumilast and roflumilast N oxide

Study type and test system	Concentrations/ Conc. Range/ Metabolising system	Result	Study Report
Gene mutations in bacteria:			
Ames test (Salmonella typhimurium: TA98, TA100, TA102, TA1535, TA1537; E. coli: WP2, WP2uvrA)	R: 33.3 - 5000 µg/plate; +/- S9	negative	127E/95
	R-NO: 31.6 - 5000 µg/plate; +/- S9	negative	225E/99
Gene mutations in mammalian cells:			
HPRT gene mutation in V79 cells	R: 1.25 - 20 µmol/L; +/- S9	negative	67/97
Genetic damage *in vitro*:			
Micronucleus test in V79 cells	R: 1 - 20 µg/mL; +/- S9	negative	113/97
	R-NO: 20 - 200 µg/mL; +/- S9	negative	135/99
Chromosomal aberrations in human lymphocytes	R: 75 - 150 µmol/L; +:- S9	negative	129/95
Genetic damage *in vivo*:			
Mouse micronucleus test	R: 100, 300, 900 mg/kg/day	positive	106/96
	ADCP: 30, 100, 300 mg/kg/day	negative	106/98
Chromosomal aberration test in mouse bone marrow	R 100, 300, 900 mg/kg	negative	92/99
DNA damage *in vivo*:			
DNA ^{32}P-postlabeling assay in rat tissues (nasal mucosa, liver, testes)	R 0.5, 2.5 mg/kg/day	negative	71E/99
	ADCP 0.5 mg/kg/day	negative	14E/99
DNA ^{32}P-postlabeling assay in hamster tissues (nasal mucosa, liver)	R 1, 8 mg/kg/day	negative	143/2002

Roflumilast induced a low number of micronuclei in polychromatic erythrocytes after 300 mg/kg/day in males and after 900 mg/kg/day in males and females. Reported values seem to be in the range of the spontaneous incidence number of micronuclei in this species. It should also be considered that weak positive in vivo micronucleus tests have been reported for compounds that induce hypothermia or cause hematopoiesis, effects observed after roflumilast administration in safety pharmacology and toxicology mechanistic studies. In a mechanistic study, roflumilast induced an activation of erythrocyte parameters (erythrocyte count, hemoglobin, hematocrit) within 24 and 48 hours after single oral administration of 300 and 900 mg/kg roflumilast to male NMRI mice. This result indicates that the low

number of micronuclei in polychromatic erythrocytes observed in the in vivo mouse micronucleus test assay have been caused by an increase in erythropoiesis rather than by a mutagenic effect. In addition, the exposure ratio in mice at 100 mg/kg/day (NOEL) is higher than 200-fold the human AUC at 500 µg/day. Therefore no clastogenic risk is expected.

The rest of in vitro and in vivo genotoxicity battery of studies with roflumilast, roflumilast N-oxide and metabolite ADCP gave negative results. Therefore, these compounds were not considered genotoxic.

2.3.4.4. Carcinogenicity

The carcinogenic potential of roflumilast was assessed in two rodent species (mouse and hamster) with daily drug administration by gavage for 2 years. Mice and hamsters were the species chosen for carcinogenicity assessment since the dose limiting olfactory mucosa toxicity in rats precluded long-term dosing of rats. In the 2-year carcinogenicity study in the B6C3F1 mice, at roflumilast doses that achieved maximum tolerated dose, there was no evidence for roflumilast-related neoplasia nor were there any statistical differences in the incidences of tumors in either sex. These results indicate that roflumilast does not exhibit carcinogenic potential in this species. Roflumilast-related tumors in olfactory mucosa were observed at 8 and 16 mg/kg/day in the 2-year carcinogenicity studies in hamsters. These effects have been demonstrated in specific mechanistic toxicity studies to be due to the formation of local SH-reactive metabolites within the nasal epithelium following the cleavage of ADCP and subsequent oxidation to ADCP N-oxide (metabolites of roflumilast) that bind to olfactory mucosa. The presence of degenerative and hyperplastic processes in the olfactory mucosa, as well as the lack of genotoxic results for ADCP and ADCP N-oxide in genotoxicity studies reflect the long-term exposure seems to be the more feasible cause of these effects. In addition, these two metabolites are not formed by human olfactory mucosa and the safety margins are large. It could be concluded that it seems to be a species-specific effect and there is no special concern regarding roflumilast use in humans.

2.3.4.5. Reproduction Toxicity

The effects of orally administered roflumilast on reproductive parameters were studied in mice (male fertility, pre- and postnatal development), rats (fertility, early embryonic development, embryo-fetal development), and rabbits (embryo-fetal development). Male fertility was tested in mice at the end of the 6-month toxicity studies with roflumilast and roflumilast N-oxide. Drug administration in the pre/postnatal study was suspended before delivery because of a pronounced tocolytic effect of roflumilast. Roflumilast is not considered teratogenic.

Effects on male reproductive performance were confined to the rat and were considered due to a disturbance of ion exchange and fluid absorption causing leakiness of the efferent ductular epithelium, emigration of sperm into the extraductular space and granuloma formation. The anatomical differences between rats and humans contribute to the assurance that this effect is rat specific. No other species showed this effect. The NOAEL for this effect was only at approximately 1 -2 fold the human AUC.

The increased incidence of incomplete ossification in the embryo-foetal development study in rats correlated with a significant maternal toxicity at roflumilast dose of 1.8 mg/kg, and thus is not regarded as a direct effect of roflumilast. The exposure multiples between pregnant rats and humans at therapeutic dose is not significantly wide. However, it was considered unlikely that the incomplete ossification noted in rat studies should present a contraindication to the use of roflumilast in pregnancy. This is based on the fact that there is much variation in skull bone ossification at term, most of skull bone ossification occurs after birth and that there are no consequences to physical and mental development.

Roflumilast treatment was associated with signs of tocolytic activity resulting in delivery retardation in the mouse. These effects occurred at systemic drug exposures in the range of those in humans. However, the relevance of these findings to humans is unknown.

2.3.4.6. Toxicokinetic data

No gender differences in exposure were noted in either the species tested. In general, roflumilast,

roflumilast N-oxide and ADCP exposure levels increased proportionally with dose. This increase was over-proportional at high doses in mice (25 mg/kg/day, 6-month oral study), and in Cynomolgus monkeys. Biotransformation of roflumilast was specially pronounced in the hamster resulting in a 23- to 38- fold higher exposure to roflumilast N-oxide, and 1.2 to 2 and 7 to 10 higher to ADCP and ADCP N-oxide than to the parent compound. ADCP N-oxide was not detectable in dog and cynomolgus monkey plasma samples. Roflumilast N-oxide was neither detected in dog plasma samples.

2.3.4.7. Local Tolerance

No significant local intolerance following intramuscular, intravenous, paravenous or intraarterial roflumilast administration in rats and rabbits. The following gastrointestinal local tolerance effects have been observed in safety pharmacology and repeat-dose toxicity studies, regarding: stomach erosions and intestine inflammation in 1 month study on rats; inflammation of the stomach 1 month study in monkeys.

2.3.4.8. Other toxicity studies

Studies on antigenicity and immunotoxicity were conducted. Neither roflumilast nor roflumilast N-oxide had skin-sensitizing properties in the guinea pig maximization test. The findings of the immunotoxicity studies did not raise concerns.

Neither of the compounds administration resulted in any direct compound-related effects on lymphohematopoietic organs in mice, rats, hamsters, dogs or monkeys even after repeat doses for up to 52 weeks.

The main roflumilast metabolites (roflumilast N-oxide, ADCP and ADCP N-oxide) toxicological profile has been adequately covered along the non-clinical roflumilast toxicity development.

The presence of five potential genotoxic impurities in roflumilast drug substance is limited by a specification limit of no more than 0.15%, consistent with the qualification threshold of the applicable guidelines. Therefore, there is no requirement for further qualification.

Impurities and residual solvents are limited to acceptable amounts as recommended in the applicable guidelines.

In line with the applicable guideline, no photosafety testing would be warranted for roflumilast.

2.3.5. Ecotoxicity/environmental risk assessment

An environment risk assessment for roflumilast was performed. Roflumilast PEC surfacewater value is 2.5 x 10-3 µg/L below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Considering the above data, roflumilast should be used according to the precautions stated in the SPC in order to minimize any potential risks to the environment.

2.4. Clinical aspects

2.4.1. Introduction

Eighteen phase II and III studies were conducted in patients with COPD to establish the therapeutic dose and to assess the efficacy and safety of roflumilast compared to placebo. The bases for the assessment of the present application are the efficacy and safety data in patients with severe COPD (associated with chronic bronchitis) in the two pivotal studies M2-124 and M2-125. Please refer to table 3.

There are four important supportive studies: two additional supportive 1-year studies M2-111 and M2-112 as well as two 6-month studies in patients with moderate to severe COPD on salmeterol (M2-127) or tiotropium (M2-128).

2.4.2. 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.

A routine GCP inspection has been performed on the request from the CHMP on 3 sponsor sites (Germany, Poland, South Africa) for Study M2-125. During this inspection, three critical deficiencies were identified However, following response from the Applicant, it was clarified that the findings from the inspection have not altered the results of the individual studies or the pooled analysis. Table 3 provides an overview of the clinical studies discussed in this report.

Table 3 - Tabular overview of clinical studies

Study code	Locations	Design	Roflumilast dose [µg/d]	Pts random / completed	Dura-tion [wks]	Gender M/F	Median Age (range)	Population FEV_1% pred.	Primary endpoints
Dose-finding studies									
FK1 101 139/2001-K1	DE, HU, ZA, NL	pbo, p, r, db dose-response	250, 500	Total: 516/442 Pbo: 172/150 Rof250: 175/147 Rof500: 169/145	26	372/144	62 (41-75)	35 to 75	pre-FEV_1, SGRQ
M2-107 26/2003 ""	AU, AT, BE, CA, FR, DE, HU, IE, ZA, ES, UK	pbo, p, r, db	250, 500	Total: 1413[e]/1155 Pbo: 280/248 Rof250: 578[e]/476 Rof500: 555/431	24	1036/375	64 (40-87)	30 to 80	post-FEV_1, SGRQ
Pivotal studies - severe to very severe COPD									
M2-124 218/2008 "AURA study"	AT, AU, DE, FR, HU, NZ, RO, RU, UK, USA	pbo, p, r, db	500	Total: 1525[a],[e]/1027 Pbo: 759[d]/525 Rof500: 766[d]/502	52	1078/445	63 (40-92)	≤50	pre-FEV_1, exac. rate (moderate or severe)
M2-125 219/2008 "HERMES study"	CA, DE, ES, IN, IT, PL, USA, ZA	pbo, p, r, db	500	Total: 1571[f]/1077 Pbo: 798[e]/550 Rof500: 773[d]/527	52	1258/310	64 (40-90)	≤50	pre-FEV_1, exac. rate (moderate or severe)

a =One patient w as randomized twice (included only once); d = One patient was randomized but did not receive treatment; e = Two patients were randomized but did not receive treatment; f = Three patients were randomized but did not receive treatment. co = cross-over, COPD = chronic obstructive pulmonary disease, d = day, db = double-blind, exac. = exacerbation, FEV_1 = forced expiratory volume in 1 second, FRC = functional residual capacity, LABD = long-acting bronchodilators, p = parallel, pbo = placebo (controlled), post = post-bronchodilator, pre = pre-bronchodilator, pred. = predicted, pts = patients, r = randomized, Sal = salmeterol (50 µg twice daily), SGRQ = St George's Respiratory Questionnaire, Tio = tiotropium (18 µg once daily).

2.4.3. Pharmacokinetics

Pharmacokinetic data were obtained from a number of clinical studies, from healthy volunteers but also patients with COPD, asthma, hepatic or renal impairment.

Roflumilast is rapidly metabolized to its N-oxide which also exerts PDE4 inhibitory activity (approximately 3-fold lower potency as compared to the parent compound) with 10-fold higher plasma AUC, and a 3-fold higher free fraction in plasma. The N-oxide contributes about 90% of the overall

PDE4 inhibitory activity and is assumed to contribute largely to the pharmacodynamic activity of roflumilast. To estimate the combined PDE4 inhibitory activities of roflumilast and roflumilast N-oxide, the concept of 'total PDE4 inhibitory activity' (tPDE4i) was established and used to characterize the pharmacokinetics of roflumilast. The tPDE4i accounts for differences in intrinsic PDE4 inhibitory activity, free concentration in plasma, and in-vivo exposures (AUC) of roflumilast and roflumilast N-oxide. The calculated tPDE4i was used to evaluate potential precautions and/or dose adjustment requirements in special populations or drug interaction scenarios.

2.4.3.1. Absorption

Absorption following single oral dosing with 500 µg roflumilast is rapid, with C_{max} occurring within 1 hour for roflumilast. Plateau-like maximum concentrations of the N-oxide metabolite are reached after 8 hours. The mean C_{max} of roflumilast and its N-oxide after repeated dosing under fasted conditions are between 5 and 10 µg/L and 22 to 43 µg/L respectively. Steady-state plasma concentrations following repeated dosing with 500 µg are reached after approximately 4 days and 6 days for roflumilast, and the N-oxide, respectively. The systemic exposure of roflumilast and roflumilast N-oxide increase proportionally after single and repeated roflumilast doses between 250 µg and 1000 µg.

2.4.3.2. Distribution

With a volume of distribution of 2.9 L/kg, binding of roflumilast and its N-oxide to human plasma proteins is approximately 99% and 97%, respectively. Distribution of roflumilast into lipophilic tissues, its potential accumulation and the associated influence of weight on the pharmacokinetics of roflumilast and roflumilast N-oxide is unknown.

Studies in rats with radiolabeled roflumilast indicated low penetration across the blood-brain barrier.

2.4.3.3. Elimination

Roflumilast is extensively metabolized via phase I (CYP450) and phase II (conjugation) reactions. The major metabolite found in human plasma is roflumilast N-oxide and its formation is catalyzed by cytochrome CYP450 3A4 and 1A2, with the former being the major contributor to the N-oxide formation.

Excretion in humans after oral or intravenous administration occurs almost exclusively in the form of roflumilast metabolites and mainly via the kidneys (~70% of the dose). The fecal elimination accounts for approximately 20% of the dose. The effective half-life of roflumilast after a 500 µg dose ranges between 8 and 31 hours; for the N-oxide the terminal half-life ranges from 11 to 47 hours, which favours the once-daily dosing regimen. The total plasma clearance of roflumilast after intravenous administration is slow.

Polymorphisms of cytochrome P450 enzymes appear to have no relevant influence on roflumilast metabolism.

2.4.3.4. Dose proportionality and time dependencies

Dose proportionality can be assumed as the systemic exposure of roflumilast and roflumilast N-oxide increased proportionally after single and repeated roflumilast doses of 250 µg and 500 µg, and after repeated doses of 500 µg, 750 µg and 1000 µg.

2.4.3.5. Special populations

Special populations are assessed based on the concept of the tPDE4i and a population-based pharmacokinetic model. Differences between observed (in studies) and predicted (derived from the model) pharmacokinetics were seen. The population model is based on a comprehensive set of all available pharmacokinetic data. Thus, the model-based values are considered to be more reliable and robust compared to observed values from single studies. A modest variability of both, observed or predicted, roflumilast pharmacokinetics was seen in some

populations but none of them is deemed to be of clinical relevance. However, the results obtained in clinical trials in some populations (patients aged > 65 years, patients with a body weight < 60 kg, women) differ significantly from the ones obtained in the pharmacokinetic population model. Hence, the robustness of this model was questioned during the assessment and, at the CHMP's request, the Applicant commits to conduct a clinical program, in the context of the post-marketing randomized controlled study, in order to better characterize the PK profile of roflumilast in populations of particular interest (elderly and very elderly patients, patients with a body weight < 60 kg, women).

Gender

No relevant differences in safety or tolerability between males and females were observed in the pooled data of COPD phase II and III studies. Hence, no dose adjustment is necessary with regard to gender.

Elderly

The tPDE4i of roflumilast was comparable in young (18 to 45 years) and middle-aged (46 to 64 years) healthy subjects. A 19% higher mean tPDE4i was observed in the elderly (65 years and older) when compared with the young. The population model predicted a 8% to 14% higher tPDE4i of roflumilast in healthy subjects aged 60 years to 80 years compared to those being 40 years of age. No relevant differences in safety or tolerability between age groups were observed in the pooled data of COPD phase II and III studies.

Race

The population model predicted a 42% and 28% higher 'total PDE4 inhibitory activity' of roflumilast in Blacks and Hispanics, respectively, as compared with Whites. No relevant differences in safety or tolerability between race groups were observed in the pooled data of COPD phase II and III studies.

Impaired liver function

Based on ex vivo data, a 18% and 87%46% higher mean tPDE4i was observed in patients with liver impairment Child-Pugh A and Child Pugh B, respectively after repeated administration of roflumilast 250 µg QD, compared to healthy controls. Metabolic in-vitro data and simulations suggest dose-proportionality between roflumilast 250 µg and 500 µg in patients with liver impairment Child-Pugh A or B. Predictions for the roflumilast 500 µg dose in this population indicate that mean tPDE4i values are similar to those extrapolated from data of the study with the 250 µg dose. As roflumilast is only available in 500µg dose, the use of roflumilast cannot be indicated in this population. The pharmacokinetics of roflumilast in patients with severe liver impairment (Child-Pugh C) has not been evaluated, and therefore its use cannot be recommended in these patients. The SPC adequately reflects this information.

Impaired renal function

In patients with severe renal impairment, the tPDE4i was 9% lower compared to healthy controls. No differences in safety or tolerability between healthy subjects and patients with renal impairment were observed.

2.4.3.6. Pharmacokinetic interaction studies

Inhibition and induction of CYP 3A4

CYP 3A4 is the main isoenzyme involved in roflumilast metabolism. Its inhibition by repeated doses of erythromycin (moderate CYP 3A4 inhibitor) or ketoconazole (strong CYP 3A4 inhibitor) did not increase tPDE4i of a single dose of roflumilast in healthy male subjects. With rifampicin (strong CYP 3A4 inducer) a 58% lower mean tPDE4i was observed compared to values when roflumilast was given alone.

Inhibition and induction of CYP 1A2

With fluvoxamine (strong CYP 1A2 inhibitor) a 59% higher mean total PDE4 inhibition was observed compared to values when roflumilast was given alone. This is reflected in the SPC.

Cigarette smoke, a CYP 1A2 inducer, resulted in a 4% lower tPDE4i. Pharmacokinetic population models indicated a 19% lower tPDE4i in smoking healthy subjects compared to non-smoking ones.

Theophylline, a CYP 1A2 substrate, did not change total PDE4 inhibition.

Co-medications

An increase of the tPDE4i of roflumilast by 47% and 25% was observed after co-administration of cimetidine (weak CYP 1A2 and 3A4 inhibitor) and enoxacin (moderate CYP 1A2 inhibitor and weak CYP 3A4 inhibitor), respectively. These increases are not assumed to result in clinically relevant interactions; however, these data are included in the SPC.

No pharmacokinetic interaction of roflumilast with digoxin (substrate for P-glycoprotein, membrane-localized drug transport mechanism) was demonstrated.

Co-administration of an antacid containing aluminium hydroxide and magnesium hydroxide which increased gastric pH, did not affect tPDE4i. Consequently roflumilast absorption is unlikely to be influenced by gastric pH.

No relevant pharmacokinetic interaction was observed with inhaled salbutamol, formoterol, budesonide, oral theophylline, montelukast, digoxin, warfarin, sildenafil, and midazolam.

A slight increase of tPDE4i was noted with a hormonal oral contraceptive (gestodene, ethinylestradiol).

These data are included in the SPC.

2.4.3.7. Pharmacokinetics using human biomaterials

An in vitro program was conducted to assess the inhibitory potential of roflumilast and its N-oxide on major human liver CYP450 enzymes (CYP 1A2, 2A6, 3A4/5, 4A9/11, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1). There was either no inhibition, or inhibition was only seen at concentrations more than 100-times higher than the maximum plasma levels at therapeutic doses. In cultured human hepatocytes, roflumilast did not cause induction of CYP 1A2, 2A6, 3A4/5, 2C9, or 2C19 and only a week induction of CYP 2B6.

2.4.4. Pharmacodynamics

The therapeutic rationale to develop roflumilast as treatment of COPD is mainly based on the chronic inflammatory nature of the disease. In in vitro and in vivo non-clinical studies, roflumilast and its N-oxide demonstrated potent anti-inflammatory activities, which are expected to have implications on the inflammatory processes of the disease. Both compounds modulated the mediator release from neutrophils, eosinophils, monocytes, macrophages, dendritic cells, CD4+ and CD8+ T-cells at concentrations achieved in human plasma with therapeutic doses. The pharmacodynamic effects of roflumilast in humans have been assessed using various biochemical markers and surrogate indicators of anti-inflammatory activity.

2.4.4.1. Mechanism of action

In-vitro studies have shown that roflumilast and roflumilast N-oxide selectively and potently inhibit PDE4 activity. The synthesis of leukotriene B4, interleukins (IL-2, IL-4, IL-5), interferon γ, and tumor necrosis factor α (TNFα), as well as the formation of reactive oxygen species in human leukocytes were reduced by both compounds. In addition to its anti-inflammatory activity, roflumilast increased ciliary beat frequency in proximal as well as distal airways in vitro, demonstrating its potential to improve mucociliary clearance of the lungs.

Assessment of biomarkers in blood, sputum, and BALF were used to provide evidence of the *in-vivo* anti-inflammatory effects of roflumilast and confirm results of *in-vitro* and animal studies. Roflumilast significantly reduced the influx of absolute numbers of neutrophils, eosinophils, and total cells into airways. In COPD patients, the reduced influx of cells into airways was paralleled by a decrease of TNFα formation (in whole blood ex vivo after in-vitro LPS stimulation).

The relationship between roflumilast plasma concentrations and effect has not been fully addressed. The tPDE4i concept should be further explored, especially to evaluate its impact on efficacy and safety and to help to establish treatment recommendations for at least black, non-smoking females, potent CYP1A2 inhibitors and dual 1A2-3A4 inhibitors in the SPC. Hence, at the CHMP's request, the Applicant committed to conduct a clinical program, in the context of the post-marketing randomized controlled study, in order to further characterize the PK/PD relationship of Daxas, in terms of both efficacy and relevant safety aspects especially in populations of special safety concern as listed above.

2.4.4.2. Primary and Secondary pharmacology

The pharmacodynamic effects of roflumilast on the abnormal inflammatory response observed in COPD, have been explored not only considering lung function variables (e.g. FEV1) or the effect on exacerbations, but evaluating various biochemical markers and surrogate indicators of anti-inflammatory activity, including TNFα formation, presence of inflammatory cells in sputum and in broncho-alveolar lavage fluid (BALF). The inference of the effects of roflumilast based on biochemical markers and surrogate indicators of inflammation, though showed a positive trend in some of the tests, failed to show consistency across all the different evaluations, especially in the in vivo tests performed in healthy volunteers that measured TNFα levels in BALF and blood. Only as a result of a post-hoc analysis, the absolute inflammatory cell numbers were proven to be reduced in sputum, while differential cell counts used to measure changes in the inflammatory indexes did not show significant differences.

A thorough QT/QTc study was performed in which administration of roflumilast up to 1,000 µg once daily for 14 days had no effect on the QTc interval. Cardiac findings after the administration of roflumilast in this study do not seem to raise safety concerns.

2.4.5. Clinical efficacy

2.4.5.1. Dose response study(ies)

Two dose-finding studies (Study FK1 101 and M2-107) were conducted. Roflumilast was used at doses of 250 µg and 500 µg in these studies as both doses were shown to be safe and well tolerated in phase I studies.

Study FK1 101
This dose ranging study was a double blind, evaluation of the safety and efficacy of placebo, roflumilast 250 µg and 500 µg, in COPD. The trial duration was 26 weeks. Eligible patients were 40– 75 years old, with an FEV_1 of 35% to 75% predicted normal, and no more than 12% response (FEV_1) to salbutamol. They had a history of at least ten pack-years cigarette smoking and stable disease as indicated by lack of change in spirometry in the two-week baseline run-in period. Patients with concurrent disease likely to interfere with study procedures were excluded.

Patients were allowed to use rescue inhaled salbutamol and inhaled anticholinergics at constant dose; other common COPD treatments were not allowed during the study.

The primary efficacy criteria were change from baseline in pre-bronchodilator-FEV_1 and in the St. George's Respiratory Questionnaire (SGRQ) total score.

The primary analysis was on the ITT population and the comparison of roflumilast 500 µg to placebo.

Changes in the primary endpoints within treatment groups, including placebo (baseline to end point), were observed; however, the between treatment differences were not statistically different. This is probably due to insufficient statistical power.

Study M2-107

The study design was similar to Study FK1 101. However, Study M2-107 was larger than Study FK1 101 and included a more representative COPD patient population.

Compared to placebo, there was a statistically significant increase in pre- and post-bronchodilator FEV1

with both roflumilast doses at end of treatment. The Jonckheere-Terpstra test demonstrated a significant dose-response relationship (ie. higher increases with higher doses) for both primary endpoints, post-bronchodilator FEV1 ($p < 0.0001$) and the SGRQ total score ($p = 0.0485$) (two-sided test). A dose ordering with a higher response to the 500 µg dose was also seen for the number of mild, moderate, or severe exacerbations per patient ($p = 0.0059$, 2-sided; Jonckheere-Terpstra test).

2.4.5.2. Main studies

This application is based on two pivotal phase III studies (M2-124, M2-125) in a total of 3,096 patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations. Both studies were 52-week, double-blind, placebo-controlled studies evaluating roflumilast 500 µg QD.

2.4.5.2.1. Methods

2.4.5.2.1.1. Study Participants

Diagnosis and main criteria for inclusion:

The main inclusion criteria were the following: age ≥ 40 years; patients with a history of COPD for at least 12 months as defined in the ATS (American Thoracic Society) / ERS (European Respiratory Society) consensus statement and chronic productive cough for 3 months in each of the 2 years prior to baseline visit V0 (if other causes of productive cough had been excluded); FEV1 / FVC (Forced vital capacity) ratio (post-bronchodilator) ≤ 70%; FEV1 (post-bronchodilator) ≤ 50% of predicted; at least one documented COPD exacerbation (as defined by the need for oral or parenteral glucocorticosteroid intake and/or hospitalization) within one year prior to study baseline visit V0; current smoker or former smoker (smoking cessation at least one year ago) with a smoking history of at least 20 pack years. Patients with emphysema only and patients with moderate COPD disease (those populations not responding to roflumilast in the earlier one-year supportive studies) were not planned to be included in pivotal trials M2-124 and M2-125.

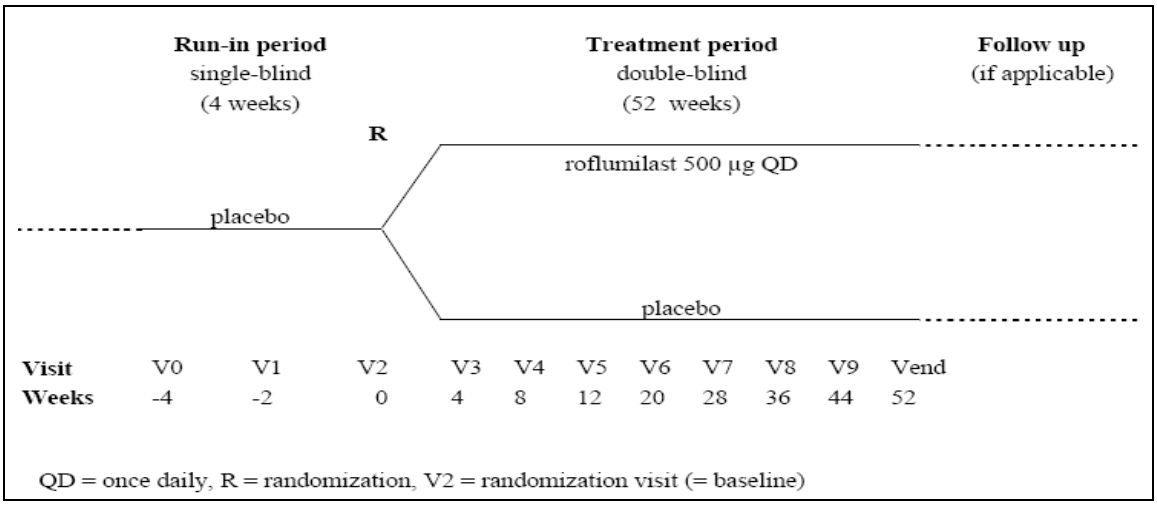
Exclusion criteria

Pregnant and lactating females as well as patients with a diagnosis of relevant lung disease were excluded.

2.4.5.2.1.2. Treatments

The two pivotal studies M2-124 and M2-125 included a run-in period of 4 weeks followed by a double-blind treatment period of 52 weeks, in which patients received roflumilast 500 µg or placebo tablets of identical appearance, orally, once-daily. Please refer to figure 1 for study details.

Figure 1 - Flow-chart of visits during pivotal studies M2-124 and M2-125



Concomitant medications allowed during the treatment period included Short-acting β2-agonists (SABAs), long-acting β2-agonists (LABAs) and short-acting anticholinergics(SAMAs) (only if patients were not taking LABAs). Inhaled corticosteroid (ICS) or oral glucocorticosteroids were not allowed during the maintenance treatment; however, they were allowed to treat the exacerbations. Oral β2-agonists, long-acting anticholinergics (LAMAs), theophylline, lipoxygenase inhibitors and leukotriene antagonists were prohibited during the studies.

2.4.5.2.1.3. Objectives

- To investigate the effect of 500 µg roflumilast od (once daily) on exacerbation rate, lung function, COPD symptoms, dyspnoea, health related quality of life and health care resource use;
- To investigate the safety and tolerability of roflumilast.

These objectives are considered appropriate for the purpose of investigating the efficacy and safety of a new compound in patients with COPD.

2.4.5.2.1.4. Outcomes/endpoints

(Co) primary efficacy endpoints:

- Mean change from baseline (V2) during the treatment period in pre-bronchodilator FEV1.
- Mean rate of COPD exacerbations requiring oral or parenteral corticosteroids (moderate), or requiring hospitalization, or leading to death (severe), per patient per year.

Secondary key endpoints of efficacy:

- Mean change in post-bronchodilator FEV1 from baseline (V2) to each post-randomization visit during the treatment period.
- Time to mortality due to any reason.
- Natural log-transformed CRP (C-reactive protein) [mg/L] (mean change from baseline (V2) to last scheduled study visit).
- Mean transition dyspnea index (TDI) focal score during the treatment period.

2.4.5.2.1.5. Sample size

The sample size calculation was based on the assumption of a rate of 1.25 moderate-/severe exacerbations in the placebo group, a reduction of 20% with roflumilast 500 µg and an overdispersion factor of 2.

2.4.5.2.1.6. Randomisation

The randomisation methods included a randomisation schedule based on a computer generated randomisation list and stratification by smoking status and pre-treatment with LABA to ensure a balanced randomisation of patients in each subgroup.

2.4.5.2.1.7. Blinding (masking)

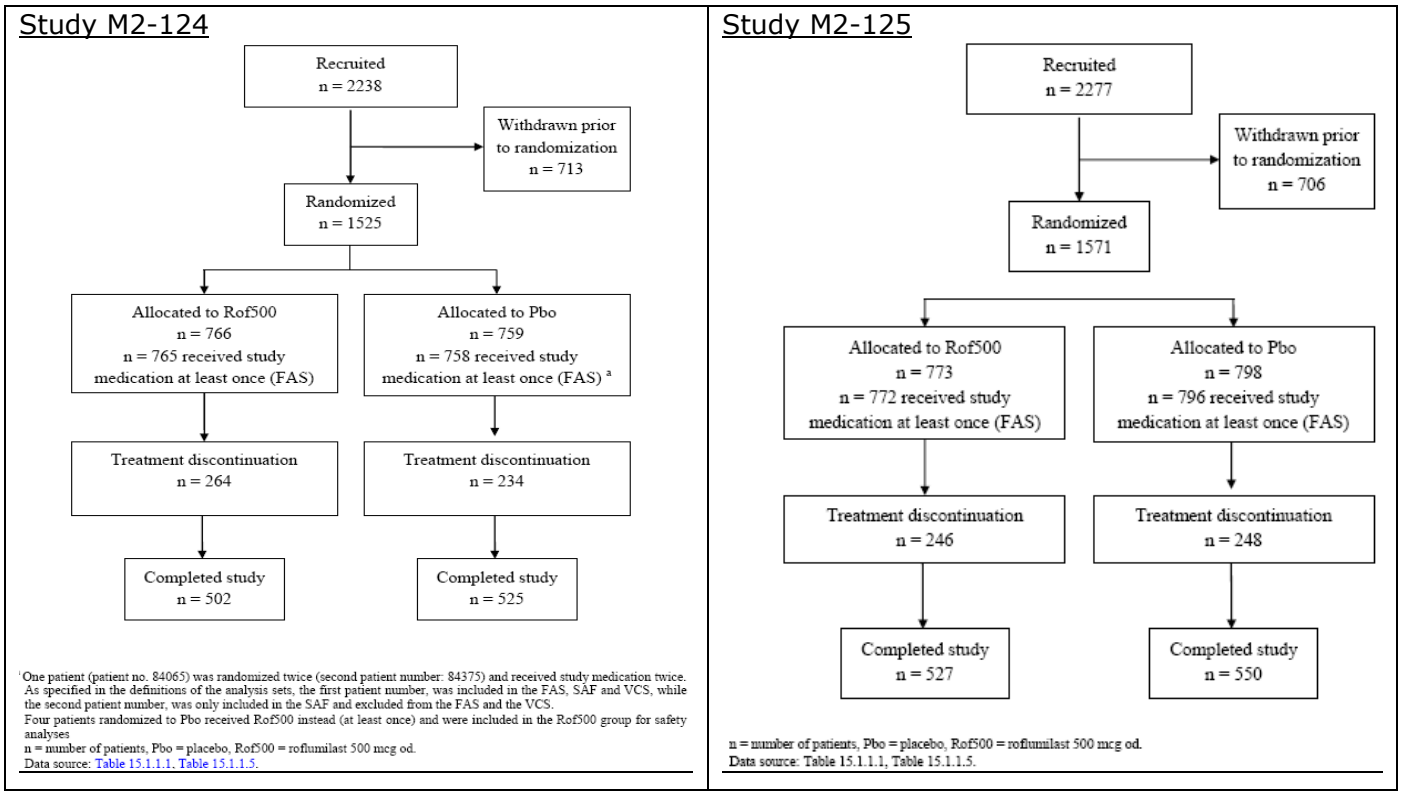
Blinding was achieved by supplying roflumilast and placebo tablets of identical appearance (both white to off-white tablets, packed in blister packs containing 10 tablets) and secondly, by means of code-labelling of the study medication.

2.4.5.2.1.8. Statistical methods

The two primary variables were tested in a hierarchical manner with a two-sided test using a significance level of 5%, and pre-bronchodilator FEV1 being tested first, on an ITT basis. If the first primary endpoint proved to be significant, the second primary endpoint, rate of moderate/severe exacerbations, was tested. For the primary analysis of the primary endpoint "pre-bronchodilator FEV1" a repeated measurements analysis of covariance (ANCOVA) model was used. For the "rate of moderate/severe COPD exacerbations" a Poisson regression model with time-in-study as an offset variable (correction for the time a patient was in the study) was used. The following factors and covariates were included in the model: treatment, country (or region), smoking status, baseline FEV1 % predicted, concomitant LABA treatment, gender and age. The Pearson Chi-Square correction for scale was applied, in order to account for potential overdispersion resulting from lack of independence of the events and/or zero inflation.

2.4.5.2.2. Results

Figure 2 - Patients disposition in pivotal studies M2-124 and M2-125



2.4.5.2.2.1. Recruitment

Study M2-124: The clinical phase of the study lasted from 27/02/2006 (first patient in) to 07/07/2008 (last patient out). A total of 2238 patients were recruited at 246 centres in 6 country pools (Australia/New Zealand/United Kingdom, Austria/Germany, France, Hungary/Romania, Russia and USA).

Study M2-125: The clinical phase of the study lasted from 02/03/2006 (first patient in) to 29/04/2008 (last patient out). A total of 2277 patients were recruited at 221 centres in 7 country pools (Canada, Germany, India, Italy/Spain, Poland, South Africa and USA)

2.4.5.2.2.2. Baseline data

Demographic characteristics are summarised in table 4.

Table 4 Demography - Studies M2-124, M2-125, and pivotal COPD studies pool

Study or pool	Treat-ment	N	Age [years] Median	Range	Age >65 [N (%)[a]]	Male [N (%)[a]]	Cur. Smoker [N (%)[a]]	BMI [kg/m^2][b] Mean ± SD
M2-124	Placebo	758	63	40-92	312 (41)	538 (71)	361 (48)	26.0 ± 5.5
	Rof500	765	63	40-89	316 (41)	540 (71)	365 (48)	26.4 ± 5.5
M2-125	Placebo	796	65	40-90	359 (45)	648 (81)	282 (35)	25.4 ± 5.9
	Rof500	772	64	40-90	343 (44)	610 (79)	270 (35)	25.2 ± 6.2
124+125 pool	Placebo	1554	64	40-92	671 (43)	1186 (76)	643 (41)	25.7 ± 5.7
	Rof500	1537	64	40-90	659 (43)	1150 (75)	635 (41)	25.8 ± 5.9

[a] Percentages (rounded to the nearest integer) are based on the total number of patients in a treatment group.
[b] Measurement at randomization.
BMI = body mass index, COPD = chronic obstructive pulmonary disease, Cur. = current, FAS = full analysis set, N = number of patients, Rof500 = 500 µg roflumilast once daily, SD = standard deviation.

Demographic characteristics were comparable for the roflumilast and placebo treatment groups in both individual studies and the pooled analyses. The majority of patients were White (≥71%). The proportion of patients of other races was generally below 5% with the exception of Asians, which comprised 23% of patients in Study M2-125 and 12% in the pooled analysis.

Baseline values for lung function and COPD severity were similar in both treatment groups of the two individual studies, of the pooled analysis, and across studies and pooled analyses.

Previous COPD treatment are summarised in Table 5.

Table 5 - Frequently used previous respiratory medication - Studies M2-124, M2-125, and pivotal COPD studies pool (FAS)

Study or Pool Treat.	N	Number of (%)[a] of patients SABA (ih)	ICS[b] (incl. comb)	Comb. CS +LABA (ih)	LAMA (ih)	ICS (only)	LABA (ih)	Xanthines
M2-124								
Placebo	758	464 (61)	335 (44)	331 (44)	234 (31)	169 (22)	150 (20)	153 (20)
Rof500	765	501 (66)	338 (44)	336 (44)	238 (31)	175 (23)	143 (19)	165 (22)
M2-125								
Placebo	796	475 (60)	322 (41)	267 (34)	168 (21)	201 (25)	215 (27)	227 (29)
Rof500	772	462 (60)	312 (40)	285 (37)	168 (22)	192 (25)	206 (27)	220 (29)
124+125 pool								
Placebo	1554	939 (60)	657 (42)	598 (39)	402 (26)	370 (24)	365 (24)	380 (25)
Rof500	1537	963 (63)	650 (42)	621 (40)	406 (26)	367 (24)	349 (23)	358 (25)

Those medications are listed which were reported by at least 25% of patients in any treatment group and within 4 weeks prior study to entry.
[a] Percentages (rounded to the nearest integer) are based on the total number of patients in a treatment group.
[b] Includes: ICS only, inhaled combinations of corticosteroids and LABAs, and inhaled combinations of corticosteroids and SABAs.
COPD = chronic obstructive pulmonary disease, comb. = combination, CS = corticosteroid, FAS = full analysis set, ICS = inhaled corticosteroid, ih = inhaled, incl. = including, LAMA = long-acting muscarinic agonist = long-acting anticholinergic, LABA = long-acting β_2-agonist, N = number of patients, Rof500 = 500 µg roflumilast once daily, SABA = short-acting β_2-agonist. Treat. = treatment.

Concomitant COPD treatment are summarised in Table 6.

Table 6 - Frequently used concomitant respiratory medication - Studies M2-124, M2-125, and pivotal COPD studies pool (FAS)

Study or Pool	Treat-ment	N	Number of (%)[a] of patients					
			SABA (ih)	CS[b] (excl. ih)	LABA[c] (incl. comb.)	LABA (ih)	SAMA[d] (incl. comb.)	SAMA (ih. only)
M2-124	Placebo	758	753 (99)	409 (54)	385 (51)	342 (45)	268 (35)	245 (32)
	Rof500	765	761 (>99)	377 (49)	378 (49)	339 (44)	266 (35)	240 (31)
M2-125	Placebo	796	791 (99)	456 (57)	408 (51)	351 (44)	348 (44)	324 (41)
	Rof500	772	769 (>99)	404 (52)	371 (48)	329 (43)	322 (42)	297 (39)
124+125	Placebo	1554	1544 (99)	865 (56)	793 (51)	693 (45)	616 (40)	569 (37)
pool	Rof500	1537	1530 (>99)	781 (51)	749 (49)	668 (44)	588 (38)	537 (35)

Those medications are listed which were reported by at least 20% of patients in any treatment group. **Please note that concomitant medication includes all medication independent of the length of time they were administered ie whether they were taken only once or over an extended time period.**

[a] Percentages (rounded to the nearest integer) are based on the total number of patients in a treatment group.
[b] Other than inhaled or nasal applications. [c] Includes patients who used LABAs only and inhaled combinations of corticosteroids and LABAs. [a] Includes patients who used inhaled SAMAs only and combinations of inhaled SAMAs and SABAs.
COPD = chronic obstructive pulmonary disease, comb. = combination, CS = corticosteroids, excl. = excluding, FAS = full analysis set, ih = inhaled, incl. = including, LABA = long-acting β_2-agonist, N = number of patients, Rof500 = 500 µg roflumilast once daily, SABA = short-acting β_2-agonist, SAMA = short-acting muscarinic agonist = short-acting anticholinergic.

The percentage of patients having taken acetylcysteine or smoking cessation drugs during the pivotal studies was small. Only few patients reported change in smoking status. These characteristics were balanced between groups.

The percentage of patients completing the study (around 70%) or discontinuing prematurely (around 30%) was comparable between treatment groups, both within the individual studies and among studies. In both pivotal studies, patients on roflumilast withdrew the study due to AEs earlier and to a higher extent than those on placebo. On the contrary, withdrawal rates due to COPD exacerbation in patients receiving placebo were higher than that of patients on roflumilast.

2.4.5.2.2.3. Outcomes and estimation

Primary endpoints

Pre-FEV1:

The LSMean changes in pre-bronchodilator FEV1 showed increases in the roflumilast by 40 mL and decreases in the placebo group by 9 mL during the treatment period (M2-124 and M2-125 pool), with a mean difference by 48 ml (95%CI: 35 to 62; $p < 0.0001$). The results were consistent in both pivotal studies (differences by 39 ml and 58 ml in favour of roflumilast versus placebo in studies M2-124 and M2-125 respectively).

Roflumilast significantly improved pre-bronchodilator FEV1 %predicted as compared to placebo in pivotal studies M2-124 and M2-125. Please refer to Table 7.

Table 7 - Change from baseline to end of treatment in pre-bronchodilator FEV1 [L] (primary endpoint) - Studies M2-124, M2-125, and pivotal COPD studies pool (ITT, rep. measures)

Study or Pool	Treatment	n	Baseline Mean	Change from baseline		Difference vs placebo		
				LSMean	95% CI	LSMean	95% CI	p-value[a]
M2-124	Placebo	745	1.061	0.008	-0.008, 0.023			
	Rof500	745	1.071	0.046	0.030, 0.062	0.039	0.018, 0.060	0.0003
M2-125	Placebo	766	0.985	-0.025	-0.039, -0.011			
	Rof500	730	0.955	0.033	0.019, 0.048	0.058	0.041, 0.075	<0.0001
124+125	Placebo	1511	1.023	-0.009	-0.019, 0 002			
pool	Rof500	1475	1.014	0.040	0.029, 0.050	0.048	0.035, 0.062	<0.0001

[a] 2-sided
CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, LS = least squares, pre = pre-bronchodilator, rep. = repeated, Rof500 = µg roflumilast once daily, vs = versus.

In patients concomitantly treated with LABA and compared to placebo, roflumilast increased pre-bronchodilator FEV1 by 49 mL in the post-hoc ITT analysis as a result of the findings from the GCP inspection (compared with 46 mL in the pre-specified analysis) and post-bronchodilator FEV1 by 50 mL

in the post-hoc ITT analysis (compared with 46 mL in the pre-specified analysis).

Moderate/severe COPD exacerbations

The results on moderate/severe exacerbations rates in the primary analysis (ITT population, Poisson regression model) were consistent in studies M2-124 and M2-125, being statistically significant in favour of roflumilast compared with placebo in individual studies as well as in the pooled analysis (mean exacerbations per patient per year: Rof. 1.142 vs Placebo 1.374; RR: 0.831; 95%CI: 0.75 to 0.92; RR reduction: 16.9%; p = 0.0003). The results are presented in Table 8.

Table 8 - Rate of moderate or severe exacerbation (primary endpoint) - Studies M2-124, M2-125, and pivotal COPD studies pool (ITT, Poisson regression)

Exacerbation	Placebo		Rof500		Rof500 vs placebo			
Study or pool	N	Rate	N	Rate	%Change	Rate ratio	95% CI	p-value[a]
M2-124	758	1.266	765	1.077	-14.9	0.851	0.737, 0.982	0.0278
M2-125	796	1.485	772	1.210	-18.5	0.815	0.710, 0.935	0.0035
124+125 pool	1554	1.374	1537	1.142	-16.9	0.831	0.752, 0.918	0.0003

[a] 2-sided
CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, Rof500 = 500 µg roflumilast once daily, vs = versus.

The effect size in the PP population is not of the same magnitude than the ITT analysis in study M2-124, in which the results in the PP population are disappointing (only a relative change by -7.8% on exacerbations versus placebo was reported with the Poisson regression model and -6.7% with the negative binomial regression model). Please refer to table 9.

Table 9 - Mean rate of moderate or severe COPD exacerbations per patient per year: Poisson regression model (ITT, PP)

	Exacerbation rate				Rate Rof500/Pbo				
	Rof500		Pbo		Rate	Change			2-sided
	n	Rate	n	Rate	ratio	[%]	SE	95% CI	p-value[a]
ITT	765	1.077	758	1.266	0.851	-14.9	0.062	0.737, 0.982	0.0278
PP	553	1.007	549	1.093	0.922	-7.8	0.079	0.780, 1.089	0.3385

[a] Two-sided p-value significance level 5%. CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, n = number of patients in the respective treatment group, Pbo = placebo, PP = per-protocol analysis, Rof500 = roflumilast 500 mcg, SE = standard error. Note: A rate ratio <1 represents a favorable outcome for the Rof500 treatment. Rates, 95% CIs, rate ratio, SE, and p-values are based on a Poisson regression with factors treatment, baseline post-bronchodilator FEV_1, (%predicted), age, sex, smoking status, concomitant treatment with long-acting β_2-agonists and country pool.

The effect size in the PP population is of the same magnitude than the ITT analysis in study M2-125 either in with the Poisson regression model or the negative binomial regression model.

Secondary endpoints

Significant results in favour of roflumilast were shown in both trials in the following secondary endpoints: post-FEV1, rates of patients with at least one moderate/severe exacerbation, time to first and second moderate/severe exacerbation, mean differences in TDI score. Significant results in favour of roflumilast were also shown in the need for rescue medication in study M2-125 only. No statistically significant differences were found in mortality rates (pooled analysis: 42 deaths each group; 2.7% each group), rate of patients with at least one point improvement in the TDI score, C-reactive protein levels, symptom scores or quality of life scores, which were similar in patients treated with roflumilast or placebo.

Patients experiencing a COPD exacerbation

The number of patients with at least one moderate/severe exacerbation during the 1-year study period was significantly lower in patients receiving roflumilast than in patients treated with placebo in both studies and the pooled analysis (risk ratio each: 0.89). The results are presented in Table 10.

Table 10 - Patients with moderate or severe exacerbations - Studies M2-124, M2-125, and pivotal COPD studies pool (ITT, log binominal regression)

Study or pool	Placebo			Rof500			Risk ratio Rof500/placebo		
	N	n (%)[a]	Risk[b]	N	n (%)[a]	Risk[b]	Ratio[c]	95% CI	p-value[d]
M2-124	758	389 (51)	0.52	765	344 (45)	0.47	0.89	0.80, 0.98	0.0196
M2-125	796	432 (54)	0.56	772	373 (48)	0.50	0.89	0.82, 0.98	0.0183
124+125 pool	1554	821 (53)	0.54	1537	717 (47)	0.48	0.89	0.83, 0.95	0.0006

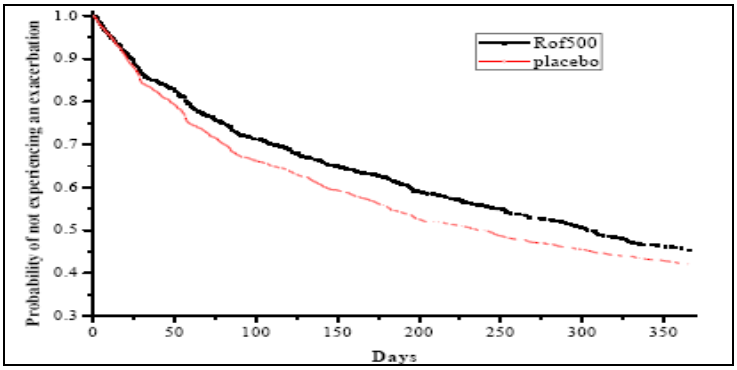
[a] Percentages (rounded to the nearest integer) are based on the total number of patients in a treatment group; [b] Risk of experiencing at least one exacerbation (rounded); [c] Rounded; [d] 2-sided.
CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, n = number of patients with at least one exacerbation, Rof500 = 500 µg roflumilast once daily.

Time to first moderate to severe exacerbation

In the pooled analysis of the two pivotal studies, differences on median time to first moderate to severe exacerbation were statistically significant in favour of roflumilast (Rof500 80 d vs placebo 71 d; Hazards ratio: 0.89; 95%CI: 0.80 to 0.98; p = 0.0185; Cox proportional hazards regression).

The Kaplan-Meier Plot for the time to first moderate or severe exacerbation based on the pooled analysis is shown in figure 3.

Figure 3 - Time to first moderate or severe exacerbation, Kaplan-Meier Plot – pivotal COPD studies pool (ITT)



Time to second moderate to severe exacerbation:

The median time to onset of second moderate or severe exacerbation was statistically significant in favor of roflumilast in study M2-124 (Rof500 172 d vs placebo 159 d; Hazard ratio: 0.79; 95%CI: 0.64 to 0.98; p = 0.0290) and study M2-125 (Rof500 188 d vs placebo 144 d; Hazard ratio: 0.79; 95%CI: 0.65 to 0.97; p = 0.0214).

2.4.5.2.2.4. Ancillary analyses

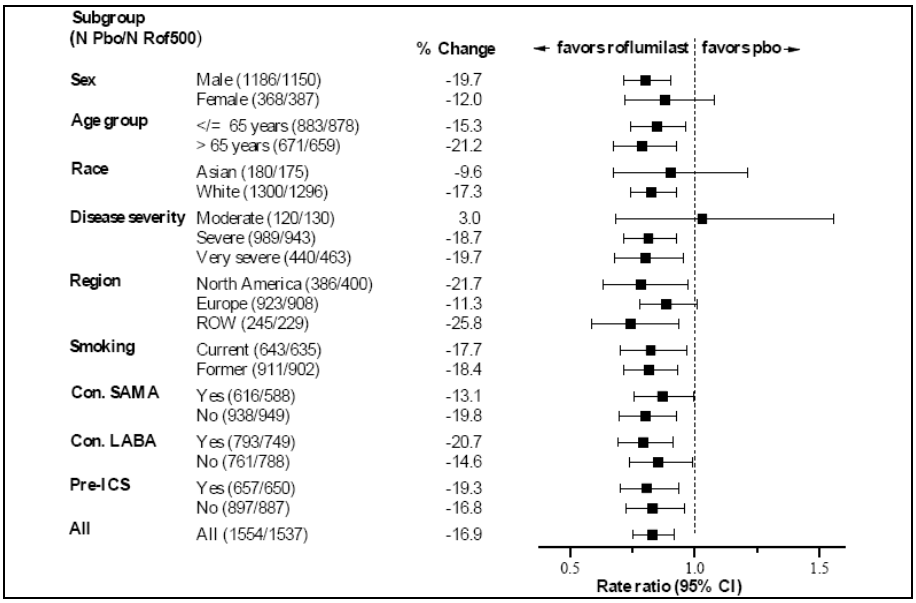
The results on exacerbations in the ancillary analysis (ITT population, negative binomial regression model) are consistent in studies M2-124 and M2-125, being statistically significant in favour of roflumilast compared with placebo.

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

The efficacy data from Phase II and Phase III studies for roflumilast were pooled. All efficacy analyses were exploratory. All analyses were made on an ITT basis. All selected efficacy endpoints were primary or key secondary endpoints, or secondary endpoints related to COPD exacerbations in the pivotal studies.

The main results from planned subgroup analyses in the COPD pivotal studies are shown in figure 4:

Figure 4 - Moderate or severe exacerbations by subgroup - pivotal COPD studies pool (ITT, Poisson regression)



CI = confidence interval, conc. = concomitant, COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroid, ITT = intention-to-treat, LABA = long-acting β2-agonist, N = number of patients, pbo = placebo, Rof500 = roflumilast 500 µg once daily, ROW = "rest of the world" (all countries except USA, Canada, and European countries), SAMA = short-acting muscarinic agonist = short-acting anticholinergic.

The modest effect of roflumilast on pre-FEV1 was generally consistent among the subgroups analysed in the planned analyses in the different pool of trials:

- The modest effect of roflumilast versus placebo on the reduction of moderate/severe exacerbations were in favour of roflumilast in patients with severe/very severe disease and consistently disappointing in patients with moderate COPD disease.
- The modest effect of roflumilast versus placebo on the reduction of moderate/severe exacerbations were consistently in favour of roflumilast in patients with bronchitis and consistently disappointing in patients with emphysema only.

Subgroup analysis of patients with frequent exacerbations (pivotal COPD studies pool)

In patients with severe COPD associated with chronic bronchitis and history of frequent exacerbations (at least 2 exacerbations in the last year), the relative risk reduction on exacerbation rates was 21.3% (absolute risk reduction: 0.415 exacerbations per patient per year; NNT: 2.4).

Secondary variables, such as the time to second moderate/severe exacerbation, change in pre-bronchodilator FEV1, post-bronchodilator FEV1 and transition dyspnoea index in the target population, were statistically significant in favour of roflumilast versus placebo in the study M2-124 + M2-125 pool.

The time to first exacerbation or death with roflumilast were not significantly different from placebo in the target population.

Responders' analysis

When all adverse events leading to study discontinuation were considered, there were no differences between roflumilast and placebo in the rate of responders. However, when only serious adverse events were considered, the rate of responders was significantly higher with roflumilast than with placebo.

Additional sensitivity analyses of moderate or severe exacerbations with imputation and simulation methods were performed to assess the impact of patient withdrawal on effect size estimates for exacerbations. The results from these studies suggest that the part of the effect size which may be due to patients dropping out is less than 2% for study M2-124 and less than 3.5% for study M2-125.

Completers analysis

The completers analysis was pre-specified in the protocol and the effect on reduction of exacerbations was similar in patients who completed the study (-13.9%) compared with the overall study population

(-16.9%).

2.4.5.4. Clinical studies in special populations

The applicant did not submit clinical studies to assess the efficacy of roflumilast in special populations.

2.4.5.5. Supportive study(ies)

Of the supportive studies provided by the Applicant, the following ones were of interest and included patients with moderate to very severe COPD. All supportive studies were double-blind, randomized, and placebo-controlled studies of 24 to 52 weeks treatment and included roflumilast at a dose of 500µg QD. Some studies in addition used roflumilast at a dose of 250µg QD.

Studies M2-111 and M2-112:

These two 1-year studies investigated the effect of roflumilast on exacerbations and lung function in patients with severe to very severe COPD. These studies were similar in design to the pivotal studies but patients in Studies M2-111 and M2-112 had a lower risk of exacerbations than that included in the pivotal studies. A total of 2,690 patients were included and randomized. A history of chronic bronchitis and of COPD exacerbations was not requested in these studies, and patients without a history of COPD exacerbations as well as patients with emphysema were included. Patients were also not required to show symptoms of cough and sputum during run-in as in the pivotal studies. ICS were used in 809 (61%) of the roflumilast treated patients, whereas the use of LABAs and theophylline was prohibited.

Daxas 500µg once daily significantly improved lung function compared to placebo, on average by 51 ml (pre-bronchodilator FEV_1, $p<0.0001$), and by 53 ml (post-bronchodilator FEV_1, $p<0.0001$). The rate of moderate or severe exacerbations was not significantly reduced by roflumilast in individual studies (relative risk reduction: 13.5% in study M2-111 and 6.6% in study M2-112; p = not significant). There was no clinically meaningful difference between treatments for SGRQ total score in both studies. Adverse events rates were independent of concomitant treatment with inhaled corticosteroids.

Studies M2-127 (228/2008) and M2-128 (225/2008):

These two 24-week studies investigated the benefit of roflumilast treatment in patients with moderate to severe COPD who were receiving maintenance therapy with either salmeterol (Study M2-127; n = 933 patients) or tiotropium (Study M2-128; n = 743 patients). The main focus of these studies was to evaluate if roflumilast adds additional benefit on lung function beyond the effects of long-acting bronchodilators.

In both studies, roflumilast significantly improved lung function in patients on long-acting bronchodilators. In study M2-128, statistically significant improvements in TDI score and SOBQ (Shortness of Breath Questionnaire) were found with roflumilast, but not in study M2-127.

2.4.6. Discussion on clinical efficacy

Though statistical significance was reached for the two primary endpoints of the pivotal trials, concerns were raised by the CHMP with regards to the modest efficacy observed with roflumilast. Moreover, the effects of the product on exacerbations were inconsistent depending on the severity of the affection and the concomitance of chronic bronchitis. Finally, the clinical relevance of the modest effect observed was difficult to interpret due to the lack of active comparator and the absence of data on top of LABAs and ICS. Hence, an ad hoc expert group meeting was convened by the CHMP to discuss the questions of the clinical relevance of the effect of roflumilast and the identification of a population for which the benefit of roflumilast could be regarded as particularly relevant.

With regards to the clinical relevance of the effect of roflumilast on the pulmonary endpoint, the experts considered that the change in FEV1 was lower than seen with other compounds. However, it was noted - also with reference to recent ATS/ERS publications - that there are no defined limits of significance for this endpoint in the concerned patient population. The issue that there are no

supportive data to further substantiate the marginal effect seen was raised and particular emphasis was laid on the lack of robust quality of life data. The experts agreed that the lack of standardisation for the concomitant medications makes the interpretation of the results difficult due to the potential confounding effects.

It was noted however that FEV1 might not be the most relevant endpoint for this compound due to its action as anti-inflammatory agent.

Overall, the experts agreed that the clinical relevance of the effect of roflumilast on FEV1 was difficult to judge based on the available data since the current first line treatment (combination of LABA / ICS) was not used in the trials, neither as concomitant medication nor as a comparator. However, taking into account the severity of the disease in the patients enrolled in the trials, in which a very small variation of FEV1 is expected according to the natural history of the disease, some experts felt that the effect shown by roflumilast on this parameter might not be negligible.

With regard to the effect of roflumilast on the second primary endpoint, exacerbation rate, the experts agreed that this was closer to demonstrate clinically relevance. However, as discussed above, the design of the trials could potentially introduce bias in the results.

On the question of the population for which would particularly benefit of treatment with roflumilast, the experts agreed that in principle the patients with severe to very severe COPD, high exacerbation rate and chronic bronchitis seem to be benefiting from treatment with roflumilast therefore representing the correct target population. For this population there is an unmet need with available therapies. However, as discussed above, the clinical relevance of the effect of the compound in this population was difficult to assess based on the available data.

Finally, the experts felt that the use of roflumilast would in principle only be foreseen as an add-on treatment to the current first line treatment (combination of LABA / ICS) in the patients with severe to very severe COPD, high exacerbation rate and chronic bronchitis. Some experts could also foresee its use as an alternative in the same patient population for which other medications (e.g. combined LABA/ICS) are contraindicated or have been shown to have limited efficacy. However, there is no data to support an efficacy demonstration in this setting.

2.4.7. Clinical safety

2.4.7.1. Patient exposure

More than 24,000 subjects were enrolled in 114 clinical studies investigating oral roflumilast, of whom more than 14,000 were exposed to roflumilast at a variety of dose levels. The majority of patients included in the clinical program were males and Caucasians. Even though the current application was intended for an indication in patients with COPD associated with chronic bronchitis, roflumilast has also been studied in asthma, and in a limited number of other affections. All these populations are considered, however the Applicant focuses on an integrated safety analysis of pooled clinical studies in patients with COPD. The broad clinical database is complemented with results from non-clinical studies, and pooled data analyses based on roflumilast studies in patients with asthma are used supportively.

Baseline characteristics and medication allowed at inclusion and during the studies reflect well an overall COPD population, though the effect of concomitant use of roflumilast and ICS was not assessed. Further information is provided in table 11.

Table 11 - Patient drug exposure – pivotal COPD and COPD safety pools

Exposure to study drug	Pivotal COPD studies pool[a]		COPD safety pool[b]		
	Placebo (N=1545) n (%)[c]	Rof500 (N=1547) n (%)[c]	Placebo (N=5491) n (%)[c]	Rof250 (N=797) n (%)[c]	Rof500 (N=5766) n (%)[c]
<1 week	24 (1.6)	36 (2.3)	53 (1.0)	13 (1.6)	119 (2.1)
≥1 week to <4 weeks	48 (3.1)	90 (5.8)	162 (3.0)	23 (2.9)	370 (6.4)
≥4 weeks to <13 weeks	132 (8.5)	164 (10.6)	710 (12.9)	100 (12.5)	883 (15.3)
≥13 weeks to <26 weeks	113 (7.3)	90 (5.8)	2045 (37.2)	549 (68.9)	2081 (36.1)
≥26 weeks to <52 weeks	468 (30.3)	446 (28.8)	1167 (21.3)	112 (14.1)	1081 (18.7)
≥52 weeks	760 (49.2)	721 (46.6)	1354 (24.7)	0 (0.0)	1232 (21.4)
Mean E per patient	293.1 ± 120.6	279.9 ± 134.0	226.5 ± 119.0	148.8 ± 47.9	206.6 ± 125.8

(days) [mean ± SD]					
Median E per patient (days)	363	363	173	168	169
Total E (patient years)	1240	1186	3405	325	3261

[a]Includes studies M2-124, M2-125. [b]Includes studies FK1 101, FK1 103,IN-108, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128. [c] Percentages are based on N. COPD – chronic obstructive pulmonary disease, ET = exposure time, N = number of patients in treatment group, n = number of patients with data available, Rof250 = 250 µg roflumilast once daily, Rof500 = 500 µg roflumilast once daily.

2.4.7.2. Adverse events

Causality

In the COPD safety data base, more than 17% of the AEs were deemed to be related to the administration of roflumilast 500 µg QD (5.4% in the placebo group).

Common adverse events

In addition to AEs such as nausea and diarrhoea, body weight decrease and insomnia are registered as common AEs. Table 12 presents the frequent AEs by system organ class and preferred term. Further information is provided in table 12.

Table 12 - Patients with frequent AEs by system organ class and preferred term (frequency ≥ 2% of patients with regard to preferred term in any treatment group) – pivotal COPD studies and COPD safety pools

System Organ Class Preferred Term (MedDRA)	Pivotal COPD studies pool		COPD safety pool		
	Placebo (N=1545) (ET=1240) n (%)[a]	Rof500 (N=1547) (ET=1186) n (%)[a]	Placebo (N=5491) (ET=3405) n (%)[a]	Rof250 (N=797) (ET=325) n (%)[a]	Rof500 (N=5766) (ET=3261) n (%)[a]
All AEs	**963 (62.3)**	**1040 (67.2)**	**3447 (62.8)**	**484 (60.7)**	**3873 (67.2)**
Infections and infestations	**422 (27.3)**	**424 (27.4)**	**1508 (27.5)**	**188 (23.6)**	**1492 (25.9)**
Nasopharyngitis	97 (6.3)	92 (5.9)	346 (6.3)	50 (6.3)	364 (6.3)
Bronchitis	64 (4.1)	56 (3.6)	192 (3.5)	25 (3.1)	177 (3.1)
Upper respiratory tract infection	59 (3.8)	49 (3.2)	234 (4.3)	32 (4.0)	219 (3.8)
Pneumonia	31 (2.0)	42 (2.7)	110 (2.0)	5 (0.6)	104 (1.8)
Influenza	38 (2.5)	39 (2.5)	132 (2.4)	16 (2.0)	145 (2.5)
Gastrointestinal disorders	**188 (12.2)**	**319 (20.6)**	**587 (10.7)**	**104 (13.0)**	**1271 (22.0)**
Diarrhoea	49 (3.2)	130 (8.4)	143 (2.6)	39 (4.9)	585 (10.1)
Nausea	30 (1.9)	62 (4.0)	79 (1.4)	18 (2.3)	297 (5.2)
Investigations	**181 (11.7)**	**281 (18.2)**	**584 (10.6)**	**55 (6.9)**	**811 (14.1)**
Weight decreased	44 (2.8)	157 (10.1)	101 (1.8)	6 (0.8)	394 (6.8)
Respiratory, thoracic and mediastinal disorders	**327 (21.2)**	**265 (17.1)**	**1607 (29.3)**	**197 (24.7)**	**1476 (25.6)**
COPD[b]	204 (13.2)	157 (10.1)	1271 (23.1)	169 (21.2)	1142 (19.8)
Dyspnoea	28 (1.8)	28 (1.8)	120 (2.2)	18 (2.3)	84 (1.5)
Musculoskeletal and connective tissue disorders	**144 (9.3)**	**181 (11.7)**	**445 (8.1)**	**62 (7.8)**	**590 (10.2)**
Back pain	35 (2.3)	50 (3.2)	117 (2.1)	22 (2.8)	176 (3.1)
Nervous system disorders	**90 (5.8)**	**150 (9.7)**	**304 (5.5)**	**45 (5.6)**	**615 (10.7)**
Headache	25 (1.6)	51 (3.3)	110 (2.0)	28 (3.5)	266 (4.6)
Dizziness	16 (1.0)	30 (1.9)	65 (1.2)	9 (1.1)	139 (2.4)
Metabolism and nutrition disorders	**60 (3.9)**	**104 (6.7)**	**186 (3.4)**	**19 (2.4)**	**311 (5.4)**
Decreased appetite	7 (0.5)	36 (2.3)	22 (0.4)	4 (0.5)	125 (2.2)
Psychiatric disorders	**55 (3.6)**	**98 (6.3)**	**164 (3.0)**	**22 (2.8)**	**344 (6.0)**
Insomnia	20 (1.3)	37 (2.4)	50 (0.9)	11 (1.4)	148 (2.6)
Vascular disorders	**80 (5.2)**	**76 (4.9)**	**229 (4.2)**	**20 (2.5)**	**196 (3.4)**
Hypertension	48 (3.1)	38 (2.5)	136 (2.5)	12 (1.5)	95 (1.6)

[a]Percentages of patients with at least one event in the category.
[b]The preferred term COPD refers to COPD exacerbation. Note, in the pivotal COPD studies only COPD exacerbations fulfilling the criterion of a serious AE were to be recorded in the AE section.
AE = adverse event, COPD = chronic obstructive pulmonary disease, ET = number of patient years of exposure, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in treatment group, n = number of patients with at least one event in the category, Rof250 = 250 µg roflumilast once daily, Rof500 = 500 µg roflumilast once daily

Diarrhea

Diarrhea, usually mild or moderate in intensity, is an identified common adverse reaction of roflumilast: 585 cases were reported in 5766 patients treated with roflumilast 500 µg (COPD safety pool). Of these, 10 cases were considered serious. The majority of patients had other causes for diarrhea, or a negative re-challenge, and resolved without sequel.

Psychiatric AEs

The rate of psychiatric AEs in the COPD safety pool is significantly higher in patients on roflumilast 500 micrograms than in patients on placebo.

Weight loss

Weight loss registered as an AE in the roflumilast-treated patients during the first year seems small in magnitude (≈ -2 kg), and did not show a relevant progression after the first 6 months of treatment. The magnitude and incidence of this effect appears to be sufficiently and consistently characterised;

however, the causality assessment remains unclear as multiple factors may contribute to the effect. Hence, given that weight loss is associated to a worse prognosis in COPD, this AE should be proactively monitored and it should be considered to stop the treatment in case of unexplained and pronounced weight decrease.

Cardiac safety

Fewer patients in the roflumilast 500 µg than in the placebo group experienced cardiac AEs of interest (5.2% vs 5.7%). In all studies, the ECG recordings at the last visit were compared with those at the baseline visit and results from the ECG analysis show no arrhythmogenic potential of roflumilast.

Infections

An increased risk of infections associated with the administration of roflumilast has not been shown. However, given the lack of clinical experience, treatment with roflumilast should not be initiated or existing treatment should be stopped in patients with severe immunological diseases, severe acute infectious diseases or patients treated with immunosuppressive medicinal products. Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster is limited.

Endocrine disorders

Gynaecomastia was observed in clinical trials. In 9 out of the 12 cases reported, a temporal relationship between the incidence of gynaecomastia and the administration of roflumilast was found, even though in 6 of these cases other drugs could also explain the event. The pharmacology studies performed were not specifically designed to explore the influence of the hormones commonly associated to gynaecomastia.

2.4.7.3. Serious adverse event/deaths/other significant events

Deaths

In the COPD safety pool, a total of 84 deaths were reported in the roflumilast 500 µg group, 7 in the 250 µg group, and 86 in the placebo group. Most of the AEs leading to death were related to respiratory, thoracic and mediastinal disorders, followed by cardiac disorders. COPD exacerbation was the most frequently documented AE leading to death in both treatment arms, balanced in both groups. No death was considered treatment-related by either the investigator or the sponsor.

Risk of suicidality

Despite the absence of presence of concomitant causes, a causal relationship between roflumilast and triggering suicide is biologically plausible from a pharmacodynamic point of view and was considered as a "potential risk" in the safety specification. Five cases of suicide (3 completed and 2 attempted) were reported in the treatment group compared to none under placebo group. Hence, a relationship between risk of triggering suicide and roflumilast cannot be excluded. Therefore, roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behavior.

Tumors

Roflumilast does not seem to have carcinogenic potential. However, as this population has been excluded from the clinical plan, roflumilast is not recommended in patients with cancer.

2.4.7.4. Laboratory findings

No evidence of medically relevant pathological laboratory findings associated with roflumilast treatment was shown, except from the slight decrease in haemoglobin. No effects on renal function were detected in the studies with roflumilast. The data does not imply an increased risk of liver toxicity.

2.4.7.5. Safety in special populations

The AE pattern in all subgroups analyzed was generally similar to that seen in the overall study population. Also, there were no noteworthy differences amongst the subgroups in the occurrence of

individual AEs with roflumilast treatment as compared to placebo. Weight decreased, diarrhoea, and nausea were generally the most frequent AEs associated with roflumilast in all subgroups. Differences observed between subgroups were small and of no clinical relevance.

2.4.7.6. Safety related to drug-drug interactions and other interactions

During the clinical program, particularly in the pivotal studies, no safety issues have been registered with the COPD co-mediations used in the clinical study program.

2.4.7.7. Discontinuation due to adverse events

Across all treatment groups, between 8.9% and 14.3% of the patients experienced AEs leading to withdrawal. The overall frequencies were slightly higher in the roflumilast 500 µg QD group compared to the placebo group. In both, roflumilast and placebo groups, COPD exacerbation was the most frequent AE leading to withdrawal. In the placebo group, pneumonia and dyspnea were other frequent AEs leading to withdrawal. Exacerbations leading to withdrawal were considered likely to be based on the underlying disease.

2.4.7.8. Post marketing experience

Roflumilast has not been approved for use in any country; therefore, there are no postmarketing reports.

2.5. Discussion on clinical safety

In both the pivotal COPD studies pool and the COPD safety pool, the overall incidence of adverse events (AEs) was higher in the roflumilast 500 µg QD groups than in the placebo groups. Adverse events judged to be causally related by the investigator, and AEs leading to study discontinuation were more frequent under roflumilast 500 µg QD than under placebo. Weight loss is of particular concern as this adverse event is associated to a worse prognosis in COPD. Deaths were infrequent with little difference observed between treatment arms, and no death was considered treatment-related by either the investigator or the sponsor. The incidence of serious adverse events (SAEs) was also low and similar for the roflumilast 500 µg QD and placebo groups. A comparable distribution of SAE incidences under roflumilast 500 µg QD and placebo was generally observed in the COPD, 1-year, 6-month, and 3-month study duration pools, with the exception of the COPD 3-month, studies pool, where the incidence of SAEs was low overall, but somewhat higher under roflumilast 500 µg QD than under placebo. A relationship between risk of triggering suicide and roflumilast cannot be excluded. In order to better address the safety profile of roflumilast, the Applicant commits to explore the feasibility of developing alternative doses.

The proposed SPC reflects information obtained from the clinical COPD pool. The same source has been considered for the description of intensity and duration of AEs. The risks identified with roflumilast are addressed in the risk management plan and the Applicant proposed educational material for Healthcare Professionals.

2.6. Pharmacovigilance

2.6.1. Detailed description of the pharmacovigilance system

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

2.6.2. Risk management plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety issue / concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk		
Weight decrease	Routine PV Close follow-up of reported cases and special section in PSUR. Long-term comparative observational post-marketing study	Section 4.4 of the SmPC: *In 1-year studies (M2-124, M2-125), a decrease of body weight occurred more frequently in patients treated with Daxas compared to placebo-treated patients. After discontinuation of Daxas, the majority of patients had regained body weight after 3 months. Body weight of underweight patients should be checked at each visit. Patients should be advised to check their body weight on a regular basis. In the event of an unexplained and clinically concerning weight decrease, the intake of Daxas should be stopped and body weight should be further followed-up.* SmPC Section 4.8: Weight decreased is included as common adverse reaction. Educational material for prescribers and patients will be distributed.
Psychiatric disorders (insomnia, anxiety, nervousness, depression)	Routine PV	Section 4.4 of the SmPC states that Daxas treatment is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression and that the risks and benefits of starting or continuing treatment with Daxas should be carefully assessed if patients reported previous or existing psychiatric symptoms or if concomitant treatment with other medications likely to cause psychiatric events is intended. In section 4.8 of the SmPC insomnia is considered as common adverse reaction of roflumilast treatment. Anxiety is labelled as uncommon adverse reaction and nervousness and depression as rare adverse reactions. Educational material for prescribers and patients will be distributed.
Important potential risk		
Malignant tumours	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas should not be initiated and existing treatment with Daxas should be stopped in patients with cancers (except basal cell carcinoma). Educational material for prescribers and patients will be distributed.

Infections	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas should not be initiated and existing treatment with Daxas should be stopped in patients with severe acute infectious diseases. Experience in patients with latent infections such as tuberculosis, viral hepatits, herpes viral infection or herpes zoster is limited. Educational material for prescribers and patients will be distributed.
Mesenteric vasculitis / ischemic colitis	Routine PV	As no specific risk for mesenteric vasculitis / ischemic colitis has been detected, no risk minimisation activities are deemed necessary.
Cardiac safety	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended. Educational material for prescribers will be distributed.
Risk of triggering suicide	Routine PV Long-term comparative observational post-marketing study Close follow-up of reported cases and special section in PSUR	In section 4.4 of the SmPC a warning is included concerning rare instances of suicidal ideation and behaviour, including completed suicide observed in clinical trials. The risks and benefits of starting or continuing treatment with Daxas should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with medicinal products likely to cause psychiatric events is intended. Patients should be instructed to notify their prescriber of any changes in behaviour or mood and of any suicidal ideation. Moreover, Daxas is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. In section 4.8 of the SmPC a statement is included to point out that in clinical studies, rare instances of suicidal thinking and behaviour (including completed suicide) were reported. Patients should be instructed to notify their prescriber of any suicidal ideation. Educational material for prescribers and patients will be distributed.
Serious diarrhoea	Routine PV Long-term comparative observational post-marketing study	Diarrhoea is considered a common adverse reaction of roflumilast treatment (section 4.8 of the SmPC). No reference to serious diarrhoea in the SmPC is deemed necessary. However, as information on serious diarrhoea is limited, further monitoring of events is considered appropriate.
Gynaecomastia	Routine PV	Gynaecomastia is considered a rare adverse reaction of roflumilast treatment (section 4.8 of the SmPC). No further risk minimisation activities are considered necessary.

Persistent intolerability in high-exposure populations	Routine PV	Use of Daxas in populations such as black, non-smoking females, might lead to an increase of exposure and persistent intolerability. In this case, Daxas treatment should be reassessed (see section 4.4 of the SmPC). Educational material for prescribers will be distributed.
Off-label use: • Asthma adult • Asthma paediatric • COPD other than indicated • Alpha 1 anti-trypsin deficiency	Routine PV	The proposed indication is defined in section 4.1 of the SmPC as: *Daxas is indicated for maintenance treatment of severe COPD (FEV_1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.* Section 4.2 of the SmPC: *There is no relevant use of Daxas in the paediatric population (under 18 years).* Educational material for prescribers will be distributed.
Important missing/limited information		
Use during pregnancy and lactation	Routine PV Close follow-up of reported cases and special section in PSUR.	Section 4.6 of the SmPC: *There are limited amount of data from the use of roflumilast in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Daxas is not recommended during pregnancy and in women of childbearing potential not using contraception.* *Roflumilast has been demonstrated to cross the placenta in pregnant rats.* *Breastfeeding* *Available pharmacokinetic data in animals have shown excretion of roflumilast or its metabolites in milk. A risk to the suckling child cannot be excluded. Daxas should not be used during breast-feeding.* Pregnancies will be closely monitored according to established company procedures. Considering the very low likelihood of a pregnancy in the indicated patients, no further risk minimisation activities were considered necessary.

Important missing/limited information (continued)		
HIV infection or active hepatitis	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas should not be initiated and existing treatment with Daxas should be stopped in patients with severe acute infectious diseases or severe immunological diseases (e.g. HIV infection). Experience in patients with latent infections such as viral hepatitis is limited. Educational material for prescribers and patients will be distributed.
Intake of immunosuppressive medication (excl. short-term systemic corticosteroids)	Routine PV	SmPC section 4.4: Due to lack of relevant experience, treatment with Daxas should not be initiated and existing treatment with Daxas should be stopped in patients being treated with immunosuppressive medicinal products (except short-term systemic corticosteroids). Educational material for prescribers and patients will be distributed.
Severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy)	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas should not be initiated and existing treatment with Daxas should be stopped in patients with severe immunological diseases. Educational material for prescribers and patients will be distributed.
Mild, moderate or severe hepatic impairment classified as Child Pugh A, B or C	Routine PV	Sections 4.2, 4.3 of the SmPC state that patients with moderate or severe hepatic impairment classified as Child Pugh B or C, respectively should not take Daxas, i.e. that these patients are contraindicated. Section 4.2 of the SmPC mentions that clinical data are considered insufficient to recommend a dose adjustment for mild hepatic impairment (Child-Pugh A). Caution is thus considered necessary in these patients. Educational material for prescribers will be distributed.
History of malignant tumours	Routine PV	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas should not be initiated and existing treatment with Daxas should be stopped in patients with cancers (except basal cell carcinoma). Educational material for prescribers and patients will be distributed.
Severe heart failure (NYHA grades 3 and 4)	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended. Educational material for prescribers will be distributed.

Severe acute infections or acute relevant lung diseases and lower respiratory tract infections (esp. tuberculosis)	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas should not be initiated and existing treatment with Daxas should be stopped in patients with severe acute infectious diseases. Educational material for prescribers and patients will be distributed.
Combination of roflumilast with theophylline for maintenance therapy	Routine PV	Section 4.4 of the SmPC: *There are no clinical data to support the concomitant treatment with theophylline for maintenance therapy. Therefore, the concomitant treatment with theophylline is not recommended.* Educational material for prescribers and patients will be distributed.
Long-term treatment	Routine PV Long-term comparative observational post-marketing study	Section 4.2 of the SmPC: *Daxas has been studied in clinical trials for up to one year*. No further risk minimisation activities are considered necessary.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to prescribe Daxas are provided with an Educational pack.

The educational pack should contain the following:

• Summary of Product Characteristics and Patient Information Leaflet for Daxas

• Educational material for the physician.

• Copies of the patient card to be given to patients before they receive Daxas

The educational material for the prescriber should include information on the following key elements:

- The specific indication approved. The fact that Daxas is not indicated for the treatment of COPD patients other than those covered by the approved indication, nor for use in patients with asthma or alpha 1 anti trypsine deficiency.
- The need to inform patients about the risks of Daxas and the precautions for safe use
- The risk of weight decrease in underweight patients and the need to monitor the body weight at each visit and to stop the treatment in the event of an unexplained and clinically concerning weight decrease. Patients should be advised to weigh themselves at regular intervals and record the weight in the patient card.
- The risk of psychiatric disorders such as insomnia, anxiety, depression in patients receiving Daxas and the potential risk of suicide. Hence, the need to carefully assess the benefit risk balance of this treatment in patients with existing psychiatric symptoms or with history of depression and to inform patients to report any changes in behaviour, mood and any suicidal ideation. Daxas is not recommended in patients with a history of depression associated with suicidal ideation or behaviour.

- The potential risk of malignant tumours and the lack of experience in patients with past history of cancer. Daxas should not be initiated or should be stopped in patients with cancers (except basal cell carcinoma).

- That increased exposure might occur in certain populations and increase the risk of persistent intolerability:
    - Special populations who have increased PDE4 inhibition such as black non smoking females
    - Patients concomitantly treated with CYP1A2 inhibitors (such as fluvoxamine) or dual CYP3A4/1A2 inhibitors (such as enoxacin and cimetidine)

- The potential risk of infections: Daxas should not be initiated, or treatment should be stopped, in patients with severe acute infectious diseases. The limited experience in patients with latent infections such as tuberculosis, viral hepatitis or herpes infections.

- The lack of experience in patients with HIV infection or active hepatitis, with severe immunological diseases (e.g.multiple sclerosis, lupus erythematous, multifocal leukoencephalopathy) or treated with immunosuppressive therapy (other than short-term systemic corticosteroids) and that Daxas should not be initiated or should be stopped in these patients.

- The potential cardiac risk: Daxas has not been studied in patients in congestive heart failure (NYHA grade 3 and 4); hence, it is not recommended in this population.

- The limited or missing information in patients with liver impairment. Daxas is contraindicated in patients with moderate or severe liver impairment (Child Pugh B or C). Clinical data are considered insufficient to recommend dose adjustment and caution should be observed in patients with mild liver impairment (child Pugh A).

- The lack of clinical data to support the combination with theophylline and that such combination is not recommended.

Patient Card

The patient card should contain the following key elements:

That they should tell their doctor if they have a history of any of the following conditions
- cancer
- insomnia, anxiety, depression, suicidal ideation or behaviour
- multiple sclerosis or SLE
- infection with tuberculosis, herpes, hepatitis, HIV

That patients should tell their doctor if they develop symptoms indicative of:
- insomnia, anxiety, depression, suicidal ideation or behaviour
- severe infection

That patients should tell their doctor if they are taking any other medicines.

That Daxas may cause weight loss and patients should weigh themselves regularly and record their weight on the patient card.

The patient card should include an area where patients can record their weight and the date they weighed themselves and they should be asked to bring the patient card with them at each visit.

2.6.3. Benefit-risk balance

Quality

The quality of Daxas is adequately established. Satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

The quality of this medicinal product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. At the time of the CHMP opinion there are no unresolved quality issues which have a negative impact on the benefit/risk balance of the product.

Non-clinical pharmacology and toxicology

Toxicity studies were conducted in mice, rats, hamsters, dogs and monkeys. Single dose toxicity studies showed that doses of 10000 times the human oral dose were required for mortality, causes of which were not established.

Subchronic and chronic repeat dose studies showed compound related histologic changes in the olfactory mucosa of rodents, in the male reproductive organs of rats, in the heart of dogs and in the gastro-intestinal tract of rats and monkeys. Nasal toxicity was dose-limiting in the rats and resulted in the mouse and hamster being selected for carcinogenicity studies.

- Olfactory toxicity was shown by mechanistic studies to be rodent specific. The dog and monkey did not demonstrate this effect. These data support the lack of risk of this effect in humans.
- Cardiac lesions were found in repeat dose studies in dogs. No such cardiac lesions were observed in other species. This effect is linked to phosphodiesterase inhibition, and is well known to be dog-specific.
- Gastrointestinal changes were seen in rats and monkeys at 50 to 200 fold the clinical dose. Effects in monkeys were considered transient.
- Effects on male reproductive performance were confined to the rat. Effects on female reproductive parameters were stress related and not considered roflumilast specific.

The product was not considered genotoxic nor has irritant potential if applied to the skin or eye. The product is neither phototoxic nor allergenic. Roflumilast does not exhibit carcinogenic potential in mice. Roflumilast-related tumors in olfactory mucosa were observed in the 2-year carcinogenicity studies in hamsters. It was concluded that this finding was a species-specific effect which did not raise special concern regarding the use of roflumilast in humans.

No embryofoetal effects were noted in the rabbit. Roflumilast is not considered teratogenic. Tocolytic effects and decreased postnatal survival were noted in mice at similar exposures to those in humans. The relevance of this finding in humans is unknown.

The impurity profile for the roflumilast product is considered qualified. No risk to the environment is considered through normal clinical use of the compound.

Efficacy

The efficacy demonstration in the two pivotal trials was based on changes to FEV1 and exacerbation rate, respectively.

Despite reaching statistical significance, the effect of roflumilast on the FEV1 parameter is modest and below the range of the changes recognised as clinically relevant. Likewise, the overall effect size on the reduction of moderate and severe exacerbations is lower than the relative change considered as minimal important differences in the literature. However, the effect of roflumilast on the lung function parameter is difficult to interpret because of the concomitant use of bronchodilators agents during the trial and the claimed anti-inflammatory properties of the compound.

Roflumilast did not show an effect in the reduction of exacerbations in patients with moderate severity of COPD disease. In patients with severe to very severe COPD, type chronic bronchitis, and history of frequent exacerbations (at least 2 exacerbations in the last year), roflumilast 500µg showed significant effect versus placebo for both endpoints. Hence, the CHMP requested that the Applicant limits the indication to the patients with severe to very severe COPD, type chronic bronchitis, and history of frequent exacerbations (at least 2 exacerbations in the last year).

Secondary outcomes were generally significant in favor of roflumilast compared with placebo. The net benefit on the reduction of moderate to severe exacerbations was generally consistent across different subgroups.

Mortality rates and time to death were similar in the roflumilast and placebo groups, with a non-significant trend in favor of placebo in the time to death. Therefore, the benefit in the reduction of exacerbations and in the improvement in FEV1 afforded by roflumilast versus placebo seems not to be translated into differences in survival.

Safety

The overall incidence of adverse events (AEs) was higher in the roflumilast 500 µg QD groups than in the placebo groups. Adverse events judged to be causally related by the investigator, and AEs leading to study discontinuation were more frequent under roflumilast 500 µg QD than under placebo. Weight loss is of particular concern as this adverse event is associated to a worse prognosis in COPD. Deaths were infrequent with little difference observed between treatment arms, and no death was considered treatment-related by either the investigator or the sponsor. The incidence of serious adverse events was also low and similar for the roflumilast 500 µg QD and placebo groups. A comparable distribution of SAE incidences under roflumilast 500 µg QD and placebo was generally observed in the COPD, 1-year, 6-month, and 3-month study duration pools, with the exception of the COPD 3-month, studies pool, where the incidence of SAEs was low overall, but somewhat higher under roflumilast 500 µg QD than under placebo. A relationship between risk of triggering suicide and roflumilast cannot be excluded.

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 performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

Benefit

Patients with severe COPD remain symptomatic and poorly controlled despite available treatment. Roflumilast has a novel mode of action working in a different way than any of the current COPD treatment. Hence, roflumilast could be a useful adjunct to currently existing COPD treatments.

Despite reaching statistical significance, the effect of roflumilast on the primary endpoint is modest. However, these effects were observed in a population with severe COPD (type chronic bronchitis) patients with very poor lung function and minimal reversibility at baseline. In addition, the effect of roflumilast on exacerbations was reached on top of bronchodilators, not in addition to placebo.

The lack of standardisation for the concomitant medications and potentially the lack of standardisation of the study population in the treatment arms were considered as a potential bias to the results. In addition, the current first line treatment (combination of LABA / ICS) was not used in the trials, neither as concomitant medication nor as a comparator. Hence, at the CHMP's request, the applicant commits to conduct a controlled study to evaluate the use of roflumilast as an add on therapy on top of LABA and ICS in the population defined in the indication of the current SPC. The design of the study should be appropriate to demonstrate a clinically relevant effect of roflumilast as add-on therapy.

An ad hoc expert group meeting was convened by the CHMP. Overall, the experts agreed that the clinical relevance of the effect of roflumilast on FEV1 was difficult to judge based on the available data since the current first line treatment was not used in the trials, neither as concomitant medication nor as a comparator. However, taking into account the severity of the disease in the patients enrolled in the trials, in which a very small variation of FEV1 is expected according to the natural history of the disease, some experts felt that the effect shown by roflumilast on this parameter might not be negligible. With regard to the effect of roflumilast on the exacerbation rate endpoint, the experts agreed that this was closer to demonstrate clinically relevance in patients with severe to very severe COPD, high exacerbation rate and chronic bronchitis.

Risk

The following adverse events were documented with higher rates in the roflumilast arm than in the placebo arm: weight decrease, diarrhoea, nausea, headache, decreased appetite, back pain, dizziness and insomnia. The intensity of these events was generally of mild to moderate intensity. Weight loss is of particular concern as this adverse event is associated to a worse prognosis in COPD. In pivotal studies, the rate of AEs leading to withdrawal was superior in the roflumilast group than in the placebo group. In addition, a relationship between risk of triggering suicide and roflumilast cannot be excluded. Hence, at the CHMP's request, the Applicant will conduct a long-term comparative observational safety study to further assess the risks associated with the use of roflumilast.

Benefit-Risk Balance

There is a medical need for new treatments for COPD. The availability of a new anti-inflammatory treatment in severe COPD may be seen as an additional chance for severe COPD patients.

Both roflumilast pivotal studies had a positive outcome on the primary endpoints. The effect of roflumilast is modest and the clinical relevance of these finding remain unclear. The limited reduction in exacerbation rate is consistent with the modest effect observed with roflumilast. The treatment benefit on the lung function parameter is below the usual limit of minimally clinically important difference. Nevertheless, this modest benefit may be of interest in a severe to very severe population and this effect was reached on top of bronchodilators. Hence, the CHMP requested to restrict the indication to the subgroup of patients with severe COPD disease, type chronic bronchitis and frequent exacerbations (at least 2 exacerbations in the last year).

The main risks associated with the use of roflumilast are diarrhea, nausea and weight loss. A relationship between risk of triggering suicide and roflumilast cannot be excluded.

Overall, the available data justify the use of roflumilast in the restricted subgroup of patients with severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations. In order to better demonstrate the clinical relevance of the effect of roflumilast as add-on therapy, the Applicant will conduct a controlled study to evaluate the use of roflumilast as an add on therapy on top of LABA and ICS in this population. In addition, the Applicant will conduct a long-term comparative observational safety study to further assess the risks associated with the use of roflumilast.

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

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see section 3.6.2.

2.6.4. Recommendation

2.6.4.1. Normal opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Daxas in the following indication:

Daxas is indicated for the maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

was favourable and therefore recommended the granting of the marketing authorisation.