22 February 2018
EMA/154975/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Daxas

International non-proprietary name: roflumilast

Procedure No. EMEA/H/C/001179/X/0035

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Daxas
MAH:	AstraZeneca AB SE-151 85 Sodertalje SWEDEN
Active substance:	ROFLUMILAST
International Non-proprietary Name/Common Name:	roflumilast
Pharmaco-therapeutic group (ATC Code):	Other systemic drugs for obstructive airway diseases (R03DX07)
Therapeutic indication(s):	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
Pharmaceutical form(s):	Tablet
Strength(s):	250 µg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PVDC/alu)
Package size(s):	28 tablets

Table of contents

List of abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ANCOVA	analysis of covariance
AUC	Area under the plasma concentration-time-curve
β_2-adrenergic agonist	beta$_2$ adrenergic receptor agonist
BMI	body mass index
BSV	Between subject variability
CAT	COPD Assessment Test
cAMP	cyclic adenosine monophosphate
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	confidence interval
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase 2
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP 3A4, CYP 1A2	cytochrome P450 3A4, 1A2
eC-SSRS	Electronic C-SSRS questionnaire
EMA	European Medicines Agency
EOD	every other day (alternate day dosing)
EU	European Union
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcome
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FDC	fixed-dose combination
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
HPLC	High performance liquid chromatography
IC_{50}	concentration at which 50% inhibition is achieved
ICS	inhaled corticosteroid
IMP	investigational medicinal product
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
KF	Karl Fischer titration
LABA	long-acting β_2-adrenergic receptor agonist
LAMA	long-acting muscarinic receptor antagonist
LOCF	last observation carried forward
LS	Least squares
mMRC	Modified British Medical Research Council
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NDA 22-522	Roflumilast original NDA approval 28 February 2011 (Reference ID 2911527)
OD	once daily
PD	pharmacodynamic
PDE (4)	phosphodiesterase (4)
PDE4I	phosphodiesterase 4 inhibitor
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PT	Preferred term
PVC	Poly vinyl chloride
PVDC	Polyvinilidene chloride

Abbreviation or special term	Explanation
SAE	serious adverse event
SAS	Safety analysis set
SE	Standard error
SmPC	Summary of Product Characteristics
sNDA	supplemental New Drug Application
SOC	System Organ Class
TEAE	treatment-emergent adverse event
tPDE4i	total PDE4 inhibitory activity
TTE	time to event
US	United States
USPI	United States Prescribing Information
UV	Ultraviolet
V	visit
VCS	valid case set
VPC	Visual predictive check
COPD	Chronic Obstructive Pulmonary Disease
CMC	Chemistry, Manufacturing, and Controls
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
QP	Qualified Person
TSE	Transmissible Spongiform Encephalopathy

1. Background information on the procedure

1.1. Submission of the dossier

The MAH AstraZeneca AB submitted on 6 March 2017 an extension of the marketing authorisation.

The MAH applied for an addition of a new strength of 250 µg in a PVC/PVDC/Alu blister of 28 tablets.

Furthermore, the PI is brought in line with the latest QRD template version 10.0. Updated RMP version 18.0 has also been submitted.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, indent 2 (c) - Extensions of marketing authorisations.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Jayne Crowe

CHMP Peer reviewer(s): N/A

- The application was received by the EMA on 6 March 2017.
- The procedure started on 23 March 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 June 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 June 2017.

- During the meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 20 July 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 10 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 15 November 2017.
- During the PRAC meeting on 31 November 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 December 2017, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 22 January 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 February 2018.
- During the meeting on 19-22 February 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Daxas on 22 February 2018.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Roflumilast, at a 500 microgram once-daily dose, is authorised in the EU since 05-Jul-2010 for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV_1 post-bronchodilator < 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

2.1.2. Epidemiology and risk factors, screening tools / prevention

COPD 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. 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.

2.1.3. Biologic features

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.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The most widely accepted classification of the severity of COPD is according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD; Available from: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/). It includes a spirometric and symptoms classification.

The GOLD classification of airflow limitation severity (spirometric classification) recognizes four grades (1: mild; 2: moderate; 3: severe; 4: very severe), being categories 3-4 those corresponding to severe (FEV1 ≤ 50% predicted) and very severe (FEV1 ≤ 30% predicted) airflow limitation, respectively.

It should be noted that there is only a weak correlation between FEV1, symptoms and impairment of a patient's health status. For this reason, formal symptomatic assessment is also required.

Current GOLD guidelines recommend the symptomatic classification of COPD patients regarding symptoms and risk of exacerbations using the "ABCD" assessment tool. Group D are patients with more symptoms at high risk of exacerbations.

The prognosis of COPD is poorer in patients with severe/very severe airflow limitation and it is correlated with the degree of dyspnoea (GOLD 2017).

2.1.5. Management

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.

Current GOLD guidelines recommend adding roflumilast to treatment regimens for patients in Group D who have chronic bronchitis and forced expiratory volume in 1 second (FEV_1) <50% of predicted whose exacerbations are not adequately controlled on a triple combination of a long-acting β_2-adrenergic agonist (LABA), a long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS). The indication for roflumilast in clinical practice is therefore for patients with GOLD spirometric grade 3-4 and group D.

2.2. About the product

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.

2.3. The development programme/compliance with CHMP guidance/scientific advice

No formal CHMP scientific advice was given. However, there were several interactions between the Rapporteur and the MAH with respect to defining the design of the OPTIMIZE pivotal study for this line extension.

With the proposed OPTIMIZE study (RO-2455-302-RD), the marketing authorization holder (MAH) intended to address and fulfill follow-up measure 004 "*The applicant commits to present a program exploring the feasibility of developing alternative doses to minimize the risk of drug interactions, poor*

tolerability and the influence of factors such as gender, age, smoking status on bioavailability of the product".

During the assessment of FUM004, the design of the OPTIMIZE study was discussed. The primary endpoint of "Percentage of subjects prematurely discontinuing study treatment due to any reason (during main period i.e., Visit V1 to Vend)" was considered adequate to investigate if patients could benefit from an up-titration regimen. Initially proposed key secondary endpoints of the study were
"Percentage of subjects with adverse events of interest to evaluate tolerability - diarrhea, nausea, headache, decreased appetite, insomnia and abdominal pain (main period, V1 to Vend)" and
"Percentage of subjects prematurely discontinuing study treatment due to any reason (during down-titration period, V0DT to VendDT)".

In addition, change in forced vital capacity (FVC) and pre-bronchodilator FEV1 and change in subject-assessed treatment satisfaction scores were proposed as secondary efficacy endpoints during the up- and down-titration period.
Furthermore, also population PK and PK/PD analysis were proposed to be performed during the whole study (up- and down-titration period) to better understand the relationship between PK and relevant safety (adverse events i.e., diarrhea, nausea, headache, decreased appetite, insomnia and abdominal pain) and efficacy (FEV1) parameters.

While accepting that the primary objective of the OPTIMIZE study is to demonstrate improved tolerability of 250mcg QD roflumilast compared with 500mcg QD roflumilast, it was also considered important that the study was also designed to demonstrate that efficacy is maintained at the lower dose. Therefore, FEV1 during the down titration was proposed by the rapporteur as key secondary endpoint.
In this regard, the use of the hierarchical testing procedure was accepted. However, if statistical significance was not achieved at a given stage, no inferential conclusions could be drawn from any of the subsequent analyses at the lower stages of the hierarchy even if they were carried out for exploratory purposes.

A mixed model repeated measures (MMRM) analysis was initially proposed by the MAH for the primary analysis of the primary efficacy endpoint, change from baseline FEV1. The Rapporteur did not endorse the proposal, as this method tends to overestimate treatment effects when a considerable amount of data is missing caused by premature discontinuation.
Therefore, analysis of covariance (ANCOVA) was proposed with an appropriate model including the baseline value as a covariate. This method had to be carried out on the ITT population where missing data had to be imputed using a suitable and justified method. Further sensitivity analyses had to be conducted to demonstrate the robustness of the findings.

As requested by the CHMP, the following changes were implemented in the protocol of the OPTIMIZE study :
- Inclusion of FEV1 as key secondary endpoint during down-titration period.
- Change from mixed model repeated measures (MMRM) analysis to analysis of covariance (ANCOVA) for the primary analysis of the primary efficacy endpoint, change from baseline FEV1.

It was planned to extend the existing PK/PD models in a two-step approach by using the data obtained from the REACT study (RO-2455-404-RD) which was performed to address follow-up measures 001 and 003, and the data obtained from the OPTIMIZE study.

Depending on the OPTIMIZE study outcome, the MAH planned to seek for changes of the posology section of the SmPC to provide recommendation for up- and/or down-titration regimens with roflumilast.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

The authorization of manufacturing for finished product manufacturer, Takeda GmbH dated 15th February 2017, has been submitted, as well as the certificate of GMP compliance of the manufacturer, dated 14th February 2017, following an inspection carried out on 22nd June 2016.

A valid QP Declaration has been submitted, updated with more recent audit dates for Siegfried Evionnaz SA and Jetpharma SA, dated 6th September 2017.

GCP

Directive 2001/83/EC (amended) Article 8.3 (ib) requires a statement to the effect that clinical trials carried out outside the European Union (EU) meet the ethical requirements of Directive 2001/20/EC. In the pivotal study supporting this line extension application (RO-2455-302-RD OPTIMIZE study), subjects were randomized at a total of 161 sites in 15 countries: Bulgaria (11 sites), Germany (9), Greece (5), Hungary (21), Republic of Korea (9), Philippines (4), Poland (15), Romania (19), Russia (17), Slovakia (12), South Africa (14), Spain (2), Thailand (3), Ukraine (14), and United Kingdom (6).

Takeda (sponsor of the clinical trial) and its representative, Quintiles, performed study RO-2455-302-RD OPTIMIZE to the same ethical standard in all countries, both within and outside the EU. This ethical standard is consistent with the ethical requirements of Directive 2001/20/EC. In the protocol, investigators were instructed to conduct the study in accordance with the current version of the Declaration of Helsinki, and the International Conference on Harmonization (ICH), harmonized tripartite guideline ICH E6 (R1): Good Clinical Practice, and any applicable local regulations.

Takeda procedures, internal quality control measures, and audit programs provide reassurance that the clinical study program was carried out in accordance with Good Clinical Practice (GCP), as documented by the International Conference on Harmonization (ICH). AstraZeneca acquired the rights to the OPTIMIZE Study from Takeda following completion of the study.

During the OPTIMIZE study, internal audits found non-compliance potentially affecting patient safety and study data integrity at a single site (site 6002), resulting in inspection by the South African Medicines Control Council in July 2015. A site inspection was also conducted by Authority for Health and Consumer Protection, Free and Hanseatic City of Hamburg, Germany in October 2015, with no significant finding of non-compliance. In addition, data from OPTIMIZE were included in a Medicines and Healthcare Products Regulatory Agency inspection of records for several studies in August 2015. Taking the above into account, the CHMP did not find sufficient reasons to trigger an inspection for this study.

2.5. Type of application and other comments on the submitted dossier

- **Legal basis**

This application is to extend the marketing authorization for roflumilast (Daxas/Daliresp/Libertek) 500 microgram tablet by adding the new strength of 250 microgram roflumilast tablets.

The application is submitted in accordance with article 8(3) in directive 2001/83/EC (i.e.: dossier with administrative, quality, pre-clinical and clinical data).

The clinical part of this submission is based on clinical data from a single study (Study RO 2455 302-RD [OPTIMIZE]) together with updated pop PK analyses based on data from OPTIMIZE and REACT (Study RO-2455-404-RD) to fulfill a Committee for Medicinal Products for Human Use (CHMP) post-authorization measure (FUM004).

The proposed indication is for the 250 micrograms tablet to be taken once daily for 28 days as a starting dose intended to reduce patient discontinuation when initiating therapy. The recommended maintenance dose is one tablet of 500 micrograms roflumilast to be taken once daily.

This line-extension including the 250 micrograms roflumilast tablet translates into the following changes in the SmPC pertaining to sections 4.2 and 5.1 (track changes).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Daxas is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (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.

4.2 Posology and method of administration

Posology

Starting dose
The recommended starting dose is one tablet of 250 micrograms roflumilast to be taken once daily, for 28 days.

This starting dose of 250 micrograms roflumilast is intended to reduce patient discontinuation when initiating therapy, but 250 micrograms per day is not the therapeutic dose.

Maintenance dose
The recommended dose is one tablet of 500 micrograms roflumilast to be taken once daily.
~~The recommended dose is 500 micrograms (one tablet) roflumilast once daily.~~

Daxas may need to be taken for several weeks to achieve its effect (see section 5.1). Daxas has been studied in clinical trials for up to one year.

Section 5.1: Addition of the description of the OPTIMIZE study:

Starting dose titration trial

The tolerability of roflumilast was evaluated in a 12-week randomised, double-blind, parallel group trial (RO-2455-302-RD) in patients with severe COPD associated with chronic bronchitis. At screening, patients were required to have had at least one exacerbation in the previous year. A total of 1323 patients were randomised to receive roflumilast 500 micrograms once a day for 12 weeks (n=443), roflumilast 500 micrograms every other day for 4 weeks followed by roflumilast 500 micrograms once a day for 8 weeks (n=439), or roflumilast 250 micrograms once a day for 4 weeks followed by roflumilast 500 micrograms once a day for 8 weeks (n=441).

Over the entire study period of 12 weeks, the percentage of patients discontinuing treatment due to any reason was statistically significantly lower in patients initially receiving roflumilast 250 micrograms once a day for 4 weeks followed by roflumilast 500 micrograms once a day for 8 weeks (18.4%) compared to those receiving roflumilast 500 micrograms once a day for 12 weeks (24.6%; Odds Ratio 0.66, 95% CI [0.47, 0.93], p=0.017). The discontinuation rate for those receiving 500 micrograms every other day for 4 weeks followed by 500 micrograms once a day for 8 weeks was not statistically significantly different to those receiving 500 micrograms once a day for 12 weeks.

Decreasing the dose in those patients who did not tolerate the 500 micrograms once a day dose to 250 micrograms reduced PDE4 inhibitor exposure to below the levels observed in patients receiving and able to tolerate the 500 micrograms once a day dose. Long term administration at the 250 micrograms dose level may not induce sufficient PDE4 inhibition to exert clinical efficacy.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with roflumilast in all subsets of the paediatric population in chronic obstructive pulmonary disease (see section 4.2 for information on paediatric use).

2.6. Quality aspects

2.6.1. Introduction

The finished product is presented as tablets containing 250 µg of roflumilast as active substance.

Other ingredients are: lactose monohydrate, maize starch, povidone, and magnesium stearate.

The product is available in PVC/PVDC aluminium blisters as described in section 6.5 of the SmPC

2.6.2. Active Substance

The active substance used to manufacture the new strength: 250 µg film tablets is the same as that used in the manufacture of the currently authorised 500 µg film coated tablets

2.6.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Daxas 250 µg tablets are uncoated tablets (immediate release). They are described as white to off-white, round tablets embossed with “D” on one side and “250” on the other. The tablet’s diameter is 5 mm.

The finished product is currently available as film-coated 500 µg tablets. The applicant is applying for uncoated 250 µg tablets which will have a different composition to the 500 µg film coated tablets. The objective of the pharmaceutical development was to develop an immediate-release, white 250 µg tablet by employing standard manufacturing technologies, to enable a recommended starting roflumilast dosage.

Roflumilast is a white to off-white, crystalline powder; it is a very stable chemical substance. The active substance is poorly soluble in aqueous solutions between pH 1 to 7. Dissolution of the active substance from the dosage form depends mainly on its solubility as well as its rate of dissolution. Therefore, the particle size of the active substance might affect rate and extent of dissolution. The use of micronized active substance was needed to provide an immediate release dissolution profile.

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 are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Tablet formulations were varied in weight and size during drug development by varying the amount of excipients. Several clinical studies and bioequivalence studies were performed during development. Finally, a small uncoated, white tablet was chosen for marketing authorisation.

Since the absorption of the drug depends mainly on its release from the tablet and on dissolution under physiological conditions, in-vitro dissolution may be relevant to the prediction of in-vivo performance. In order to establish a suitable dissolution method, different factors have to be taken into account. These include the physicochemical characteristics of the drug as well as different testing

conditions. Importantly, the dissolution method was able to discriminate between different, bio-inequivalent formulations, are consistent with the corresponding pharmacokinetic characteristics.

In order to link the formulation of the finished product used in pivotal clinical trials to the original formulation intended for commercialisation, a bioequivalence study was performed showing bioequivalence. There was also no difference in the in-vitro dissolution profiles of the tablets used in pivotal clinical trials and Formula E film-coated tablets.

Due to the low active substance content of the tablets, special focus was taken on blend and content uniformity during manufacturing development, scale-up and validation, and the homogeneous distribution of the active substance and homogeneity of the granules was determined during release testing by content uniformity. Therefore, the manufacturing process for the granules was adapted during scale-up to the commercial batch scale.

The primary packaging is PVC/PVDC aluminum blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 4 main steps: production of the granulation solution, production of the granulate, production of the tableting mixture, tableting and packaging. The process is considered to be a non-standard manufacturing process.

As a unit-dose form contains less than 2% active substance by weight the manufacturing process is considered non-standard. As such, normally, the granulation should be considered as a critical step however the applicant has provided process validation data showing that all batches comply with specifications and no deviations were detected. The validation data provided supports the robustness of the manufacturing process and in process controls with regard to blend uniformity and assay of the tablet. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), dimension (measuring device), water content (KF), identity (HPLC, UV), purity (HPLC), microbiological purity (Ph. Eur.), assay (HPLC or UV), content uniformity (Ph. Eur.), dissolution (Ph. Eur.) .

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 4 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Additionally, they were tested at 30 ºC / 75% RH for 48 months. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same specification as release. The analytical procedures used are stability indicating. No obvious trends were detectable and the results were well within the proposed specification under long term and accelerated conditions.

In addition, one batch (stored without primary packaging material) was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed. Data confirmed that no additional storage recommendations regarding light protection were necessary.

Based on available stability data, the proposed shelf-life of 48 months without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.6.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out 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 clinical use.

2.6.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.6.6. Recommendations for future quality development

No applicable

2.7. Non-clinical aspects

2.7.1. Introduction

The Applicant has submitted no additional nonclinical data supporting a lower starting dose. No modification of the benefit risk profile of Roflumilast is expected.

With regards to the Environmental Risk Assessment, no additional studies were submitted. The Applicant estimates that no increase in the environmental exposure is anticipated, given that the proposed starting dose is lower than the previously approved.

2.7.2. Pharmacology

N/A

2.7.3. Pharmacokinetics

N/A

2.7.4. Toxicology

N/A

2.7.5. Ecotoxicity / environmental risk assessment

N/A

2.7.6. Discussion and conclusion on non-clinical aspects

The only modification presented in this line extension is the substitution of the starting dose of 500mcg of Roflumilast for a lower one, i.e. 250 mcg. Given the positive risk benefit profile obtained in the initial assessment of the substance, no additional concerns are expected from a nonclinical point of view.

The documentation and rationale for not conducting additional ERA studies is considerable acceptable.

2.8. Clinical aspects

2.8.1. Introduction

This line extension application is based on the study RO-2455-302-RD (OPTIMIZE). This multicentre, randomized, double blind, Phase III study comprised an initial 4 week period in which patients received roflumilast 250 µg once daily (OD), 500 µg every other day (EOD), or the currently approved dosage of 500 µg OD; followed by 8 weeks of dosing at 500 µg OD for all subjects. For patients unable to tolerate the approved maintenance dose of roflumilast 500 µg OD during the Main Period, the lower dosage of 250 µg OD was to be administered in a Down-titration Period.

Pharmacokinetic (PK) and pharmacodynamic (PD) data were collected in both Main and Down-titration Periods to update the developed population PK (pop-PK) and PK–PD models, and specifically to evaluate exposures in patients unable to tolerate roflumilast 500 µg OD both before and after transitioning to a 250 µg OD relative to exposures in patients tolerating the approved dosage. OPTIMIZE was performed using the US formulation of roflumilast 500 µg and 250 µg tablets. Evaluations included treatment discontinuations for any reason as a primary variable; other safety evaluations included AEs of interest (preferred terms associated with Diarrhoea, Nausea, Headache, Decreased appetite, Insomnia, Abdominal pain, Vomiting, Angioedoema, Anxiety, Depression, and Weight loss), GI tolerability, and patient-assessed outcomes. Other assessments included effects on lung function, PK, and PK-PD relationships with AEs and lung function.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH 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.

Table 1. Tabular overview of clinical studies

Type of study	Study code; location of study report	Objectives of the study	Study design	Test product; dosage regimen	Number of subjects randomised /treated	Population	Duration of treatment	Study status type of report
Safety, efficacy, PK, and PK/PD	RO-2455-302-RD (OPTIMIZE); Module 5.3.5.1	Evaluate efficacy, safety, tolerability and PK of: roflumilast 500 µg OD in COPD patients using up-titration regimen and roflumilast 250 µg OD using down-titration regimen in subjects not tolerating 500 µg OD	Randomised, double-blind, active-controlled, parallel-group study with an open-label down- titration period	**Main period**: roflumilast 250 µg tablet OD PO/500 µg tablet OD PO	Total: 1323/ 1321 N=441/441	Patients with severe COPD (postbronchodilator FEV_1 ≤50% predicted) associated with chronic productive cough. Patients were former or current smokers; all received standard of care COPD maintenance treatment.	**Total:** maximum of 20 weeks **Main period:** 12 weeks **Down-titration period:** 8 weeks	Complete, Full
				roflumilast 500 µg tablet EOD PO/500 µg tablet OD PO	N=439/437			
				roflumilast 500 µg tablet OD PO	N=443/443			
				Down-titration period: roflumilast 250 µg tablet OD PO	N=104 treated			

COPD chronic obstructive pulmonary disease; EOD every other day; FEV_1 forced expiratory volume in 1 second; OD once daily; PD pharmacodynamics; PK pharmacokinetics; PO orally.

2.8.2. Pharmacokinetics

In the original submission, the PK profile of roflumilast and its metabolite were assessed using PK samples taken across 21 Phase I studies, 1 Phase II study and 1 Phase III study.

In humans, roflumilast is rapidly metabolised to its N-oxide metabolite. The latter exerts PDE4 inhibitory activity (approximately 3-fold lower potency compared with the parent compound) with 10-fold higher area under the plasma concentration-time curve (AUC), and a 3-fold higher free fraction in plasma. The N-oxide metabolite contributes about 90% of the overall PDE4 inhibitory activity and is assumed to contribute largely to the pharmacodynamics (PD) activity of roflumilast. Thus, during development, pharmacokinetic (PK) data were evaluated for both the parent compound and its N-oxide metabolite.

Roflumilast is converted to roflumilast N-oxide by cytochrome P450 (CYP) 3A4 and 1A2 isoenzymes (von Richter et al 2007, Lahu et al 2008). CYP3A4 is primarily responsible for clearance of roflumilast N-oxide, with some contribution from CYP2C19 and extrahepatic CYP1A1. The activity of CYP3A4 and CYP1A2 can be affected by covariates such as age and sex (Bebia et al 2004, Mangoni and Jackson 2004, Cotreau et al 2005) and smoking (Funck-Brentano et al 2006), and these covariate effects have been demonstrated on the PK profile 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 additionally used to characterise the PK of roflumilast (Hermann et al 2007, Lahu and Facius 2013). The tPDE4i accounts for differences in intrinsic PDE4 inhibitory activity, free concentration in plasma, and in vivo systemic exposures (AUC) of roflumilast and roflumilast N-oxide.

More recently, the population PK model was updated with data obtained in the Phase IIIb/IV REACT study which tested the utility of adding roflumilast 500 µg once daily to a fixed dose combination (FDC) of long-acting β2-agonist (LABA)/inhaled corticosteroid (ICS). Now, the population PK model has been updated with data from OPTIMIZE.

Total PDE4i was calculated according to the following equation:

$$tPDE4i = \frac{f_{u,p}\,dose}{CL^{k}{}_{p}\,IC_{50,p}\,\tau} + \frac{f_{u,m}\,dose}{CL^{k}{}_{m}\,IC_{50,m}\,\tau}$$

where fu,p/fu,m is the in vitro fraction unbound for parent/metabolite (fu,p=0.011, fu,m=0.034), IC50,p/IC50,m is the in vitro 50% inhibitory concentration for parent/metabolite (IC50,p=0.3 µg/L; IC50,m=0.8 µg/L), $CL^{k}{}_{p}/CL^{k}{}_{m}$ is the individual apparent clearance for parent/metabolite (estimated by the population PK model), dose is the daily oral dose, and τ is the dosing interval (24 hours).

The population PK analyses from the original submission described the PK of roflumilast parent and metabolite in 2 independent models. In the population PK covariate analyses, race had the greatest impact on tPDE4i, and females were estimated to have higher tPDE4i than males. Smokers were shown to have a lower tPDE4i than non-smokers/former smokers. In addition, an exposure-response relationship was identified for FEV1 from exposure-response analyses using data from 4 Phase II/III studies. A significant exposure-response relationship was identified for the adverse events (AEs) of diarrhoea, nausea and headache.

The new information is generated from the OPTIMIZE study. OPTIMIZE had the following PK-related objectives:

- To characterize the PK of roflumilast and roflumilast N-oxide with an up-titration regimen
- To characterize the PK of roflumilast and roflumilast N-oxide with roflumilast 250 µg once daily in patients not tolerating the 500 µg once daily dose
- To characterize the PK/PD relation with respect to relevant safety and efficacy parameters

In OPTIMIZE, the PK of both roflumilast and roflumilast N-oxide were measured. Bioanalytics of roflumilast and roflumilast N-oxide were performed using a validated high performance liquid

chromatography tandem mass spectrometer method. The lower limit of quantitation in plasma is 0.100 microg/L using a sample volume of 0.2 mL.

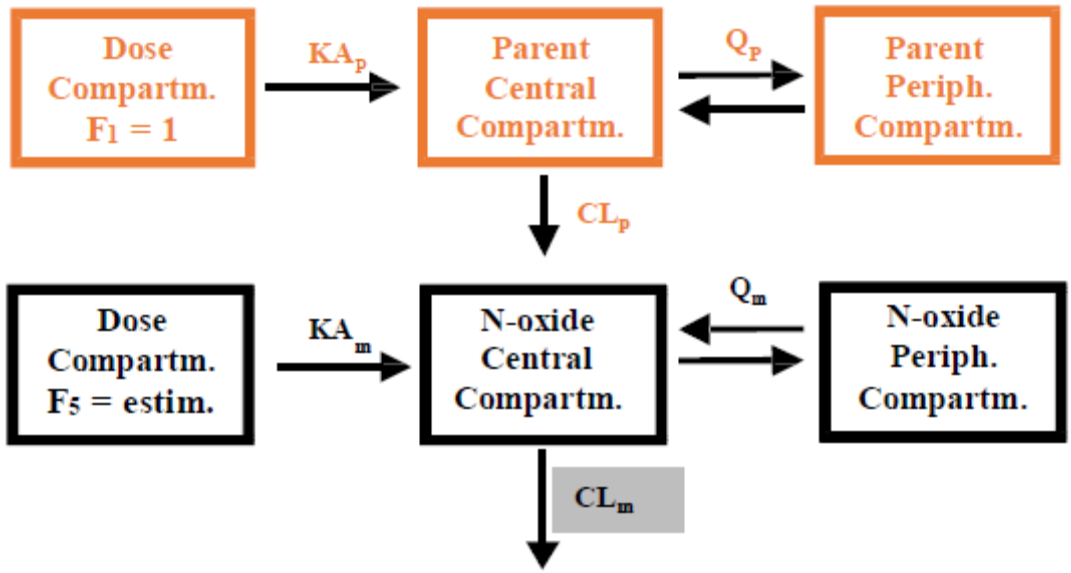
The OPTIMIZE population PK model

The resulting integrated PK model is shown schematically in Figure 1. The base REACT model consisted of two distribution compartments with first-order absorption and elimination for the parent and two additional distribution compartments with first order elimination for the metabolite. The absorption of the parent was described by a first-order process and a lag-time.

In the absence of IV data for both roflumilast and the N-oxide, absolute bioavailability cannot be estimated and therefore only apparent clearances and volumes can be used. This is the reason why in the model roflumilast is transformed completely into the N-oxide metabolite, although other metabolic routes are known to exist. In addition to systemic formation of roflumilast N-oxide, pre-systemic formation was also identified, which is described by first order absorption from an additional dose compartment, with a separate fraction (F5). The bioavailability of the additional dose compartment for the N-oxide metabolite was estimated.

This parameter describes the contribution of pre-systemic formation relative to systemic formation of roflumilast N-oxide. The bioavailability of roflumilast was fixed to 1 (F1).

Figure 1. Integrated population PK model for roflumilast (parent) and roflumilast n-oxide (metabolite)



CLm clearance of metabolite; CLp clearance of parent; compartm. compartment; F1 the relative bioavailability of roflumilast, fixed to 1; F5 presystemic formation of metabolite; KAm absorption rate of metabolite; KAp absorption rate of parent; Qm intercompartmental clearance of metabolite; Qp intercompartmental clearance of parent.

The base REACT model was applied on the OPTIMIZE data and the effect of patients versus healthy volunteers were fixed to the values estimated for the REACT study. The base REACT population PK model without covariates described individual plasma concentration data in OPTIMIZE well. Therefore, the model developed on combined REACT and OPTIMIZE data used the same structure while covariates were investigated anew.

Systemic exposure to parent and metabolite were integrated in the tPDE4i, because this parameter is directly derived from model parameters.

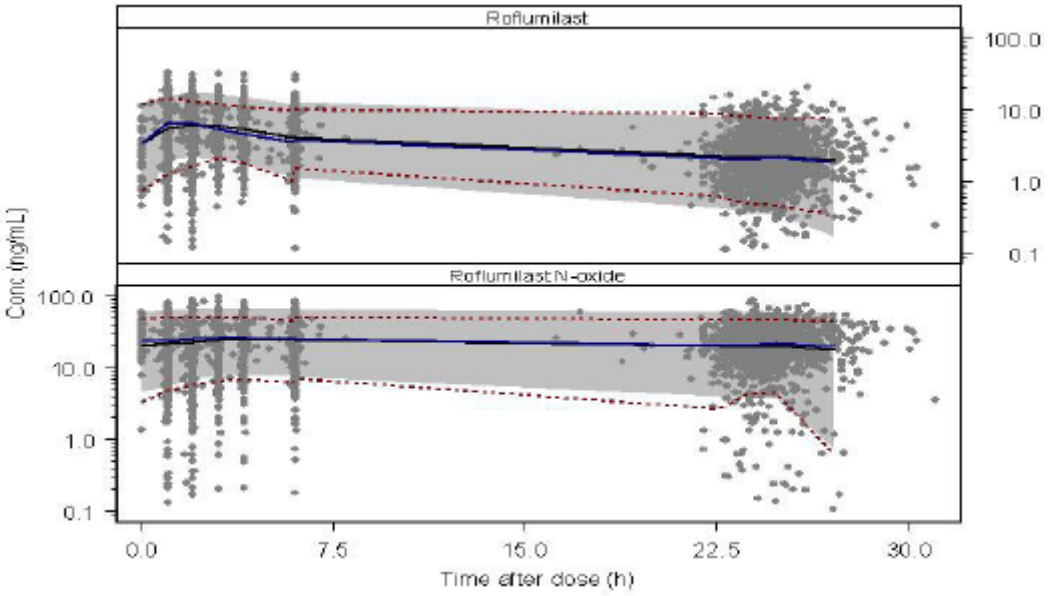
Both roflumilast parent and metabolite total plasma concentrations were described by the integrated population PK model with adequate precision. As compared to the final REACT model results obtained on the REACT data only, similar parameter estimates were obtained for the combined dataset, the percent change of parameters being overall below 21%. A larger difference (61%) was found between

the estimates of the Phase II/III effects on the volume of the central compartment for the N-oxide obtained on the REACT data only and on the combined dataset.

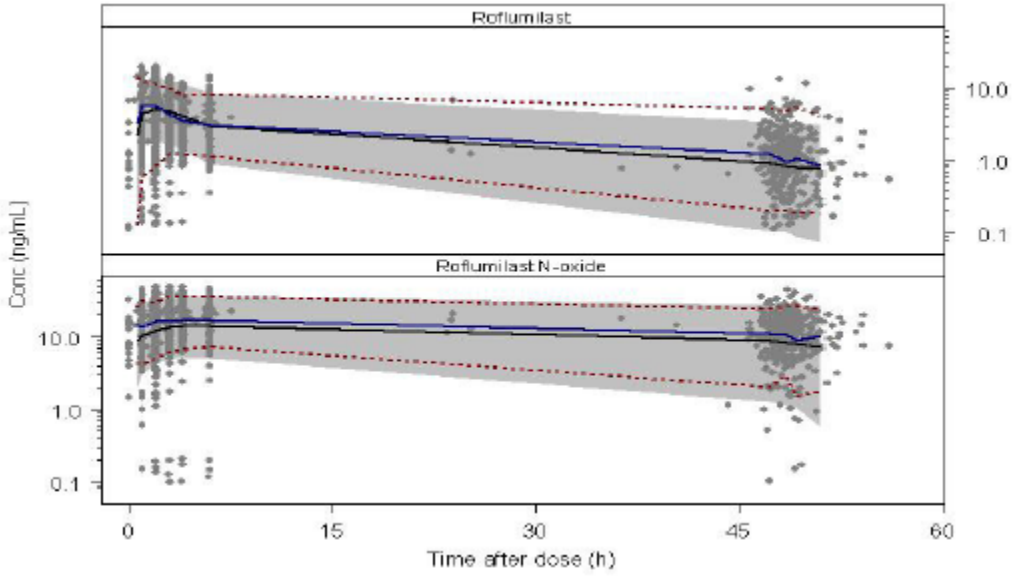
The OPTIMIZE model was able to describe the between-subject variability (BSV) across treatment phases (up-titration, maintenance, and down-titration) and dose regimens (OD or EOD), as shown in the Visual Predictive Checks (VPCs) (Figure 2 and Figure 3). Time axes for the VPC plots were restricted to the period of time where the majority of observations was available (first 30 or 60 hours after dose, depending on the treatment arm).

Figure 2. Visual Predictive Checks for roflumilast (top panel) and roflumilast N-oxide (bottom panel) for patients receiving roflumilast 500 µg OD from all treatment arms in OPTIMIZE

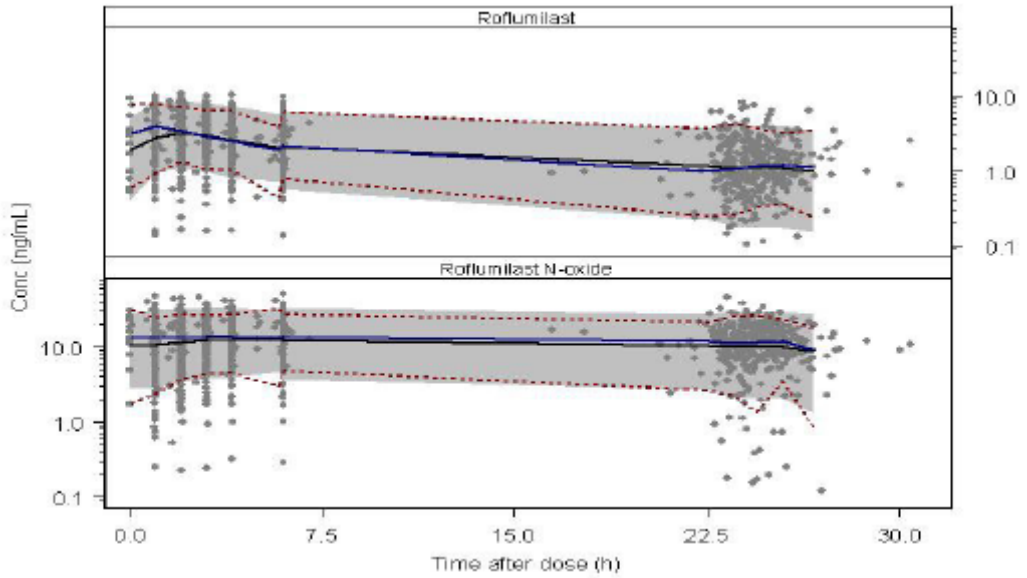
(a) Roflumilast 500 µg OD from all treatment arms



(b) Roflumilast 500 µg EOD (up-titration phase [Main Period] of treatment arm 2)

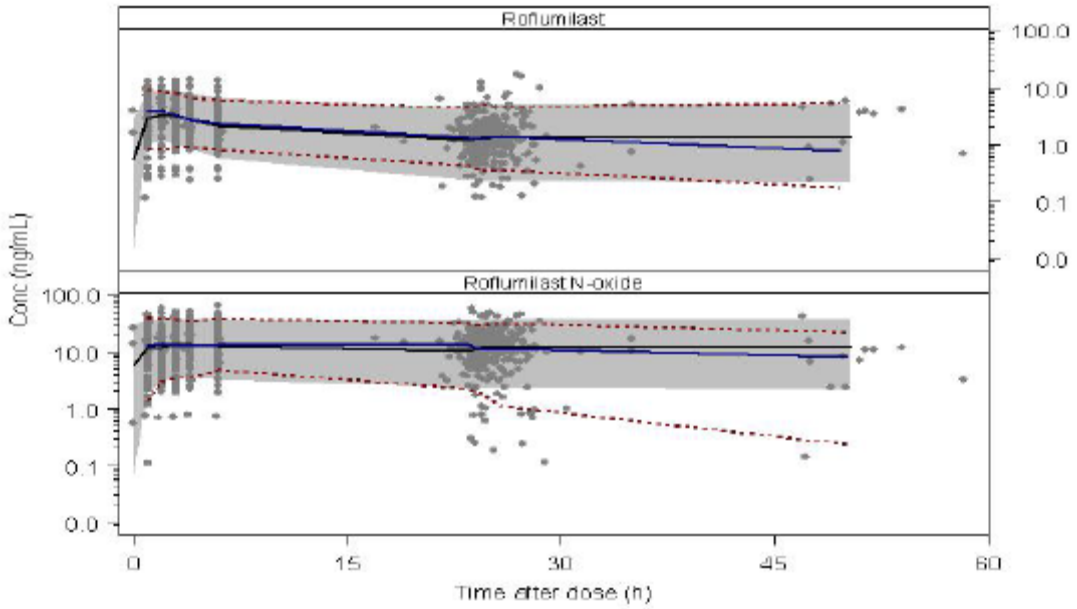


(c) Roflumilast 250 µg OD (up-titration phase [Main Period] of treatment arm 3)



EOD every other day; OD once daily.
The model is able to describe between-subject variability across dose regimens. Black line and grey area: median prediction and 90% prediction interval, respectively; blue and red dotted lines: median observation and 5th and 95th percentiles of observations, respectively; grey dots: observations of OPTIMIZE Source: see Module 5.3.4.2, PK and PK/PD analysis of exposure and efficacy report (OPTIMIZE).

Figure 3. Visual Predictive Checks for roflumilast (top panel) and roflumilast Noxide (bottom panel) for patients who started the Down-Titration Period (roflumilast 250 µg OD) in OPTIMIZE



EOD every other day; OD once daily.
The model is able to describe between-subject variability in the Down-Titration Period for both parent and metabolite. Black line and grey area: median prediction and 90% prediction interval, respectively; blue and red dotted lines: median observation and 5th and 95th percentiles of observations, respectively; grey dots: observations of OPTIMIZE.

Covariate Effects

A covariate analysis was performed on the combined REACT and OPTIMIZE dataset, and new covariates of age and sex were added as compared to the final REACT model. Table 4 shows patient counts and characteristics for the combined dataset, as well as for OPTIMIZE and REACT separately.

Table 2. Demographic and baseline characteristics for OPTIMIZE and REACT.

		OPTIMIZE	REACT	Total
Patients, n (%[a])		1238 (72.9%)	461 (27.1%)	1699 (100.0%)
Samples, n (%[a])	Roflumilast	9416 (85.6%)	1589 (14.4%)	11005 (100.0%)
	Roflumilast N-oxide	9553 (85.8%)	1587 (14.2%)	11140 (100.0%)
Age (years)	Mean (SD)	64.5 (8.10)	64.2 (8.38)	64.4 (8.18)
	Median (Min, Max)	64.0 (40,90)	64.0 (41,92)	64.0 (40,92)
Sex, n (%[b])	Male	921 (74.4%)	354 (76.8%)	1275 (75.0%)
	Female	317 (25.6%)	107 (23.2%)	424 (25.0%)
Smoking, n (%[b])	Current	577 (46.6%)	220 (47.7%)	797 (46.9%)
	Former	661 (53.4%)	241 (52.3%)	902 (53.1%)
Race, n (%[b])	Asian	82 (6.6%)	8 (1.7%)	90 (5.3%)
	Black or African American	9 (0.7%)	4 (0.9%)	13 (0.8%)
	White	1132 (91.4%)	447 (97.0%)	1579 (92.9%)
	Other	9 (0.7%)	2 (0.4%)	11 (0.6%)
	Hispanic	6 (0.5%)	0 (0.0%)	6 (0.4%)
Weight (kg)	Mean (SD)	75.4 (17.80)	75.0 (17.60)	75.3 (17.74)
	Median (Min, Max)	74.0 (33.5,160)	73.0 (39,155)	74.0 (33.5,160)

percentages relative to total number in combined dataset
percentages relative to total number in study
Max maximum; Min minimum; SD standard deviation.
Source: see Module 5.3.4.2, PK and PK/PD analysis of exposure and efficacy report (OPTIMIZE), Table 5, for original table, from which this table has been produced.

The covariate 'race' was tested according to the covariate analysis, and each race category was included in the model as a binary relationship. However, in the single covariate addition procedure, race did not show a statistically significant result.

The covariates included in the model according to the combined dataset showed that:

- The clearance of the N-oxide is 11.2% lower for females
- The clearance of roflumilast and its metabolite are lower for patients older than 60 years old. For example, a 70-year-old patient is characterized by 9% and 8% lower clearance of parent and metabolite, respectively. However, 10% higher clearances were estimated for a 50-year-old patient with respect to the estimate obtained for the 60-year-old patient.
- Concerning the covariates already included in the final REACT model and re-estimated on the combined dataset, the results showed that clearance of parent and metabolite were 15.1% higher for current smokers as compared to former smokers.
- Based on a reference value of weight of 70 kg, a patient weighing 80 kg is characterized by a 3.7% and 18% higher clearance of the metabolite and all volume terms, respectively. Lower clearance of N-oxide (-4%) and volume (-17%) were found for a patient weighing 60 kg.

These differences were not considered to be clinically relevant, and no changes to the current approved maintenance dose of roflumilast are warranted.

For each covariate included in the final model for the combined dataset, the single covariate effect on the tPDE4i was assessed, assuming a 500 µg once daily treatment.

This analysis showed that tPDE4i values decreased for increasing weight, ranging from 1.012 to 0.681 corresponding to the minimum (i.e., 33.5 kg) and maximum (i.e., 160 kg) body weight, respectively.

The single effect of age on clearance of parent and metabolite provided tPDE4i values between 0.675 and 1.055 corresponding to the minimum (40 years) and the maximum (92 years) values of the covariate AGE.
The smoking status affected both clearances and determined a lower tPDE4i value for current smoker (ie, 0.729) as compared to former/never smoker (ie, 0.839). Females were characterized by higher tPDE4i values (ie, 0.937) as compared to males (ie, 0.839).

Systemic exposure
The tPDE4i was calculated for 1238 patients with quantifiable PK samples in the OPTIMIZE trial. The individual tPDE4i was estimated for each treatment phase and dose regimen administered to the patients. In the roflumilast 250 µg OD up-titration phase of the Main Period (treatment arm 3), tPDE4i values were found to be approximately half of the values estimated for patients who underwent the 500 µg continuous treatment (treatment arm 1).
Similar but slightly higher tPDE4i values were obtained in the roflumilast 500 µg EOD up-titration phase of the Main Period (treatment arm 2) as compared to the roflumilast 250 µg OD up-titration phase (treatment arm 3). Although similar tPDE4i values were estimated in the up-titration phase of the roflumilast 500 µg EOD and roflumilast 250 µg OD treatment arms, higher maximum and lower minimum concentrations are expected due to the dose regimen.
Furthermore, estimated tPDE4i values were comparable for roflumilast 500 µg OD in the maintenance phase across all treatment arms. As compared to the Down-Titration Period, similar tPDE4i values were estimated in the roflumilast 500 µg EOD and roflumilast 250 µg OD up-titration treatment arms in the Main Period.

Systemic exposure – Down-Titration
For patients who did not tolerate roflumilast 500 µg OD and enrolled in the Down-Titration Period, the analysis showed that, when receiving 250 µg OD, patients have a tPDE4i exposure approximately half that observed in patients treated with 500 µg OD (ie, patients who tolerated 500 µg OD and did not down-titrate).

However, for all subgroup pairs with sufficient number of patients, the average tPDE4i in 'non-tolerators' is slightly higher when compared with 'tolerators' at the same dose. For example, when considering the subgroup of patients who dropped out due to any reason, the median tPDE4i after 500 µg OD is 1.16 and 1.23 (+6%) in 'tolerators' and 'non-tolerators', respectively.
Nevertheless, comparing 'tolerators' of roflumilast 500 µg OD (median tPDE4i of 1.16 at 500 µg OD) with 'non-tolerators' of roflumilast 500 µg OD (median tPDE4i of 0.60 at 250 µg OD, ie, during the Down-Titration Period), the latter have still a markedly lower tPDE4i systemic exposure (-48.3%).

Table 5 shows summary statistics of observed individual tPDE4i activity after roflumilast 250 µg OD or 500 µg OD.

Table 3. Summary statistics of observed tPDE4i after roflumilast 250 µg OD or 500 µg OD

Subgroup definition		tPDE4i					
		500 µg OD			250 µg OD		
		N	Med	(5%, 95%)	N	Med	(5%, 95%)
All patients		1114	1.17	(0.352, 2.03)	76	0.611	(0.197, 1.243)
DO due to AE of interest	Yes	67	1.28	(0.427, 2.22)	62	0.647	(0.201, 1.239)
	No	1047	1.16	(0.339, 2.02)	14	0.436	(0.212, 1.069)
DO due to any AE	Yes	77	1.29	(0.464, 2.10)	64	0.647	(0.204, 1.237)
	No	1037	1.16	(0.337, 2.02)	12	0.408	(0.209, 1.006)
DO due to any reason	Yes	106	1.23	(0.416, 2.06)	75	0.600	(0.197, 1.243)
	No	1008	1.16	(0.332, 2.02)	1	0.626	(0.626, 0.626)
At least 1 AE of interest	Yes	536	1.23	(0.453, 2.09)	75	0.600	(0.197, 1.243)
	No	578	1.12	(0.297, 1.98)	1	0.929	(0.929, 0.929)
At least 1 AE of any PT	Yes	693	1.22	(0.416, 2.07)	76	0.611	(0.197, 1.243)
	No	421	1.08	(0.294, 1.97)	0	-	(-, -)

AE adverse event; DO dropout; OD once daily; PT preferred term; tPDE4i: total phosphodiesterase 4 inhibition.

Only patients who received the roflumilast 500 µg OD treatment are used. These patients were split into 'tolerators' or 'non-tolerators' based on 5 different definitions (see OPTIMIZE CSR, Section 9.7.1.7.1). Summary statistics (median and 5th to 95th percentiles) were derived for each of the 5 × 2 subgroups and tPDE4i. The same statistics are shown for all patients as a reference.

Subgroup: overall population treated with roflumilast 500 µg OD and roflumilast 250 µg OD and subpopulations defined according to dropout and AE: discontinuation due to AE of interest; discontinuation due to AE of any PT; discontinuation due to any reason; at least one AE of interest; at least one AE of any PT

DO: dropout (discontinuation from the Main Period irrespective of starting the Down-Titration Period)

Comparison of population PK results

The population PK analyses from the original submission described the PK of roflumilast parent and metabolite in 2 independent models.

The current OPTIMIZE model simultaneously describes parent and metabolite. Benefits of this approach are that correlations, e.g., between the clearance of parent and metabolite are captured by the model, which should result in more reliable tPDE4i simulations. Also sparse data can be described with more certainty, because parent and metabolite data simultaneously inform all individual PK parameters.

The covariate analysis in the original models was built on PK data collected in healthy volunteers, whereas the covariate analysis of the current OPTIMIZE population PK model is based on patient data only.

Comparison of covariate findings between the original and the OPTIMIZE population PK model: A high level overview of the original covariate findings is described here. In the original submission, the impact of individual covariates was determined as relative change in tPDE4i values from a reference subject, which was defined as male, non-smoking, non-black/non-Hispanic, healthy, aged 40-years old. In OPTIMIZE, the reference patient was a male, 60-year old, former smoker, baseline body weight of 70 kg.

In the original analysis, of the single covariates, black (race) had the greatest impact on tPDE4i, with a 42% higher mean tPDE4i than non-black/non-Hispanic patients. Similarly, but to a lesser extent, Hispanic patients were estimated to have a 28% higher mean tPDE4i than non-black/non-Hispanic patients. Female patients were estimated to have a 19% higher mean tPDE4i than male patients. To the contrary, smokers were estimated to have a 19% lower mean tPDE4i than non-smokers/former smokers.

Using the population PK model with REACT and OPTIMIZE combined data, the assessment of the single covariate effect, assuming the 500 µg OD treatment, showed that tPDE4i ranges between 1.012 and 0.681 according to range of body weight observed in the studied population (ie, 33.5 to 160 kg) (no

effect of weight was seen in the original analysis). Race was not identified as a covariate (due to the low numbers of black patients). As in the original analysis, higher tPDE4i values were estimated for females (+12% as compared to males) and lower tPDE4i values were obtained for current smokers (-13% as compared to former/never smokers). For the age range between 40 and 92 years, tPDE4i ranged between 0.675 and 1.055.

2.8.3. Pharmacodynamics

Roflumilast is a PDE4 inhibitor, a non-steroid, anti-inflammatory active substance designed to target both the systemic and pulmonary inflammation associated with COPD. The mechanism of action is the inhibition of PDE4, a major cyclic adenosine monophosphate (cAMP)-metabolizing enzyme found in structural and inflammatory cells important to the pathogenesis of COPD (Daxas SmPC).

Roflumilast targets the PDE4A, 4B and 4D splicing variants with similar potency in the nanomolar range. The affinity to the PDE4C splicing variants is 5 to 10-fold lower. This mechanism of action and the selectivity also apply to roflumilast N-oxide, which is the major active metabolite of roflumilast (Daxas SmPC).

PK-PD relationship

Three types of analyses were performed to characterize the relationship of systemic exposure with
a) post-BD FEV1 observations (PK/FEV1 models),
b) the percentage of patients with at least one AE (PK/AE models), and
c) the time to treatment discontinuation due to AEs (PK/TTE models).

Methods

a) PK/FEV1 dataset
In the OPTIMIZE study, out of 1238 patients with valid PK samples, all had FEV1 measurements. Therefore, all 1238 patients were also included in the PK/FEV1 analysis. In total, the OPTIMIZE PK/FEV1 dataset consists of 6093 FEV1 observations: 1991 observations from the 500 µg OD subset, 2053 observations from the 500 µg EOB subset, and 2049 observations from the 250 µg OD subset.

The PK/FEV1 dataset was created from the OPTIMIZE data with minor modifications; post-bronchodilator observations and FEV1 observations at screening were removed.

Treatment phases and Visit numbers were assigned to allow differentiation between treatment phases (up-titration, maintenance, and down-titration), for graphical evaluation and modelling purposes. Empirical Bayesian Estimates of PK parameters for individual patients using the final PK model were used to compute tPDE4i values for each of the treatment phases. These were added to the PK/FEV1 dataset to be used as PK input.

Additional columns were added to identify patients in potential special interest categories, such as COPD severity, body weight, and age. In addition, new columns were created for the percentage of the study period during which there was concomitant LABA/ICS use and a flag to indicate concomitant LABA/ICS use at each observation.

The PK/FEV1 model was developed using the following stepwise approach:
1. First, the previously developed base and final REACT models were applied to the OPTIMIZE data according to a Bayesian Feedback procedure (i.e. MAXEVAL = 0 in the NONMEM code, meaning that estimation is not performed but parameters already available are used to provide predictions for the new OPTIMIZE dataset);

2. Description of FEV1 was then optimized on the OPTIMIZE dataset using the REACT covariate model as a starting point.

Due to the absence of placebo group data in the OPTIMIZE data, all disease progression and placebo-related fixed-effect parameters were fixed at REACT values. Covariate effect parameters on BSL and SLP4 were re-estimated, but not those on E0, because of the shorter time period over which FEV1

observations were available. This is due to the different duration of the OPTIMIZE study as compared to the REACT one, being 12 weeks (plus 8 weeks if the patients started the down-titration period) and 52 weeks, respectively.

All random effect parameters (BSV on BSL and E0, and WSV) were re-estimated. Differences in PK between up-titration dose regimens were evaluated by estimating separate treatment parameters (SLP4 and ThalfP4) for 500 µg EOD and 250 µg OD versus 500 µg OD dose regimens; 3. A formal covariate analysis was performed on BSL (the only parameter for which a BSV was estimated on OPTIMIZE data). A forward inclusion/backward elimination procedure was followed. Forward inclusion was done on top of the covariates already present in the REACT model. During backward elimination, all covariates were removed one-by-one (including those already present in the REACT model).

b) PK/AE dataset

There were 1238 patients in the PK/AE dataset. The binary response variable AE was set to 'yes' for patients with at least 1 AE with Medical Dictionary for Regulatory Activities preferred term (PT) in 'Any AE (all PTs)' during the Main Period of the study. Systemic exposure in the model was defined as the predicted tPDE4i with the 500 µg OD treatment. In total, 797 (64.4%) of patients reported at least 1 AE. Patient counts (and percent) for each arm of the study were: 257 (62.1%) in the 250 µg OD treatment arm, 269 (65.0%) in the 500 µg EOD treatment arm, 271 (66.1%) in the 500 µg OD treatment arm.

To assess the incidence and timing of AEs of interest, a list of 'AEs of interest' was compiled consisting of 6 groups of related PTs: headache, diarrhoea, nausea, decreased appetite, insomnia, and abdominal pain. For the analysis that explored the relationship between PK and AEs of interest, an additional 5 groups of related PTs were included in a list referred to as 'AEs of interest' (extended list) to ensure consistency with previous PK/AE analyses, consisting of 11 groups of related PTs: headache, diarrhoea, nausea, abdominal pain, appetite disorders, sleep disorders, vomiting, angioedema, anxiety, depression, weight loss. In total, 633 (51.1%) patients reported at least 1 of these AEs. The 'AEs of interest' category was used in the safety statistics analysis of OPTIMIZE and the 'Any AE' category was used for sensitivity analyses.

c) PK/TTE dataset

There were 1238 patients in the PK/TTE dataset. The PK/TTE analysis was based on all discontinuation events due to 'AEs of Interest (extended list)' during the Main Period from all patients. Any AE that led to discontinuation from the Main Period was recorded with event time defined as days after treatment start until last Main Period study medication intake (days on MP), excluding potential later study medication intakes during the Down-Titration Period. For each patient *i* and every AE group *X*, the time to discontinuation *TTE_Xi* was defined as "censored" if no AE in group *X* lead to treatment discontinuation of patient *i* from the Main Period. In case patient *i* had an AE in group *X* which lead to discontinuation from the Main Period, *TTE_Xi* was set to the number of days that the patient was treated during the Main Period.

For each subject, the tPDE4i predicted for the treatment phase at which this patient discontinued was chosen as systemic exposure variable. If discontinuation happened during up-titration phase of the Main Period, tPDE4i predicted for the respective up-titration treatment was used (tPDE4i_250OD, tPDE4i_500EOD, or tPDE4i_500OD), if discontinuation happened during the maintenance phase of the Main Period, tPDE4i_500OD was used. In case a patient either completed the Main Period or discontinued due to another reason, the respective tPDE4i predicted for the last day of the patient's Main Period was used.

Results

a) Exposure-response model for FEV1

The previous exposure-response model for FEV1 was developed based on data from the REACT study, and described the relative change from baseline in FEV1, as a function of roflumilast systemic exposure expressed as tPDE4i. The REACT model has now been applied to PK and FEV1 data from the OPTIMIZE study to further characterize the exposure FEV1 response of roflumilast and roflumilast N-oxide.

The final OPTIMIZE model

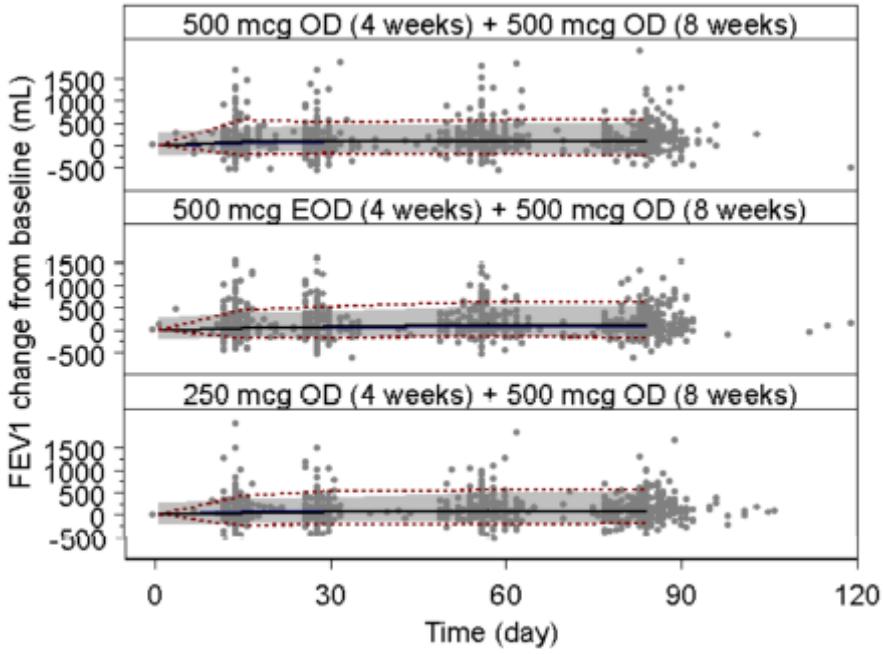
The final OPTIMIZE FEV1 model contains the following covariate effects:

- COPD status, concomitant long acting muscarinic antagonist (LAMA) use, percent reversibility (for short-acting bronchodilators), age, weight, sex and race on baseline FEV1
- Weight on placebo effect
- Smoking status on treatment effect slope.

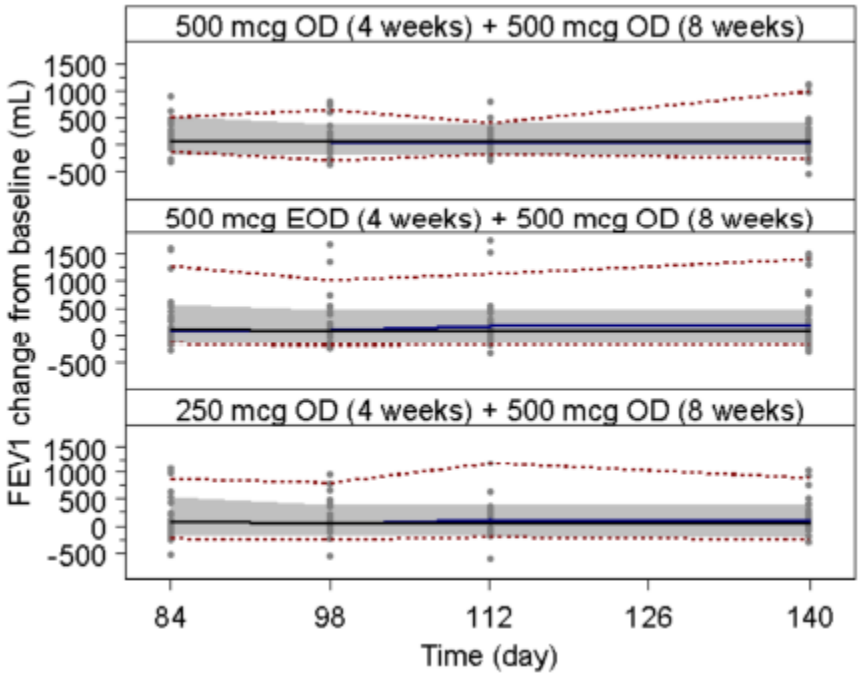
All parameters could be estimated with good precision (CV<50%). The final model described OPTIMIZE data well (Figure 4).

Figure 4. Visual Predictive Checks for FEV1 change from baseline (a and b) and mean change from baseline (c and d), during up-titration and maintenance phases of the Main Period (a and c) and the Down-Titration Period (b and d) using the current final FEV1 model

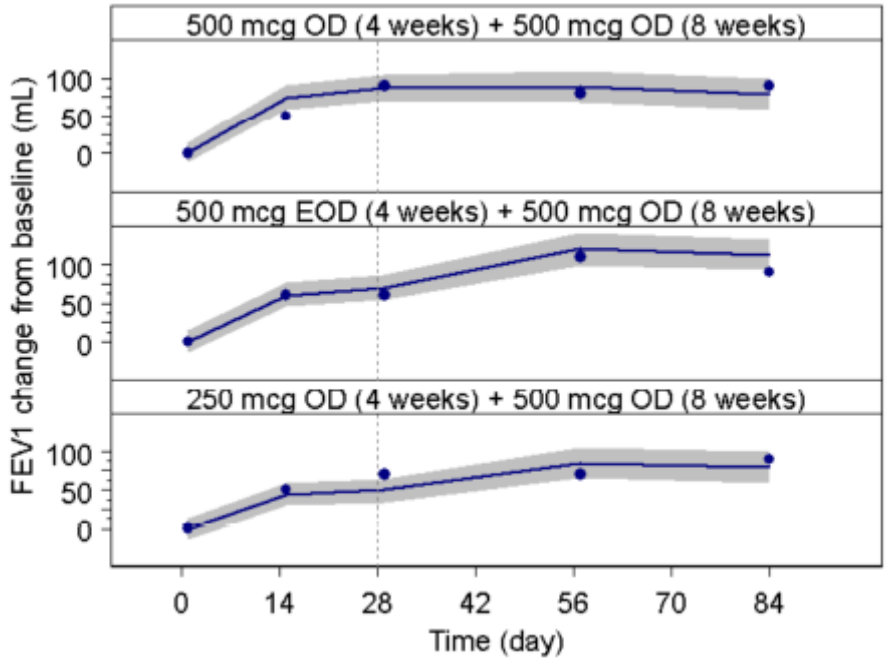
(a) All observations, Main Period



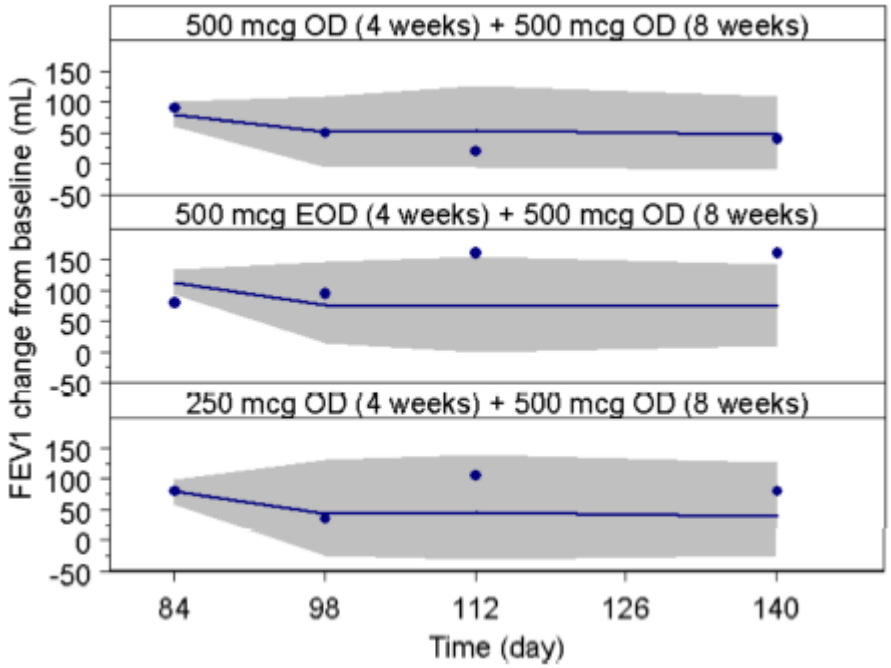
(b) All observations, Down-Titration Period



(c) Mean, Main Period



(d) Mean, Down-Titration Period



(a) and (b): Solid line and grey area: median prediction and 90% prediction interval, respectively; blue and red dotted lines: median observation and 5th and 95th percentiles of observations, respectively; grey dots: observations.
(c) and (d): Solid line and grey area: median prediction and 90% prediction interval, respectively; dots: mean FEV1 values. Vertical dashed line (c) indicates the time point between the Up-Titration phase and the Maintenance phase.
(b) and (d): For the Down-Titration Period, data were plotted at Visit Day assuming start of down-titration at Day 84.
Source: see Module 5.3.4.2, PK and PK/PD analysis of exposure and efficacy report (OPTIMIZE), Figure 8.

The observed FEV1 changes in the OPTIMIZE study are well described by the FEV1 model developed for the REACT study in the treatment phases (up-titration, maintenance, and down-titration) and across the different treatment arms. Model simulations showed that change of FEV1 from baseline is lower at the end of the 4-week up-titration treatment phase with roflumilast 250 µg OD than roflumilast 500 µg OD (Figure 4, [c]), and is predicted to decrease after down-titration from roflumilast 500 µg OD to roflumilast 250 µg OD (Figure 4, [d]).

Covariate Effects:
To evaluate the influence of covariates in the PD model, FEV1 and FEV1 change from baseline (ΔFEV1) estimates for a 500 µg OD dose regimen at steady state, after 4 weeks and after 12 weeks of treatment, were calculated assuming a typical tPDE4i value, accounting for patient covariates.

Covariates weight, COPD severity, and percent reversibility for short-acting bronchodilators resulted in the largest change in FEV1 at baseline parameter, followed by the effect of age, sex, race and the use of LAMA at baseline, while smoking affected the proportionality coefficient for roflumilast tPDE4i. The range of predicted FEV1 change from baseline at week 4 and week 12 (resulting from covariates in the PK/FEV1 model) was largest for weight and smoking.
For example, ΔFEV1 after 12 weeks ranged from 32.0 to 157 mL for a 33.5 to 160 kg weight range, and was dependent on smoking status (96.5 versus 56.0 mL for current versus former/never smokers).

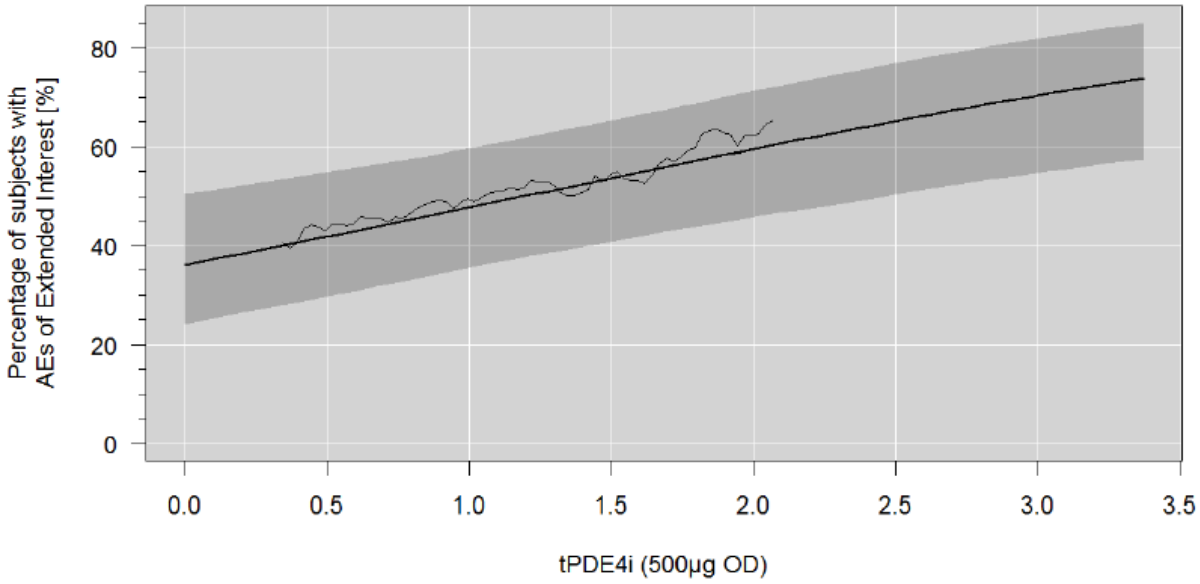
b) Results of the PK / AE analysis

b1. AEs of interest

The final model quantifies a significant increase in the percentage of subjects with AEs of Interest with increased exposure (see Figure 5). The plot show the mean model response (thick line) together with a shaded ribbon indicating the 95% confidence intervals around the mean response. The erratic thin line represents the local fit (local fit is a locally averaged percentage of subjects with adverse events and

it's variability is not directly related to the shaded 95% CIs, i.e. it is not expected to have approximately 95% of the local fits within the shaded area, as it would be with standard VPC plots).

Figure 5. Model response from the logistic regression model for the percentage of subjects with AEs of Interest (extended list) as a function of tPDE4i (500µg OD).



In addition covariates LAMAC and SMOK indicated that percentages of subjects with AEs of Interest were

- Higher in subjects concomitantly treated with LAMAs when compared with subjects not taking LAMAs.
- Higher in former smokers when compared with current smokers.

Total PDE4i was a significant predictor of the percentage of patients with AEs in 7 out of 9 tested PT groups. Logistic regression analysis indicates that the percentage of patients with AEs of interest (extended list), Any AE (all PTs), diarrhoea, appetite disorders, insomnia, nausea, and weight loss, according to the model, depends on tPDE4i. The percentage of patients with headache and abdominal pain was not found to depend on tPDE4i, according to the model. Smoking habit was a significant predictor in 5 models.

In addition, covariates Asian and concomitant use of LAMA or LABA/ICS were significant for one PT group each (RO-2455-302-RD: Expert Report to Characterize PK/AE).

Moreover, variable treatment arm (250 µg OD/500 µg EOD) was not found as a covariate in any model, ie, the percentages of patients with AEs are not affected by treatment arm but were sufficiently characterized by tPDE4i as a descriptor of systemic exposure.
Simulations of the PK/AE models were performed to assess the probability of a patient to develop AEs in dependence of their characteristics and roflumilast systemic exposure. Relative risks over placebo were derived from these simulations. Placebo effects were predicted since there was no placebo arm included in OPTIMIZE.

Among all simulated scenarios for the "AEs of interest (extended list)", the median predicted RR (to placebo) for a reference patient (male, age 64 years, former smoker, body weight 74 kg, and concomitant treatment with LAMA) when treated with 500 µg OD is1.31 with a 90% prediction interval of [0.43, 4.67].

The lowest average RR of 1.27 [0.41, 4.56] was predicted for young patients (age=51 years) and the highest average RR of 1.38 [0.38, 5.66] was predicted for patients concomitantly treated with LAMAs. Relative differences of both extremes when compared with the reference were -3% and +5% and not considered clinically relevant.

Table 4. Simulated tPDE4i, percentages of subjects with AEs of Interest (extended list), and relative risk to placebo in subgroups defined by PK and PD covariates for typical subjects.

Scenario	$tPDE4i_0$	AE_0	$tPDE4i_{250}$	AE_{250}	RR_{250}	$tPDE4i_{500}$	AE_{500}	RR_{500}
WT=48	0.00	44.5%	0.72	53.2%	1.17	1.45	61.8%	1.34
(PK-Covariate)	[0.00, 0.00]	[13.4, 80.7]	[0.69, 0.76]	[18.0, 85.5]	[0.35, 4.27]	[1.38, 1.53]	[23.8, 89.4]	[0.46, 4.76]
WT=74	0.00	44.5%	0.65	52.3%	1.16	1.30	60.1%	1.31
(PK-Covariate)	[0.00, 0.00]	[13.3, 80.7]	[0.62, 0.68]	[17.4, 85.1]	[0.34, 4.22]	[1.25, 1.36]	[22.4, 88.7]	[0.43, 4.67]
WT=105	0.00	44.5%	0.60	51.7%	1.14	1.19	58.8%	1.28
(PK-Covariate)	[0.00, 0.00]	[13.4, 80.6]	[0.57, 0.63]	[17.1, 84.8]	[0.34, 4.18]	[1.14, 1.26]	[21.6, 88.1]	[0.42, 4.58]
Former Smoker	0.00	44.5%	0.65	52.3%	1.15	1.30	60.1%	1.31
(PK&PD-Covariate)	[0.00, 0.00]	[13.4, 80.7]	[0.62, 0.68]	[17.4, 85.0]	[0.34, 4.22]	[1.25, 1.36]	[22.5, 88.7]	[0.44, 4.66]
Current Smoker	0.00	35.9%	0.56	42.5%	1.17	1.13	49.2%	1.33
(PK&PD-Covariate)	[0.00, 0.00]	[9.7, 74.5]	[0.54, 0.60]	[12.4, 79.3]	[0.29, 4.96]	[1.07, 1.20]	[15.7, 83.5]	[0.36, 5.51]
Males	0.00	44.5%	0.65	52.3%	1.15	1.30	60.1%	1.31
(PK-Covariate)	[0.00, 0.00]	[13.4, 80.7]	[0.62, 0.68]	[17.4, 85.0]	[0.34, 4.22]	[1.25, 1.36]	[22.5, 88.7]	[0.44, 4.66]
Females	0.00	44.5%	0.72	53.2%	1.17	1.45	61.8%	1.34
(PK-Covariate)	[0.00, 0.00]	[13.3, 80.7]	[0.69, 0.77]	[18.0, 85.5]	[0.35, 4.27]	[1.38, 1.53]	[23.7, 89.4]	[0.46, 4.76]
AGE=51	0.00	44.5%	0.58	51.4%	1.14	1.15	58.4%	1.27
(PK-Covariate)	[0.00, 0.00]	[13.4, 80.7]	[0.55, 0.60]	[16.9, 84.6]	[0.33, 4.17]	[1.10, 1.21]	[21.3, 87.9]	[0.41, 4.56]
AGE=64	0.00	44.5%	0.65	52.3%	1.16	1.30	60.1%	1.31
(PK-Covariate)	[0.00, 0.00]	[13.3, 80.7]	[0.62, 0.68]	[17.4, 85.1]	[0.34, 4.22]	[1.25, 1.36]	[22.4, 88.7]	[0.43, 4.67]
AGE=77	0.00	44.5%	0.72	53.2%	1.17	1.44	61.7%	1.34
(PK-Covariate)	[0.00, 0.00]	[13.4, 80.6]	[0.68, 0.76]	[17.9, 85.5]	[0.35, 4.26]	[1.37, 1.52]	[23.7, 89.3]	[0.46, 4.74]
With Conc. LAMA	0.00	44.5%	0.65	52.3%	1.15	1.30	60.1%	1.31
(PD-Covariate)	[0.00, 0.00]	[13.4, 80.7]	[0.62, 0.68]	[17.4, 85.0]	[0.34, 4.22]	[1.25, 1.36]	[22.5, 88.7]	[0.44, 4.66]
W/o Conc. LAMA	0.00	36.0%	0.65	43.5%	1.19	1.30	51.4%	1.38
(PD-Covariate)	[0.00, 0.00]	[9.7, 74.5]	[0.62, 0.68]	[12.9, 80.0]	[0.30, 5.04]	[1.25, 1.36]	[16.9, 84.6]	[0.38, 5.66]

$tPDE4i_{dose}$ is the simulated total PDE4 inhibitory activity in subjects treated with *dose* (0µg,250µg,500µg) OD. AE_{dose} is the simulated percentage of subjects with AEs of Interest (extended list), treated with *dose*. RR_{dose} is the simulated risk relative to placebo of subjects with AEs of Interest (extended list), treated with *dose*. All simulation scenarios are summarized as median and 90% prediction interval (5^{th} to 95^{th} percentile of all predictions).

b.2 Any AE:

For any AE, the logit of probability depended on tPDE4i and race (Asian versus non-Asian). As with AEs of interest, LAMA use and smoking were also found to be covariates. In addition, covariates of the PK model result in different tPDE4i levels and hence translate into differences in RR when comparing simulations stratified by these variables. Nevertheless, these differences are small in all cases and do not indicate clinically relevant differences across all investigated subgroups.

For "Any AEs", the predicted RR (to placebo) for a reference patient when treated with 500 µg OD is 1.31 [0.48, 4.43]. The lowest and highest predicted RRs in all scenarios were 1.15 [0.65, 2.64] for Asian patients and 1.34 [0.51, 4.52] for patients with a body weight of 48 kg. This corresponds to a -12% and +2% difference from the reference. Numerically the same highest RRs were also predicted for females and patients aged 77 years. The high variability in AEs translated into the prediction of RRs causing largely overlapping prediction intervals in all cases that included 1 (no effect). Given this variability, RRs were very similar among all simulated scenarios.

Table 5. Simulated tPDE4i, percentages of subjects with Any AE (all PTs), and relative risk to placebo in subgroups defined by PK and PD covariates for typical subjects.

Scenario	$tPDE4i_0$	AE_0	$tPDE4i_{250}$	AE_{250}	RR_{250}	$tPDE4i_{500}$	AE_{500}	RR_{500}
WT=48	0.00	47.8%	0.72	57.5%	1.18	1.45	66.7%	1.34
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.69, 0.76]	[20.6, 87.5]	[0.38, 4.05]	[1.38, 1.53]	[27.8, 91.3]	[0.51, 4.52]
WT=74	0.00	47.8%	0.65	56.5%	1.16	1.30	64.9%	1.31
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.62, 0.68]	[20.0, 87.1]	[0.37, 4.00]	[1.25, 1.36]	[26.2, 90.6]	[0.48, 4.43]
WT=105	0.00	47.8%	0.60	55.8%	1.15	1.19	63.6%	1.29
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.57, 0.63]	[19.5, 86.8]	[0.36, 3.96]	[1.14, 1.26]	[25.1, 90.1]	[0.46, 4.35]
Former Smoker	0.00	47.8%	0.65	56.5%	1.16	1.30	64.9%	1.31
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.62, 0.68]	[20.0, 87.1]	[0.37, 4.00]	[1.25, 1.36]	[26.2, 90.6]	[0.48, 4.43]
Current Smoker	0.00	47.8%	0.56	55.4%	1.14	1.13	62.8%	1.27
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.54, 0.60]	[19.3, 86.6]	[0.36, 3.94]	[1.07, 1.20]	[24.4, 89.8]	[0.45, 4.32]
Males	0.00	47.8%	0.65	56.5%	1.16	1.30	64.9%	1.31
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.62, 0.68]	[20.0, 87.1]	[0.37, 4.00]	[1.25, 1.36]	[26.2, 90.6]	[0.48, 4.43]
Females	0.00	47.8%	0.72	57.5%	1.18	1.45	66.7%	1.34
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.69, 0.77]	[20.6, 87.6]	[0.38, 4.05]	[1.38, 1.53]	[27.7, 91.3]	[0.50, 4.52]
AGE=51	0.00	47.8%	0.58	55.5%	1.14	1.15	63.1%	1.28
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.55, 0.60]	[19.3, 86.6]	[0.36, 3.95]	[1.10, 1.21]	[24.7, 89.9]	[0.45, 4.33]
AGE=64	0.00	47.8%	0.65	56.5%	1.16	1.30	64.9%	1.31
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.62, 0.68]	[20.0, 87.1]	[0.37, 4.00]	[1.25, 1.36]	[26.2, 90.6]	[0.48, 4.43]
AGE=77	0.00	47.8%	0.72	57.4%	1.18	1.44	66.6%	1.34
(PK-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.68, 0.76]	[20.6, 87.5]	[0.38, 4.04]	[1.37, 1.52]	[27.7, 91.2]	[0.50, 4.50]
Non-Asian	0.00	47.8%	0.65	56.5%	1.16	1.30	64.9%	1.31
(PD-Covariate)	[0.00, 0.00]	[14.9, 82.7]	[0.62, 0.68]	[20.0, 87.1]	[0.37, 4.00]	[1.25, 1.36]	[26.2, 90.6]	[0.48, 4.43]
Asian	0.00	69.9%	0.65	76.7%	1.08	1.30	82.4%	1.15
(PD-Covariate)	[0.00, 0.00]	[30.7, 92.4]	[0.62, 0.68]	[38.8, 94.5]	[0.54, 2.48]	[1.25, 1.36]	[47.3, 96.1]	[0.65, 2.64]

tPDE4i_{dose} is the simulated total PDE4 inhibitory activity in subjects treated with dose (0µg,250µg,500µg) OD. AE_{dose} is the simulated percentage of subjects with Any AE (all PTs), treated with dose. RR_{dose} is the simulated risk relative to placebo of subjects with Any AE (all PTs), treated with dose.

c) Results of the PK/TTE analysis

Time-to-event models with a log-normal hazard adequately described discontinuation times from the Main Period (up-titration and maintenance phases) and from the up-titration phase of the Main Period only due to AEs of interest (extended list) and due to Any AEs.

The variable 'treatment arm 250 µg OD' was a significant covariate in all models, indicating that patients treated with roflumilast 250 µg OD for 4 weeks before increasing the dose to roflumilast 500 µg OD had significantly lower discontinuation rates due to AEs of interest (extended list) and due to Any AEs during the Main Period compared to patients in the 500 µg EOD or 500 µg OD treatment arms.

In addition, variables Asian, sex, and age were found as significant covariates when characterizing discontinuation events during the Main Period; discontinuation rates due to AEs were higher for Asians, females, and with increasing age. However, when characterizing discontinuation events during the up-titration phase of the Main Period only, only body weight was found beside 'treatment arm 250 µg OD' as a covariate; early treatment discontinuation due to AEs in OPTIMIZE (within the up-titration phase) was found to be co-dependent on other patient characteristics rather than late discontinuation events.

Despite up-titration with 250 µg OD, systemic exposure (as characterized by tPDE4i) was not found to significantly affect discontinuation rates.

Discussion about the PK-response models:

a) Comparison of findings between the original and OPTIMIZE PK/FEV1 analyses:

The originally developed exposure-response models for FEV1 were based on data from 4 Phase II/III studies testing roflumilast compared with placebo without PK sampling. These models were developed as dose/response models and then extended using simulated typical systemic exposure as a PK variable. In contrast, the OPTIMIZE PK/FEV1 analyses is an individual exposure response model describing the change in FEV1 over time as a function of tPDE4i and therefore cannot be directly compared with the original model. In addition, there were differences in treatment duration and background therapy between OPTIMIZE and the originally reported studies.

b) Comparison of findings between the original and OPTIMIZE PK/AE analyses:

In the PK/AE analyses in the original submission, a significant exposure-response relationship was identified for diarrhoea, nausea, and headache. In OPTIMIZE PK/AE analyses, systemic exposure, as measured by tPDE4i, was a significant predictor of the percentage of patients with AEs in 7 out of 9

tested PT groups; AEs of interest (extended list), Any AE (all PTs), diarrhoea, appetite disorders, insomnia, nausea, and weight loss depends on tPDE4i. The percentages of patients with headache and abdominal pain were not found to depend on tPDE4i.

However, the originally reported and OPTIMIZE PK/AE models cannot be directly compared in detail due to the difference in the dosing regimen compared to that currently approved for roflumilast.

2.8.4. Discussion on clinical pharmacology

This application is based on the study RO-2455-302-RD (OPTIMIZE), 'a multicenter, randomized, double-blind, Phase 3 study to evaluate tolerability and pharmacokinetics of 500 µg roflumilast once daily with an up-titration regimen in COPD, including an open-label Down-Titration Period evaluating tolerability and PK of 250 µg roflumilast once daily in patients not tolerating 500 µg roflumilast once-daily'.

The OPTIMIZE population pharmacokinetic (PK) analyses used OPTIMIZE data combined with PK data from the REACT study (Study RO 2455-404-RD). Parameters of the final population PK model were estimated with good precision (coefficient of variation of the estimates less than 25%) and estimates were consistent with previous findings. The model was able to adequately describe average PK concentrations as well as the BSV across all treatment phases (up-titration, maintenance, and down-titration) and dosing schemes.

Reducing the dose of roflumilast to 250 µg OD in patients who did not tolerate roflumilast 500 µg OD markedly reduced tPDE4i to below those typically observed in patients who tolerated 500 µg OD. Therefore, administration of roflumilast 250 µg OD may not induce sufficient PDE4 inhibition to exert clinical efficacy.

Although the applicant states that dose adjustment for patient covariates (such as gender, age and smoking status) is not warranted, it does not prevent from updating section 5.2 of the SmPC.
In addition, the need for dose adjustment should be further discussed for some special populations.

The Applicant has submitted the requested pre-study validation report ACTC2 including two addendum (Analyte Stability in Frozen Matrix Sodium Heparin and Stability of Standards in Solution).
In general, the pre-study or method validation of the bioanalytical method was consistent and demonstrated an adequate linearity, precision and accuracy (both intra- and inter-day) within the calibrated range, which showed also an adequate selectivity, absence of significant carry-over and matrix effect and adequate dilution linearity. In addition, the analyte long-term stability was demonstrated for 716 days at -20 ºC and -70 ºC.

New PK data generated from OPTIMIZE in almost 19.000 samples from 1238 COPD patients are robust and may be of interest for prescribers. In this respect, section 5.2 of the SmPC must be updated with respect to: a) PK data of the 250 microgram dose. It should be stated that these levels are sub-therapeutic and therefore not recommended for maintenance treatment, with cross reference to section 5.1 and 4.2;
b) The influence of intrinsic/extrinsic factors on PDE4 inhibitory activity (i.e.: age, weight, race, gender and smoking status) (subsection of special populations).
Upon request, adiscussion about potential need for dose adjustments was provided (e.g.: whether obese patients may require maintenance doses > 500 micrograms or if Asian patients and/or patients with low body weight may require maintenance doses < 500 micrograms.
The company provided a new population PK model on the combined REACT and OPTIMIZE dataset and identified no clinically relevant changes of systemic exposure levels in populations of particular interest (eg, elderly patients, female patients, or patients with high [>80 kg] or low [<60 kg] baseline body weight).

With respect to race, Asian patients tend to have a lower body weight than patients from Western countries. Asian race was not a significant covariate in population PK analysis, whereas in subgroup analyses of pivotal studies (Study M2-124 and Study M2-125), the effect of roflumilast versus placebo on the rate of moderate or severe exacerbations showed no heterogeneity depending on race. Therefore, is was concluded that the approved maintenance dose of roflumilast 500 µg OD does not need to be adjusted in these populations.

The mechanism of action, primary and secondary pharmacology of roflumilast are well established and were already assessed in the roflumilast 500 microg MAA. The new line extension application is based on a single pivotal study (OPTIMIZE study) that included combined PK, PD, efficacy and safety data. Only the new PD data pertaining to the OPTIMIZE PK-PD model have been described and assessed in this section.

Three types of analyses were performed to characterize the relationship of systemic exposure of 3 roflumilast starting regimes (250 microg OD or 500 microg EOD for 4 weeks followed by 500 for 8 additional weeks versus standard regime of roflumilast 500 microg OD for 12 weeks) with
a) post-BD FEV1 observations (PK/FEV1 models); b) the percentage of patients with at least one AE (PK/AE models), and c) the time to treatment discontinuation due to AEs (PK/TTE models).

The population PK/FEV1 model predicted a reduced improvement in FEV1 at roflumilast 250 µg OD compared to roflumilast 500 µg OD during the 4-week up-titration phase of the Main Period. The model also predicted a decrease of FEV1 change from baseline in subjects down-titrating from 500 µg OD to 250 µg OD in the Down-Titration Period. In accordance with reducing the dose of roflumilast to 250 µg once daily in patients who did not tolerate roflumilast 500 µg once daily, total PDE4 inhibition (tPDE4i) was markedly reduced by approximately 50% to below that typically observed in patients who tolerated 500 µg once daily, and this led to a smaller change in forced expiratory volume in the first second (FEV1) from baseline. Therefore, administration of roflumilast 250 µg once daily may not induce sufficient phosphodiesterase 4 (PDE4) inhibition to exert clinical efficacy. This is further discussed in the efficacy section.

PK/PD models of incidence of adverse events (AEs) and time-to event models for discontinuation from the study were also developed. Covariate analyses using these models found weighted plasma exposure of roflumilast and its metabolite to be a significant predictor of AE incidence, and dose in the up-titration phase to be a significant predictor of discontinuations. The models were based on average concentrations and were unable to explain the differences in discontinuation rates between the two up-titration regimes (250 microg OD vs. 500 microg EOD), despite average concentrations were similar. Other PK characteristics (e.g. Cmax) might be required in addition to characterize the PK/safety relationship. The sparse data used to build the population PK model did not allow a robust prediction of C_{max}. and therefore cannot analyze a potential relationship between C_{max} and discontinuation rates. It was concluded that, even if further analyses of PK/safety data based on C_{max} were possible, these would not change the position regarding the benefit of introducing a starting dose of roflumilast 250 µg OD.

On the other hand, time to event models attempt to characterize the (discontinuation) time (dependent variable) as a function of so called predictor or independent variables.

These data provided supporting evidence that starting roflumilast treatment with 250 µg once daily for 4 weeks followed by up-titration to the 500 µg once daily dose results in lower discontinuation rates and AEs of interest, compared to starting with roflumilast 500 µg once daily. This is applicable for the 12 week study period. No assumptions can be made beyond this period.
Nevertheless, in previous roflumilast clinical trials, Kaplan-Meier plots of time to onset of AEs show that the majority of events in the roflumilast treated-patients occur early, and that there is a plateau after 4 weeks. Therefore, the first 4 weeks of treatment represents the dosing period most relevant to the aims of the study (ie, to improve tolerability of roflumilast through use of alternative dosing regimens). After this time, there is no evidence to support a need for further improvements, as the frequency of AEs with roflumilast is not higher than with placebo, and the rate of withdrawals from study treatment are low.

2.8.5. Conclusions on clinical pharmacology

New PK data generated from OPTIMIZE in almost 19.000 samples from 1238 COPD patients are robust. Results from the new population PK model on the combined REACT and OPTIMIZE dataset identified no clinically relevant changes of systemic exposure levels in populations of particular interest (eg, elderly patients, female patients, or patients with high [>80 kg] or low [<60 kg] baseline body weight). With respect to race, Asian patients tend to have a lower body weight than patients from Western countries. Asian race was not a significant covariate in population PK analysis, whereas in subgroup analyses of pivotal studies (Study M2-124 and Study M2-125), the effect of roflumilast versus placebo on the rate of moderate or severe exacerbations showed no heterogeneity depending

on race. Therefore, the approved maintenance dose of roflumilast 500 µg OD does not need to be adjusted in these populations.

With respect to PK-PD relationship, three types of analyses were performed to characterize the relationship of systemic exposure of 3 roflumilast starting regimes (250 microg OD or 500 microg EOD for 4 weeks followed by 500 for 8 additional weeks versus standard regime of roflumilast 500 micrograms OD for 12 weeks) with: a) post-BD FEV1 observations (PK/FEV1 models); b) the percentage of patients with at least one AE (PK/AE models), and c) the time to treatment discontinuation due to AEs (PK/TTE models).

Results from the new population PK model and PK-PD model of pre-BD FEV1 also indicates that 250 micrograms roflumilast is associated to sub-therapeutic levels and therefore should not be used for maintenance treatment. The SmPC has been ammended accordingly in secctions 4.2 and 5.1 to warn against the use of the 250 microgram dose as maintenance dose. The applicant has been requested to discuss about what are considered therapeutic and subtherapeutic levels (e.g. levels of PDE4 inhibitory activity) and make a revised proposal to include these levels in the SmPC for the 250 microg (subtherapeutic) and 500 microg (therapeutic) (see LoI).

PK/PD models of incidence of adverse events (AEs) and time-to event models for discontinuation from the study were also developed. The models were based on average concentrations. Covariate analyses using these models found weighted plasma exposure of roflumilast and its metabolite to be a significant predictor of AE incidence, and dose in the up-titration phase to be a significant predictor of discontinuations.

2.9. Clinical efficacy

2.9.1. Dose-response studies and main clinical studies

This submission is based on data from a single study (Study RO 2455 302-RD [OPTIMIZE]) conducted to fulfil a Committee for Medicinal Products for Human Use (CHMP) post-authorization measure (FUM004) to explore alternative doses of roflumilast to minimise the risk of drug interactions, poor tolerability, and the influence of factors such as gender, age, and smoking status on the bioavailability of the product in patients with chronic obstructive pulmonary disease (COPD).

The single pivotal OPTIMIZE study was a multicenter, randomized, double-blind, Phase III study that comprised a 12-week Main Period, including an initial 4-week up-titration regimen to assess if alternative dosing strategies (roflumilast 250 µg once daily or 500 µg every other day) could minimise the risk of poor tolerability of the approved dose of 500 µg once daily (primary safety objective).

The primary endpoint was the percentage of patients prematurely discontinuing study treatment due to any reason during the Main Period (see Module 2.7.4). The study also included an 8-week Down-Titration Period in patients not tolerating the approved dose of roflumilast 500 µg once daily during the Main Period, to assess if a lower maintenance dose of 250 µg once daily could be proposed to minimise the risk of poor tolerability (secondary safety objective).

CLINICAL STUDY REPORT RO-2455-302-RD

Study Title: A Multicenter, Randomized, Double-Blind Phase 3 Study to Evaluate Tolerability and Pharmacokinetics of 500 µg Roflumilast Once Daily With an Up-Titration Regimen in COPD, including an Open-Label Down-Titration Period Evaluating Tolerability and Pharmacokinetics of 250 µg Roflumilast Once Daily in Subjects Not Tolerating 500 µg Roflumilast Once-Daily.

Methods:

Study Sites: 161 ex-US sites in 15 countries had subjects enrolled in the double-blind treatment period

Study Periods: Double-blind treatment period (4 weeks), single-blind treatment period (8 weeks), open-label Down-Titration Period (8 weeks), safety follow-up (30 days).

Study Dates:
- Date first subject signed informed consent form: 30 April 2014.
- Date of last subject's last visit/contact (from the Clinical database): 21 October 2015.
- Date of last subject's last procedure for collection of data for primary endpoint: 18 September 2015

Study Duration: A maximum of 20 weeks plus a 30-day safety follow-up period.

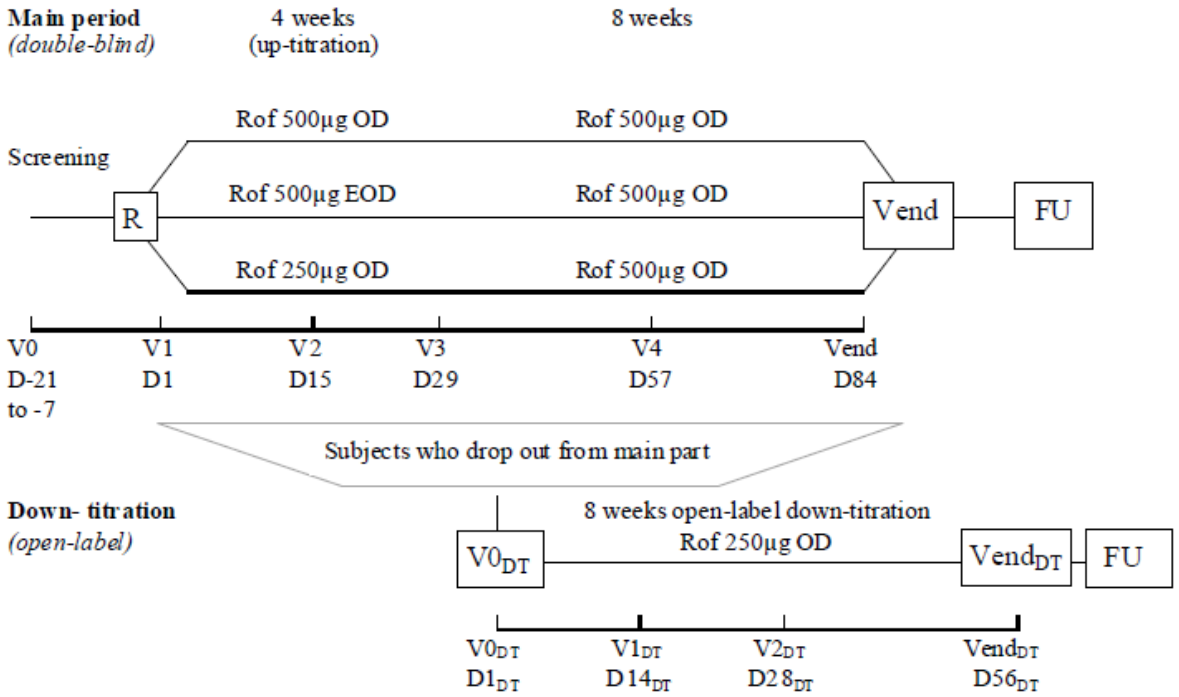
Methods

OPTIMIZE was a multicenter, randomized, double-blind, 3-arm, parallel group, phase 3 study with an open-label Down-Titration Period for subjects who withdrew from the Main Period of the study. During the Main Period, subjects were randomized receive 1 of the 3 treatments consisting of 2 up-titration treatment groups: 250 µg OD or 500 µg EOD for the first 4 weeks followed by 500 µg OD for 8 weeks, and the currently approved roflumilast regimen of 500 µg OD administered for 12 weeks.

During the Main Period, the first 4 weeks (up-titration) was double-blinded, and the following 8 weeks (maintenance period) was single-blinded. All subjects discontinuing from the Main Period were permitted to enter an 8-week open-label Down-Titration Period where they received roflumilast 250 µg OD.

Spirometry and subject-assessed treatment satisfaction for efficacy assessments were performed at Screening (V0, Days -21 to -7), Randomization (V1, Day 1), and at Weeks 2, 4, 8, and 12 (Visits V2, V3, V4, and Vend) of the Main Period, and at Baseline (V0DT=Vend of Main Period) and at Weeks 2, 4 and 8 (Visits V1DT, V2DT and VendDT) of the Down-Titration Period. Six milliliter blood samples for PK analysis were drawn at Visits V2, V4, Vend/V0DT, V1DT, V2DT and VendDT.

Figure 6. Schematic of RO-2455-302-RD (OPTIMIZE) study design



D = day, D_{DT} = day of the down-titration period, DT = down-titration, EOD = every other day, OD = once daily, R = randomization, Rof = roflumilast, V = Visit, V_{DT} = visit of the down-titration period, Vend = last visit, FU = safety follow-up phone call

D day, DDT day of the down-titration period, DT down-titration, EOD every other day, FU safety follow-up phone

call; OD once daily, R randomisation, Rof roflumilast, V Visit, VDT visit of the down-titration period, Vend last visit.

- **Study participants**

Number of Subjects:

Planned: 1323 subjects planned for randomization

Enrolled in the Main Period: 1323 subjects

Enrolled in Down-Titration Period: 104 subjects including 80 subjects who withdrew from the Main Period while receiving roflumilast 500 µg OD (the analysis of main interest for Down-Titration Period).

Analyzed:
Safety analysis set (SAS) for Main Period: 1321 subjects,
Full analysis set (FAS): 1323 subjects,
SAS for Down-Titration Period: 104 subjects including 80 subjects who withdrew from the Main Period while receiving roflumilast 500 µg OD (the analysis of main interest for Down-Titration Period);
Valid case set (VCS) for Main Period: 1156 subjects, PK set: 1238 subjects.

Diagnosis and Main Criteria for Inclusion:

This study included patients aged ≥40 years with a history of chronic obstructive pulmonary disease (COPD) (at least 12 months prior to Screening Visit [V0] with post-bronchodilator forced expiratory volume in the first second [FEV1]/forced vital capacity [FVC] ratio <70% and FEV1 ≤50% of predicted) associated with chronic productive cough (for 3 months in each of the 2 years prior to V0) and a history of exacerbations (at least 1 documented COPD exacerbations within 1 year prior to V0), and were concomitantly treated with a fixed combination of long-acting β2-agonist and inhaled corticosteroid. Patients also were former or current smokers.

Exclusion criteria:

a) Criteria affecting the read-out parameters of the study:
1. The subject had a COPD exacerbation ongoing at Screening (Visit V0), or has a COPD exacerbation between V0 and V1.
2. The subject had a lower respiratory tract infection not resolved 4 weeks prior to Screening (Visit V0).
3. The subject had a diagnosis of asthma and/or other relevant lung disease (eg, history of primary bronchiectases, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease [eg, fibrosis, silicosis, sarcoidosis], or active tuberculosis).
4. The subject had a known α1-antitrypsin deficiency.
5. The subject had taken roflumilast within 6 months of Screening (Visit V0).

b) Criteria within ethical considerations in terms of general health:
6. The subject had clinically relevant abnormal laboratory values suggesting an undiagnosed disease requiring further clinical evaluation (as assessed by the investigator).
7. The subject had a history of severe psychiatric or neurological disorders.

- **Treatments**

During the Main Period, subjects were randomized receive 1 of the 3 treatments consisting of 2 up-titration treatment groups: 250 µg OD or 500 µg EOD for the first 4 weeks followed by 500 µg OD for 8 weeks, and the currently approved roflumilast regimen of 500 µg OD administered for 12 weeks. All subjects discontinuing from the Main Period were permitted to enter an 8-week open-label Down-Titration Period where they received roflumilast 250 µg OD.

Table 6. Study treatments in OPTIMIZE clinical trial.

Test Product, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number
Roflumilast	250 µg, tablet	250 µg OD	Oral	10883205 and 11056250
Roflumilast	500 µg, tablet	500 µg OD	Oral	10883213 and 11056242
Roflumilast	500 µg, tablet	500 µg EOD	Oral	10883213 and 11056242

Reference Therapy, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength	Study Dosage	Mode of Administration	Drug Product Lot Number
Placebo	0 µg, tablet	0 µg EOD	Oral	10883221 and 11056253

- **Objectives**

Primary:

- To evaluate discontinuation rates of roflumilast 500 µg once daily (OD) using an up-titration regimen with either 250 µg OD or 500 µg every other day (EOD) for the first 4 weeks of treatment followed by 500 µg OD for 8 weeks compared with continuous treatment of 500 µg OD during the entire 12-week Main Period.
- To evaluate if subjects who do not tolerate roflumilast 500 µg OD have a drug exposure with 250 µg roflumilast OD similar to that observed in other subjects with the 500 µg OD dose.

Secondary:

- To evaluate the gastrointestinal tolerability of roflumilast 500 µg OD with an up-titration regimen compared with continuous treatment of 500 µg OD.
- To evaluate the safety, discontinuations and tolerability especially the gastrointestinal tolerability of roflumilast 250 µg OD in subjects not tolerating the 500 µg OD dose.
- To evaluate the safety of roflumilast 500 µg OD with an up-titration regimen compared with continuous treatment of 500 µg OD.
- To evaluate the efficacy of roflumilast 500 µg OD with an up-titration regimen on lung function compared with continuous treatment of 500 µg OD.
- To characterize the efficacy of roflumilast 250 µg OD on pulmonary function during a Down-Titration Period, in subjects who do not tolerate roflumilast 500 µg OD.
- To evaluate subject-assessed treatment satisfaction with an up-titration regimen compared with continuous treatment of roflumilast 500 µg OD.
- To characterize subject-assessed treatment satisfaction of roflumilast 250 µg OD during a Down-Titration Period, in subjects who do not tolerate roflumilast 500 µg OD.
- To characterize the pharmacokinetics (PK) of roflumilast and roflumilast N-oxide with an up-titration regimen.
- To characterize the PK of roflumilast and roflumilast N-oxide with roflumilast 250 µg OD in subjects not tolerating the 500 µg OD dose.
- To characterize the PK/pharmacodynamic (PD) relation with respect to relevant safety and efficacy parameters

- **Outcomes / endpoints**

Primary Endpoint

- The primary endpoint was the percentage of subjects prematurely discontinuing study treatment due to any reason (during Main Period, [Visit V1 to Vend]).

Key Secondary Endpoints

- Percentage of subjects with adverse events (AEs) of interest to evaluate tolerability during Main Period (V1 to Vend). For the purposes of safety analysis, the treatment-emergent adverse events (TEAEs) of interest were defined as diarrhea, nausea, headache, decreased appetite, insomnia, and abdominal pain.
- Change in prebronchodilator FEV1 during Down-Titration Period (V0DT to VendDT).
- Percentage of subjects prematurely discontinuing study treatment due to any reason during Down-Titration Period (V0DT to VendDT).

Other secondary endpoints were:
- Change in prebronchodilator FEV1 from V1 to V2, V3, V4, and Vend (during Main Period of the study) and also from V1 to VendDT (including Down-Titration Period).
- Change in prebronchodilator FVC from V1 to V2, V3, V4, and Vend (during Main Period of the study) and also from V0DT to VendDT and V1 to VendDT (including Down-Titration Period).
-
- Change in subject-assessed treatment satisfaction scores from V1 to V2, V3, V4, and Vend (during Main Period of the study) and also from V0DT to VendDT and V1 to VendDT (including Down-Titration Period).

Pharmacokinetic secondary endpoints:
- PK profiles of roflumilast and roflumilast N-oxide.
- Individual and population PK parameters for roflumilast and roflumilast N-oxide (the active metabolite) and total phosphodiesterase 4 (PDE4) inhibitory activity (tPDE4i) of both active moieties including covariate effects on these parameters (where 'tPDE4i' activity includes the PDE inhibitory activity of roflumilast itself as well as roflumilast N-oxide).
- Relationship between PK and relevant safety (AEs of interest [extended list] to evaluate tolerability, ie, diarrhea, nausea, headache, decreased appetite, insomnia, abdominal pain, vomiting, angioedema, anxiety,and weight loss) and efficacy (FEV1) parameters.

Safety:
- Safety was assessed by evaluation of AEs, changes in laboratory values, vital signs, physical examination findings, body weight and body mass index (BMI), as well as changes on the Columbia Suicide Severity Rating Scale (C-SSRS).

- **Sample size**

The sample size for the Main Period was based on the primary endpoint of the percentage of subjects discontinuing study treatment due to any reason, during the Main Period of the study, up to Week 12. Discontinuation rates for the sample size calculation were estimated from data of the roflumilast COPD pivotal studies pool (M2-124 and M2-125), which included a very similar subject population as the OPTIMIZE study. The discontinuation rates after the initial 12 weeks of treatment were used to reflect the treatment duration of the OPTIMIZE study (total treatment duration of the pivotal studies was 1 year).
With these assumptions, Kaplan-Meier estimates revealed discontinuation rates of 20% with roflumilast and 13% with placebo.
Based on these data, a total of 441 subjects per treatment arm, 1323 overall, will provide 80% power to declare superiority of each of:

- Roflumilast 250 µg OD/500 µg OD vs. reference.
- Roflumilast 500 µg EOD/500 µg OD vs. reference.

Where the reference is defined as roflumilast 500 µg OD for 12 weeks. It refers to a 2-group chi-square test of equal proportions (OR =1), assuming discontinuation rates of 13% on each of the up-titration arms and 20% on the reference arm, and a 2-sided significance level of 5.0% using a closed testing procedure with hierarchical evaluation (roflumilast 250 µg OD/500 µg OD being tested first followed by roflumilast 500 µg EOD/500 µg OD).

The expected sample size for the Down-Titration Period was based on the above assumption that 13% to 20% of subjects prematurely discontinue roflumilast treatment. Including about 1323 subjects in the Main Period will thus lead to approximately 150 subjects in the Down-Titration Period assuming that 75% of subjects who discontinue from the Main Period will continue into the Down-Titration Period.

- **Randomisation**

In this study, a 1:1:1 randomization was employed. Eligible subjects were randomized by means of interactive voice response system/interactive web response system (IVRS/IWRS). At each dispensing visit, the system assigned an appropriate investigational medicinal product (IMP) kit(s) from the stock available at the study center for each subject.

- **Blinding (masking)**

The first 4 weeks of the main treatment period was double-blind. The following 8 weeks of the main treatment period was single-blinded with the sponsor and investigators aware that all subjects were receiving roflumilast 500 µg OD. All subjects discontinuing from the main treatment period were permitted to enter an 8-week, Down-Titration Period where subjects received open-label roflumilast 250 µg OD. In all cases, the original randomized treatment regimen remained blinded to all parties for the duration of the study.

Roflumilast 250 µg and 500 µg tablets as well as the placebo tablets were identical in appearance, shape and color, and had identical labeling and packaging. The investigational drug blind was maintained using the IVRS/IWRS, and was not to be broken unless information concerning the investigational drug was necessary for the medical treatment of a subject, or in the event of a medical emergency (Section 8.5 of the protocol).

- **Statistical methods**

In this study, all confirmatory decisions were taken to assess superiority. For this purpose, the primary and key secondary endpoints in safety were based on the SAS, where as the key secondary endpoint in efficacy was based on the FAS (Intention-to-treat analysis). To analyze robustness of results, analyses based on the VCS (Per-protocol analysis) was generally performed in addition and interpreted as supportive analysis.

For hypothesis testing, a hierarchical testing procedure was prespecified to control the overall type I error rate of 5% for the primary and key secondary endpoints as described in above is as follows:
The null hypotheses to be tested in a fixed order at the 2-sided 0.05 significance level were:

- H01: the percentage of discontinuations by Week 12 on roflumilast 250 µg OD/500 µg OD was not lower than or equal to that on roflumilast 500 µg OD.
- H02: the percentage of discontinuations by Week 12 on roflumilast 500 µg EOD/500 µg OD was not lower than or equal to that on roflumilast 500 µg OD.
- H03: the percentage of AEs of interest by Week 12 on roflumilast 250 µg/500 µg OD was not lower than or equal to that on roflumilast 500 µg OD.
- H04: the percentage of AEs of interest by Week 12 on roflumilast 500 µg EOD/500 µg OD was not lower than or equal to that on roflumilast 500 µg OD.
- In addition, the change from Baseline (V0DT) in pre-bronchodilator FEV1 during the open-label down-titration period was estimated.

The above testing procedure controlled the 5% error rate; each subsequent hypothesis would be tested for confirmatory basis only if all previously tested hypotheses had been rejected. As a result, the principle of closed testing implied that the overall 2-sided false-rejection rate of the study was maintained at 5%. If any test could not be performed on a confirmatory basis, because a previous test had failed, the test was performed in an exploratory manner.

For statistical interpretation, the default significance level was 5%, CIs for point estimates were 95% and all tests were interpreted as 2-sided.

The analyses of ‘main interest’ for the Down-Titration Period were those conducted in only those subjects who were taking roflumilast 500 µg OD during the Main Period at the time of discontinuation (thus excluding subjects who discontinued whilst taking roflumilast 250 µg OD or 500 µg EOD during the Main Period for the Down-Titration Period).

Safety:

The primary endpoint (percentage of subjects prematurely discontinuing study treatment for any reason during the Main Period from V1 to Vend) was analyzed using a logistic regression model, with study treatment, country and baseline FEV1 as explanatory variables. Superiority analyses were performed using a hierarchical testing procedure.

Comparisons were made at the 2-sided 5% significance level. As a supportive analysis, the hazard ratio for each up-titration arm compared with the roflumilast 500 µg OD arm and the associated 95% CI were estimated using a Cox proportional hazards model with study treatment and country as class effects and baseline FEV1 as a continuous covariate. Subjects who did not discontinue study treatment during the Main Period were censored at Vend (final visit of Main Period). A sensitivity analysis was performed for the primary and key secondary endpoints.

The percentage of subjects with AEs of interest (diarrhea, nausea, headache, decreased appetite, insomnia, and abdominal pain) was analyzed using a logistic regression analysis as part of the hierarchical approach as described for the primary safety endpoint. Time to onset, duration and intensity of AEs of interest to evaluate tolerability was summarized descriptively. Descriptive statistics were used to analyze the endpoint of percentage of subjects prematurely discontinuing study treatment due to any reason (from V0DT to VendDT).

Analyses of AEs, clinical laboratory values, vital signs, body weight and BMI, as well as C-SSRS were performed descriptively.

Efficacy:
The key secondary endpoint (change in pre-bronchodilator FEV1 from V0DT to VendDT) was assessed with an analysis of variance (ANCOVA) model using the last observation carried forward (LOCF) value, as described by Ebutt and Frith. The robustness of the primary method for the key-secondary endpoint was assessed using another ANCOVA model for repeated measurements, as described by Verbeke and Molenberghs. These analyses were repeated for change in pre-bronchodilator FEV1 from Baseline (V1) to the end of the Main Period (Vend), as well as for the endpoints of change from Baseline in pre-bronchodilator FVC and subject-assessed treatment satisfaction.

Also, as a sensitivity analysis, change in pre-bronchodilator FEV1 from baseline (V0DT) to the last scheduled post-randomization visit was analyzed with a pattern mixture model implemented by multiple imputation replacing LOCF in accounting for missing data.

- **Changes in study conduct or in the planned analyses**

There was 1 protocol amendment: Protocol Amendment 1 with the following changes:

- All procedures outlined in the Vend visit were to be performed at V0DT for subjects continuing into the open-label Down-Titration Period of the study.
- Clarified that the 'Liver Function Test Abnormalities' were not be a separate subject discontinuation/withdrawal category.
- Clarified that an additional dose of study drug was not to be provided at Vend for subjects discontinuing prematurely from the Main Period without continuing into the Down-Titration Period, and that only 1 PK sample was to be taken at this visit.

Results

- **Participant flow**

The disposition of randomized subjects is summarized in Table 9. Of the 1323 subjects who went on to be randomized, 2 subjects (0.2%) were never treated. In total, 1043 subjects (79%) completed the Main Period. Of the 278 subjects (21.0%) who discontinued during the Main Period, 146 subjects (11.1%) discontinued during the first 4 weeks of the Main Period (up to Visit 3).

A total of 104 subjects (7.9%) who withdrew from the Main Period entered the Down-Titration Period (where they received roflumilast 250 µg OD). Approximately one-quarter of these subjects went on to discontinue from this Down-Titration Period, with the most common reason for discontinuation from this period due to an AE. Of the 104 subjects who entered the Down-Titration Period, 80 subjects

(comprising of 20, 22 and 38 subjects from the 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively) entered after not tolerating at least 1 dose of roflumilast 500 µg OD during the Main Period. The remaining 24 subjects (104-80=24) who entered the Down Titration Period did not receive roflumilast 500 µg OD in the Main Period but received either 250 µg OD or 500 µg EOD, during the first 4 weeks of low dose roflumilast.

Table 7. Disposition of Subjects (All Randomized Subjects)

	Roflumilast 250 µg OD/ 500 µg OD (N=441)	Roflumilast 500 µg EOD/ 500 µg OD (N=439)	Roflumilast 500 µg OD (N=443)	Total (N=1323)
	Number of Subjects (%)			
Randomized and treated	441 (100.0)	437 (99.5)	443 (100.0)	1321 (99.8)
Randomized but not treated	0	2 (0.5)	0	2 (0.2)
Completed study drug (a)(c)(d)	360 (81.6)	349 (79.9)	334 (75.4)	1043 (79.0)
Prematurely discontinued study drug (b)(c)(d)	82 (18.6)	88 (20.1)	109 (24.6)	279 (21.1)
Subjects in the SAS for Main Period	**441 (100.0)**	**437 (99.5)**	**443 (100.0)**	**1321 (99.8)**
Subjects discontinuing Main Period (c)	81 (18.4)	88 (20.1)	109 (24.6)	278 (21.0)
Discontinued during first 4 weeks of Main Period (V1-V3) (c)	34 (7.7)	42 (9.6)	70 (15.8)	146 (11.1)
Reason for Main Period discontinuation (e)				
PTE/AE	44 (54.3)	57 (64.8)	68 (62.4)	169 (60.8)
Major/significant protocol deviation	0	1 (1.1)	3 (2.8)	4 (1.4)
Lost to follow-up	4 (4.9)	2 (2.3)	1 (0.9)	7 (2.5)
Voluntary withdrawal	23 (28.4)	23 (26.1)	21 (19.3)	67 (24.1)
Study termination	0	0	0	0
Pregnancy	0	0	0	0
Lack of efficacy	2 (2.5)	0	0	2 (0.7)
Other	8 (9.9)	5 (5.7)	16 (14.7)	29 (10.4)
Subjects in the SAS for Down-Titration Period (c)	**27 (6.1)**	**39 (8.9)**	**38 (8.6)**	**104 (7.9)**
Subjects discontinuing Down-Titration Period (e)	7 (25.9)	11 (28.2)	7 (18.4)	25 (24.0)
Reason for Down-Titration Period discontinuation (f)				
AE	4 (57.1)	10 (90.9)	3 (42.9)	17 (68.0)
Major/significant protocol deviation	0	0	0	0
Lost to follow-up	0	0	0	0
Voluntary withdrawal	2 (28.6)	1 (9.1)	2 (28.6)	5 (20.0)
Study termination	0	0	0	0
Pregnancy	0	0	0	0
Lack of efficacy	0	0	0	0
Other	1 (14.3)	0	2 (28.6)	3 (12.0)

Source: Table 15.1.5.
(a) Subjects are defined as having completed study drug if they did not discontinue from the Main Period.
(b) Subjects are defined as having prematurely discontinued study drug if they discontinued from either the Main Period or the Down-Titration Period.
(c) Percentages are based on SAS for the Main Period.
(d) One subject who completed the Main Period and therefore was not eligible to enter the Down-Titration Period was mistakenly enrolled in this period. This subject was then prematurely discontinued from the Down-Titration Period, and is thus counted as having completed and discontinued study drug.
(e) Percentages are based on SAS for the Down-Titration Period
(f). Percentages for reason for discontinuation of study drug are based on the total number of subjects who prematurely discontinued the study drug during the associated period.

- **Recruitment and study conduct**

In total, 1585 subjects were screened, of which 1323 subjects (83.5%) from 161 sites in 15 countries were eligible for randomization and included in the FAS. The most common reason for exclusion was not meeting inclusion criteria (in 162 of 262 subjects [61.8%]).

Subjects were randomized into the double-blind main treatment period at a total of 161 sites in 15 countries: Bulgaria (11 sites), Germany (9), Greece (5), Hungary (21), Republic of Korea (9), Philippines (4), Poland (15), Romania (19), Russia (17), Slovakia (12), South Africa (14), Spain (2), Thailand (3), Ukraine (14), and United Kingdom (6).

For statistical analyses, countries were divided into 4 regions as follows: Western Europe (Germany, Spain, United Kingdom), North-Eastern Europe (Poland, Russia, Ukraine), South-Eastern Europe (Bulgaria, Greece, Hungary, Romania, Slovakia), and Non-European (South Korea, Philippines, South Africa, Thailand).

During the study, persistent noncompliance was noted at site 6002, which was based in South Africa. Following routine monitoring of the site a number of significant noncompliance issues were noted including inadequate source documentation confirming the eligibility of 3 subjects, a subinvestigator who was not a listed delegate obtaining informed consent, and the incorrect storing of PK samples. Study recruitment at the site was paused while corrective action, including the retraining of staff was undertaken. The recruitment hold was subsequently lifted, and the site was permitted to recruit one subject. Three days later, the site monitor reported persistent noncompliance at the site, resulting in Takeda conducting an audit at the study site. At the time of the investigation, the site had screened 5 subjects; 1 subject was a screen failure, and 4 subjects had completed the study. The audit was rated as 'unsatisfactory' due to significant noncompliance issues, and the site was closed from further participation in the study protocol.

The noncompliance issues/site closure had been reported to the Ethics Committee and the Regulatory Authority (Medicines Control Council) of South Africa. At the time of the investigation, the site had screened 5 subjects; 1 subject was a screen failure, and 4 subjects had completed the study. Although subject data was included in the primary intention-to-treat (ITT) analysis, to account for any impact on data integrity, a sensitivity analysis excluding subject data from South African Site 6002, which was suspected of scientific misconduct, was carried out.

- **Baseline data**

Main Period
Demographic and baseline characteristics are summarized in Table 10 for the Main Period. Overall, demographic characteristics were similar across the 3 treatment groups. The majority of subjects in each treatment group were White (405 subjects [91.8%] in the roflumilast 250 µg OD/500 µg OD group, 399 subjects [91.3%] in the roflumilast 500 µg EOD/500 µg OD group and 405 subjects [91.4%] in the roflumilast 500 µg OD group). The mean (SD) age of subjects was 64.2 (7.81), 65.0 (8.21), and 64.6 (8.36) years in the roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD groups, respectively. The 250 µg OD/ 500 µg OD dose group was comprised of more subjects aged 40 to 64 years (54.9% of subjects) than the other 2 dose groups (46.2% and 50.6% for 500 µg EOD/ 500 µg OD and 500 µg OD, respectively). The majority of subjects in each treatment group were male (72.6% in roflumilast 250 µg OD/500 µg OD group,74.4% in roflumilast 500 µg EOD/500 µg OD group, and 76.3% in roflumilast 500 µg OD group).

Table 8. Demographic and Baseline Characteristics (SAS, Main Period)

		Roflumilast 250 µg OD/ 500 µg OD (N=441)	Roflumilast 500 µg EOD/ 500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)	Total (N=1321)
Age (years)	Mean (SD)	64.2 (7.81)	65.0 (8.21)	64.6 (8.36)	64.6 (8.13)
	Median (min, max)	64.0 (43, 84)	65.0 (40, 83)	64.0 (40, 90)	64.0 (40, 90)
Age group, n (%)	40-64 years	242 (54.9)	202 (46.2)	224 (50.6)	668 (50.6)
	65-84 years	199 (45.1)	235 (53.8)	217 (49.0)	651 (49.3)
	≥85 years	0	0	2 (0.5)	2 (0.2)
Sex, n (%)	Male	320 (72.6)	325 (74.4)	338 (76.3)	983 (74.4)
	Female	121 (27.4)	112 (25.6)	105 (23.7)	338 (25.6)
Ethnicity, n (%)	Hispanic or Latino	1 (0.2)	2 (0.5)	5 (1.1)	8 (0.6)
	Not Hispanic and Latino	428 (97.1)	423 (96.8)	426 (96.2)	1277 (96.7)
	Missing	12 (2.7)	12 (2.7)	12 (2.7)	36 (2.7)
Race, n (%)	American Indian or Alaskan Native	0	1 (0.2)	0	1 (0.1)
	Asian	32 (7.3)	30 (6.9)	32 (7.2)	94 (7.1)
	Black or African American	3 (0.7)	3 (0.7)	3 (0.7)	9 (0.7)
	Native Hawaiian/Other Pacific Islander	1 (0.2)	4 (0.9)	3 (0.7)	8 (0.6)
	White	405 (91.8)	399 (91.3)	405 (91.4)	1209 (91.5)
Height (cm)	Mean (SD)	169.1 (8.73)	168.8 (8.66)	169.1 (8.55)	169.0 (8.64)
	Median (min, max)	170.0 (140, 198)	170.0 (146, 194)	170.0 (120, 191)	170.0 (120, 198)
Weight (kg)	Mean (SD)	75.68 (18.686)	74.40 (17.804)	75.74 (16.900)	75.28 (17.808)
	Median (min, max)	74.00 (38.0, 160.0)	74.00 (33.5, 134.0)	74.00 (38.9, 131.0)	74.00 (33.5, 160.0)
BMI (kg/m^2) (a)	Mean (SD)	26.39 (5.987)	26.01 (5.618)	26.46 (5.880)	26.29 (5.830)
	Median (min, max)	25.30 (13.6, 58.8)	25.70 (14.1, 49.7)	25.90 (14.9, 83.8)	25.60 (13.6, 83.8)

Source: Table 15.1.8.1.
(a) Subject with a BMI of 83.5 kg/m^2 had a baseline weight of 120 kg and height of 120 cm.
Baseline is the assessment taken on the reference start date (Randomization Visit V1 for the Main Period and final visit of Main Period V_{end}/V_{0DT} for the Down-Titration Period) or the last assessment taken prior to the start of study drug intake in the study period.

Other baseline characteristics are summarized in Table 11 for the Main Period. With the exception of 3 subjects whose information is missing, all subjects had a history of COPD exacerbation, although the majority of subjects had experienced ≤2 episodes within the 1 year prior to Screening. A small proportion of subjects (6.5%-6.9% across the 3 treatment groups) had previously received roflumilast treatment, though none of these had stopped due to intolerability. Baseline lung function results (FEV1, FVC, FEV1/FVC, and %FEV1 reversibility) were broadly similar across the 3 treatment groups.

Table 9. Other Baseline Characteristics (SAS, Main Period)

		Roflumilast 250 µg OD/ 500 µg OD (N=441)	Roflumilast 500 µg EOD/ 500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)	Total (N=1321)
Smoking classification, n (%)	Never smoked	0	0	0	0
	Current smoker	213 (48.3)	198 (45.3)	196 (44.2)	607 (46.0)
	Ex smoker	228 (51.7)	239 (54.7)	247 (55.8)	714 (54.0)
Cigarette pack years (amount) (a)	Mean (SD)	38.1 (17.49)	40.2 (19.22)	37.6 (17.70)	38.6 (18.17)
	Median (min, max)	37.0 (10, 113)	39.0 (10, 160)	35.0 (10, 142)	37.0 (10, 160)
Interpretation of chest x-ray, n (%)	Within normal limits	188 (42.6)	176 (40.3)	185 (41.8)	549 (41.6)
	Abnormal, not clinically significant	223 (50.6)	230 (52.6)	236 (53.3)	689 (52.2)
	Abnormal, clinically significant	8 (1.8)	6 (1.4)	5 (1.1)	19 (1.4)
	Not done	21 (4.8)	25 (5.7)	17 (3.8)	63 (4.8)
	Missing	1 (0.2)	0	0	1 (0.1)
COPD exacerbation history, n (%)	Yes	441 (100.0)	436 (99.8)	441 (99.5)	1318 (99.8)
	No	0	0	0	0
	Missing	0	1 (0.2)	2 (0.5)	3 (0.2)
>2 exacerbation episodes, n (%)	Yes	6 (1.4)	9 (2.1)	9 (2.0)	24 (1.8)
	No	435 (98.6)	427 (97.7)	432 (97.5)	1294 (98.0)
Previous roflumilast treatment, n (%)	Yes	29 (6.6)	30 (6.9)	29 (6.5)	88 (6.7)
	No	411 (93.2)	407 (93.1)	414 (93.5)	1232 (93.3)
	Missing	1 (0.2)	0	0	1 (0.1)
Stopped due to intolerability, n (%)	Yes	0	0	0	0
	No	440 (99.8)	437 (100.0)	443 (100.0)	1320 (99.9)
	Missing	1 (0.2)	0	0	1 (0.1)
Prebronchodilator FEV_1, (L)	n	440	436	443	1319
	Mean (SD)	1.022 (0.3177)	1.028 (0.3173)	1.018 (0.3289)	1.023 (0.3211)
	Median (min, max)	0.980 (0.32, 2.27)	1.000 (0.28, 1.90)	0.990 (0.26, 1.98)	0.990 (0.26, 2.27)
Predicted FEV_1 (%) (b)	n	440	436	443	1319
	Mean (SD)	35.94 (8.823)	36.66 (8.803)	36.03 (9.533)	36.21 (9.060)
	Median (min, max)	36.45 (10.0, 69.0)	37.55 (10.3, 75.9)	37.00 (3.3, 75.3)	37.00 (3.3, 75.9)
Prebronchodilator FVC (L)	n	440	436	443	1319
	Mean (SD)	2.304 (0.7418)	2.303 (0.7091)	2.314 (0.6822)	2.307 (0.7109)
	Median (min, max)	2.210 (0.65, 4.76)	2.200 (0.80, 4.82)	2.250 (0.69, 5.05)	2.220 (0.65, 5.05)
Postbronchodilator FEV_1/FVC ratio (derived)	n	438	433	440	1311
	Mean (SD)	0.460 (0.1362)	0.465 (0.1078)	0.456 (0.1096)	0.460 (0.1186)
	Median (min, max)	0.450 (0.17, 2.26)	0.453 (0.22, 0.78)	0.444 (0.21, 0.81)	0.450 (0.17, 2.26)
% FEV_1 reversibility	n	440	436	443	1319
	Mean (SD)	7.108 (12.0016)	6.452 (14.4437)	7.390 (11.4071)	6.986 (12.6737)
	Median (min, max)	5.485 (-27.27, 90.59)	4.310 (-28.05, 147.06)	5.380 (-24.14, 59.55)	5.130 (-28.05, 147.06)

Source: Table 15.1.8.1.
(a) Number of pack-years = (number of cigarettes smoked per day/20) × number of years smoked.
(b) According to the study database, 1 subject reported a predicted FEV_1 of 3.3%, which appears to have been miscalculated and incorrectly entered by the study site. This data point should read 33%.

Concomitant medications

Nearly all subjects in the Main Period (1320 subjects, 99.9%) were receiving an ongoing concomitant medication at Baseline. Overall, the type and frequency of concomitant medication was broadly similar across treatment groups (Table 12).

Table 10. Summary of Relevant COPD Medications Used Before, During the Main Period, or After Treatment in ≥10% of Subjects in Any Treatment Group (SAS, Main Period)

Extended ATC Code (Medication Group)	Pretreatment	Main Period	Posttreatment
	Number of Subjects (%)		
Roflumilast 250 µg OD/ 500 µg OD (N=441)			
Subjects with any relevant COPD medications	430 (97.5)	430 (97.5)	428 (97.1)
R03AC (Inhaled short-acting beta-2-agonists)	314 (71.2)	314 (71.2)	293 (66.4)
R03BAL (Inhaled combination of corticosteroids and long-acting beta-2-agonists)	301 (68.3)	299 (67.8)	296 (67.1)
R03BD (Inhaled long-acting anticholinergics)	277 (62.8)	277 (62.8)	274 (62.1)
R03ACL (Inhaled long-acting beta-2-agonists)	116 (26.3)	115 (26.1)	114 (25.9)
R03DA (Xanthines)	111 (25.2)	85 (19.3)	80 (18.1)
R03BA (Inhaled Corticosteroids)	71 (16.1)	71 (16.1)	70 (15.9)
R03ACC (Inhaled combination of short acting beta-2-agonists and short-acting anticholinergics)	76 (17.2)	67 (15.2)	67 (15.2)
H02 (Corticosteroids [excluding inhaled and nasal applications])	77 (17.5)	26 (5.9)	5 (1.1)
Roflumilast 500 µg EOD/500 µg OD (N=437)			
Subjects with any relevant COPD medications	429 (98.2)	428 (97.9)	427 (97.7)
R03AC (Inhaled short-acting beta-2-agonists)	310 (70.9)	310 (70.9)	284 (65.0)
R03BAL (Inhaled combination of corticosteroids and long-acting beta-2-agonists)	297 (68.0)	296 (67.7)	296 (67.7)
R03BD (Inhaled long-acting anticholinergics)	257 (58.8)	259 (59.3)	259 (59.3)
R03ACL (Inhaled long-acting beta-2-agonists)	97 (22.2)	96 (22.0)	97 (22.2)
R03DA (Xanthines)	110 (25.2)	89 (20.4)	86 (19.7)
R03BA (Inhaled Corticosteroids)	76 (17.4)	77 (17.6)	75 (17.2)
R03ACC (Inhaled combination of short acting beta-2-agonists and short-acting anticholinergics)	78 (17.8)	73 (16.7)	71 (16.2)
H02 (Corticosteroids [excluding inhaled and nasal applications])	86 (19.7)	31 (7.1)	9 (2.1)
Roflumilast 500 µg OD (N=443)			
Subjects with any relevant COPD medications	436 (98.4)	436 (98.4)	434 (98.0)
R03BAL (Inhaled combination of corticosteroids and long-acting beta-2-agonists)	298 (67.3)	299 (67.5)	298 (67.3)
R03AC (Inhaled short-acting beta-2-agonists)	302 (68.2)	295 (66.6)	278 (62.8)
R03BD (Inhaled long-acting anticholinergics)	254 (57.3)	254 (57.3)	253 (57.1)
R03ACL (Inhaled long-acting beta-2-agonists)	99 (22.3)	98 (22.1)	97 (21.9)
R03DA (Xanthines)	107 (24.2)	89 (20.1)	85 (19.2)
R03ACC (Inhaled combination of short acting beta-2-agonists and short-acting anticholinergics)	90 (20.3)	83 (18.7)	80 (18.1)
R03BA (Inhaled Corticosteroids)	84 (19.0)	81 (18.3)	77 (17.4)
H02 (Corticosteroids [excluding inhaled and nasal applications])	84 (19.0)	39 (8.8)	12 (2.7)

Source: Table 15.1.12.5.1.
Subjects receiving a particular medication during more than 1 period were counted in all relevant periods.
The posttreatment period includes concomitant medications taken posttreatment for all subjects, including those who entered the down-titration period, who had a follow-up assessment.
ATC=Anatomical Therapeutic Chemical.

Down-Titration Period

Demographic and baseline characteristics are summarized in Table 13 for subjects who did not tolerate roflumilast 500 µg OD during the Main Period and subsequently entered the Down-Titration Period (N=80).

Overall, demographic characteristics were similar across the 3 treatment groups in the Down-Titration Period. As shown in Table 13, the majority of subjects in each treatment group were White (18 subjects [90.0%] in the roflumilast 250 µg OD/500 µg OD group, 21 subjects [95.5%] in the roflumilast 500 µg EOD/500 µg OD group, and 34 subjects [89.5%] in the roflumilast 500 µg OD group). The mean (SD) age of subjects was 65.6 (8.82), 63.5 (5.93), and 66.0 (7.78) years in the roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD groups, respectively. The

500 µg EOD/500 µg OD and 500µg OD treatment groups were comprised of more subjects aged 40 to 64 years (50.0% and 52.6% of subjects, respectively) than the 250 µg OD/ 500 µg OD dose group (40.0%). The majority of subjects in each treatment group were male (60.0% in roflumilast 250 µg OD/500 µg OD group, 54.5% in roflumilast 500 µg EOD/500 µg OD group, and 63.2% in roflumilast 500 µg OD group).

Table 11. Demographic and Baseline Characteristics of Subjects in the Down-Titration Period Who Did Not Tolerate Roflumilast 500 µg OD in the Main Period (SAS, Down-Titration Period)

		Roflumilast 250 µg OD/ 500 µg OD (N=20)	Roflumilast 500 µg EOD/ 500 µg OD (N=22)	Roflumilast 500 µg OD (N=38)	Total (N=80)
Age (years)	Mean (SD)	65.6 (8.82)	63.5 (5.93)	66.0 (7.78)	65.2 (7.58)
	Median (min, max)	65.5 (50, 77)	64.0 (54, 76)	63.5 (50, 82)	65.0 (50, 82)
Age group, n (%)	40-64 years	8 (40.0)	11 (50.0)	20 (52.6)	39 (48.8)
	65-84 years	12 (60.0)	11 (50.0)	18 (47.4)	41 (51.3)
	≥85 years	0	0	0	0
Sex, n (%)	Male	12 (60.0)	12 (54.5)	24 (63.2)	48 (60.0)
	Female	8 (40.0)	10 (45.5)	14 (36.8)	32 (40.0)
Ethnicity, n (%)	Hispanic or Latino	0	0	0	0
	Not Hispanic and Latino	20 (100.0)	22 (100.0)	37 (97.4)	79 (98.8)
	Missing	0	0	1 (2.6)	1 (1.3)
Race, n (%)	Asian	2 (10.0)	1 (4.5)	3 (7.9)	6 (7.5)
	Black or African American	0	0	1 (2.6)	1 (1.3)
	White	18 (90.0)	21 (95.5)	34 (89.5)	73 (91.3)
Height (cm)	Mean (SD)	166.5 (7.42)	167.0 (8.85)	166.7 (8.79)	166.8 (8.39)
	Median (min, max)	167.5 (148, 180)	168.0 (150, 185)	167.5 (149, 185)	168.0 (148, 185)
Weight (kg)	Mean (SD)	76.74 (24.321)	80.08 (21.280)	74.45 (15.423)	76.57 (19.485)
	Median (min, max)	83.50 (38.0, 129.0)	74.85 (46.6, 134.0)	74.30 (38.9, 102.0)	75.85 (38.0, 134.0)
BMI (kg/m^2)	Mean (SD)	27.41 (7.540)	28.64 (7.037)	26.72 (5.145)	27.42 (6.315)
	Median (min, max)	26.70 (13.6, 44.6)	27.45 (17.5, 44.3)	26.60 (15.8, 39.3)	27.05 (13.6, 44.6)

Source: Table 15.1.8.2A.
Baseline is the assessment taken on the reference start date (Randomization Visit V1 for the Main Period and final visit of Main Period V_{end}/V_{0DT} for the Down-Titration Period) or the last assessment taken prior to the start of study drug intake in the study period.

As shown in Table 14, all subjects had a history of COPD exacerbation, although no subject had experienced >2 episodes within the 1 year prior to Screening. In total, 5.0%, 9.1%, and 13.2% of subjects in the roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively, had previously received roflumilast treatment, though none of these had stopped due to intolerability. There was an imbalance between treatment groups in baseline %FEV1 reversibility, probably due to the small sample size (N=80).

Table 12. Other Baseline Characteristics (SAS, Down-titration Period)

		Roflumilast 250 µg OD/ 500 µg OD (N=20)	Roflumilast 500 µg EOD/ 500 µg OD (N=22)	Roflumilast 500 µg OD (N=38)	Total (N=80)
Smoking classification, n (%)	Never smoked	0	0	0	0
	Current smoker	9 (45.0)	14 (63.6)	18 (47.4)	41 (51.3)
	Ex smoker	11 (55.0)	8 (36.4)	20 (52.6)	39 (48.8)
Cigarette pack years (amount) (a)	Mean (SD)	44.4 (24.44)	35.9 (10.32)	36.4 (12.91)	38.3 (16.20)
	Median (min, max)	40.0 (18, 113)	35.0 (20, 57)	40.0 (13, 80)	40.0 (13, 113)
Interpretation of chest x-ray, n (%)	Within normal limits	7 (35.0)	7 (31.8)	16 (42.1)	30 (35.7)
	Abnormal, not clinically significant	13 (65.0)	13 (59.1)	19 (50.0)	45 (56.3)
	Abnormal, clinically significant	0	1 (4.5)	1 (2.6)	2 (2.5)
	Not done	0	1 (4.5)	2 (5.3)	3 (3.8)
COPD exacerbation history, n (%)	Yes	20 (100.0)	22 (100.0)	38 (100.0)	80 (100.0)
	No	0	0	0	0
>2 exacerbation episodes, n (%)	Yes	0	0	0	0
	No	20 (100.0)	22 (100.0)	38 (100.0)	80 (100.0)
Previous roflumilast treatment, n (%)	Yes	1 (5.0)	2 (9.1)	5 (13.2)	8 (10.0)
	No	19 (95.0)	20 (90.9)	33 (86.8)	72 (90.0)
Stopped due to intolerability, n (%)	Yes	0	0	0	0
	No	20 (100.0)	22 (100.0)	38 (100.0)	80 (100.0)
Prebronchodilator FEV_1, (L)	Mean (SD)	0.886 (0.2675)	1.019 (0.2787)	0.930 (0.3236)	0.944 (0.2990)
	Median (min, max)	0.810 (0.46, 1.36)	1.015 (0.58, 1.46)	0.890 (0.39, 1.72)	0.900 (0.39, 1.72)
Predicted FEV_1 (%)(b)	Mean (SD)	33.51 (8.974)	37.07 (7.690)	34.71 (10.977)	35.06 (9.660)
	Median (min, max)	30.90 (13.9, 49.0)	37.70 (24.0, 50.0)	33.50 (3.3, 59.0)	33.60 (3.3, 59.0)
Prebronchodilator FVC (L)	Mean (SD)	1.860 (0.5609)	2.206 (0.6266)	2.078 (0.5652)	2.059 (0.5881)
	Median (min, max)	1.700 (1.08, 3.01)	2.090 (1.43, 3.56)	1.995 (0.96, 3.19)	1.990 (0.96, 3.56)
Postbronchodilator FEV_1/FVC ratio (derived)	Mean (SD)	0.470 (0.1019)	0.481 (0.1256)	0.471 (0.1287)	0.473 (0.1202)
	Median (min, max)	0.479 (0.27, 0.67)	0.458 (0.28, 0.67)	0.479 (0.28, 0.69)	0.477 (0.27, 0.69)
% FEV_1 reversibility	Mean (SD)	5.113 (11.8264)	3.470 (16.0616)	5.486 (9.8107)	4.838 (12.1670)
	Median (min, max)	4.135 (-25.20, 26.60)	0.380 (-24.14, 37.23)	5.100 (-24.14, 31.58)	4.220 (-25.20, 37.23)

Source: Table 15.1.8.2A.
(a) Number of pack-years = (number of cigarettes smoked per day/20) × number of years smoked.
(b) According to the study database, 1 subject reported a predicted FEV_1 of 3.3% which appears to have been miscalculated and incorrectly entered by the study site. This data point should read 33%.

- **Numbers analysed**

The number of subjects in each analysis set is shown in Table below.

Table 13. Number of Subjects

	Roflumilast 250 µg OD/ 500 µg OD n (%)	Roflumilast 500 µg EOD/ 500 µg OD n (%)	Roflumilast 500 µg OD n (%)	Total n (%)
FAS	441	439	443	1323
SAS for Main Period (a)	441 (100.0)	437 (99.5)	443 (100.0)	1321 (99.8)
SAS for Down-Titration Period (b)(c)	27 (6.1)	39 (8.9)	38 (8.6)	104 (7.9)
VCS (a)	386 (87.5)	383 (87.2)	387 (87.4)	1156 (87.4)
PK dataset (d)	409	408	392	1238

Source: Table 15.1.7 and Appendix 16.1.10.3 Table 2.
Note: Definitions of analysis sets are provided in Section 9.7.1.1.
(a) Percentages are based on FAS.
(b) Percentages are based on SAS for the Main Period.
(c) 80 subjects were included in the SAS for the Down-Titration Period for subjects who entered the period after not tolerating at least 1 dose of roflumilast (comprising of 20, 22 and 38 subjects from the 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively).
(d) There were 29 subjects who discontinued the Main Period before first visit for PK blood draws, but entered into the Down-Titration Phase.

Protocol Deviations

The number of subjects with ≥1 protocol deviation was broadly similar across treatment groups, and did not have any clinically significant impact on the interpretation of the study data or subject safety. In all treatment groups, the most common protocol deviation was "selection criteria not met".

Table 14. Significant Protocol Deviations (FAS)

	Roflumilast 250 µg OD/ 500 µg OD (N=441)	Roflumilast 500 µg EOD/ 500 µg OD (N=439)	Roflumilast 500 µg OD (N=443)	Total (N=1323)
	Number of Subjects (%)			
Subjects with at least 1 protocol deviation	55 (12.5)	56 (12.8)	56 (12.6)	167 (12.6)
Excluded concomitant medication	3 (0.7)	5 (1.1)	4 (0.9)	12 (0.9)
Procedure not performed as per protocol	18 (4.1)	13 (3.0)	7 (1.6)	38 (2.9)
Selection criteria not met	22 (5.0)	27 (6.2)	28 (6.3)	77 (5.8)
Subject not withdrawn as per protocol	0	1 (0.2)	0	1 (0.1)
Treatment deviation	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Overall Main Period compliance is <75% or >125%	15 (3.4)	14 (3.2)	23 (5.2)	52 (3.9)
Overall Down-Titration Period compliance is <75% or >125%	0	2 (0.5)	1 (0.2)	3 (0.2)

Source: Table 15.1.6.
Subjects may have more than 1 protocol deviation, but are counted only once per category and in the total.

Measurements of Treatment Compliance

Compliance to study medication was similarly high across treatment groups during the Main Period and Down-Titration Period. During the Main Period, at least 95% of subjects in all treatment groups having compliance between ≥75% and ≤125% of study medication: mean (SD) treatment compliance was 104.42% (91.623%), 100.92% (14.138%), and 102.36% (20.549%) in roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively. During the Down-Titration Period, mean (SD) treatment compliance was 99.21% (4.177%), 107.75% (26.381%), and 102.91% (33.432%) in roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD

treatment groups, respectively, with at least 90.9% of subjects in all treatment groups taking between ≥75% and ≤125% of study medication.

A significant protocol deviation of treatment compliance <75% or >125% was reported in 52 of 1323 subjects (3.9%) during the Main Period and in 3 of 1323 (0.2%) during the Down-Titration Period. Treatment noncompliance led to discontinuation in 2 subjects (both in the 250 µg OD/500 µg OD treatment group).

- **Outcomes and estimation**

The primary endpoint of this study was the percentage of subjects prematurely discontinuing study treatment due to any reason (during Main Period, ie, Visit V1 to Vend). Although this is a safety endpoint, it is described first in this assessment report to follow the same hierarchy as in the clinical study.

Efficacy was assessed as a 'key secondary endpoint', and 'other secondary endpoint' in this study. The key secondary efficacy endpoints were assessed using hierarchical statistical testing procedures. However, as a result of the failure to reach statistical significance for the second hierarchical test, all efficacy endpoints tested using this procedure were performed in an exploratory manner.

Primary endpoint

Primary Analysis of the Primary Endpoint: Percentage of Subjects Prematurely Discontinuing Study Treatment Due to Any Reason During the Main Period

A logistic regression model was used with terms for study treatment, country and baseline FEV1 as explanatory variables. Treatment comparisons were made at a 5% significance level, 2-sided, following hierarchical testing procedure. As a supportive analysis for the primary results, results based on Cox proportional hazards model were also presented.

The result of the statistical analyses for the primary endpoint is shown in Table 17. Compared with roflumilast 500 µg OD [H01] the odds of discontinuing the Main Period were statistically significantly lower in the roflumilast 250 µg OD/500 µg OD treatment group at the 5% significance level (24.6% vs. 18.4% of subjects, OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017, primary endpoint). At the 5% significance level, there was no statistically significant difference between roflumilast 500 µg OD and roflumilast 500 µg EOD/500 µg OD treatment groups [H02] (OR 0.76, 95% CI: 0.55, 1.07; p-value 0.114). Supportive analysis Cox proportional hazards model found a similar result for roflumilast 250 µg OD/500 µg OD (HR=0.68, 95 % CI: 0.51, 0.92) and roflumilast 500 µg EOD/500 µg OD (HR=0.77, 95% CI: 0.58, 1.02) versus roflumilast 500 µg OD.

Table 15. Statistical Analysis and Hierarchical Testing of the Primary Safety Endpoint: Percentage of Subjects Prematurely Discontinuing Study Treatment Due to Any Reason During the Main Period (SAS, Main Period)

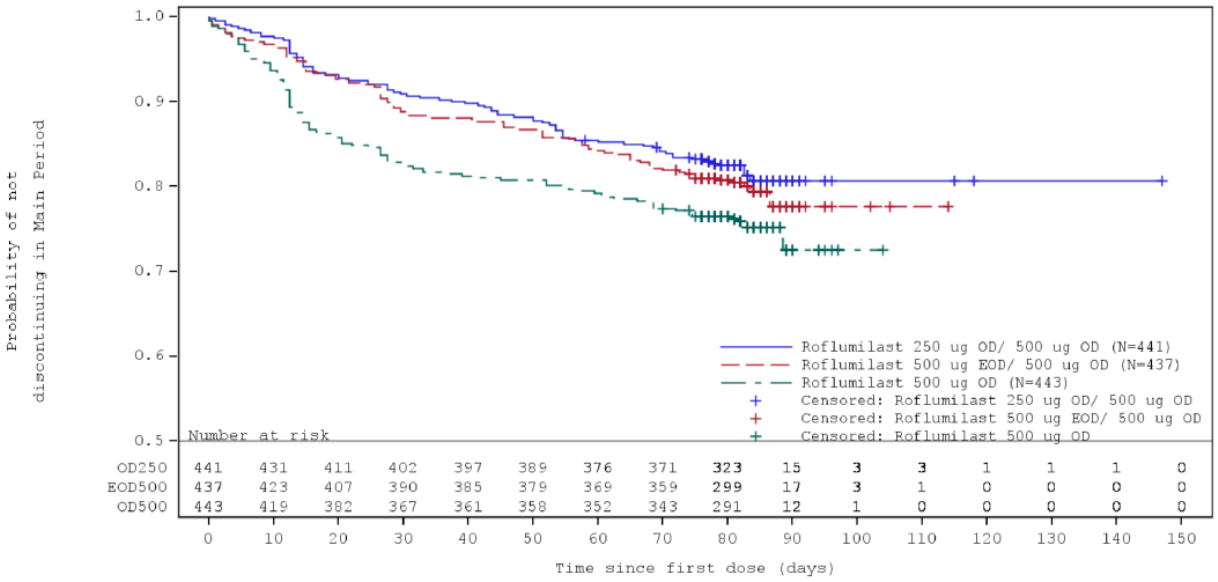
	Roflumilast 250 µg OD/500 µg OD (N=441)	Roflumilast 500 µg EOD/500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)
Subjects prematurely discontinuing Main Period, n (%)	81 (18.4)	88 (20.1)	109 (24.6)
p-value for comparison against Reference 500 µg OD (a)	0.017 (H01)	0.114 (H02)	
OR (95% CI) for comparison against Reference (a)	0.66 (0.47, 0.93)	0.76 (0.55, 1.07)	
HR (95% CI) for comparison against Reference (b)	0.68 (0.51, 0.92)	0.77 (0.58, 1.02)	

Source: Table 15.2.1.1.
H01, H02 = Order of hierarchical testing.
(a) Logistic regression model with study treatment, country and baseline FEV_1 as explanatory variables.
(b) Cox proportional hazards model with study treatment and country as class effects, and baseline FEV_1 as a continuous variable.

A summary of the time to discontinuation during the Main Period is displayed in Figure 7.

Compared with either up-titration treatment group, the frequency of discontinuation in the 500 µg treatment group was greater and started to occur earlier. The Kaplan-Meier plot is based on the Main Period data only and, as indicated by the plot, some subjects had 150 days for their Main Period and were censored at that time point.

Figure 7. Kaplan-Meier Plot for Prematurely Discontinuing Study Treatment Due to Any Reason During the Main Period (SAS, Main Period)



Source: Figure 15.2.1.1.1.
Time to discontinuation is calculated from date of first dose in the Main Period until the date of last dose in the Main Period. Subjects who did not discontinue from the Main Period will be censored at the time of their last Main Period dose date. The plot is based on the Main Period data only and, as indicated by the plot, some subjects had 150 days for their Main Period and were censored at that time point.
EOD500=Roflumilast 500 µg EOD/500 µg OD, OD250=Roflumilast 250 µg OD/500 µg OD, OD500=Roflumilast 500 µg OD.

Sensitivity analyses of the primary endpoint:

The results based on the logistic regression model with region as a covariate, instead of country, were consistent with the primary analysis results; compared with roflumilast 500 µg OD, the odds of discontinuing from the Main Period were lower in the roflumilast 250 µg OD/500 µg OD treatment group (OR=0.70, 95% CI: 0.50, 0.97; p-value 0.032).

The results of the sensitivity analyses by excluding the South African site (Site 6002) for the primary endpoint supported the results of the primary analysis. Compared with roflumilast 500 µg OD, the odds of discontinuing from the Main Period were lower in the roflumilast 250 µg OD/500 µg OD treatment group (OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017).
This is not unexpected, as this site only included 5 patients and only 2 of them had a primary event (one in group 2 and one in group 3)

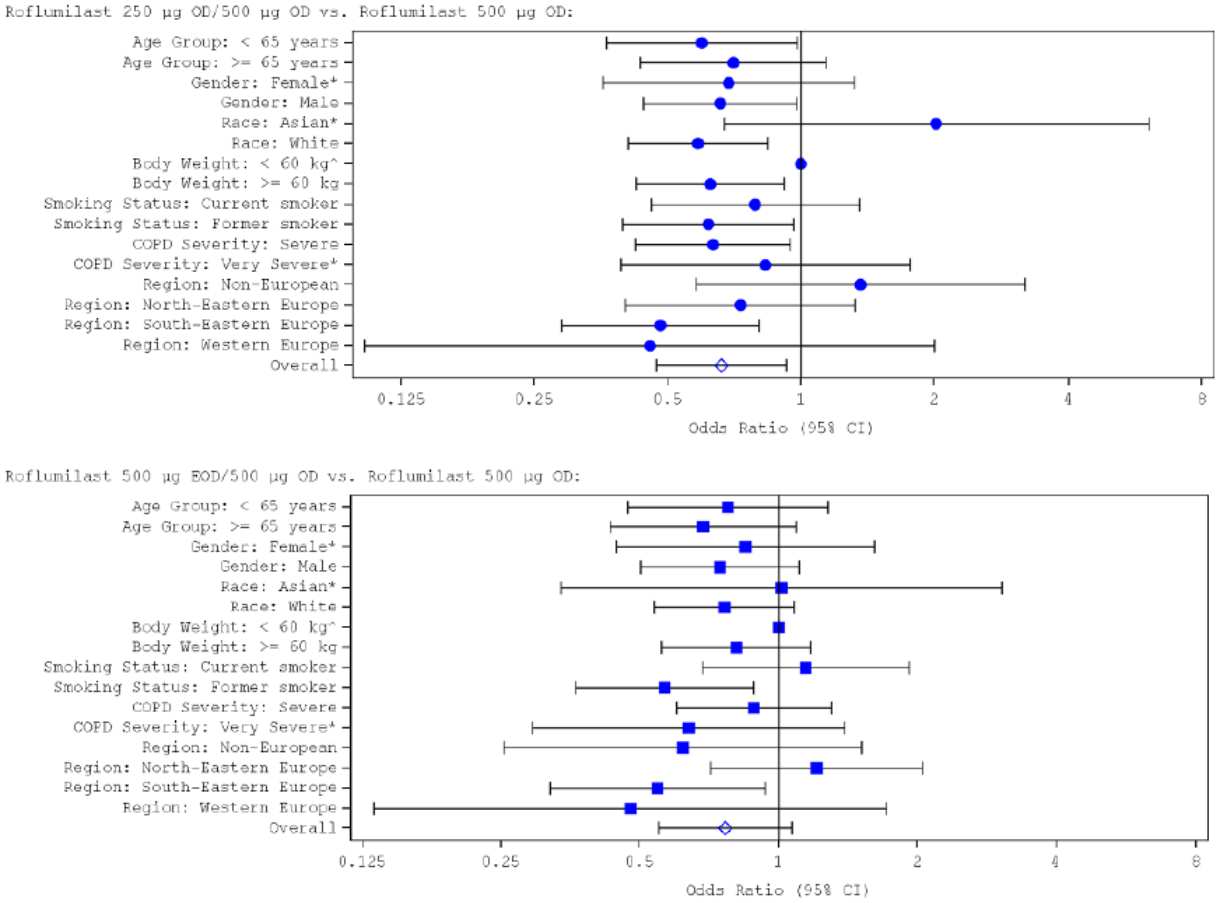
Subgroup Analyses of the Primary Endpoint
Subgroup analysis of the primary endpoint is displayed in Figure 8. In the majority, analyses of subgroups tended to support the primary finding, such that the odds of premature discontinuation from the Main Period were lower in the up-titration groups compared with the reference treatment.

The subgroups that trended towards favoring reference treatment (roflumilast 500 µg OD) were non-European region and Asian race (versus roflumilast 250 µg OD/500 µg OD), and north-Eastern Europe

region and current smoking status (versus roflumilast 500 µg EOD/500 µg OD). Logistic regression could not be performed for the subgroup body weight <60 kg as complete convergence was not obtained, or for Black and Other race subgroups due to the low number of subjects in these subgroups.

CIs were wide for some subgroups, predominantly due to the small number of subjects in each of the subgroups. In particular, Asian race (32, 30, 32 subjects in the roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively), and Western Europe (20, 33, and 19 subjects, respectively).

Figure 8. Forest Plot of ORs (95% CI) for Subjects Prematurely Discontinuing Study Treatment Due to Any Reason in the Main Period, by Subgroup and Overall (SAS, Main Period)



Source: Figure 15.2.2.1.1.
An OR of <1 favors the up-titration treatment 250 µg OD/500 µg OD or 500 µg EOD/500 µg OD. An OR >1 favors 500 µg OD.
A logistic regression model with study treatment, country and baseline FEV_1 as explanatory variables has been used.
The 'Black' and 'Other' race subgroup categories were not considered for the logistic regression because of their significantly low counts.
*=Used Firth Logistic Regression, ^=Results not used as complete convergence not obtained.

Key Secondary Safety Endpoint: TEAEs of Interest during the Main Period

The results of the statistical analysis of TEAEs of Interest (diarrhea, nausea, headache, reduced appetite, insomnia, or abdominal pain) during the Main Period are considered exploratory based on insufficient evidence to reject the null hypothesis for the primary endpoint at the 5% significance level [H02] in the framework of hierarchical testing (i.e.: no statistically significant differences were found for the comparison between groups 2 and 3 for the primary endpoint of premature discontinuations).

Compared with roflumilast 500 µg OD, the odds of experiencing a 'TEAE of interest' was significantly lower at the 5% significance level in the roflumilast 250 µg OD/500 µg OD treatment group (54.2% versus 45.4% of subjects, OR=0.63, 95% CI: 0.47, 0.83; p-value = 0.001). This difference was not observed between roflumilast 500 µg EOD/500 µg OD (48.3% of subjects) and the roflumilast 500 µg OD (54.2%) treatment groups in the analysis of AEs of interest.

The more frequent TEAEs of interest were diarrhea, decreased appetite, nausea and headache, all of them occurring more frequently and starting soon in the control group than in the roflumilast 250 µg OD/500 µg OD experimental group (Table 18).

Table 16. Statistical Analysis of the Key Secondary Endpoint: TEAEs of Interest to Evaluate Tolerability During the Main Period (SAS, Main Period)

	Roflumilast 250 µg OD/ 500 µg OD (N=441)	Roflumilast 500 µg EOD/ 500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)	Total (N=1321)
Subjects with TEAEs of interest to evaluate tolerability	200 (45.4)	211 (48.3)	240 (54.2)	651 (49.3)
Diarrhea				
Subjects with ≥1 TEAE, n (%)	108 (24.5)	114 (26.1)	134 (30.2)	356 (26.9)
Subjects with severe TEAE, n (%)	1 (0.2)	6 (1.4)	5 (1.1)	12 (0.9)
Median time to onset of first TEAE, days (min, max)	8.0 (0, 81)	10.0 (0, 90)	5.5 (0, 73)	8.0 (0, 90)
Median duration of TEAE, days (min, max)	3.0 (1, 88)	3.0 (1, 90)	3.0 (1, 95)	3.0 (1, 95)
Nausea				
Subjects with ≥1 TEAE, n (%)	87 (19.7)	92 (21.1)	110 (24.8)	289 (21.9)
Subjects with severe TEAE, n (%)	1 (0.2)	2 (0.5)	3 (0.7)	6 (0.5)
Median time to onset of first TEAE, days (min, max)	10.0 (0, 84)	14.0 (0, 74)	6.5 (0, 66)	9.0 (0, 84)
Median duration of TEAE, days (min, max)	2.0 (1, 84)	2.0 (1, 90)	3.5 (1, 90)	3.0 (1, 90)
Headache				
Subjects with ≥1 TEAE, n (%)	107 (24.3)	115 (26.3)	115 (26.0)	337 (25.5)
Subjects with severe TEAE, n (%)	3 (0.7)	0	3 (0.7)	6 (0.5)
Median time to onset of first TEAE, days (min, max)	9.0 (0, 84)	10.0 (0, 84)	5.0 (0, 79)	9.0 (0, 84)
Median duration of TEAE, days (min, max)	2.0 (1, 97)	2.0 (1, 90)	3.0 (1, 93)	2.0 (1, 97)
Decreased appetite				
Subjects with ≥1 TEAE, n (%)	100 (22.7)	105 (24.0)	129 (29.1)	334 (25.3)
Subjects with severe TEAE, n (%)	2 (0.5)	1 (0.2)	5 (1.1)	8 (0.6)
Median time to onset of first TEAE, days (min, max)	10.0 (0, 84)	15.0 (0, 76)	7.0 (0, 65)	9.0 (0, 84)
Median duration of TEAE, days (min, max)	4.0 (1, 98)	3.5 (1, 124)	4.0 (1, 117)	4.0 (1, 124)
Insomnia				
Subjects with ≥1 TEAE, n (%)	98 (22.2)	106 (24.3)	110 (24.8)	314 (23.8)
Subjects with severe TEAE, n (%)	3 (0.7)	4 (0.9)	2 (0.5)	9 (0.7)
Median time to onset of first TEAE, days (min, max)	10.0 (0, 73)	7.0 (0, 74)	7.0 (0, 73)	8.0 (0, 74)
Median duration of TEAE, days (min, max)	2.0 (1, 137)	3.0 (1, 80)	4.0 (1, 117)	3.0 (1, 137)
Abdominal pain				
Subjects with ≥1 TEAE, n (%)	85 (19.3)	72 (16.5)	89 (20.1)	246 (18.6)
Subjects with severe TEAE, n (%)	2 (0.5)	7 (1.6)	4 (0.9)	13 (1.0)
Median time to onset of first TEAE, days (min, max)	10.0 (0, 84)	16.0 (0, 81)	7.0 (0, 76)	10.0 (0, 84)
Median duration of TEAE, days (min, max)	3.0 (1, 96)	3.0 (1, 80)	3.0 (1, 87)	3.0 (1, 96)

Source: Table 15.3.1.16.1.
A TEAE in the Main Period is defined as any AE, regardless of relationship to study medication that occurs after the first dose of study medication in the Main Period and within 30 days after the last study medication in the Main Period or before the first dose of study medication in the Down-Titration Period.
The PTs included under each AE of interest is listed in Section 16.2 of the SAP (Appendix 16.1.9).

Secondary endpoints

Change From Baseline in Prebronchodilator FEV1

Main period:
Improvements in prebronchodilator FEV1 from V1 to each Main Period postrandomization visit were clinically relevant (approximately 100 mL) and showed minimal differences across the 3 treatment groups (LS means of 0.09 L, 0.13 L, and 0.11 L for roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and roflumilast 500 µg OD treatment groups, respectively; Table 19 FAS). Similar results were shown when subjects for both Main Period and Down-Titration Period were evaluated (LS means of 0.07 L, 0.14 L, and 0.10 L for roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and roflumilast 500 µg OD treatment groups, respectively; Table 19 FAS).

Table 17. Statistical Analysis of the change in FEV1 during the study.

		Roflumilast 250 µg OD/500 µg OD	Roflumilast 500 µg EOD/500 µg OD	Roflumilast 500 µg OD
Change in Prebronchodilator FEV_1 (L) From Baseline (V1) to Each Main Period Postrandomization Visit, FAS				
Subjects in the FAS, N		441	439	443
LS means (a)		0.09	0.13	0.11
Treatment difference vs reference arm (a)	LS mean (SE)	-0.03 (0.017)	0.02 (0.017)	
	95% CI	(-0.06, 0.00)	(-0.01, 0.05)	
	p-value	0.093	0.252	
Change in Prebronchodilator FEV_1 (L) From Baseline (V1) to Each Main Period Postrandomization Visit, VCS				
Subjects in the VCS, N		386	383	387
LS means (b)		0.08	0.13	0.11
Treatment difference vs reference arm (a)	LS mean (SE)	-0.03 (0.018)	0.02 (0.017)	
	95% CI	(-0.06, 0.00)	(-0.02, 0.05)	
	p-value	0.090	0.306	
Change in Prebronchodilator FEV_1 (L) From Baseline (V1) to Each Postrandomization Visit, FAS				
Subjects in the FAS, N		441	439	443
LS means (a)		0.07	0.14	0.10
Treatment difference vs reference arm (a)	LS mean (SE)	-0.03 (0.021)	0.04 (0.021)	
	95% CI	(-0.07, 0.01)	(0.00, 0.08)	
	p-value	0.133	0.068	
Change in Prebronchodilator FEV_1 (L) From Baseline (V1) to Each Postrandomization Visit, VCS				
Subjects in the VCS, N		386	383	387
LS means (a)		0.06	0.14	0.10
Treatment difference vs reference arm (a)	LS mean (SE)	-0.04 (0.022)	0.04 (0.021)	
	95% CI	(-0.08, 0.01)	(0.00, 0.08)	
	p-value	0.092	0.074	

Source: Table 15.2.1.1A.
SAS and FAS Down-Titration Period analyses are based on a subgroup of 80 subjects (250 µg OD/500 µg OD [n=20], 500 µg EOD/500 µg OD [n= 22], 500 µg OD [n= 38]), who received 500 µg OD and discontinued during the Main Period. VCS Down-Titration Period analyses are based on a subgroup of 69 subjects (250 µg OD/500 µg OD [n=16], 500 µg EOD/500 µg OD [n= 18], 500 µg OD [n=35]), who received 500 µg OD and discontinued during the Main Period.
(a) ANCOVA model (Verbeke and Molenberghs) including study treatment, baseline value, time and treatment-by-time interaction as fixed factors and covariates.

Down-Titration Period: the analysis of main interest was for those patients who did not tolerate roflumilast 500 µg OD during the Main Period and subsequently entered the down-Titration period (n=80), in order to ascertain whether a the 250 microgram dose, administered to all of them, could be

effective (i.e.: whether it could produce improvements in pre-BD FEV1 from the start of down-titration to end of down-titration). Eighty subjects (of 1321 subjects, 6.0%) who did not tolerate roflumilast 500 µg OD in the Main Period were treated with roflumilast 250 µg OD for 8 weeks (n=20 for the roflumilast 250 µg OD/500 µg OD group, n=22 for roflumilast 500 µg EOD/500 µg OD group, and n=38 for the roflumilast 500 µg OD group at Baseline, V0DT). The analyses indicated no effect of the 250 microgram low-dose roflumilast in pre-BD FEV1 (Table 20).

Table 18. Change in pre-BD FEV1 (L) from baseline down-titration to last scheduled down-titration period visit (FAS and VCS).

		Roflumilast 250 µg OD/500 µg OD	Roflumilast 500 µg EOD/500 µg OD	Roflumilast 500 µg OD
Change in Prebronchodilator FEV_1 (L) From Baseline ($V0_{DT}$) to Last Scheduled Down-Titration Period Visit ($Vend_{DT}$), FAS				
Subjects in the FAS, N		441	439	443
Subjects in the FAS analyzed, n		20	22	38
LS means (a)		0.01	0.13	0.00
Treatment difference vs reference arm (a)	LS mean (SE)	0.02 (0.095)	0.13 (0.093)	
	95% CI	(-0.17, 0.20)	(-0.05, 0.32)	
	p-value	0.871	0.162	
Change in Prebronchodilator FEV_1 (L) From Baseline ($V0_{DT}$) to Last Scheduled Down-Titration Period Visit ($Vend_{DT}$), VCS				
Subjects in the VCS, N		386	383	387
Subjects in the VCS analyzed, n		16	18	35
LS means (a)		0.05	0.09	0.02
Treatment difference vs reference arm (a)	LS mean (SE)	0.03 (0.094)	0.07 (0.092)	
	95% CI	(-0.16, 0.22)	(-0.11, 0.26)	
	p-value	0.747	0.428	

Source: Table 15.2.1.1A.
SAS and FAS Down-Titration Period analyses are based on a subgroup of 80 subjects (250 µg OD/500 µg OD [n=20], 500 µg EOD/500 µg OD [n= 22], 500 µg OD [n= 38]), who received 500 µg OD and discontinued during the Main Period. VCS Down-Titration Period analyses are based on a subgroup of 69 subjects (250 µg OD/500 µg OD [n=16], 500 µg EOD/500 µg OD [n= 18], 500 µg OD [n=35]), who received 500 µg OD and discontinued during the Main Period.
(a) ANCOVA model (Ebbutt and Frith [10]) using LOCF with study treatment as fixed factor and baseline value as covariate.

The lack of effect on pre-BD FEV1 of a lower roflumilast maintenance dose was consistent in the per-protocol analysis based on the VCS and in several sensitivity analyses.

Other efficacy endpoints:

FVC: In all treatment groups, mean FVC increased from V1 to Vend. Improvements in mean FVC from V1 to each Main Period post-randomization visit showed minimal differences across the 3 treatment groups (LS Means of 0.09L, 0.15L, and 0.15L for roflumilast 250 µg OD/ 500 µg OD, 500 µg EOD/500 µg OD, and roflumilast 500 µg OD treatment groups, respectively). Similar results were shown when subjects for both Main Period and Down-Titration Period were evaluated (LS means of 0.09 L, 0.17 L, and 0.14 L for roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and roflumilast 500 µg OD treatment groups, respectively.

Patients' satisfaction with treatment: Subject treatment satisfaction was assessed by asking subjects to assess their satisfaction with their COPD therapy at each visit on a 7-point scale ranging from 0 indicating very satisfied to 6 indicating very dissatisfied. Therefore, a within group negative change from baseline indicates increased satisfaction with study treatment compared with previous treatment at baseline, while a between group negative difference indicates an increased change in satisfaction with experimental treatment versus baseline compared with the corresponding change in the control treatment.

At baseline, patients had a mean 1.8 score, which indicates that the majority were between 1 (Satisfied) and 2 (Somewhat satisfied), but closer to 2.

Analyses without adjustment for multiplicity found a statistically significant difference at the 5% significance level for the change in subject-assessed treatment satisfaction scores from V1 to each post-randomization visit during the Main Period favoring roflumilast 250 µg OD/500 µg OD versus roflumilast 500 µg (LS mean for treatment difference -0.20, 95% CI: -0.33, -0.06; p-value 0.004; see Table below). Therefore, patients on the control group still remained closer to score 2 (somewhat satisfied) while patients on the group 1 became closer to score 1 (satisfied).

Table 19. Statistical Analysis of the Change in Subject-Assessed Treatment Satisfaction

		Roflumilast 250 µg OD/500 µg OD	Roflumilast 500 µg EOD/500 µg OD	Roflumilast 500 µg OD
Change in Subject Treatment Satisfaction From Baseline (V1) to Each Main Period Postrandomization Visit, FAS				
Subjects in the FAS, N		441	439	443
LS means (b)		-0.40	-0.30	-0.21
Treatment difference vs reference arm (b)	LS mean (SE)	-0.20 (0.067)	-0.09 (0.065)	
	95% CI	(-0.33, -0.06)	(-0.22, 0.03)	
	p-value	0.004	0.150	

Looking at the descriptive data at D84, there are numerically more patients in up-titration group1 that are satisfied (score 0-2) (89.1%) than in the control group (85.7%). On the contrary, there are more patients dissatisfied (score 4-6) in the control group (7.5%) than in up-titration group 1 (3.7%) (Table 15.2.4.3)

Table 20. Summary of Subject Treatment Satisfaction Assessment (FAS)

Visit/Response	Roflumilast 250 µg OD/ 500 µg OD (N=441)	Roflumilast 500 µg EOD/ 500 µg OD (N=439)	Roflumilast 500 µg OD (N=443)
Baseline (V1) (n[%])	441	438	443
0. Very satisfied	72 (16.3)	76 (17.4)	79 (17.8)
1. Satisfied	149 (33.8)	143 (32.6)	146 (33.0)
2. Somewhat satisfied	96 (21.8)	95 (21.7)	107 (24.2)
3. Neither satisfied nor dissatisfied	81 (18.4)	72 (16.4)	62 (14.0)
4. Somewhat dissatisfied	29 (6.6)	34 (7.8)	29 (6.5)
5. Dissatisfied	12 (2.7)	14 (3.2)	17 (3.8)
6. Very dissatisfied	2 (0.5)	4 (0.9)	3 (0.7)
Vend (Day 84) (n[%])	407	416	412
0. Very satisfied	114 (28.0)	109 (26.2)	98 (23.8)
1. Satisfied	167 (41.0)	155 (37.3)	167 (40.5)
2. Somewhat satisfied	82 (20.1)	93 (22.4)	89 (21.6)
3. Neither satisfied nor dissatisfied	29 (7.1)	38 (9.1)	27 (6.6)
4. Somewhat dissatisfied	7 (1.7)	11 (2.6)	10 (2.4)
5. Dissatisfied	6 (1.5)	9 (2.2)	19 (4.6)
6. Very dissatisfied	2 (0.5)	1 (0.2)	2 (0.5)

Source: Table 15.2.4.3 of the OPTIMIZE CSR

- **Ancillary analyses**

See previous section for sensitivity analyses and subgroup analyses of the main endpoint. No other relevant ancillary analyses are available.

- **Summary of main efficacy results**

The following table summarises the efficacy/safety results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21. Summary of efficacy for trial RO-2455-302-RD (OPTIMIZE)

Title: A Multicenter, Randomized, Double-Blind Phase 3 Study to Evaluate Tolerability and Pharmacokinetics of 500 µg Roflumilast Once Daily With an Up-Titration Regimen in COPD, Including an Open-Label Down-Titration Period Evaluating Tolerability and Pharmacokinetics of 250 µg Roflumilast Once Daily in Subjects Not Tolerating 500 µg Roflumilast Once-Daily			
Study identifier	Study No. RO-2455-302-RD (OPTIMIZE)		
Design	A Multicenter, Randomized, controlled, Double-Blind, Phase 3 Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		84 days (up-titration 28 days + maintenance 56 days) 21 days (prior to randomization) 8-week down-titration period
Hypothesis	Superiority (on discontinuation rates during the 12-week main period).		
Treatments groups	Group 1: 250 µg OD for 4 weeks followed by 500 µg OD for 8 weeks		N= 441
	Group 2: 500 µg every other day (EOD) followed by 500 µg OD for 8 weeks		N= 437
	Group 3: 500 µg OD during the entire 12-week main period		N= 443
Endpoints and definitions	Primary endpoint	Percentage of subjects prematurely discontinuing study treatment for any reason during the Main Period (from V1 to Vend) (from baseline to end of treatment, D84)	OR between treatment groups was analyzed using a logistic regression model, with study treatment, country and baseline FEV1 as explanatory variables. Hierarchical approach: group 1 vs. group 3 followed by Group 2 vs. group 3.
	Key secondary endpoint 1	Percentage of subjects with adverse events (AEs) of interest to evaluate tolerability during Main Period (V1 to Vend).	The percentage of subjects with AEs of interest (diarrhea, nausea, headache, decreased appetite, insomnia, and abdominal pain) was analyzed using a logistic regression analysis as part of the hierarchical approach as described for the primary safety endpoint.
	Key secondary endpoint 2	change in prebronchodilator FEV1 during the 8-week down-titration period (V0DT to VendDT)	Difference between treatment groups was assessed with an analysis of variance (ANCOVA) model using the last observation carried forward (LOCF) value
	Key secondary endpoint 3	Percentage of subjects prematurely discontinuing study treatment due to any reason during the 8-week down-titration period (V0DT to VendDT)	Descriptive, disaggregated by prior treatment during main period.
Database lock	N/A. Last patient's last visit/contact on 18 October 2015		
Results and Analysis			

Analysis description	Primary Analysis
Analysis population and time point description	Subjects prematurely discontinuing main period. Intent to treat (Full analysis set: FAS), from baseline to day 84

	Roflumilast 250 µg OD/500 µg OD (N=441)	Roflumilast 500 µg EOD/500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)
Subjects prematurely discontinuing Main Period, n (%)	81 (18.4)	88 (20.1)	109 (24.6)
p-value for comparison against Reference 500 µg OD (a)	0.017 (H01)	0.114 (H02)	
OR (95% CI) for comparison against Reference (a)	0.66 (0.47, 0.93)	0.76 (0.55, 1.07)	
HR (95% CI) for comparison against Reference (b)	0.68 (0.51, 0.92)	0.77 (0.58, 1.02)	

H01, H02 = Order of hierarchical testing.
(a) Logistic regression model with study treatment, country and baseline FEV_1 as explanatory variables.
(b) Cox proportional hazards model with study treatment and country as class effects, and baseline FEV_1 as a continuous variable.

Analysis description	Key secondary endpoint 1
Analysis population and time point description	Subjects with AEs of interest Intent to treat (Full analysis set: FAS), from baseline to day 84

	Roflumilast 250 µg OD/500 µg OD (N=441)	Roflumilast 500 µg EOD/500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)
Subjects with AEs of interest, n (%)	200 (45.4)	211 (48.3)	240 (54.2)
p-value for comparison against Reference 500 µg OD (a)	0.001	0.091	
OR (95% CI) for comparison against Reference (a)	0.63 (0.47, 0.83)	0.78 (0.59, 1.04)	

(a) Logistic regression model with study treatment, country and baseline FEV_1 as explanatory variables.

Analysis description	Key secondary endpoint 2
Analysis population and time point description	Change in pre-BD FEV1 during down-titration period. Intent to treat (Full analysis set: FAS), during the 8-week open-label down-titration period

		Roflumilast 250 µg OD/500 µg OD	Roflumilast 500 µg EOD/500 µg OD	Roflumilast 500 µg OD
Change in Prebronchodilator FEV_1 (L) From Baseline ($V0_{DT}$) to Last Scheduled Down-Titration Period Visit ($Vend_{DT}$), FAS				
Subjects in the FAS, N		441	439	443
Subjects in the FAS analyzed, n		20	22	38
LS means (a)		0.01	0.13	0.00
Treatment difference vs reference arm (a)	LS mean (SE)	0.02 (0.095)	0.13 (0.093)	
	95% CI	(-0.17, 0.20)	(-0.05, 0.32)	
	p-value	0.871	0.162	

Analysis description	Key secondary endpoint 3

Analysis population and time point description	Subjects prematurely discontinuing the 8-week open-label down-titration period, Intent to treat (Full analysis set: FAS) (all patients received roflumilast 250 microg during this period; disaggregated data are shown according to prior treatment during main phase)

Endpoint/Test	Roflumilast 250 µg OD/ 500 µg OD	Roflumilast 500 µg EOD/ 500 µg OD	Roflumilast 500 µg OD
No. of subjects in the SAS for Down-Titration Period, N	20	22	38
No. of subjects prematurely discontinuing Down-Titration Period, SAS	4 (20.0%)	4 (18.2%)	7 (18.4%)

Source: Table 15.2.1.1A of the OPTIMIZE CSR.

2.9.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This submission is based on data from a single study (Study RO 2455 302-RD [OPTIMIZE]) conducted to fulfil a Committee for Medicinal Products for Human Use (CHMP) postauthorisation measure (FUM004) to explore alternative doses of roflumilast to minimise the risk of drug interactions, poor tolerability, and the influence of factors such as gender, age, and smoking status on the bioavailability of the product in patients with chronic obstructive pulmonary disease (COPD).

OPTIMIZE was a multicenter, randomized, double-blind, 3-arm, parallel group, phase 3 study with an open-label Down-Titration Period for subjects who withdrew from the Main Period of the study. During the Main Period, subjects were randomized receive 1 of the 3 treatments consisting of 2 up-titration treatment groups: 250 µg OD or 500 µg EOD for the first 4 weeks followed by 500 µg OD for 8 weeks, and the currently approved roflumilast regimen of 500 µg OD administered for 12 weeks. During the Main Period, the first 4 weeks (up-titration) was double-blinded, and the following 8 weeks (maintenance period) was single-blinded. All subjects discontinuing from the Main Period were permitted to enter an 8-week open-label Down-Titration Period where they received roflumilast 250 µg OD.

Spirometry and subject-assessed treatment satisfaction for efficacy assessments were performed at Screening (V0, Days -21 to -7), Randomization (V1, Day 1), and at Weeks 2, 4, 8, and 12 (Visits V2, V3, V4, and Vend) of the Main Period, and at Baseline (V0DT=Vend of Main Period) and at Weeks 2, 4 and 8 (Visits V1DT, V2DT and VendDT) of the Down-Titration Period. Six milliliter blood samples for PK analysis were drawn at Visits V2, V4, Vend/V0DT, V1DT, V2DT and VendDT.

Inclusion and exclusion criteria in OPTIMIZE study are in line with the indication (severe COPD and a history of exacerbations) and contraindications/non-recommendation of use detailed in the Daxas SmPC. Study medications included roflumilast 250 µg tablet, 500 µg tablet and placebo (roflumilast 0 µg tablet). Placebo was used only during the 4-week up-titration period (the only phase that was double-blinded) (the 8 week continuation after initial 4-week up-titration was single blinded, as investigators knew that all patients were receiving the roflumilast 500 µg tablet, although they were unaware of the type of initial 4-week treatment that patients had received).

Primary Endpoint was the percentage of subjects prematurely discontinuing study treatment due to any reason during Main Period. Key Secondary Endpoints included the percentage of subjects with adverse events (AEs) of interest to evaluate tolerability during Main Period, the change in prebronchodilator FEV1 during Down-Titration Period (V0DT to VendDT) and the percentage of subjects prematurely discontinuing study treatment due to any reason during Down-Titration Period (V0DT to VendDT). Other secondary endpoints were: change in prebronchodilator FEV1 during Main Period of the study, change in prebronchodilator FVC during Main Period and also including Down-Titration Period; change in subject-assessed treatment satisfaction scores during Main Period of the study and also including Down-Titration Period.

Randomisation and blinding/masking methods were appropriate.

Subjects were randomized into the double-blind main treatment period at a total of 161 sites in 15 countries: Bulgaria (11 sites), Germany (9), Greece (5), Hungary (21), Republic of Korea (9), Philippines (4), Poland (15), Romania (19), Russia (17), Slovakia (12), South Africa (14), Spain (2), Thailand (3), Ukraine (14), and United Kingdom (6). During the study, persistent noncompliance was noted at site 6002, which was based in South Africa. At the time of the investigation, the site had screened 5 subjects; 1 subject was a screen failure, and 4 subjects had completed the study. The site was closed from further participation in the study protocol. A request for triggered GCP inspection was proposed by the Rapporteur for the following clinical study: RO-2455-302-RD (OPTIMIZE) and was discussed at CHMP. It should be ruled out that the non compliance on GCP is an isolated finding in center 6002 in South-Africa or if it is systemic to the whole trial. The CHMP did not find sufficient reasons to trigger an inspection for this study.

Efficacy data and additional analyses

A total of 1321 randomized patients received at least one dose of study drug (441 in 250/500 microg group 1; 437 in 500 microg EOD group 2; 443 in the 500 microg OD control group). Overall, demographic characteristics were similar across the 3 treatment groups. The majority of subjects in each treatment group were White (405 subjects [91.8%] in the roflumilast 250 µg OD/500 µg OD group, 399 subjects [91.3%] in the roflumilast 500 µg EOD/500 µg OD group and 405 subjects [91.4%] in the roflumilast 500 µg OD group). The mean (SD) age of subjects was 64.2 (7.81), 65.0 (8.21), and 64.6 (8.36) years in the roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD groups, respectively. The 250 µg OD/ 500 µg OD dose group was comprised of more subjects aged 40 to 64 years (54.9% of subjects) than the other 2 dose groups (46.2% and 50.6% for 500 µg EOD/ 500 µg OD and 500 µg OD, respectively). The majority of subjects in each treatment group were male (72.6% in roflumilast 250 µg OD/500 µg OD group,74.4% in roflumilast 500 µg EOD/500 µg OD group, and 76.3% in roflumilast 500 µg OD group).

Nearly all subjects in the Main Period (1320 subjects, 99.9%) were receiving an ongoing concomitant medication at Baseline. Overall, the type and frequency of concomitant medication was broadly similar across treatment groups. About 67% of patients was receiving a dual ICS+LABA combination during the main period, and 63% of patients were receiving a LAMA. However, no data about the aggregated number of patients receiving the ICS+LAMA combination or ICS+LABA+LAMA combination were reported. Tolerability may differ (be worse) at increasing number of concomitant medications. In fact, concomitant LAMA use was a covariate in the PK/PD model of adverse events.

During the procedure, the applicant was requested to analyse the main endpoint and key secondary safety endpoint in the target population included in the product labelling (i.e.: severe COPD patients treated with ICS plus LABA and/or LAMA), separately for dual combination (ICS+LABA or LAMA) and triple combination (ICS+LABA+LAMA) and to discuss the findings. The results were hampered by its post-hoc nature and lack of statistical power due to small sample sizes. Anyway, the analysis provided justify for all of the subgroups studied to take advantage of the 250 µg OD/500 µg OD up-titration regimen, regardless of concomitant LAMA or multiple concomitant medication use.

Percentage of Subjects Prematurely Discontinuing Study Treatment Due to Any Reason During the Main Period (main endpoint): Compared with roflumilast 500 µg OD [H01] the odds of discontinuing the Main Period using a logistic regression model were statistically significantly lower in the roflumilast 250 µg OD/500 µg OD treatment group at the 5% significance level (24.6% vs. 18.4% of subjects, OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017, primary endpoint). At the 5% significance level, there was no statistically significant difference between roflumilast 500 µg OD and roflumilast 500 µg EOD/500 µg OD treatment groups [H02] (OR 0.76, 95% CI: 0.55, 1.07; p-value 0.114). Supportive analysis Cox proportional hazards model found a similar result for roflumilast 250 µg OD/500 µg OD (HR=0.68, 95 % CI: 0.51, 0.92) and roflumilast 500 µg EOD/500 µg OD (HR=0.77, 95% CI: 0.58, 1.02) versus roflumilast 500 µg OD.

The results based on the logistic regression model with region as a covariate, instead of country, were consistent with the primary analysis results. Compared with roflumilast 500 µg OD [H01The odds of discontinuing from the Main Period were lower in the roflumilast 250 µg OD/500 µg OD treatment group (OR=0.70, 95% CI: 0.50, 0.97; p-value 0.032). The results of the sensitivity analyses by

excluding the South African site (Site 6002) for the primary endpoint supported the results of the primary analysis also yielded significant differences (OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017).

Strictly speaking, the single pivotal trial supporting this application does not fulfill with the level of statistical significance (considerably stronger than <0.05) normally required for application based on a single pivotal trial (Points to consider on application with 1. meta-analyses; 2. one pivotal study; CHMP/EWP/2330/99). However, it has to bear in mind that, on the one hand, the results on the primary (safety) endpoint were quite robust, with all sensitivity and ancillary analyses of the main endpoint showing a benefit, and with all secondary endpoint showing also a benefit in safety and patient's satisfaction and no detrimental effect on efficacy (pre-BD FEV1). On the other hand, the efficacy of roflumilast is out of question at this stage, and the line extension is restricted to improve the initial tolerability and decrease early withdrawal rates with treatment by starting with a lower dose. It is concluded that starting with a halved dose for the first 4 weeks followed by the 500 microg maintenance dose is safer than starting with 500 microg dose. In addition, no claims of efficacy are made for this starting dose.

Anyway, while recognizing that a streamlined posology aimed to minimize adverse events and treatment discontinuations is a positive goal, the applicant was requested to discuss about the clinical relevance and impact of decreasing the number of discontinuations by 6.2% in terms of preventing exacerbations. With a 6.2% reduction of discontinuations in the current population treated with roflumilast would translate into a 12.9% reduction in exacerbations during the first year. According to market share of roflumilast in different regions, this would translate in the prevention of additional 340 exacerbations in Europe and 1031 exacerbations globally, compared with starting with the 500 microg dose. This benefit is added to the adverse events (mainly gastrointestinal) prevented.

During the procedure, the applicant was requested to discuss whether the results at 3 months would be sustained in the long term. In roflumilast clinical trials, Kaplan-Meier plots of time to onset of AEs show that the majority of events in the roflumilast treated-patients occur early, and that there is a plateau after 4 weeks. Therefore, the first 4 weeks of treatment represents the dosing period most relevant to the aims of the study (ie, to improve tolerability of roflumilast through use of alternative dosing regimens). After this time, there is no evidence to support a need for further improvements, as the frequency of AEs with roflumilast is not higher than with placebo, and the rate of withdrawals from study treatment are low.

The results of the per protocol analysis provided during the procedure wer consistent with the results of the primary analysis and supported the finding that protocol deviations had no impact on the interpretation of the study data.

Most subgroups trended towards favouring the 250/500 microg OD up-titration regimen with some exceptions. The subgroups that trended towards favoring reference treatment (roflumilast 500 µg OD) were non-European region and Asian race (versus roflumilast 250 µg OD/500 µg OD), and north-Eastern Europe region and current smoking status (versus roflumilast 500 µg EOD/500 µg OD).

Race was not a significant covariate in population PK analysis, whereas in subgroup analyses of pivotal studies (Study M2-124 and Study M2-125), the effect of roflumilast versus placebo on the rate of moderate or severe exacerbations showed no heterogeneity depending on race. Results from the new population PK model on the combined REACT and OPTIMIZE dataset identified no clinically relevant changes of systemic exposure levels in other populations of particular interest (eg, elderly patients, female patients, smoking status, or patients with high [>80 kg] or low [<60 kg] baseline body weight). With respect to race, Therefore, the approved maintenance dose of roflumilast 500 µg OD does not need to be adjusted in these populations.

Elderly patients seem under-represented in the OPTIMIZE study, and they are a special population at risk of adverse events and withdrawals. The applicant clarified that only 115 patients were between 75 to 84 years and only 2 patients were >85 years old. With the limitations of small sample sizes, the subgroup analyses by age showed some small increases in adverse events with age with all dosing regimes, but the benefit of the new dosing regime in avoiding adverse events and discontinuations was consistently in favour of the new roflumilast regime regardless of age.

TEAEs of Interest during the Main Period (Key Secondary Safety Endpoint):

The more frequent TEAEs of interest were diarrhea, decreased appetite, nausea and headache, all of them occurring more frequently and starting soon in the control group than in the roflumilast 250 µg OD/500 µg OD experimental group. Compared with roflumilast 500 µg OD, the odds of experiencing a 'TEAE of interest' was significantly lower at the 5% significance level in the roflumilast 250 µg OD/500 µg OD treatment group (54.2% versus 45.4% of subjects, OR=0.63, 95% CI: 0.47, 0.83; p-value = 0.001). This difference was not observed between roflumilast 500 µg EOD/500 µg OD (48.3% of subjects) and the roflumilast 500 µg OD (54.2%) treatment groups in the analysis of AEs of interest.

The results of the statistical analysis of TEAEs of Interest (diarrhea, nausea, headache, reduced appetite, insomnia, or abdominal pain) during the Main Period are supportive and consistent with the results on the main study endpoint. However, they are considered exploratory based on insufficient evidence to reject the null hypothesis for the primary endpoint at the 5% significance level [H02] in the framework of hierarchical testing (i.e.: no statistically significant differences were found for the comparison between groups 2 and 3 for the primary endpoint of premature discontinuations).

Change From Baseline in Prebronchodilator FEV1:

a) ***Main treatment period:***

Improvements in prebronchodilator FEV1 from V1 to each Main Period postrandomization visit were clinically relevant (approximately 100 mL) and showed minimal differences across the 3 treatment groups (LS means of 0.09 L, 0.13 L, and 0.11 L for roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and roflumilast 500 µg OD treatment groups, respectively). Similar results were shown when subjects for both Main Period and Down-Titration Period were evaluated (LS means of 0.07 L, 0.14 L, and 0.10 L for roflumilast 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and roflumilast 500 µg OD treatment groups, respectively).

b**) Down-Titration Period:**

The analysis of main interest was for those patients who did not tolerate roflumilast 500 µg OD during the Main Period and subsequently entered the down-Titration period (n=80), in order to ascertain whether a the 250 microgram dose, administered to all of them, could be effective (i.e.: whether it could produce improvements in pre-BD FEV1 from the start of downtitration to end of downtitration). Eighty subjects (of 1321 subjects, 6.0%) who did not tolerate roflumilast 500 µg OD in the Main Period were treated with roflumilast 250 µg OD for 8 weeks (n=20 for the roflumilast 250 µg OD/500 µg OD group, n=22 for roflumilast 500 µg EOD/500 µg OD group, and n=38 for the roflumilast 500 µg OD group at Baseline, V0DT). The analyses indicated no effect of the 250 microgram low-dose roflumilast in pre-BD FEV1. The lack of effect on pre-BD FEV1 of a lower roflumilast maintenance dose was consistent in the per-protocol analysis based on the VCS and in several sensitivity analyses.

During the procedure, it was introduced in the product information that the 250 micrograms dose is subtherapeutic and should not be used for maintenance treatment.

FVC: In all treatment groups, mean FVC increased from V1 to Vend with minimal differences across the 3 treatment groups. Similar results were shown when subjects for both Main Period and Down-Titration Period were evaluated.

Patients' satisfaction with treatment: The secondary outcome of mean treatment difference in increased patient's satisfaction with treatment is difficult to interpret in terms of clinical relevance, as the mean values at study time-point compared with baseline remain between 1 (satisfied) and 2 (somewhat satisfied) regardless of dosing schedule applied. Looking at the descriptive data at D84, there are numerically more patients in up-titration group1 that are very satisfied or satisfied (89.1%) than in the control group (85.7%). On the contrary, there are more patients dissatisfied (score 4-6) in the control group (7.5%) than in the up-titration group 1 (3.7%). Therefore, it seems that patient's satisfaction tended to be improved with the up-titration regime than with the standard regime. These results are consistent with the primary endpoint of treatment withdrawals and the key secondary endpoint of AEs of interest (less risk of diarrhoea, insomnia, nausea). Patient's satisfaction with up-titration probably reflects a better tolerability (less adverse events with the 250 microg to 500 microg up-titration) at similar efficacy in terms of lung function improvement (i.e.: similar improvement in pre-BD FEV1 regardless of dosing schedule, close to +100 ml).

2.9.3. Conclusions on clinical efficacy

This submission is based on data from a single study (Study RO 2455 302-RD [OPTIMIZE]) conducted to fulfil a Committee for Medicinal Products for Human Use (CHMP) post-authorization measure (FUM004) to explore alternative doses of roflumilast to minimize the risk of poor tolerability, and to investigate the influence of factors such as gender, age, and smoking status on the bioavailability of the product in patients with chronic obstructive pulmonary disease (COPD).

Compared with standard dosing (roflumilast 500 µg OD), patients on the roflumilast 250 µg OD/500 µg OD up-titration dosing regimen had statistically significant lower odds of discontinuing the Main Period using a logistic regression model (24.6% vs. 18.4% of subjects, OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017, primary endpoint). Supportive analysis Cox proportional hazards model found a similar result for roflumilast 250 µg OD/500 µg OD (HR=0.68, 95 % CI: 0.51, 0.92). The results were consistent using region as a covariate, instead of country. In addition, the results of the sensitivity analyses by excluding the South African site (Site 6002) for the primary endpoint also yielded significant differences (OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017). On the contrary, the second up-titration regime tested (roflumilast 500 µg EOD/500 µg OD) was not superior to the standard dosing regime in reducing discontinuations (OR 0.76, 95% CI: 0.55, 1.07; p-value 0.114).

While recognizing that a streamlined posology aimed to minimize adverse events and treatment discontinuations is a positive goal, the applicant was requested to discuss about the clinical relevance and impact of decreasing the number of discontinuations by 6.2% in terms of preventing exacerbations. The applicant considered that, 6.2% reduction of discontinuations in the current population treated with roflumilast would translate into a 12.9% reduction in exacerbations during the first year. According to market share of roflumilast in different regions, this would translate in the prevention of additional 340 exacerbations in Europe and 1031 exacerbations globally, compared with starting with the 500 microg dose. This benefit is added to the adverse events (mainly gastrointestinal) prevented.

Most subgroups trended towards favouring the 250/500 microgram OD up-titration regimen with some exceptions (non-European region and Asian race). Race was not a significant covariate in population PK analysis, whereas in subgroup analyses of pivotal studies (Study M2-124 and Study M2-125), the effect of roflumilast versus placebo on the rate of moderate or severe exacerbations showed no heterogeneity depending on race. Results from the new population PK model on the combined REACT and OPTIMIZE dataset identified no clinically relevant changes of systemic exposure levels in other populations of particular interest (eg, elderly patients, female patients, smoking status, or patients

with high [>80 kg] or low [<60 kg] baseline body weight). With respect to race, Therefore, the approved maintenance dose of roflumilast 500 µg OD does not need to be adjusted in these populations.

With respect to lung function, the three dosing regimens were associated to similar improvements in pre-BD FEV1 versus baseline, thus suggesting that all treatment approaches had similar efficacy. The analysis of FEV1 during down-titration period in patients who did not tolerate roflumilast in the main period indicated no effect of the 250 microgram low-dose roflumilast in pre-BD FEV1. The lack of effect on pre-BD FEV1 of a lower roflumilast maintenance dose was consistent in the per-protocol analysis based on the VCS and in several sensitivity analyses. In the product information it has been reinforced the message that the 250 micrograms dose is sub-therapeutic and should not be used for maintenance treatment.

2.9.4. Clinical safety

Patient exposure

A summary of the duration of exposure to study drug (in weeks) during the Main Period is described in Table 24. The mean and median duration of exposure was broadly similar across treatment groups. The roflumilast 500 µg OD treatment group tended to have a greater number of subjects (72 of 443 subjects, 16.3%) who received treatment for ≤4 weeks compared with the up-titration treatment groups. More than 80% of subjects in each treatment group had exposure to roflumilast for more than 8 weeks during the Main Period (Table 24).

Table 22. Main Period Study Medication Exposure (SAS, Main Period)

	Roflumilast 250 µg OD/500 µg OD (N=441)	Roflumilast 500 µg EOD/500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)
Duration of Exposure in Main Period (weeks)			
Mean (SD)	10.836 (3.0715)	10.647 (3.1956)	10.040 (3.8944)
Median (minimum, maximum)	12.000 (0.14, 21.14)	11.857 (0.14, 16.43)	11.857 (0.14, 15.00)
Duration of Exposure Categories in Main Period, n (%)			
≤4 weeks	35 (7.9)	42 (9.6)	72 (16.3)
>4 weeks - ≤8 weeks	28 (6.3)	20 (4.6)	16 (3.6)
>8 weeks	378 (85.7)	375 (85.8)	355 (80.1)

Source: Table 15.1.14.1.
Study drug exposure is calculated as (the date of last dose - date of first dose + 1)/7).

Down-Titration Period
Patients were exposed to roflumilast 250 micrograms for a mean between 6.7 to 7.2 weeks in subgroups by prior treatment. At least 80% of subjects were exposed to roflumilast 250 micrograms for more than 4 weeks during the Down-Titration Period in subgroups by prior treatment. Only 12 patients were exposed for less than 4 weeks.

Adverse events

Summary of AEs by relatedness and severity

Main Period: An overview of TEAEs occurring during the Main Period is summarized in Table 25. Overall, 61.2%, 64.3%, and 65.7% of subjects receiving 250 µg OD/500 µg OD, 500 µg EOD/ 500 µg OD, and 500 µg OD, respectively, experienced at least 1 TEAE during the Main Period (Table 25). The

majority of TEAEs were investigator-assessed as unrelated to study treatment, and were rated mild-to-moderate intensity. In 15.3% of subjects, the TEAE led to study drug discontinuation.

Serious TEAEs occurred in a similar proportion of subjects across treatment groups (4.3%-5.0% of subjects); the majority of SAEs were investigator-assessed as unrelated to study treatment.

Overall, 6 subjects (0.5%) died (1 further subject died ≥30 days after the last dose of roflumilast and is not included in Table 25, but is discussed in next section about SAES and death.

Table 23. Overview of TEAEs Occurring in the Main Period (SAS, Main Period)

	Roflumilast 250 µg OD/ 500 µg OD (N=441)		Roflumilast 500 µg EOD/ 500 µg OD (N=437)		Roflumilast 500 µg OD (N=443)		Total (N=1321)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAE	270 (61.2)	1575	281 (64.3)	1613	291 (65.7)	1676	842 (63.7)	4864
Related	145 (32.9)	556	159 (36.4)	632	177 (40.0)	690	481 (36.4)	1878
Not related	125 (28.3)	1019	122 (27.9)	981	114 (25.7)	986	361 (27.3)	2986
Mild	132 (29.9)	1250	135 (30.9)	1272	142 (32.1)	1321	409 (31.0)	3843
Moderate	115 (26.1)	293	120 (27.5)	292	122 (27.5)	311	357 (27.0)	896
Severe	23 (5.2)	32	26 (5.9)	49	27 (6.1)	44	76 (5.8)	125
Leading to study drug discontinuation (a)	58 (13.2)	138	67 (15.3)	157	77 (17.4)	209	202 (15.3)	504
Serious TEAEs	19 (4.3)	24	22 (5.0)	30	20 (4.5)	27	61 (4.6)	81
Related	1 (0.2)	1	1 (0.2)	1	1 (0.2)	1	3 (0.2)	3
Not related	18 (4.1)	23	21 (4.8)	29	19 (4.3)	26	58 (4.4)	78
Leading to study drug discontinuation (a)	4 (0.9)	5	4 (0.9)	6	7 (1.6)	7	15 (1.1)	18
Deaths	3 (0.7)	3	1 (0.2)	1	2 (0.5)	2	6 (0.5)	6

Source: Table 15.3.1.1.1 and Appendix 16.2.7.1.
A TEAE in the Main Period is defined as any AE, regardless of relationship to study medication that occurs after the first dose of study medication in the Main Period and within 30 days after the last study medication in the Main Period or before the first dose of study medication in the Down-Titration Period.
For each summary only the worst case per subject is counted.
(a) TEAEs leading to study drug discontinuation include both temporary drug interruption and permanent discontinuation, with a subject counted just once for multiple interruptions and permanent discontinuation.

Down-Titration Period: As shown in Table 26, TEAEs occurred in 45.0%, 50.0%, and 65.8% of subjects who entered the Down-Titration Period after receiving roflumilast 250 µg OD/500 µg OD (N=20), 500 µg EOD/500 µg OD (N=22), and 500 µg OD (N=38), respectively, during the Main Period. In 12.5% of subjects, the TEAE led to study drug discontinuation. One subject in the roflumilast 250 µg OD/500 µg OD treatment group experienced a serious and treatment-related TEAE (of COPD). There were no deaths during the Down-Titration Period.

Table 24. Overview of TEAEs Occurring in the Down-Titration Period in Subjects Who Did Not Tolerate Roflumilast 500 µg OD in the Main Period (SAS, Down-Titration Period)

	Roflumilast 250 µg OD/500 µg OD (N=20)		Roflumilast 500 µg EOD/500 µg OD (N=22)		Roflumilast 500 µg OD (N=38)		Total (N=80)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAE	9 (45.0)	22	11 (50.0)	41	25 (65.8)	100	45 (56.3)	163
Related	5 (25.0)	7	6 (27.3)	21	20 (52.6)	77	31 (38.8)	105
Not related	4 (20.0)	15	5 (22.7)	20	5 (13.2)	23	14 (17.5)	58
Mild	3 (15.0)	11	6 (27.3)	33	16 (42.1)	87	25 (31.3)	131
Moderate	6 (30.0)	11	5 (22.7)	8	8 (21.1)	12	19 (23.8)	31
Severe	0	0	0	0	1 (2.6)	1	1 (1.3)	1
Leading to study drug discontinuation (a)	2 (10.0)	2	2 (9.1)	5	6 (15.8)	10	10 (12.5)	17
Serious TEAEs	1 (5.0)	1	0	0	0	0	1 (1.3)	1
Related	1 (5.0)	1	0	0	0	0	1 (1.3)	1
Not related	0	0	0	0	0	0	0	0
Leading to study drug discontinuation (a)	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0

Source: Table 15.3.1.1.2A and Appendix 16.2.7.1.
A TEAE in the down-titration period is defined as any AE, regardless of relationship to study medication, that occurs after the first dose of study medication in the down-titration period and within 30 days after the last study medication in the down-titration period.
For each summary only the worst case per subject is counted.
(a) TEAEs leading to study drug discontinuation include both temporary drug interruption and permanent discontinuation, with a subject counted just once for multiple interruptions and permanent discontinuation.

Overview of TEAEs by System Organ Class (SOC)

Main Period: TEAEs reported in ≥2% of subjects in any treatment group are summarized in Table 27 for the Main Period. The most frequently reported TEAEs during the Main Period were in the SOCs of Gastrointestinal disorders (36.5%, 38.2%, and 44.2% of subjects in 250 µg OD/500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively), Nervous system disorders (27.0%, 30.9%, and 29.3% of subjects, respectively), Metabolism and nutrition disorders (23.1%, 24.9%, and 30.0%, respectively), and Psychiatric disorders (22.9%, 24.9%, and 25.5% of subjects, respectively). TEAEs in the SOC Cardiac disorders were infrequent (1.2% of 1321 subjects), occurring in 1.6%, 1.1%, and 0.9% of subjects in 250 µg OD 500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively. TEAEs in the SOC Infections and infestations occurred in 8.8%, 10.8%, and 9.5% of subjects in 250 µg OD/ 500 µg OD, 500 µg EOD/500 µg OD, and 500 µg OD treatment groups, respectively (9.7% of 1321 subjects).

Table 25. Most Frequent (≥2% of Subjects in Any Treatment Group) TEAEs Occurring in the Main Period by SOC and PT (SAS, Main Period)

SOC PT (MedDRA)	Roflumilast 250 µg OD/500 µg OD (N=441)		Roflumilast 500 µg EOD/ 500 µg OD (N=437)		Roflumilast 500 µg OD (N=443)		Total (N=1321)	
	n (%)	n'	n (%)	n'	n (%)	n'	n (%)	n'
Subjects with any most frequent TEAEs	**239 (54.2)**	**1435**	**248 (56.8)**	**1460**	**272 (61.4)**	**1537**	**759 (57.5)**	**4432**
Gastrointestinal disorders	154 (34.9)	573	157 (35.9)	587	190 (42.9)	626	501 (37.9)	1786
Diarrhea	107 (24.3)	216	113 (25.9)	233	134 (30.2)	259	354 (26.8)	708
Nausea	87 (19.7)	183	92 (21.1)	201	110 (24.8)	192	289 (21.9)	576
Abdominal pain	69 (15.6)	145	58 (13.3)	126	64 (14.4)	141	191 (14.5)	412
Abdominal pain upper	19 (4.3)	29	15 (3.4)	27	27 (6.1)	34	61 (4.6)	90
General disorders and administration site conditions	4 (0.9)	4	10 (2.3)	10	5 (1.1)	9	19 (1.4)	23
Fatigue	4 (0.9)	4	10 (2.3)	10	5 (1.1)	9	19 (1.4)	23
Infections and infestations	13 (2.9)	15	15 (3.4)	15	20 (4.5)	21	48 (3.6)	51
Nasopharyngitis	7 (1.6)	8	11 (2.5)	11	12 (2.7)	12	30 (2.3)	31
Bronchitis	6 (1.4)	7	4 (0.9)	4	9 (2.0)	9	19 (1.4)	20
Investigations	10 (2.3)	10	9 (2.1)	9	17 (3.8)	17	36 (2.7)	36
Weight decreased	10 (2.3)	10	9 (2.1)	9	17 (3.8)	17	36 (2.7)	36
Metabolism and nutrition disorders	100 (22.7)	201	105 (24.0)	204	129 (29.1)	251	334 (25.3)	656
Decreased appetite	100 (22.7)	201	105 (24.0)	204	129 (29.1)	251	334 (25.3)	656
Musculoskeletal and connective tissue disorders	26 (5.9)	32	27 (6.2)	30	27 (6.1)	33	80 (6.1)	95
Pain in extremity	20 (4.5)	24	21 (4.8)	23	20 (4.5)	23	61 (4.6)	70
Arthralgia	8 (1.8)	8	7 (1.6)	7	9 (2.0)	10	24 (1.8)	25
Nervous system disorders	117 (26.5)	294	131 (30.0)	299	124 (28.0)	289	372 (28.2)	882
Headache	107 (24.3)	278	115 (26.3)	279	115 (26.0)	271	337 (25.5)	828
Dizziness	16 (3.6)	16	20 (4.6)	20	14 (3.2)	18	50 (3.8)	54
Psychiatric disorders	97 (22.0)	253	100 (22.9)	252	106 (23.9)	234	303 (22.9)	739
Insomnia	97 (22.0)	253	100 (22.9)	252	106 (23.9)	234	303 (22.9)	739
Respiratory, thoracic and mediastinal disorders	47 (10.7)	53	51 (11.7)	54	47 (10.6)	57	145 (11.0)	164
Chronic obstructive pulmonary disease	34 (7.7)	38	39 (8.9)	41	38 (8.6)	45	111 (8.4)	124
Dyspnea	15 (3.4)	15	13 (3.0)	13	11 (2.5)	12	39 (3.0)	40

Source: Table 15.3.1.5.1 and Appendix 16.2.7.1.
A TEAE in the Main Period is defined as any AE, regardless of relationship to study medication that occurs after the first dose of study medication in the Main Period and within 30 days after the last study medication in the Main Period or before the first dose of study medication in the Down-Titration Period.
If a subject experienced more than 1 AE within a PT, the subject is counted once in that PT.
PTs are sorted in decreasing order of incidence based on the total number of subjects with AEs within that PT.
n'=number of events for specified category.

Down-Titration Period: For subjects in the roflumilast 250 µg OD/500 µg OD (N=20), 500 µg EOD/500 µg OD (N=22), and 500 µg OD (N=38) treatment groups who did not tolerate roflumilast 500 µg OD in the Main Period, the most frequently reported TEAEs during the Down-Titration Period were Gastrointestinal disorders (10.0%, 27.3%, and 47.4% of subjects, respectively), Nervous system disorders (15.0%, 18.2%, and 26.3% of subjects, respectively), Metabolism and nutrition disorders (15.0%, 18.2%, and 23.7%, respectively), and Psychiatric disorders (10.0%, 22.7%, and 15.8% of subjects, respectively). These most frequent events were consistent with those observed in the Main Period. No subjects experienced a TEAE in the SOC Cardiac disorders during the Down-Titration Period. TEAEs in the SOC Infections and infestations occurred in 15.0%, 0%, and 15.8% of subjects in 250 µg OD/500 µg OD (N=20), 500 µg EOD/500 µg OD (N=22), and 500 µg OD (N=38) treatment groups, respectively.

Treatment-Related TEAEs

Main Period: Overall, 145 subjects (32.9%), 159 subjects (36.4%), and 177 subjects (40.0%) receiving roflumilast 250 µg OD/500 µg OD, 500 µg EOD 500 µg OD, and 500 µg OD, respectively,

experienced a TEAE that was investigator-assessed as related to roflumilast (Table 28). The most frequent treatment-related TEAEs were in the SOCs Gastrointestinal disorders, Metabolism and nutrition disorders, Psychiatric disorders, and Nervous system disorders (Table 28). TEAEs occurring in ≥1% of subjects in any treatment group are shown in Table 28.

Table 26. TEAEs Investigator-Assessed as Treatment-Related Occurring in ≥1% of Subjects in Any Treatment Group During the Main Period by SOC and PT (SAS, Main Period)

SOC	Roflumilast 250 µg OD/ 500 µg OD (N=441)	Roflumilast 500 µg EOD/ 500 µg OD (N=437)	Roflumilast 500 µg OD (N=443)	Total (N=1321)
PT (MedDRA)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal disorders	**96 (21.8)**	**110 (25.2)**	**131 (29.6)**	**337 (25.5)**
Diarrhea	61 (13.8)	76 (17.4)	96 (21.7)	233 (17.6)
Nausea	50 (11.3)	56 (12.8)	72 (16.3)	178 (13.5)
Abdominal pain	38 (8.6)	34 (7.8)	43 (9.7)	115 (8.7)
Abdominal pain upper	11 (2.5)	10 (2.3)	17 (3.8)	38 (2.9)
General disorders and administration site conditions	**4 (0.9)**	**11 (2.5)**	**1 (0.2)**	**16 (1.2)**
Asthenia	1 (0.2)	5 (1.1)	1 (0.2)	7 (0.5)
Investigations	**10 (2.3)**	**8 (1.8)**	**16 (3.6)**	**34 (2.6)**
Weight decreased	9 (2.0)	7 (1.6)	15 (3.4)	31 (2.3)
Metabolism and nutrition disorders	**60 (13.6)**	**64 (14.6)**	**79 (17.8)**	**203 (15.4)**
Decreased appetite	58 (13.2)	64 (14.6)	78 (17.6)	200 (15.1)
Musculoskeletal and connective tissue disorders	**8 (1.8)**	**15 (3.4)**	**11 (2.5)**	**34 (2.6)**
Pain in extremity	8 (1.8)	9 (2.1)	10 (2.3)	27 (2.0)
Nervous system disorders	**49 (11.1)**	**58 (13.3)**	**61 (13.8)**	**168 (12.7)**
Headache	41 (9.3)	47 (10.8)	53 (12.0)	141 (10.7)
Dizziness	10 (2.3)	10 (2.3)	8 (1.8)	28 (2.1)
Psychiatric disorders	**54 (12.2)**	**51 (11.7)**	**64 (14.4)**	**169 (12.8)**
Insomnia	50 (11.3)	48 (11.0)	62 (14.0)	160 (12.1)

Source: Table 15.3.1.8.1.
A TEAE in the Main Period is defined as any AE, regardless of relationship to study medication that occurs after the first dose of study medication in the Main Period and within 30 days after the last study medication in the Main Period or before the first dose of study medication in the Down-Titration Period.
If a subject experienced more than 1 AE within a PT, the subject is counted once in that PT.
PTs are sorted in decreasing order of incidence based on the total number of subjects with AEs within that PT.

Down-titration period

The most frequent events were consistent with those observed in the Main Period.

Serious adverse events and deaths

Deaths

Seven subjects died over the duration of this study. Of the 7 deaths, 6 subjects (of a total of 1321 subjects, 0.5%) died in the Main Period. The remaining death (Subject 6164/004 in treatment group 250 µg OD/ 500 µg OD) occurred ≥30 days after the last dose of study medication. None of the SAEs leading to death were investigator-assessed as related to study treatment.

Main Period

There were 6 deaths in the Main Period: 3 subjects (of 441 subjects, 0.7%) in the roflumilast 250 µg/500 µg OD treatment group, 1 subject (of 437 subjects, 0.2%) in the roflumilast 500 µg EOD/500 µg OD treatment group, and 2 subjects (of 443 subjects, 0.5%) in the 500 µg OD roflumilast treatment group (Table 29).

Table 27. Fatal SAEs Occurring in the Main Period (Randomized Subjects)

Subject Number/ Sex/Age	MedDRA PT	Day of Onset	Day of Death	Investigator-Assessed Relationship	Comments
Roflumilast 250 µg OD/500 µg OD					
6076/006 (M/56)	COPD	84	86	Not related	Previous AEs included concurrent moderate pneumonia (Day 84, ongoing)
6178/008 (F/62)	Cardiac failure	46	51	Not related	Previous AEs included moderate COPD (Day 27)
6196/017 (M/78)	Cardiopulmonary failure	23	23	Not related	Previous AEs included moderate COPD (Day 10, ongoing)
Roflumilast 500 µg EOD/500 µg OD					
6203/011 (M/71)	Pneumothorax spontaneous	82	102	Not related	No clinically relevant previous AEs
Roflumilast 500 µg OD					
6084/001 (M/69)	Lung adenocarcinoma	57	91	Not related	Previous AEs included concurrent moderate hemoptysis (Days 57-91)
6163/013 (M/61)	Myocardial infarction	78	78	Not related	Previous AEs included severe syncope (Day 72)

Source: Appendices 16.2.7.1 and 16.2.7.4.
F=Female, M=Male.

None of the 104 subjects who entered the Down-Titration Period died during the study.

Other serious adverse events

In total, 61 of 1321 subjects (4.6%) experienced 81 SAEs, including 19 (4.3%), 22 (5.0%), and 20 (4.5%) subjects in the roflumilast 250 µg OD/500 µg OD (24 SAEs), 500 µg EOD/500 µg OD (30 SAEs), and 500 µg OD (27 SAEs) treatment groups, respectively (Table 30).

Table 28. Treatment-Emergent SAEs During the Main Period by SOC and PT (SAS, Main Period)

SOC	Roflumilast 250 µg OD/ 500 µg OD (N=441)		Roflumilast 500 µg EOD/ 500 µg OD (N=437)		Roflumilast 500 µg OD (N=443)		Total (N=1321)	
PT (MedDRA)	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Subjects with any serious TEAEs	**19 (4.3)**	**24**	**22 (5.0)**	**30**	**20 (4.5)**	**27**	**61 (4.6)**	**81**
Cardiac disorders	**3 (0.7)**	**3**	**2 (0.5)**	**2**	**2 (0.5)**	**2**	**7 (0.5)**	**7**
Myocardial infarction	1 (0.2)	1	0	0	1 (0.2)	1	2 (0.2)	2
Myocardial ischemia	0	0	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Atrial fibrillation	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Cardiac failure	1 (0.2)	1	0	0	0	0	1 (0.1)	1
Cardiopulmonary failure	1 (0.2)	1	0	0	0	0	1 (0.1)	1
Ear and labyrinth disorders	**1 (0.2)**	**2**	**0**	**0**	**0**	**0**	**1 (0.1)**	**2**
Vertigo	1 (0.2)	2	0	0	0	0	1 (0.1)	2
Gastrointestinal disorders	**2 (0.5)**	**2**	**0**	**0**	**1 (0.2)**	**2**	**3 (0.2)**	**4**
Abdominal mass	1 (0.2)	1	0	0	0	0	1 (0.1)	1
Colitis ulcerative	1 (0.2)	1	0	0	0	0	1 (0.1)	1
Femoral hernia incarcerated	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Small intestinal obstruction	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Infections and infestations	**4 (0.9)**	**5**	**4 (0.9)**	**4**	**3 (0.7)**	**3**	**11 (0.8)**	**12**
Pneumonia	2 (0.5)	2	1 (0.2)	1	1 (0.2)	1	4 (0.3)	4
Infective exacerbation of chronic obstructive airways disease	1 (0.2)	2	0	0	1 (0.2)	1	2 (0.2)	3
Acute sinusitis	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Appendicitis	1 (0.2)	1	0	0	0	0	1 (0.1)	1
Bronchopneumonia	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Respiratory tract infection	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Upper respiratory tract infection	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Injury, poisoning and procedural complications	**0**	**0**	**1 (0.2)**	**1**	**0**	**0**	**1 (0.1)**	**1**
Lower limb fracture	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Metabolism and nutrition disorders	**0**	**0**	**0**	**0**	**2 (0.5)**	**2**	**2 (0.2)**	**2**
Decreased appetite	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Gout	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (0.2)**	**1**	**0**	**0**	**1 (0.1)**	**1**
Spinal osteoarthritis	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (0.2)**	**1**	**3 (0.7)**	**3**	**4 (0.3)**	**4**
Lung adenocarcinoma	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Malignant melanoma	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Prostate cancer	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Transitional cell carcinoma	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Nervous system disorders	**0**	**0**	**1 (0.2)**	**1**	**2 (0.5)**	**2**	**3 (0.2)**	**3**
Sciatica	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Syncope	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Transient ischaemic attack	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Psychiatric disorders	**0**	**0**	**1 (0.2)**	**1**	**0**	**0**	**1 (0.1)**	**1**
Anxiety	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Respiratory, thoracic and mediastinal disorders	**10 (2.3)**	**12**	**14 (3.2)**	**17**	**11 (2.5)**	**12**	**35 (2.6)**	**41**
Chronic obstructive pulmonary disease	8 (1.8)	8	13 (3.0)	14	7 (1.6)	8	28 (2.1)	30
Dyspnea	3 (0.7)	3	0	0	3 (0.7)	3	6 (0.5)	6
Acute respiratory failure	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Hemoptysis	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Pleural effusion	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Pneumothorax spontaneous	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Pulmonary hypertension	1 (0.2)	1	0	0	0	0	1 (0.1)	1
Vascular disorders	**0**	**0**	**2 (0.5)**	**2**	**1 (0.2)**	**1**	**3 (0.2)**	**3**
Hypertension	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Hypertensive crisis	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Vasculitis	0	0	1 (0.2)	1	0	0	1 (0.1)	1

Source: Table 15.3.1.12.1.
A TEAE in the Main Period is defined as any AE, regardless of relationship to study medication that occurs after the first dose of study medication in the Main Period and within 30 days after the last study medication in the Main Period or before the first dose of study medication in the Down-Titration Period.

Down-Titration Period: Of the 80 subjects that entered the Down-Titration Period after not tolerating roflumilast 500 µg OD in the Main Period, 1 subject (1.3%) who entered this period in the 250 µg OD/500 µg OD treatment group experienced 1 serious TEAE. The SAE of (worsening) COPD was investigator-assessed as treatment-related.

Other significant AEs:

Columbia-Suicide Severity Rating Scale

No completed or attempted suicide was reported during the treatment period. Suicidal ideation was reported in 1 subject in the roflumilast 500 µg OD group during the Main Period (Subject 6146/015), and resulted in discontinuation from the study. There was no suicide or suicidal ideation reported during the Down-Titration Period.

Laboratory findings

There were no clinically relevant changes in mean or median serum chemistry or hematology values from V1 at Vend for any treatment group during the Main Period, or from V1 or V0DT to VendDT in the Down Titration Period. No more than 2.2% of subjects in any treatment group had serum chemistry values that met criteria for 'markedly abnormal' during the Main Period and no more than 2% of subjects in any treatment group had hematology values that met criteria for 'markedly abnormal' during the Main Period (see Clinical AR).

The mean body weight loss was around 1 kg in the 3 treatment groups during the main study period. No significant mean weight loss was reported during the down-titration period. In total, 36 of the 1321 subjects (2.7%) experienced the TEAE of "weight decreased" during the Main Period, with incidence higher in 500 µg OD than either up-titration group (3.8% versus 2.3% and 2.1% of subjects in 250 µg OD/500 µg OD and 500 µg EOD/500 µg OD, respectively). A TEAE of weight loss was only reported in 2 subjects during the Down Titration period (see Clinical AR).

Safety in special populations

Regarding the primary endpoint, premature discontinuations were more frequent in patients > 65 years (23-27% across treatment groups) than in patients < 65 years (15-22% across treatment groups) but the odds ratio of discontinuations favor up-titration group 1 versus reference both in patients > 65 years (OR point estimate 0.70) and in patients < 65 years (Table 31).

The same applies for the key secondary safety endpoint of rate of patients with AEs of interest, which is more frequent in patients > 65 years (48-56% across treatment groups) than in patients < 65 years (43-53% across treatment groups) but the odds ratio of discontinuations favor up-titration group 1 versus reference both in patients > 65 years (47.7% vs 55.7%) and in patients < 65 years (43.4% vs. 52.7%) (Table 31).

Table 29. Primary and Key Secondary Analysis of Safety, by Subgroup

Age Group: >= 65 years

Endpoint/Test	Roflumilast 250 µg OD/ 500 µg OD	Roflumilast 500 µg EOD/ 500 µg OD	Roflumilast 500 µg OD
No. of subjects in the SAS for Main Period, N	199	235	219
No. of subjects prematurely discontinuing Main Period, SAS	46 (23.1%)	53 (22.6%)	60 (27.4%)
P-value for comparison against Reference 500 µg OD (a)	0.151	0.111	
Odds Ratio [95% CI] for comparison against Reference (a)	0.70 [0.43 , 1.14]	0.69 [0.43 , 1.09]	
Hazard Ratio [95% CI] for comparison against Reference (b)	0.74 [0.50 , 1.10]	0.69 [0.47 , 1.01]	
AEs of Interest to Evaluate Tolerability during Main Period, SAS			
No. of subjects with AEs of interest	95 (47.7%)	121 (51.5%)	122 (55.7%)
No. of subjects in the SAS for Down-Titration Period, N	12	11	18
No. of subjects prematurely discontinuing Down-Titration Period, SAS	2 (16.7%)	3 (27.3%)	3 (16.7%)

Note 1: Down-Titration period summaries are based on a subgroup of 80 subjects (250 µg OD/500 µg OD: 20, 500 µg EOD/500 µg OD: 22, 500 µg OD: 38), who received 500 µg OD and discontinued during the Main Period.
Note 2: * = Used Firth logistic regression, ^ = Results not used as complete convergence not obtained, CI = Confidence Interval, AE = Adverse Event, SAS = Safety Analysis Set, NC = Not Calculated
Note 3: The 'Black' and 'Other' race subgroup categories were not considered for the logistic regression or proportional hazards models because of their significantly low counts.
(a) Logistic regression model with study treatment, country and baseline FEV1 as explanatory variables.
(b) Cox proportional hazards model with study treatment and country as class effects, and baseline FEV1 as a continuous variable.

Age Group: < 65 years

Endpoint/Test	Roflumilast 250 µg OD/ 500 µg OD	Roflumilast 500 µg EOD/ 500 µg OD	Roflumilast 500 µg OD
No. of subjects in the SAS for Main Period, N	242	202	224
No. of subjects prematurely discontinuing Main Period, SAS	35 (14.5%)	35 (17.3%)	49 (21.9%)
P-value for comparison against Reference 500 µg OD (a)	0.042	0.320	
Odds Ratio [95% CI] for comparison against Reference (a)	0.60 [0.36 , 0.98]	0.78 [0.47 , 1.28]	
Hazard Ratio [95% CI] for comparison against Reference (b)	0.61 [0.39 , 0.95]	0.77 [0.49 , 1.19]	
AEs of Interest to Evaluate Tolerability during Main Period, SAS			
No. of subjects with AEs of interest	105 (43.4%)	90 (44.6%)	118 (52.7%)
No. of subjects in the SAS for Down-Titration Period, N	8	11	20
No. of subjects prematurely discontinuing Down-Titration Period, SAS	2 (25.0%)	1 (9.1%)	4 (20.0%)

Note 1: Down-Titration period summaries are based on a subgroup of 80 subjects (250 µg OD/500 µg OD: 20, 500 µg EOD/500 µg OD: 22, 500 µg OD: 38), who received 500 µg OD and discontinued during the Main Period.
Note 2: * = Used Firth logistic regression, ^ = Results not used as complete convergence not obtained, CI = Confidence Interval, AE = Adverse Event, SAS = Safety Analysis Set, NC = Not Calculated
Note 3: The 'Black' and 'Other' race subgroup categories were not considered for the logistic regression or proportional hazards models because of their significantly low counts.
(a) Logistic regression model with study treatment, country and baseline FEV1 as explanatory variables.
(b) Cox proportional hazards model with study treatment and country as class effects, and baseline FEV1 as a continuous variable.

Pregnancy

There were no subjects with a positive pregnancy test throughout the duration of the study.

Immunological events

No specific section is dedicated to immunological events in the dossier. Anyway, looking at the TEAEs by SOC, either frequent or serious, there was no indication of immunological events with roflumilast in OPTIMIZE study beyond some mild skin reactions.

Safety related to drug-drug interactions and other interactions

No information provided initially. During the procedure, the applicant was requested to show the results of the main endpoint and key secondary safety endpoint by subgroups according to concomitant medications (i.e.: concomitant ICS only, concomitant ICS+LABA, concomitant ICS+LAMA, concomitant ICS+LABA+LAMA) by treatment groups and to discuss whether the 250/500 microgram up-titration regime could provide a particular advantage in patients with multiple concomitant medications. The Applicant submitted the requested subgroup analyses by concomitant medication use. The analyses were hampered by their post-hoc nature and lack of statistical power due to small sample sizes. Anyway, the analysis provided justify for all of the subgroups studied to take advantage of the 250 µg OD/500 µg OD up-titration regimen, regardless of concomitant LAMA or multiple concomitant medication use.

Discontinuation due to AES

This was an important component of the main endpoint (all withdrawals) in OPTIMIZE. Please see the outcomes estimation in the efficacy section.

2.9.5. Discussion on clinical safety

The comparative results of the main and key secondary (safety) study endpoints (rate of withdrawals and TEAEs of interest have already been described in the efficacy section. The following sections will focus on the description of patient exposures, adverse events, laboratory findings, safety in special populations, safety related to drug-drug interactions and post-marketing experience.

The roflumilast up-titration groups (250 µg OD/500 µg OD and 500 µg EOD/ 500 µg OD) tended to have a greater number of subjects (378 and 375 subjects; 85.7 and 85.8%, respectively) who received treatment for >8 weeks compared with the standard treatment group (355 of 443; 80.1%). The roflumilast 500 µg OD treatment group tended to have a greater number of subjects (72 of 443 subjects, 16.3%) who received treatment for ≤4 weeks compared with the up-titration treatment groups (7.9% and 9.6%, respectively). This is consistent with the results of the primary endpoint, showing less early withdrawals with the 250 µg OD/500 µg OD dosing regimen than with the other dosage schedules.

Most patients (63.7%) experienced TEAEs during treatment with roflumilast (61.2% in group 1, 64.3% in group 2 and 65.7% in control group). Most frequent TEAEs were gastrointestinal (diarrhoea, nausea, abdominal pain) (occurring in 37.9% of patients overall) (34.9% in group 1, 35.9% in group 2 and 42.9% in control group). SAES were reported in 4.6% of subjects. Only 0,2% of patients had a SAE related to study medication (1 patient in each group).

Overall, 145 subjects (32.9%), 159 subjects (36.4%), and 177 subjects (40.0%) receiving roflumilast 250 µg OD/500 µg OD, 500 µg EOD 500 µg OD, and 500 µg OD, respectively, experienced a TEAE that was investigator-assessed as related to roflumilast. The most frequent treatment-related TEAEs were in the SOCs Gastrointestinal disorders (diarrhoea 17.6%, nausea 13.5%, abdominal pain 11.6%), Metabolism and nutrition disorders (decreased appetite 15.1%), Psychiatric disorders (insomnia, 12.1%) and Nervous system disorders (headache 10.7%, dizziness 2.1%). The benefit of the roflumilast 250 µg OD/500 µg OD up-titration regime versus the standard roflumilast 500 µg OD

regime was largely driven by less related TEAEs of diarrhoea (13.8% vs. 21.7%; -7.9% difference) and nausea (11.3% vs. 16.3%; -5% difference).

Seven subjects died over the duration of this study. Of the 7 deaths, 6 subjects (of a total of 1321 subjects, 0.5%) died in the Main Period. The remaining death (Subject 6164/004 in treatment group 250 µg OD/ 500 µg OD) occurred ≥30 days after the last dose of study medication. None of the SAEs leading to death were investigator-assessed as related to study treatment.

In total, 61 of 1321 subjects (4.6%) experienced 81 SAEs, including 19 (4.3%), 22 (5.0%), and 20 (4.5%) subjects in the roflumilast 250 µg OD/500 µg OD (24 SAEs), 500 µg EOD/500 µg OD (30 SAEs), and 500 µg OD (27 SAEs) treatment groups, respectively. Most SAES were related to worsening COPD. No safety signal is apparent from these data.

There were no clinically relevant changes in mean or median serum chemistry or hematology values from V1 at Vend for any treatment group during the Main Period, or from V1 or V0DT to VendDT in the Down Titration Period. No more than 2.2% of subjects in any treatment group had serum chemistry values that met criteria for 'markedly abnormal' during the Main Period and no more than 2% of subjects in any treatment group had hematology values that met criteria for 'markedly abnormal' during the Main Period.

The mean body weight loss was around 1 kg in the 3 treatment groups during the main study period. No significant mean weight loss was reported during the down-titration period. In total, 36 of the 1321 subjects (2.7%) experienced the TEAE of "weight decreased" during the Main Period, with incidence higher in 500 µg OD than either up-titration group (3.8% versus 2.3% and 2.1% of subjects in 250 µg OD/500 µg OD and 500 µg EOD/500 µg OD, respectively). A TEAE of weight loss was only reported in 2 subjects during the Down Titration period.The dossier has no dedicated section to safety in special populations or in the elderly. The only data available is about primary and key secondary analysis of safety by age group in the subgroup analysis of the main endpoint (withdrawals in patients > 65 years) and in some tables in the appendixes. Looking at subgroups of primary and key secondary endpoint, premature discontinuations were more frequent in patients > 65 years (23-27% across treatment groups) than in patients < 65 years (15-22% across treatment groups), but the odds ratio of discontinuations favoured up-titration group 1 versus reference both in patients > 65 years (OR point estimate 0.70) and in patients < 65 years (Table 31). The same applies for the key secondary safety endpoint of rate of patients with AEs of interest, which tended to be more frequent in patients > 65 years (48-56% across treatment groups) than in patients < 65 years (43-53% across treatment groups), but consistently less frequent in the up-titration group 1 versus reference both in patients > 65 years (47.7% vs. 55.7%) and in patients < 65 years (43.4% vs. 52.7%) (Table 31). During the procedure, the applicant wa also invited to discuss about the apparent under-representation of elderly patients in the pivotal OPTIMIZE study, particularly taking into account that they are a special population at the highest risk of having a primary outcome study event (i.e.: withdrawal due to intolerability). The applicant clarified that only 115 patients were between 75 to 84 years and only 2 patients were >85 years old. With the limitations of small sample sizes, the data showed some small increases in adverse events with age with all dosing regimes, but the benefit of the new dosing regime in avoiding adverse events and discontinuations was consistently in favour of the new roflumilast regime regardless of age.

No specific section is dedicated to immunological events in the dossier. Anyway, looking at the TEAEs by SOC, either frequent or serious, there was no indication of immunological events with roflumilast in OPTIMIZE study beyond some mild skin reactions.

With respect to safety related to drug-drug interactions, the company is also requested to show the results of the main endpoint and key secondary safety endpoint by subgroups according to concomitant medications (i.e.: concomitant ICS only, concomitant ICS+LABA, concomitant ICS+LAMA, concomitant ICS+LABA+LAMA) by treatment groups and to discuss whether the 250/500 microgram up-titration regime could provide a particular advantage in patients with multiple concomitant medications. This analysis is of special interest, as a higher incidence in weight decrease, decreased appetite, headache and depression has been reported with roflumilast in patients receiving concomitant LAMA as compared to those not receiving LAMA (REACT study data already included in the SmPC) (see also efficacy section).

During the procedure, the applicant was invited to comment on the potential benefit of recommending the administration of roflumilast with food in reducing gastrointestinal intolerability. The applicant answered that clinical data available with roflumilast does not indicate a protective effect of meal on gastrointestinal adverse effects or other intolerability symptoms. Therefore, it is endorsed that a specific recommendation to take roflumilast with food is not needed.

The cumulative clinical trial exposure to roflumilast in the COPD program, asthma program and other indications (tablet and cream formulations) is 17396 patients, as of 5 January 2017. Cumulative post-marketing exposure to roflumilast globally since first marketing launch in 2010 has been estimated to be over 804,498 patient-years, with the majority of exposure occurring in North America and Europe. Post-marketing surveillance data with roflumilast at the time of this submission shows that the AE pattern in post-marketing surveillance reports does not deviate from the experience from clinical studies. The most frequently reported ADRs from roflumilast post-marketing reports are well-known reactions associated with PDE-4 inhibitors (i.e.: gastrointestinal adverse reactions, insomnia, decreased appetite) and/or are expected events for this patient population, clinical manifestations of the underlying disease and its progression. Weight decrease, psychiatric disorders including suicide risk, and angioedema as important identified risks, and cardiac safety, malignancy and infection risks to be clinically important potential risks for roflumilast. No new safety data have been received during the latest post-marketing safety reporting period to alter the current understanding and assessment of these safety risks.

2.9.6. Conclusions on clinical safety

The analysis of safety data from OPTIMIZE study does not raise any new concern about the safety of roflumilast. Most patients (63.7%) experienced TEAEs during treatment with roflumilast (61.2% in group 1, 64.3% in group 2 and 65.7% in control group), with most frequent TEAEs being gastrointestinal (diarrhoea, nausea, abdominal pain) (occurring in 37.9% of patients overall) (34.9% in group 1, 35.9% in group 2 and 42.9% in control group). SAES were reported in 4.6% of subjects. Only 0,2% of patients had a SAE related to study medication (1 patient in each group). These data are consistent with the known safety profile of roflumilast.

The analysis of TEAEs related to study drug indicated a safety advantage of the roflumilast 250 µg OD/500 µg OD up-titration regime versus the standard roflumilast 500 µg OD regime, which was largely driven by less related TEAEs of diarrhoea (13.8% vs. 21.7%; -7.9% difference) and nausea (11.3% vs. 16.3%; -5% difference).

The summary of safety concerns after the addition of the 250 microg dose remain the same as for the 500 microgram dose, which is endorsed, because no new safety concerns related to new or increased adverse reactions are expected with the use of a lower roflumilast dose. However, with respect to the

safety specification, the main concern due to the availability of the new (ineffective) 250 microgram dose, is the potential for off-label use with respect to the maintenance dose.

On the one hand, the information included in the RMP provides evidence that up-titration has been done off-label since the approval of roflumilast 500 microgr with the use every second day or half a tablet each day. Therefore, current line extension is expected to put in the SmPC a practice already extended among prescribers, but now with evidence from a randomized trial. The product information was ammended during the procedure to reinforce the message that the 250 micrograms dose is subtherapeutic and should not be used for maintenance treatment.

2.9.7. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.10. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Weight decrease
	Psychiatric disorders (insomnia, anxiety, panic attack, nervousness, depression, suicidal ideation and behaviour)
	Angioedema
Important potential risks	Malignant tumours
	Infections
	Cardiac safety
	Risk of triggering suicide
	Serious Diarrhoea
	Gynaecomastia
	Pancreatitis
	Persistent intolerability in high exposure populations
	Off-label use: • Asthma adult • Asthma paediatric • COPD other than indicated • Alpha 1 anti-trypsin deficiency • Use at lower than indicated doses
Missing information	Use during pregnancy and lactation
	Intake of immunosuppressive medication (excl. short-term systemic corticosteroids)
	Severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy)

Summary of safety concerns	
	Mild, moderate or severe hepatic impairment classified as Child Pugh A, B or C
	Combination of roflumilast with theophylline for maintenance therapy
	Long-term treatment

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Long-term post-marketing observational study of roflumilast (D7120R00003 [RO-2455-403-RD]); Category 1 (FUM002)	To evaluate the long-term safety of roflumilast in the treatment of COPD, with focus primarily on all-cause mortality. In addition, the study will evaluate potential risks, including potential safety issues identified during the clinical trials of roflumilast. Specifically this study aims to compare the incidences of all-cause mortality, major cardiovascular events, new diagnosis of cancer, all-cause hospitalisation, hospitalisation related to respiratory disease, suicide or hospitalisation for suicide attempt, abnormal, unexplained weight loss, serious diarrhoea of non-infections origin and new diagnosis of depression, tuberculosis or viral hepatitis B or C in roflumilast treated (exposed) COPD patients compared with matched COPD patients not treated with roflumilast (non-exposed). The exposed and non-exposed cohorts will be followed for five to nine years.	Long-term treatment safety data will be generated aiming at investigating the 5-year mortality and morbidity of roflumilast in the COPD patient population	Started	The first interim analysis is planned for 2017; The final study report is planned to be available in 2021.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Weight decrease	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/Daliresp/Libertek compared to placebo-treated patients. After discontinuation of Daxas/Daliresp/Libertek, 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/Daliresp/Libertek 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 is distributed at market introduction and made available thereafter.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Psychiatric disorders (insomnia, anxiety, panic attack, nervousness, depression, suicidal ideation and behaviour)	SmPC section 4.4 states: Daxas/Daliresp/Libertek is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression. Rare instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression, usually within the first weeks of treatment. The risks and benefits of starting or continuing treatment with Daxas/Daliresp/Libertek should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. Daxas/Daliresp/Libertek is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. Patients and caregivers should be instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with Daxas/Daliresp/Libertek. Section 4.8 of the SmPC: Insomnia is considered as common adverse reaction of Daxas/Daliresp/Libertek treatment. Anxiety is labelled as uncommon adverse reaction and panic attack, nervousness, depression, and suicidal ideation and behaviour as rare adverse reactions. Furthermore, a statement is included to point out that in clinical studies and post-marketing experience, rare instances of suicidal ideation and behaviour (including suicide) were reported. Patients and caregivers should be instructed to notify the prescriber of any suicidal ideation.	Educational material was updated and re-distributed after adding the risk of triggering suicide. A system for tracking the distribution of the Educational Material was implemented at the same time. For suicidal ideation and behaviour, the success of the risk minimisation activities will also be evaluated in the interim and final analyses of the long-term post-marketing study.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Angioedema	Angioedema is considered a rare adverse reaction of roflumilast treatment (section 4.8 of the SmPC). No further risk minimisation activities are considered necessary.	Not applicable.
Important potential risk		
Malignant tumours	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas/Daliresp/Libertek should not be initiated and existing treatment with Daxas/Daliresp/Libertek should be stopped in patients with cancers (except basal cell carcinoma).	Educational material for prescribers and patients is distributed at the time of market introduction and made available thereafter.
Infections	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas/Daliresp/Libertek should not be initiated and existing treatment with Daxas/Daliresp/ Libertek should be stopped in patients with severe acute infectious diseases. Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection or herpes zoster is limited.	Educational material for prescribers and patients is distributed at the time of market introduction and made available thereafter.
Cardiac safety	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 is distributed at the time of market introduction and made available thereafter.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Risk of triggering suicide	In section 4.4 of the SmPC a warning is included concerning rare instances of suicidal ideation and behaviour, including suicide which have been observed in patients with or without a history of depression, usually within the first weeks of treatment. The risks and benefits of starting or continuing treatment with Daxas/Daliresp/Libertek 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. Daxas/Daliresp/Libertek is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. Patients and caregivers should be instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with Daxas/Daliresp/Libertek. In section 4.8 of the SmPC a statement is included to point out that in clinical studies and post-marketing experience, rare instances of suicidal ideation and behaviour (including suicide) were reported. Patients and caregivers should be instructed to notify the prescriber of any suicidal ideation.	Educational material for prescribers and patients is provided at market introduction. For those countries where this risk was not included in the original materials, materials have been updated and redistributed. Materials are also made available thereafter. Effectiveness is assessed through periodic evaluation of spontaneous ADRs received from the EU.
Serious Diarrhoea	Diarrhoea is considered a common adverse reaction of roflumilast treatment (section 4.8 of the SmPC).	Not applicable
Gynaecomastia	Gynaecomastia is considered a rare adverse reaction of roflumilast treatment (section 4.8 of the SmPC). No further risk minimisation activities are considered necessary.	Not applicable.
Pancreatitis	Not applicable (a potential need for risk minimisation measures will be assessed with each PSUR)	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Persistent intolerability in high exposure populations	Use of Daxas/Daliresp/Libertek in populations such as black, non-smoking females, might lead to an increase of exposure and persistent intolerability. In this case, Daxas/Daliresp/Libertek treatment should be reassessed (see section 4.4 of the SmPC).	Educational material for prescribers is distributed at the time of market introduction and made available thereafter.
Off-label use: • Asthma adult • Asthma paediatric • COPD other than indicated • Alpha 1 anti-trypsin deficiency • Use at lower than indicated doses	The indication is defined in section 4.1 of the SmPC as: *Daxas/Daliresp/Libertek 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.* The posology is defined in section 4.2 of the SmPC as: *Starting dose - The recommended starting dose is one tablet of 250 micrograms roflumilast to be taken once daily, for 28 days. This starting dose is intended to reduce adverse events and patient discontinuation when initiating therapy, but it is a sub-therapeutic dose. Therefore, the 250 micrograms dose should be used only as a starting dose.* *Maintenance dose - After 28 days of treatment with the 250 micrograms starting dose, patients must be up-titrated to one tablet of 500 micrograms roflumilast, to be taken once daily.* Section 4.2 of the SmPC: *There is no relevant use of Daxas/Daliresp/Libertek in the paediatric population (under 18 years).*	Educational material for prescribers is distributed at the time of market introduction and made available thereafter.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
Use during pregnancy and lactation	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/Daliresp/Libertek 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/Daliresp/Libertek should not be used during breast-feeding. Pregnancies will be monitored according to the procedures described in Part III.2 of this document. Considering the very low likelihood of a pregnancy in the indicated patients, no further risk minimisation activities were considered necessary.	Not applicable.
Intake of immunosuppressive medication (excl. short-term systemic corticosteroids)	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas/Daliresp/Libertek should not be initiated and existing treatment with Daxas/Daliresp/ Libertek should be stopped in patients being treated with immunosuppressive medicinal products (except short-term systemic corticosteroids).	Educational material for prescribers and patients is distributed at the time of market introduction and made available thereafter.
Severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy)	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Daxas/Daliresp/Libertek should not be initiated and existing treatment with Daxas/Daliresp/ Libertek should be stopped in patients with severe immunological diseases.	Educational material for prescribers and patients is distributed at the time of market introduction and made available thereafter.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Mild, moderate or severe hepatic impairment classified as Child Pugh A, B or C	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/Daliresp/Libertek, 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 is distributed at the time of market introduction and made available thereafter.
Combination of roflumilast with theophylline for maintenance therapy	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 is distributed at the time of market introduction and made available thereafter.
Long-term treatment	Section 4.2 of the SmPC: Daxas/Daliresp/Libertek has been studied in clinical trials for up to one year. Long term data will be acquired in an epidemiological long-term study.	Not applicable.

Conclusion

The CHMP and PRAC considered that the risk management plan version 18.3 is acceptable.

2.11. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.12. Product information

2.12.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the patient leaflet as a result of the introduction of 250 µg tablet are minor and do not change the readability of the document.

2.12.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Daxas (roflumilast) is included in the additional monitoring list as it has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)].

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Place of roflumilast in therapy

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. It has a mechanism of action that is complimentary to the anti-inflammatory effect of ICS and the bronchodilatory effect of LABA and LAMA, which are the standard of care in patients with severe COPD at risk of exacerbations. Exacerbations of COPD are worsenings of the patient's respiratory symptoms beyond normal day-to-day variation that lead to changes in medication, and possibly, hospitalization and death.

Current GOLD guidelines recommend adding roflumilast to treatment regimens for patients in Group D who have chronic bronchitis and forced expiratory volume in 1 second (FEV_1) <50% of predicted whose exacerbations are not adequately controlled on a triple combination of a long-acting β_2-adrenergic agonist (LABA), a long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS). The indication for roflumilast in clinical practice is therefore for patients with GOLD spirometric grade 3-4 and group D.

Roflumilast was approved for use in 2010. During clinical studies, the rate of discontinuations with roflumilast in pivotal studies was quite high, around 30%, with withdrawals due to intolerability accounting for the majority of discontinuations (Daxas EPAR, 2010). As follow-up measure (FUM004), the MAH was encouraged to present a program exploring the feasibility of developing alternative doses to minimize the risk of drug interactions and poor tolerability. This line extension application is the result of studies aimed to address this issue.

3.1.1. Disease or condition

Roflumilast, at a 500 microgram once-daily dose, is authorised in the EU since 05-Jul-2010 for maintenance treatment of severe chronic obstructive pulmonary disease (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.

COPD 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. 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.

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.

The most widely accepted classification of the severity of COPD is according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD; Available from: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/). It includes a spirometric and symptoms classification.

The GOLD classification of airflow limitation severity (spirometric classification) recognizes four grades (1: mild; 2: moderate; 3: severe; 4: very severe), being categories 3-4 those corresponding to severe (FEV1 ≤ 50% predicted) and very severe (FEV1 ≤ 30% predicted) airflow limitation, respectively.

It should be noted that there is only a weak correlation between FEV1, symptoms and impairment of a patient's health status. For this reason, formal symptomatic assessment is also required.

Current GOLD guidelines recommend the symptomatic classification of COPD patients regarding symptoms and risk of exacerbations using the "ABCD" assessment tool. Group D are patients with more symptoms at high risk of exacerbations. The prognosis of COPD is poorer in patients with severe/very severe airflow limitation and it is correlated with the degree of dyspnoea (GOLD 2017).

3.1.2. Available therapies and unmet medical need

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.

3.1.3. Main clinical studies

This submission is based on data from a single study (Study RO 2455 302-RD [OPTIMIZE]) conducted to fulfill a Committee for Medicinal Products for Human Use (CHMP) post-authorization measure (FUM004) to explore alternative doses of roflumilast to minimize the risk of poor tolerability, and to explore the influence of factors such as gender, age, and smoking status on the bioavailability of the product in patients with chronic obstructive pulmonary disease (COPD).

OPTIMIZE was a multicenter, randomized, double-blind, 3-arm, parallel group, phase 3 study with an open-label Down-Titration Period for subjects who withdrew from the Main Period of the study. During the Main Period, subjects were randomized receive 1 of the 3 treatments consisting of 2 up-titration treatment groups: 250 µg OD or 500 µg EOD for the first 4 weeks followed by 500 µg OD for 8 weeks, and the currently approved roflumilast regimen of 500 µg OD administered for 12 weeks. All subjects discontinuing from the Main Period were permitted to enter an 8-week open-label Down-Titration Period where they received roflumilast 250 µg OD.

Inclusion and exclusion criteria in OPTIMIZE study were in line with the indication (severe COPD and a history of exacerbations) and contraindications/non-recommendation of use detailed in the Daxas SmPC. Study medications included roflumilast 250 µg tablet, 500 µg tablet and placebo of identical appearance. Placebo was used only during the 4-week up-titration period (the only phase that was double-blinded) (the 8 week continuation after initial 4-week up-titration was single blinded, as investigators knew that all patients were receiving the roflumilast 500 µg tablet, although they were unaware of the type of initial 4-week treatment that patients had received).

Primary Endpoint was the percentage of subjects prematurely discontinuing study treatment due to any reason during Main Period. Key Secondary Endpoints included the percentage of subjects with adverse events (AEs) of interest to evaluate tolerability during Main Period, the change in pre-bronchodilator (pre-BD) FEV_1 during Down-Titration Period (V0DT to VendDT) and the percentage of subjects prematurely discontinuing study treatment due to any reason during Down-Titration Period (V0DT to VendDT). Other secondary endpoints were: change in pre-BD FEV_1 during Main Period of the study, change in pre-BD FVC during Main Period and also including Down-Titration Period; change in subject-assessed treatment satisfaction scores during Main Period of the study and also including Down-Titration Period.
Study methods were appropriate, and one study site was closed due to GCP non compliance issues.

3.2. Favourable effects

Compared with roflumilast 500 µg OD [H01] the odds of discontinuing the Main Period using a logistic regression model were statistically significantly lower in the roflumilast 250 µg OD/500 µg OD treatment group at the 5% significance level (24.6% vs. 18.4% of subjects, OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017, primary endpoint). At the 5% significance level, there was no statistically significant difference between roflumilast 500 µg OD and roflumilast 500 µg EOD/500 µg OD treatment groups [H02] (OR 0.76, 95% CI: 0.55, 1.07; p-value 0.114). Supportive analysis Cox proportional hazards model found a similar result for roflumilast 250 µg OD/500 µg OD (HR=0.68, 95 % CI: 0.51, 0.92) and roflumilast 500 µg EOD/500 µg OD (HR=0.77, 95% CI: 0.58, 1.02) versus roflumilast 500 µg OD. A per-protocol analysis also supported the robustness of the results on the primary study endpoint.

The results of the main endpoint based on the logistic regression model with region as a covariate, instead of country, were consistent with the primary analysis results. Compared with roflumilast 500 µg OD [H01The odds of discontinuing from the Main Period were lower in the roflumilast 250 µg OD/500 µg OD treatment group (OR=0.70, 95% CI: 0.50, 0.97; p-value 0.032). The results of the sensitivity analyses by excluding the South African site for the primary endpoint supported the results of the primary analysis also yielded significant differences (OR=0.66, 95% CI: 0.47, 0.93; p-value 0.017). Most subgroups trended towards favouring the 250/500 microg OD up-titration regimen.

The analysis of TEAEs of Interest during the Main Period (Key Secondary Safety Endpoint) was entirely consistent with those of the primary endpoint. Compared with roflumilast 500 µg OD, the odds of experiencing a 'TEAE of interest' was significantly lower in the roflumilast 250 µg OD/500 µg OD treatment group (54.2% versus 45.4% of subjects, OR=0.63, 95% CI: 0.47, 0.83; p-value = 0.001). This difference was not observed between roflumilast 500 µg EOD/500 µg OD (48.3% of subjects) and the roflumilast 500 µg OD (54.2%) treatment groups in the analysis of AEs of interest.

During the main treatment period (D0-D84Vend), all the 3 treatment groups experienced statistically significant and relevant absolute mean improvements in pre-BD FEV1 versus baseline (group 1: +117 ml; group 2: +141 ml; group 3, control = +122 ml), having in mind that they were patients who had a baseline pre-BD FEV1 around 1018 ml to 1028 ml (≈10% relative increase. There were no statistically significant differences for the change in pre-bronchodilator FEV1 from baseline to end of treatment visit, between roflumilast 250 µg OD/500 µg OD versus roflumilast 500 µg OD (LS mean for treatment difference 0.02 L, 95% CI: -0.17, 0.20; p=0.871) or roflumilast 250 µg EOD/500 µg OD versus roflumilast 500 µg OD-group 3 (LS mean for treatment difference 0.13 L, 95% CI: -0.05, 0.32; p=0.162), thus suggesting that all treatment approaches had similar efficacy. Per-protocol analysis based on the VCS also found similar results.

There were numerically more patients in up-titration group that are very satisfied or satisfied (89.1%) than in the control group (85.7%). On the contrary, there were more patients dissatisfied in the control group (7.5%) than in the up-titration group 1 (3.7%). Therefore, it seems that patient's satisfaction tended to be improved with the up-titration regime than with the standard regime, and this is consistent with the primary endpoint of treatment withdrawals and the key secondary endpoint of AEs of interest (less risk of diarrhoea, insomnia, nausea). Patient's satisfaction with up-titration probably reflects a better tolerability (less adverse events with the 250 micrograms to 500 micrograms up-titration) at similar efficacy in terms of lung function improvement (i.e.: similar improvement in pre-BD FEV_1 regardless of dosing schedule, close to +100 ml). However, no definitive conclusions can be drawn due to the exploratory nature of the analysis.

3.3. Uncertainties and limitations about favourable effects

About 67% of patients was receiving a dual ICS+LABA combination during the main period, and 63% of patients were receiving a LAMA. However, no data about the aggregated number of patients receiving the ICS+LAMA combination or ICS+LABA+LAMA combination were reported initially. Submitted subgroup analyses by concomitant medication use submitted during the procedure were hampered by its post-hoc nature and lack of statistical power due to small sample sizes. Anyway, the analysis provided justify for all of the subgroups studied to take advantage of the 250 µg OD/500 µg OD up-titration regimen, regardless of concomitant LAMA or multiple concomitant medication use. In addition, patients on polypharmacy (on ≥4 concomitant medications) had a small increase (approximately 10%) in the predicted tPDE4i and could not explain the observed increase in number of AEs of interest for these patients. Therefore, no conclusion can be drawn on higher benefit of the new roflumilast dosing regime in patients on polypharmacy.

Strictly speaking, the single pivotal trial supporting this application does not fulfill with the level of statistical significance (considerably stronger than <0.05) normally required for application based on a single pivotal trial (Points to consider on application with 1. meta-analyses; 2. one pivotal study; CHMP/EWP/2330/99). However, on the one hand, the results on the primary safety endpoint were quite robust, with all sensitivity and ancillary analyses of the main endpoint showing a benefit, and with key secondary endpoint showing also a benefit in safety (e.g.: significant lower rates of TEAEs of interest) and patient's satisfaction, with no detrimental effect on efficacy (pre-BD FEV_1). On the other hand, the line extension is restricted to improve the initial tolerability and decrease early withdrawal rates with treatment by starting with a lower dose.

There are no data to ascertain whether the benefit shown at 3 months will be sustained in the long term. Even if the effect is sustained overtime, and while recognizing that a streamlined posology aimed to minimize adverse events and treatment discontinuations is a positive goal. It is agreed with the applicant that a 6.2% reduction of discontinuations in the current population treated with roflumilast would translate into a 12.9% reduction in exacerbations during the first year. According to market share of roflumilast in different regions, this would translate in the prevention of additional 340 exacerbations in Europe and 1031 exacerbations globally, compared with starting with the 500 microg dose. This benefit is added to the adverse events prevented (mainly gastrointestinal).

Although most subgroups trended towards favouring the 250/500 microg OD up-titration regimen, there were two exceptions (i.e.: non-European region and Asian race in the comparison versus roflumilast 500 µg OD). Asian patients tend to have a lower body weight than patients from Western countries. Asian race was not a significant covariate in population PK analysis, whereas in subgroup analyses of pivotal studies, the effect of roflumilast versus placebo on the rate of moderate or severe exacerbations showed no heterogeneity depending on race. Results from the new population PK model on the combined REACT and OPTIMIZE dataset identified no clinically relevant changes of systemic exposure levels in other populations of particular interest (eg, elderly patients, current smokers, female patients, or patients with high [>80 kg] or low [<60 kg] baseline body weight). Therefore, the approved maintenance dose of roflumilast 500 µg OD does not need to be adjusted in these populations.

Elderly patients seem under-represented in the OPTIMIZE study, and they are a special population at risk of adverse events and withdrawals. The applicant clarified that only 115 patients were between 75 to 84 years and only 2 patients were >85 years old. With the limitations of small sample sizes, the subgroup analyses by age showed some small increases in adverse events with age with all dosing regimes, but the benefit of the new dosing regime in avoiding adverse events and discontinuations was consistently in favour of the new roflumilast regime regardless of age.

The analysis of main interest for the down-titration phase was for those patients who did not tolerate roflumilast 500 µg OD during the Main Period and subsequently entered the down-Titration period (n=80), in order to ascertain whether a the 250 microgram dose, administered to all of them, could be effective (i.e.: whether it could produce improvements in pre-BD FEV1 from the start of down-titration to end of down-titration). Eighty subjects (of 1321 subjects, 6.0%) who did not tolerate roflumilast 500 µg OD in the Main Period were treated with roflumilast 250 µg OD for 8 weeks (n=20 for the roflumilast 250 µg OD/500 µg OD group, n=22 for roflumilast 500 µg EOD/500 µg OD group, and n=38 for the roflumilast 500 µg OD group at Baseline, V0DT). The analyses indicated no effect of the 250 microgram low-dose roflumilast in pre-BD FEV1. The lack of effect on pre-BD FEV1 of a lower roflumilast maintenance dose was consistent in the per-protocol analysis based on the VCS and in several sensitivity analyses. Product information was ammended to reinforce the message that the 250 micrograms dose is subtherapeutic and should not be used for maintenance treatment.

The results of the statistical analysis of TEAEs of Interest (diarrhea, nausea, headache, reduced appetite, insomnia, or abdominal pain) during the Main Period are supportive and consistent with the results on the main study endpoint. However, they are considered exploratory based on insufficient evidence to reject the null hypothesis for the primary endpoint at the 5% significance level [H02] in the framework of hierarchical testing (i.e.: no statistically significant differences were found for the comparison between groups 2 and 3 for the primary endpoint of premature discontinuations).

3.4. Unfavourable effects

The analysis of safety data from OPTIMIZE study does not raise any new concern about the safety of roflumilast. Most patients (63.7%) experienced TEAEs during treatment with roflumilast (61.2% in group 1, 64.3% in group 2 and 65.7% in control group), with most frequent TEAEs being gastrointestinal (diarrhoea, nausea, abdominal pain) (occurring in 37.9% of patients overall) (34.9% in group 1, 35.9% in group 2 and 42.9% in control group). SAES were reported in 4.6% of subjects. Only

0,2% of patients had a SAE related to study medication (1 patient in each group). These data are consistent with the known safety profile of roflumilast.

The analysis of TEAEs related to study drug indicated a safety advantage of the roflumilast 250 µg OD/500 µg OD up-titration regime versus the standard roflumilast 500 µg OD regime, which was largely driven by less related TEAEs of diarrhoea (13.8% vs. 21.7%; -7.9% difference) and nausea (11.3% vs. 16.3%; -5% difference).

3.5. Uncertainties and limitations about unfavourable effects

Although the OPTIMIZE study showed a benefit of the roflumilast 250 µg OD/500 µg OD up-titration regime versus the standard roflumilast 500 µg OD regimen, it was based on the assessment at 3 months. The first 4 weeks of treatment represents the dosing period most relevant to the aims of the study (i.e., to improve tolerability of roflumilast through use of alternative dosing regimens). After this time, there is no evidence to support a need for further improvements, as the frequency of AEs with roflumilast is not higher than with placebo, and the rate of withdrawals from study treatment are low.

The 250 micrograms dose is subtherapeutic and should not be used for maintenance treatment.

3.6. Effects Table

Table 30. Effects Table for roflumilast 250 microg tablets OD for up-titration phase to 500 microg OD (effective dose for severe COPD patients at risk of exacerbations despite ICS and LABD)

Effect	Short Description	Unit	Treatment (250 microg OD for 4 weeks followed by 500 microg OD for 8 weeks)	Control (500 microg OD for 12 weeks)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Premature discontinuations	Subjects prematurely discontinuing main period. Intent to treat (Full analysis set: FAS), from baseline to day 84	N (%)	81 (18.4%)	109 (24.6%)	OR: 0.66; 95%CI: 0.47 to 0.93	OPTIMIZE study report
AEs events of interest	Subjects with AEs of interest Intent to treat (Full analysis set: FAS), during the 8-week main period	N (%)	200 (45.4%)	240 (54.2%)	OR: 0.63; 95%CI: 0.47 to 0.83	OPTIMIZE study report
Unfavourable Effects (lack of beneficial effect)						

Effect	Short Description	Unit	Treatment (250 microg OD for 4 weeks followed by 500 microg OD for 8 weeks)		Control (500 microg OD for 12 weeks)	Uncertainties/ Strength of evidence	References
Effect on pre-BD FEV1 in intolerants to roflumilast who received the 250 microg dose during down-titration	Change in pre-BD FEV1 (L) versus baseline during the 8-week down-titration period Intent to treat (Full analysis set: FAS)	Litres, mean	0.01		0.00	0.02 (-0.17 to 0.20)	OPTIMIZE study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Adherence to COPD medications is a key goal in the management of COPD, as it is associated with reduced risk of death and admission to hospital due to COPD exacerbations [Vestbo et al. Thorax. 2009;64:939-43]. Therefore, any measure to improve adherence to roflumilast is welcomed to minimize the high withdrawal rates, about 30%, found in pivotal studies with roflumilast (Daxas EPAR, 2010).

The OPTIMIZE pivotal study was designed to answer that question. The study showed a better adherence (less early withdrawals: 18.4% vs. 24.6%; Diff: -6.2%) with the roflumilast 250 µg OD/500 µg OD up-titration regime versus the standard roflumilast 500 µg OD regimen. The results were further supported by a lower risk of TEAEs of interest (45.4% vs. 54.2: Diff.: -8.8%) and trend towards a better patients' satisfaction with treatment, probably related to a better tolerability.

3.7.2. Balance of benefits and risks

The analysis of TEAEs related to study drug indicated a safety advantage of the roflumilast 250 µg OD/500 µg OD up-titration regime versus the standard roflumilast 500 µg OD regime, which was largely driven by less related TEAEs of diarrhoea (13.8% vs. 21.7%; -7.9% difference) and nausea (11.3% vs. 16.3%; -5% difference). The positive effect is further supported by sensitivity analyses of the main endpoint as well as for the results of secondary endpoints of TEAEs of interest and patient-reported outcomes.

The analysis of safety data from OPTIMIZE study does not raise any new concern about the safety of roflumilast. Most patients (63.7%) experienced TEAEs during treatment with roflumilast (61.2% in group 1, 64.3% in group 2 and 65.7% in control group), with most frequent TEAEs being gastrointestinal (diarrhoea, nausea, abdominal pain) (occurring in 37.9% of patients overall) (34.9% in group 1, 35.9% in group 2 and 42.9% in control group). SAES were reported in 4.6% of subjects. These data are consistent with the known safety profile of roflumilast.

Finally, there is a risk of off-label use with the roflumilast 250 microgram as maintenance dose. The 250 micrograms dose is sub-therapeutic and should not be used for maintenance treatment. This has been adequately mentioned in section 4.2 of the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Although the OPTIMIZE study showed a benefit of the roflumilast 250 µg OD/500 µg OD up-titration regime versus the standard roflumilast 500 µg OD regime for withdrawals and TEAEs of interest, the study does not provide data beyond 3 months. In roflumilast clinical trials, Kaplan-Meier plots of time to onset of AEs show that the majority of events in the roflumilast treated-patients occur early, and that there is a plateau after 4 weeks. Therefore, the first 4 weeks of treatment represents the dosing period most relevant to the aims of the study (i.e., to improve tolerability of roflumilast through use of alternative dosing regimens). After this time, there is no evidence to support a need for further improvements, as the frequency of AEs with roflumilast is not higher than with placebo, and the rate of withdrawals from study treatment are low**.** With a 6.2% reduction of discontinuations in the current population treated with roflumilast would translate into a 12.9% reduction in exacerbations during the first year. According to market share of roflumilast in different regions, this would translate in the prevention of additional 340 exacerbations in Europe and 1031 exacerbations globally, compared with starting with the 500 microg dose. This benefit is added to the adverse events (mainly gastrointestinal) prevented.

3.8. Conclusions

The overall B/R of Daxas is positive for the lower strength 250 µg in the currently approved indication.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Daxas 250 µg, is favourable in the following indication:

Daxas is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (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.

The CHMP therefore recommends the extension of the marketing authorisation for Daxas subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The Marketing Authorisation Holder shall agree the content and format of the updated educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that all Healthcare Professionals who are expected to prescribe Daxas are provided with an updated 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 or caregivers 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 outside of the approved indication, nor for use in patients with asthma or alpha-1 antitrypsin deficiency.
- The need to inform patients about the risks of Daxas and the precautions for safe use including:
- 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. Rare instances of suicidal ideation and behaviour, including completed suicide, have been observed in patients with and without a history of depression, usually in the first weeks of treatment. Physicians should carefully assess the benefit risk balance of this treatment in patients with existing psychiatric symptoms or with history of depression. Daxas is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. If patients suffer from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt, it is recommended to discontinue treatment with Daxas.
- Patients and caregivers should be requested to report any changes in the patient`s behaviour or mood or suicidal ideation.
- 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 CYP1A2/2C19/3A4 inhibitors (such as fluvoxamine and cimetidine) or CYP1A2/3A4 inhibitors (such as enoxacin).
- 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 erythematosus, 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 or their caregivers should tell their doctor if the patient develops symptoms indicative of:
- insomnia, anxiety, depression, changes in behaviour or mood, 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
ANX 2.1 - The MAH commits to conduct a long-term comparative observational safety study. This study should be appropriate to compare the incidences of all-cause mortality, major cardiovascular events, new diagnosis of cancer, all-cause hospitalisation, hospitalisation related to respiratory disease, suicide or hospitalisation for suicide attempt, and new diagnosis of depression, tuberculosis or viral hepatitis B or C in roflumilast treated COPD patients compared with COPD patients not treated with roflumilast.	Interim Study Reports - with each PSUR Final study report by 31/03/2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable