2 Synopsis

Title of the study:

Effect of 500 µg roflumilast on exercise tolerance and respiratory reserve in patients with chronic obstructive pulmonary disease. A 12 weeks double blind study with roflumilast once daily versus placebo. The INSPIRE Study.

Investigators:

Investigators at 22 centers.

Study center(s):

Multi-center study at 22 investigational sites in 4 countries (Canada, France, Germany, Hungary).

Publication (reference): Not yet published.

Studied period (years): 29-Oct-2003 (first patient in) to 18-Feb-2005 (last patient out).

Clinical phase: IIIb

Objectives:

The aims of the present study were to investigate the effect of roflumilast 500 µg od (once daily) in the morning *versus* placebo on exercise tolerance, respiratory reserve, exertional dyspnea intensity, lung function, and quality of life; in addition, the safety and tolerability of roflumilast were examined.

Methodology:

This study was a 12-week, randomized, double-blind, multi-center, phase IIIb study. It included a 2 to 3-week single-blind baseline period and a 12-week treatment period.
During the **baseline period**, patients with stable COPD who had met the inclusion criteria received placebo tablets. Disallowed COPD medication was withdrawn at study entry or 4 weeks prior to baseline in case of long-acting anticholinergics. Patients were allowed to continue with inhaled glucocorticosteroids of up to 2000 µg/d (ex valve) of BDP-CFC (beclomethasone dipropionate - chlorofluorocarbons) equivalent if taken on a regular basis at a constant daily dose for at least 3 months prior to study entry. Short-acting anticholinergics were allowed at a constant daily dose if taken previously for at least 4 weeks prior to study entry. Rescue medication (salbutamol) was used throughout the entire study 'as-needed'.
A routine physical examination, resting ECG (electrocardiogram) and blood pressure measurement, standard laboratory work-up and pregnancy test were performed at the first

baseline Visit B0. In addition to lung function tests performed at all baseline visits (Visit B0, B1 [1 week after B0], B2 [1 week after B1], and, if applicable, B3 [1 week after B2]), single-breath diffusing capacity for carbon monoxide and the peak work capacity from an incremental cycle exercise test were determined at Visit B0. At Visit B1, B2, and the optional Visit B3, safety variables were assessed, the CCQ (Clinical COPD Questionnaire) was completed, and constant-load cycle exercise tests performed. The BDI (Baseline Dyspnea Index) was assessed at Visit B2 and optionally Visit B3.

Patients who met all randomization criteria were stratified according to their smoking status (current smokers; ex-smokers) and randomly assigned to receive either one tablet of roflumilast 500 µg od in the morning, or one tablet of placebo od in the morning during **the treatment period**. Cardiopulmonary constant-load cycle exercise tests, lung function tests, and completion of CCQ and TDI (Transition Dyspnea Index) questionnaires were done at the investigational sites 4, 8, and 12 weeks (Visit T4, T8, and T12, respectively) after the randomization visit. Safety status was assessed by monitoring of AEs (adverse events) and vital signs (all visits), laboratory tests and physical examination including ECG (for randomized patients at study termination).

Number of patients (total and for each treatment):

	Rof500	Pbo	Total
Full analysis set	**127**	**123**	**250**
Valid cases set	**109**	**109**	**218**

Pbo = placebo, Rof500 = roflumilast 500 µg once daily.

Diagnosis and criteria for inclusion:

Inclusion into the baseline period

Patients of either sex with a history of COPD of at least 6 months, ≥40 years old, who had given their written informed consent. Post-bronchodilator FEV_1/FVC (forced expiratory volume in 1 second / forced vital capacity) had to be ≤70%, FRC (functional residual capacity) ≥120% of predicted, and VO_2 (oxygen consumption) peak ≤85% of VO_2 max predicted. Included were current smokers or ex-smokers with a smoking history of at least 10 pack years, who did not suffer from any concomitant disease that interfered with study procedures or evaluation, and whose COPD was clinically stable within 4 weeks prior to Visit B0.

Exclusion criteria

The main exclusion criteria were COPD exacerbation indicated by treatment with systemic glucocorticosteroids not stopped 4 weeks prior to Visit B0; lower respiratory tract infection not resolved 4 weeks prior to Visit B0; diagnosis of asthma and/or other relevant lung disease; concurrent participation in or completion of a pulmonary rehabilitation program within 2 months preceding the baseline Visit B0; known alpha-1-antitrypsin deficiency; need for supplemental oxygen therapy; clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation; known infection with HIV, active

hepatitis and/or liver insufficiency; clinically significant cardiopulmonary abnormalities that were not related to COPD and that required further evaluation; pregnancy, breast feeding, oocyte donation or oocyte implantation planned during the study; female patient of childbearing potential and not using and not willing to continue to use a medically reliable method of contraception for the entire study duration; participation in another study within 30 days preceding baseline Visit B0, or re-entry of patients previously enrolled in this study; suspected inability or unwillingness to comply with study procedures; drug abuse; use of not allowed drugs or washout times of drugs not adhered to; suspected hypersensitivity to the study medication.

Inclusion into the treatment period (randomization criteria)

Patients were randomized 2 to 3 weeks after baseline Visit B0 if they were judged to be clinically stable and the two highest pre-bronchodilator EETs (exercise endurance times) measured at two different baseline visits had been within 10% or 2 minutes, whichever was greater.

Test product: roflumilast
Dose: 500 µg once daily in the morning
Mode of administration: tablet
Batch No.: 420210
Duration of treatment: 12 weeks

Reference product: placebo
Dose: not applicable
Mode of administration: tablet
Batch No.: 130290
Duration of administration: 12 weeks

Criteria for evaluation:

Primary variable of efficacy

Change (endpoint minus baseline value) in pre-bronchodilator EET (exercise endurance time) during constant-load symptom-limited cycle exercise.

Key secondary variables (efficacy)

Change in pre-bronchodilator FRC_{pl} (functional residual capacity determined by plethysmography), pre-bronchodilator IC (inspiratory capacity determined by slow spirometry), and pre-bronchodilator exertional dyspnea intensity at isotime.

Secondary variables (efficacy)

Secondary variables were based on the change to endpoint as well as on change to each scheduled treatment visit (except for the TDI, which was already defined as change from baseline, and exacerbations).

Post-bronchodilator EET; metabolic/cardiopulmonary parameters during constant-load exercise: pre- and post-bronchodilator VO_2, VCO_2 (carbon dioxide production), V_E (ventilation), F (breathing frequency), VT (tidal volume), SaO_2 (oxygen saturation); lung function parameters from forced spirometry: pre- and post-bronchodilator FEV_1, FVC, $FEF_{25-75\%}$ (mean forced expiratory flow between 25% and 75% of vital capacity), PEF (peak expiratory flow), FEV_1/FVC; lung function parameters from slow spirometry: post-bronchodilator IC, pre- and post-bronchodilator SVC (slow vital capacity); lung function parameters from plethysmography: post-bronchodilator FRC_{pl}, pre- and post-bronchodilator TLC (total lung capacity) and RV (residual volume), SR_{aw} (specific airway resistance); variables from single breath diffusing capacity: pre-bronchodilator D_LCO (diffusing capacity of the lungs for carbon monoxide) and KCO (gas transfer coefficient); post-bronchodilator exertional dyspnea intensity and pre- and post-bronchodilator leg discomfort; exercise IC from the constant-load exercise test; total score and domain scores of the CCQ; focal score and component scores of the TDI; number of patients with a moderate or severe COPD exacerbation and time to first moderate or severe COPD exacerbation.

Secondary variables (safety)
AEs, blood biochemistry, hematology, urine analysis, blood pressure, heart rate, physical examination.

Statistical methods:

Given a normal distribution of the primary variable pre-bronchodilator EET, a sample size of 115 patients per group was sufficient to ensure a power of 90% in correctly detecting a significant difference between the two treatments under the following assumptions: $\alpha = 0.025$, one-sided, improvement in roflumilast compared to placebo in group means = 100 seconds, common standard deviation = 230 seconds (resulting in an effect size of 100/230 = 0.435). Under similar assumptions and when the common standard deviation = 269 seconds (resulting in an effect size of 0.372), a power of 80% results when evaluating 115 patients per treatment arm.

An ANCOVA (analysis of covariance) was performed to test the hypotheses for the difference of the treatments in the primary variable. The dependent variable was the difference of the value at the endpoint visit to the value at the randomization Visit T0. Besides the treatment, the following factors and co-variables (all fixed) were included in the model: value at Visit T0, age, sex, smoking status (current smokers; ex-smokers), country, and pretreatment with ICS (inhaled corticosteroids). Smoking status was included in the model as this had been used as stratification variable in randomization. The factor pretreatment with ICS was included in the model as this was considered relevant for the patients' outcome in EET. In line with ICH E9, no interaction term was included in the primary model. The ANCOVA was also used to analyze the key secondary variables as well as the secondary variables post-bronchodilator EET, metabolic and cardiopulmonary parameters, lung function variables, and scores from CCQ and TDI, each for the endpoint as well as for the analyses for

each visit. In addition, to identify a possible heterogeneity of between-treatment effects across countries, individual country results were provided for the primary variable and the key secondary variables for the change from baseline to endpoint analysis only.

An additional repeated measurement model was analyzed to investigate the robustness of the results for all variables except for variables from single breath diffusing capacity and exacerbations. The dependent variable was the change at each scheduled visit from baseline and the factors and covariables analogous to the model described above were included. Time and a treatment-by-time interaction were included. An additional model not including the interaction term was performed for a further robustness check.

Non-parametric between-group comparisons were performed for the modified Borg scale, FEV_1/FVC, and for the scores from TDI using the Mann-Whitney U-Test to check the robustness of the results. Non-parametric within-group comparisons were done with Pratt's modification of Wilcoxon's signed rank test, where the null hypothesis was that of no difference.

The hypothesis of equality between two independent samples was analyzed with the logrank test for time to study withdrawal and time to LOE (lack of efficacy). Exacerbations were investigated based on the frequency of patients having experienced an escape criterion (LOE) or not, using Fisher's Exact Test. Categories for changes in CCQ scores and TDI scores were analyzed by Fisher's Exact Test.

SUMMARY - CONCLUSIONS

All patients included in the study had a history of COPD of at least six months. Demographic data and baseline characteristics of the full analysis set and the valid cases set were essentially comparable. The treatment groups were well balanced for most variables. The percentage of men was 2.7 times the percentage of women in the roflumilast group and 5.1 times the percentage of women in the placebo group in the full analysis set. A higher percentage of patients in the roflumilast group had been pretreated with ICS or received concomittant ICS during the study than patients in the placebo group. Results are reported for the ITT analysis, which was the primary analysis for this placebo-controlled study.

Efficacy

Primary variable pre-bronchodilator exercise endurance time

The primary variable was the change in pre-bronchodilator EET during constant-load symptom-limited cycle exercise from Visit T0 to T_{last}. Pre-bronchodilator EET increased by 14.6 s in the roflumilast and by 50.6 s in the placebo group. The within-treatment increases were not statistically significant in either group. Superiority of roflumilast over placebo was not shown for the primary variable (difference between treatments -36.0 s, one-sided $p = 0.8906$).

Change in pre-bronchodilator EET [s]: within- and between-treatment differences, endpoint analysis (ITT)

WITHIN		T0		$T_{last/end}$	T_{last} - T0		
	n	Mean	LSMean	LSMean	LSMean ± SE	95% CI	p-value[a]
ITT analysis							
Rof500	121	473.0	477. 5	492.1	14.6 ± 23.7	-32.1, 61.3	0.5380
Pbo	118	482.1	477. 5	528.1	50.6 ± 26.5	-1.5, 102.8	0.0571

BETWEEN			n	n	Difference Test - Ref for T_{last} - T0		
	Test	Ref	Test	Ref	LSMean ± SE	95% CI	p-value[b]
ITT analysis	Rof500	Pbo	121	118	-36.0 ± 29.2	-93.5, 21.5	0.8906

[a] Two-sided p-value for within-treatment differences, significance level 5%.
[b] One-sided p-value for superiority, significance level 2.5%.
Note that EET values were rounded to one digit after the decimal point.
CI = confidence interval, EET = exercise endurance time, LS = least squares, n = number of patients with data available at T0 and endpoint, Pbo = placebo, Rof500 = roflumilast 500 µg once daily, SE = standard error, T0 = randomization visit, T_{last} = last visit (ITT analysis).

Key secondary variables

Pre-bronchodilator FRC_{pl} from plethysmography showed slight decreases that were not statistically significant in either treatment group (roflumilast -0.010 L, placebo -0.057 L). Between-treatment analysis (difference between treatments 0.047 L) did not show superiority of roflumilast.

Neither the roflumilast group (-0.051 L) nor the placebo group (-0.007 L) demonstrated an improvement in **pre-bronchodilator IC** from slow spirometry at rest in within-treatment analysis. Superiority of roflumilast was not shown (between-treatment difference -0.044 L).

Patients rated **exertional dyspnea intensity during exercise** on the modified Borg scale. **At pre-bronchodilator isotime,** minor decreases indicating improvement were observed within both treatment groups (roflumilast -0.281, placebo -0.226), but were not statistically significant. Roflumilast treatment was not superior to placebo with respect to pre-bronchodilator dyspnea on exertion (difference between treatments -0.055).

Secondary variables

For secondary variables determined during exercise testing, the results at isotime are described here. Between-treatment differences for pre- and end-exercise timepoints are only mentioned where they differ in statistical significance from isotime results.

Post-bronchodilator exercise endurance time

Roflumilast-treated patients experienced a small decrease and patients in the placebo group a small increase in **post-bronchodilator EET**. Superiority of roflumilast to placebo was not demonstrated. The between-treatment difference of -64.5 s was in favor of placebo (95% CI [-123.9, -5.2]).

Metabolic and cardiopulmonary parameters during exercise

Pre- as well as **post-bronchodilator VO_2 and VCO_2** did not change significantly in either treatment group; between-treatment differences (pre- and post-bronchodilator VO_2 -0.001 L/min and -0.019 L/min, VCO_2 -0.011 L/min and -0.016 L/min) did not show superiority of roflumilast.

V_E increased in the **pre-bronchodilator** exercise tests of the roflumilast group (1.074 L/min), while placebo-receiving patients showed a decrease (-0.422 L/min); both changes were not statistically significant. The one-sided p-value of roflumilast for pre-bronchodilator V_E at isotime (between-treatment difference 1.496 L/min, p = 0.0252) was close to, but did not reach the significance level of 0.025. Roflumilast was superior to placebo at the end-exercise timepoint (between-treatment difference 1.853 L/min, one-sided p = 0.0068), but was not superior before exercise (difference 0.241 L/min). A small, statistically significant improvement in **post-bronchodilator V_E** was seen in roflumilast-treated patients (1.978 L/min, two-sided p = 0.0022), while the increase in the placebo group was lower and not statistically significant (0.843 L/min, two-sided p = 0.2283). Roflumilast did not show superiority over placebo for post-bronchodilator V_E (between-treatment difference 1.135 L/min).

Roflumilast-treated patients raised their **pre-bronchodilator F** statistically significantly (1.076 breaths/min, two-sided p = 0.0134) while patients in the placebo group had a smaller increase that was not statistically significant (0.118 breaths/min). The increase in **post-bronchodilator F** was statistically significant in the roflumilast (2.732 breaths/min, two-sided p <0.0001) and not significant in the placebo group (0.698 breaths/min, two-sided p = 0.2328). Superiority of roflumilast to placebo was not shown for pre- or post-bronchodilator F. Placebo was favored for post-bronchodilator F (between-treatment difference of 2.034 breaths/min, 95% CI [0.752, 3.315]).

Pre-bronchodilator VT did not improve in either treatment group; the between-treatment difference of 2.763 mL was in favor of roflumilast, superiority was not shown. **Post-bronchodilator VT** decreased statistically significantly in roflumilast-treated patients (-53.050 mL, two-sided p = 0.0122) and showed a minor increase in the placebo group (4.885 mL, two-sided p = 0.8321). Between-treatment analysis did not demonstrate superiority of roflumilast; at isotime, not at the pre- and end-exercise timepoints, placebo was favored for post-bronchodilator VT (difference -57.935 mL, 95% CI [-107.526, -8.344]).

SaO_2 measured **prior to bronchodilator** inhalation improved with roflumilast treatment (0.3%) while it decreased with placebo (-0.4%); both within-treatment changes were not statistically significant. Superiority of roflumilast to placebo was demonstrated for pre-bronchodilator SaO_2 at isotime (between-treatment difference 0.7%, one-sided p = 0.0098). Roflumilast was superior to placebo at the end-exercise timepoint (difference 0.7%, one-sided p = 0.074) and not superior at the pre-exercise timepoint (difference 0.4%). A statistically significant improvement was seen in **post-bronchodilator SaO_2** in roflumilast-treated patients (0.4%, two-sided p = 0.0441) and not in the placebo group (-0.1%, two-sided

p = 0.7991). The results were numerically in favor of roflumilast, but superiority was not shown at isotime (between-treatment difference 0.5%, 95% CI [-0.0, 1.0], one-sided p = 0.0325). Roflumilast was superior with respect to pre-exercise (between-treatment difference 0.5%, one-sided p = 0.0145) and end-exercise timepoints (difference 0.5%, one-sided p = 0.0192) for post-bronchodilator SaO_2.

Variables from forced spirometry

Roflumilast-treated patients experienced a statistically significant improvement (0.056 L, two-sided p = 0.0312) in **pre-bronchodilator FEV_1** in contrast to patients who had received placebo (-0.028 L, two-sided p = 0.3424). Roflumilast demonstrated superiority to placebo with respect to pre-bronchodilator FEV_1 (difference between treatments 0.084 L, one-sided p = 0.0037).The within-treatment increase in **post-bronchodilator FEV_1** in the roflumilast group (0.033 L) and the decrease in the placebo group (-0.042 L) were not statistically significant. Roflumilast was superior to placebo in between-treatment analysis of post-bronchodilator FEV_1 (difference 0.075 L, one-sided p = 0.0149).

Within-treatment changes for **pre- and post-bronchodilator FVC** were not statistically significant for either treatment group and superiority of roflumilast in between-treatment analysis was not demonstrated (between-treatment difference pre-bronchodilator FVC 0.043 L, post-bronchodilator 0.036 L).

Pre-bronchodilator FEV_1/FVC increased in the roflumilast group (1.3%, two-sided p = 0.0241) and decreased with placebo (-0.5%, two-sided p = 0.3888). Roflumilast was superior to placebo for pre-bronchodilator FEV_1/FVC (between-treatment difference 1.8%, one-sided p = 0.0044). **Post-bronchodilator FEV_1/FVC** increased in the roflumilast group with statistical significance (1.2%, two-sided p = 0.0237), and decreased in the placebo group (-0.2%, two-sided p = 0.7203). Roflumilast was superior to placebo in terms of post-bronchodilator FEV_1/FVC (difference 1.4%, one-sided p = 0.0143). Similar results were seen in the **non-parametric analysis of FEV_1/FVC**. Superiority of roflumilast over placebo was demonstrated for pre- and post-bronchodilator FEV_1/FVC (between-treatment difference 2.0%, one-sided p = 0.0003 and difference 1.0%, p = 0.0037, respectively).

Pre-bronchodilator $FEF_{25-75\%}$ increased in the roflumilast group (0.017 L/s) and decreased in the placebo group (-0.044 L/s) without statistical significance. Roflumilast showed superiority over placebo for pre-bronchodilator $FEF_{25-75\%}$ (difference 0.062 L/s, one-sided p = 0.0180). The rise in **post-bronchodilator $FEF_{25-75\%}$** in roflumilast patients was not statistically significant (0.007 L/s), while the placebo group experienced a statistically significant decrease (-0.068 L/s, two-sided p = 0.0154). Superiority of roflumilast treatment was seen with this parameter (difference between treatments 0.075 L/s, one-sided p = 0.0069).

PEF values before bronchodilator inhalation decreased within each treatment group, with a stronger, statistically significant reduction in the placebo group (roflumilast -1.5 L/min, two-sided p = 0.7136; placebo -10.3 L/min, two-sided p = 0.0276). Superiority of roflumilast was not shown for pre-bronchodilator PEF. **Post-bronchodilator PEF** decreased to a larger extent in patients who had received placebo (roflumilast -0.8 L/min, two-sided p = 0.8573; placebo

-9.7 L/min, two-sided p = 0.0479). Superiority for roflumilast was not shown (difference 9.0 L/min, one-sided p = 0.0457).

Variables from slow spirometry

Pre- and post-bronchodilator SVC did not exhibit statistically significant changes in within-treatment analysis and superiority for roflumilast was not demonstrated (between-treatment differences pre-bronchodilator SVC -0.020 L, post-bronchodilator SVC 0.004 L). **Post-bronchodilator IC** changes in either treatment group were small and not statistically significant; superiority of roflumilast was not demonstrated (difference between treatments -0.015 L).

Variables from plethysmography

Post-bronchodilator FRC_{pl} showed a minor, not statistically significant increase in the roflumilast and a small decrease in the placebo group; roflumilast was not superior to placebo (between-treatment difference 0.073 L).

Minor changes that were not statistically significant were observed for **pre- and post-bronchodilator TLC and RV** in both treatment groups; superiority of roflumilast was not shown for these variables (between-treatment difference pre- and post-bronchodilator TLC: -0.016 L, 0.034 L; RV: -0.011 L, 0.009 L).

Pre-bronchodilator SR_{aw} was more reduced in the roflumilast group (-0.187 kPa x s, two-sided p = 0.0377) than in the placebo group (-0.023 kPa x s, two-sided p = 0.8243); superiority of roflumilast was not demonstrated (between-treatment difference -0.165 kPa x s). Roflumilast-treated patients improved in **post-bronchodilator SR_{aw}** with statistical significance (-0.159 kPa x s, two-sided p = 0.0356), while patients in the placebo group increased in SR_{aw} (0.031 kPa x s, two-sided p = 0.7145); superiority of roflumilast was demonstrated for post-bronchodilator SR_{aw} (difference between treatments -0.190 kPa x s, one-sided p = 0.0214).

Variables from single breath diffusing capacity

The within-treatment decreases of **D_LCO** were small and not statistically significant. **KCO** decreased to a small extent in the roflumilast group, while it increased somewhat in the placebo group. Changes were not statistically significant in either treatment group. Between-treatment differences were small (D_LCO -0.210 mL/min/mmHg, KCO -0.087 mL/min/mmHg/L lung volume) and superiority of roflumilast was not demonstrated.

Level of discomfort during exercise (modified Borg scale)

Within-treatment increases for **pre-bronchodilator leg discomfort** were higher in the roflumilast group (0.355) than in the placebo group (0.011), but not statistically significant in either group; superiority of roflumilast was not shown. The level of **leg discomfort at post-bronchodilator isotime** was statistically significantly increased in the roflumilast (0.859, two-sided p = 0.0001), but not the placebo group (0.011, two-sided p = 0.9627). Superiority of roflumilast was not shown, between-treatment analyses favored placebo at isotime

(difference of 0.848, 95% CI [0.315, 1.380]) and the end-exercise timepoint. Roflumilast led to a statistically significant increase (0.463, two-sided p = 0.0490) of post-bronchodilator exertional dyspnea intensity at isotime, while a minor reduction was observed for placebo (-0.006). Superiority of roflumilast was not seen (between-treatment difference 0.469).

Exercise IC [L] (from the constant-load exercise test)

There was no improvement in exercise IC within the treatment groups at pre- or post-bronchodilator isotime. **Pre-bronchodilator exercise IC** decreased less in the roflumilast (-0.025 L, two-sided p = 0.5123) than in the placebo group (-0.149 L, two-sided p = 0.0007). Roflumilast demonstrated superiority to placebo for pre-bronchodilator exercise IC at isotime (between-treatment difference 0.124 L, one-sided p = 0.0042), not at pre- and end-exercise timepoints. **Post-bronchodilator** within-treatment decreases of **exercise IC** were similar and statistically significant in the two treatment groups (roflumilast -0.122 L, two-sided p = 0.0031; placebo -0.121 L, two-sided p = 0.0121); superiority of roflumilast was not demonstrated.

Clincal COPD Questionnaire

No statistically significant changes in **CCQ** domain scores or total score occurred in either treatment group. Between-treatment analyses (difference in total score -0.07) did not show superiority of roflumilast.

Baseline/Transition Dyspnea Index

The primary analysis for the **BDI/TDI** dyspnea indexes was non-parametric. TDI focal or individual domain scores did not indicate clinically relevant changes in either treatment group; point estimates for between-treatment differences were zero in all instances.

Parametric analyses revealed statistically significant within-treatment improvements in the roflumilast, but not in the placebo group. Superiority of roflumilast was not shown for T_{last} (focal score between-treatment difference 0.68, one-sided p = 0.0388). Superiority of roflumilast for the focal score of the TDI was demonstrated for Visit T8 (difference between treatments 0.81, one-sided p = 0.0106) and Visit T12 (difference between treatments 0.84, one-sided p = 0.0147).

Parametric repeated measurement analyses demonstrated superiority of roflumilast for the focal score (between-treatment difference 0.68, one-sided p = 0.0078) and all domain scores.

COPD exacerbations

Moderate or severe **COPD exacerbations** were experienced by 6 out of 127 patients in the roflumilast treatment group and by 4 out of 123 patients in the placebo group (FAS).

Safety

During the present study, 115 (46.0%) patients experienced treatment-emergent AEs. The percentage of patients with AEs was higher in the roflumilast-treated (49.6%) than in the placebo group (42.3%).

AEs that were balanced between roflumilast and placebo belonged most frequently to the System Organ Classes ‘infections and infestations’ (roflumilast 17.3%, placebo 16.3%) and

'respiratory, thoracic and mediastinal disorders' (roflumilast 12.6%, placebo 14.6%). The following AEs had a more than 2% higher frequency in patients treated with roflumilast than with placebo, by MedDRA preferred terms: diarrhoea (roflumilast 10.2%, placebo 1.6%), chronic obstructive airways disease exacerbated (roflumilast 6.3%, placebo 4.1%), dizziness (roflumilast 6.3%, placebo 1.6%), headache (roflumilast 5.5%, placebo 1.6%), anxiety (roflumilast 3.9%, placebo 0%), weight decreased (roflumilast 3.9%, placebo 0%), insomnia (roflumilast 3.1%, placebo 0%), tremor (roflumilast 2.4%, placebo 0%), asthenia (roflumilast 2.4%, placebo 0%), and fatigue (roflumilast 2.4%, placebo 0%). Dyspnoea exacerbated was an AE in 4.9% of placebo-treated, but only in 0.8% of roflumilast-treated patients.

Most patients experienced AEs which were assessed as not related or unlikely related to study medication by the investigator. At least likely related AEs occurred more frequently in patients treated with roflumilast (15.7%) than in patients in the placebo group (5.7%). AEs assessed by the investigator as definitely related were experienced by two patients in the roflumilast group (one patient with headache, one patient with two episodes of diarrhea).

No patients died during the study. During treatment, eight SAEs were reported in five roflumilast-treated patients and eight SAEs in seven patients in the placebo group. All SAEs in roflumilast-treated patients were assessed as not related to study medication by investigator and sponsor.

In the roflumilast group, nine patients with non-serious AEs left the study prematurely. In four of these cases the AEs were assessed as unlikely or not related by the investigator. Five of the roflumilast-treated patients experienced AEs assessed as likely or definitely related to study medication, including, by MedDRA preferred term, decreased appetite, diarrhoea, dizziness, dry mouth, fatigue, gastrointestinal disorder, headache, nausea, and weight decreased. Six patients with non-serious AEs from the placebo group discontinued the study.

SAEs caused three patients in the roflumilast group and three patients in the placebo group to leave the study prematurely. The SAEs of the roflumilast-treated patients that discontinued (one patient with adenocarcinoma pancreas, one patient with chronic obstructive airways disease exacerbated and lung neoplasm, one patient with orchitis and epididymitis) were assessed as not related.

There were no major changes in laboratory values over time in either treatment group. Laboratory AEs were reported for three patients in the roflumilast group and for four patients in the placebo group. All laboratory AEs were not serious and mild or moderate in intensity. One case of 'hemoglobin decreased' in the roflumilast group was assessed as likely related to study medication by the sponsor and as unlikely related by the investigator. All other laboratory AEs were assessed as not or unlikely related to study medication.

Mean blood pressure and heart rate were stable during the study. There were no major differences between the treatment groups.

Conclusions

The present study did not show superiority of roflumilast 500 µg/d, given od orally in the morning, over placebo for the primary variable pre-bronchodilator EET during constant-load symptom-limited cycle exercise or the key secondary variables pre-bronchodilator FRC_{pl}, pre-bronchodilator IC at rest, and pre-bronchodilator exertional dyspnea intensity at isotime. Superiority of roflumilast was demonstrated with respect to the secondary variables pre-bronchodilator FEV_1, FEV_1/FVC, FEF_{25-75}, exercise IC (at isotime), SaO_2 (at isotime and end-exercise timepoint), and post-bronchodilator FEV_1, FEV_1/FVC, FEF_{25-75}, SR_{aw}, and SaO_2 (at the pre- and end-exercise timepoint). The known safety profile of roflumilast was not changed by this study.