1 Title Page Clinical Study Report No. 134/2006 Version (2.0)

Title: Effect of roflumilast on exacerbation rate in patients with chronic obstructive pulmonary disease. The OPUS Study		Version date:	23-Dec-2008
		INN:	Roflumilast
		Program/Project No.:	BY217
		Compound No.:	B9302-107
		Batch No.: Roflumilast 500 µg Placebo	 320190 320200, 420210 420240, 130280
Study Protocol No.:	**BY217/M2-111**	Development phase:	III
EudraCT No:	not applicable	Indication studied:	COPD
Study initiation date:	09-Dec-2003	Date of early termination:	not applicable
Study completion date:	02-Dec-2005	Summary of modifications:	No. 1

Name and country of investigators:
188 centers in Canada, France, Germany, Poland, South Africa and the United States of America participated.
Coordinating investigator:
[redacted] Nycomed GmbH, Konstanz, Germany (until 29-Apr-2005), Nebraska Medical Center, Omaha, NE 68198-5125, USA (from 29-Apr-2005).

Name of sponsor's responsible medical officer: Dr Dirk Bredenbröker, Nycomed GmbH, Konstanz, Germany (until March 2008), Dr Udo-Michael Göhring, Nycomed GmbH (RDM/MR), Konstanz, Germany (from March 2008)

Person(s) responsible for study report:
Dr Klaus Fichtner, Nycomed GmbH (formerly ALTANA Pharma AG), Konstanz, Germany

Sponsors contact persons:
See accompanying letter of the regulatory approval application

Statement of GCP compliance:
This study was performed in accordance with Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95)

Archiving responsibility for essential documents:
Department RDM/CK at Nycomed GmbH, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

2 Synopsis

Title of the study: Effect of roflumilast on exacerbation rate in patients with chronic obstructive pulmonary disease.

The OPUS Study.

Investigator(s) and study center(s): A total of 188 investigators at 188 centers located in Canada (13), France (12), Germany (14), Poland (10), South Africa (15), and the USA (124) participated in the study.

Coordinating investigator(s): [redacted] ALTANA Pharma AG (until 29-Apr-2005), followed by [redacted] Department of Internal Medicine – Pulmonary, 985125 Nebraska Medical Center, Omaha, NE 68198-5125, USA

Publication (reference): Not applicable

Studied period: 09-Dec-2003 (first patient in) to 02-Dec-2005 (last patient out)

Clinical phase: III

Objectives:

- To compare the effects of 500 µg roflumilast od (once daily) vs (versus) placebo administered over 52 weeks on exacerbation rate, lung function, quality of life, and health economics in patients with COPD (chronic obstructive pulmonary disease);
- to investigate the safety and tolerability of roflumilast.

Methodology:

Multicenter, multinational, double-blind, randomized, parallel group study (with a single-blind placebo baseline period).

No. of patients (total and for each treatment) planned and analyzed:

It was planned to randomize 1100 patients (550 per treatment group).

Analyzed sets:

	Enrolled	Randomized	Safety set	Full analysis set	Valid cases set
Rof500		568	567	567	417
Pbo		608	606	606	468
Total	1801	1176	1173	1173	885

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

Diagnosis and main criteria for inclusion:

Inclusion criteria:

Patients meeting the following criteria were considered for inclusion in the baseline period:

- written informed consent was given;
- age ≥40 years;
- post-bronchodilator FEV_1 (forced expiratory volume in 1 second)/FVC (forced vital capacity) ratio ≤70%;
- post-bronchodilator FEV_1 % predicted ≤50;
- current smoker or ex-smoker (smoking cessation at least one year ago) with a smoking history of at least 10 pack years;
- not suffering from any concomitant disease that could have interfered with study procedures or evaluation;
- clinically stable COPD indicated by no exacerbation and no change in COPD treatment within 4 weeks prior to Baseline Visit B0;
- availability of a chest x-ray dated a maximum of 6 months prior to Baseline Visit B0 or willingness to have a chest x-ray performed before Visit B0.

Randomization criteria

Patients were randomized after 4 weeks of the baseline period, if the following criteria were fulfilled:

- judged to be clinically stable and no moderate/severe exacerbations between B0 and T0;
- negative hemoccult (guaiac) test at B0;
- medication compliance ≥80% and ≤125%.

Test product, dose, mode of administration, batch no.: Roflumilast tablet, 500 µg od, orally, 320190, 320200, and 420210

Reference product, dose, mode of administration, batch no.: Placebo tablet, od, orally, 420240 and 130280

Duration of treatment: 52 weeks

Criteria for evaluation:

Efficacy evaluation (primary)

- mean change from baseline (T0) during the treatment period in pre-bronchodilator FEV_1 [L] (repeated measurements ANCOVA including all scheduled visits from T0 to the final visit [T52 or early termination]);
- number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year (Poisson regression model).

Efficacy evaluation (key-secondary):

- mean change from baseline (T0) during the treatment period in post-bronchodilator FEV_1 [L] (repeated measurements ANCOVA including all visits from T0 to the final visit [T52 or early termination]);
- number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in the population of patients with post-bronchodilator FEV_1 <30% of predicted at T0 (Poisson regression model);
- number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in the population of patients with a medical history of chronic bronchitis with or without a medical history of emphysema (Poisson regression model);
- number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in the population of patients with a mean daily cough score of ≥2 in the week before randomization (T0; Poisson regression model);
- number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in the population of patients with a mean daily cough score of ≥1 in the week before randomization (T0; Poisson regression model).
- number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in the population of patients with a history of at least one moderate or severe COPD exacerbation in the year prior to B0 (Poisson regression model);
- number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids and/or antibiotics or severe COPD exacerbations per patient per year (Poisson regression model);
- number of mild or moderate or severe COPD exacerbations per patient per year (Poisson regression model).

Efficacy evaluation (secondary):

- pre- and post-bronchodilator expiratory lung function variables: $FEV_{1,}$[1] FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$ (forced expiratory flow at 25, 50, or 75% of vital capacity), $FEF_{25-75\%}$ (forced expiratory flow between 25% and 75% of vital capacity), $FEF_{200-1200}$ (forced expiratory flow between 200 and 1200 mL of vital capacity), PEF (peak expiratory flow), FEV_3, FEV_6 (forced expiratory volume in 3 or 6 seconds), AEX (area under the expiratory curve), SVC (slow vital capacity), FEV_1/FVC, ERV (expiratory reserve volume), TV (tidal volume);
- pre- and post-bronchodilator inspiratory lung function variables: IC (inspiratory capacity), FIV_1 (forced inspiratory volume in 1 second), PIF (peak inspiratory flow), FVC_{in} (forced vital capacity, inspiratory), IRV (inspiratory reserve volume);
- COPD exacerbations: moderate (treated with oral or parenteral glucocorticosteroids) or severe exacerbations,[1] moderate (treated with oral or parenteral glucocorticosteroids and/or antibiotics) or severe exacerbations,[1] severe exacerbations, moderate (treated with oral or parenteral glucocorticosteroids) exacerbations, moderate (treated with oral or parenteral glucocorticosteroids and/or antibiotics) exacerbations, severe or moderate (treated with oral or parenteral glucocorticosteroids and/or antibiotics) or mild exacerbations,[1] moderate (treated with oral or parenteral glucocorticosteroids and/or antibiotics) or mild exacerbations, mild exacerbations;
- BDI (baseline dyspnea index)/TDI (transition dyspnea index): focal score, component scores (functional impairment, magnitude of task, magnitude of effort);
- diary variables: morning PEF, daily use of rescue medication, COPD symptom scores (score sum, breathlessness, cough, sputum), COPD symptom-free days, rescue medication-free days;
- SGRQ (St Georges Respiratory Questionnaire): total score, component scores (activity, impact, symptoms);
- mortality;
- time to study withdrawal: time to study withdrawal due to any reason,[2] time to study withdrawal due to a COPD exacerbation, time to study withdrawal due to AE[2] (adverse event).

Safety evalution (secondary):

AEs, standard laboratory, hemoccult/guaiac test, ECG (electrocardiogram), 24-h Holter ECG, vital signs, physical examination, body weight and BMI (body mass index).

[1] Analyses other than the primary and key-secondary analyses.

[2] These variables were not analyzed for efficacy but for completeness reasons.

Statistical methods:

For all variables statistical tests comparing roflumilast 500 µg od vs placebo were performed. For the lung function parameters, the scores from BDI/TDI and SGRQ, as well as for morning PEF from diary repeated measurements and endpoint ANCOVAs (analyses of covariance) were done. Repeated measurements ANCOVAs were also performed for the daily use of rescue medication and the COPD symptom scores. The number of COPD exacerbations was analyzed with a Poisson regression model and a Wilcoxon rank-sum test. Furthermore, survival analyses were performed using Cox-regression models and log-rank tests. Patients with or without an event were analyzed with a log-binomial regression model and Fisher's exact test. Additional non-parametric analyses were performed for the ratio of FEV_1/FVC, for the scores from BDI/TDI, and the diary parameters (except morning PEF).

The primary variables were tested in an a-priori order, so that superiority of roflumilast 500 µg od to placebo needed to be shown first for pre-bronchodilator FEV_1 before superiority of roflumilast 500 µg od to placebo was tested for the number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations in a confirmatory manner. If both primary variables proved to be significant, the key-secondary variables were tested hierarchically in a confirmatory manner. The ITT (intention-to-treat) analysis was the primary analysis for the superiority testing. The PP (per-protocol) analysis was used to assess the robustness of the results.

The secondary efficacy variables were analyzed in an exploratory manner. AEs were analyzed using descriptive statistics.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

In total, 1176 patients were randomized (1:1) and 1173 patients were included in the FAS (full analysis set) for the ITT analysis (roflumilast 500 µg: 567 patients, placebo: 606 patients). In general, the two treatment groups were well comparable with respect to patient disposition, demographic and other baseline characteristics (see Table below).

Demographic and other baseline characteristics by treatment

		FAS		VCS	
		Rof500 (N = 567)	**Pbo (N = 606)**	**Rof500 (N = 417)**	**Pbo (N = 468)**
Age [years]	Median (range)	65 (40, 87)	64 (41, 86)	64 (40, 83)	64 (42, 84)
Weight [kg][a]	Mean ± SD	75 ± 18.3	75 ± 19.1	76 ± 18.1	75 ± 19.2
Height [cm]	Mean ± SD	170 ± 9.5	170 ± 9.3	170 ± 9.1	170 ± 9.3
BMI [kg/m^2][a]	Mean ± SD	26 ± 5.7	26 ± 5.7	26 ± 5.7	26 ± 5.7
Sex [n (%)][b]	Female	180 (31.7)	206 (34.0)	115 (27.6)	153 (32.7)
	Male	387 (68.3)	400 (66.0)	302 (72.4)	315 (67.3)
Race [n (%)][b]	American Indian or Alaska Native	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
	Asian	3 (0.5)	1 (0.2)	2 (0.5)	1 (0.2)
	Black	20 (3.5)	21 (3.5)	15 (3.6)	13 (2.8)
	Caucasian	532 (93.8)	564 (93.1)	392 (94.0)	436 (93.2)
	Hispanic or Latino	5 (0.9)	5 (0.8)	3 (0.7)	5 (1.1)
	Native Hawaiian, other Pacific Islander	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
	Other	7 (1.2)	13 (2.1)	5 (1.2)	12 (2.6)
COPD severity (GOLD) [n (%)][b]	Very severe	137 (24.2)	165 (27.2)	93 (22.3)	126 (26.9)
	Severe	366 (64.6)	396 (65.3)	278 (66.7)	313 (66.9)
	Moderate	64 (11.3)	45 (7.4)	46 (11.0)	29 (6.2)
Smoking status [n (%)][b]	Ex-smokers	327 (57.7)	341 (56.3)	231 (55.4)	272 (58.1)
	Current smokers	240 (42.3)	265 (43.7)	186 (44.6)	196 (41.9)
Pack years [n]	Mean ± SD	50 ± 28.2	51 ± 26.7	50 ± 26.3	50 ± 25.5
Pre-BD FEV_1 at T0 [L]	Mean ± SD	0.96 ± 0.4	0.93 ± 0.3	0.99 ± 0.4	0.93 ± 0.3
[% of pred.]	Mean ± SD	31.3 ± 9.9	30.8 ± 9.1	31.7 ± 9.6	30.6 ± 8.7
Post-BD FEV_1 at T0 [L]	Mean ± SD	1.12 ± 0.4	1.09 ± 0.4	1.16 ± 0.4	1.09 ± 0.3
[% of pred.]	Mean ± SD	36.8 ± 10.7	36.0 ± 9.8	37.2 ± 10.4	35.8 ± 9.3
FEV_1 rev. at T0 [mL increase]	Mean ± SD	162.6 ± 143.9	157.4 ± 155.3	167.7 ± 146.0	161.3 ± 151.8
[% increase]	Mean ± SD	18.9 ± 16.7	18.8 ± 17.7	18.8 ± 16.6	19.2 ± 18.0
Post-BD FEV_1/FVC at T0 [%]	Mean ± SD	43.17 ± 10.6	42.82 ± 9.9	43.34 ± 10.0	42.60 ± 9.7
SGRQ total score at T0[a]	Mean ± SD	48.12 ± 17.2	49.13 ± 16.6	47.74 ± 17.6	49.17 ± 16.6
Mean cough score at W0[a,c]	Mean ± SD	1.14 ± 0.8	1.14 ± 0.7	1.19 ± 0.8	1.15 ± 0.7
Mean sputum score at W0[a,d]	Mean ± SD	1.06 ± 0.8	1.10 ± 0.8	1.09 ± 0.8	1.13 ± 0.7

[a] These baseline parameters did not necessarily include data from all patients in the analysis sets.
[b] Percentages are based on the number of patients in a treatment group.
[c] Cough scores: 0 = no cough, 1 = mild cough (at some time a day), 2 = moderate cough (regularly during the day), 3 = severe cough.
[d] Sputum scores: 0 = no sputum production, 1 = mild sputum production, 2 = moderate sputum production, 3 = severe sputum production.
BD = bronchodilator, BMI = body mass index, FAS = full analysis set, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, N = number of patients in respective treatment group, n = number of patients, Pbo = placebo, pred. = predicted, rev. = reversibility, Rof500 = roflumilast 500 µg once daily, SD = standard deviation, T0 = randomization visit, VCS = valid cases set, W0 = week before randomizaton visit.

Efficacy

For most variables, efficacy results are summarized for the repeated measurements analysis and the Poisson regression model, which were the primary efficacy analyses. The analysis of change from baseline generally supported the results of the repeated measurements analysis.

If not indicated otherwise, results of the ITT analysis are reported which was the primary analysis in this superiority study.

Primary efficacy variables

Pre-bronchodilator FEV_1

Pre-bronchodilator FEV_1 increased with roflumilast (LSMean: 29 mL) whereas it deteriorated with placebo (LSMean: -7 mL). The analysis of between-treatment differences demonstrated superiority of roflumilast 500 µg od to placebo (difference in LSMeans: 36 mL, one-sided p = 0.0001, ITT, confirmed by PP; see table below).

Change from T0 in pre-bronchodilator FEV_1 [L]: within- and between-treatment differences, repeated measurements analysis (ITT, PP)

WITHIN				Mean	Within-treatment difference	
		n	n obs	at T0	LSMean ± SE	95% CI
ITT	Rof500	488	2957	0.950	0.029 ± 0.008	0.014, 0.044
	Pbo	541	3526	0.920	-0.007 ± 0.007	-0.021, 0.007
PP	Rof500	352	2220	0.986	0.026 ± 0.009	0.009, 0.044
	Pbo	405	2574	0.920	-0.011 ± 0.008	-0.027, 0.005

BETWEEN					Difference Test - Ref			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	1-sided p-value[a]	2-sided p-value[b]
ITT	Rof500	Pbo	488	541	0.036 ± 0.010	0.016, 0.055	0.0001	0.0003
PP	Rof500	Pbo	352	405	0.037 ± 0.011	0.015, 0.059	0.0006	0.0011

[a] One-sided p-value for superiority, significance level 2.5%.

[b] Two-sided p-value for between-treatment differences, significance level 5%.

CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, LS = least squares, n = number of patients with data available, n obs = number of observations, Pbo = placebo, Rof500 = roflumilast 500 µg once daily, SE = standard error of the LSMean, T0 = randomization visit.

Number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year

The Poisson regression model (primary analysis) revealed that the rate of moderate steroid-treated exacerbations or severe exacerbations per patient per year was lower in the roflumilast treatment group than in the placebo group (0.623 vs 0.720, see table below). The reduction compared with placebo was –13.5% in the ITT and –16.4% in the PP analysis. The differences between treatments were not statistically significant.

Frequency of moderate steroid-treated exacerbations or severe exacerbations per patient per year: Poisson regression model (ITT, PP)

	Rof500		Pbo		Ratio Rof500/Pbo					
	n	Rate	n	Rate	Rate ratio	Change [%]	SE	95% CI	1-sided p-value[a]	2-sided p-value[b]
ITT	567	0.623	606	0.720	0.865	-13.5	0.086	0.713, 1.051	0.0720	0.1440
PP	417	0.552	468	0.660	0.836	-16.4	0.097	0.666, 1.050	0.0618	0.1237

[a] One-sided p-value for superiority, significance level 2.5%.
[b] Two-sided p-value for between-treatment differences, significance level 5%.
Steroid-treated was defined by treatment with oral or parenteral glucocorticosteroids.
CI = confidence interval, n = number of patients included in analyses, Pbo = placebo, Rof500 = roflumilast 500 µg once daily, SE = standard error.

Key-secondary efficacy variables

Since superiority of roflumilast 500 µg od to placebo was not shown for the primary variable number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in the primary Poisson regression analysis, confirmatory hypothesis testing was stopped and the key-secondary variables were analyzed only in an exploratory manner.

Post-bronchodilator FEV_1

Post-bronchodilator FEV_1 increased over the treatment period with roflumilast (LSMean: 21 mL) and decreased with placebo (LSMean: -17 mL). A statistically significant between-treatment difference in favor of roflumilast was observed (difference in LSMeans: 38 mL, p = 0.0001, one-sided, ITT, confirmed by PP).

Number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in subgroups

In patients with **very severe COPD** a small increase (+8.6%) in the number of moderate exacerbations treated with oral or parenteral glucocorticosteroids or severe exacerbations was seen with roflumilast when compared with placebo (one-sided p = 0.6767; see Table below). A reduction (-19%) in the frequency of moderate exacerbations treated with glucocorticosteroids or severe exacerbations could be observed in patients with a **history of chronic bronchitis with or without emphysema** with roflumilast when compared with placebo (one-sided p = 0.0518). For patients with a **mean cough score ≥2 during W0** superiority of roflumilast to placebo was shown with -38.5% fewer moderate exacerbations treated with oral or parenteral glucocorticosteroids or severe exacerbations reported with roflumilast when compared with placebo (p = 0.0130, one-sided, ITT, not confirmed by PP). In patients with a **mean cough score of ≥1 during W0** the treatment effect was less prominent (-9.8% fewer moderate steroid-treated exacerbations or severe exacerbations with roflumilast when compared with placebo, one-sided p = 0.1945). Patients with a **history of ≥1**

exacerbation in the year prior to B0 experienced 0.910 and 1.018 moderate steroid-treated exacerbations or severe exacerbations per patient per year with roflumilast and placebo, respectively, resulting in a 10.6% reduction in these type of exacerbations with roflumilast when compared with placebo (one-sided p = 0.2107).

Frequency of moderate steroid-treated exacerbations or severe exacerbations per patient per year in subgroups: Poisson regression model (ITT)

	Rof500		Pbo		Ratio Rof500/Pbo					
Subgroup	n	Rate	n	Rate	Rate ratio	Change [%]	SE	95% CI	1-sided p-value[a]	2-sided p-value[b]
COPD severity										
Very severe	137	1.054	165	0.971	1.086	8.6	0.194	0.764, 1.542	0.6767	0.6466
History of COPD										
Chronic bronchitis with or without emphysema	374	0.614	372	0.758	0.810	-19.0	0.105	0.629, 1.044	0.0518	0.1036
Mean cough score during W0										
≥2	124	0.631	117	1.026	0.615	-38.5	0.134	0.401, 0.944	0.0130	0.0261
≥1	376	0.714	419	0.792	0.902	-9.8	0.108	0.713, 1.141	0.1945	0.3889
History of COPD exacerbations in the year prior to B0										
≥1 COPD exacerbation	217	0.910	229	1.018	0.894	-10.6	0.125	0.680, 1.175	0.2107	0.4214

[a] One-sided p-value for superiority, significance level 2.5%.
[b] Two-sided p-value for between-treatment differences, significance level 5%.
Steroid-treated was defined by treatment with oral or parenteral glucocorticosteroids.
B0 = first baseline visit, CI = confidence interval, COPD = chronic obstructive pulmonary disease, n = number of patients included in analyses, Pbo = placebo, Rof500 = roflumilast 500 µg once daily, SE = standard error, W0 = week before randomization visit.

Number of moderate or severe COPD exacerbations and number of mild, moderate or severe COPD exacerbations per patient per year

The rate of moderate (including those treated with antibiotics only) or severe COPD exacerbations per patient per year was lower in the roflumilast treatment group than in the placebo group (0.838 vs 0.932, Poisson regression model). The reduction compared with placebo was 10.0%. The rate of mild, moderate or severe exacerbations decreased by –13.6% with roflumilast when compared with placebo. The differences between treatments were not statistically significant in the Poisson regression model.

Secondary efficacy variables

All secondary variables were analyzed in an exploratory manner.

Lung function parameters

In the roflumilast treatment group a within-treatment improvement was seen for most pre- and post-bronchodilator expiratory lung function variables. In the placebo group all expiratory variables with the exception of pre-bronchodilator $FEF_{200-1200}$ and FEV_1/FVC deteriorated. Superiority of roflumilast to placebo was shown for pre- and post-bronchodilator FVC, $FEF_{50\%}$, $FEF_{25-75\%}$, $FEF_{200-1200}$, FEV_3, FEV_6, AEX, and FEV_1/FVC, as well as for pre-bronchodilator $FEF_{75\%}$ and post-bronchodilator $FEF_{25\%}$ and PEF (all $p < 0.025$, one-sided). For pre- and post-bronchodilator SVC and ERV, for pre-bronchodilator $FEF_{25\%}$ and PEF, as well as for post-bronchodilator $FEF_{75\%}$ the differences between treatments were in favor of roflumilast but not statistically significant.

The inspiratory lung function parameters (both pre- and post-bronchodilator) decreased in both treatment groups with the decrease being more profound in the placebo group. No statistically significant between-treatment differences were detected for the inspiratory lung function variables with the exception of pre-bronchodilator IC (difference in LSMeans: 40 mL, $p = 0.0137$, one-sided).

COPD exacerbations

The results of the secondary analyses on COPD exacerbations were in line with the results seen for the primary and key-secondary analyses.

BDI/TDI

An increase in TDI scores from BDI and thus an improvement in dyspnea was found for both treatments with the improvement being more pronounced in the roflumilast treatment group. Superiority of roflumilast to placebo was shown for the focal score (difference in LSMeans: 0.38 units, $p = 0.0010$, one-sided, ITT) and all component scores (all $p < 0.025$, one-sided). The differences between the treatment groups with regard to the number of patients with a clinically relevant improvement in TDI (ie an increase in focal score of ≥1 unit) were statistically significant and in favor of roflumilast ($p = 0.0063$).

SGRQ

An improvement in quality of life (corresponding to a decrease in SGRQ total score) was observed in the roflumilast treatment group (LSMean: -1.83 units) and in the placebo group (LSMean: -0.34 units). Furthermore, improvements were seen with roflumilast in the activity score, and with roflumilast and placebo in the impact and symptoms score. Superiority of roflumilast 500 µg od to placebo was demonstrated for the total score (difference in LSMeans: -1.48 units, one-sided $p = 0.0081$), the impact score (difference in LSMeans: -1.60 units, one-sided $p = 0.0098$), and the symptoms score (difference in LSMeans: -2.09 units, one-sided $p = 0.0095$). For the activity score, the difference between treatments was in favor of roflumilast but not statistically significant (difference in LSMeans:

-1.24 units, one-sided p = 0.0524). There were no statistically significant differences between the treatment groups with regard to the number of patients with or without a clinically relevant improvement in SGRQ total score (ie a decrease of ≥4 units).

Morning PEF (diary)

Morning PEF improved over the treatment period with roflumilast (LSMean: 26 mL) and deteriorated with placebo (LSMean: -0.4 mL). The difference between treatments was statistically significant (difference in LSMeans: 3.0 L/min, p = 0.0202, one-sided).

Daily use of rescue medication (diary)

The daily use of rescue medication did not change over the treatment period with roflumilast but increased with placebo (LSMean: 0.5 puffs/d). The between-treatment difference was statistically significant (difference in LSMeans: -0.5 puffs/d, p = 0.0002, one-sided).

COPD symptom scores (diary)

The COPD symptom scores (breathlessness, cough, sputum production, and score sum) tended to decrease during the study in both treatment groups, indicating an improvement in COPD symptoms. The difference between roflumilast 500 µg od and placebo was statistically significant and in favor of placebo for the sputum production score (difference in LSMeans: 0.1 units, p = 0.0017, two-sided). No statistically significant differences between the treatments were observed for the other symptom scores.

COPD symptom- and rescue medication-free days (diary)

No differences between the treatment groups were detected for the percentage of COPD symptom- and rescue medication-free days.

Mortality

The number of patients who died during the study was similar in the roflumilast 500 µg od (11 out of 567 [1.9%] patients) and the placebo group (12 out of 606 [2.0%] patients) and no statistically significant difference between the treatment groups was detected with regard to mortality.

Time to study discontinuation

The time to study discontinuation due to any reason and due to AE was statistically significantly shorter in the roflumilast treatment group than in the placebo group (both

$p < 0.05$).[3] No statistically significant difference between the treatment groups was observed for time to study withdrawal due to a COPD exacerbation.

Safety

A summary of AEs is given in the following table:

Frequency of treatment-emergent AEs (safety set)

	Rof500 (N = 567)	Pbo (N = 606)	Total (N = 1173)
Number of patients (%)[a] with:			
AEs	489 (86.2)	505 (83.3)	994 (84.7)
SAEs: all	126 (22.2)	132 (21.8)	258 (22.0)
deaths	11 (1.9)	12 (2.0)	23 (2.0)
AEs with causality[b] suggested	150 (26.5)	70 (11.6)	220 (18.8)
AEs leading to discontinuation	111 (19.6)	62 (10.2)	173 (14.7)
AEs not yet known to be recovered	181 (31.9)	179 (29.5)	360 (30.7)
Changes in study medication due to AEs	81 (14.3)	42 (6.9)	123 (10.5)
Changes in conc. medication due to AEs	385 (67.9)	440 (72.6)	825 (70.3)

[a] Percentages are based on the total number of patients in a treatment group.
[b] AEs assessed as likely or definitely related to the study medication by the investigator.
AE = adverse event, conc. = concomitant, N = number of patients in each treatment group, Pbo = placebo, Rof500 = roflumilast 500 µg once daily, SAE = serious adverse event.

The overall incidence of AEs was slightly higher in patients taking roflumilast 500 µg od (86.2%) than in patients taking placebo (83.3%). The most frequently reported AEs were respiratory, thoracic and mediastinal disorders. These AEs occurred more frequently in patients taking placebo (53.5%) than in patients taking roflumilast 500 µg od (46.4%). On the other hand, AEs relating to gastrointestinal disorders showed higher incidences in the roflumilast 500 µg od group (30.9%) than in the placebo group (14.5%), largely due to a difference in the incidence of diarrhoea and nausea.

The frequency of patients with AEs considered to be causally related to study medication (assessed as "likely" or "definitely related" by the investigator) was higher in the roflumilast 500 µg od group (26.5%) than in the placebo group (11.6%). The most frequent "likely" or "definitely related" AE in the roflumilast treatment group was diarrhoea, followed by weight decreased and nausea. In the placebo group ECG QTc interval prolonged, diarrhoea, and weight decreased were the most frequent AEs assessed to be at least "likely related" to study medication. Overall, the incidence of AEs assessed as at least "likely related" to roflumilast treatment was consistent with observations made in earlier studies in patients with COPD.

The majority of patients with AEs experienced events with mild or moderate severity. The vast majority of AEs (81%) in each treatment group resolved during the study.

[3] These variables were not evaluated for efficacy but for completeness reasons.

In total, 23 patients died during the treatment period of the study (11 [1.9%] in the roflumilast 500 µg group and 12 [2.0%] in the placebo group); all of the deaths were assessed to be "not" or "unlikely related" to the study medication by the investigator and the sponsor. Additionally, one patient who was enrolled in the baseline period, but not randomized, died.

SAEs (serious adverse events) were reported during the treatment period for 126 (22.2%) patients in the roflumilast 500 µg od group and 132 (21.8%) patients in the placebo group. Overall, COPD was the most frequent SAE in both treatment groups, followed by pneumonia.

The percentage of patients who were withdrawn from the study due to AEs was lower in patients taking placebo (10.2%) than in patients taking roflumilast 500 µg (19.6%). The most common reason for study discontinuation was COPD followed by (in the roflumilast treatment group) diarrhoea and nausea.

Overall, for all clinical chemistry and hematology parameters analyzed, the mean changes from baseline were small and not clinically relevant. There were no major differences in the incidence of clinically significant abnormalities in laboratory values between the two treatment groups and most of these were considered "not" or "unlikely related" to study medication by the investigator. Review of hemoccult findings revealed no hint for any gastrointestinal bleeding tendencies.

Vital signs, physical examination, and ECG did not reveal any clinically significant changes due to study drug administration and no influence of roflumilast on QT/QTc intervals was seen. A decrease in weight was observed more often in the roflumilast group than in the placebo group (70 vs 31 patients, respectively). However, the median weight loss was low with –1 kg in the roflumilast group and 0 kg in the placebo group.

In the 24-h Holter ECG no significant drug-related effects on HR (heart rate), superventricular ectopy, and ventricular ectopy were observed. Furthermore, time-domain measures of HR variability were evaluated. The lack of effect of roflumilast on HR variability suggests that the drug does not impair normal autonomic HR control.

These results were comparable to those observed in previous studies and support a favorable safety profile for roflumilast.

Conclusions:

This study demonstrated that roflumilast administered in od doses of 500 µg was superior to placebo in improving the primary efficacy variable pre-bronchodilator FEV_1 in patients with COPD. For the other primary endpoint frequency of moderate exacerbations treated with oral or parenteral glucocorticosteroids or severe exacerbations per patient per year a reduction of 14% with roflumilast vs placebo was seen, which, however, was not statistically significant in the primary Poisson regression model. Amongst the (key-)secondary outcome parameters consistent improvements with roflumilast vs placebo were also demonstrated, eg for post-bronchodilator FEV_1 and the pre- and post-bronchodilator lung function parameters FVC, FEV_6 or $FEF_{25-75\%}$. Improved lung function was associated with an improvement in

symptomatic measures such as a relief in dyspnea (as assessed with the BDI/TDI), a lower need for rescue medication, and an improved quality of life (as assessed with the SGRQ) in the roflumilast treatment group when compared with the placebo group.

In total, 86.2% of patients treated with roflumilast 500 µg od and 83.3% of patients treated with placebo experienced AEs. However, the number and type of AEs were not unexpected for the patient population under investigation. Most of the AEs were judged “not” or “unlikely related” to the study medication. The majority of AEs was of mild or moderate severity and resolved during the study. There was no apparent clinically relevant influence on vital signs, ECG parameters or physical examination. Thus, the study supported a favorable benefit to risk ratio for roflumilast.

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