1 Title Page — Clinical Study Report No. 25/2008 — Version 1.0

Title: A 12-week, double-blind, randomized study to investigate the effect of 500 µg roflumilast tablets once daily versus placebo on pulmonary function in patients with chronic obstructive pulmonary disease The JADE Study		Version date:	09-Jul-2008
		INN:	Roflumilast
		Program/Project No.:	BY217
		Compound No.:	B9302-107
		Batch Code No.:	BY217-265
Study Protocol No.:	**BY217/M2-119**	Development phase:	III
EudraCT No.:	Not applicable	Indication studied:	COPD
Study initiation date:	31-Aug-2005	Date of early termination:	Not applicable
Study completion date:	13-Mar-2007	Summary of modifications:	Not applicable

Name and country of investigators:

32 centers in Hong Kong, Malaysia, Philippines, South Korea and Taiwan participated

Coordinating investigator:

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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: A 12-week, double-blind, randomized study to investigate the effect of 500 µg roflumilast tablets once daily versus placebo on pulmonary function in patients with chronic obstructive pulmonary disease.

The JADE Study

Investigators and study centers: A total of 32 investigators in 32 centers in Hong Kong, Malaysia, Philippines, South Korea, and Taiwan participated in the study.

Coordinating investigator: [redacted] Department of Pulmonary & Critical Care Medicine, ASAN Medical Center, University of Ulsan, College of Medicine, 388-1 Pungnap-2dong, Songpa-gu, Seoul 138-736, Korea

Publication (reference): Not applicable

Studied period: 31-Aug-2005 (first patient in) to 13-Mar-2007 (last patient out)

Clinical phase: phase III

Objectives:

- To investigate the effect of 500 µg oral roflumilast versus placebo on pulmonary function in patients suffering from chronic obstructive pulmonary disease (COPD)
- To provide more data on the safety and tolerability of roflumilast

Methodology:

Multicenter, randomized, double-blind, placebo-controlled, parallel-group, multi-national, multi-center study with two treatment arms. Patients were randomized to one of the two treatment groups 500 µg roflumilast or placebo in a 1:1 randomization scheme.

The study consisted of a single-blind 4-week baseline period (visits V0, V1 and V2) and a double-blind 12-week treatment period (visits V3, V4 and V5) and an additional safety follow-up, if necessary.

Eligible patients entered the single-blind baseline period. Disallowed medication was withdrawn upon study entry. Short-acting anticholinergics were allowed at a constant daily dosage if already taken on a constant daily dosage for at least 4 weeks prior to the study. Rescue medication (salbutamol) could be used throughout the entire study on an "as-needed" basis.

During the baseline period, the patients received placebo tablets. On completion of the baseline period, patients were re-evaluated and those who met all randomization criteria were

randomized in a 1:1 ratio to receive once daily either, roflumilast 500 µg, or placebo. There was a stratification of patients according to their smoking status (smoker/ former smoker).

Lung function tests were performed at baseline visit V0 to determine eligibility. Tests were repeated at visits V1 and V2 and during the treatment period after 4, 8 and 12 weeks (V3, V4 and V5, respectively). Safety assessments were performed at each regular clinic visit.

The primary endpoint was the mean change in post-bronchodilator FEV_1 (forced expiratory volume in one second) from baseline (V2) to each post-randomization visit during the treatment period. Mean change in pre-bronchodilator FEV_1 from baseline (V2) to each post-randomization visit during the treatment period was analyzed as the key-secondary endpoint. All other data were evaluated as secondary endpoints. Safety status was assessed by clinical laboratory tests, vital signs, physical examination (including electrocardiogram [ECG]), and monitoring of adverse events (AEs).

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

According to the sample size calculation, 195 randomized patients were needed per treatment arm.

Analyzed sets:

	Enrolled	Randomized	Safety set	Full analysis set	Valid cases set
Rof500		204	203	203	160
Pbo		207	207	207	177
Total	551	411	410	410	337

Pbo= placebo, Rof500 = roflumilast 500 µg od.
Data source: Table 15.1.1.2.

Diagnosis and main criteria for inclusion:

- Written informed consent;
- Age ≥40 years;
- Patients with a history of chronic obstructive pulmonary disease as defined by the GOLD criteria (2003);
- Post-bronchodilator FEV_1/ forced vital capacity (FVC) ratio ≤70%;
- Post-bronchodilator FEV_1 30 – 80% of predicted;
- Fixed airway obstruction (defined as an FEV_1 increase of ≤15% and/or ≤200 mL after receiving 400 µg salbutamol);
- Current smoker or former 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 might interfere with study procedures or evaluation;
- Clinically stable COPD within 4 weeks prior to baseline visit V0;
- Availability of a chest x-ray dated a maximum of 6 months prior to study baseline visit V0 or a willingness to have a chest x-ray performed at visit V0.

Inclusion in the treatment period (randomization criteria):

Patients were randomized 4 weeks after the baseline visit V0, if the following criteria were fulfilled:

- No moderate or severe COPD exacerbation between V0 and V2;
- Medication compliance ≥80% and ≤125%.

Patients who did not fulfill the randomization criteria 4 weeks after the baseline visit (V0) were excluded from further participation in the study.

Test product, dose, mode of administration, batch no.: Roflumilast, one 500 µg tablet, once daily, oral administration in the morning after breakfast, batch code number BY217-265[1].

Reference product, dose, mode of administration, batch no.: Placebo, one tablet, once daily, oral administration in the morning after breakfast, batch code number BY217-265[1].

Duration of treatment: 4 weeks baseline (placebo) and 12 weeks treatment (randomized 1:1)

Criteria for evaluation:

The primary endpoint was the mean change in post-bronchodilator FEV_1 [liters (L)] from baseline (V2) to each post-randomization visit during the treatment period.

The key-secondary endpoint was the mean change in pre-bronchodilator FEV_1 [L] from baseline (V2) to each post-randomization visit during the treatment period.

Secondary endpoints of efficacy:

Expiratory lung function endpoints (pre- and post-bronchodilator)

- Forced expiratory volume in 6 seconds (FEV_6) [L] mean change from baseline (V2) to each post-randomization visit;
- FVC [L] mean change from baseline (V2) to each post-randomization visit;
- FEV_1/FVC [%] mean change from baseline (V2) to each post-randomization visit;
- Mean forced expiratory flow between 25-75% of vital capacity ($FEF_{25-75\%}$) [L/s] mean change from baseline (V2) to each post-randomization visit;
- Peak expiratory flow (PEF) [L/min] mean change from baseline (V2) to each post-randomization visit.

COPD exacerbations during the treatment period

[1] Batch code number BY217-265 applies to all study medications, including those administered during the baseline period.

- Time to first moderate COPD exacerbation;
- Time to first severe COPD exacerbation;
- Time to first moderate or severe COPD exacerbation;
- Proportion of patients experiencing at least one moderate COPD exacerbation;
- Proportion of patients experiencing at least one severe COPD exacerbation;
- Proportion of patients experiencing at least one moderate or severe COPD exacerbation.

Time to study withdrawal

- Time to study withdrawal;
- Time to study withdrawal due to an AE.

Endpoints for safety and tolerability:

- AEs;
- Standard laboratory variables;
- ECG;
- Vital signs (blood pressure and pulse rate);
- Routine physical examination;
- Body weight and body mass index (BMI).

Statistical methods:

For all endpoints, statistical tests comparing roflumilast 500 µg od versus placebo were performed. The primary endpoint, mean change in post-bronchodilator FEV_1, was analyzed using a repeated measurements analysis of covariance (ANCOVA) including all visits from baseline (V2) to the final scheduled visit (V5). The key-secondary endpoint, mean change in pre-bronchodilator FEV_1 from baseline to the final scheduled visit (V5), and other secondary endpoints (pre- and post-bronchodilator spirometry assessments) were similarly analyzed using a repeated measurements ANCOVA model. Additionally, supportive analyses were performed using an ANCOVA model including the last-observation-carried-forward (LOCF) method. For repeated measurements ANCOVA analyses, the change in FEV_1 from baseline (V2) to the final scheduled visit (V5) was of primary interest, whereas changes from V2 to other study visits were performed for completeness.

The primary and key-secondary endpoints were tested in an a-priori order, such that the superiority of roflumilast 500 µg od over placebo was first demonstrated for post-bronchodilator FEV_1 before superiority of roflumilast 500 µg od over placebo was tested for pre-bronchodilator FEV_1 in a confirmatory manner. ITT (intention-to-treat) analyses were the primary analyses for superiority testing. The PP (per-protocol) analyses were used to assess the robustness of the results.

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

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

In total, 411 patients were randomized (1:1). 410 patients took at least one dose of the study medication, and were included in the FAS (full analysis set) for ITT analyses. As summarized in the table below, patients in the two treatment groups were well comparable with respect to patient disposition, demographic, and other baseline characteristics.

Demographic and other baseline characteristics (FAS and VCS)

Treatment variable[a]		FAS		VCS	
		Rof500 (N = 203)	Pbo (N = 207)	Rof500 (N = 160)	Pbo (N = 177)
Age [years]	Median (range)	68 (41− 91)	67 (41 − 84)	67 (41 − 91)	67 (41 − 84)
Height [cm]	Mean ± SD	163 ± 8	163 ± 7	163 ± 7	163 ± 7
Weight [kg]	Mean ± SD	60 ± 12	59 ± 10	59 ± 12	58 ± 11
BMI [kg/m^2]	Mean ± SD	22.39 ± 3.7	22.14 ± 3.4	22.31 ± 3.7	22.04 ± 3.4
Sex [n (%)][b]	Male	188 (92.6)	195 (94.2)	149 (93.1)	165 (93.2)
	Female	15 (7.4)	12 (5.8)	11 (6.9)	12 (6.8)
Race [n (%)][b]	Asian	203 (100.0)	207 (100.0)	160 (100.0)	177 (100.0)
COPD severity [n (%)][b]	Very severe	12 (5.9)	14 (6.8)	8 (5.0)	12 (6.8)
	Severe	75 (36.9)	73 (35.3)	62 (38.8)	67 (37.9)
	Moderate	106 (52.2)	104 (50.2)	83 (51.9)	90 (50.8)
	Mild	10 (4.9)	16 (7.7)	7 (4.4)	8 (4.5)
Smoking status [n (%)][b]	Current	69 (34.0)	69 (33.3)	60 (37.5)	61 (34.5)
	Former	134 (66.0)	138 (66.7)	100 (62.5)	116 (65.5)
Pack years[c]	Mean ± SD	42 ± 22.1	45 ± 28.9	42 ± 22.7	44 ± 30.0
Pre-bronchodilator FEV_1 [L]	Mean ± SD	1.29 ± 0.4	1.28 ± 0.5	1.30 ± 0.4	1.25 ± 0.5
Post-bronchodilator FEV_1 [L]	Mean ± SD	1.41 ± 0.5	1.40 ± 0.5	1.41 ± 0.5	1.36 ± 0.5
Pre-bronchodilator FEV_1 [% of predicted]	Mean ± SD	50.6 ± 16.3	50.3 ±16.3	50.3 ± 15.6	48.6 ± 14.9
Post-bronchodilator FEV_1 [% of predicted]	Mean ± SD	55.1 ± 16.5	54.9 ± 16.8	54.7 ± 15.7	53.1 ± 15.0
FEV_1 reversibility [mL]	Mean ± SD	119.21 ± 131.3	119.28 ± 135.1	114.50 ± 124.4	114.01 ± 133.6
FEV_1 reversibility [% increase]	Mean ± SD	10.3 ± 11.8	10.8 ± 13.9	9.9 ± 10.6	10.7 ± 14.5
Post-bronchodilator FEV_1/FVC [% increase]	Mean ± SD	50.5 ± 11.8	49.3 ± 11.2	50.6 ± 11.9	48.7 ± 11.0

[a] FEV_1 measurements were taken at V2; all other measurements were recorded at V0.
[b] Percentages are based on the number of patients in the respective treatment group.
[c] Pack years = duration of smoking history [years] × average number of cigarettes per day/20.
BMI = body mass index, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, FAS = full analysis set, FVC = forced vital capacity, N = number of patients in the respective treatment group, n = number of patients in the respective category, Pbo = placebo, Rof500 = roflumilast 500 µg, od, VCS = valid cases set.
Data source: Table 15.1.2.1 and Table 15.1.2.2.

Study results

Efficacy

For most endpoints, efficacy results are summarized for the repeated measurements analysis (ITT), which was the primary efficacy analysis. Last value analysis including the LOCF method generally supported the results of repeated measurements analyses.

Primary efficacy endpoint

Post-bronchodilator FEV_1

Post-bronchodilator FEV_1 increased among patients in the roflumilast 500 µg od group (least squares mean adjusted for covariates (LSMean): 52 mL; confidence interval (CI): 13, 91 mL;

ITT), but decreased among patients in the placebo group (LSMean: -27 mL; CI -66, 12 mL; ITT).

A statistically significant between-treatment difference in post-bronchodilator FEV_1 demonstrated the superiority of roflumilast 500 µg od over placebo (LSMean: 79 mL; p-value, one-sided: <0.0001; ITT, confirmed by PP).

Within- and between-treatment differences for post-bronchodilator FEV_1 are provided in the table below.

Change from baseline to the final scheduled visit in post-bronchodilator FEV_1 [L]: within- and between-treatment differences, repeated measurements analyses (ITT, PP)

WITHIN				Within-treatment difference	
	n	n obs	Mean at baseline	LSMean ± SE	95% CI
ITT					
Rof500	189	524	1.415	0.052 ± 0.020	0.013, 0.091
Pbo	202	591	1.401	-0.027 ± 0.020	-0.066, 0.012
PP					
Rof500	156	447	1.408	0.044 ± 0.020	0.006, 0.083
Pbo	176	514	1.359	-0.024 ± 0.019	-0.061, 0.014

BETWEEN					Difference Test – Ref			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	1-sided[a] p-value	2-sided[b] p-value
ITT	Rof500	Pbo	189	202	0.079 ± 0.016	0.048, 0.110	<0.0001	<0.0001
PP	Rof500	Pbo	156	176	0.068 ± 0.016	0.037, 0.099	<0.0001	<0.0001

[a] One-sided p-value for superiority, significance level 2.5%.
[b] Two-sided p-value for between-treatment differences, significance level 5.0%.
CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, ITT = intension-to-treat analysis, L = liters, LSMean = least squares mean adjusted for covariates, n = number of patients with data available, n obs = number of observations, Pbo = placebo, PP = per-protocol analysis, Ref = reference, Rof500 = roflumilast 500 µg od, SE = standard error of the LSMean.
Note: The final scheduled visit refers to V5, which occurred 12 weeks after the baseline (V2) visit.
Data source: Table 15.2.2.1 and Table 15.2.2.2.

Key-secondary efficacy endpoint

Pre-bronchodilator FEV_1

Since superiority of roflumilast 500 µg od was demonstrated for the primary endpoint, the key-secondary endpoint was analyzed also in a confirmatory manner.

Pre-bronchodilator FEV_1 increased for patients in the roflumilast treatment group (LSMean: 54 mL; CI: 13, 94 mL; ITT), but decreased for patients in the placebo treatment group (LSMean: -42 mL; CI -82, -1 mL; ITT).

A statistically significant between-treatment difference in pre-bronchodilator FEV_1 demonstrated the superiority of roflumilast 500 µg od over placebo (LSMean: 95 mL; p-value, one-sided: <0.0001; ITT, confirmed by PP).

Within- and between-treatment differences for pre-bronchodilator FEV_1 are provided in the table below.

Change from baseline to the final scheduled visit in pre-bronchodilator FEV_1 [L]: within- and between-treatment differences, repeated measurements analyses (ITT, PP)

WITHIN				Within-treatment difference	
	n	n obs	Mean at baseline	LSMean ± SE	95% CI
ITT					
Rof500	189	525	1.291	0.054 ± 0.021	0.013, 0.094
Pbo	202	592	1.279	-0.042 ± 0.021	-0.082, -0.001
PP					
Rof500	156	448	1.292	0.051 ± 0.020	0.011, 0.091
Pbo	176	515	1.243	-0.034 ± 0.020	-0.074, 0.005

BETWEEN					Difference Test – Ref			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	1-sided[a] p-value	2-sided[b] p-value
ITT	Rof500	Pbo	189	202	0.095 ± 0.016	0.063, 0.127	<0.0001	<0.0001
PP	Rof500	Pbo	156	176	0.085 ± 0.016	0.053, 0.118	<0.0001	<0.0001

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

[b] Two-sided p-value for between-treatment differences, significance level 5.0%.

CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat analysis, L = liters, LSMean = least squares mean adjusted for covariates, n = number of patients with data available, n obs = number of observations, Pbo = placebo, PP = per-protocol analysis, Ref = reference, Rof500 = roflumilast 500 µg od, SE = standard error of the LSMean.

Note: The final scheduled visit refers to V5, which occurred 12 weeks after the baseline (V2) visit.

Data source: Table 15.2.2.1 and Table 15.2.2.2.

Secondary endpoints

All secondary endpoints were analyzed in an exploratory manner.

Pre- and post-bronchodilator expiratory lung function variables

For pre- and post-bronchodilator FEV_6, FVC, and PEF, as well as post-bronchodilator FEF_{25-75} and FEV_1/FVC, between-treatment differences were in favor of roflumilast 500 µg od over placebo (p-value, one-sided <0.025; ITT, confirmed by PP except for FEV_1/FVC). For pre-bronchodilator FEF_{25-75} and pre-bronchodilator FEV_1/FVC, between-treatment difference analyses were in favor of roflumilast 500 µg, but were not statistically significant.

COPD exacerbations

Due to the low number of events and the short treatment duration, the results of analyses of COPD exacerbations should be interpreted with care. The frequency of moderate or severe COPD exacerbations was comparable among patients of the two treatment groups: 6.9% of patients in the roflumilast 500 µg od group and 8.2% of patients in the placebo group experienced at least one moderate or severe COPD exacerbation. Cox proportional hazards regression showed a hazard ratio in favor of roflumilast 500 µg od for onset of a moderate and for a moderate or severe COPD exacerbation. The hazard ratio for onset of a severe COPD exacerbation was in favor of placebo, but this finding should be interpreted with caution due

to the low number of events (3 patients treated with placebo [1.4%] and 4 patients treated with roflumilast 500 µg [2.0%] experienced a severe COPD exacerbation).

Time to study discontinuation

Cox proportional hazards regression showed a hazard ratio of 2.352, i.e. the risk for early study discontinuation was much higher for patients in the roflumilast 500 µg od group compared with patients in the placebo group. The risk for early study discontinuation due to AE was also considerably higher (3.185 hazard ratio) for patients in the roflumilast 500 µg od group compared with patients in the placebo group. However, due to the relatively low number of patient discontinuations due to AEs, these results should be interpreted with care.

Subgroup analyses

Subgroup analyses of the primary endpoint, change in post-bronchodilator FEV_1, were in favor of roflumilast 500 µg od for all except the female subgroup, where a between-treatment difference in favor of placebo was observed. However, this finding has to be interpreted cautiously due to the small patient number (24 patients with data available) in this subgroup.

Subgroup analyses of the key-secondary endpoint, pre-bronchodilator FEV_1 provided similar results to those obtained for post-bronchodilator FEV_1.

Safety

A summary of AEs is provided in the table below.

Frequency of treatment-emergent AEs (safety set)

	Rof500 (N = 203)	Pbo (N = 207)	Total (N = 410)
Number of patients (%)[a] with at least one:			
AE	134 (66.0)	90 (43.5)	224 (54.6)
SAE: all	18 (8.9)	6 (2.9)	24 (5.9)
deaths	2 (1.0)	0 (0)	2 (0.5)
AE with causality[b] suggested	47 (23.2)	11 (5.3)	58 (14.1)
AE leading to discontinuation	18 (8.9)	6 (2.9)	24 (5.9)
AE not yet known to be recovered	26 (12.8)	13 (6.3)	39 (9.5)
Change in study medication due to AEs	11 (5.4)	5 (2.4)	16 (3.9)
Change in concentration of medication due to AEs	100 (49.3)	65 (31.4)	165 (40.2)

[a] Percentages are based on the number of patients in the respective treatment group.
[b] Assessed by the investigator as likely or definitely related to the study medication.
N = number of patients in respective treatment group, Pbo = placebo, Rof500 = roflumilast 500 µg od, SAF = safety set.
Data source: Table 15.3.1.4 and Listing 16.2.4.8.

The overall incidence of treatment-emergent AEs was higher in patients in the roflumilast 500 µg od group (66.0%) compared with patients in the placebo group (43.5%). At the SOC level, the most commonly documented AEs were infections and infestations, which occurred slightly more frequently among patients taking roflumilast 500 µg od group (24.1%) than

among patients taking placebo (15.5%). At the PT level, the most commonly reported treatment-emergent AE among patients in the roflumilast 500 µg od group was upper respiratory tract infection (13.3%), followed by diarrhoea (11.3%), and COPD exacerbation (10.8%). COPD exacerbation was the most frequent treatment-emergent AE among patients in the placebo group (11.1%). AEs that were frequently documented in patients in the roflumilast 500 µg od group, such as diarrhoea, weight decreased, decreased appetite, and anorexia, were rare in patients treated with placebo.

The frequency of patients with AEs considered to be causally related to the study medication (assessed as likely or definitely related by the investigator) was higher among patients in the roflumilast 500 µg od group (23.2%) compared with patients in the placebo group (5.3%). The most common causally related AE among patients in the roflumilast 500 µg od group was diarrhoea, followed by decreased weight, anorexia, and decreased appetite. COPD exacerbation was the most common causally related AE among patients in the placebo group.

Most patients with treatment-emergent AEs experienced events that were mild or moderate in severity. The vast majority of AEs in both treatment groups resolved during the study period.

2 patients in the roflumilast 500 µg od group (1.6%) died during the treatment period. None of the AEs that resulted in the death of these patients were considered likely or definitely related to the study medication by either the investigator or the sponsor. In addition, 1 patient died during the baseline period.

SAEs (serious adverse events) were reported during the study period for 18 patients in the roflumilast 500 µg od group (8.9%) and 6 patients in the placebo group (2.9%). COPD exacerbation was the most frequent SAE in both treatment groups, followed by pneumonia, and anorexia among patients in the roflumilast 500 µg od group.

The percentage of patients who withdrew due to AEs was higher in patients in the roflumilast 500 µg od group (8.9%) compared with patients in the placebo group (2.9%). The most common reason for study discontinuation among patients in the roflumilast 500 µg od group was diarrhoea followed by COPD exacerbation. The AE that most frequently resulted in withdrawal among patients in the placebo group was COPD exacerbation (2.9%).

Mean body weight of patients in the placebo group was unchanged during the treatment period, whereas that of patients in the roflumilast 500 µg od group decreased by 1.6 kg from baseline to the final study visit. The between-treatment difference was statistically significant (LSMean: -1.57 kg; p-value, two-sided: <0.0001; SAF). Weight loss was more frequently documented as an AE in the roflumilast 500 µg od group (5.4%) than in the placebo group (0.5%). Most cases of weight decreased among patients treated with roflumilast 500 µg od were assessed as likely related to the study medication by the investigator. None of the decreased weight occurrences among patients in the roflumilast 500 µg od group were severe in intensity. The most common AEs concurrent with decreased weight among patients in the roflumilast 500 µg od group were constipation, upper respiratory tract infection, and anorexia.

The number of patients who experienced AEs of special interest other than weight loss (infections and tumors related to TNF-α inhibition, mesenteric vasculitis, and cardiac safety) was small, and no conclusion could be drawn from the data accumulated in this study.

In both treatment groups, median changes from baseline to end of treatment in hematology and clinical chemistry values were small and not clinically relevant. Laboratory values were

rarely outside the sponsor-defined alert range. The frequency of laboratory AEs was low in both treatment groups, and most of these AEs were considered not related or unlikely related to study medication.

Vital signs, ECG, and physical examinations did not reveal any clinically relevant changes due to administration of study medication.

Conclusions:

This study demonstrated superiority of roflumilast 500 µg od over placebo in improving post-bronchodilator FEV_1, the primary efficacy endpoint, among patients with COPD. Roflumilast 500 µg was also shown to be superior to placebo in improving pre-bronchodilator FEV_1, the key-secondary endpoint. Consistent improvement of pre- and post-bronchodilator FEV_6, FVC, FEV_1/FVC, PEF, and FEF_{25-75} confirmed the superiority of roflumilast 500 µg over placebo.

In total, 66.0% of patients in the roflumilast 500 µg od group and 43.5% of patients in the placebo group experienced AEs during the treatment period. However, the number and types of AEs were not unexpected for the patient population under investigation. Most of the AEs were of mild or moderate severity, were assessed as not related or unlikely related to the study medication, and resolved during the study. Analyses of AEs, laboratory variables, ECG, vital signs, and physical examinations did not reveal any new safety findings beyond those already known for roflumilast. The results are consistent with those of previous studies, and support a favorable risk-benefit assessment for roflumilast 500 µg od.

Date of report: 09-Jul-2008