1 Title Page

Clinical Study Report No. 193/2006

Version 2.0

Title: A 24-week, double blind, randomized study to investigate the effect of 500 µg Roflumilast tablets once daily versus placebo on parameters indicative of hyperinflation in patients with chronic obstructive pulmonary disease. The HERO Study		Version date:	23-Dec-2008
		INN:	Roflumilast
		Program/Project No.:	BY217
		Compound No.:	B9302-107
		Batch No.: Roflumilast 500 µg Roflumilast placebo	 130220 130270
Study Protocol No.:	**BY217/M2-121**	Development phase:	IIIb
EudraCT No:	2004-000288-89	Indication studied:	COPD
Study initiation date:	12-Oct-2004	Date of early termination:	not applicable
Study completion date:	08-Nov-2005	Summary of modifications:	No. 1

Name and country of investigators:
89 centers in Canada, Spain, France, Portugal, Poland, United Kingdom, South Africa and the United States of America
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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 24-week, double-blind, randomized study to investigate the effect of 500 µg Roflumilast tablets once daily vs placebo on parameters indicative of hyperinflation in patients with chronic obstructive pulmonary disease. The Hero Study (BY217/M2-121).

Investigator(s) and study center(s):

89 centers in Canada, France, Poland, Portugal, South Africa, Spain, United Kingdom (UK) and United States of America (USA).

Coordinating investigator(s):

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[redacted] (from 26-Jan-2005), Kingston General Hospital, Canada.

Publication (reference): Not applicable.

Study period: 12-Oct-2004 (first patient in) to 08-Nov-2005 (last patient out).

Clinical phase: Phase IIIb

Objectives:

The main objective of the study was to investigate the effect of roflumilast 500 µg od (once daily) vs placebo on parameters indicative for hyperinflation, lung function, dyspnea, and QoL (quality of life). In addition, safety and tolerability were investigated.

Methodology:

This was a multi-center, double-blind, placebo-controlled, randomized, two-arm, parallel-group comparison of roflumilast 500 µg od po (*per os,* orally) vs placebo od po.

The study consisted of a single-blind baseline period of 4 weeks (Visits B0, B2, and B4), a double-blind treatment period of 24 weeks (Visits T0 [on the same day as Visit B4], T4, T8, T12, T18, and T24), and a follow-up period (if considered necessary by the investigator). Patients were allowed to use salbutamol (albuterol in the US) rescue medication throughout the study. During the baseline period, patients took one placebo tablet od in the morning and withdrew all disallowed concomitant medication. At Visit T0, all eligible patients were randomized to one of two treatment groups (ratio 1:1) and took either roflumilast 500 µg od or placebo od in the morning.

Lung function tests including spirometry (FEV_1 [forced expiratory volume in 1 s], FVC [forced vital capacity], FEV_1/FVC, $FEF_{25-75\%}$ [mean forced expiratory flow between 25 and 75% of vital capacity], PEF [peak expiratory flow]), plethysmography (FRC_{pl} [functional residual capacity plethysmography], TLC [total lung capacity], RV [residual volume], RV/TLC, IC [inspiratory capacity]), SVC (slow vital capacity), and pulse oximetry (SpO_2 [oxygen saturation]) were performed at Visit B0 to determine eligibility. Tests were repeated at Visit B4 and Visits T4, T8, T12, T18 and T24.

Health outcomes were determined using the CCQ (Clinical COPD Questionnaire), which assessed the patient's QoL and BDI/TDI (Baseline and Transition Dyspnea Index), which

assessed the patient's dyspnea. Health outcomes were assessed at Visit B2 (CCQ only), and B4, and Visits T4, T8, T12, T18, and T24 (or on early termination). AEs (adverse events) and the use of concomitant medication were documented by the investigator throughout the study. Standard laboratory investigations (biochemistry, hematology, and urinalysis) were made at Visit B0 (with verification of laboratory values at B2 if required) and at Visit T24 (or on early termination). A physical examination and 12-lead ECG (electrocardiogram) were performed at Visit B0 and at treatment Visit T24 (or on early termination). A chest X-ray (if not conducted in the previous 6 months or if results were unavailable) was performed at Visit B0. Vital signs were assessed at each visit. The laboratory investigations, physical examination, 12-lead ECG, and vital signs were re-assessed at a follow-up visit if considered necessary by the investigator.

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

It was planned to enroll approximately 680 patients, with approximately 550 patients randomized to one of the two treatment groups (275 patients allocated per treatment arm).

	Enrolled	Randomized	Safety set	Full analysis set	Valid case set
Roflumilast 500 µg od		301	301	301	225
Placebo od		299	299	299	245
Total	774	600	600	600	470

od = once daily

Diagnosis and main criteria for inclusion:

Inclusion criteria (at Visit B0)

Patients of either sex who met the following criteria were considered for inclusion in the baseline period:

- gave written informed consent;
- a history of COPD for at least 12 months as defined by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria 2003;
- age ≥40 y;
- FEV_1/FVC ratio (post-bronchodilator) ≤70%;
- FEV_1 (post-bronchodilator) ≤65% of predicted;
- FRC (post-bronchodilator) ≥120% of predicted;
- clinically stable COPD disease within 4 weeks prior to Visit B0;
- availability of a chest X-ray dated a maximum of 6 months prior to Visit B0 or a willingness to have a chest X-ray performed at Visit B0.

Randomization criteria (at Visit T0)

Patients were randomized 4 weeks after Visit B0, if the following criteria were fulfilled:

- judged to be clinically stable;
- no moderate or severe COPD exacerbations had occurred between Visit B0 and Visit T0;
- medication compliance ≥80% and ≤125%;

- ability to perform valid, reproducible and acceptable lung function tests in particular FRC_{pl}.

Patients who did not fulfill the randomization criteria after 4 weeks of baseline treatment were excluded from further participation in the study.

Test product: Roflumilast, 500 µg od, po, batch no. 130220

Reference product: Matched placebo, od, po, batch no. 130270

Duration of treatment: 4 weeks baseline period followed by 24 weeks treatment period

Criteria for evaluation:

Primary efficacy variables

- the mean change from baseline (T0) during the treatment period in post-bronchodilator FEV_1;
- the mean change from baseline (T0) during the treatment period in post-bronchodilator FRC_{pl}.

Key secondary efficacy variables

- the mean TDI focal score during the treatment period;
- the mean change from baseline (T0) during the treatment period in post-bronchodilator RV.

Other secondary efficacy variables

- spirometry (FEV_1[1], FVC, FEV_1/FVC, $FEF_{25–75\%}$, and PEF; all analyzed pre- and post-bronchodilator);
- plethysmography (FRC_{pl}[1], TLC, RV[1], RV/TLC, IC; all analyzed pre- and post-bronchodilator);
- SVC (pre- and post-bronchodilator);
- pulse oximetry (SpO_2; analyzed pre- and post-bronchodilator);
- BDI/TDI (focal score[1] and component scores [functional impairment, magnitude of task, magnitude of effort]);
- CCQ (total score and domain scores [symptoms, functional state, mental state]);
- COPD exacerbations (severe or moderate exacerbations, EROS [exacerbations requiring oral or parenteral glucocorticosteroids]);
- time to study withdrawal (overall, due to escape criterion met or due to an AE).

Safety variables

- AEs;
- laboratory assessments (biochemistry, hematology and urinalysis);
- physical examination (including weight and BMI [body mass index]);
- vital signs.

[1] These variables were partially included in the primary or key secondary efficacy variables

Statistical methods:

The primary efficacy analysis of the primary and key secondary variables and most of the other secondary variables (other lung function parameters, BDI/TDI scores, CCQ scores) was performed using a repeated measurement ANCOVA (analysis of covariance). This model included all observed measurements from the scheduled visits during the treatment period. The dependent variable was the change at each scheduled visit from baseline (T0). As well as the treatment, the following factors and covariables (all fixed) were included in the model: value at T0, smoking status, age, sex, country, and time, as well as a treatment by time interaction. Smoking status was included in the model as this was used as a stratification variable in randomization. Time was used as a categorical variable and represented the scheduled number of weeks the measurements were performed after randomization. The repeated correlation structure in the visit time points was unstructured, allowing for maximum flexibility in estimation. In addition, a repeated measurement analysis not including the treatment-by-time interaction term, was performed for all lung function variables, and for health outcome measures (BDI/TDI and CCQ) in order to check the robustness of the results in an exploratory manner.

An additional ANCOVA of change from baseline to individual study visits was performed for reasons of robustness. This was performed for the endpoint analysis as well as for each individual scheduled visit for all lung function variables, as well as for health outcome measures (BDI/TDI and CCQ). The dependent variable was the difference of the endpoint to the value at Visit T0 (randomization). Besides the treatment, the following factors and covariables (all fixed) were included in the model: value at T0, smoking status, age, sex, and country.

Non-parametric between-group comparisons were performed for the ratio FEV_1/FVC and RV/TLC, as well as for the scores from TDI, using the Mann-Whitney U-Test to check the robustness of the results. Non-parametric within-group comparisons were performed with Pratt's modification of the Wilcoxon's signed rank test.

Survival analyses on time to exacerbation and time to study withdrawal were performed using Cox regression models and log-rank tests. Patients with or without an event were analyzed with log-binomial regressions and Fisher's exact tests. Categories for changes in TDI scores and CCQ scores were analyzed using Fisher's exact test.

All tests described for secondary efficacy variables were exploratory and were performed one-sided at a level of 2.5% (or equivalently 5% two-sided).

The ITT (intention-to-treat) analysis (based on the FAS [full analysis set] was the primary analysis for this study. The PP (per-protocol) analysis (based on the VCS [valid case set]) was secondary and performed to check the robustness of the data.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

The treatment groups were well balanced for most demographic and baseline variables.

		FAS	
		Rof500 (N = 301)	**Placebo (N = 299)**
Age [years]	Median (range)	65 (42,92)	65 (42,87)
Weight [kg]	Mean ± SD	74.07 ± 16.5	72.71 ± 16.6
Height [cm]	Mean ± SD	170.03 ± 8.5	169.09 ± 8.7
Sex [n (%)]a	Male	231 (76.7)	217 (72.6)
	Female	70 (23.3)	82 (27.4)
Race [n (%)][a]	American Indian or Alaska Native	2 (0.7)	0
	Asian	0	2 (0.7)
	Black	4 (1.3)	3 (1.0)
	Caucasian	293 (97.3)	292 (97.7)
	Other	2 (0.7)	2 (0.7)
Smoking status [n (%)][a]	Current smokers	112 (37.2)	108 (36.1)
	Ex–smokers	189 (62.8)	191 (63.9)
Pack years [n][b]	Mean ± SD	48.47 ± 26.9	48.73 ± 27.3
Concomitant therapy with inhaled corticosteroids [n (%)][a]	No	123 (40.9)	138 (46.2)
	Yes	178 (59.1)	161 (53.8)
Concomitant therapy with inhaled short acting anticholinergics [n (%)][a]	No	143 (47.5)	147 (49.2)
	Yes	158 (52.5)	152 (50.8)
COPD severity [n (%)][a]	Very severe	34 (11.3)	24 (8.0)
	Severe	149 (49.5)	150 (50.2)
	Moderate	115 (38.2)	123 (41.1)
	Mild	1 (0.3)	1 (0.3)
	Not available	2 (0.7)	1 (0.3)
FEV_1 at T0 [L][c]	Mean ± SD	1.31 ± 0.4[d]	1.31 ± 0.4[d]
[% of predicted][c]	Mean ± SD	46.21 ± 13.1[d]	47.05 ± 12.2[d]
FEV_1 rev at B0 [% increase][c]	Mean ± SD	16.08 ± 15.3[d]	17.32 ± 16.0[d]
FRC_{pl} at T0 [L][c]	Mean ± SD	5.14 ± 1.1[e]	5.05 ± 1.2
[% of predicted][c]	Mean ± SD	154.26 ± 27.2	153.64 ± 29.1

[a] Percentages are based on the number of patients in a treatment group.

[b] Subset current and ex–smokers.

[c] Post–bronchodilator measurement

[d] N=299 for Rof500 and N=298 for placebo in FAS

B0 = baseline, COPD = chronic obstructive pulmonary disease, FAS = full analysis set, FEV_1 = forced expiratory volume in 1 second, FRC_{pl} = functional residual capacity plethysmography, N = number of patients in a treatment group, n = number of patients with data available, rev = reversibility, Rof500 = roflumilast 500 µg od, SD = standard deviation, T0 = randomization visit.

Efficacy results

Primary efficacy variable: post-bronchodilator FEV_1

The first primary efficacy variable was the mean change from baseline during the treatment period for post-bronchodilator FEV_1. Post-bronchodilator FEV_1 increased by 0.024 L in the roflumilast 500 µg od group, and decreased by 0.011 L in the placebo group (ITT). The difference between treatment groups during 24 weeks of treatment was statistically significant in favor of roflumilast 500 µg od over placebo (0.036 L, one-sided p-value = 0.0030, ITT). The PP analysis confirmed the results of the ITT analysis.

Change from T0 to T24 in post-bronchodilator FEV_1 [L]: within- and between-treatment differences, repeated measurements analysis (ITT, PP)

WITHIN					Within-treatment difference	
		n	n obs	Mean at T0	LSMean ± SE	95% CI
ITT	Rof500	272	1168	1.324	0.024 ± 0.011	0.002, 0.047
	Placebo	281	1277	1.316	–0.011 ± 0.011	–0.033, 0.010
PP	Rof500	210	918	1.334	0.032 ± 0.012	0.008, 0.056
	Placebo	235	1063	1.327	–0.016 ± 0.011	–0.038, 0.007

BETWEEN					Difference Test – Ref			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	p-value sup[a]	p-value 2-sided[b]
ITT	Rof500	Placebo	272	281	0.036 ± 0.013	0.010, 0.061	0.0030	0.0061
PP	Rof500	Placebo	210	235	0.048 ± 0.013	0.022, 0.074	0.0002	0.0004

[a] One-sided p-value for superiority, significance level 2.5%.
[b] Two-sided p-value, significance level 5%.
CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, LS = least squares, n = number of patients with data available, n obs = number of observations, PP = per-protocol, Ref = reference, Rof500 = roflumilast 500 µg od, SE = standard error, sup = superiority, T0 = randomization visit, T24 = visit 24 weeks after randomization visit T0.

Primary efficacy variable: post-bronchodilator FRC_{pl}:

The second primary efficacy variable was the mean change from baseline during the treatment period for post-bronchodilator FRC_{pl} An improvement in post-bronchodilator FRC_{pl} (as indicated by a lower value) was seen in both treatment groups; post-bronchodilator FRC_{pl} decreased by 0.011 L with roflumilast 500 µg od, and decreased by 0.048 L with placebo (ITT). The difference between treatment groups (0.037 L, ITT) was in favor of placebo, but not statistically significant. The PP analysis confirmed the results of the ITT analysis.

As FRC_{pl} was not proven to be statistically significant for roflumilast 500 µg od compared with placebo, the hypothesis testing cascade was stopped, and all additional analyses of key secondary and secondary variables were exploratory.

Change from T0 to T24 in post-bronchodilator FRC_{pl} [L]: within- and between-treatment differences, repeated measurements analysis (ITT, PP)

WITHIN					Within-treatment difference	
		n	n obs	Mean at T0	LSMean ± SE	95% CI
ITT	Rof500	261	1114	5.110	–0.011 ± 0.029	–0.067, 0.045
	Placebo	263	1183	5.012	–0.048 ± 0.028	–0.102, 0.006
PP	Rof500	205	882	5.170	–0.016 ± 0.031	–0.078, 0.046
	Placebo	228	1017	5.030	–0.026 ± 0.030	–0.085, 0.033

BETWEEN					Difference Test - Ref			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	p-value sup[a]	p-value 2-sided[b]
ITT	Rof500	Placebo	261	263	0.037 ± 0.032	–0.026, 0.101	0.8768	0.2464
PP	Rof500	Placebo	205	228	0.010 ± 0.035	–0.058, 0.078	0.6155	0.7690

[a] One-sided p-value for superiority, significance level 2.5%.
[b] Two-sided p-value, significance level 5%.

CI = confidence interval, FRC_{pl} = functional residual capacity plethysmography, ITT = intention-to-treat, LS = least squares, n = number of patients with data available, n obs = number of observations, PP = per-protocol, Ref = reference, Rof500 = roflumilast 500 µg od, SE = standard error, sup = superiority, T0 = randomization visit, T24 = visit 24 weeks after randomization visit T0.

Key secondary variable: mean change in TDI focal score

TDI focal score increased by 0.53 in the roflumilast 500 µg od group, and increased by 0.54 in the placebo group (ITT). The difference between treatment groups for mean change in TDI focal score during 24 weeks of treatment (-0.01, ITT) was in favor of roflumilast 500 µg od, but not statistically significant. The PP analysis confirmed the results of the ITT analysis

Key secondary variable: mean change in post-bronchodilator RV

An improvement in post-bronchodilator RV (as indicated by a lower value) was seen in both treatment groups; post-bronchodilator RV decreased by 0.094 L with roflumilast 500 µg od, and decreased by 0.069 L with placebo (ITT). The difference between treatment groups for change in post-bronchodilator RV during 24 weeks of treatment was in favor of roflumilast 500 µg od, but not statistically significant (-0.025 L, ITT). The PP analysis confirmed the results of the ITT analysis.

Other secondary variables

Superiority of roflumilast 500 µg od over placebo was shown for post-bronchodilator FEV_1/FVC (0.740%, one-sided p-value = 0.0181) and SVC (0.062 L, one-sided p-value = 0.0178). For post-bronchodilator FVC, $FEF_{25-75\%}$, PEF, RV/TLC, and SpO_2, the difference between treatment groups was in favor of roflumilast 500 µg od, but superiority was not seen.

Superiority of roflumilast 500 µg od over placebo was shown for pre-bronchodilator FEV_1 (0.039 L, one-sided p-value = 0.0022), FVC (0.080 L, one-side p-value = 0.0027), $FEF_{25-75\%}$ (0.036 L/s, one-sided p-value = 0.0032), RV/TLC (-0.952%, one-sided p-value = 0.0076), and SVC (0.104 L, one-sided p-value = 0.0002). For pre-bronchodilator FRC_{pl}, FEV_1/FVC, PEF, RV, RV/TLC, and IC, the difference between treatment groups was in favor of roflumilast 500 µg od, but superiority was not observed.

For TDI component scores of impairment, magnitude of task, and effort, similar improvements were seen in the roflumilast 500 µg od and placebo groups. No statistically significant between-treatment differences were seen.

For CCQ scores, small improvements were observed for roflumilast 500 µg od compared with placebo in total score, symptom score, and functional state. For CCQ mental state, deteriorations were seen for roflumilast 500 µg od compared with placebo. No statistically significant between-treatment differences were shown.

The percentage patients with moderate or severe COPD exacerbations were similar with roflumilast 500 µg od (24.58%) and placebo (24.75%). The mean time to onset of the first moderate or severe COPD exacerbation was 75.66 days in the roflumilast 500 µg od group and 80.97 days in the placebo group.

During the treatment period, 14.62% of patients in the roflumilast 500 µg od group experienced an exacerbations requiring oral or parenteral glucocorticosteroids (EROS) compared with 15.38% of patients in the placebo group. The mean time to onset of first moderate or severe COPD EROS was longer in patients treated with roflumilast 500 µg od compared with placebo (67.25 vs 60.65 days).

The mean and median number of days to withdrawal was similar between the roflumilast 500 µg od and placebo treatment groups. The Cox proportional hazards analysis indicated that the risk of being withdrawn early from the study was higher in the roflumilast 500 µg od group than in the placebo group (hazard ratio 1.520 [95% CI: 1.089, 2.122]).

A total of 32 patients (13 in the roflumilast 500 µg od group and 19 in the placebo group) withdrew from the study due to a COPD exacerbation (escape criterion). The hazard ratio of 0.733 indicated that withdrawal due to a COPD exacerbation (escape criterion) was less likely to be earlier in patients taking roflumilast 500 µg od than in patients taking placebo, but this was not statistically significant.

A total of 79 patients (50 in the roflumilast 500 µg od group and 29 in the placebo group) withdrew from the study due to an AE. The hazards ratio of 1.800 (95% CI: 1.136, 2.852) suggested that withdrawal due to an AE was likely to be earlier in patients taking roflumilast 500 µg od.

Safety results

The following table summarizes the treatment-emergent AEs reported during the double-blind treatment period:

Treatment-emergent adverse events (SAF)

	Number (%) of patients		
	Rof500 (N = 301)	**Placebo (N = 299)**	**Total (N = 600)**
AEs	215 (71.4)	188 (62.9)	403 (67.2)
SAEs	24 (8.0)	21 (7.0)	45 (7.5)
AEs with definitely or likely causality suggested by the investigator	80 (26.6)	23 (7.7)	103 (17.2)
AEs leading to discontinuation	50 (16.6)	29 (9.7)	79 (13.2)
AEs not yet known to be recovered	59 (19.6)	47 (15.7)	106 (17.7)
Changes in study medication due to AEs	38 (12.6)	21 (7.0)	59 (9.8)
Changes in concomitant medication due to AEs	157 (52.2)	151 (50.5)	308 (51.3)

Percentages are based on the total number of patients in a treatment group
AE = adverse event, N = number of patients in a treatment group, Rof500 = roflumilast 500 µg od, SAE = serious adverse event, SAF = safety set.

Most frequently, AEs affected the respiratory system, with COPD exacerbation (note that COPD exacerbation is the low level MedDRA term for this event, which is coded as preferred term COPD in the AE tables) being the most commonly reported AE for patients in the roflumilast 500 µg od and placebo group (24.6% and 25.8%, respectively). Bronchitis, diarrhoea, nausea, weight decrease, headache, tremor and insomnia were more frequently reported in the roflumilast 500 µg od group than in the placebo group. Except for bronchitis, this is in line with the current known safety profile of roflumilast 500 µg od. As AEs referring to the MedDRA system organ class 'infections and infestations' are similarly distributed between the treatment groups, no major safety concerns can be deduced from the higher frequency of 'bronchitis' in the roflumilast 500 µg od group.

The majority of AEs reported by patients in the roflumilast 500 µg od and placebo group were of moderate intensity (41.2% and 32.1%, respectively). AEs that were considered by the investigator to be likely or definitely related to study medication were reported by 80 patients (26.6%) in the roflumilast 500 µg od group and 23 patients (7.7%) in the placebo group.

During treatment, 24 patients (8.0%) in the roflumilast 500 µg od group reported 32 SAEs and 21 patients (7.0%) reported 32 SAEs in the placebo group. These SAEs included three patients who died; one in the roflumilast 500 µg od group due to COPD exacerbation (CRF ID 81110), and two patients in the placebo group, one from an injury (CRF ID 80258), and one from myocardial ischaemia and coronary artery atherosclerosis (CRF ID 81541). All three deaths were considered unrelated to study medication.

The percentage of patients who discontinued study medication due to AEs was higher in the roflumilast 500 µg od group compared with the placebo group (16.6% and 9.7%, respectively).

Overall, no clinically relevant changes in hematology, biochemistry, and urinalysis were observed in either the roflumilast 500 µg od or placebo group. During treatment, 18 instances of AEs associated with abnormal laboratory values were reported for patients in the roflumilast 500 µg od group compared with 24 instances for patients in the placebo group.

Physical examination during the study period did not reveal any clinically relevant results. There were no clinically significant changes in BP or HR; changes in systolic and diastolic blood pressure during the treatment period were similar for patients in the roflumilast 500 µg od group and placebo group, with slight increases in mean HR between Visit B0 and Visit T24 seen in the roflumilast 500 µg od group, compared with the placebo group. During the treatment period, there was a mean loss of weight of 1.6 kg in the roflumilast 500 µg od group compared with a mean weight gain of 0.4 kg in the placebo group, and a corresponding reduction of BMI from 25.5 kg/m^2 to 24.9 kg/m^2 in the roflumilast 500 µg od treatment group. Weight decrease is an acknowledged common side-effect of roflumilast 500 µg od.

Conclusions:

In conclusion, this multi-center study that looked at the parameters of lung function and hyperinflation for roflumilast 500 µg od compared with placebo showed that after 24 weeks of treatment, roflumilast 500 µg od demonstrated superiority over placebo for the primary efficacy parameter of FEV_1, which is indicative of airway obstruction in obstructive lung disease. However, roflumilast 500 µg od was not effective in reducing hyperinflation, as indicated by the absence of superiority over placebo for the co-primary efficacy variable of FRC_{pl}. No clinically relevant improvements in health outcome measures of BDI/TDI and CCQ were seen. Overall, there were no differences between treatment groups in the incidence of COPD exacerbation or time to first COPD exacerbation.

The observed safety data for roflumilast 500 µg od in this study were in line with the known safety profile of roflumilast 500 µg od.

Date of report: 23-Dec-2008