Synopsis of study report: 26/2003
Location in Module 5:

Study Code:
BY217 M2-107

Report Version:
2.0

Title of the study:

A comparison of treatment with 250 µg roflumilast versus 500 µg roflumilast versus placebo over 24 weeks in patients with chronic obstructive pulmonary disease (COPD)

Investigators:

A total of 159 investigators in Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, South Africa, Spain and the UK.

Study center(s):

A total of 159 centers in Australia (9), Austria (9), Belgium (10), Canada (26), France (14), Germany (17), Hungary (10), Ireland (6), South Africa (11), Spain (15) and the UK (32).

Publication (reference):

Not applicable

Studied period (years):

05 April 2002 to 17 June 2003

Clinical phase:

III

Objectives:

- to investigate the effect of 250 µg vs. 500 µg roflumilast vs. placebo on pulmonary function, exacerbation rate, quality of life, symptoms, and use of rescue medication
- to investigate the safety and tolerability of roflumilast

Methodology:

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

No. of subjects (total and for each treatment):

	Full analysis set	Valid cases set
	n	n
Total	1411	1070
Placebo	280	220
Roflumilast 250 µg	576	440
Roflumilast 500 µg	555	410

Diagnosis and criteria for inclusion:

Inclusion criteria

Patients of either sex were considered for the trial if they met the following criteria:

- history of chronic obstructive pulmonary disease for at least 12 months as defined by the GOLD criteria (2001)
- written informed consent
- age ≥ 40 years
- FEV_1/FVC ratio (post-bronchodilator) ≤ 70%
- FEV_1 (post-bronchodilator) 30 – 80% of predicted
- fixed airway obstruction (defined as an FEV_1 increase of ≤ 12% and/or ≤ 200 ml after receiving 400 µg salbutamol with a spacer)
- current smoker or ex-smoker (smoking cessation at least one year prior to recruitment) with a smoking history of at least 10 pack years
- stable clinical state with no change in COPD treatment during the last 4 weeks and
- not suffering from any concomitant disease that might interfere with study procedures or evaluation
- availability of a chest x-ray dated within 6 months prior to the study baseline visit or willingness to have a chest x-ray performed at visit B0.

Exclusion criteria

Patients meeting any of the following criteria were excluded from study enrolment. Any waiver of these criteria had to be approved both by the investigator and sponsor prior to patient entry:

- poorly controlled COPD as indicated by an exacerbation that:
  - required a course of systemic glucocorticosteroids during the 4 week period prior to the baseline visit B0, or

  - involved hospital admission (including treatment in an emergency room) in the 4 week period prior to the baseline visit B0

- lower respiratory tract infection in the 4 week period prior to the baseline visit B0
- diagnosis of asthma and/or other relevant lung disease (e.g. history of bronchiectasis, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease [e.g. fibrosis, silicosis, sarcoidosis] and active tuberculosis)
- known alpha-1-antitrypsin deficiency
- need for long-term oxygen therapy
- clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation (as assessed by the investigator)
- known infection with HIV
- active hepatitis
- diagnosis or history of cancer
- clinically significant cardiopulmonary abnormalities (diagnosed clinically or by x-ray/ECG) that were not related to COPD and that required further evaluation
- pregnancy, breast-feeding or lack of effective contraception in either females of childbearing potential or females who were < 1 year postmenopausal; effective contraception included abstinence, hormonal contraception (pill, Depo-Provera, Norplant), intra-uterine devices (IUD), "double-barrier" method or surgical sterilization such as tubal ligation or hysterectomy. Females of childbearing potential who were not sexually active (at study entry and in the 4 week period prior to the study) had to consent to use effective contraception if they became sexually active during the study.
- participation in another study (use of investigational product) within 30 days preceding the baseline visit B0 or re-entry of patients already enrolled in this trial
- suspected inability or unwillingness to comply with study procedures
- alcohol or drug abuse
- regular use of >8 puffs/day rescue medication
- inability to follow the procedures of the study due to e.g. language problems, psychological disorders
- suspected hypersensitivity to the study medication
- liver insufficiency
- use of not allowed drugs.

Randomization criteria
Patients were randomized after a 4-week baseline period, if the following criteria were fulfilled:

- FEV_1 (post-bronchodilator) 30 – 80% of predicted
- medication compliance ≥ 80% and ≤ 125%.

Test product:

Roflumilast

Dose:

250 µg and 500 µg, one tablet o.d. (once daily) in the morning

Mode of administration:

Oral administration

Batch No.:

101180 (roflumilast 250 µg) or 101160 (roflumilast 500 µg)

Duration of treatment:

Baseline period: 4 weeks; treatment period: 24 weeks

Reference product:

Placebo

Dose:

One tablet o.d. in the morning

Mode of administration:

Oral administration

Batch No.:

410190 or 101160

Criteria for evaluation:

Efficacy evaluation (primary)
- post-bronchodilator FEV_1
- co-primary: St. George's Respiratory Questionnaire (SGRQ)

Efficacy evaluation (secondary):
- pre- and post-bronchodilator FEV_1[1]
- pre- and post-bronchodilator spirometric lung function parameters: FVC, PEF, FEF_{25-75}, $FEF_{200-1200}$, FEV_3, FEV_6, AEX, FIV_1, PIF, FVC_{in}
- morning PEF (diary)
- exacerbations (number and time to event)
- SGRQ total[2] and component scores
- symptom score and use of rescue medication (diary)
- proportion of symptom-free days and rescue medication-free days
- Global Rating Scale (GRS)

Safety evalution (secondary):
Adverse events (AEs), electrocardiogram (ECG), changes in laboratory values and in physical examination findings.

Statistical methods:

Efficacy analysis was done as intention-to-treat (ITT) and per-protocol (PP) analysis, with the ITT analysis being the primary analysis for efficacy evaluation.
The within- and between-treatment differences for the (co-) primary efficacy and most of the secondary efficacy variables (lung function parameters, component scores of the SGRQ, GRS and morning PEF from diary) were evaluated using an analysis of covariance (ANCOVA) with the factors and/or covariables treatment, value at visit T0, age, sex, smoking status, and (pooled) center included in the model. The dependent variable was the change from visit T0. The last observation carried forward method (LOCF) was applied to replace missing values for the endpoint analysis of efficacy. As the co-primary variable total score of SGRQ was only tested on a confirmatory basis, if the primary variable post-bronchodilator FEV_1 proved superiority of roflumilast 500µg over placebo, no adjustment of the level α was required.

The secondary efficacy variables symptom score and daily use of rescue medication were analyzed non-parametrically using Pratt's modification of Wilcoxon's signed rank test for within-group comparisons and the Mann-Whitney test for between-group comparisons. The

[1] Analyses other than the primary analysis.

[2] Analyses other than the co-primary analysis.

number of rescue-medication and symptom free days and the number of COPD exacerbations were analyzed with the Mann-Whitney U-Test. The time to event analysis for exacerbations and drop-out was done by the log rank test. Fisher's Exact Test was used to analyze categories for the change in SGRQ scores.

For lung function parameters, SGRQ and GRS, a 'time averaged excess area under curve' (AUC) analysis using an ANCOVA model was done in addition to the analysis of differences.

The three treatments were compared with the above described tests in a pairwise manner. Furthermore, tests for trend were applied in order to investigate for a monotone dose-response relationship: the variables from spirometry (for differences and AUC), the scores from SGRQ and the GRS (also for the differences and AUC), morning PEF, use of rescue medication, the symptom scores, the percentage of rescue medication free and symptom free days and the number of COPD exacerbations were analyzed with the Jonckheere-Terpstra Test and the Cochran-Armitage test for trend was used to investigate the scores from SGRQ categorized into 'improvement of at least 4' and 'improvement of less than 4' percent. Furthermore, trend tests for survival were applied for time to first exacerbation analysis.

SUMMARY - CONCLUSIONS

Summary:

Efficacy results

Efficacy results are summarized for the ITT analysis, which was used for the primary efficacy analysis. The results of the PP analysis were generally comparable to those of the ITT analysis. The results focus on the respective endpoint analyses, if not indicated otherwise.

Primary and co-primary efficacy variable

Post-bronchodilator FEV_1 (primary efficacy variable) increased statistically significantly (increase being greater in the roflumilast 500 µg than in the roflumilast 250 µg group) in both roflumilast doses in the ITT endpoint analysis, whereas it decreased statistically significantly in the placebo group. Statistically significant between-treatment differences in favor of roflumilast were observed for the comparisons of roflumilast 500 µg with placebo (difference in LSMeans: 97 ml) and roflumilast 250 µg with placebo (difference in LSMeans: 74 ml; Table 1). A statistically significant monotone dose-response relationship in favor of roflumilast was observed in the Jonckheere-Terpstra test ($p < 0.0001$).

Table 1: Post-bronchodilator FEV_1 [l] - between-treatment differences in change from T0 to T_{last} (ITT last-value analysis)

		n	n	ΔTest – ΔReference		
Test	Reference	Test	Reference	LSMean ± SEM	95%CI	p-value[a]
Rof500	Placebo	501	257	0.097 ± 0.018	0.062, 0.131	<0.0001
Rof500	Rof250	501	528	0.023 ± 0.014	-0.006, 0.051	0.1166
Rof250	Placebo	528	257	0.074 ± 0.018	0.039, 0.108	<0.0001

[a] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.
CI = confidence interval, Δ = within-treatment difference, FEV_1 = forced expiratory volume in one second, LS = least squares, n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).
Data source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.7, Table 14.2.1.10.

The results of the time averaged excess AUC analysis were similar to those of the analysis of differences and thus supported the results obtained. In addition, the difference between the two roflumilast doses reached statistical significance in the AUC analysis.

Total SGRQ score (co-primary efficacy variable): Statistically significant improvements (corresponding to a decrease in score) were observed in all three treatment groups from T0 to T_{last} with the changes being higher in both roflumilast groups than in the placebo group. In the roflumilast groups the changes were close to the level of clinical significance (i.e. change of at least 4). The between-treatment differences between roflumilast 500 µg and placebo approached statistical significance in the ITT analysis (p = 0.0532, Table 2) and reached statistical significance in the PP analysis (p = 0.0492). The Jonckheere-Terpstra test revealed a statistically significant monotone dose-response relationship in favor of roflumilast.

Table 2: SGRQ total score - between-treatment differences change from T0 to T_{last} (ITT last-value analysis)

		n	n	ΔTest – ΔReference		
Test	Reference	Test	Reference	LSMean ± Std Err	95%CI	p-value[a]
Rof500	Placebo	496	267	-1.7 ± 0.9	-3.5, 0.0	0.0532
Rof500	Rof250	496	522	-0.2 ± 0.7	-1.6, 1.3	0.8270
Rof250	Placebo	522	267	-1.6 ± 0.9	-3.3, 0.2	0.0770

[a] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.
CI = confidence interval, Δ = within-treatment difference, LS = least squares, n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).
Data source: Table 14.2.3.7.

Secondary efficacy variables

If not indicated otherwise, the results summarized for the secondary efficacy parameters focus on the ITT analysis of differences. The results for the AUC analysis were similar to those of the analysis of differences.

Expiratory lung function parameters: FEV_3, FEV_6, AEX, $FEF_{200-1200}$, FEF_{25-75}, FVC and PEF increased in both roflumilast groups with the exception of FVC in the roflumilast 250 µg group in the ITT analysis. The increase reached statistical significance for AEX and $FEF_{200-1200}$ in the roflumilast 250 µg group and for all post-bronchodilator expiratory parameters with the exception of FVC and PEF in the roflumilast 500 µg group. In the placebo group all expiratory lung function parameters tended to decrease reaching statistical significance for FEV_3, FEV_6, FVC and PEF. Statistically significant differences between both roflumilast groups and the placebo group in favor of roflumilast were found for all expiratory parameters. The difference between both roflumilast groups reached statistical significance in favor of roflumilast 500 µg for FEV_3 and FEV_6. The Jonckheere-Terpstra test for trends revealed a statistically significant dose-response relationship in favor of roflumilast for all post-bronchodilator expiratory lung functions.

The analysis of the pre-bronchodilator expiratory lung function parameters showed similar results to those of the post-bronchodilator lung function parameters.

Inspiratory lung function parameters FIV_1, PIF, FVC_{in} tended to decrease rather than increase in all treatment groups during the course of the study with the decrease being higher in the placebo group than in the roflumilast groups. Statistically significant between-treatment differences in favor of roflumilast were found between the roflumilast groups and the placebo group for FVC_{in} and FIV_1. The Jonckheere-Terpstra test for trend revealed a statistically significant monotone dose-response relationship for post-bronchodilator FVC_{in} in favor of roflumilast.

Morning PEF increased statistically significantly in both roflumilast groups from W0 to W_{last} (with a higher increase in the roflumilast 500 µg than in the 250 µg group), whereas it remained approximately the same in the placebo group. Statistically significant between-treatment differences were observed between both roflumilast groups and the placebo group. The Jonckheere-Terpstra test for trends revealed a statistically significant dose-response relationship in favor of roflumilast for morning PEF ($p < 0.025$, one-sided).

SGRQ component scores (activity, impact and symptoms) decreased in all three treatment groups. The improvement (i.e. decrease) in both roflumilast groups was more pronounced than that in the placebo group. A statistically significant improvement was found for all three scores for both roflumilast groups and for the symptoms score for the placebo group. A clinically relevant improvement (i.e. decrease of at least 4) was found for the symptoms score

for both roflumilast groups. No statistically significant between-treatment differences were seen with the exception of the difference between the roflumilast 500 µg and the placebo group in the PP analysis for the impacts score. The Jonckheere-Terpstra test for trend revealed a statistically significant dose-response relationship in favor of roflumilast for the impacts score.

Exacerbations: The Jonckheere-Terpstra test for dose-response relationship showed a dose-dependent reduction of the total number of exacerbations ('severe, moderate or mild exacerbations') with increasing doses of roflumilast. In the roflumilast 500 µg group the reduction amounted to 34% as compared to placebo, predominantly due to a reduction of mild exacerbations. This could be expected because the inclusion criteria aimed towards a population with moderate COPD in a stable clinical state.

The GRS score improved from T0 to T_{last} in all three treatment groups with the increase in score being slightly higher in the roflumilast groups than in the placebo group. The within-treatment differences for all three treatment groups reached statistical significance. No statistically significant differences between the three treatment groups were observed and no statistically significant dose-response relationship was found.

COPD symptom score: The decrease in the COPD symptom score sum, indicating an improvement, was slightly more pronounced in the roflumilast 500 µg group than in the other two groups and reached statistical significance for both roflumilast groups for the score sum, the breathlessness score and the cough score, but not the sputum score. In the placebo group, the decrease was only statistically significant for the score sum. No statistically significant differences between the three treatment groups were seen and no statistically significant dose-response relationship for the COPD symptom score was found.

Daily use of rescue medication showed a statistically significant increase in the placebo group but not the roflumilast groups. No statistically significant between-treatment differences were seen.

Symptom and rescue medication free days: No statistically significant differences between the three treatment groups could be found for the percentage of symptom and rescue medication free days.

Subgroup analysis by smoking status: In total, the results for both subgroups by smoking status were comparable to those of the overall analysis. Statistically significant differences were observed between both treatments and placebo for FEV_1 in both subgroups. For SGRQ total score no statistically significant differences between treatments were seen.

Subgroup analysis by use of anticholinergics: Post-bronchodilator FEV_1 tended to increase under roflumilast treatment and to decrease under placebo irrespective of the subgroup analyzed. Statistically significant differences between either of the two roflumilast groups and the placebo group as well as statistically significant differences between the two roflumilast groups were observed in patients without use of anticholinergics. The differences in LSMeans were 128 ml (roflumilast 500 µg vs. placebo), and 80 ml (roflumilast 250 µg vs. placebo), indicating an even greater effect of roflumilast in patients not currently using anticholinergics. Improvements in SGRQ total score were more pronounced in both roflumilast groups than in the placebo group and tended to be greater in patients without use of anticholinergics than in those with use of anticholinergics. No statistically significant differences in total score of SGRQ were observed between the three treatment groups.

Safety results

In total, 2259 AEs were reported during the treatment period of this study: 174 patients taking placebo (62.1%) experienced 419 AEs, 382 patients (66.3%) taking roflumilast 250 µg experienced 896 AEs and 370 patients (66.7%) taking roflumilast 500 µg experienced 944 AEs. Thus, the overall incidence of AEs was slightly higher in patients taking roflumilast than in patients taking placebo. An overview of AEs is provided below in Table 3.

Table 3: Overview of treatment-emergent AEs

	Number (%) of patients[a]			
	Placebo (n = 280)	**Roflumilast 250 µg (n = 576)**	**Roflumilast 500 µg (n = 555)**	**Total (n = 1411)**
No. of AEs	419	896	944	2259
No. of patients reporting at least one AE	174 (62.1)	382 (66.3)	370 (66.7)	926 (65.5)
No. of patients with SAEs	21 (7.5)	41 (7.1)	53 (9.5)	115 (8.2)
No. of patients with AEs judged to be at least 'likely' related to study drug[b]	12 (4.3)	46 (8.0)	92 (16.6)	150 (10.6)
No. of patients with AEs leading to premature study discontinuation	23 (8.2)	56 (9.7)	82 (14.8)	161 (11.4)
No. of patient with AEs not yet known to be recovered	22 (7.9)	54 (9.4)	55 (9.9)	131 (9.3)

[a] Percentages are based on the total number of patients in the respective treatment group.
[b] by investigator
n = number of patients.
Data source: Table 14.3.1.2, Table 14.3.1.3.

The most frequently reported AEs were related to the respiratory system and thus due to the underlying disease. AEs affecting the gastro-intestinal tract occurred more frequently in patients taking roflumilast (15.8% in the roflumilast 250 µg group and 22.5% in the roflumilast 500 µg group) than in patients taking placebo (11.1%). Diarrhea nos and nausea showed dose-dependently higher incidences in the roflumilast groups (diarrhea: 4.9% in the roflumilast 250 µg group and 9.0% in the roflumilast 500 µg group, nausea: 2.8% in the

roflumilast 250 µg group and 4.9% in the roflumilast 500 µg group) than in the placebo group (diarrhea: 2.1%, nausea 0.7%).

The incidences of AEs considered to be at least 'likely' related to study medication (assessed as 'likely' or 'definitely' related by the investigator) were higher in the roflumilast groups (8.0% in the roflumilast 250 µg group and 16.6% in the roflumilast 500 µg group) than in the placebo group (4.3%). The most frequent 'likely' or 'definitely' related AE was diarrhea followed by nausea, headache and dizziness.

The vast majority of patients experienced AEs with mild or moderate severity. The percentage of patients experiencing severe AEs ranged from 8.6% in the placebo group to 12.8% in the roflumilast 500 µg group. The vast majority of AEs (> 90%) in each treatment group resolved during the course of the study.

In total, 13 patients died during the treatment period of the study (two [0.7%] in the placebo group, six [1.0%] in the roflumilast 250 µg group, and five [0.9%] in the roflumilast 500 µg group), all of which were judged to be 'not' or 'unlikely' related to the study medication by the sponsor and the investigator. Additionally, two patients who had been enrolled in the baseline period but were not randomized died later.
SAEs were reported during the treatment period for 7.1% of patients in the roflumilast 250 µg group, 7.5% of patients in the placebo group, and 9.5% of patients in the roflumilast 500 µg group.

The percentage of patients who were withdrawn from the study due to AEs was lower in patients taking placebo (8.2%) than in patients taking roflumilast 250 µg (9.7%) or roflumilast 500 µg (14.8%). The most common reason for study discontinuation was COPD exacerbation followed by diarrhea and nausea.

Physical examination, vital signs, ECG and laboratory values did not reveal any apparent clinically significant changes as a result of roflumilast administration. 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 once-daily doses of 250 or 500 µg was an effective treatment of patients with COPD. When compared to placebo, both 250 and 500 µg roflumilast effectively improved the post-bronchodilator lung function parameters FEV_1, FEV_3, FEV_6, AEX, $FEF_{200-1200}$, FEF_{25-75}, FVC, as well as PEF. Furthermore, roflumilast treatment increased morning PEF, improved quality of life, and lowered the

incidence of COPD exacerbations. For all of these parameters a statistically significant monotone dose-response relationship in favor of roflumilast could be seen.

In total, 62.1% of patients treated with placebo, 66.3% of patients receiving 250 µg roflumilast and 66.7% of patients treated with 500 µg roflumilast experienced AEs. Most of these AEs were judged 'not related' or 'unlikely related' to the study medication. The vast majority of AEs was of mild or moderate severity and resolved during the study. There was no apparent clinically relevant influence on laboratory parameters, vital signs, ECG or physical examination. Thus, the study supported a favorable benefit-to-risk ratio for roflumilast.