Synopsis of study report: 296/2004
Location in Module 5:

Study Code:
BY217/M2-112

Report Version:
1.0

Title of the study:

Effect of roflumilast on exacerbation rate in patients with chronic obstructive pulmonary disease.
A 52 weeks double blind study with 500 µg roflumilast once daily versus placebo.
RATIO Study.

Investigator(s):

A total of 159 investigators in Australia, Austria, Canada, France, Hungary, Italy, Netherlands, Poland, Portugal, Russian Federation, South Africa, Spain, Switzerland, and United Kingdom participated in the study.

Study center(s):

A total of 159 centers in Australia (11), Austria (7), Canada (21), France (17), Hungary (7), Italy (9), Netherlands (12), Poland (9), Portugal (4), Russian Federation (9), South Africa (13), Spain (16), Switzerland (9), and United Kingdom (15) were included in the study.

Publication (reference):

Not applicable

Studied period (years):

24-Jan-2003 to 27-Oct-2004.

Clinical phase:

IIIa

Objectives:

- to investigate the effect of 500 µg roflumilast *vs* placebo on exacerbation rate and pulmonary function, and additionally

- quality of life
- safety and tolerability of roflumilast
- health-economic evaluation (out of the scope of this report)

Methodology:

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

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

	Roflumilast 500 µg	**Placebo**	**Total**
	n	**n**	**n**
Total set			1829
Safety set	760	753	1513
Full analysis set	760	753	1513
Valid cases set	514	536	1050

Diagnosis and criteria for inclusion:

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

- Chronic obstructive pulmonary disease (COPD) as defined by GOLD: COPD is considered as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an inflammatory response of the lungs to noxious particles or gases. The characteristic symptoms of COPD are cough, sputum production and dyspnoea upon exertion.
- written informed consent has been obtained
- age ≥ 40 years
- forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio (post-bronchodilator) ≤ 70%
- FEV_1 (post-bronchodilator) ≤ 50% of predicted
- fixed airway obstruction (defined as an FEV_1 increase of ≤ 15% and/or ≤ 200 mL after receiving 200 µg salbutamol)
- current smoker or ex-smoker (smoking cessation at least 1 year ago) with a smoking history of at least 10 pack years (smoking of 20 cigarettes per day for 1 year corresponds to 1 ‘pack year’)

- not suffering from any concomitant disease that might 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 month prior to study baseline Visit B0 or willingness to have a chest x-ray performed before Visit B0.

Exclusion Criteria

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

- COPD exacerbation indicated by a treatment with systemic glucocorticosteroids not stopped 4 weeks prior to the baseline Visit B0
- lower respiratory tract infection not resolved within 4 weeks 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)
- use of not allowed drugs
- known alpha-1-antitrypsin deficiency
- need for long-term oxygen therapy defined as ≥ 16 hours/day
- 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
- liver insufficiency
- diagnosis or history of cancer or recurrence within 5 years

- clinically significant cardiopulmonary abnormalities (diagnosed clinically or by x-ray/electrocardiogram [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), intrauterine devices, '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
- inability to follow the procedures of the study due to e.g. language problems, psychological disorders
- suspected hypersensitivity to the study medication.

Randomization Criteria

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

- judged to be clinically stable and no moderate/severe exacerbations between B0 and T0
- medication compliance ≥80% and ≤125%.

Test product:

Roflumilast

Dose:

500 µg, one tablet once daily (od) in the morning

Mode of administration:

Oral administration

Batch No.:
120170 and 120180

Duration of treatment:
Baseline period: 4 weeks; treatment period: 52 weeks

Reference product:
Placebo

Dose:
One tablet od in the morning

Mode of administration:
Oral administration

Batch No.:
410190, 320220, and 320230

Criteria for evaluation:
Efficacy evaluation (primary)[1]
- frequency of moderate or severe exacerbations per patient per year
- change (endpoint minus baseline value) in post-bronchodilator FEV_1

Efficacy evaluation (secondary):
- -key secondary: change in total score of St. George's Respiratory Questionnaire (SGRQ; endpoint minus baseline value)[2]
- pre- and post-bronchodilator spirometric lung function parameters: FEV_1[3], FVC, peak expiratory flow (PEF), forced expiratory flow rate at 25, 50, or 75% of the vital capacity (FEF_{25}, FEF_{50}, or FEF_{75}), forced expiratory flow between 25% and 75% of the vital capacity (FEF_{25-75}), forced expiratory flow between 200 and 1200 mL ($FEF_{200-1200}$), forced expiratory volume in the first 3 or 6 seconds (FEV_3, FEV_6), area under the expiratory

[1] Primary variables changed as described in Amendment 1 and Amendment 5 to the Study Protocol (see Section 9.8, Appendix 16.1.1.2, and Appendix 16.1.1.6).

[2] Total score of SGRQ was stipulated as key secondary variable in Amendment 5 to the Study Protocol (see Section 9.8 and Appendix 16.1.1.6).

[3] Analyses other than the primary analysis.

curve (AEX), forced inspiratory volume in 1 second (FIV_1), peak inspiratory flow (PIF), forced inspiratory vital capacity (FVC_{in}), inspiratory capacity (IC)
- exacerbations (severe, moderate, and mild)[3]
- SGRQ total[4] and component scores
- morning PEF (diary)
- COPD symptom score and use of rescue medication (diary)
- proportion of symptom-free days and rescue medication-free days
- Baseline/Transition Dyspnoea Index (BDI/TDI) focal and component scores

Safety evalution (secondary):
Adverse events (AEs), vital signs, 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 primary variable frequency of moderate or severe exacerbations per patient per year was evaluated non-parametrically using the Wilcoxon rank-sum test. Furthermore, a Poisson regression model that included the factors and covariables treatment, age, sex, smoking status, country, and pretreatment with ICS was applied. The within- and between-treatment differences for the primary efficacy variable post-bronchodilator FEV_1 and most of the (key-)secondary efficacy variables (other lung function parameters, SGRQ, and morning PEF from diary) were evaluated using an analysis of covariance (ANCOVA) with above mentioned factors and covariables included in the model. The dependent variable was the change from visit T0. In the ITT analysis the last observation carried forward method (LOCF) was applied to replace missing values for the endpoint analysis of efficacy. For lung function parameters and SGRQ, a repeated measurement analysis and a 'time averaged excess area under curve' (AUC) analysis was done in addition to the analysis of differences. As the key secondary variable total score of SGRQ was only tested on a confirmatory basis if both of the two primary variables proved superiority of roflumilast 500µg over placebo, no adjustment of the level α was required.
The secondary efficacy variables BDI/TDI, 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 U-test for between-group comparisons. The number of rescue-medication and symptom free days were analyzed with the Mann-Whitney U-Test. The time to event analysis for exacerbations was done by the log rank test. Fisher's Exact Test was used to analyze frequencies of patients with or without exacerbations and for categories of the change in SGRQ scores.

[4] Analyses other than the key secondary analysis.

SUMMARY - CONCLUSIONS

Summary:

If not indicated otherwise, the results described here refer to the ITT analysis.

Primary efficacy variables:

Post-bronchodilator FEV_1 increased from T0 to T_{last} with roflumilast, whereas in the placebo group a statistically significant decrease was seen. Differences in LSMeans between roflumilast and placebo ranged from 45 to 70 mL and were statistically significant at the different visits. A statistically significant between-treatment difference in favor of roflumilast was found for the comparison of roflumilast 500 µg with placebo at the endpoint as well (difference in LSMeans: 39 mL; see Table 1). This result was confirmed by the repeated measurement and the AUC analysis (difference in LSMeans for both analyses: 48 mL).

Table 1: Post-bronchodilator FEV_1 [L] - within- and between-treatment differences (ITT last-value analysis)

WITHIN		**T0**		**T_{last}**	**T_{last} – T0**		
	n	**Mean % pred.**	**LSMean**	**LSMean**	**LSMean ± SEM**	**95%CI**	**p-value[a]**
Rof500	701	1.131 41%	1.138	1.150	0.012 ± 0.011	-0.009, 0.033	0.2478
Placebo	720	1.145 41%	1.138	1.112	-0.026 ± 0.011	-0.047, -0.005	0.0149
BETWEEN			**n**	**n**	**ΔTest – ΔReference**		
	Test	**Reference**	**Test**	**Reference**	**LSMean ± SEM**	**95%CI**	**p-value[b]**
	Rof500	Placebo	701	720	0.039 ± 0.012	0.016, 0.062	0.0005

[a] p-value for within-treatment differences (ANCOVA), two-sided, significance level 5%.

[b] p-value referring to superiority, one-sided, significance level 2.5%.

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} Rof500 = roflumilast 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).

Data source: Table 15.2.7.1, Table 15.2.7.2, Table 15.2.7.9, and Table 15.2.7.13.

Patients treated with roflumilast 500 µg od had fewer moderate or severe COPD exacerbations per year than those treated with placebo (see Table 2).

Table 2: Frequency of exacerbations per patient per year (Wilcoxon rank-sum test, ITT analysis)

Exacerbation severity	n		Standardized value[a]	Relative effect p[b]	p-value[c]	p-value[d]
	Rof500	Placebo				
Moderate or severe	760	753	0.753	0.5101	0.4514	0.2257
Severe	760	753	-0.775	0.4947	0.4383	0.7808
Moderate	760	753	1.247	0.5162	0.2123	0.1062
Mild	760	753	1.460	0.5178	0.1442	0.0721

[a] Standardized Wilcoxon-Mann-Whitney statistic: values > 0 indicate an improvement with roflumilast compared to placebo.
[b] Relative effect p of placebo to roflumilast: values > 0.5 indicate an improvement with roflumilast compared to placebo.
[c] Asymptotic p-value, two-sided, significance level 5%.
[d] Asymptotic p-value, one-sided, significance level 2.5%.
n = number of patients included in analyses, Rof500 = roflumilast 500 µg once daily.
Data source: Table 15.2.2.1.

Using a Poisson-regression model the reduction compared with placebo was found to be –7% in the ITT and –11% in the PP analysis (see Table 3).

Table 3: Frequency of exacerbations per patient per year (Poisson regression model, ITT analysis)

Exacerbation severity	Test			Reference			Ratio test/reference		
		n	Rate		n	Rate	Risk ratio ± SE	95%CI	p-value[a]
Moderate or severe	Rof500	760	0.857	Placebo	753	0.918	0.934 ± 0.075	0.798, 1.092	0.3901
Severe	Rof500	760	0.083	Placebo	753	0.076	1.090 ± 0.242	0.705, 1.686	0.6970
Moderate	Rof500	760	0.760	Placebo	753	0.833	0.913 ± 0.077	0.774, 1.076	0.2758
Mild	Rof500	760	1.683	Placebo	753	1.915	0.878 ± 0.102	0.700, 1.103	0.2640

[a] p-value for between-treatment differences, two-sided, significance level 5%.
CI = confidence interval, n = number of patients included in analyses, Rof500 = roflumilast 500 µg once daily, SE = standard error.
Data source: Table 15.2.3.2.

The difference between roflumilast and placebo was not statistically significant in the primary Wilcoxon rank-sum test (see Table 2). When analyzing a pre-defined subset of exacerbations that were treated with oral glucocorticosteroids, roflumilast reduced the rate of moderate exacerbations to a statistically significant extent when compared with placebo (p = 0.0147, one-sided, Wilcoxon rank-sum test). In the Poisson-regression model this reduction of moderate exacerbations was found to be -18% (estimated rates per year: roflumilast 0.395, placebo 0.483, p = 0.0668, two-sided).

Key-secondary efficacy variable:

Since superiority of roflumilast over placebo could not be shown for the primary variable frequency of moderate or severe exacerbations per year on a confirmatory basis, the key secondary variable total score of SGRQ was tested in an exploratory manner.

For the change in SGRQ total score from T0 to T_{last} statistically significant improvements (corresponding to a decrease in score) were observed in both treatment groups. There was no difference between roflumilast 500 µg and placebo.

Secondary efficacy variables:

The rate of moderate and mild exacerbations per year numerically decreased with roflumilast when compared with placebo by –9% and –12%, respectively (Poisson regression model). The rate of severe exacerbations increased in the roflumilast treatment group by 9% *vs* placebo (Poisson regression model). However, this estimate was based on a low number of events. The changes in exacerbation frequencies were not statistically significant (Wilcoxon rank-sum test).

Post-bronchodilator FEV_3, FEV_6, and FVC decreased during the study in both treatment groups. The decrease was statistically significant for the placebo group. Statistically significant differences in favor of roflumilast were found for FEV_3 and FEV_6 in the ITT endpoint analysis and for FVC in the PP analysis. AEX, $FEF_{200-1200}$, FEF_{25}, and FEF_{50} increased in the roflumilast 500 µg group during the course of the study. On the other hand, these secondary lung function parameters decreased in the placebo group. The comparison of roflumilast 500 µg with placebo revealed statistically significant between-treatment differences in favor of roflumilast for the parameters AEX, $FEF_{200-1200}$, FEF_{25-75}, FEF_{25}, and FEF_{50}.

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

Morning PEF improved statistically significantly in the roflumilast and the placebo group from W0 to W_{last}. Statistically significant between-treatment differences in favor of roflumilast were observed in the analysis of AUC.

Similar to the total score, a decrease in the SGRQ component scores (activity, impacts and symptoms) was also found for both treatment groups. No statistically significant between-treatment differences were seen.

A statistically significant increase in TDI scores from BDI and thus an improvement in dyspnoea was found for both treatments with the improvement being more pronounced in the roflumilast treatment group. A statistically significant difference between the treatments in favor of roflumilast was observed for the effort score but not for the focal score.

The decrease in the COPD symptom score sum, indicating an improvement of COPD symptoms, was slightly more pronounced in the roflumilast 500 µg group than in the placebo group.

A statistically significant increase in the daily use of rescue medication was seen for the roflumilast and the placebo group. The between-treatment difference was statistically significant in favor of roflumilast in the PP analysis.

The results of the subgroup analyses of exacerbations (according to smoking status and concomitant ICS treatment) were comparable to those of the overall analysis: The frequency of moderate or severe exacerbations per patient per year decreased with roflumilast when compared with placebo, but not to a statistically significant extent. The greatest effect of roflumi-

last could be seen in smokers: using the Poisson regression model, the reduction of moderate or severe exacerbations was found to be –18% and for mild exacerbations –25% when compared with placebo. For patients not using ICS during the study, the reduction in the rate of moderate or severe exacerbations was –11%, whereas the rate of moderate or severe exacerbations was reduced by –5% when patients were taking concomitant ICS.

For post-bronchodilator FEV_1, a beneficial effect of roflumilast could be observed when compared with placebo throughout the different subgroups (according to smoking status, concomitant ICS treatment, and exacerbation frequency).

Safety

In total, 3897 AEs were reported during the treatment period. Out of 760 patients receiving roflumilast 500 µg 592 (77.9%) experienced 1997 AEs, and 584 of 753 patients (77.6%) receiving placebo experienced 1900 AEs. Thus, the incidence of patients experiencing AEs was comparable between patients taking roflumilast and in patients taking placebo.

The most frequently reported AEs were related to the respiratory system and thus due to the underlying disease. AEs affecting the gastro-intestinal tract and nervous system disorders occurred more frequently in patients taking roflumilast than in patients taking placebo as expected from the results of other clinical trials. On the preferred term level, diarrhea, nausea and headache showed higher incidences in the roflumilast group (diarrhea: 9.3%, nausea: 5.0%, headache: 6.2%) than in the placebo group (diarrhea: 2.7%, nausea: 1.3%, headache: 2.4%).

The majority of patients experienced AEs with mild or moderate severity. Most AEs in each treatment group resolved during the study.

The incidence of AEs considered to be at least ‘likely’ related to study medication was higher in the roflumilast group (17.8%) than in the placebo group (5.6%). The most frequent ‘likely’ or ‘definitely’ related AE was diarrhea followed by nausea, which reflects the overall high incidence of these AEs in the study. In total, 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.

In total, 32 patients died during the treatment period of the study (12 patients [1.6%] in the roflumilast 500 µg group and 20 patients [2.7%] in the placebo group). All deaths were judged to be ‘not’ or ‘unlikely’ related to the study medication by the sponsor and the investigator. Additionally, 8 patients who were enrolled but were not randomized died during the baseline period.

SAEs were reported during the treatment period for 18.0% of patients in the roflumilast 500 µg group and 17.5% of patients in the placebo group. The percentage of patients who were withdrawn from the study due to AEs was lower in patients taking placebo (9.8%) than in patients taking roflumilast 500 µg (16.3%). The most common reason for study discontinuation was COPD exacerbation followed by diarrhea and nausea.

An influence of roflumilast on vital signs, ECG, laboratory values or physical examination during treatment was not apparent.

Conclusions:

This study demonstrated that roflumilast administered in once daily doses of 500 µg was superior to placebo in improving the primary efficacy variable FEV_1 in patients with COPD. Although for the other primary endpoint frequency of moderate or severe exacerbations superiority of roflumilast over placebo could not be shown in a confirmatory manner, roflumilast showed a significant reduction *vs* placebo in the predefined analysis of moderate exacerbations treated with oral/parenteral glucocorticosteroids by –18%. Amongst the secondary outcome parameters consistent improvements with roflumilast *vs* placebo could be demonstrated, e.g. for the post-bronchodilator lung function parameters FEV_6 or FEF_{25-75}.

In total, 77.9% of patients treated with 500 µg roflumilast and 77.6% 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 related' 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 laboratory parameters, vital signs, ECG or physical examination. Thus, the study supported a favorable benefit to risk ratio for roflumilast.