Synopsis of study report: 139/2001 K1
Location in Module 5:

Study Code:
BY217/FK1 101

Report Version:
3.0

Title of the study:

26 weeks treatment with 250 µg vs. 500 µg roflumilast vs. placebo in patients with chronic obstructive pulmonary disease (dose range finding trial)

Investigators:

A total of 47 investigators participated in four countries: Germany (17), Hungary (8), South Africa (9) and The Netherlands (13).

Study centers:

A total of 47 centers in four countries: Germany (17), Hungary (8), South Africa (9) and The Netherlands (13).

Publication (reference):

Not applicable.

Studied period:

08 October 1999 - 12 February 2001

Clinical phase:

II/III

Objectives:

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

Methodology:

This was a double-blind, randomized parallel-group multicenter study. After a single-blind baseline period of 2 weeks (visits B0, B1, if applicable, and B2 i.e. visits at start of the baseline period, 1 and 2 weeks after the start of the baseline period, respectively), eligible patients were randomized (at visit T0 = B2) to receive a once daily (OD) dose of either 500 µg roflumilast, 250 µg roflumilast or placebo. During the 26-week treatment period patients recorded their morning PEF, use of rescue medication and their symptoms on a diary. After 1, 3, 6, 10, 14, 18, 22 and 26 weeks (T1, T3, T6, T10, T14, T18, T22 and T26) patients underwent further lung function testing (FEV_1, FVC, PEF, FEF_{25-75}) and safety assessments at a clinic visit. Additionally, at selected visits blood gas analysis and an exercise test were performed and health-related quality of life as well as pharmacoeconomic data were assessed.

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

Intention-to-treat	n = 516	Per-protocol	n = 436
Placebo	n = 172	Placebo	n = 145
250 µg roflumilast	n = 175	250 µg roflumilast	n = 149
500 µg roflumilast	n = 169	500 µg roflumilast	n = 142

Diagnosis and criteria for inclusion:

Inclusion:
- COPD patients, aged 40 to 75 years,
- post-bronchodilator[a] FEV_1 between 35% to 75% of predicted,
- FEV_1/FVC ratio pre-bronchodilator[a] ≤ 70%,
- irreversible airways obstruction, defined as an increase ≤ 12% and ≤ 200 ml of initial value after receiving 400 µg salbutamol (with a spacer),
- current or ex-smokers (history of at least 10 pack years),
- stable clinical state with no change in COPD treatment during the previous 4 weeks,
- no concomitant disease which might interfere with study related procedures.

Randomization:
- pre-bronchodilator[a] FEV_1 within ± 15% of that at B0,

[a] Spirometric measurements were done after withholding bronchodilators for at least 4 hours prior to measurements (pre-bronchodilator measurement) and 30 min after inhalation of 400 µg salbutamol (post-bronchodilator measurement).

- post-bronchodilator[a] FEV_1 between 35% and 75% of predicted and an increase in FEV_1 ≤ 12% and ≤ 200 ml after inhalation of 400 µg salbutamol,
- compliance during the baseline period ≥ 80% and ≤ 120%.

Test product:

Roflumilast 250 or 500 µg/tablets

Dose:

One tablet OD in the morning

Mode of administration:

Oral

Batch No.:

BY217-45-1-1 (250 µg), BY217-46-4-1 (500 µg)

Duration of treatment:

Baseline period two weeks; treatment period 26 weeks.

Reference product:

Placebo

Dose:

One tablet, OD, in the morning

Mode of administration:

Oral

Batch No.:

BY217-43-3-1

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[a] Spirometric measurements were done after withholding bronchodilators for at least 4 hours prior to measurements (pre-bronchodilator measurement) and 30 min after inhalation of 400 µg salbutamol (post-bronchodilator measurement).

Criteria for evaluation:

Efficacy:

- *primary variables:*
  - pre-bronchodilator[a] FEV_1 at end of treatment as compared to T0 (T_{last} - T0),
  - Quality of life (St George's Respiratory Questionnaire [SGRQ], total score) at end of treatment as compared to T0.
- *secondary variables:*
  - pre-and post-bronchodilator spirometry (FVC, PEF, FEF_{25-75}),
  - post-bronchodilator FEV_1,
  - morning PEF from diary cards,
  - symptoms and use of rescue medication from the diary cards,
  - component scores from SGRQ,
  - component score from the Short Form 36 questionnaire,
  - breathlessness and exercise test,
  - blood gas analysis (optional),
  - pre-defined "escape" criteria (occurrence of three moderate and/or one severe exacerbation),
  - number of exacerbations,
  - Global Rating Scale.

Safety:

Adverse events, ECG, changes in laboratory values and in physical examination findings.

Statistical methods:

Efficacy analysis was done for the ITT and PP population, with the ITT population being the primary population for efficacy evaluation. Additionally, a so-called extended ITT analysis was performed for lung function measurements, which included invalid lung function measurements not included in the ITT analysis. For the primary variables, the secondary lung function variables, morning PEF from diaries, component and total scores of the SGRQ and results of the SF-36 an ANCOVA with the factors and/or covariates treatment, age, sex, smoking status and center was performed. Based on the $T_{last(end)}$ - T0 differences, where T_{last} and T_{end} corresponds to the endpoint analysis of the ITT and PP evaluation, respectively, a test for monotone dose-response using the pairwise contrasts was performed.

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[a] Spirometric measurements were done after withholding bronchodilators for at least 4 hours prior to measurements (pre-bronchodilator measurement) and 30 min after inhalation of 400 µg salbutamol (post-bronchodilator measurement).

Statistical methods (continued):

Adjusted least squares (LS) means and 95%-confidence limits were given for treatment differences. With respect to spirometric measurements a post-hoc analysis demonstrated a non-normal distribution. Thus, a post-hoc non-parametric analysis including the Jonckheere-Terpstra test and the Mann-Whitney U-test was performed additionally for these variables. The type-I-error was set to $\alpha = 0.025$, one-sided. Since significance for both endpoints was to be demonstrated, multiplicity adjustments to the significance level were not indicated. The sample size of approximately 150 patients per group ensured a power of approximately 90% for concluding superiority of 500 µg over placebo with regard to both primary variables.

SUMMARY - CONCLUSIONS

Summary:

Efficacy results:

Efficacy results are summarized for the ITT analysis, which was primary. Results form the PP analysis were comparable.

Primary variables:

Pre-bonchodilator FEV_1: In addition to the parametric analysis as specified in the protocol a non-parametric analysis was performed as suggested by the non-normal distribution of the FEV_1 values. The improvements seen were higher in the roflumilast groups as compared to placebo (with respect to LSMeans and medians), reaching statistical significance on the 2.5%-level (one-sided) with respect to both doses, but not for placebo (see below). Differences between roflumilast and placebo were more pronounced when analyzed non-parametrically. A trend towards dose-dependency was found (LS Mean).

Pre-bronchodilator FEV_1 (l): Within treatment differences: T_{last} - T0 (ITT last value analysis)

Treatment group	n	LS Mean ± Std Err (median)	95% CI	p-value[a] parametric (non-parametric)
Placebo	169	0.029 ± 0.023 (-0.020)	-0.017, 0.075	0.2183 (0.8222)
250 µg roflumilast	173	0.064 ± 0.022 (0.030)	0.020, 0.108	0.0045 (0.0104)
500 µg roflumilast	167	0.069 ± 0.023 (0.030)	0.024, 0.114	0.0026 (0.0110)

[a] Two-sided.

SUMMARY - CONCLUSIONS (continued)

Summary (continued):

Efficacy results - Primary variables (continued):

Pre-bronchodilator FEV_1 (l): Between-treatment differences for T_{last} - T0 (ITT last value analysis)

Treatment group	n	LS Mean ± Std Err	95% CI	p-value[a] parametric (non-parametric)
250 µg roflumilast vs placebo	[b]	0.035 ± 0.030	-0.024, 0.094	0.1199 (0.0475)
500 µg roflumilast vs placebo	[b]	0.041 ± 0.030	-0.018, 0.099	0.0884 (0.0471)
500 µg vs 250 µg roflumilast	[b]	0.005 ± 0.030	-0.053, 0.064	0.4284 (0.4980)

[a] one-sided [b] n = 169, 173, 167 for placebo, 250 µg and 500 µg roflumilast, respectively.

SGRQ - total score: There were no differences between treatments. A comparable statistically significant and clinically relevant decrease in LSMean was seen in all three treatment groups amounting to -4.45, -4.41, and -4.73 in the placebo, 250 µg roflumilast and 500 µg roflumilast group, respectively.

Secondary variables:

Lung function measurements: Improvements in *post-bronchodilator FEV_1* were greater on roflumilast as compared to placebo (see below), with a trend towards dose dependency and with the difference being more pronounced when medians are analyzed as compared to LSMeans.

Post-bronchodilator FEV_1 (l): Within treatment differences: T_{last} - T0 (ITT last value analysis)

Treatment group	n	LS Mean ± Std Err (median)	95% CI	p-value[a] parametric (non-parametric)
Placebo	167	0.057 ± 0.024 (0.020)	0.010, 0.104	0.0180 (0.1071)
250 µg roflumilast	169	0.093 ± 0.023 (0.070)	0.048, 0.139	0.0001 (0.0001)
500 µg roflumilast	160	0.109 ± 0.024 (0.075)	0.062, 0.156	<0.0001 (<0.0001)

[a] Two-sided.

SUMMARY - CONCLUSIONS (continued)

Summary (continued):

Efficacy results - Secondary variables (continued):

Post-bronchodilator FEV_1 (l): Between-treatment differences for T_{last} - T0 (ITT last value analysis)

Treatment group	n	LS Mean ± Std Err	95% CI	p-value[a] parametric (non-parametric)
250 µg roflumilast vs placebo	[b]	0.037 ± 0.031	-0.023, 0.097	0.1155 (0.0639)
500 µg roflumilast vs placebo	[b]	0.052 ± 0.031	-0.009, 0.113	0.0465 (0.0180)
500 µg vs 250 µg roflumilast	[b]	0.015 ± 0.031	-0.045, 0.076	0.3096 (0.3329)

[a] One-sided.
[b] n = 167, 169, 160 for placebo, 250 µg and 500 µg roflumilast, respectively.

As seen for FEV_1 the improvements with respect to FEF_{25-75} and PEF from spirometry and diaries were consistently higher in the roflumilast groups as compared to placebo, for both pre- and post-(see below) bronchodilator measurements, with a trend towards dose-dependency for most variables. For FVC, deteriorations were seen, but less pronounced under roflumilast, or FVC even improved under roflumilast.

Lung function variables: within-treatment changes (T_{last} – T0 [W0]) - ITT last value analysis

		Placebo	Roflumilast 250 µg	Roflumilast 500 µg
FEF_{25-75} (l/s)	LSMean (95% CI)	0.006 (-0.060, 0.072)	0.061 (-0.004, 0.126)	0.071 (0.004, 0.138)
	Median	-0.010	0.040	0.025
FVC (l)	LSMean (95% CI)	-0.064 (-0.132, 0.004)	-0.003 (-0.068, 0.063)	0.019 (-0.050, 0.087)
	Median	-0.020	0.050	0.075
PEF (l/min)[a]	LSMean (95% CI)	13 (2, 24)	27 (16, 37)	16 (5, 27)
	Median	7	19	13
Morning PEF (l/min)[b]	LSMean (95% CI)	2 (-5, 9)	9 (2, 16)	10 (3, 17)
	Median	0	7	10

For spirometric measurements the post-bronchodilator value is given. PEF values are rounded. CI = confidence interval, W0 = week prior to T0.
N = 167, 169, 160 (spirometry), 162, 169, 164 (morning PEF) for the placebo, 250 µg and 500 µg roflumilast group, respectively
[a] from spirometry [b] from diaries.

SUMMARY - CONCLUSIONS (continued)

Summary (continued):

Efficacy results - Secondary variables (continued):

Symptom score and use of rescue medication: The total symptom score (median) decreased in all treatment groups, numerically more pronounced under placebo (see below). For the individual scores breathlessness, cough and sputum production, no differences between groups were seen. The use of rescue medication remained constant during the treatment period in all three treatment groups, as measured by the number of puffs per day.

Symptom score and use of rescue medication within-treatment changes (T_{last} – W0) in median (95% CI) - ITT

	Placebo	Roflumilast 250 µg	Roflumilast 500 µg
Symptom score (change in score sum)	-0.50 (-0.79, -0.29)	-0.43 (-0.79, -0.31)	-0.29 (-0.64, -0.20)
Rescue medication (no of puffs)	0.00 (-0.14, 0.43)	0.00 (-0.29, 0.14)	0.00 (-0.36, 0.07)

CI = confidence interval, W0 = week prior to T0.

Exacerbations ("escape" criteria): The number of patients meeting "escape" criteria were three each in the placebo and 250 µg roflumilast, and two in the 500 µg roflumilast group. The overall number of exacerbations was reduced on 500 µg roflumilast as compared to the other two treatment groups. The corresponding numbers were 26, 25 and 15 exacerbations on placebo, 250 µg and 500 µg roflumilast, respectively, experienced by 16, 19 and 13 patients.

6-minute walk (Borg scale) and blood gas analysis: There were no significant differences between the three treatment groups with respect to the walking test. Blood gas analysis revealed slight differences in favor of roflumilast.

Individual symptom scores of the SGRQ: Individual symptom scores improved significantly in each treatment group with a monotone dose-response for the activity domain.

SF-36: Differences were seen in each of the nine health concepts covered by the SF-36 in either treatment group without any clear trend with the exception of the general health and physical functioning with more pronounced improvement on roflumilast, particularly with the 500 µg dose.

Health utility - Global Rating Scale: Small improvements without any differences between treatment groups were seen.

SUMMARY - CONCLUSIONS (continued)

Summary (continued):

Efficacy results - Secondary variables (continued):

Subgroup analyses: The differences in favor of roflumilast were slightly more pronounced in the subgroup of smokers with a trend towards dose-dependency for FEV_1, FVC (both pre- and post-bronchodilator), pre-bronchodilator PEF (spirometry) and use of rescue medication. Other subgroup analyses (i.e. patients with a moderate or severe state of the disease, with or without anti-inflammatory pre-treatment, with or without concomitant use of anticholinergics) revealed also slight differences but without any clear trend in favor of any subgroup thus indicating rather a robust efficacy of roflumilast across patient populations studied. However note, that the sample size of the subgroups were small.

Safety results:

In total there were 528 AEs experienced by 252/516 patients (49%) during the treatment period. The incidence of AEs and SAEs (based on the number of patients with at least one AE) was well comparable between groups. The great majority of AEs was judged to be "not" related to study medication. An overview of AEs is shown below:

Overview of AEs

	Placebo (N = 172)	Roflumilast 250 µg (N = 175)	Roflumilast 500 µg (N = 169)
No. of patients with AEs[a]	85 (49%)	85 (49%)	82 (49%)
No. of AEs	182	170	176
"likely" and "definitely" related AEs[b]	6 (3%)	8 (5%)	30 (17%)
"unlikely" and "not" related AEs[b]	176 (97%)	162 (95%)	146 (83%)
No. of patients withdrawn due to AE[a]	10 (6%)	13 (7%)	12 (7%)
No. of patients with SAEs[a]	11 (6%)	14 (8%)	9 (5%)
No. of SAEs	14	18	12

[a] Percentages are based on the number of patients in each treatment group.
[b] Percentages are based on the total number of AEs in the respective treatment group.

Overall the most frequently reported AEs were bronchitis (including COPD exacerbations) and upper respiratory tract infection in each treatment group. Of those AEs which were considered to be at least "likely" related to roflumilast intake, headache, nausea and diarrhea were the most commonly reported AEs with an incidence of 2% (headache, nausea) and 1% (diarrhea), respectively (based on the total number of AEs in the roflumilast groups).

SUMMARY - CONCLUSIONS (continued)

Summary (continued):

Safety results (continued):

Most of the AEs were mild or moderate in intensity. Five (3%), 16 (9%) and 10 (6%) of the reported AEs in the placebo, 250 µg and 500 µg roflumilast group, respectively were severe in nature, all judged by the investigator and Sponsor to be "not" or "unlikely" related to study medication as were all SAEs.

Physical examinations, vital signs, ECG and laboratory values did not reveal any clinically significant changes as a result of roflumilast administration. Electrocardiographic findings did not indicate an influence of roflumilast on the QTc interval.

Conclusions:

This study demonstrated that both doses, 250 µg/d and 500 µg/d roflumilast increase the lung function in patients with COPD. Although superiority of roflumilast vs placebo could not be shown at the 2.5% level (one-sided) for the primary variables, patients receiving roflumilast performed consistently better than those on placebo with respect to all lung function measurements (spirometry and morning PEF from diaries). Additionally, the results demonstrated a trend towards dose-dependency for some of these variables.

Differences between treatments were even more pronounced when spirometric lung function variables were analyzed non-parametrically as suggested by the non-normal distribution. This holds true in particularly for post-bronchodilator FEV_1, for which the differences 500 µg roflumilast vs placebo reached statistical significance. Post-bronchodilator FEV_1 is considered to be a more relevant survival predictor than the pre-bronchodilator value, which was chosen as primary variable, and is now recommended by current guidelines to characterize COPD. Differences between treatments in quality of life assessments were not observed probably due to the patients' poor perception of moderate differences in their state of COPD. With respect to safety, roflumilast showed a favorable safety profile and was very well tolerated in patients with COPD.