Synopsis of study report: 93/2002
Location in Module 5:

Study Code:
BY217/FK1 103

Report Version:
2.0

Title of the study:

Withdrawal of 500 µg roflumilast after 12 weeks of treatment versus continued treatment for 24 weeks versus placebo in patients with chronic obstructive pulmonary disease

Investigators:

A total of 46 investigators participated in four countries: Germany (17), Hungary (15), The Netherlands (10), and Poland (4).

Study center(s):

A total of 46 centers participated in four countries: Germany (17), Hungary (15), The Netherlands (10), and Poland (4).

Publication (reference):

Not applicable.

Studied period (years):

28 Oct 2000 to 07 Apr 2002

Clinical phase:

III

Objectives:

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

Methodology:

The study was a 24 week double-blind, randomized parallel group study with a single-blind baseline period. According to the sample size calculation 480 patients were needed. The protocol specified that preferably 18 to 42 patients - but at least six patients - were to be included per center. In the 1st amendment to the protocol (September 18, 2000), the number of patients per center were changed to "preferably 18 to 48 patients should be included per center, but at least six patients per center

The study consisted of a baseline period of two weeks (Visits B0, - if applicable B1 -, and B2) a treatment period of 24 weeks (Visits T0 [= B2 visit], T1, T4, T8, T12, T13, T16, T20 and T24) and a follow-up period, if necessary.

Eligible patients received salbutamol on demand, and were randomly assigned to one of the three groups:

- Placebo: tablet, once daily, oral,
- Roflumilast: 500 µg tablet, once daily, oral,
- Roflumilast/placebo: roflumilast 500 µg tablet, once daily, oral for the first 12 weeks, followed by placebo tablet, once daily, oral for the second 12 weeks.

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

Intention-to-treat	n = 581	Per-protocol	n = 483
roflumilast	n = 200	roflumilast	n = 167
roflumilast/placebo	n = 195	roflumilast/placebo	n = 159
placebo	n = 186	placebo	n = 157

Diagnosis and criteria for inclusion:

Inclusion criteria:

- written informed consent has been obtained,
- history of chronic obstructive pulmonary disease (COPD) as defined by European respiratory Society (ERS) criteria (European Respiratory Society, 1995) for more than one year (reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and exhibits minimal reversibility with bronchodilators. Patients show symptoms like cough and/or sputum production and/or breathlessness at rest or after exertion),
- age 40 to 75 years,
- FEV_1 / FVC ratio pre-bronchodilator ≤ 70% and
- FEV_1 35% to 75% of predicted post-bronchodilator (after receiving 400 µg salbutamol via metered dose inhaler (MDI) with a spacer measured after 30 minutes ± five minutes) in patients fulfilling the wash-out definitions with respect to current treatment,
- patients had to show fixed airways obstruction, defined as an increase of less or equal to 12% of initial value **and** less or equal to 200 ml after receiving salbutamol (400 µg via MDI with a spacer, see above),

- current smokers or ex-smokers (stable for at least six months prior to Visit B0) **and** smoking history (≥ 10 pack years),
- no change in COPD treatment in the last four weeks,
- patients in a stable clinical state (no exacerbation or history of lower airway infection four weeks prior to the baseline visit),
- patients who, with the exception of COPD, do not suffer from any additional disease(s) which might interfere with study related procedures, assessed by the investigator.

Randomization criteria:

- post-bronchodilator FEV_1 is between 35% and 75% of predicted at random Visit T0 (= time range reference value for the following visits) when salbutamol was withheld for at least four hours (anticholinergics at least six hours),
- FEV_1 value **pre-bronchodilator** measured at Visit T0 is within a range of ± 15% of Visit B0 value,
- increase in FEV_1 of less or equal to 12% of initial value **and** less or equal to 200 ml (30 minutes ± five minutes after inhalation of 400 µg salbutamol using an MDI with spacer),
- compliance ≥ 80% and ≤ 120%.

Test product:

Roflumilast

Dose:

500 µg

Mode of administration:

One tablet o.d. (once daily) in the morning, oral administration

Batch No.:

499110

Duration of treatment:

Baseline period: two weeks, treatment period: 24 weeks.

Reference product:

Placebo

Dose:

Not applicable.

Mode of administration:

One tablet o.d. (once daily) in the morning, oral administration

Batch No.:

199110, 200130

Criteria for evaluation:

Efficacy evaluation (primary):
- Post-bronchodilator FEV_1 (Comparison A),
- St George's Respiratory Questionnaire – total score (Comparison A).

Efficacy evaluation (secondary):
- Pre-bronchodilator FEV_1 (Comparison A, B, C, D, E),
- Post-bronchodilator FEV_1 (Comparison B, C, D, E),
- Lung function parameters: pre- and post-bronchodilator FEV_2, FEV_3, FIV_1, FVC, FVCin, FEF_{25-75}, PEF, PIF (Comparison A, B, C, D, E),
- Morning PEF (Comparison A),
- St George's Respiratory Questionnaire – total score (Comparison B, C, D),
- St George's Respiratory Questionnaire – component scores (Comparison A, B, C, D),
- SF36 scores (Comparison A),
- COPD symptom scores (Comparison A),
- Daily use of rescue medication (Comparison A),
- Blood gas analysis (Comparison A),
- Six-minute walking test and modified Borg scale (Comparison A),
- "Escape" criteria and exacerbations (Comparison A).

Safety evaluation (secondary): Adverse events, vital signs, electrocardiogram (ECG), changes in laboratory values, and in physical examination findings.

Statistical methods:

The analysis of treatment effects was based on the following comparisons:

- Comparison A: T24 to T0 for the groups roflumilast vs. placebo,

- Comparison B: T24 to T12 for the groups roflumilast vs. roflumilast/placebo,
- Comparison C: T12 to T0 for the pooled groups roflumilast and roflumilast/placebo vs. placebo,
- Comparison D: T24 to T0 for the groups roflumilast/placebo vs. placebo
- Comparison E: T24 to T0 for the groups roflumilast vs. roflumilast/placebo (only for lung function parameters).

The efficacy analysis was performed for the intention-to-treat (ITT) and per-protocol (PP) population with the ITT population being the primary population for efficacy evaluation. In addition, for spirometric lung function variables an extended ITT analysis was performed including invalid data. An analysis of covariance (ANCOVA) was performed for the primary efficacy variables and the secondary efficacy variables FEV_1, FEV_2, FEV_3, FVC, FEF_{25-75}, PEF, FVCin, FIV_1, PIF, SGRQ (St George's Respiratory Questionnaire) and SF-36 (MOS 36 Item Short-Form Health Survey) with the factors and/or covariables treatment, value at T0 (randomization visit), age, sex, smoking status at B0 (baseline, two weeks prior randomization) and center. The results focus on the endpoint analysis (T_{last} for the ITT and extended ITT analysis, T_{end} for the PP analysis) including last observation carried forward (LOCF) values.
Since the statistical analysis was based on the $T_{last(end)}$ – T0 (or T12, respectively, in Comparison B) differences, only patients with paired T0 (T12) and $T_{last(end)}$ values, respectively, were included. Least-squares Means (LSMeans) and 95% confidence intervals (CIs) were given for treatment differences. Since significance for both endpoints was to be demonstrated, multiplicity adjustments of the significance level were not indicated. The sample size of approximately 160 patients per group ensured a power of approximately 90% for concluding superiority of roflumilast 500 µg over placebo with regard to both primary efficacy variables.

SUMMARY - CONCLUSIONS

Summary:

Efficacy results:

Results from the ITT and PP endpoint analysis were similar unless indicated otherwise.

Comparison A (roflumilast vs. placebo, T0 to T24)

Primary variables

A statistically significant increase in post-bronchodilator FEV_1 was observed in the roflumilast group. In the PP endpoint analysis, but not in the ITT endpoint analysis, a statistically significant between-treatment difference in favor of roflumilast was shown. Furthermore, statistically significant differences between the treatment groups in favor of roflumilast were shown at each visit from T4 to T24, except for T20 in the ITT analysis.

Post-bronchodilator FEV_1: within and between-treatment differences

WITHIN			T0 (paired)		$T_{last(end)}$	$T_{last(end)}$ – T0		
		n	Mean	LSMean	LSMean	LSMean ± SEM	95%CI	p-value[a]
ITT	Rof500	191	1.602	1.581	1.659	0.078 ± 0.017	0.044, 0.111	<0.0001
	Placebo	176	1.558	1.581	1.620	0.039 ± 0.018	0.004, 0.074	0.0312
PP	Rof500	148	1.587	1.578	1.666	0.088 ± 0.020	0.049, 0.126	<0.0001
	Placebo	140	1.570	1.578	1.616	0.037 ± 0.020	-0.002, 0.077	0.0657

BETWEEN			n	n	ΔTest – ΔReference		
	Test	Reference	Test	Reference	LSMean ± SEM	95%CI	p-value[b]
ITT	Rof500	Placebo	191	176	0.039 ± 0.022	-0.005, 0.083	0.0810
PP	Rof500	Placebo	148	140	0.051 ± 0.025	0.002, 0.100	0.0434

[a] p-value for within-treatment differences (ANCOVA), two-sided, significance level 5%.
[b] 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}, FEV_1 = forced expiratory volume in one second, Rof500 = roflumilast 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis), T_{end} = last visit (PP endpoint analysis).

An exploratory post-hoc analysis based on time-averaged AUC for post-bronchodilator FEV_1 revealed a clear and statistically significant difference between the treatment groups in favor of roflumilast.

Treatment with roflumilast led to an improvement in health-related quality of life: the SGRQ total score improved statistically significantly. The difference between the treatment groups was not statistically significant.

Secondary spirometry variables

Pre-bronchodilator FEV_1 increased in the roflumilast group, but decreased in the placebo group. Furthermore, statistically significant increases were observed for roflumilast, with respect to the expiratory post-bronchodilator spirometry parameters FEV_2, FEV_3, FEF_{25-75}, and PEF. For placebo, increases were consistently lower and not statistically significant (both except for PEF). A statistically significant difference between the treatments in favor of roflumilast could be shown for pre-bronchodilator FEV_1 (PP analysis only).

Quality of life

All SGRQ component scores showed improvements with roflumilast treatment (statistically significant for activity and symptom score in the ITT analysis and for impact and symptom score in the PP analysis). Improvements were also observed with placebo treatment. The assessment of general quality of life with the SF36 questionnaire showed improvements in most items in both treatment groups. There were no statistically significant differences between the treatment groups in the SGRQ scores and in the SF36 scores, except for social functioning (in favor of placebo in the ITT but not in the PP analysis).

Diary variables

Morning PEF from patient diaries increased statistically significantly with roflumilast and with placebo. The COPD symptom score sum and the individual scores for breathlessness, cough, and sputum production decreased or were stable in both treatment groups. Median

daily use of rescue medication did not change during the study in either treatment group. The median percentage of symptom free days was zero in both groups, while the median percentage of rescue medication free days was twice as high in the roflumilast group than in the placebo group. Statistically significant differences between the treatment groups were not observed for any of the diary variables.

Blood gases and exercise test

Blood gas analysis indicated a better oxygenation after roflumilast treatment: PaO_2 and SaO_2 increased statistically significant and $PaCO_2$ tended to decrease. In the placebo group, PaO_2 and SaO_2, but also $PaCO_2$ tended to increase (not statistically significant). The increases in PaO_2 and SaO_2 were numerically lower as compared with the roflumilast group. A statistically significant difference in favor of roflumilast was found for PaO_2 in the PP analysis, but not in the ITT analysis.

In the six-minute walk test, the median walked distance increased with roflumilast treatment but not with placebo. There were no statistically significant differences between the treatment groups.

Exacerbations

The number of patients experiencing exacerbations was similar in both treatment groups. In the placebo group, one patient fulfilled the "escape" criteria.

Comparison B (roflumilast vs. roflumilast/placebo, T12 to T24)

From T12 to the endpoint, no statistically significant changes were observed for the expiratory post-bronchodilator spirometry parameters in the roflumilast group. By contrast, after withdrawal of roflumilast, FEV_1, FEV_2, FEV_3, and FEF_{25-75} decreased statistically significantly. In the PP analysis, a statistically significant difference between the groups in favor of roflumilast was found for FEV_1.

In the roflumilast group the SGRQ scores remained at the same level. In the withdrawal group (roflumilast/placebo), a deterioration was observed after withdrawal of roflumilast. The differences between the treatment groups were not statistically significant.

Comparison C (roflumilast pooled vs. placebo, T0 to T12)

For this comparison, data from all patients who received roflumilast up to T12 were pooled. This resulted in a higher statistical power to detect differences between roflumilast and placebo.

All expiratory post-bronchodilator spirometry parameters showed a statistically significant increase in the pooled roflumilast group. In the placebo group, no statistically significant changes were observed, except for an increase in FEF_{25-75}. Statistically significant differences between the treatment groups in favor of roflumilast were found for FEV_1, FEV_2, FEV_3, FEF_{25-75}, and FVC.

With roflumilast treatment, all SGRQ scores improved statistically significantly. Less marked improvements were observed with placebo. There was no statistically significant difference between the treatment groups.

Comparison D (roflumilast/placebo vs. placebo, T0 to T24)
The changes from T0 to the endpoint were higher in the withdrawal group than in the placebo group for most expiratory post-bronchodilator lung spirometry parameters (except FEV_2 and PEF). For FVC, an increase from T0 was observed in the withdrawal group (roflumilast/placebo), but a decrease in the placebo group. There were no statistically significant differences between the treatment groups.
A higher improvement from T0 in SGRQ total score was seen in the withdrawal group (roflumilast/placebo) as compared with the placebo group. This was mainly due to an improvement in impact score. The differences between the treatment groups were not statistically significant.
Comparison E (roflumilast/placebo vs. roflumilast, T0 to T24, post-hoc analysis)
In the roflumilast group, statistically significant increases from T0 to the endpoint were found for all expiratory post-bronchodilator spirometry parameters except for FVC. In the withdrawal group (roflumilast/placebo), all parameters increased (statistically significant for FEV_1, FEV_2, and PEF). No statistically significant between-treatment differences were observed.
Subgroup analysis
Two subgroup analyses were performed, one stratified by smoking status and the other stratified by concomitant use of a constant dose of anticholinergics.
Improvements in post-bronchodilator FEV_1 and SGRQ total score were more pronounced in smokers as compared with ex-smokers.
Patients taking concomitantly a constant dose of anticholinergics responded with a higher increase in post-bronchodilator FEV_1 to roflumilast treatment. In this subgroup, a statistically significant between-treatment difference in favor of roflumilast was found.
The improvement in SGRQ total score observed for roflumilast treatment was similar in the subgroups with and without concomitant intake of anticholinergics. The difference between the treatment groups was statistically significant in favor of roflumilast in patients taking concomitant anticholinergics only.

Safety results:
The percentage of patients experiencing AEs during the treatment period was similar with continuous roflumilast (43%) and continuous placebo (41%) treatment. In the withdrawal arm, more patients experienced AEs before roflumilast withdrawal (32%) than after roflumilast withdrawal (23%). The majority of AEs in all treatment groups were mild or moderate in intensity. The most frequent AE was bronchitis (including COPD exacerbations) in all treatment groups. Diarrhea did not occur in patients treated with placebo but was reported for 4% of patients taking roflumilast continuously and for 1.5% of patients receiving roflumilast during the first 12 weeks in the withdrawal arm. Headache, vomiting, back pain, pain in extremity, tachycardia, tremor, rash, and malaise, were more frequent (one to 2% higher frequencies) with roflumilast than with placebo treatment.

Most AEs were judged as “unrelated” or “unlikely related” to the study medication. AEs assessed as “likely” or “definitely related” to roflumilast treatment in more than one patient were diarrhea, nausea, headache, increased liver enzymes, tremor, pain in extremity, vertigo, and malaise.
During the study, 5 patients (3 on roflumilast, 2 on placebo) died. In addition, 11 patients treated with roflumilast and 12 patients taking placebo reported SAEs. All SAEs were assessed as “unrelated” to the study medication except for one case of atrial fibrillation which was judged as “unlikely related”.
In total, 32 patients discontinued roflumilast treatment because of AEs; 9 of these AEs were assessed as “likely” or “definitely related” to the study drug.
There was no apparent influence of roflumilast on vital signs, ECG, laboratory values, or physical examination during the 24 weeks of treatment.
These results are comparable to those observed in previous studies and support the good safety profile of roflumilast.

Conclusions:

This study demonstrated that roflumilast improves lung function in patients with COPD. For post-bronchodilator FEV_1, statistically significant between-treatment differences in favor of roflumilast were shown in the PP but not in the primary ITT endpoint analysis. Pooling of data from all patients receiving roflumilast until T12 showed statistically significant differences between the treatments in favor of roflumilast for post-bronchodilator FEV_1.
Most lung function parameters decreased after withdrawal of roflumilast but remained at a higher level as compared with placebo. These findings suggest that roflumilast treatment leads not only to symptomatic relief but may reduce disease progression. No rebound effect was observed after discontinuation of roflumilast.
With respect to safety, roflumilast showed a favorable safety profile and was well tolerated in patients with COPD.