Synopsis of study report: 327/2003
Location in Module 5:

Study Code:
BY217 IN-108

Report Version:
2.0

Title of the study:

Comparison of safety and efficacy of 250 µg roflumilast versus 500 µg roflumilast versus placebo over 12 weeks in patients with chronic obstructive pulmonary disease (COPD).

Investigators:

Five investigators from India participated in this study.

Study center(s):

Multicenter study, five centers in India

Publication (reference):

Not applicable

Studied period:

05 August 2002 to 01 July 2003

Clinical phase:

II

Objectives:

- To study the safety and tolerability of roflumilast 250 µg vs. roflumilast 500 µg vs. placebo.
- To investigate the effect of roflumilast 250 µg vs. roflumilast 500 µg vs. placebo on pulmonary function, efficacy rating, and exacerbation rate.
- To evaluate plasma levels of roflumilast and its major metabolite roflumilast N-oxide.

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	118	89
Roflumilast 500 µg	47	35
Roflumilast 250 µg	46	40
Placebo	25	14

Diagnosis and criteria for inclusion:

Inclusion criteria

Patients with a history of COPD for at least 12 months as defined by the GOLD criteria (2001) were considered for the trial if they met the following criteria:

- written informed consent
- age 40 to 75 years
- FEV_1/FVC ratio (post-bronchodilator) ≤ 70%
- FEV_1 (post-bronchodilator) 30 to 80% of predicted
- fixed airway obstruction (defined as an FEV_1 increase of ≤ 12% and/or ≤ 200 ml after receiving salbutamol 400 µg with a spacer)
- current smoker or ex-smoker (smoking cessation at least one year ago) with a smoking history of at least 10 pack years
- in a stable clinical state with no change in COPD treatment during the last four weeks and
- not suffering from any concomitant disease that might interfere with study procedures or evaluation
- availability of a chest x-ray done within six 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:
  a) required a course of systemic glucocorticosteroids during the four week period prior to the baseline visit B0, or
  b) involved hospital admission (including treatment in an emergency room) in the four

week period prior to the baseline visit B0

- inability to adhere to the washout times of drugs
- use of not allowed drugs
- lower respiratory tract infection in the four 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], active tuberculosis and old tuberculosis with involvement of more than one zone or more than 10% of involvement of lung, based on x-ray, chest)
- liver insufficiency
- 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 are not related to COPD and that require further evaluation
- pregnancy, breast feeding or lack of effective contraception in either females of childbearing potential or females who are postmenopausal less than one year
- 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
- planning a participation in a smoking cessation program
- suspected inability or unwillingness to comply with study procedures
- inability to follow study procedures due to e.g. language problems, psychological disorders
- alcohol or drug abuse
- regular use of more than eight puffs/day of rescue medication
- suspected hypersensitivity to the study medication.

Randomization criteria

Patients were randomized after a two week baseline period, if the following criteria were fulfilled:

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

Test product:

Roflumilast

Dose:

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

Mode of administration:

oral

Batch No.:

120190 (roflumilast 250 µg) or 120170 (roflumilast 500 µg)

Duration of treatment:

Baseline period: 2 weeks; treatment period: 12 weeks

Reference product:

Placebo

Dose:

One tablet o.d. in the morning

Mode of administration:

oral

Batch No.:

410190

Criteria for evaluation:

Primary variable:

Safety and tolerability assessed by:

- adverse events
- laboratory values
- electrocardiogram/blood pressure measurements

Secondary variables

- mean change from randomization to endpoint in forced expiratory volume in one second (FEV_1, post-bronchodilator)
- mean change from randomization to endpoint in forced expiratory volume in one second (FEV_1, pre-bronchodilator)

- exacerbations (frequency and time to event)
- mean change from randomization to endpoint in forced vital capacity (FVC), peak expiratory flow (PEF), and forced expiratory flow between 25 and 75% of vital capacity (FEF_{25-75}) (pre- and postbronchodilator spirometry)
- effectiveness rating (patient/investigator)

Pharmacokinetics:
Plasma levels of roflumilast and its major metabolite roflumilast N-oxide

Statistical methods:

The primary safety parameters were analyzed in a descriptive manner including summary statistics such as frequencies and percentages, or median, 68%-range, mean, SD or SEM, where appropriate. No inferential statistics were performed.
The efficacy analysis was primarily based on the ITT analysis; the PP analysis was used to check the robustness of the results. The primary variable of efficacy was the change from T0 (randomization visit) to T_{last} in post-bronchodilator FEV_1, applying the LOCF principle.
The lung function parameters pre-bronchodilator FEV_1, pre- and post-bronchodilator FEV_{25-75}, FVC and PEF were secondary variables of efficacy and like the primary variable of efficacy evaluated by an analysis of covariance including – besides treatment - baseline (randomization) value, age, sex, smoking status and center.
The three treatments were compared in a pair-wise manner. Furthermore, tests for trend were applied in order to investigate for a monotone dose-response relationship: the variables from spirometry and the number of COPD exacerbations were analyzed with the Jonckheere-Terpstra Test. Furthermore, time to first exacerbation was analyzed.

SUMMARY - CONCLUSIONS

Summary:

Efficacy

The primary efficacy analysis was based on the ITT analysis. The results focus on the respective endpoint analyses, if not indicated otherwise.

Primary variable of efficacy

The primary variable of efficacy post-bronchodilator FEV_1 increased from T0 to T_{last} in patients treated with both roflumilast doses, whereas a decrease was seen in the placebo group. The improvement was greater in the roflumilast 500 µg than in the roflumilast 250 µg group. Statistically significant between-treatment differences in favor of roflumilast were found for the comparisons of roflumilast 500 µg with placebo (difference in LSMeans: 152 ml) and roflumilast 250 µg with placebo (difference in LSMeans: 137 ml; see Table below). The Jonckheere Terpstra trend test (analysis of differences and AUC analysis)

revealed a statistically significant monotone dose-response relationship in favor of roflumilast for the primary variable of efficacy post-bronchodilator FEV_1. The results of the PP analysis of post-bronchodilator FEV_1 were comparable to those of the ITT analysis.

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
Rof500	Placebo	42	25	0.152 ± 0.050	0.053, 0.251	0.0028
Rof500	Rof250	42	43	0.015 ± 0.043	-0.070, 0.100	0.7300
Rof250	Placebo	43	25	0.137 ± 0.049	0.040, 0.235	0.0064

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).

Results of the AUC analysis were similar to those of the analysis of differences and thus supported the results obtained by the analysis of difference.

Secondary variables of efficacy

If not mentioned otherwise, the results for the ITT analysis of the secondary variables of efficacy are described.

All the secondary post-bronchodilator expiratory lung function parameters, FEF_{25-75}, FVC, and PEF, showed statistically significant between treatment differences when comparing the roflumilast groups vs. the placebo group except for the difference in FVC between the roflumilast 500 µg group vs. the placebo group. The time averaged excess AUC analysis revealed statistically significant between-treatment differences in FVC and FEF_{25-75} (ITT and PP) and in PEF (PP) for the comparison of roflumilast 500 µg treatment vs. placebo. Furthermore, a statistically significant difference in FEF_{25-75} between the roflumilast 250 µg treatment group and the placebo group could be seen.

The Jonckheere-Terpstra test for trend (analysis of differences) revealed a statistically significant dose-response relationship in favor of roflumilast for post-bronchodilator expiratory lung function variables FVC and FEF_{25-75}.
Furthermore, the Jonckheere-Terpstra test for trend (time averaged excess AUC) showed a statistically significant dose-response relationship in favor of roflumilast for post-bronchodilator FVC in both the ITT and the PP analyses and for FEF_{25-75} in the PP analysis.

Pre-bronchodilator expiratory lung function parameters, FEV_1, FEF_{25-75} and PEF showed statistically significant between-treatment improvements for the roflumilast 500 µg and

250 µg treatment groups vs. the placebo group in the PP analysis (analysis of differences and the AUC analysis). Furthermore, the ITT analysis (analysis of differences) revealed a statistically significant between-treatment improvement in FEV_1 for roflumilast 500 µg vs. placebo and for roflumilast 250 µg vs. placebo.

Exacerbations

Only few exacerbations occurred with a slight tendency towards a lower percentage of patients experiencing a severe or moderate exacerbation in the roflumilast 500 µg group and a lower percentage of patients receiving roflumilast 250 µg experiencing mild exacerbations. An exacerbation leading to drop-out occurred only in the placebo group. However, due to the small sample size, the short treatment period, and the low number of exacerbations no firm conclusion could be made.

Effectiveness Rating Scale

There were no differences between the treatment groups regarding effectiveness rating.

Safety

Sixty-seven AEs were reported in 42 (35.6%) patients during the treatment period. Out of the 25 patients receiving placebo, seven (28%) experienced 12 AEs, 17 (37%) of 46 patients receiving roflumilast 250 µg experienced 26 AEs and 18 (38.3%) of 47 patients receiving roflumilast 500 µg experienced 29 AEs. Thus, the incidence of patients experiencing AEs was slightly higher in patients taking roflumilast than in patients taking placebo. An overview of AEs is provided below.

Overview of treatment-emergent adverse events

	Number (%) of patients[a]			
	Roflumilast 500 µg od (n = 47)	**Roflumilast 250 µg od (n = 46)**	**Placebo (n = 25)**	**Total (n = 118)**
No. of AEs	29	26	12	67
No. of patients reporting at least one AE	18 (38.3)	17 (37.0)	7 (28.0)	42 (35.6)
No. of patients with SAEs	1 (2.1)	2 (4.3)	1 (4.0)	4 (3.4)
No. of patients with AEs judged to be at least 'likely' related to study drug[b]	2 (4.3)	0 (0.0)	0 (0.0)	2 (1.7)
No. of patients with AEs leading to premature study discontinuation	0 (0)	2 (4.3)	1 (4.0)	3 (2.5%)
No. of patients with AEs not yet known to be recovered	1 (2.1)	0 (0)	0 (0)	1 (0.8)

[a] Percentages are based on the total number of patients in the respective treatment group.
[b] by investigator.
n = number of patients.

The most frequently reported AEs were related to the respiratory system (25.4%) and thus due to the underlying disease. AEs affecting the gastro-intestinal tract (6.8%) occurred in patients

taking roflumilast (10.9% in the roflumilast 250 µg group and 6.4% in the roflumilast 500 µg group), whereas none were reported in patients taking placebo. A trend towards a dose dependency was observed for AEs concerning the SOC 'nervous system disorders' (incidence 0% in the placebo group vs. 2.2% in the roflumilast 250 µg group vs. 4.3% in the roflumilast 500 µg group).

Only two patients of the entire FAS experienced AEs, which were assessed by the investigator as 'definitely related' (headache) and 'likely related' (hyperpigmentation of the skin) to the study medication. Both of these patients belonged to the roflumilast 500 µg treatment group. Four patients, one in the roflumilast 500 µg treatment group and three in the roflumilast 250 µg treatment group experienced 'unlikely related' AEs. All other AEs were unrelated to the study medication.

Four patients, one patient (2.1%) in the roflumilast 500 µg treatment group, two patients (4.3%) in the roflumilast 250 µg treatment group and one patient (4.0%) in the placebo group, experienced severe AEs. All other patients experienced mild or moderate AEs (10 patients, 21.3%; 7 patients, 14.9% in the roflumilast 500 µg treatment group; 7 patients, 15.2%; 8 patients, 17.4% in the roflumilast 250 µg treatment group and 4 patients, 16.0%; 2 patients, 8.0% in the placebo group).

The majority of AEs (12, 41.4%) in the roflumilast 500 µg treatment group and in the placebo group (5, 41.7%) had an onset time of more than four and up to twelve weeks. However, in the roflumilast 250 µg treatment group, the number of patients having an onset after the first day and up to one week (10, 38.5%) was almost equal to the number of patients (9, 34.6%) having an onset time of more than four and up to twelve weeks.

Most of the AEs had a duration ranging from one day to one week and resolved during the study (16, 55.2%; in the roflumilast 500 µg treatment group; 10, 38.5% in the roflumilast 250 µg treatment group; 8, 66.7% in the placebo group). Only one AE (3.4%) out of 29 AEs occurring in the roflumilast 500 mg group was still ongoing at the end of the study.

Six SAEs were reported in four patients, one out of 25 patients (4%) in the placebo group, two out of 46 patients (4.3%) in the roflumilast 250 µg group and one out of 47 patients (2.1%) in the roflumilast 500 µg group.
One patient, belonging to the placebo group, died due to an acute COPD exacerbation, which was judged to be unrelated to the study medication by both the investigator and the sponsor. The patient also had a recurring lower respiratory tract infection.

Three patients discontinued the study prematurely due to AEs: two patients in the roflumilast 250 µg group were withdrawn, one due to colicky abdominal pain and the other

one due to a COPD exacerbation. One patient in the placebo group experienced a COPD exacerbation with fatal outcome.

Physical examination, vital signs, ECG and laboratory values did not reveal any apparent clinically significant changes as a result of roflumilast administration.

Thus, both roflumilast doses were tolerated well by the patients. 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 and well-tolerated therapy in Indian patients with COPD.

When compared to placebo, both roflumilast 250 µg and roflumilast 500 µg improved the post-bronchodilatory lung function parameters FEV_1, FVC, PEF, and FEF_{25-75}. A statistically significant monotone dose-response relationship in favor of roflumilast was observed for FEV_1, FVC, and FEF_{25-75}.

In total, 28% of patients treated with placebo, 37% of patients receiving roflumilast 250 µg and 38.3% of patients treated with roflumilast 500 µg experienced AEs. More than 90% of these AEs were assessed to be unrelated to the study medication. Only four patients experienced severe AEs, of which three were COPD exacerbations. One patient in the placebo group died during the study due to a COPD exacerbation. No clinically relevant influence on laboratory parameters, vital signs, ECG or physical examination was seen. This study showed that roflumilast was safe and well tolerated.

Thus, a favorable benefit-to-risk ratio was established for roflumilast in Indian patients with COPD.