Synopsis of study report: 77/2002
Location in Module 5:

Study Code:

BY217/FK1 102

Report Version:

3.0

Title of the study:

26 weeks treatment with 500 µg roflumilast in patients with chronic obstructive pulmonary disease

Investigators:

A total of 39 investigators in four countries

Study center(s):

A total of 39 investigators in four countries located in Germany (16), Hungary (8), The Netherlands (8) and South Africa (7).

Publication (reference):

Not applicable.

Studied period (years):

18 April 2000 to 08 November 2001

Clinical phase:

II / III

Objectives:

To investigate the long-term safety of roflumilast in patients with chronic obstructive pulmonary disease. Furthermore, the study investigated the long-term effect of roflumilast on pulmonary function and quality of life.

Methodology:

This open-label, multi-center, multinational phase II/III study was the open-label extension of study BY217/FK1 101 (a double-blind, 26 week, dose-finding study investigating the effects of 250 µg, 500 µg roflumilast and placebo on lung function, quality of life, symptoms and use rescue medication in patients with COPD). The study consisted of a 26-week treatment period starting with Visit T26 (last visit of the previous study). After 4, 13, and 26 weeks (T30, T39, and T52) patients underwent 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):

N = 397 (all treated with 500 µg roflumilast)

Diagnosis and criteria for inclusion:

Patients with chronic obstructive pulmonary disease who had completed the previous study BY217/FK1 101 according to protocol, who had given their written consent, who had not started or stopped smoking during the last 6 months, and who were at least 40 years old were eligible.

Test product:

Roflumilast

Dose:

500 µg per tablet.

Mode of administration:

One tablet once daily in the morning.

Batch No.:

BY217-46-2-1, BY217-46-6-1 (Germany), BY217-46-4-1, BY217-46-6-1 (Hungary), BY217-46-2-1, BY217-46-4-1, BY217-46-6-1 (The Netherlands), BY217-46-2-1, BY217-46-6-1 (South Africa).

Duration of treatment:

26 weeks

Reference product:

Not applicable.

Dose:

Not applicable.

Mode of administration:

Not applicable.

Batch No.:

Not applicable.

Criteria for evaluation:

Safety evaluation (primary):	Adverse events, laboratory values, physical examination, vital signs, ECG
Efficacy evaluation (secondary):	Spirometric lung function tests, St. George's respiratory Questionnaire, SF-36 Questionnaire, 6-minute walk, blood gas analysis, exacerbation rate

Statistical methods:

An ITT, and for spirometry parameters an additional extended ITT analysis, were performed. Safety parameters were analyzed in a descriptive manner.
For the secondary spirometry variables, the differences to T0 (start of the previous study BY217/FK1 101) and to T_{start} (start of present trial, for most patients T26) were calculated and an analysis of covariance (ANCOVA) was carried out. In addition, analyses separated by treatment groups of the previous study were carried out. All tests were performed two-sided at the significance level $\alpha = 0.05$. If applicable, the last observation was carried forward for the last-value analysis.

SUMMARY - CONCLUSIONS

Summary:

This open-label extension of the 26-week randomized, double-blind, parallel group study BY217/FK1 101 assessed the safety of roflumilast over a treatment period of further 26 weeks in patients with COPD. A total of 397 patients who had regularly terminated the previous study BYK217/FK1 101 were included in the study. Safety variables were of primary interest.
Efficacy results:
For the analysis of the secondary efficacy parameters, patients were stratified into three groups according to their treatment in the preceding study BY217/FK1 101 (placebo, 250 µg roflumilast, or 500 µg roflumilast).
With respect to post-bronchodilator lung function measurements, statistically significant increases in FEV1 and FVC from start to endpoint of the open-label extension were observed in patients previously on placebo ($p < 0.05$). This provides further evidence for the efficacy of roflumilast.

Post-bronchodilator FEV_1 (within-treatment differences $T_{last} - T_{start}$)

Treatment group of BY217/FK1 101	n	LS Mean ± Std Err	95% CI	p-value two-sided
Placebo	134	0.05 ± 0.02	0.01, 0.09	0.0186
250 µg roflumilast	127	-0.03 ± 0.02	-0.07, 0.02	0.2395
500 µg roflumilast	123	-0.05 ± 0.02	-0.10, -0.01	0.0189

The pre-bronchodilator measurements showed no statistically significant within-treatment changes during the open-label extension, except for a decrease in FEF_{25-75} in the previously with 250 µg roflumilast treated group ($p < 0.01$). In patients previously treated with placebo, a numerical increase in all parameters was noted after the switch to 500 µg roflumilast in the open-label extension.

During the open-label extension, 32 COPD exacerbations were experienced by 27 (7%) patients.
Results from the 6-min walk showed no statistically significant changes in the median distance walked during the open label extension. Blood gas analysis revealed a statistically significant increase in oxygen saturation and a statistically significant decrease in $PaCO_2$ in patients previously treated with placebo.
The assessment of health-related quality of life (St. George's Respiratory Questionnaire) showed no statistically significant changes during the open-label extension, except a decrease in symptom score in patients previously on placebo. General quality of life, which was assessed with the SF 36 questionnaire, did not show consistent changes during the open-label extension except for a numerical increase in the physical functioning score in all groups.
Safety results:
Roflumilast was tolerated very well. The incidence of adverse events (41%) during the open-label extension was not unusual for this type of patient population and was slightly lower than in the randomized study BY217/FK1 101 (49%). The most frequently reported adverse events were bronchitis (including COPD exacerbations) and upper respiratory tract infection.
Most adverse events (96%) were assessed as "unrelated" or "unlikely related" to the study medication. Eleven AEs were judged "likely related" to roflumilast. The respective symptoms were insomnia, increased SGOT and SGPT, diarrhea, abdominal pain, vomiting, nausea, increased BUN, and tremor. In only two of 161 patients with AEs, the events (vertigo and headache) were assessed as "definitely related".
Three deaths (due to a massive hemorrhage after bypass surgery, metastatic adenocarcinoma of the lung, convulsions) occurred during the study. The events were judged "unrelated" or "unlikely related" to the study medication.
In total, twenty-four patients were reported with 32 serious AEs (including the three deaths); all serious AEs were assessed as being "unrelated" or "unlikely related" to the study medication.
Sixteen patients withdrew prematurely due to AEs. Three AEs leading to discontinuation (insomnia, abdominal pain, diarrhea) were judged "likely related" to the study drug.
Overall, clinical chemistry and hematology parameters showed no clinically significant changes. The same held true for vital signs and ECG findings.

Conclusions:

This open-label extension of a randomized, 26-week study with administration of placebo, 250 µg, or 500 µg roflumilast, assessed the safety of roflumilast over a further 26 week treatment with 500 µg roflumilast in patients with COPD.
Roflumilast was tolerated very well. Safety data collected over one year of roflumilast treatment did not indicate any treatment-related negative effects.