Synopsis of study report: 85/2002
Location in Module 5:

Study Protocol No.:
BY217/FK1 021

Report Version:
Version 1.0

Title of the study:
12 weeks treatment with 125 µg roflumilast versus 250 µg roflumilast versus placebo in patients with asthma.

Investigators:
A total of 148 investigators in the US and 17 investigators in Argentina enrolled patients.

Study centers:
Multicenter – 148 centers in the US and 17 centers in Argentina enrolled patients.

Publication (reference):
Not applicable

Study period (years):
First Patient Included: 09 January 2002
Last Patient Out: 21 April 2004
Clinical Phase:
III; IND 57,883

Objectives:
- To investigate the effect of 125 µg versus 250 µg roflumilast versus placebo on pulmonary function, quality of life, symptoms, use of rescue medication and drop-outs due to "lack of efficacy (LOE)/escape criteria" in patients suffering from bronchial asthma, and
- To investigate the safety and tolerability of roflumilast.

Methodology:
This was a multinational, multicenter, double-blind, randomized, parallel group study. The study consisted of a single-blind Baseline Period of two weeks (Visits B0 and B2), a double-blind Treatment Period of 12 weeks (Visits T0, T3, T6, T9, and T12), a Wash-out Period of two weeks (W2), and a safety follow-up (Visit F) visit, if necessary. At B0 all asthma medications, except rescue medication on demand, were withdrawn, and the single-blind placebo medication was administered. During the double-blind, placebo-controlled Treatment Period (starting with T0=baseline Visit B2), patients received one of the following:

- 250 µg roflumilast tablet administered orally once daily in the morning, or
- 125 µg roflumilast tablet administered orally once daily in the morning, or
- Placebo tablet once in the morning

Rescue medication, a short acting β_2-agonist (albuterol), was available to all patients.

No. of patients (total and for each treatment):
1601 enrolled patients
695 randomized patients (three patients were randomized but not treated)
237 patients in the roflumilast 250 µg group, 221 patients in the roflumilast 125 µg group, and 234 patients in the placebo group were included in the intent-to-treat (ITT) population.

Diagnosis and criteria for randomization and inclusion into treatment:
Diagnosis: history of bronchial asthma as defined by the National Institute of Health criteria (1997)

- Written informed consent,
- Age 18 to 70 years,
- Baseline Visit (B0) Forced expiratory volume in one second (FEV_1) (% predicted) must be:
  - 50-100% in patients either untreated or receiving short-acting bronchodilators, cromones, leukotriene antagonists, anticholinergics, lipoxygenase inhibitors, long-acting bronchodilators, theophylline, less than or equal to 420 µg/day beclomethasone dipropionate (BDP) ex mouthpiece (or equivalent) alone or in their combinations,
- No change in asthma treatment during the last four weeks prior to B0,
- Except for asthma, in good health,
- In a stable clinical state, and
- Non-smokers or ex-smokers (smoking cessation more than one year and smoking history less than 10 pack years).

Randomization Criteria:

- FEV_1 was between 50 and 85% predicted at randomization Visit T0 (= reference value) when albuterol was withheld for at least four hours prior to the measurement,

- FEV_1 at T0 within a range of +/-20% of baseline Visit B0 value,
- At least one puff/day albuterol on average during the last seven days of the Baseline Period prior to randomization Visit T0,
- Symptom score ≥1 per day on average during the last seven days of the Baseline Period prior to randomization Visit T0,
- Increase of initial FEV_1 ≥12% and ≥200 mL 15 to 30 min after inhalation of 0.18 mg to 0.36 mg albuterol ex mouthpiece (which was determined within six months prior to B0 or during baseline), and
- Medication compliance ≥80% and ≤125%.

Criteria for exclusion from treatment :

- Diagnosed with chronic obstructive pulmonary disease (COPD) and/or other relevant lung diseases (e.g., history of bronchiectasis, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease, and active tuberculosis),
- Clinically relevant abnormal laboratory values that suggested an unknown disease and required further clinical evaluation (as assessed by the investigator),
- Poorly controlled asthma which required either:

1. a course of oral corticosteroids during four weeks prior to baseline Visit B0, or
2. hospitalization for asthma (including treatment in an emergency room) in the four weeks prior to baseline Visit B0,

- Exacerbation of asthma or lower airway infection in the four-week period prior to the baseline Visit B0,
- Use of any of the following pre-medications:
    1. oral or parenteral steroids in the four-week period prior to Visit B0,
    2. inhaled steroids >420 µg/day BDP ex mouthpiece (or equivalent) in the four-week period prior to Visit B0,
    3. used any concomitant drugs that were not allowed by the protocol (see Section 9.4.7),
    4. used any corticosteroids with the exception of nasal/ophthalmic/dermal steroids during the study, or
    5. used inhaled and oral cromones, oral long-acting antihistamines, theophylline, lipoxygenase inhibitors, leukotriene antagonists, inhaled long-acting β2-agonists, oral β2-agonists, inhaled anticholinergics, or any short acting β_2-agonists (with exception of albuterol supplied by the Sponsor) during the trial.
- Pregnancy, breast-feeding, or lack of effective contraception in either females of childbearing potential or in females who were less than one year postmenopausal; effective contraception included abstinence, hormonal contraception (pill, Depo-Provera, Norplant), intra-uterine devices (IUD), “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 four-week period prior to the

study) had to consent to using effective contraception in case they became sexually active during the study.

- Patients who were participating in another study (use of an investigational product) within 30 days preceding the baseline Visit B0 or the reentry of patients already randomized in this trial. However, patients who failed to meet the randomization criteria after the Baseline Period could be re-enrolled for a second time. Patients participating in an observational or epidemiologic study could be included if no blinded and/or not yet approved drug had been administered.
- Current smokers or ex-smokers with either smoking cessation ≤1 year or with a smoking history of 10 pack years or more,
- Suspected non-compliance,
- Alcohol or drug abuse,
- Patients who were continuously using more than 8 puffs/day rescue medication,
- Patients who were not able to follow the procedures of the study, e.g., due to language problems or psychological disorders,
- Suspected hypersensitivity to the study medication, or
- Oocyte donation or oocyte implantation planned during the trial.

Test product:	Tablets with roflumilast: 250 µg and 125 µg
Dose:	250 µg or 125 µg/ day in the morning
Mode of administration:	Oral
Batch No.:	Roflumilast 250 µg tablets: 101180 Roflumilast 125 µg tablets: 301160 and 200140
Duration of treatment:	12 weeks

Reference product:	Identical tablets with placebo
Dose:	One tablet/day in the morning
Mode of administration:	Oral
Batch No.:	Placebo tablets: 320230 and 101160

Criteria for evaluation:

- Primary efficacy variable: Mean change from randomization to endpoint in FEV_1
- Secondary efficacy variables:
  - Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), and Maximum Expiratory Flow (MEF) 25-75% at endpoint,
  - FEV_1, at Visits T3, T6, T9, T12, and W2,
  - FEV_1, FVC, MEF 25-75%, and PEF at Visits T3, T6, T9, and T12,
  - Morning and evening PEF from diary cards,

- Diurnal PEF variability,
- Use of rescue medication,
- Proportion of symptom-free days/ rescue medication free days,
- Asthma symptom scores,
- Time to lack of efficacy (LOE)/escape criteria,
- Drop-outs due to LOE/escape criteria, and
- Quality of life (Asthma Quality of Life Questionnaire [AQLQ(s)]).

- Safety Variables:
- Adverse events (AEs), and
- Changes in laboratory values, change in physical examination findings, ECG (PR, QRS, QT, QT_c intervals), BP and HR.
- Pharmacokinetics:
- Plasma levels of roflumilast and its major metabolite roflumilast N-oxide.

Statistical methods:

The primary and secondary efficacy variables of pulmonary function were analyzed by Analysis of Covariance (ANCOVA). Non-parametric analyses (Wilcoxon signed rank test and Mann-Whitney test) were performed on the secondary efficacy variables of PEF variability, asthma symptom score, and rescue medication use. Asthma Quality of Life Questionnaire [AQLQ(s)] data were analyzed using Analysis of Variance (ANOVA) and paired t-test. Pairwise group comparisons on Time to LOE was done by Log-Rank test. Additionally, the Jonckheere-Terpstra trend test was performed on endpoint changes from baseline (T0) for pulmonary function measurements, selected diary assessments, and Asthma Quality of Life overall score. The time averaged excess AUC between treatment groups were compared by ANOVA for all pulmonary function variables and the selected diary variables. For safety parameters, descriptive statistics were summarized.

SUMMARY – CONCLUSIONS:

Efficacy Conclusions:

The primary efficacy result on FEV_1 change from baseline to endpoint from the ITT analysis showed no statistically significant treatment difference (-0.003 L, p=0.535) when comparing 250 µg roflumilast with placebo. The exploratory assessments of the comparisons between the two roflumilast dose groups and between 125 µg roflumilast and placebo also showed differences that were not statistically significant. Statistically significant increases in FEV_1 from baseline to endpoint were observed in all treatment groups (all $p<0.001$). No statistically significant dose trend was detected. Similar conclusions were drawn from the per protocol (PP) analysis. A numerically better result of the time averaged excess AUC was shown for the 250 µg roflumilast group than the 125 µg roflumilast and placebo groups for both the ITT and PP analyses. The pairwise treatment difference between the 250 µg roflumilast and

placebo groups was statistically significant for the PP analysis (0.055 L, p=0.044) but failed to reach statistical significance for the ITT analysis (0.028 L, p=0.170).

For the secondary spirometry efficacy variables (i.e., changes from baseline of FEV_1 at each visit, FVC, MEF 25-75%, and PEF at each visit and endpoint) in the ITT analysis, numerically better results were generally observed for the 250 µg roflumilast group than the 125 µg roflumilast and placebo in all visits (except Visits T12 and W2). However, no statistically significant treatment differences could be shown at endpoint or any visit. No statistically significant dose trend was detected in any of the variables. For the PP analysis, a statistically significant treatment difference between 250 µg roflumilast and placebo groups was observed for FVC endpoint (0.090 L, p=0.021). Although numerically better ITT results of the time averaged excess AUC were noted for the 250 µg roflumilast group than the 125 µg roflumilast and placebo groups at all visits and endpoint for these variables, the pairwise treatment differences failed to reach statistical significance. The PP analysis showed similar results with the exception of treatment differences between 250 µg roflumilast and placebo groups on MEF 25-75% at Week 12 (0.083 L/s, p=0.049) and endpoint (0.092 L/s, p=0.019).
In general, the between-group comparisons on diary efficacy assessments showed no statistically significant treatment differences at any week or at endpoint for either ITT or PP analyses. Statistically significant changes from baseline within each treatment group were observed at all or most timepoints for all diary efficacy assessments. The time averaged excess AUC for the selected diary parameters were not statistically significant between treatment groups. The trend test was not statistically significant.

No statistically significant treatment differences on any of the AQLQ(s) scores were observed at endpoint for either the ITT or PP analysis, even though the 250 µg roflumilast group showed a numerical advantage over the 125 µg roflumilast and placebo groups. The pairwise treatment comparisons were not statistically significant at other visits on any of the AQLQ(s) scores as well. Statistically significantly higher score changes from baseline were observed within each treatment group in all of the AQLQ(s) parameters at all timepoints (including endpoint). No statistically significant trend was observed on the overall score.

The ITT median time to LOE was shorter in 250 µg roflumilast (32 days) than 125 µg roflumilast and placebo groups (both 43 days). However, the pairwise comparison on time to LOE did not show statistically significant differences between any of the two treatment groups for either the ITT or PP analysis.

The percentage of patients who reported asthma exacerbation was lower in the 250 µg roflumilast group (5.9%) and about the same for the 125 µg roflumilast group (9.0%) and the placebo group (9.4%) in the ITT population. The median times to the first exacerbation were

longer in the 250 µg roflumilast group (30 days) and the 125 µg roflumilast group (39 days) than in the placebo group (22 days).

In summary, although orally administered 250 µg roflumilast was not statistically significantly different from placebo for the primary and secondary efficacy variables from the ITT analyses, results from PP endpoint analyses revealed statistically significant better FVC and better time averaged excess FEV_1 AUC when comparing 250 µg roflumilast with placebo. In general, numerically better results were seen for the 250 µg roflumilast than for 125 µg roflumilast and placebo groups in spirometry evaluations, diary assessments, and percentage of asthma exacerbation.

Safety Conclusions:
All patients of the ITT population were included in the safety analyses for this study. For the 250 µg roflumilast, the 125 µg roflumilast, and placebo groups, respectively, 68.8%, 70.1%, and 70.5% of patients were exposed to treatment for at least 11 weeks.
Roflumilast was safe and well tolerated. The total percentage of patients with treatment-emergent AEs was slightly higher in the 250 µg roflumilast group (47.7%) than in the 125 µg roflumilast (43.9%) and placebo (43.6%) groups. The proportions of patients reporting AEs by system organ class and individually were comparable among treatment groups with the exception of gastrointestinal disorders, which were reported by 13.1%, 6.3%, and 6.8% of patients in the 250 µg roflumilast, 125 µg roflumilast, and placebo groups, respectively.

Serious adverse events were reported for five patients in the 250 µg roflumilast group, two patients in the 125 µg roflumilast group, and two patients in the placebo group. One SAE of asthma aggravated in the 125 µg roflumilast group was considered to have a likely relationship to study medication. There were no deaths during the study.

A total of 66 patients withdrew from the study due to AEs: 8.0% in the 250 µg roflumilast group, 10.9% in the 125 µg roflumilast group, and 9.8% in the placebo group. Asthma aggravated was the most frequently reported AE leading to discontinuation for 3.8% of patients in the 250 µg roflumilast group, 6.8% in the 125 µg roflumilast group, and 6.4% in the placebo group. Eight of the 19 patients (3.4%) in the 250 µg roflumilast group, 6 of the 24 patients (2.7%) in the 125 µg roflumilast group, and 3 of the 23 patients (1.3%) in the placebo group who discontinued had AEs that were considered by the investigator to be likely or definitely related to study medication.

No clinically significant deviations were observed for the roflumilast and placebo groups for hematology, biochemistry, or urinalysis parameters. In all groups, no apparent changes from baseline to Visit T12 in systolic or diastolic blood pressure were observed, and there were no significant changes in body weight during the study. No significant changes in ECG intervals

from baseline to Visit T12 were noted for the roflumilast or placebo groups. There were no unexpected clinically significant physical examination findings at T12 which were not present at B0 for any treatment group.

In conclusion, the known safety profile of roflumilast was confirmed, and no additional safety concerns were identified during this study.

Conclusions

Thus, the following can be concluded from the study:

- The increase in the primary efficacy variable (FEV_1 change from baseline to endpoint) in patients treated with roflumilast was similar to that seen with placebo. There was also no relevant difference between roflumilast doses. A statistical significant difference versus placebo in favor of roflumilast was noted for the 250 µg dose when the comparison was based on time averaged AUC (PP).
- Most of the secondary efficacy variable results showed a numerical advantage of the 250 µg roflumilast dose over the 125 µg dose and placebo but failed to show statistical significance; and
- Roflumilast was well tolerated by the patients in this study.