Synopsis of study report: 303/2003
Location in Module 5:

Study Protocol No.:
BY217/FK1 020

Report Version:
1.0

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

Study centers:
Multicenter – 111 centers in the US, and 8 centers in Hungary

Publication (reference): not applicable

Study period (years):
First Patient Included: 19 November 2001
Last Patient Out: 18 August 2003

Clinical Phase:
III; IND 57,883

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

Methodology:
This was a multinational, multicenter, randomized, parallel group study. The trial consisted of a single-blind Baseline Period of 2 weeks (Visits B0 and B2), a double-blind Treatment Period of 12 weeks (Visits T0, T3, T6, T9, and T12), and safety follow-up (Visit F). At B0 all asthma medications, except rescue medication, were withdrawn, and the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 either:

- 250 µg roflumilast tablets administered orally once daily in the morning, or
- placebo tablet once in the morning

Rescue medication, a short acting β2-agonist (albuterol), was available to all patients.

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

495 randomized patients

252 patients in the roflumilast group; 243 patients in the placebo group

Diagnosis and criteria for randomization and inclusion/exclusion into treatment:

Diagnosis: history of bronchial asthma defined by the National Institute of Health (NIH) criteria (1997)

Inclusion criteria:

- 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 4 weeks prior to B0
- in a stable clinical state
- except for asthma in good health
- non-smokers or ex-smokers (smoking cessation more than 1 year and smoking history less than 10 pack years)

Exclusion criteria:

- 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:
  - a course of oral corticosteroids during 4 weeks prior to baseline Visit B0, or
  - hospitalization for asthma (including treatment in an emergency room) in the 4 weeks prior to baseline Visit B0, or
- Exacerbation of asthma or lower airway infection in the 4 week period prior to the baseline Visit B0

- Used any of the following pre-medications:
  - oral or parenteral steroids in the 4 week period prior to Visit B0
  - inhaled steroids >420 µg/day BDP ex mouthpiece (or equivalent) in the 4 week period prior to Visit B0
  - used any concomitant drugs that were not allowed by the protocol
  - used any corticosteroids with exception of nasal/ophthalmic/dermal steroids during the study
  - used inhaled and oral cromones, oral long-acting antihistamines, theophylline, lipoxygenase inhibitors, leukotriene antagonists, inhaled long-acting β2-agonists, oral β2-agonists, inhaled anticholinergics, and 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 <1 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 4 week period prior to the study) had to consent to using effective contraception in case they became sexually active during the study.
- Current smokers or ex-smokers with either smoking cessation ≤1year or with a smoking history of 10 pack years or more
- Suspected non-compliance
- Alcohol or drug abuse
- Patients who were continuously using >8 puffs/day rescue medication
- Patients who were not able to follow the procedures of the study due to e.g. language problems and psychological disorders
- Suspected hypersensitivity to the study medication
- Participation in another study (use of an investigational product) within 30 days preceding the baseline Visit B0 or re-entry of patients already randomized in this trial However, patients who fail to meet randomization criteria after the baseline period might be re-enrolled for a second time. Patients participating in an observational/epidemiologic study may be included if no blinded and/or not yet approved drug is administered
- Oocyte donation or oocyte implantation planned during the trial

Randomization criteria:

- FEV_1 was between 50 and 85% predicted at random Visit T0 (= reference value) when albuterol was withheld for at least 4 hours prior to the measurement
- FEV_1 at T0 was within a range of +/-20% of baseline Visit B0 value
- ≥1 puffs/day albuterol on average during the last 7 days of the Baseline Period prior to random Visit T0

- symptom score ≥1 per day on average during the last 7 days of the Baseline Period prior to random Visit T0
- increase of initial FEV_1 ≥12% and ≥200 ml 15 to 30 minutes after inhalation of 0.18 mg to 0.36 mg albuterol ex mouthpiece (which was determined within 6 months prior to B0 or during baseline)
- medication compliance was ≥80% and ≤125%.

Test product: Tablets with roflumilast
Dose: 250 µg/day in the morning
Mode of administration: oral
Batch No.: Roflumilast 250 µg tablets: 101180

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:
101160, 410190, 320220

Criteria for evaluation:
- Primary variable: Mean change from randomization to endpoint in FEV_1
- Secondary variables:
  - FEV_1 at earlier visits than the endpoint
  - Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), Maximum Expiratory Flow (MEF) 25-75% (spirometry)
  - Morning and evening PEF, PEF variability from diary cards
  - Asthma symptoms and use of rescue medication (diary cards)
  - Proportion of symptom-free days / rescue medication-free days
  - Drop-outs due to Lack of Efficacy (LOE)/Escape criteria
  - Quality of life (Asthma Quality of Life Questionnaire [AQLQ])

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. The time points of drop-outs due to the predefined LOE/escape criteria will be analyzed for a difference between treatments using pairwise logrank test. Asthma Quality of Life Questionnaire (AQLQ) data were analyzed using Analysis of Variance (ANOVA) and paired t-test. The time averaged

excess AUC between treatment groups were compared by ANCOVA for all pulmonary function and selected diary variables (post-hoc analysis). For safety parameters, descriptive statistics were summarized.

SUMMARY – CONCLUSIONS:

This was a Phase III, placebo-controlled, double-blind, study in which patients with bronchial asthma were randomized to receive either 250 µg roflumilast or placebo. Patients received albuterol metered dose inhaler (MDI) for use as rescue medication throughout the study. The primary objective of this 12-week study was to compare the effects of oral roflumilast (250 µg once daily) versus placebo on pulmonary function, quality of life, symptoms, and use of rescue medication, and drop-outs due to "LOE/escape criteria" in adult patients with bronchial asthma. This study was also designed to provide information on the safety and tolerability of roflumilast in patients with bronchial asthma.

Disposition and Demographics

A total of 495 patients were randomized in this study and included in the Intent-To-Treat (ITT) population. Of the 495 patients, 69.4% (175/252) of patients in the roflumilast group, and 72.0% (175/243) of patients in the placebo group completed the study. The inclusion of patients in the Per-Protocol (PP) population was decided by the Blinded Data Review Committee, based on their review of protocol violations and deviations. Of the 495 patients, 407 patients were included in the PP population. Forty-eight patients withdrew from the study due to treatment emergent adverse events (AEs) in both the roflumilast (9.9%) and the placebo (9.5%) groups. Exacerbation of asthma of mild, moderate, and severe intensity was the most commonly reported AE leading to discontinuation in both the roflumilast (7.9%) and placebo groups (8.2%).

There were no significant differences in demographic and baseline characteristics between the two treatment groups for both the ITT and PP populations. The mean baseline pulmonary test variables were also similar among the treatment groups in both analysis populations. In the ITT population, the most frequently used medications were selective β_2-adrenoceptor agonists in 96.0% (242/252) of patients in the roflumilast group, and 95.9% (233/243) of patients in the placebo group.

Efficacy Results

Statistically significant improvement in FEV_1 changes from baseline to endpoint were observed in both 250 µg roflumilast (0.103 L, $P < 0.001$) and placebo (0.061 L, $P = 0.015$) groups. However, the FEV_1 change from baseline to endpoint showed no statistically significant difference ($P = 0.224$) between treatment groups for the ITT analysis. Similar conclusions were reached from the PP analysis. However, a post-hoc analysis, which

compared time averaged excess AUC, showed statistically significant differences between treatments in favor of roflumilast (0.043 L, P = 0.031) in the ITT analysis.

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 shown for 250 µg roflumilast group than placebo in all visits and endpoint. However, treatment differences failed to reach statistical significance at endpoint for these variables and results were not statistically significant for most visits except for FVC. The PP analysis showed similar results. A statistically significant difference between treatments was shown for FVC when the comparison was based on time averaged excess AUC.

For the secondary diary efficacy assessments, statistically significant changes from baseline within each treatment group were observed at all or most timepoints except morning PEF. In general, the between-group comparisons on diary efficacy assessments showed no statistically significant treatment differences at any week or endpoint for either ITT or PP analyses. The time averaged excess AUC for diary parameters was not statistically significant between treatment groups.

Statistically significant changes from baseline were shown within each treatment group in all AQLQ domain and overall scores at all timepoints. No statistically significant treatment differences on any of the AQLQ scores were observed in either the ITT or PP analysis.

The pairwise comparison on time to LOE did not show a statistically significant difference between the two groups for either the ITT or PP analysis. The percentages of ITT patients reporting asthma exacerbation were similar in the roflumilast (10.3%) and placebo (9.9%) groups. The median time to the first exacerbation was 21.0 days for the roflumilast group and 39.5 days for the placebo group.

Safety Results

For the safety analyses, all patients in the ITT population were included. Of the 252 patients in the roflumilast group 181 patients (71.8%) were exposed to >11 weeks of treatment. Of the 243 patients in the placebo group, 180 patients (74.1%) were exposed to >11 weeks of treatment. Twenty-seven patients in the roflumilast group and 26 patients in the placebo group reported lack of treatment compliance.

The overall percentage of patients with AEs was 43.3% and 46.1% in the roflumilast and placebo groups, respectively. The percentage of patients with treatment emergent AEs likely or definitely related to study medication was low in both roflumilast (5.2%) and placebo (3.7%) groups. In general, the overall percentages of patients with AEs were highest for AEs

of the respiratory, thoracic, and mediastinal system, reported for 18.7% and 21.8% of patients in the roflumilast and placebo groups, respectively.

Serious adverse events (SAEs) were reported in 4 patients who were in the roflumilast group and 6 patients in the placebo group. Only 1 patient in the roflumilast group withdrew from the study due to a SAE. No patient died during this study. Nausea (2 patients), headache (2 patients), diarrhea (1 patient) and dyspepsia (1 patient) were the only significant other AEs that led to patient withdrawal and were considered to be likely or definitely related to the study medication in patients in the roflumilast group. Four of these significant six adverse events were reported by one patient (one episode each of nausea, headache, diarrhea, dyspepsia).
For the laboratory evaluations, no clinically significant changes between the roflumilast and placebo groups were observed.

Mean ECG intervals at Visit T12 did not change in both roflumilast and placebo groups when compared to findings at baseline. All other changes in vital signs, body weight, or ECG (including HR) values were not significant during the study.

Conclusions
Thus, it can be concluded from this study that following 12 weeks of oral administration of 250 µg roflumilast in patients with asthma that:

- The primary efficacy variable (FEV_1 change from baseline to endpoint) measured in patients treated with roflumilast was numerically superior to the placebo but failed to reach statistical significance. in the primary analysis based on differences. However, statistical significance was reached when the comparison was based on time averaged AUC.
- Most of the secondary efficacy variable results also indicated numerical advantage of roflumilast over placebo but failed to show statistical significance; and
- Roflumilast was well tolerated by the patients in this study.