2 SYNOPSIS

Title of the study:
Safety and efficacy of Roflumilast versus placebo in subjects with bronchial asthma (Study No.: BY217/FK1 011)

Study centers:
A total of five centers participated, all located in the USA: New England Clinical Studies, North Dartmouth; Bernstein Clinical Research Center, Ohio; USCD Clinical Trial Center, University of California, San Diego; Valley Clinical Research Center, Easton; Allergy & Asthma Care of Florida Clinical Research Division, Ocala.

Publication (reference):
Not applicable.

Study period (years):
1 October 1999 – 28 December 1999

Clinical Phase: II

Objectives:
The main objective was to compare the safety and tolerability of once daily, orally administered 0.5 mg roflumilast with placebo over a period of four weeks in patients with mild to moderate asthma. Further, the effects of roflumilast on pulmonary function, symptoms of asthma and use of rescue medication were assessed.

Methodology:
This was a multi-center, parallel, randomized, double-blind phase II study. Eligible patients entered a single-blinded baseline period of 1-3 weeks duration (visits B0, B1, B2, B3), during which they had all anti-asthmatic medication other than albuterol withdrawn and received placebo. Patients whose FEV_1 was between 50 and 80% of predicted normal, who did not fulfill pre-defined "escape" criteria, who showed a reversible obstruction (FEV_1 increase $\geq$ 12% and $\geq$ 200 ml in response to 200 µg albuterol within 15 min) and treatment compliance between 80 and 120% were randomized to receive either a once daily dose of 0.5 mg roflumilast or placebo (visit T0). During the 4-week treatment period, patients recorded their morning and evening PEF, use of beta-agonist, night- and day-time symptoms of asthma. After 2 and 4 weeks (T2 and T4, respectively), patients underwent further lung function testing (FEV_1, FVC, PEF) and safety assessment at a clinic visit. Possible effects of trial medication on cardiac function were evaluated by monitoring heart rate, blood pressure and ECG over a period of 2 hours after tablet intake at clinic visits.

Number of subjects (total and for each treatment):

Intention-to-treat	N = 47	Per-protocol	N = 46
Roflumilast	N = 25	Roflumilast	N = 25
Placebo	N = 22	Placebo	N = 21

Diagnosis and criteria for inclusion:
Patients with stable, mild to moderate asthma (otherwise healthy), aged 18 - 70 years, non-or ex-smokers (smoking cessation > 1 year prior to study start), who were currently not treated with inhaled or systemic corticosteroids, and who showed a FEV_1 of 50-90% of predicted normal. At the end of the baseline period, patients were required to have an FEV_1 between 50 and 80% of predicted, a reversible obstruction (FEV_1 increase $\geq$ 12% and $\geq$ 200 ml in response to 200 µg albuterol within 15-30 min), a treatment compliance between 80 and 120%, and no "escape" criteria (decrease in FEV_1 of at least 20% of that at B0/T0, or use of albuterol > 12 puffs/d) present.

Test product, dose, mode of administration, batch no.:
Roflumilast, 0.25 mg/tablet, 2 tablets od in the morning, oral administration batch no.: BY217-45-4-1.

Duration of treatment:
Baseline period: 1-3 weeks; treatment period: 4 weeks.

Synopsis (continued)

Reference therapy, dose, mode of administration, batch no.:
Placebo, 2 tablets od in the morning, oral administration, batch nos.: BY217-43-1-1, BY217-43-3-1.

Criteria for evaluation:
Efficacy evaluation:
Spirometric lung function tests (FEV_1, FVC, PEF) at T2 and T4, morning and evening PEF (derived from diaries), PEF variability, symptoms of asthma and use of rescue medication.

Safety (primary variable):
Safety variables included laboratory values, physical examination (ECG, BP, HR monitored over a period of 2 hours after medication intake on clinic visit days), and adverse event (AE) monitoring.

Statistical methods:
An ITT, extended ITT (if applicable) and PP analysis was performed. For spirometric lung function variables (FEV_1, FVC, and PEF) the differences T2-T0, T4-T0, and $T_{END/LAST}$-T0 were calculated, and the null hypothesis that the respective mean differences were equal versus the alternative, that they were unequal was tested using an ANCOVA with the factors/covariables value at T0, age, and sex. Within group differences were analyzed by the same model. Adjusted means and two-sided 95%-confidence limits were given for within- and between-treatment comparisons. The same procedure was applied for the analysis of morning and evening PEF derived from diaries.

The number of daily use of rescue medication, the sum of symptom scores averaged or cumulated, as well as PEF variability were analyzed for each week by non-parametric test procedures. Between-treatment comparisons were done by the Mann-Whitney U-test. Within-group comparisons were done with the Wilcoxon's signed-rank test modified according to Pratt. The number of symptom-free and rescue medication-free days was also analyzed non-parametrically. Adverse events, clinical chemistry, vital signs, and ECGs were analyzed in a descriptive manner.

SUMMARY - CONCLUSIONS:

Efficacy Results:

While the sample size of the study was too low to allow for firm statistical and clinical conclusions, the study demonstrated that the lung function variables FEV_1, FVC and PEF (derived from either spirometry or diaries) increased over the treatment period in both groups, with the improvement being more pronounced on roflumilast as compared to placebo in all analyses performed (PP, ITT, and if applicable, ext. ITT). However, neither within- nor between-treatment differences proved to be statistically significant in the endpoint analysis at the 5% level, with the exception of the within-treatment effect of roflumilast on FVC in the ITT and ext. ITT analysis ($p = 0.0342$ and $p = 0.0270$, respectively).

Results for FEV_1 endpoint analysis are shown below:

FEV_1 (l/min) endpoint analysis (ITT)

Treatment	N	Within-treatment differences T_{LAST} – T0		Between-treatment differences Test - Ref	
		LSMean (95%-CI)	p-value	LSMean (95%-CI)	p-value
Placebo (Ref.)	22	0.06 (-0.12, 0.24)	0.4938	0.08 (-0.17, 0.33)	0.5119
Roflumilast (Test)	24	0.14 (-0.03, 0.32)	0.1102		

The improved lung function was even more marked at T2. For FEV_1/FVC within- (all analyses) and between- (ITT and ext. ITT analysis) treatment differences reached statistical significance at T2 (unadjusted p-value); for PEF, the within-treatment differences in the ITT and ext. ITT analysis. Neither within- nor between-treatment differences were statistically significant in the placebo group.

Synopsis (continued)

Efficacy results (continued):

With respect to the other efficacy variables, PEF variability, asthma symptom scores and use of rescue medication, marginal improvements were seen over the treatment period, with the placebo group presenting with slightly better improvements as compared to roflumilast. Statistical significance was reached occasionally for within-treatment differences in both groups, but not for any of the between-treatment comparisons.

Note, that the study was primarily designed to show tolerability and not efficacy and thus, statistically significant or clinically relevant differences were not expected to be obtained since the sample size was too small.

Safety Results:

In total there were 34 AEs experienced by 14/25 patients (56%) on roflumilast, and 9 AEs experienced by 6/22 patients (27%) on placebo during the double-blind treatment period. The most frequently reported AEs of patients on roflumilast were gastro-intestinal disorders and headache, which were, in the great majority of cases, judged to be "likely" related to study medication. Remaining AEs were considered to be "unlikely" or "not" related, as were all AEs experienced by patients on placebo treatment. Most of the AEs were of mild or moderate intensity. There were seven AEs experienced by two patients on roflumilast which were of severe intensity (gastro-intestinal disorders and headache) and led to premature discontinuation of study medication. The AEs resolved upon withdrawal, however. Two severe AEs were reported by two patients in the placebo group (headache and back pain). Death or other serious AEs were not reported.

There were no clinically significant alterations in vital signs, laboratory values, or physical examination during the 4 weeks of treatment. Blood pressure and heart rate were stable throughout the trial as well as during the 2 hours directly following drug intake. No clinically relevant abnormality in ECG was found during the treatment and the 2h observation period after roflumilast intake. Electrocardiographic findings did not indicate an influence of roflumilast on the QTc interval.

Conclusion:

The study supports the good safety profile and acceptable tolerability of roflumilast. The incidence of AEs was higher on roflumilast treatment as compared to placebo, but all AEs could be easily managed and thus do not place asthmatic patients at an unreasonable or intolerable risk. The AEs experienced were primarily those expected on roflumilast, as seen in previous studies. Roflumilast did not influence cardiovascular function; more specifically, repeated measurements of 12-lead resting ECG, blood pressure and heart rate did not show any clinically relevant alterations under treatment with roflumilast. The PQ, QRS, QT, and QTc intervals were not affected by roflumilast. With respect to efficacy, the sample size was not sufficient to prove significance between roflumilast and placebo at the 5% level at any endpoint-analysis (which at this patient number level could have only been expected if the differences would have been very large), but it can be concluded that roflumilast has the potential to improve lung function.