Synopsis of study report: 43/2002 K1
Location in Module 5:

Study Code:
BY217/FK1 010

Report Version:
2.0

Title of the study:
Effect of roflumilast on allergen challenge in patients with bronchial asthma

Study center(s):
Medical School, University of Stellenbosch, Tygerberg, South Africa

Publication (reference):
Not applicable.

Studied period (years):
02 November 1999 to 26 September 2001

Clinical phase:
II

Objectives:
This study aimed to assess the extent of reduction of allergen-induced early asthmatic reaction (EAR) and late asthmatic reaction (LAR) in patients with mild allergic asthma after repeated dosing of roflumilast at daily doses of 0.25 mg or 0.5 mg vs. placebo. Furthermore, airway responsiveness and safety parameters were analyzed.

Methodology:
This was a double-blind, randomized, three-period crossover study consisting of a baseline period (2 to 14 days, visits B0 and B1) and three treatment periods (each 7 days, visits V1 and V2, V3 and V4, V5 and V6, respectively) separated by washout periods of 2 to 5 weeks.

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

PP population: n = 23
ITT population: n = 23

Diagnosis and criteria for inclusion:

Patients with allergic asthma of either sex who gave their written consent could be included if they fulfilled the following criteria: aged 18 to 50 years, healthy with the exception of asthma, history of episodes of wheezing consistent with the clinical diagnosis of mild asthma, currently under treatment with short-acting inhaled bronchodilators only, hyper-reactive to metacholine ($PC_{20}FEV_1 \leq 16$ mg/ml), FEV1 ≥ 70% of predicted, positive prick test with the tested allergens, and who experience an EAR (decrease in $FEV_1 \geq 25\%$ from post-saline value within first 2 h after allergen inhalation) and LAR (decrease in $FEV_1 \geq 15\%$ from post-saline value at ≥ 2 recording times (between 2 to 12 h after allergen inhalation) *and* showing a typical gradual deterioration in FEV_1).

Test product:

Roflumilast

Dose:

0.25 or 0.5 mg roflumilast

Mode of administration:

Tablets; administered orally once daily in the morning after breakfast;

Batch No.:

0.25 mg roflumilast: BY217-45-1-1
0.5 mg roflumilast: BY217-46-1-1

Duration of treatment:

One week for each treatment.

Reference product:

Placebo tablets identical in appearance to roflumilast

Dose:

Not applicable.

Mode of administration:

Tablets, administered orally once daily in the morning after breakfast.

Batch No.:

BY217-43-3-1

Criteria for evaluation:

Efficacy evaluation (primary):	extent of LAR, determined as $AUC_{2-12\,h}$ of the FEV_1 decrease
Efficacy evaluation (secondary):	extent of EAR, determined as $AUC_{0-2\,h}$ of the FEV_1 decrease, $PC_{20}FEV_1$ ratios of second treatment visit vs. first treatment visit,
Safety evaluation (secondary):	adverse events, laboratory tests, ECG, vital signs, physical examination

Statistical methods:

Pair-wise tests were used to analyze treatment effects. The first test compared 0.5 mg roflumilast vs. placebo. If, and only if, this test showed significant results, 0.25 mg roflumilast was compared vs. placebo, and the two roflumilast doses were compared with each other. Due to the principle of closed testing procedures, there was no need to adjust the α-level. However, in accordance with the ICH E9 guideline on Statistical Consideration in the Design of Clinical Trials a 2.5%-level for the type I error rate (half the conventional 5%-level) is recommended in the case of one-sided tests.

The AUCs of the FEV_1 decrease over time as the primary characteristic of the extent of the LAR were compared by the analysis of variance for the three-period crossover design. An additive model was used. Means and two-sided 95%-confidence intervals are given for the differences roflumilast - placebo of population means.

The following hypothesis were considered, where μ denotes the expected mean of the FEV_1 area decrements:

H_0': $\mu_{Placebo} \leq \mu_{500\mu g\ roflumilast}$

H_1': $\mu_{Placebo} > \mu_{500\mu g\ roflumilast}$ (0.5 mg roflumilast is superior to placebo)

and

H_0'': $\mu_{Placebo} \leq \mu_{250\mu g\ roflumilast}$

H_1'': $\mu_{Placebo} > \mu_{250\mu g\ roflumilast}$ (0.25 mg roflumilast is superior to placebo)

and

H_0'': $\mu_{250\mu g\ roflumilast} \leq \mu_{500\mu g\ roflumilast}$

H_1'': $\mu_{250\mu g\ roflumilast} > \mu_{500\mu g\ roflumilast}$ (0.5 mg roflumilast is superior to 0.25 mg roflumilast)

The extent of the EAR was analyzed analogously, however with an exploratory intention.
The other secondary variables were analyzed in a descriptive manner, if appropriate by means and 95%-confidence intervals.
With respect to the $PC_{20}FEV_1$ (metacholine) values, the ratios V2/V1, V4/V3, and V6/V5 were calculated and used to test for treatment effects. The closed testing procedure described above for the primary variable, was performed based on a multiplicative model. Geometric means and two-sided 95%-confidence intervals were given for the respective ratios of population medians. For the analysis of the secondary efficacy variables, no adjustment for multiplicity was made.
Clinical laboratory data were presented as individual data and were marked according to the normal ranges provided by the central laboratory. Nature, incidence, and intensity, as well as the investigator's and the Sponsor's causality assessment were reported for each adverse event.

SUMMARY - CONCLUSIONS

Summary:

Efficacy results:

Characteristic reductions in lung function after allergen inhalation corresponding to an EAR and LAR were seen in the recorded FEV_1 profiles. Analysis of the $AUC_{2-12\,h}$ of the FEV_1 decrease showed a reduction of LAR by 43% compared with placebo in patients treated with 0.5 mg roflumilast ($p = 0.0009$, PP analysis). Under 0.25 mg roflumilast, LAR was reduced by 27% ($p = 0.0110$, PP analysis). Since the LAR is believed to be predominantly caused by inflammatory airway changes, the attenuating effect of roflumilast is well in line with its expected anti-inflammatory effect. The difference between the two roflumilast dosages was not statistically significant.

Between-treatment differences in LAR ($AUC_{2-12\,h}$; parametric PP analysis)

Test	Reference	n	$AUC_{2-12\,h}$ Test - Reference		% Reduction from reference
			point estimate (95% CI)	p-value[a]	
0.5 mg Rofl.	Placebo	19	-0.243 (-0.3817, -0.1040)	0.0009	43%
0.25 mg Rofl.	Placebo	21	-0.148 (-0.2724, -0.0237)	0.0110	27%
0.5 mg Rofl.	0.25 mg Rofl.	19	-0.084 (-0.2228, 0.0557)	0.1113	21%

[a] one-sided

The effect on EAR was evaluated based on the $AUC_{0-2\,h}$ of the FEV_1 decrease. A statistically significant attenuation of EAR ($p < 0.025$, PP analysis) in comparison with placebo was observed both for 0.5 mg roflumilast (reduction by 28%) and 0.25 mg roflumilast (reduction by 25%).
Treatment effects on airway responsiveness after allergen exposure were analyzed by comparing $PC_{20}FEV_1$ values at the start of each treatment period and after the allergen challenge per-

formed at the end of each treatment period. Patients treated with placebo showed an increased airway responsiveness after allergen exposure. By contrast, roflumilast treatment seemed to attenuate this response. However, no statistically significant difference was found between 0.5 mg roflumilast and placebo.

Safety results:

In total, 52 AEs occurred during the three treatment periods. The incidence was lowest under placebo (10 AEs in 9 patients), followed by 0.25 mg roflumilast (19 AEs in 12 patients), and 0.5 mg roflumilast (23 AEs in 14 patients).

There were no deaths, serious AEs, or AEs leading to discontinuation from the trial. Furthermore, there was only one AE of severe intensity. However, this was assessed "not related" to the treatment with 0.5 mg roflumilast.

The most frequent AEs observed under roflumilast treatment affected the gastrointestinal tract (diarrhea, gastrointestinal disorder) or nervous system (headache). However, all were mild to moderate in intensity and did not lead to discontinuation.

There were no AEs judged "definitely related" to the study medication. Most AEs (8/10 [80%] under placebo, 13/19 [68%] under 0.25 mg roflumilast, and 11/23 [48%] under 0.5 mg roflumilast) were judged "not" or "unlikely related". In total, 18 AEs (6 AEs under 0.25 mg roflumilast and 12 AEs under 0.5 mg roflumilast) were assessed "likely related" to roflumilast intake.

Routine laboratory test did not reveal clinically relevant changes during treatment. Furthermore, no influence on vital signs, ECG, or physical examination findings was seen. Overall, roflumilast treatment was well tolerated.

Conclusions:

Taken together, 0.25 and 0.5 mg roflumilast administered once daily for one week showed to be effective in attenuating both LAR and EAR after allergen exposure in patients with allergic asthma. The effect on LAR seemed to be dose-dependent (n.s.) and is well in line with the expected anti-inflammatory effect of roflumilast. Furthermore, the results suggest that roflumilast leads to a reduction in allergen-induced airway responsiveness.