Synopsis of study report: 38/2001 K2
Location in Module 5:

Study Code:
BY217/FK1 006

Version Date:
20 Jul 2004

Title of the study:

12 weeks treatment with 0.1 mg or 0.25 mg or 0.5 mg roflumilast in patients with asthma (dose range finding study)

Investigators:

A total of 68 investigators in 6 countries.

Study center(s):

A total of 68 centers participated, located in Austria (5), Germany (29), Hungary (10), Poland (6), South Africa (9), Spain (9).

Publication (reference):

Not applicable

Studied period (years):

14 September 1998 (first patient in the study) – 21 December 1999 (last patient out of the study)

Clinical phase:

II/III

Objectives:

- This study was a dose-range finding study. Its objective was to investigate the effects of 0.1 mg, 0.25 mg and 0.5 mg roflumilast administered once daily over 12 weeks on pulmonary function, asthma symptoms and use of rescue medication in patients with asthma. Additionally, safety and tolerability of roflumilast was assessed.

Methodology:

This was a parallel, randomized, double-blind, multi-center, multi-national phase II/III study. After a single-blind baseline period of 1 - 3 weeks during which placebo was administered, eligible patients were allocated to one of the three treatment groups for a treatment period of 12 weeks. Patients recorded their morning and evening PEF, use of beta-agonist, night- and day-time symptoms of asthma daily on a diary throughout the entire study. Further lung function testing (FEV_1, FVC, PEF) and safety assessment were performed at clinic visits scheduled at 1, 3, 6, 9, and 12 weeks after treatment start (T0, T1, T3, T6, T9, T12).

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

Intention-to-treat:	n = 690	Per-protocol:	n = 617
0.1 mg roflumilast:	n = 229	0.1 mg roflumilast:	n = 201
0.25 mg roflumilast:	n = 228	0.25 mg roflumilast:	n = 203
0.5 mg roflumilast:	n = 233	0.5 mg roflumilast:	n = 213

Diagnosis and criteria for inclusion:

Patients with stable asthma (otherwise healthy), aged 15 - 70 years and who showed a FEV_1 between 50 and 100% of predicted dependant on the pre-treatment, were eligible to enter the study. At the end of the baseline period, patients were required to have an FEV_1 between 50 and 85% of predicted and either a reversible airway obstruction (FEV_1 increase ≥ 15% in response to 0.2 to 0.4 mg salbutamol) *or* a diurnal PEF variability of at least 15% during at least 3 days of the last 7 days directly preceding the randomization visit.

Duration of treatment:

Baseline period: 1 to 3 weeks
Treatment period: 12 weeks

Test product:

Roflumilast

Dose:

1 tablet (0.1, 0.25 and 0.5 mg/tablet) once-daily in the morning

Mode of administration:

Oral administration

Batch No.:

0.1 mg: BY217-44-1-1
0.25 mg: BY217-45-4-1
0.5 mg: BY217-46-2-1

Reference product:

Not applicable

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

Efficacy evaluation:

Primary variable: FEV_1 at end of treatment compared to baseline (T_{last}-T0)

Secondary variables: Spirometric lung function tests (FVC, PEF), morning and evening PEF (derived from diaries), PEF variability, symptoms of asthma and use of rescue medication, drop-outs due to pre-defined "lack of efficacy" criteria, subjective efficacy rating (patient/physician) at end of treatment and scheduled visits T1, T3, T6, T9 and T12; FEV_1 at T1, T3, T6, T9, and T12.

Safety:

Clinical laboratory (biochemistry, hematology, urinalysis), physical examination, vital signs, electrocardiogram (ECG), and adverse event (AE) monitoring.

Statistical methods:

An ITT, extended ITT (if applicable) and PP analysis was performed, with the ITT analysis being primary for efficacy evaluation.

For the primary variable FEV_1 and the secondary lung function variables FVC, PEF, and morning/evening PEF from diaries an ANCOVA with the factors/covariates treatment, sex, center, value at T0, and age was performed. Based on the $T_{last/end}$ - T0 differences, where T_{last} corresponds to the last value analysis of the ITT, and T_{end} to the endpoint analysis of the PP evaluation, a test for monotone dose-response using the pairwise contrast was performed. Adjusted means and 95%-confidence limits were given for treatment differences. Within- and between group comparisons followed the two-sided approach with $\alpha = 0.05$.

For the number of patients with LOE, a monotone dose-dependency was established by means of the logrank test for trend and, if applicable, subsequent pairwise logrank tests.

The daily use of rescue medication, the sum of symptom scores between W0 (week prior to T0) and the week prior to the last visit (T_{last}) as well as between each week and W0, PEF variability as well as the number of symptom-free and rescue medication-free days were analyzed by non-parametric test procedures. Between-treatment comparisons were done by the Mann-

Whitney U-test. Within-group comparisons were done with Pratt's modification of the Wilcoxon's signed-rank test.
The subjective efficacy rating, adverse events, as well as vital signs were analyzed in a descriptive manner.

SUMMARY – CONCLUSIONS

Summary:

Efficacy results:

Efficacy results are summarized for the ITT last value analysis (T_{last}), which were well comparable to those obtained in the PP endpoint analysis.

Primary efficacy variable FEV1

FEV_1 increased to a statistically significant and clinical relevant degree in all three dose groups, showing a clear dose-response. Superiority could be demonstrated for the 0.5 mg dose over the 0.1 mg dose. A statistical significant improvement was seen already after one week of treatment.

Summary statistics for FEV_1 (l) - ITT last value analysis

Treatment	n	LSMean ± Std Err	95%-CI	p-value[a]
Within treatment differences: T_{last} - T0				
0.1 mg	227	0.26 ± 0.03	0.20, 0.32	< 0.0001
0.25 mg	224	0.32 ± 0.03	0.26, 0.39	< 0.0001
0.5 mg	228	0.40 ± 0.03	0.34, 0.46	< 0.0001
Between treatment differences for T_{last} - T0				
0.25 mg vs 0.1 mg	b	0.06 ± 0.04	-0.02, 0.15	0.1601
0.5 mg vs 0.1 mg	b	0.14 ± 0.04	0.05, 0.22	0.0017
0.5 mg vs 0.25 mg	b	0.07 ± 0.04	-0.01, 0.16	0.0856

[a] two-sided. b n=227, 224, 228 for the 0.1, 0.25, and 0.5 mg group. CI = confidence interval, LS = least squares, n = number of patients, Std err = standard error, T_{last} = ITT last value analysis, T0 = randomization visit.
Note, numbers were rounded.

Secondary efficacy variables

A statistically significant improvement in most of the secondary variables was observed at T_{last} (see table below). The 0.5 mg dose was superior to the 0.1 mg for PEF (morning and evening PEF derived from diary as well as PEF from spirometry), the 0.25 mg to the 0.1 mg only for spirometric PEF. An early onset of efficacy (statistically significant after week 1 or 2) was found for almost all variables, for morning PEF as early as one day after treatment start for all roflumilast doses.

Secondary variables – changes in ITT last value analysis

	0.1 mg roflumilast		0.25 mg roflumilast		0.5 mg roflumilast	
	LSMean or mean	95%-CI	LSMean or mean	95%-CI	LSMean or mean	95%-CI
FVC (LSMean, l)	0.31*	0.25, 0.38	0.38*	0.31, 0.45	0.39*	0.32, 0.46
PEF (LSMean l/min) - spirometry	50*	38, 62	68**	56, 80	70**	58, 81
Morning PEF (LSMean l/min) - diary	10*	3, 17	12*	5, 19	20**	13, 27
Symptom score (mean change in score sum)	-0.26*	-0.44, -0.17	-0.31*	-0.48, 0.21	-0.17*	-0.33, -0.07
Rescue medication (mean change no. of puffs)	-0.05*	-0.29, -0.05	0.03	-0.29, 0.00	0.12	-0.14, 0.08

LSMean=Least squares mean, CI=Confidence Interval. *p<0.05 for within treatment comparison. **p<0.05 for within- and between treatment comparison vs 0.1 mg. P-values are to be considered to be descriptive in nature.

The probability of not experiencing *LOE* increased in a dose-dependent manner from 0.88 for the 0.1 mg to 0.92, and 0.94 for the 0.25 and 0.5 mg group, respectively. The results of the logrank trend test approached but did not reach statistical significance (p = 0.0253, one-sided).

With respect to the efficacy evaluation by patient and investigator, there were no differences between the dose groups, with the efficacy rated as very effective or effective for approximately 90% of the patients irrespective if evaluated by patients or investigators.

Safety results:

In general, roflumilast was well tolerated across all dose groups. The incidence of AEs was higher in the 0.5 mg roflumilast group as compared to the lower dose groups with 57% vs ~48% (based on the number of patients reporting at least one AE). The most frequently reported AE in the two lower dose groups was a respiratory tract infection, while in the 0.5 mg group it was headache. The number of adverse events related to the nervous and to the digestive system such as headache, diarrhea, and nausea were higher in the 0.5 mg as compared to the lower dose groups.

The majority of AEs was judged to be “not” related to study medication in each dose group. However, the incidence of AEs considered by the investigator to be “likely” related to study medication amounted to 10% in the two lower dose groups as compared to 23% in the 0.5 mg group. Headache, nausea, and diarrhea (expected AEs) accounted for most of those AEs considered to be “likely” related to study medication.

Most of the AEs were mild or moderate in nature and transient. A total of 50 AEs were classified as severe with a comparable incidence in all three treatment groups.

No death occurred during the study. A total of 16 patients experienced a SAE, all judged to be either “not” or “unlikely” related to study medication, without any specific trend across dose groups.

There was no clinical evidence that roflumilast has an effect on liver or cardiac function.
The number of patients withdrawn due to AEs was higher in the 0.5 mg (16) as compared to the two lower dose groups (10 each). The most common AE leading to premature withdrawal was a deterioration of asthma, without any reasonable relationship to roflumilast. Headache, diarrhea, and nausea were the second most common AEs leading to discontinuations, mainly experienced by patients in the 0.5 mg group.
Most of the events were transient meaning that they had been resolved either spontaneously or upon treatment.
Overall, for all clinical chemistry and hematology parameters analyzed, the mean changes from baseline were small and not clinically relevant. The number of patients presenting with clinically significant abnormalities, was less then 10% in each treatment group, without any apparent dose-dependency. Additionally, the great majority of these AEs were considered to be “not” or “unlikely” related to study medication.
Vital signs and ECG did not reveal any apparent trends.

Conclusions:

Roflumilast in doses of 0.1, 0.25, and 0.5 mg O.D. was shown to be effective in the enrolled asthma patients. At this dose range statistically significant improvements were evident in pulmonary function that clearly reached clinical relevance for 0.25 and 0.5 mg. A dose-response could be demonstrated for the primary variable as well as for PEF (derived from spirometry and diaries) with the 0.5 mg dose showing significantly greater improvements than the 0.1 mg dose. The incidence of AEs was higher on 0.5 mg roflumilast as compared to the lower doses, but all AEs were easily manageable and thus bear no unreasonable or intolerable risk for asthmatic patients. The AEs experienced were primarily those expected on roflumilast as seen in previous studies. Thus the study confirmed the good safety profile and good tolerability of roflumilast.
In summary the findings suggest that most patients with mild to moderate asthma can be treated adequately with doses of 0.25 or 0.5 mg O.D. roflumilast. The results additionally indicate that a dose of 0.1 mg roflumilast O.D. might also be effective, but since no placebo arm was included in this trial, no firm conclusion on the efficacy of the 0.1 mg dose can be drawn.