Synopsis of study report: 137/2001 K2
Location in Module 5:

Study Code:
BY217/FK1 008

Report Version:
3.0

Title of the study:
12 weeks treatment with 500 µg roflumilast versus 10 mg montelukast in patients with asthma

Investigators:
A total of 48 investigators in 4 countries.

Study center(s):
A total of 48 centers participated, located in Austria (9), Canada (13), Germany (24), and France (2).

Publication (reference):
Not applicable.

Studied period (years):
05 Nov 1999 (first patient in the study), 09 Oct 2000 (last patient out of the study)

Clinical phase: III

Objectives:
The objective of the present study was to compare 0.5 mg roflumilast with 10 mg montelukast with respect to the effect on pulmonary function, symptoms, and use of rescue medication. Furthermore, the study aimed to provide information on the safety and tolerability of roflumilast.

Methodology:
This was a randomized, double-blind, double-dummy, parallel-group study with a single-blind placebo baseline period. Patients with a history of bronchial asthma were screened for inclusion in the study. After a single-blind baseline period of 1 to 3 weeks during which placebo was administered, eligible patients were allocated to one of the two treatment groups for a treatment period of 12 weeks. Patients recorded their morning and evening PEF, use of beta-agonist, as well as 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 3, 6, 9, and 12 weeks after treatment start (T0, T3, T6, T9, T12).

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

	Intention-to-treat	Per-protocol
Total	n = 445	n = 332
0.5 mg Roflumilast	n = 216	n = 159
10 mg Montelukast	n = 229	n = 173

Diagnosis and criteria for inclusion:
Patients with a history of asthma (otherwise healthy), aged 15 - 70 years and who showed a FEV_1 between 50 and 100% of predicted dependent 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 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.

Test product:
Roflumilast

Dose:
0.25 mg/tablet (first week of treatment), and 0.5 mg/tablet (from second week on).

Mode of administration:
One tablet once-daily in the morning, oral administration.

Batch No.:
BY217-45-1-1 (0.25 mg); BY217-46-2-1 (0.5 mg)

Duration of treatment:
12 weeks

Reference product:
Montelukast

Dose:
10 mg. tablet encapsulated.

Mode of administration:
One capsule once-daily in the evening; oral administration.

Batch No.:
BY217-95-1-1 and BY217-95-2-1

Criteria for evaluation:

Efficacy evaluation (primary): mean change of the forced expiratory volume in one second (FEV_1) between visit T0 (randomization) and the endpoint of the study

Efficacy evaluation (secondary):	spirometry: FEV_1 before the endpoint, FVC and PEF; derived from diaries: morning and evening PEF, PEF variability, symptoms and use of rescue medication; proportion of symptom-free days, drop-outs due to "lack of efficacy" criteria, number and time of asthma exacerbations, effectiveness rating
Safety evaluation (secondary):	laboratory values, physical examination, ECG, blood pressure, heart rate, and adverse event (AE) monitoring

Statistical methods:
An analysis of covariance including baseline (randomization) value, age, sex, and center, as well as subsequent tests for non-inferiority and superiority of roflumilast vs. montelukast (non-inferiority acceptance limit for FEV_1: 200 mL) were performed. Descriptive statistics were done for safety parameters.

SUMMARY - CONCLUSIONS

Summary:

Efficacy results:

Primary efficacy variable
The lung function variable FEV_1 at the end of the study (T_{last}) was analyzed in comparison to T0. The within-treatment comparison revealed a statistically significant increase of FEV_1 during treatment in both treatment groups. The increase was more pronounced in patients treated with roflumilast. Hypothesis testing of the between-treatment differences demonstrated non-inferiority but not superiority of roflumilast compared with montelukast. A subgroup analysis revealed that roflumilast was superior to montelukast in smokers and ex-smokers.

FEV_1 (L): ITT last value analysis vs. T0

		Differences (T_{last} – T0)		
Treatment group	**n**	**LS Mean ± SEM**	**95% CI**	**p-value two-sided**
Within-treatment differences				
10 mg Montelukast	219	0.22 ± 0.03	0.16, 0.28	<0.0001
0.5 mg Roflumilast	205	0.28 ± 0.03	0.22, 0.34	<0.0001
Between-treatment differences				**one-sided**
Roflumilast / Montelukast	205 /219	0.06 ± 0.04	-0.01, 0.14	0.0484

T_{last} = last value of analysis; LS Mean = least squares mean; SEM = standard error of the mean; CI = confidence interval;

Secondary efficacy variables

Both FVC and PEF from spirometry increased during treatment in both treatment groups (statistically significant). The between-treatment analysis demonstrated non-inferiority of roflumilast for both variables as well as superiority of roflumilast with respect to FVC.

ITT last value analysis of spirometry variables vs. T0

			Differences (T_{last} – T0)		
Variable	**Treatment group**	**n**	**LS Mean ± SEM**	**95% CI**	**p-value two-sided**
Within-treatment differences					
FVC (L)	10 mg Montelukast	219	0.23 ± 0.03	0.17, 0.30	<0.0001
	0.5 mg Roflumilast	205	0.34 ± 0.03	0.27, 0.40	<0.0001
PEF (L/min)	10 mg Montelukast	219	60 ± 6	48, 72	<0.0001
	0.5 mg Roflumilast	205	60± 6	48, 72	<0.0001
Between-treatment differences					**one-sided**
FVC (L)	Roflumilast / Montelukast	205 / 219	0.11 ± 0.04	0.02, 0.19	0.0066
PEF (L/min)	Roflumilast / Montelukast	205 / 219	-0.07 ± 7.81	-15.4, 15.3	0.5038

T_{last} = last value of analysis; LS Mean = least squares mean; SEM = standard error of the mean; CI = confidence interval;

The diary variable morning PEF showed a statistically significant increase during both roflumilast and montelukast treatment (comparison T_{last} to week before T0). However, the increase in evening PEF was only statistically significant in patients treated with roflumilast. Non-inferiority could be demonstrated for roflumilast, but the between-treatment comparison revealed no statistically significant differences for both morning and evening PEF.

PEF variability, asthma symptom score sum, and use of rescue medication improved in both treatment groups (statistically significant). There were no statistically significant differences between the treatment groups.

The majority of patients (80%) and investigators (81%) rated the roflumilast treatment “very effective” or “effective” at the end of the trial. Furthermore, the majority of randomized patients and investigators rated the effectiveness “improved” at the end of the trial compared to the start (T0).

Safety results:

During the trial, 209 (47%) patients experienced 426 AEs; 358 AEs occurred during the treatment period. The percentages of patients experiencing AEs were similar in both treatment groups (roflumilast: 44%, montelukast: 41%). Most AEs were mild to moderate in intensity, 5% to 6% of AEs in each treatment group were severe.

The majority of AEs in both treatment groups affected the respiratory system and, thus, were related to the underlying disease. In addition, headache and gastrointestinal symptoms (diarrhea, nausea, abdominal pain) occurred in the roflumilast group. However, these AEs were only transient, occurring most frequently at treatment start and declining throughout the study. Most AEs (89% in the montelukast group and 69% in the roflumilast group) were rated “not” or “unlikely related” to the study medication. The investigators considered 11% of AEs

"likely related" to montelukast treatment and 29% of AEs "likely related" to roflumilast treatment. In total, 3 AEs (nausea, diarrhea, abdominal pain) experienced by one patient were judged "definitely related" to roflumilast medication (investigators' assessment).
Overall, 5 serious AEs, 2 in the montelukast group and 3 in the roflumilast group, were reported for 5 patients. All were "not related" to the study drug according to the investigators' assessment.
In addition, 43 AEs experienced by 28 (13%) patients in the roflumilast group led to premature discontinuation. The investigators rated most of these "mild" to "moderate" in intensity. With respect to causality, 28 AEs were assessed "likely" or "definitely related" to roflumilast treatment by the investigator. In the montelukast group, 16 AEs led to premature withdrawal of 12 (5%) patients. All were "mild" to "moderate" in intensity and most were rated "not" or "unlikely related" to the study drug; six were assessed "likely related".
Laboratory tests revealed no apparent changes in laboratory parameters during the trial. However, there were individual abnormalities reported as AE in 7 (3%) patients treated with montelukast and in 5 (2%) patients treated with roflumilast. Measurement of vital signs and physical examination did not reveal any apparent changes during the trial. Both montelukast and roflumilast had no influence on ECG parameters.

Conclusions:

This study demonstrated that 0.5 mg/day roflumilast is effective for treatment of asthmatic patients. Both roflumilast and montelukast effectively increased the lung function parameters FEV_1, FVC, and PEF. The increase was more pronounced in patients treated with roflumilast. However, the predefined level of significant superiority of roflumilast was only reached for the primary variable (change in FEV_1 from T0 to endpoint) in the subgroup (ex-)smokers and for the secondary variable FVC. PEF variability, asthma symptoms, and use of rescue medication improved in both treatment groups.
In total, 41% of patients treated with montelukast and 44% treated with roflumilast experienced AEs. Most of these were judged "unlikely" or "not related" to the study medication. All AEs were easy to manage and did not bear any intolerable risk for the patients. Further, their pattern was expected from similar findings during earlier trials. There was no apparent influence on laboratory parameters, vital signs, ECG or physical examination. Thus the study confirmed the good safety profile and good tolerability of roflumilast.