Synopsis of study report: 27/2003
Location in Module 5:

Study Code:
BY217 M2-026

Report Version:
2.0

Title of the study:

A 12 weeks comparison of 250 µg roflumilast versus 10 mg montelukast in patients with asthma.

Study center(s):

A total of 59 centers participated, located in France (12), Germany (16), Hungary (9), Spain (12), and United Kingdom (10).

Publication (reference):

Not applicable.

Studied period (years):

28-Feb-2002 – 21-Feb-2003.

Clinical phase:

IIIb

Objectives:

The objective of the present study was to compare 250 µg roflumilast with 10 mg montelukast with respect to the effect on pulmonary function, symptoms, use of rescue medication, and quality of life. 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 baseline period of 1 to 3 weeks 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 rescue medication, as well as asthma symptoms daily in a diary throughout the entire study. Further lung function testing (FEV_1, FVC, PEF and $MEF_{25-75\%}$) and safety assessments were performed at clinic visits at start of the treatment period (T0) and 3, 6, 9, and 12 weeks after treatment start (T3, T6, T9, T12).

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

	Planned Per-Protocol	**Intention-to-treat**	**Per-protocol**
Total	n = 346	n = 573	n = 481
250 µg Roflumilast	n = 173	n = 289	n = 241
10 mg Montelukast	n = 173	n = 284	n = 240

Diagnosis and criteria for inclusion:

Patients with a history of asthma (otherwise healthy), aged 15 to 70 years and who showed a FEV_1 between 50 and 80% or 60 and 90% 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 80% of predicted. Furthermore, patients had to show a reversible obstruction (FEV_1 increase ≥ 12% and ≥ 200 ml in response to 0.4 mg salbutamol) on a baseline visit or within 6 month prior to baseline. Patients had to inhale an average of ≥ 1 puff of salbutamol (rescue medication) per day during the last 7 days directly preceding the randomization visit.

Test product:

Roflumilast, 250 µg/tablet.

Dose:

One tablet once daily in the morning.

Mode of administration:

Oral administration.

Batch No.:

Batch nos.: 101180 (roflumilast 250 µg tablets); 101160 (roflumilast placebo tablets).

Duration of treatment:

12 weeks.

Reference product:

Montelukast, 10 mg tablet overencapsulated.

Dose:

One capsule once daily in the evening.

Mode of administration:

Oral administration.

Batch No.:

Batch nos.: 108301 (montelukast 10 mg capsules); 107301 (montelukast placebo capsules).

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.
Efficacy evaluation (secondary):	Spirometry: FEV_1 at earlier visits than endpoint, FVC and PEF, $MEF_{25-75\%}$. Derived from diaries: morning and evening PEF, PEF variability, symptoms and use of rescue medication; proportion of symptom-free days, asthma exacerbations, AQLQ(S)
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 over montelukast (non-inferiority acceptance limit for FEV_1: 200 mL) were performed. Safety parameters were analyzed descriptively.

SUMMARY - CONCLUSIONS

Summary:

Efficacy results:

Primary efficacy variable

The lung function variable FEV_1 at the end of the study ($T_{end/last}$) was analyzed in comparison to T0. The within-treatment comparison revealed a statistically significant FEV_1 increase of 370 ml at T_{end} in both treatment groups. Comparison of treatment groups demonstrated non-inferiority of roflumilast to montelukast. Superiority of roflumilast with regard to the change in FEV_1 could not be shown. A subgroup analysis in non-smokers and (ex-)smokers revealed similar results.

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

Treatment group	n	Differences (T_{end} – T0) LS Mean ± SEM	95% CI	p-value two-sided
Within-treatment differences				
250 µg Roflumilast	207	0.37 ± 0.04	0.30, 0.45	<0.0001
10 mg Montelukast	214	0.37 ± 0.04	0.30, 0.44	<0.0001
Between-treatment differences				
Roflumilast / Montelukast	207 / 214	0.01 ± 0.05	-0.08, 0.10	0.8907

LS Mean = least squares mean; SEM = standard error of the mean;
CI = confidence interval.

Secondary efficacy variables

An increase in FEV_1 in comparison to T0 was seen at the different visits (T3, T6, T9, T12). This increase was statistically significant in both treatment groups. Non-inferiority of roflumilast could be demonstrated at all visits. FVC, $MEF_{25-75\%}$, and PEF from spirometry increased during treatment in both groups to a similar extend. The between-treatment analysis at T_{end} revealed non-inferiority of roflumilast for FVC and PEF. For $MEF_{25-75\%}$ no differences between treatment groups were found.

PP last value analysis of spirometry variables vs. T0

Variable	Treatment group	n	Differences (T_{end} – T0) LS Mean ± SEM	95% CI	p-value two-sided
Within-treatment differences					
FVC (L)	250 µg Roflumilast	207	0.36 ± 0.04	0.27, 0.44	<0.0001
	10 mg Montelukast	214	0.33 ± 0.04	0.25, 0.42	<0.0001
$MEF_{25-75\%}$ (L)	250 µg Roflumilast	207	0.41 ± 0.05	0.31, 0.51	<0.0001
	10 mg Montelukast	214	0.40± 0.05	0.30, 0.50	<0.0001
PEF (L/min)	250 µg Roflumilast	207	78 ± 6	66, 90	<0.0001
	10 mg Montelukast	214	79± 6	67, 92	<0.0001
Between-treatment differences					
FVC (L)	Roflumilast / Montelukast	207 / 214	0.02 ± 0.05	-0.08, 0.12	0.6820
$MEF_{25-75\%}$ (L)	Roflumilast / Montelukast	207 / 214	0.01 ± 0.07	-0.12, 0.14	0.8426
PEF (L/min)	Roflumilast / Montelukast	207 / 214	-1.25 ± 7.99	-17.0, 14.5	0.8758

LS Mean = least squares mean; SEM = standard error of the mean; CI = confidence interval.

The diary variables morning and evening PEF showed a statistically significant increase during both roflumilast and montelukast treatment (comparison $W_{end/last}$ to week before T0). For both variables non-inferiority could be demonstrated for roflumilast, and 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. There was no statistically significant difference between the treatment groups for all diary variables except for the proportion of symptom-free days in favor of montelukast. Quality of life improved in a statistically significant way in both the roflumilast and the montelukast treatment group. Differences between the groups were statistically significant, i.e. quality of life was rated higher in patients treated with montelukast. However, differences between treatment groups did not reach the threshold of the minimal important difference.

There were no marked differences between treatment groups concerning number, duration and onset of asthma exacerbations.

Safety results:

During the trial, 272 (47%) patients experienced 476 AEs; 437 AEs occurred during the treatment period. The percentages of patients experiencing AEs were similar in both treatment groups (roflumilast: 48%, montelukast: 41%). Most AEs were mild to moderate in intensity, 8% (roflumilast treatment group) and 10% (montelukast montelukast treatment group) of AEs were severe.

The majority of AEs in both treatment groups affected the respiratory system (worsening of asthma, bronchitis, and upper respiratory infection) and was therefore related to the underlying disease. In addition, 2% of patients in both treatment groups experienced allergic

reactions, which were mostly related to the underlying allergic predisposition. Headache occurred in at least 5 (2%) patients in both treatment groups. Further AEs in at least 2% of patients treated with roflumilast were diarrhea (2.4%) and back pain (2.1%).
Most AEs (91% in the roflumilast group and 98% in the montelukast group) were rated “not” or “unlikely related” to the study medication. The investigators considered 7% of AEs “likely related” to roflumilast treatment and 2% of AEs “likely related” to montelukast treatment. In total, 4 AEs (diarrhea, dyspepsia) experienced by 2 patients were judged “definitely related” to roflumilast medication (investigators’ assessment).
Overall, 7 serious AEs, three in the roflumilast group and four in the montelukast group, were reported for 6 patients. All were “not related” or “unlikely related” to the study drug according to the investigators’ assessment.
In addition, 41 AEs experienced by 37 (13%) patients in the roflumilast group led to premature discontinuation. The investigators rated most of these AEs “moderate” to “severe” in intensity. With respect to causality, 11 (27%) AEs were assessed “likely” or “definitely related” to roflumilast treatment by the investigator. In the montelukast group, 30 AEs led to premature withdrawal of 24 (9%) patients. All were “moderate” to “severe” in intensity; most (97%) were rated “not” or “unlikely related” to the study drug; 1 AE (3%) was assessed “likely related”. In both treatment groups, the most frequent AE leading to discontinuation was worsening of asthma.

Laboratory tests revealed no apparent changes in laboratory parameters during the study. However, there were individual abnormalities reported as AE in 7 (2%) patients treated with roflumilast and in 11 (4%) patients treated with montelukast. Measurement of vital signs and physical examination did not reveal any apparent changes during the trial. There were no clinically relevant ECG findings after 12 weeks of treatment with either roflumilast or montelukast according to the investigators.

Conclusions:

This study demonstrated that 250 µg/day roflumilast is as effective for treatment of patients with asthma as montelukast 10 mg/day. Both 250 µg roflumilast and 10 mg montelukast increased the lung function parameters FEV_1, FVC, $MEF_{25-75\%}$ and PEF to a similar statistically significant and clinically relevant extend. PEF variability, asthma symptoms, use of rescue medication, and quality of life improved in both treatment groups.

In total, 48% of patients treated with roflumilast and 41% treated with montelukast 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. There was no apparent or clinically relevant influence on laboratory parameters, vital signs, ECG or physical examination. Thus the study confirmed the good safety profile and good tolerability of 250 µg roflumilast, which is comparable to that of 10 mg montelukast.