Synopsis of study report: 45/2005
Location in Module 5:

Study Protocol No.:
BY217/M2-017

Report Version:
1.0

Title of the study:

A comparison of 500 µg Roflumilast versus 10 mg Montelukast. A 24 weeks, double-blind study in patients with Asthma. The PRIME-study (BY217/M2-017)

Investigators:

94 centers in Austria, Brazil, France, Germany, Hungary, India, Mexico, South Africa, Spain, and the United Kingdom.

Study center(s):

Multicenter study at 94 investigational sites in 10 countries (Austria, Brazil, France, Germany, Hungary, India, Mexico, South Africa, Spain, and the United Kingdom).

Publication (reference): Not yet published.

Studied period (years): 23-Oct-2003 (first patient in) to 23-Nov-2004 (last patient out)

Clinical phase: Phase IIIb

Objectives:

The main objective of this study was to compare the effect of roflumilast 500 µg in the morning po (per os) od (once daily) with montelukast 10 mg in the evening po od, administered for 24 weeks, on lung function, symptoms, QoL (quality of life), health economics, and use of rescue medication in patients suffering from asthma.

Further, the safety and tolerability of roflumilast were investigated.

Methodology:

The present study has a randomized, double-blind, double-dummy, parallel group design. It consisted of a single-blind placebo baseline period of one to three weeks (Visits B0, B1, if

applicable B2 and B3), followed by a 24-week treatment period (Visits T0, T4, T8, T12, T16, T20, and T24), and a follow-up period (if necessary). Patients were allowed to use salbutamol as rescue medication throughout the study. During baseline, they withdrew their previous controller medication, if applicable, and received placebo. At Visit T0, eligible patients were randomized to one of the treatment groups (ratio 1:1). During the treatment period they took either roflumilast 500 µg od in the morning or montelukast 10 mg od in the evening.

Lung function (FEV_1, FVC, $MEF_{25-75\%}$, and PEF) was measured during baseline at Visits B0, B1, B2, and B3 (the latter two visits only if applicable) and during treatment at Visits T4, T8, T12, and T16, T20, T24/T_{end}). Throughout the study patients recorded their morning and evening PEF, use of rescue medication, and asthma-related symptoms in an electronic diary. QoL was assessed at Visits B0, B1, (B2 and B3, if applicable), T12, and T24/T_{end}. Adverse events (AEs) and use of concomitant medication were documented by the investigator throughout the study. Standard laboratory investigations were made at baseline, Visits T12, and T_{end}, and a follow-up visit, if necessary. Physical examination was performed at Visits B0 and T_{end}, and a follow-up visit (if applicable). Vital signs (blood pressure [BP] and heart rate [HR]) were assessed at each study visit.

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

	Enrolled	Randomized	Safety set	Valid cases set
Roflumilast 500 µg		472	472	349
Montelukast 10 mg		486	485	354
Total	**1213**[1]	**958**	**957**	**703**

No patient was randomized more than once, therefore the safety set was identical to the full analysis set.

Diagnosis and criteria for inclusion:

Inclusion criteria (at Visit B0)

Outpatients (aged 15 to 70 years) of either sex who gave written informed consent and who met the following criteria were included into the study:

- diagnosis of persistent chronic bronchial asthma (with reference to the GINA [Global Initiative for Asthma] guidelines 2002);
- baseline FEV_1 % predicted had to be:
  - 50 to 80 % in patients either untreated or receiving any asthma medication except ICS; eg short-acting bronchodilators, DSCG (disodiumchromoglycate), nedocromil, anticholinergics, long-acting bronchodilators, theophylline/aminophylline, lipoxygenase inhibitors, alone or in combination;

[1] One patient was additionally included in the total set who experienced an SAE before baseline.

- ♦ 60 to 90 % in patients receiving not more than 500 µg (ex actuator) BDP-CFC (beclomethasone dipropionate-chlorofluorocarbon) or equivalent; and/or in combination with any other asthma medication mentioned above;
- no change in the asthma treatment 4 weeks prior to baseline period;
- patients who were in good health, with the exception of asthma.

Randomization criteria (at Visit T0)
After the baseline period (1 to 3 weeks), patients were randomized if they fulfilled the following criteria:

- FEV_1 between 50 and 80 % predicted at Randomization Visit T0, ie the last baseline visit, when salbutamol (rescue medication) was withheld for at least 4 h prior to the measurement;
- positive reversibility test within 6 months before or during baseline, ie an increase of initial FEV_1 ≥12% and ≥0.200 L at 15 to 30 min after inhalation of 200 to 400 µg salbutamol;
- ≥1 puff/d salbutamol (rescue medication) on average during the last week directly preceding the Randomization Visit T0. Visit Days B0 and T0 were not taken in account.

Patients who did not fulfill the randomization criteria after 3 weeks of baseline were excluded from further study participation.

Test product: roflumilast

Dose: one tablet of 500 µg od in the morning
Mode of administration: oral administration
Batch No.: 420210
Duration of treatment: 24 weeks

Reference product: montelukast

Dose: one capsule of 10 mg od in the evening
Mode of administration: oral administration
Batch No.: 230457
Duration of treatment: 24 weeks

Criteria for evaluation:

Efficacy
Primary variable
- FEV_1 (time-averaged excess AUC between T0 and endpoint);

Secondary variables
- FEV_1 (change from baseline [T0]);
- FVC, PEF, $MEF_{25-75\%}$ (AUC, change from baseline);
- AQLQ(S) overall and domain scores (AUC, change from baseline);

- morning PEF and evening PEF (AUC and change from baseline), and diurnal PEF variability (diary);
- asthma symptom scores (diary);
- daily use of rescue medication (diary);
- proportion of asthma symptom- and rescue medication-free days;
- asthma exacerbations requiring intake of oral or parenteral steroids.

Safety

Secondary variables

- AE assessment;
- standard laboratory workup;
- physical examination;
- BP and HR.

Statistical methods:

Spirometric lung function variables, AQLQ(S) scores, as well as morning and evening PEF from diary were analyzed with an ANCOVA. The dependent variable was calculated either as time-averaged excess AUC or change between T0 and endpoint. Beside the treatment, the following factors and co-variables were included in the model: value at T0, age, sex, country, and smoking status. No interaction term was included in this model. An analogous ANCOVA model was calculated using change from baseline. With regard to the primary variable FEV_1, the comparison between treatments was based on the differences of T_{end} (PP [per-protocol] analysis) or T_{last} (ITT [intention-to-treat] analysis) and the baseline value at randomization (Visit T0). These between-treatment comparisons for non-inferiority and superiority were performed in a closed test procedure. The PP analysis was the primary efficacy analysis for non-inferiority testing and the ITT analysis for superiority testing, respectively. The non-inferiority acceptance limit for FEV_1 was -0.100 L. Note that for interpretation the lower limit of the 95% confidence interval has to be above that margin.

Diurnal PEF variability, asthma symptom scores, daily use of rescue medication, and proportion of symptom- and rescue medication-free days were analyzed non-parametrically (change from T0) and parametrically (time-averaged excess AUC). Differences between treatments were analyzed with the Mann-Whitney U-Test; within-group differences were analyzed with Pratt's modification of Wilcoxon’s signed rank test.

Frequencies and percentages of occurrence of asthma exacerbations were provided and between-treatment differences of the time to onset of the first asthma exacerbation were analyzed using a logrank test.

Descriptive statistics were given for AEs, laboratory variables, and vital signs.

A sample size of at least 464 patients per group was chosen to achieve a power of 90% in correctly concluding non-inferiority of roflumilast 500 µg to montelukast 10 mg with regard to the primary variable 'difference in FEV_1'.

SUMMARY - CONCLUSIONS

Summary:

In total, 958 patients were randomized, and 957 patients were included in the full analysis set (472 patients treated with roflumilast 500 µg and 485 patients treated with montelukast 10 mg). Of these, 703 patients (349 patients in the roflumilast 500 µg group and 354 patients in the montelukast 10 mg group) had no major protocol violations and were included in the valid cases set.

In demography data no differences were observed between the two treatment groups. The majority of patients were Caucasian (≥78%). Most patients had severe persistent asthma (≥69%) and were described as non-smokers (≥73%), with smaller numbers of patients classified as ex-smokers or current smokers.

Demographic and other baseline characteristics by treatment (full analysis set)

		Rof500 (N = 472)	Mon10 (N = 485)
Age [years]	Median (range)	42 (15, 70)	42 (15, 70)
Weight [kg]	Mean ± SD	75 ± 18.1	76 ± 19.2
Height [cm]	Mean ± SD	167 ± 10.1	168 ± 10.0
Sex [n (%)]	Female	255 (54.0)	242 (49.9)
	Male	217 (46.0)	243 (50.1)
Race [n (%)]	Asian	70 (14.8)	72 (14.8)
	Black	15 (3.2)	14 (2.9)
	Caucasian	371 (78.6)	378 (77.9)
	Other	16 (3.4)	21 (4.3)
Asthma severity (GINA) [n (%)][a]	Mild persistent	4 (0.8)	2 (0.4)
	Moderate persistent	55 (11.7)	59 (12.2)
	Severe persistent	326 (69.1)	333 (68.7)
	Not available	87 (18.4)	91 (18.8)
Smoking status [n (%)]	Non-smokers	346 (73.3)	356 (73.4)
	Ex-smokers	82 (17.4)	83 (17.1)
	Current smokers	44 (9.3)	46 (9.5)
Pack years [n][b]	Mean ± SD	5 ± 3.2	5 ± 2.9
FEV_1 at T0 [L][c]	Mean ± SD	2.127 ± 0.581	2.164 ± 0.611
predicted [%][d]	Mean ± SD	68.1 ± 9.1	67.8 ± 9.3
FEV_1 rev. at B0 [% increase][e]	Mean ± SD	20.4 ± 12.5	20.3 ± 13.0

[a] The classification according to GINA was not performed as planned in the Study Protocol, but as post-hoc stipulated. [b] Rof500: n = 126, Mon10: n = 129 (subset current and ex-smokers). [c] Rof500: n = 459; Mon10: n = 460 (ITT analysis). [d] Rof500: n = 458; Mon10: n = 459 (ITT analysis). [e] Rof500: n = 455; Mon10: n = 463.
Mon10 = montelukast 10 mg od, n = number of patients with data available, rev. = reversibility, Rof500 = roflumilast 500 µg od, SD = standard deviation.

Efficacy results

The primary variable FEV_1 (calculated as time-averaged excess AUC) increased in both treatment groups between T0 and $T_{end/last}$ (by 0.180 L in the roflumilast 500 µg group and by 0.212 L in the montelukast 10 mg group, PP). Non-inferiority of roflumilast 500 µg to montelukast 10 mg was demonstrated (one-sided p = 0.0112). The results were confirmed in the ITT analysis: increases of 0.181 L under roflumilast 500 µg and 0.188 L under montelukast 10 mg were observed. Superiority of roflumilast 500 µg over montelukast 10 mg was not shown. In the secondary analysis of FEV_1, within-treatment changes between T0 and T_{last} revealed improvements in both treatment groups (endpoint and repeated measurement analyses), confirming the primary analysis. The difference between treatments was not statistically significant.

Time-averaged excess AUC of FEV_1 [L]: endpoint analysis (PP, ITT)

WITHIN			Time-averaged excess $AUC_{(T0, T_{end/last})}$		
		n	LSMean ± SE	95% CI	p-value[a]
PP	Rof500	241	0.180 ± 0.023	0.135, 0.225	<0.0001
	Mon10	265	0.212 ± 0.023	0.167, 0.257	<0.0001
ITT	Rof500	450	0.181 ± 0.018	0.145, 0.217	<0.0001
	Mon10	448	0.188 ± 0.018	0.152, 0.224	<0.0001

BETWEEN					Difference Test - Ref.			
	Test	Ref.	n Test	n Ref.	LSMean ± SE	95% CI	p-value non-inf.[b]	p-value sup.[c]
PP	Rof500	Mon10	241	265	-0.032 ± 0.030	-0.090, 0.027	0.0112	0.8573
ITT	Rof500	Mon10	450	448	-0.007 ± 0.024	-0.054, 0.040	0.0001	0.6122

[a] Two-sided p-value for within-treatment differences, significance level 5%.
[b] One-sided p-value for non-inferiority, significance level 2.5%, margin = -100 mL
[c] One-sided p-value for superiority, significance level 2.5%.
AUC = area under the curve (calculated as time-averaged excess), CI = confidence interval, FEV_1 = forced expiratory volume in one second, LS = least squares, Mon10 = montelukast 10 mg od, n = number of patients with data available at endpoint, Ref. = reference, Rof500 = roflumilast 500 µg od, SE = standard error of the LSMean, T0 = randomization visit, T_{end} = last visit PP analysis, T_{last} = last visit ITT analysis.

Statistically significant improvements within both treatments were seen in the AUC of the secondary spirometry variables FVC, PEF, and $MEF_{25-75\%}$. The differences between treatment groups were not clinically relevant (all not statistically significant). The results were confirmed in the change from baseline and repeated measurement analyses.

The AUC of morning PEF showed improvements within both treatments (statistically significant with montelukast 10 mg); evening PEF improved slightly with montelukast 10 mg and decreased slightly with roflumilast 500 µg. The between-treatment differences were numerically in favor of montelukast 10 mg. Results were similar in the change from baseline analysis. PEF variability decreased numerically in both treatment groups. The between-treatment difference was in favor of montelukast 10 mg.

Asthma symptom scores (sum, daytime, and nighttime) decreased with both treatments statistically significantly (analyzed as AUC), indicating an improvement. The small differences between treatments were numerically in favor of montelukast 10 mg. Results were similar in the change from baseline. The same holds true for the use of rescue medication and the % of asthma symptom-free and rescue medication-free days.

Improvements in QoL (assessed by AQLQ(S)) were statistically significant for the overall score and all domain scores in both treatment groups (change from baseline). The improvements were numerically small and did not reach the minimal important difference of 0.5. Differences between the treatment groups were in favor of montelukast 10 mg, but were not clinically relevant.

The percentages of patients experiencing asthma exacerbations were similar in both treatment groups (6.6% in the roflumilast 500 µg and 7.0% patients in the montelukast 10 mg group).

The median time to onset of the first asthma exacerbation was longer in patients treated with roflumilast 500 µg (58 days) than in patients treated with montelukast 10 mg (38 days). There was no relevant difference in the duration of severe asthma exacerbations and the sum of exacerbation days during treatment.

Safety results

During the treatment period, 358 (75.8%) patients in the roflumilast 500 µg group and 322 (66.4%) patients in the montelukast 10 mg group experienced AEs. Most frequently, AEs affected the respiratory system; asthma aggravated was the most common AE reported by 37.5% of patients in the roflumilast 500 µg group and by 36.7% of patients in the montelukast 10 mg group. Gastrointestinal disorders and headache were more frequently reported in the roflumilast 500 µg group than in the montelukast 10 mg group. This is in line with the known safety profile of roflumilast.

Most AEs were moderate in intensity in the roflumilast 500 µg group and mild in the montelukast 10 mg group. AEs at least likely related to study medication were reported for 69 (14.6%) patients in the roflumilast treatment group and 23 (4.7%) patients in the montelukast treatment group.

During treatment, 17 (3.6%) patients experienced 21 SAEs in the roflumilast 500 µg group and 9 (1.9%) patients reported 11 SAEs in the montelukast 10 mg group. One patient treated with roflumilast 500 µg (CRF ID 81308) died of the SAEs bronchiolitis with consecutive acute pulmonary hyperinflation (increased expiratory reserve volume). Two SAEs were reported after the end of the treatment period (one in each treatment group).

More patients discontinued due to AEs in the roflumilast 500 µg group (104 [22.0%] patients) than in the montelukast 10 mg group (69 [14.2%] patients). Of these, six patients in the roflumilast 500 µg group (including the dead) and four patients in the montelukast 10 mg group discontinued due to SAEs.

Overall, no clinically relevant changes in hematology, biochemistry, and urinalysis values were observed in both treatment groups during the course of the study. During treatment, 29 patients in the roflumilast 500 µg group and 31 patients in the montelukast 10 mg group experienced AEs associated with abnormal laboratory values.

Physical examination, BP, and HR measured during the study period did not reveal any influence of the two different treatments.

Conclusions:

Both treatments were effective in improving lung function and the majority of secondary efficacy variables in asthma. Non-inferiority of roflumilast to montelukast was demonstrated regarding the primary variable FEV_1. The known safety profile of roflumilast was not changed by this study.