Synopsis of study report: 70/2002
Location in Module 5:

Study Code:
BY217/FK1 009

Report Version:
Version 2.0

Title of the study:
12 weeks treatment with 500 µg roflumilast versus 400 µg beclomethasone dipropionate in patients with asthma. A double-blind, double-dummy, randomized parallel group study.

Study center(s): Multinational: 51 centers in France, Germany, Spain, and the United Kingdom

Publication (reference): Not applicable.

Studied period (years):
09 October 2000 - 31 October 2001

Clinical phase:
III

Objectives:
- To compare the effect of oral roflumilast (500 µg/day during 12 weeks) in comparison to 400 µg inhaled BDP on pulmonary function, asthma symptoms and concomitant use of rescue medication in patients with bronchial asthma.
- To assess the safety and tolerability of the 12-week treatment with oral roflumilast.

Methodology:

The trial was conducted as a double-blind, double-dummy, randomized parallel group multicenter study with a single-blind placebo baseline period. After a baseline period of 1-3 weeks (visits B0 to B3), eligible patients were randomly allocated to one of two treatments (at a ratio of 1:1), so that they received either 500 µg/day roflumilast (1 tablet of 500 µg, s.i.d., p.o.) or else 400 µg/day BDP (MDI, 2 x 100 µg/puff, b.i.d.) for a treatment duration of 12 weeks. According to the double-dummy design, patients of the roflumilast group inhaled placebo (2 puffs, b.i.d.) and patients of the BDP group were given placebo tablets (1 tablet, s.i.d., p.o.). Lung function (FEV_1, FVC, PEF) was measured at baseline (B0 and B1; at B2 and B3 only if applicable) and at each subsequent visit (T0, T3, T6, T9, T12, where T0 corresponds to the last baseline visit). Patients also recorded morning and evening PEF throughout the trial. Further, they documented their daily use of rescue medication and their asthma symptoms in a diary.

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

In total, 633 patients were enrolled into the study, and 499 of them were randomized (n=253 roflumilast, n=246 BDP). From these patients, 485 (n=243 roflumilast, n=242 BDP) had paired T0 and Tlast values and were considered in the extended intention-to-treat (itt) analysis of the primary variable FEV_1. In the itt-analysis of FEV_1, there were 466 patients (n=230 roflumilast, n=236 BDP) with paired T0 and Tlast values. The per-protocol (pp) population consisted of 421 patients (n=207 roflumilast, n=214 BDP); 326 of them (n=153 roflumilast, n=173 BDP) had paired T0 and Tend values and were available for the pp-analysis of FEV_1.

Diagnosis and criteria for randomization and inclusion into treatment:

Patients with bronchial asthma, aged 12-70 years, and having baseline FEV_1-values between 50-100% predicted depending on pretreatment, were eligible. For randomization (at visit T0), patients were required to have FEV_1-values between 50-85% predicted when salbutamol had been withheld 4 hours prior to the measurement; during the last 7 days before randomization, patients also had to be characterized by asthma symptom scores ≥ 1, and by the use of salbutamol as rescue medication ≥ 1 puff/day. In addition, patients had to show **either** a reversibility of FEV_1 ≥ 15% initial (at baseline or 3 months prior to B0) **or** a diurnal PEF variability ≥ 15% during at least 3 of the 7 days preceding randomization.

Test product:

Roflumilast

Dose and mode of administration:

One tablet of 500 µg (s.i.d.), p.o.

Batch No.: 499110

Group 1: One tablet roflumilast was taken on each of day of the treatment period; additionally, placebo was inhaled (MDI, 4 puffs/day i.e. 2 puffs b.i.d.; batch No. CT991001)

Duration of treatment:

12 weeks

Active reference product:

Beclomethasone dipropionate (BDP)

Dose:

400 µg (2 x 100 µg b.i.d.)

Mode of administration:

p. inh. with an MDI device

Batch No.: D004856

Group 2: BDP (200 µg b.i.d.) was inhaled with an MDI device (2 puffs of 100 µg BDP in the morning and 2 puffs in the evening). Patients of this reference group were also given placebo tablets (1 tablet s.i.d.; batch No. 199110)

Criteria for evaluation:

- primary variable: mean change of the forced expiratory volume in one second (FEV_1) between visit T0 (randomization) and the endpoint of the study.
- secondary variables: FEV_1 at visits earlier than endpoint, FVC, PEF from spirometry, morning and evening PEF from diaries, PEF variability, asthma symptoms, proportion of symptom-free days, use of rescue medication (puffs/day, %rescue medication-free days), effectiveness rating by investigators/patients, dropouts rate due to escape criteria, number and timepoint of asthma exacerbations, safety parameters (laboratory values, physical examination, ECG, BP, HR), adverse events.

Statistical methods:

To analyze lung functions and test non-inferiority of roflumilast to BDP, an analysis of covariance was applied, including treatment, gender and center/country as factors, and the value at randomization and age as covariates. Non-inferiority acceptance limits were 200 mL for FEV_1 and FVC, and 25 L/min for PEF. Changes in PEF variability, asthma symptom scores, symptom-free days, use of rescue medication and rescue medication-free days were analyzed non-parametrically (Wilcoxon-Pratt signed-rank test within groups, Mann-Whitney

U-test between groups). The timepoints of dropouts due to escape crietria were analyzed by means of the log-rank test (survival analysis). All other secondary variables were analyzed in a descriptive manner.

SUMMARY - CONCLUSIONS

Efficacy results:

The present study suggests that a daily dose of 500 µg roflumilast taken over 12 weeks is statistically non-inferior to 400 µg BDP in its therapeutical efficacy. This holds true for the primary variable FEV_1. In both treatment groups, improvements in lung function were observed already after three weeks of double-blind treatment. After 12 weeks of treatment, the mean FEV_1 of 72% predicted could be raised to about 82% predicted in patients of both groups: this clinically relevant increase in FEV_1 (LS means) amounted to 300 ml in the roflumilast group and 370 ml in the BDP group.

FEV_1 (L), pp-analysis:

		$T0_{(paired)}$	T0	Tend	Tend-T0	p-value
		Mean	LS-Mean		LS-Mean (95%-CI*)	two-sided
500 µg roflumilast	(n=153)	2.34	2.29	2.59	0.30 (0.23, 0.37)	<0.0001
400 µg BDP	(n=173)	2.25	2.29	2.66	0.37 (0.30, 0.43)	<0.0001

*CI: confidence interval

A statistically significant increase in FVC and PEF from spirometry was observed in both treatment groups.

Analogous results were obtained for all secondary variables (e.g. increased morning and evening PEF from diaries, decrease in the use of rescue medication, reduction in asthma symptoms, improved effectiveness rating by patients and by investigators).

Morning PEF from diary (L/min), pp-analysis:

		$W0^*_{(paired)}$	W0	Tend	Tend-W0	p-value
		Mean	LS-Mean		LS-Mean (95%-CI*)	two-sided
500 µg roflumilast	(n=172)	352	356	378	22 (13, 30)	<0.0001
400 µg BDP	(n=193)	359	356	383	27 (19, 35)	<0.0001

*W0: Week 0 (prior to T0); CI: confidence interval

There was a statistically significant decrease in **PEF variability** in both treatment groups (median changes: -2.35% in the roflumilast group vs -1.85% in the BDP group for the pp-analysis).

Regarding asthma control, roflumilast was comparable to BDP in reducing the **use of rescue medication** (decrease in median of 1.29 puffs/day in each treatment group) and the **asthma symptoms** (with a decrease in the score sum of 1.01 for roflumilast and 1.07 for BDP).

Rescue medication, no. puffs/day (median change within treatments), pp-analysis:

		$W0_{(paired)}$ Median	Tend	Tend-W0 Median (95%-CI*)	p-value two-sided
500 µg roflumilast	(n=171)	2.57	0.86	-1.29 (-1.43, -0.93)	<0.0001
400 µg BDP	(n=193)	2.57	0.71	-1.29 (-1.64, -1.14)	<0.0001

*CI: confidence interval (non-parametric)

Asthma symptoms (median change within treatments), pp-analysis:

		$W0_{(paired)}$ Median	Tend	Tend-W0 Median (95%-CI*)	p-value two-sided
500 µg roflumilast	(n=160)	2.33	1.14	-1.01 (-1.22, -0.83)	<0.0001
400 µg BDP	(n=179)	2.00	1.00	-1.07 (-1.25, -0.85)	<0.0001

*CI: confidence interval (non-parametric)

Effectiveness ratings: The 12-week roflumilast treatment was rated as "very effective" or "effective" by 72% of the patients and 72% of the investigators. This is comparable to the effectiveness ratings of "very effective" or "effective" obtained in 76% of the patients and of the investigators for the BDP treatment.

Asthma exacerbations: There were overall 17 patients (13 [5%] from the roflumilast group, 4 [1.6%] from the BDP group) who experienced asthma exacerbations. The duration of these asthma exacerbations was comparable in the two treatment groups (median: 8 days in the roflumilast group and 7 days in the BDP group). The time to onset of asthma exacerbations was earlier in the roflumilast group (median:27 days) than in the BDP group (median: 36 days). In 10 cases (9 patients from the roflumilast group and one patient from the BDP group), asthma exacerbations did lead to dropout.

The exploratory subgroup analyses indicated that "non-smokers" and "smokers/ex-smokers" did not differ from the total population with regard to the improvement in FEV_1 in the two treatment groups.

Safety results:

Safety data indicate that oral roflumilast (500 µg s.i.d.) as well as inhaled BDP (200 µg b.i.d.) administered during 12 weeks were in general well tolerated in the present trial. During the

treatment period, AEs were reported by 45% of the patients treated with roflumilast and by 30% of those treated with BDP.

In general, the reported adverse events were mild in intensity and were considered as unrelated or unlikely related to the trial medication by the investigator. AEs were reported more frequently for the respiratory system (asthma, upper respiratory infection, bronchitis, rhinitis, sinusitis, increased cough, and pharyngitis). Among the most frequently reported AEs, the symptoms which were considered "likely or definitely related" to the study medication by investigators included nausea (n=11 roflumilast group; n=1 BDP group), headaches (n=7 roflumilast group; n=1 BDP group) and diarrhea (n=5 roflumilast group).

There was no death during the present study, and there was no serious AE (SAE) with likely or definite causal relationship to the study medication. A total of 6 SAEs were experienced by 5 patients (3 in the roflumilast group and 2 in the BDP group) during the treatment period.

Overall, 46 AEs experienced by 37 patients of the roflumilast group and 9 AEs experienced by 8 patients of the BDP group led to withdrawal from the study. Only in two patients were these AEs serious. In both groups, patients withdrew most often due to asthma worsening.

In the present study, a 12-week treatment with roflumilast or BDP was not associated with clinically relevant alterations in laboratory values. In addition, physical examination, ECG, blood pressure and heart rate measured during treatment did not reveal any influence of study medication.

Conclusions:

In the present study, roflumilast administered during 12 weeks was statistically non-inferior to BDP in its therapeutic efficacy. Both roflumilast and BDP significantly improved lung function as measured by FEV_1, FVC, PEF from spirometry. Both treatments also resulted in significant improvements regarding the morning and evening PEF from diary. Regarding asthma control, roflumilast was comparable to BDP in reducing asthma symptoms and the need for rescue medication.

Overall, results indicate that once-daily doses of 500 µg roflumilast is non-inferior to twice-daily doses of 200 µg BDP (400 µg/day) in treating bronchial asthma. Further, the safety data point to a good tolerability of roflumilast during a 12-week treatment.