Synopsis of study report: 366/2003
Location in Module 5:

Study Protocol No.:
BY217/M2-014

Report Version:
1.0

Title of the study:

Efficacy and safety of roflumilast 500 µg once daily compared with placebo as an add-on therapy to fluticasone propionate 125 µg twice daily over 24 weeks in patients with asthma

Investigators:

Investigators at 126 centers in Australia, Belgium, Czech Republic, Germany, Hungary, The Netherlands, Poland, Russia, Spain, and the United Kingdom.

Study center(s):

A total of 126 centers were initiated for this study. The sites were located in Australia, Belgium, Czech Republic, Germany, Hungary, The Netherlands, Poland, Russia, Spain, and the United Kingdom

Publication (reference):

Not applicable

Studied period (years):

09-DEC-2002 (first patient in) to 02-DEC-2003 (last patient out)

Clinical phase:

IIIa

Objectives:

The study compared the effect of roflumilast 500 µg once daily (od) with placebo as an add-on therapy to FP 125 µg bid, administered for 24 weeks, on pulmonary function, asthma symptoms, quality of life, health economics evaluation, and use of rescue medication in patients suffering from asthma. Safety and tolerability of roflumilast were also monitored.
Forced expiratory volume in one second (FEV_1), was the primary variable, i.e. change between randomization (Visit T0) and endpoint. The change from baseline (W0) in the average weekly amount of rescue medication used per day was assessed as a co-primary variable. All other data were evaluated as secondary variables.

Methodology:

This was a multi-center, double-blind, randomized, parallel-group study with a single-blind placebo baseline period consisting of 2 weeks (baseline visits at weeks 0 and 2 [B0 and B2]). All patients received FP at a dose of 125 µg bid during the study. During the treatment period of 24 weeks (treatment visits at 0, 2, 4, 8, 12, 18 and 24 weeks after randomization [T0, T2, T4, T8, T12, T18, T24]) patients received either roflumilast (500 µg od) or placebo added to FP 125 µg bid.

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

	Full Analysis Set (FAS)	Valid Cases Set (VCS)
FP+roflumilast 500 µg	322	268
FP+placebo	339	292
Total	661	560

Diagnosis and criteria for inclusion:

Patients of either sex who gave their written informed consent, 18 to 70 years old, with diagnosed bronchial asthma (NIH guideline criteria), and a baseline FEV_1 (% predicted) of 50 to 80% in patients receiving ≥ 400 µg to ≤ 500 µg beclomethasone dipropionate-chlorofluorocarbons (BDP-CFC or equivalent) or 60 to 90% in patients receiving between > 500 µg and ≤ 1000 µg BDP-CFC (or equivalent), who had no change in the asthma treatment in the 4 weeks prior to visit B0, and were, with the exception of asthma, in good health, could enter the study.

After 2 weeks of baseline treatment, patients were randomized if their FEV_1 was ≥ 50% and ≤ 80% predicted, if reversibility of FEV1 was ≥ 15% after salbutamol inhalation, and ≥ 1 puff/d salbutamol was taken on average during the 7 d directly preceding Visit T0 **and** asthma symptom score (24 h) was ≥ 1 on average during the 7 d directly preceding Visit T0.

Main exclusion criteria were: poorly controlled asthma, lower airway infection in the last 4 weeks, use of oral or parenteral steroids or inhaled steroids < 400 µg/d or > 1000 µg/d BDP (or equivalent) during the last 4 weeks, COPD or other relevant lung diseases, heavy smoking, and pregnancy, breast feeding or lack of reliable contraception.

Test product: Roflumilast added to FP 125 µg bid (Flixotide® (FP) Evohaler®, batch no. D029647)
Dose: 500 µg od in the morning
Mode of administration: oral tablet
Batch No.: 120170

Duration of treatment:

Two weeks baseline, 24 weeks treatment (randomized 1:1)

Reference product: Matched placebo added to FP 125 µg bid (Flixotide® (FP) Evohaler®, batch no. D029647)
Dose: od in the morning
Mode of administration: oral tablet
Batch No.: 410190, 320220

Criteria for evaluation:

Primary efficacy variable:

FEV_1 [L] (change between randomization visit T0 and endpoint)

Co-primary efficacy vaiable:

Weekly average of rescue medication use [puffs/d] (change between baseline and endpoint)

Secondary efficacy variables:

AUC of FEV_1; absolute values and AUC of FVC, PEF, $FET_{100\%}$, MEF_{25-75}; morning and evening PEF, PEF variability, AQLQ(S) overall and inidvidual scores, asthma symptom scores, symptom and rescue medication free days, severe asthma exacerbations

Safety:

Adverse events, routine laboratory tests (hematology, biochemistry, urinalysis), ECG, vital signs, physical examination

Statistical methods:

The primary variable, secondary lung function variables, and AQLQ(S) were analyzed with an ANCOVA. Beside treatment, the following factors were included in the model: baseline value of the respective variable, age, gender, and center. The co-primary variable was analyzed using a Mann-Whitney U-test and Wilcoxon signed-rank test.
Non-parametric analyses were also performed for asthma symptom score, symptom-free or rescue medication-free days, AQLQ(S), and severe exacerbations. For the primary and the co-primary variable, a hierarchical testing procedure was followed. The overall level of significance was 5% (two-sided), corresponding to 2.5% (one-sided).

SUMMARY - CONCLUSIONS

Summary:

Demographic characteristics of the treatment groups are shown below

Demographic characteristics (FAS, N = 661)

		FP+roflumilast 500 µg	FP+placebo
Median age (range) [y]		47.0 (18 – 70)	46.0 (18 – 70)
Gender, N (%)	male / female	114 (35) / 208 (65)	144 (42) / 195 (58)
Smoking, N (%)	non- / ex- / current smoker	250 (78) / 50 (16) / 22 (7)	254 (75) / 48 (14) / 37 (11)
FEV_1 % predicted at T0, mean ± SD		71.5 ± 9.1	70.4 ± 8.8

FAS = full analysis set, FEV_1 = forced expiratory volume in one second, SD = standard deviation

Efficacy

Results are summarized for the primary ITT analysis.

The primary variable was the change in **FEV_1** (T0 to endpoint). Statistically significant increases in FEV_1 were observed in both treatment groups. The increase was greater with FP+roflumilast 500 µg (LSMean = 0.378 L) than with FP+placebo (LSMean = 0.311 L). The difference between the groups was in favor of FP+roflumilast 500 µg (difference in LSMeans = 0.068 L) but did not reach statistical significance (one-sided p = 0.0555). However, a secondary analysis of FEV_1 based on the time-averaged excess AUC showed statistically significant between-treatment differences in favor of FP+roflumilast 500 µg (mean difference = 0.068 L, one-sided p = 0.0205).

Change in FEV_1 [L] from T0 - endpoint analysis (ITT)

WITHIN		**T0**			**T_{last}**	**T_{last} – T0**		
	n	**Mean**	**% pred.**	**LSMean**	**LSMean**	**LSMean ± SEM**	**95%CI**	**p-value[a]**
FP+rof500	313	2.173	71.2	2.202	2.581	0.378 ± 0.035	0.309, 0.448	<0.0001
FP+pbo	336	2.229	70.4	2.202	2.513	0.311 ± 0.034	0.244, 0.377	<0.0001
BETWEEN				**n**	**n**	**Difference Test - Ref. for T_{last} - T0**		
	Test	**Reference**		**Test**	**Reference**	**LSMean ± SEM**	**95%CI**	**p-value[b]**
	FP+rof500	FP+pbo		313	336	0.068 ± 0.043	-0.016, 0.151	0.0555

[a] p-value for within-treatment differences (ANCOVA), two-sided, significance level 5%;
[b] p-value for between-treatment differences (ANCOVA), one-sided, significance level 2.5%.
CI = confidence interval, FEV_1 = forced expiratory volume in one second, FP = fluticasone propionate 125 µg bid, LS = least squares, n = number of patients with data available at T0 and endpoint, pbo = placebo, rof500 = roflumilast 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).

With respect to within-treatment changes in FEV_1 at each visit, consistently higher increases were seen with FP+roflumilast 500 µg than with FP+placebo. A statistically significant difference between the treatment groups in favor of FP+roflumilast 500 µg was seen at Visit T18 (difference in LSMeans = 0.112 L, one-sided p = 0.0063).

The co-primary variable was the change in the weekly average of the daily number of puffs of **rescue medication use** from W0 to study endpoint. As the hypothesis of the first comparison for the primary variable could not be rejected, the results for the co-primary analysis are merely descriptive. In both groups, the weekly average of daily rescue medication use decreased statistically significantly. The decrease was greater with FP+roflumilast 500 µg (-1.00 puffs/d) compared with FP+placebo (-0.95 puffs/d). There was no statistically significant difference between the treatment groups.

Secondary spirometry variables were FVC, PEF, $FET_{100\%}$, and $MEF_{25-75\%}$. For all these variables, statistically significant increases were seen in both treatment groups. The increases were consistently higher with FP+roflumilast 500 µg. Although numerically in favor of FP+roflumilast 500 µg, the differences between the groups were not statistically significant.

Throughout the study, consistently higher increases from W0 in **morning PEF** were observed with FP+roflumilast 500 µg than with FP+placebo. The endpoint analysis showed an increase in morning PEF, which was statistically significant in the FP+roflumilast 500 µg group (LSMean = 8 L/min, two-sided p = 0.0461), but not in the FP+placebo group (LSMean

= 2 L/min). The difference between the treatment groups was not statistically significant. With respect to **evening PEF**, similar changes were observed during the study in both treatment groups. The difference between the treatment groups was in favor of FP+roflumilast 500 µg in the endpoint analysis but did not reach statistical significance.

Improvements in **asthma symptoms** were seen in both treatment groups as indicated by statistically significant decreases in symptom score sum, as well as in the nighttime and the daytime score. The decreases were consistently greater with FP+roflumilast 500 µg than with FP+placebo. The between-treatment analysis showed no statistically significant differences.

The median percentage of **symptom-free days** was higher with FP+roflumilast 500 µg (11.7%) compared with FP+placebo (10.0%), while the median percentage of **rescue-medication-free days** was lower with FP+roflumilast 500 µg (13.0%) compared with FP+placebo (14.6%). There were no significant between-treatment differences.

The **AQLQ(S)** overall score showed statistically significant within-treatment increases (indicating an improvement) in both treatment groups. The increases were similar with FP+placebo (LSMean = 0.49) than with FP+roflumilast 500 µg (LSMean = 0.44). The between-treatment differences were small and not statistically significant, neither for the overall score nor for any individual score.

The percentage of patients who experienced **severe asthma exacerbations** was similar in the FP+roflumilast 500 µg group [67 (20.8%)] and in the FP+placebo group [71 (20.9%)]. The time to onset of the first severe exacerbation was longer with FP+roflumilast 500 µg (median = 53 d) than with FP+placebo (median = 44 days). The median number of days that patients experienced severe exacerbations was 4 d for the FP+roflumilast 500 µg group and 3 d for the FP+placebo group.

Subgroup analyses were performed according to smoking status and asthma severity (post-hoc). Similar to the overall analysis, statistically significant increases in FEV_1, which were consistently higher with FP+roflumilast 500 µg than with FP+placebo, were observed in both smokers/ex-smokers and in non-smokers. The differences between-treatment differences numerically favored FP+roflumilast 500 µg in both subgroups (non-smokers: difference in LSMeans = 0.064 L; smokers/ex-smokers: difference in LSMeans = 0.063 L).

Both, patients with moderate persistent and patients with severe persistent asthma showed statistically significant increases in FEV_1. In patients with moderate persistent asthma, the increases were similar with both treatments, while in patients with severe persistent asthma greater increases were observed with FP+roflumilast 500 µg than with FP+placebo. The differences between the treatments were numerically in favor of FP+roflumilast 500 µg in patients with severe persistent asthma (difference in LSMeans = 0.082 L) but not in patients with moderate persistent asthma (difference in LSMeans = -0.007 L).

Increases in morning PEF were seen with both treatments in patients with moderate persistent asthma, while in patients with severe persistent asthma, an increase was only observed with FP+roflumilast 500 µg but not with FP+placebo. The difference between the treatment groups was in favor of FP+roflumilast 500 µg and statistically significant in patients with severe

persistent asthma only (difference in LSMeans = 11 L/min, one-sided p = 0.0190). The between-treatment comparison showed similar results for evening PEF.

Safety

During the study, a total of 763 AEs were reported. More AEs occurred in the FP+roflumilast 500 µg group (405 AEs in 184 [57.1%] patients) than in the FP+placebo group (358 AEs in 162 [47.8%] patients). Most patients had AEs of mild to moderate intensity in both groups; 46 (14.3%) and 44 (13.0%) patients reported AEs of severe intensity in the FP+roflumilast 500 µg and in the FP+placebo group, respectively.

The most frequently reported AE in both treatment groups was asthma aggravated. Diarrhea NOS, headache, nasopharyngitis, and nausea were reported by more patients in the FP+roflumilast 500 µg group than in the FP+placebo group (difference of ≥ 2% of patients). Nasopharyngitis is the only unexpected adverse event among these symptoms according to the current Investigator's Brochure. Although the percentage of patients with nasopharyngitis was higher in the FP+roflumilast 500 µg group compared to the FP+placebo group, nasopharyngitis is not considered as roflumilast-induced effect. The small number of patients in both groups does not allow a final conclusion on this symptom. Furthermore, there is no plausible mechanism to support a causal relationship between roflumilast and nasopharyngitis.

In both treatment groups, most patients reported AEs that were assessed as not related or unlikely related to the study medication by the investigator. In total, 46 (14.3%) patients in the FP+roflumilast 500 µg group had AEs that were assessed as likely related. In addition, 4 (1.2%) patients had AEs that were assessed as definitely related to the study medication. All AEs with a definite relationship were mild and non-serious. The respective symptoms were nausea, dizziness, headache, and dyspepsia. In total, 23 (6.8%) patients reported AEs that were assessed as likely related to treatment with FP+placebo by the investigator; AEs with a definite relationship were not reported in the FP+placebo group.

No deaths occurred in this study. In total, 10 (3.1%) patients in the FP+roflumilast 500 µg group experienced 10 SAEs and 7 (2.1%) patients in the FP+placebo group experienced 9 SAEs. All SAEs in both treatment groups were judged as not related or unlikely related to the study medication. In either treatment group, 4 patients discontinued due to SAEs. The number of patients who discontinued due to AEs was higher in the FP+roflumilast 500 µg group (47 [14.6%]) than in the FP+placebo group (36 [10.6%]). Most of the AEs leading to withdrawal were assessed as not related or unlikely related to the study medication (38 [65.5%] AEs in the FP+roflumilast 500 µg and 26 [66.7%] AEs in the FP+placebo group).

Laboratory tests revealed no major changes in laboratory variables over the course of the study. There were abnormalities reported as treatment-emergent AEs in 9 (2.8%) patients in the FP+roflumilast 500 µg group and 16 (4.7%) patients in the FP+placebo group. However, the majority of these were considered either unlikely or not related to study medication. No new safety signal arose from the laboratory data.

Evaluation of ECG parameters did not indicate any study drug related effect. Over the course of the study changes were similar between the two treatment groups and there were no clinically relevant ECG findings in patients treated with FP+roflumilast 500 µg. Vital signs did not show apparent changes over the course of the study in either treatment group, and the results for physical examination showed no clinically relevant results.

Conclusions:

The analysis of the treatment effects of the primary variable FEV_1 was numerically greater for FP+roflumilast 500 µg compared with FP+placebo, but did not reach statistical significance. One potentially confounding factor to demonstrating statistical significance was the large and statistically significant placebo response. However, statistically significant improvements were observed between treatment groups in the pre-specified AUC-analysis of FEV_1. Similar trends of non-statistically significant improvements were also observed with respect to the co-primary and most secondary variables for roflumilast 500 µg compared with placebo as add-on therapies to FP 125 µg bid.

No new safety signals arose from the evaluation of adverse events, laboratory data, vital signs, ECG parameters, or physical examination. Overall, roflumilast 500 µg od as add-on therapy to FP 125 µg bid was well tolerated.