Synopsis of study report: 242/2000
Location in Module 5:

Study Code:
BY217/FK1 004

Report Version:
2.0

Title of the study:
6 weeks treatment with 0.5 mg B9302-107 versus placebo in patients with asthma.

Investigators:
Nine investigators in South Africa

Study center(s):
A total of nine centers participated, all located in South Africa

Publication (reference):
Not applicable

Studied period (years):
03 Sep 1997 (first patient in the study) – 16 Sep 1998 (last patient out of the study)

Clinical phase:
II

Objectives:
- The main objective was to compare the effects of roflumilast on pulmonary function, symptoms of asthma, and use of rescue medication over six weeks treatment period with placebo in patients with mild to moderate bronchial asthma. Further, the safety and tolerability of roflumilast was assessed.

Methodology:
This was a multi-center, parallel, randomized, double-blind phase II study. After a single-blind baseline period of 2 - 4 weeks, eligible patients were allocated to treatment groups according to a 2:1 randomization scheme, receiving either 0.5 mg roflumilast/d or placebo. The

double-blind treatment period lasted 6 weeks, followed by a single-blind observation period of 2 weeks. During the baseline and observation period, all patients received placebo. Patients recorded their morning and evening PEF, use of beta-agonist, 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 and 1, 3, and 6 weeks after treatment start (T0, T1, T3, T6) and at the end of the observation period (O2).

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

Intention-to-treat:	n = 72	Per-protocol:	n = 53
Roflumilast:	n = 47	Roflumilast:	n = 37
Placebo:	n = 25	Placebo:	n = 16

Diagnosis and criteria for inclusion:

Patients with stable, mild to moderate asthma (however, mild asthmatics were predominately recruited), aged 18 - 65 years, not having used inhaled or systemic glucocorticosteroids within the last 4 or 12 weeks, respectively (dependent on the dosage previously used), and who showed a FEV_1 of 60-90% of predicted were eligible to enter the study. At the end of the baseline period, patients were required to have an FEV_1 between 60 and 90% of predicted, a reversible obstruction (FEV_1 increase ≥ 15% in response to 0.2 mg salbutamol), the absence of pre-defined "lack of efficacy" criteria, and a sum of symptom scores of ≥ 2 per day *or* a diurnal PEF variability of at least 15% during at least 3 days of the last 7 days directly preceding the randomization visit.

Duration of treatment:

Baseline:	2 to 4 weeks
Treatment period:	6 weeks
Observation period:	2 weeks

Test product:

Roflumilast

Dose:

2 tablets (0.25 mg/tablet) o.d. in the morning

Mode of administration:

Oral administration

Batch No.:

BY217-26-1-1

Reference product:

Placebo

Dose:

2 tablets o.d. in the morning

Mode of administration:

Oral administration

Batch No.:

BY217-21-2-1

Criteria for evaluation:

Efficacy evaluation:

Primary variable: Morning PEF from diary at T6 as compared to the baseline value (T0)
Secondary variables: Spirometric lung function tests (FEV_1, FVC, PEF), evening PEF (derived from diaries), PEF variability, symptoms of asthma and use of rescue medication at T1, T3 and T6, morning PEF (form diary) at T1 and T3, drop-out rate due to pre-defined "lack of efficacy" criteria, subjective efficacy rating by patient and investigator and serum levels of sE-selectin.

Safety evaluation:

Laboratory values, physical examination (ECG, BP, HR), and adverse event (AE) monitoring.

Statistical methods:

An ITT, extended ITT (if applicable) and PP analysis was performed, with the ITT analysis being primary for efficacy evaluation. For the primary and secondary lung function variables, the ratios T6/T0, T3/T0, T1/T0, O2/T0 and T0/O2 were calculated, and the null hypothesis that the respective median ratio of roflumilast was ≤ than that of placebo was tested versus the alternative that the ratio of roflumilast was > than that of placebo. The hypotheses were tested with the independent t-test after logarithmic transformation. The ratios were compared within-groups by the paired t-test and between groups by the Student's two-sample t-test or its Welch modification in case of variance inhomogeneity. Point estimates and 95%-confidence limits were given for the respective treatment ratios for within- and between-treatment comparisons. The within-group comparisons were done two-sided; the between group comparisons followed the one-sided approach. For spirometric lung function variables additionally an ANCOVA with the factors/covariables treatment, value at T0, age, sex and center was performed. The number of daily use of rescue medication, the sum of symptom scores averaged or cumulated, as well as PEF variability were analyzed for each week by non-parametric test procedures. Between-treatment comparisons were done by the Wilcoxon Mann-Whitney test. Within-group comparisons were done with the Wilcoxon's signed-rank test modified accord-

ing to Pratt. The number of symptom-free and rescue medication-free days as well as serum levels of sE-selectin was also analyzed non-parametrically. Adverse events, clinical chemistry, vital signs, and ECGs were analyzed in a descriptive manner.

SUMMARY – CONCLUSIONS

Summary:

Efficacy results:

While the results of the study are compromised by the small sample size, the study demonstrated that the spirometric variables as well as morning PEF (from diaries) increased during the treatment period in both groups, reaching statistical significance at T6 in the ITT analysis for roflumilast (with the exception of morning PEF), while only non-significant improvements were seen in the placebo group (with the exception of PEF from spirometry). Although, between treatment differences did occasionally reach statistical significance on the unadjusted 5% level at some time-points, none of the between-treatment group comparisons at T6 in the ITT analysis proved to be statistical significant, with the exception of FEV_1, when values were adjusted for different baseline characteristics ($p = 0.0476$).
Results for the primary variable morning PEF and for the secondary variable FEV_1 are shown below for the ITT analysis:

Variable/Treatment	n	Within-treatment		Between-treatment differences	
		T6/T0 of geom. means (95%-CI)	p-value[a]	Test/ref. ratio of geom. means (lower 95%-CL)[b]	p-value[b] (superiority)
Morning PEF (l/min)					
Roflumilast (Test)	47	1.02 (0.97, 1.06)	0.4491	1.01 (0.96)	0.3344
Placebo (Ref.)	25	1.00 (0.95, 1.05)	0.9464		
FEV_1 (l)					
Roflumilast (Test)	47	1.06 (1.03, 1.10)	0.0002	1.04 (1.00)	0.0652
Placebo (Ref.)	25	1.02 (0.97, 1.07)	0.3759		

[a] two-sided, unadjusted [b] one-sided, unadjusted CI: confidence interval; CL: confidence limit.

Upon withdrawal of roflumilast spirometric lung function variables decreased in the roflumilast group, reaching statistical significance as compared to placebo for FEV_1 and FVC.
With respect to the other efficacy variables, PEF variability, asthma symptom scores and use of rescue medication, small improvements were seen over the treatment period. Although the improvements on roflumilast were slightly more pronounced for some variables and time-points, it was not consistently found.
Statistical significance was reached occasionally for within-treatment differences in both groups, but not for any of the between-treatment comparisons. The effectiveness rating indicated better effectiveness of roflumilast vs placebo in the judgement of both, the patient and

the investigator. For patients presenting with LOE during the treatment period no significant difference was seen.
Soluble E-selectin levels were significantly reduced on roflumilast treatment, indicating an anti-inflammatory effect of roflumilast.

Safety results:

In total there were 139 adverse events (AEs) experienced by 53/72 patients (74%) during the treatment period. Of these 139 AEs, 111 AEs were reported by 38/47 patients (81%) on roflumilast, 28 AEs by 15/25 patients (60%) on placebo. The most frequently reported AEs on roflumilast and placebo treatment were headache and gastrointestinal disorders.
Approximately 40% of the AEs experienced by patients receiving roflumilast were considered to be “likely” related to study medication by the investigator, the remaining, were either “not” or “unlikely” related, with the exception of 12 AEs, all experienced by one patient, which were judged to be “definitely” related by the investigator but “likely” or “unlikely” by the Sponsor. In the placebo group approximately 30% of all AEs were considered to be ”likely” related, all remaining AEs were “not” or “unlikely” related, as judged by the investigator.
The majority of AEs was of “mild” or “moderate” intensity. There were 4 AEs (nausea, headache, pleural disorders, back pain) experienced by 4 patients in the roflumilast, and 2 AEs (nausea, dysuria) experienced by 2 patients in the placebo group, which were severe in nature. There was no death. One serious AE (surgery) was recorded in the roflumilast group without any reasonable causal relationship to study drug. Seven (7/47) and two (2/25) roflumilast (15%) and placebo (8%) recipients, respectively were withdrawn due to AEs.
Physical examinations and clinical chemistry did not reveal any clinically significant changes as a result of study drug administration or any apparent trends. There was one event of mild tachycardia which was judged to be “likely” related to roflumilast.

Conclusions:

In summary, although superiority of roflumilast vs placebo could not be demonstrated at the 5% level for the primary variable, it can be concluded that roflumilast has the potential to improve lung function in patients with mild asthma. Moreover, the results indicate a beneficial anti-inflammatory effect of roflumilast. The incidence of AEs appeared to be higher on roflumilast as compared to placebo, but all AEs were easily manageable and therefore do not place asthmatic patients at an unreasonable or intolerable risk. The AEs experienced were primarily those expected on roflumilast, as seen in other studies. Thus the study confirmed the good safety profile and acceptable tolerability of roflumilast.