Synopsis of study report: 32/99
Location in Module 5:

Study Code:
BY217/FK1 003

Report Version:
Version 2.0 (dated 05-Aug-2004)

Title of the study:

Six weeks treatment with 0.5 mg (500 µg) B9302-107 versus placebo added to 500 µg beclomethasone dipropionate (BDP) in patients with asthma. A double-blind, randomized parallel group study

Study center(s):

Multinational: 41 centers in Austria, Germany, Hungary, Poland, Spain

Publication (reference):

Not applicable

Studied period (years):

26 May 1997 – 18 May 1998

Clinical phase:

II

Objectives:

- To study the effect of oral roflumilast (500 µg/day during 6 weeks) vs placebo, added to 500 µg inhaled beclomethasone dipropionate (BDP) on pulmonary function, asthma symptoms and concomitant use of rescue medication in patients with mild to moderate bronchial asthma.

- To provide further information on the safety and tolerance of oral roflumilast (500 µg/day).

Methodology:

The trial was conducted as a prospective double-blind, randomized parallel-group multicenter study with a single-blind baseline period. After a baseline period of 1-4 weeks, all eligible subjects were randomly allocated to one of two treatments at a ratio of 2:1, i.e. 2/3 of the patients received 500 µg/day roflumilast (2 tablets of 250 µg, s.i.d, p.o.) and 1/3 received placebo (2 tablets s.i.d.) in addition to the basal therapy involving for all patients inhaled BDP (250 µg b.i.d.). The treatment period lasted 6 weeks. Lung function (FEV1, FVC, PEF) was measured at baseline (B0 and B1; at B2, B3, B4 only if applicable) and at each subsequent visit (T0, T1, T3, T6 where T0 corresponds to the last baseline visit). Patients also recorded morning and evening PEF (Pulmotest®, Roland). Further, they documented their daily use of rescue medication and their asthma symptoms. Diary variables were recorded at baseline (B0-B4) and during treatment (T0-T6).

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

The safety population consisted of 265 patients (n=177 roflumilast + BDP, n=88 placebo + BDP). For the extended intention-to-treat (itt) analysis of the primary variable FEV1 259 of these patients were considered. In the itt analysis of FEV1 there were 257 patients (n=170 roflumilast + BDP, n=87 placebo + BDP) with paired T0 and T6 values; in the per-protocol analysis 203 of them (n=135 roflumilast + BDP, n=68 placebo + BDP) were included.

Diagnosis and criteria for inclusion:

Patients with mild to moderate asthma having FEV_1-values between 50-85% predicted when inhaled rescue medication had been withheld for at least 4 hours and, in addition, showing **either** a reversibility of $FEV_1 \geq 15\%$ initial (at baseline or else 12 weeks prior to B0) **or** a diurnal PEF variability ≥ 15% during at least 3 of the 7 days preceding randomization.

Duration of treatment:

The treatment lasted 6 weeks. All patients inhaled 500 µg/day BDP (250 µg b.i.d.) as a basal therapy (batch No. 004497/1 with inhaler batch No. 7K886/1; batch No. 064197/1 with inhaler batch No. 6K187/1).

Test product:

Roflumilast

Dose:

500 µg roflumilast (2 tablets containing 250 µg, s.i.d.). Patients of the test group **(Group 1)** took two tablets **roflumilast** per day during treatment in addition to inhaled BDP (250 µg b.i.d.).

Mode of administration:

p.o.

Batch No.:

071496/1, 072496/1 and 073496/1

Reference product:

Placebo

Dose:

Patients of the reference group **(Group 2)** were given **placebo** tablets (2 tablets s.i.d.) in addition to BDP which was inhaled as basal therapy (250 µg b.i.d)

Mode of administration:

p.o.

Batch No.:

189396/1, 209396/1

Criteria for evaluation:

- Primary variable: FEV_1 (T6/T0-ratio)
- Secondary variables: FEV_1 (T1/T0 and T3/T0 ratios), FVC, PEF from spirometry, morning and evening PEF from diaries (T1/T0, T3/T0, T6/T0 ratios), PEF variability, asthma symptom score (mean, %symptom-free days), use of rescue medication (puffs/day, %rescue medication-free days), effectiveness rating by investigators/patients, dropout rate due to lack of efficacy (LOE), safety parameters (laboratory values, physical examination, ECG, BP, HR), adverse events.

Statistical methods:

- Primary variable: Comparison between treatments was performed by means of the independent t-test after logarithmic transformation of T6/T0-ratios. Geometric mean and lower one-sided 95%-confidence limit were given for the treatment ratio roflumilast + BDP / placebo + BDP; superiority was concluded when this limit was above 1.00.
- Secondary variables: Lung function variables, with the exception of PEF-variability, were analyzed in analogy to the primary variable. 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). Group comparison of the dropout rate due to LOE was made by means of the log-rank test (survival analysis). All other secondary variables were analyzed in a descriptive manner.

SUMMARY – CONCLUSIONS

The present study indicates that a six-week treatment with roflumilast (500 µg/day, s.i.d.) added to a basal therapy with inhaled BDP (250 µg b.i.d.) significantly improves lung function. Statistical superiority of roflumilast to placebo as adjunct to BDP after 6 weeks treatment was found for the primary variable FEV_1 in the itt- and extended itt-analysis. Superiority was also demonstrated for FEV_1 in all three (pp, itt, extended itt) analyses performed after 3 weeks therapy. Additionally, the increase in FVC and PEF from spirometry as well as the reduction in asthma symptoms and concomitant use of rescue medication were highly significant in patients treated with roflumilast. In both treatment groups, improvements in lung function were observed already after one week of double-blind treatment. After 6 weeks treatment the mean FEV_1 of 73% predicted could be raised to 82% predicted in the roflumilast + BDP group and to 79% predicted in the placebo + BDP group: This clinically relevant increase in FEV_1 amounted to 280 ml in patients receiving roflumilast + BDP compared to only 190 ml in those receiving placebo + BDP.

This improvement in lung function in the roflumilast + BDP group was not only reflected by a reduction in the asthma symptom scores but also in the use of rescue medication. However, in the placebo + BDP group the reduction in asthma symptom scores was smaller and accompanied by a marked increase in the use of rescue medication. This suggests that patients might have controlled their asthma by using more rescue medication in order to compensate for the lower efficacy of placebo + BDP treatment.

The subgroup of "non-smokers" did not differ from the total population with regard to the improvement in FEV_1 within the two treatment groups. However, in smokers/ex-smokers there was a significant increase in FEV_1 only for patients treated with roflumilast + BDP.

The reported adverse events were in general mild in intensity. With regard to safety data, a six-week treatment with repeated daily doses of 500 µg roflumilast as adjunct to daily inhalation of 500 µg BDP was not associated with any clinically significant alterations in vital signs, laboratory values, or physical examination including ECG, thus speaking for a good tolerability of the treatment.