Synopsis of study report: 321/98
Location in Module 5:

Study Code:
BY217/FK1 005

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 500 µg beclomethasone dipropionate (BDP) in patients with asthma. A double-blind, double dummy, randomized parallel group study

Study center(s):

Multinational: 38 centers in Austria, Germany, Hungary, Poland, Spain

Publication (reference):

Not applicable

Studied period (years):

05 June 1997 – 17 August 1998

Clinical phase:

II

Objectives:

- To study the effect of oral roflumilast (500 µg/day during 6 weeks) in comparison to 500 µg inhaled BDP on pulmonary function, asthma symptoms and concomitant use of rescue medication in patients with mild to moderate bronchial asthma.
- To evaluate the safety and tolerance of a six weeks treatment with oral roflumilast (500 µg/day).

Methodology:

The trial was conducted as a double-blind, double dummy, randomized parallel-group multicenter study with a single-blind baseline period. After a baseline period of 1-4 weeks, 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 BDP (250 µg b.i.d., p.inh. with spacer) for a treatment duration of 6 weeks. According to the double dummy design, patients of the roflumilast group inhaled placebo (one puff b.i.d.) and patients of the BDP group were given placebo tablets (2 tablets s.i.d.). Inhalation of BDP was made by means of a metered dose inhaler (MDI). Lung function (FEV_1, FVC, PEF) were 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 232 patients (n=159 roflumilast, n=73 BDP). All 232 patients were considered in the extended intention-to-treat (itt) analysis of variable FEV_1. In the itt-analysis of FEV_1 there were 227 patients (n=154 roflumilast, n=73 BDP) with paired T0 and T6 values. The per-protocol (pp) population consisted of 199 patients; 171 of them (n=115 roflumilast, n=56 BDP) had paired T0 and T6 values and were available for the pp analysis of FEV_1.

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 double dummy treatment lasted 6 weeks.

Test product:

Roflumilast

Dose:

Group 1: 500 µg roflumilast; two tablets (containing 250 µg each, s.i.d.) were taken on each of these days (s.i.d.); additionally, placebo (batch No. 082197/1) was inhaled (one puff b.i.d.), inhaler batch No. W0045LL/1.

Mode of administration:

p.o.

Batch No.:

072496/1, 073496/1

Reference product:

Beclomethasone diproprionate

Dose:

Group 2: 500 µg beclomethasone diproprionate (BDP, 250 µg b.i.d.) inhaled with an MDI device (inhaler batch No. W2695MA/1). Patients of this reference group were also given placebo tablets (2 tablets s.i.d.), batch No. 189396/1 and batch No. 209396/1.

Mode of administration:

Inhalation with an MDI

Batch No.:

BDP: 085197/1

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:
Student's two-sample *t*-test or its Welch modification to test for non-inferiority (at-least-equivalence) of roflumilast compared with BDP and subsequently for superiority after logarithmic transformation of T6/T0-ratios. Geometric mean and lower one-sided 95%-

confidence limit were given for the treatment ratio roflumilast/BDP, for which 0.90 had been stipulated as at-least-equivalence acceptance limit.

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 suggests that a daily dose of 500 µg roflumilast taken over 6 weeks is statistically non-inferior (at least equivalent) to 500 µg BDP in its therapeutical efficacy. This holds true for the primary variable FEV_1. Additionally, analogous results were obtained for all secondary variables (e.g. reduction in asthma symptoms and decrease in the use of rescue medication). 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 72% predicted could be raised to about 80% predicted: This clinically relevant increase in FEV_1 amounted to 300 ml and 360 ml in the roflumilast and the BDP groups, respectively.

The subgroups of "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. However, non-inferiority could not be shown in "smokers/ex-smokers" due to a higher variability and the small sample sizes of this subgroup.

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 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 roflumilast administered over 6 weeks.