Synopsis of study report: 178/98
Location in Module 5:

Study Code:
BY217/FK1 001

Report Date:
02-Mar-1999

Title of the study:
Effect of B9302-107 on allergen challenge in subjects with bronchial asthma

Study center(s):
Medical School Stellenbosch, University of Stellenbosch, RSA-Tygerberg

Publication (reference):
Not applicable

Studied period (years):
05 August 1996 – 08 August 1997

Clinical phase:
II

Objectives:
- To study wether a single oral dose (1 mg) of roflumilast reduces the allergen-induced early and late asthmatic reaction (referred to as EAR and LAR, respectively) as well as the hyperreactivity to histamine in patients with mild allergic asthma
- To evaluate the safety and tolerance of roflumilast

Methodology:
The trial was conducted as a double-blind, randomized crossover study, wherein eligible subjects were randomly allocated to one of two treatment sequences (roflumilast/placebo, placebo/roflumilast). After a two-day baseline there was a first washout period lasting 2-5 weeks

(W1); thereafter, single dose administration of roflumilast or else placebo (4 tablets x 0,25 mg roflumilast or 4 tablets placebo) took place only on the first day of a two-day treatment period (i.e. drug intake at visits V1 and V3). Treatment periods (TI and TII) were separated from one another by a washout of 2-5 weeks (W2). An allergen challenge was performed 1 hour after drug intake and followed by a histamine challenge 25 hours after drug intake (at visits V2 and V4).

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

13 subjects were randomized and included in the intention-to-treat (ITT) analysis of safety parameters; 12 subjects were included in the ITT efficacy analysis and 7 in the per-protocol analysis.

Diagnosis and criteria for inclusion:

Subjects with mild allergic asthma ($FEV_1 \geq 70\%$ predicted) currently treated only with short-acting inhaled bronchodilators, hyperresponsive to histamine ($PC_{20}FEV_1 \leq 16$ mg/ml) and exhibiting an early and late phase reaction after allergen challenge.

Duration of treatment:

Each crossover treatment period lasted 2 days; tablets were taken only on the first of these days (single dose).

Test product:

Roflumilast

Dose:

1 mg (4 tablets)

Mode of administration:

p.o.

Batch No.:

BY217-14-1-1

Reference product:

Placebo

Dose:

4 tablets

Mode of administration:

p.o.

Batch No.:

BY217-13-1-1

Criteria for evaluation:

- Primary parameter: Extent of LAR (FEV_1 decrement by reference to diluent inhalation: AUC 2-9 hours after allergen challenge).
- Secondary parameters: Extent of EAR: AUC 0-2 hours after allergen challenge, $PC_{20}FEV_1$ (histamine)-values, safety parameters (laboratory values, physical examination, ECG, BP, HR), adverse events, kinetics (serum levels).

Statistical methods:

- Primary parameter: The extent of LAR measured under roflumilast and under placebo were compared by means of an analysis of variance for the two-period crossover design. Two-sided 90%-confidence intervals (corresponding to one-sided 95%-confidence intervals) were given for the differences "roflumilast – placebo" of population medians.
- Secondary parameters: Exploratory (rather than confirmatory) analyses were carried out for all other parameters by applying similar procedures: analysis of variance and 90%-confidence intervals, where appropriate.

SUMMARY – CONCLUSIONS

The present study suggests that a single oral dose (1 mg) of roflumilast attenuates the hyperresponsiveness to histamine and reduces the early and the late components of the allergen-induced asthmatic reaction.

The reduction in $PC_{20}FEV_1$ (ratio "end/start of period") was smaller under roflumilast than under placebo, i.e. the $PC_{20}FEV_1$–values were reduced to 65% of the initial value under roflumilast and to 44% under placebo in the PP analysis (77% and 50%, respectively, in the ITT efficacy analysis). The level of suppression of the asthmatic reaction due to roflumilast as compared to placebo was 36% for the EAR and 27% for the LAR in the PP analysis (17% for the EAR and 27% for the LAR in the ITT efficacy analysis).

Tolerability data indicate that the adverse events reported under roflumilast alone and additionally to the allergen challenge were mild in intensity. With regard to safety data, there were no clinically significant alterations in vital signs, laboratory values, or physical examination including ECG.