Synopsis of study report: 20E/98K1
Location in Module 5:

Study Code:
BY217/FHP003

Report Date:
01-Oct-1998

Title of the study:
Safety, tolerability and efficacy of the new phosphodiesterase inhibitor roflumilast (B9302-107) administered to asthmatic subjects as repeated oral doses over 4 weeks

Study center(s):
ASTER, 3/5 rue Eugène Millon, 75015 Paris

Publication (reference):
Not available

Studied period (years):
3 March 1997 – 7 July 1997

Clinical phase:
I

Objectives:
To assess safety, tolerability and efficacy of roflumilast (B9302-107) during repeated oral administration during 4 weeks

Methodology:
Monocenter, randomized, double-blind, placebo-controlled, 2-period, crossover study

No. of subjects (total and for each treatment):
Total number of subjects planned: 16

Total number of subjects included: 16

Diagnosis and criteria for inclusion:

Subjects with exercise-induced asthma, presenting a moderately decreased lung function that was reversible by means of inhaled salbutamol (FEV_1 improvement was ≥ 15%; 30 min after inhalation of 2 puffs of 100 µg salbutamol), and presenting a reduction of the percentage fall index (% FI) of 10-20% during an exercise test.

Duration of treatment:

Two 4-week administration periods (roflumilast and placebo in random order) separated by a washout period of between 2 and 4 weeks

Test product:

Roflumilast (B9302-107)

Dose:

0.5 mg (2 x 0.25 mg tablets of roflumilast) per day sid

Mode of administration:

Repeated oral administration

Batch No.:

057396

Reference product:

Placebo

Dose:

2 placebo tablets per day sid

Mode of administration:

Repeated oral administration

Batch No.:

058396

Criteria for evaluation:

Tolerability:
Well-being questionnaire
Safety:
Clinical and biological parameters, spontaneous adverse events (AEs) reporting

Efficacy:
Exercise-induced bronchial provocation, PEF, FEV_1, TNFα
Pharmacokinetics:
Plasma levels of roflumilast (B9302-107)

Statistical methods:

Descriptive statistics, analysis of variance (ANOVA) for the crossover design, for percentage fall index and ($AUC_{0\text{-}12min}$/12 min)/resting FEV_1 on study days 1, 14 and 28; ANOVA for the crossover design for TNFα on study days 1 and 28.

SUMMARY – CONCLUSIONS

Summary:

Population:

Number of subjects	23 selected
	16 randomized
	16 who completed the study
	0 who discontinued treatment prematurely

Pharmacology results:

Pharmacodynamics: Evaluation of the percentage fall index, the ratio ($AUC_{0\text{-}12\ min}$/12min)/resting FEV_1 and the determination of TNFα in whole blood indicated that 28-day treatment with roflumilast (B9302-107) was effective in the treatment of exercise-induced asthma. On study days 14 and 28, the percentage fall index and the ratio ($AUC_{0\text{-}12\ min}$/12 min)/resting FEV_1 revealed an improved FEV_1 in both periods following exercise for those subjects receiving roflumilast (B9302-107) as compared to those receiving placebo. On day 28, the ANOVA for the crossover design indicated that both the percentage fall index and ($AUC_{0\text{-}12\ min}$/12 min)/resting FEV_1 were significantly improved under roflumilast treatment as compared to placebo.
TNFα levels decreased clearly under roflumilast treatment ($p<0.009$; Wilcoxon signed rank test), whereas there was only a slight decline under placebo. On day 28, the ANOVA for the crossover design indicated that TNFα levels were significantly lower under roflumilast treatment as compared to placebo.

Pharmacokinetics (compliance assessment): Pre-dose measurements of B9302-107 plasma concentrations complied with the study protocol for all subjects throughout the study with all concentration values within the expected range. Comparison of the mean concentrations of B9302-107 showed approximately constant values from day 7 to day 28.

Safety results:

No deaths or serious adverse events (SAEs) were reported and none of the AEs led to the discontinuation of the study treatment. In total, 61 mild or moderate, non-serious AEs were reported in 15 subjects during the study. All of these resolved spontaneously. Of the 61 AEs, 40 occurred in subjects treated with roflumilast (B9302-107), 19 in those treated with placebo and 2 occurred between the two periods. This relatively large number of AEs was reported during a period of at least 10 weeks. The most commonly reported AEs among the 16 subjects treated with roflumilast (B9302-107) were: headache (12 AE in 8 subjects), liquid stools (5 AE in 3 subjects), insomnia (4 AE in 3 subjects), irritability (2 AE in 2 subjects), lumbago (2 AE in 2 subjects) and asthma attacks (4 AE in 3 subjects). Under the placebo treatment, headache (1 AE in 1 subject), liquid stools (1 AE in 1 subject), lumbago (1 AE in 1 subject) and asthma attacks (1 AE in 1 subject). Episodes of headache, diarrhoea (liquid stools), insomnia and nervousness (irritability) were considered to be drug-related. Some isolated AEs were reported under both treatments. Of these, abdominal pain and nausea were also considered to be related to roflumilast (B9302-107) treatment. Well-being questionnaire results showed that 10 of the 16 subjects felt better under placebo than under treatment with the active compound, which was in agreement with the higher occurrence of AEs under roflumilast (B9302-107). Repeated measurements of vital signs, ECG recordings, clinical laboratory investigations and olfactometry assessments did not reveal any drug-related alterations.

Conclusions:

From the results of this study, it can be concluded that 28-day treatment with roflumilast (B9302-107) was effective in the treatment of exercise-induced asthma. On day 28, the evaluation of the percentage fall index and of the ratio ($AUC_{0\text{-}12min}$/12 min)/resting FEV_1 indicated a significant improvement of FEV_1 under roflumilast (B9302-107) treatment as compared to placebo. This result was confirmed by the significant reduction of TNFα levels in whole blood from day 1 to day 28 under roflumilast (B9302-107) treatment. A tendency towards an improvement of lung function already existed on days 1 and 14, however statistical significance could not be stated on these days.

AEs appeared to be more frequent under treatment with roflumilast (B9302-107) than under the placebo treatment. However, 28-day treatment with roflumilast (B9302-107) was safe and well-tolerated.