Synopsis of study report: 10/98
Location in Module 5:

Study Code:
BY217/FHP007

Report Date:
08-May-1998

Title of the study:

Influence of the new phosphodiesterase inhibitor roflumilast (B9302-107) on cardiovascular function after repeated oral sid administration in healthy male volunteers. A double-blind randomized placebo-controlled cross-over study

Study center(s):

Dept. of Clinical Pharmacology/Phase I Unit, Byk Gulden GmbH, Byk-Gulden-Str. 2, 78467 Konstanz, Germany

Publication (reference):

Not available

Studied period (years):

February 1997 – July 1997

Clinical phase:

I

Objectives:

Primary:

- Investigation of the possible influence of roflumilast on impedance cardiography parameters cardiac output (CO) and QS2I.

Secondary:

- Investigation of the possible influence of roflumilast on all other impedance cardiography parameters as well as on exercise ECG, resting ECG, blood pressure and heart rate; safety and tolerability as assessed by clinical laboratory investigation and adverse events; inves-

tigation of the pharmacokinetics of roflumilast and metabolite B9202-045 after repeated dose administration.

Methodology:

Placebo-controlled, randomized, double-blind, 2-period crossover design

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

Intention-to-treat analysis:
13 healthy male subjects (median age: 29 years, median body weight: 74 kg)
Per-protocol analysis:
12 healthy male subjects (median age: 30 years, median body weight: 74 kg)

Diagnosis and criteria for inclusion:

Healthy male subjects

Duration of treatment:

5 days

Test product:

Roflumilast

Dose:

0.5 mg roflumilast (2 tablets of 0.25 mg each) s.i.d.

Mode of administration:

p.o.

Batch No.:

047197

Reference product:

Placebo tablets of identical appearance

Dose:

2 tablets s.i.d.

Mode of administration:

p.o.

Batch No.:

048197

Criteria for evaluation:

Cardiovascular function:

Impedance cardiography (with phonocardiogram and determination of carotis pulse curve) was performed on day 4 of each study period at predose and at 2 h post dose. A 6-lead exercise ECG (2 min at 50 W, 6 min at 100 W) was recorded on day 5 of each study period at 2 h and 4 h post dose. A 12-lead resting ECG was recorded repeatedly on days 1, 4 and 5 of each study period as well as on day 11 in the morning. Blood pressure and heart rate were measured on days 1, 4 and 5 of each study period as well as on day 11 in the morning.

Other safety parameters:

Clinical laboratory investigations were performed on days 1 and 11 of each study period as well as at pre and final check. Adverse events were recorded continuously in standardized form.

Pharmacokinetics:

The plasma levels of roflumilast (B9302-107) and metabolite B9202-045 were determined on day 5 up to 144 h after administration of roflumilast.

Statistical methods:

Impedance cardiography parameters CO, QS2I (primary variables):

Point estimate and two-sided 95%-confidence limits were given for the difference of the population medians for Test and Reference using an additive model and a parametric analysis for the two-period, two-treatment crossover design.

Other cardiovascular and safety parameters (secondary variables):

Descriptive

Pharmacokinetics (secondary variables):

The following pharmacokinetic characteristics were calculated: $t_{½}$, t_{max}, C_{max}, AUC for parent compound roflumilast (B9302-107) and metabolite B9202-045 each, and AUC ratio "metabolite/parent compound" with point estimate and 90%-confidence limits.

SUMMARY - CONCLUSIONS

Summary:

Cardiovascular function:

For the impedance cardiography parameters CO and QS2I (primary variables) no significant difference was found between roflumilast treatment and placebo treatment at 0 h (day 4) and at +2 h (day 4). The differences "2 h-0 h" of this two parameters did also not differ significantly between roflumilast treatment and placebo treatment. Moreover, there was no signifi-

cant change in CO and QS2I from 0 h (day 4) to +2 h (day 4) under each treatment. An influence of roflumilast on secondary impedance cardiography parameters did not become apparent.
Excess AUC of heart rate obtained during exercise at +2 h and +4 h on day 5 was not influenced by roflumilast treatment as compared to placebo. In Subject No. 12 monotopic ventricular extrasystoles (VES) were found sporadically in all exercise ECG recordings. These findings were considered not to be causally related to roflumilast treatment as the VES did already occur in the first study period under placebo treatment.
Repeated measurements of 12-lead resting ECG, blood pressure and heart rate revealed no clinically significant findings. Minor fluctuations of some individual values did not exceed the physiological degree of variation.

Other safety parameters:
Subject No. 07 terminated the study on his own request due to stomach pain, abdominal cramps and diarrhea. The symptoms had occurred both on the first and second treatment day with 0.5 mg/d roflumilast. Other adverse events reported under roflumilast treatment were: headache (4 of 12 subjects), gastrointestinal complaints [heartburn, meteorism] (2 of 12 subjects), tiredness (1 of 12 subjects), muscle ache at the back (1 of 12 subjects). Under placebo treatment headache was reported by 2 of 12 subjects.
Individual and median values of clinical chemistry parameters remained essentially constant during the study. Some minor deviations from reference range were without clinical relevance and remained within the range usually observed in clinical trials.

Pharmacokinetics:
Geom. means with 68%-range (mean ± SEM for t_{max}):

	Parent compound roflumilast (B9302-107)	**Metabolite B9202-045**
$t_{½}$ [h]	10.4 (8.3 - 13.0)	not ascertainable
t_{max} [h]	0.56 ± 0.06	3.42 ± 0.96
C_{max} [µg/l]	9.748 (7.298 - 13.021)	0.168 (0.127 - 0.222)
AUC [µg/l*h]	34.11 (26.71 - 43.55)	2.37 (1.50 - 3.72) [N=7]

AUC ratio metabolite/parent compound (point estimate and 90%-confidence limits): 0.07 (0.05 - 0.10)

Conclusions:

Cardiovascular function:
Repeated oral administration of 0.5 mg/d roflumilast over 5 days did not influence cardiovascular function as assessed by impedance cardiography, exercise ECG and repeated implementation of 12-lead resting ECG, blood pressure and heart rate.

Other safety parameters:
Safety and tolerability of 0.5 mg/d roflumilast administered orally over 5 days was good.

Pharmacokinetics:
Following repeated oral administration of 0.5 mg/d roflumilast over 5 days, the pharmacokinetic characteristics are comparable to those obtained after 7 day-administration of 0.5 mg/d roflumilast (RR 128E/97).