Synopsis of study report: 213/2001
Location in Module 5:

Study Code:
BY217/CP-042

Report Version:
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Title of the study:

Bioequivalence of two tablet formulations (pentagonal vs. round) of 500 µg roflumilast - an open, randomized, two-period crossover study

Study center(s): Swiss Pharma Contract Ltd., 4123 Allschwil, Switzerland

Publication (reference): Not applicable

Studied period (years):
31 July 2001 to 26 September 2001

Clinical phase: I

Objectives:

The main aim of the present study was to evaluate, in healthy volunteers, the bioequivalence of two different galenical tablet formulations (**pentagonal** tablet with 130 mg inactive ingredients vs. **round** tablet with 65 mg inactive ingredients) containing 500 µg roflumilast each. Further, the study also provided information on the safety and tolerability of this roflumilast treatment.

Methodology:

The study was conducted according to an open, randomized, two-period crossover design. Subjects received on Study Day 1 either Treatment A (test) i.e. one **pentagonal** tablet of 500 µg roflumilast or Treatment B (reference) i.e. one **round** tablet of 500 µg roflumilast as single morning dose. The treatment periods were separated by a washout period of at least

10 days. Blood samplings for pharmacokinetic purposes were performed on Study Day 1 at pre-dose, and 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 10h and 24h after oral administration of the study medication.

No. of subjects: In total, 17 healthy subjects (11 men and 6 women) were included in the study.

Diagnosis and criteria for inclusion:

Healthy female or male Caucasians, aged 18 to 45 years, with a normal body weight, who gave their written informed consent were eligible.

Test product (Treatment A): Roflumilast **pentagonal** tablet
Dose: 500 µg
Mode of administration: oral administration with 240 ml water, s.i.d., in the morning
Batch No.: 101131

Duration of treatment:

Single dose on Study Day 1

Reference product (Treatment B): Roflumilast **round** tablet
Dose: 500 µg
Mode of administration: oral administration, s.i.d., in the morning
Batch No.: 499130

Criteria for evaluation:

Primary variables: $AUC_{(0-24h)}$ and C_{max} of roflumilast. $AUC_{(0-24h)}$ instead of $AUC_{(0-inf)}$ first planned in the study protocol was used as primary variable. This was necessary because blood withdrawal was limited up to 24 hours after administration and thus, extrapolation to infinity resulted in extrapolated AUC fractions in a few subjects of more than 30% for the individual subjects.
Secondary variables: $t_{1/2}$ and t_{max} of roflumilast, safety measurements and adverse events.

For all variables, it was decided to extend the evaluation of the pharmacokinetic characterictics to roflumilast N-oxide.

Statistical methods:

The pharmacokinetic characteristics were evaluated using the validated 'KINTPC' program (Version 2.0). The area under the curve [$AUC_{(0-24h)}$] was calculated by the trapezoidal formula up to the last sampling time with a concentration above the limit of quantitation. Maximum

plasma concentrations, C_{max} and the times of their occurrence, t_{max}, were directly obtained from the plasma concentration – time profiles. The terminal elimination half-life was evaluated by $t_{1/2}= \ln 2/\lambda_z$, where λ_z denotes the terminal rate constant estimated by log-linear regression.

The biostatistical analysis was performed employing the 'BIOQPC' program (Version 1.2.2). Point estimates and 90%-confidence limits are given for the Test/Reference ratios of the population medians for Treatment A (Test, pentagonal tablet) and Treatment B (Reference, round tablet) using a multiplicative model and a parametric analysis. In the parametric approach, the residual variance was calculated by means of the corresponding ANOVA model after a logarithmic transformation.

The safety variables were analyzed descriptively, including summary statistics (mean, median, 68% range, SD, SEM, geometric mean, and geometric 68%-range).

SUMMARY - CONCLUSIONS

Pharmacokinetic results:

For roflumilast, the two administered galenical tablet formulations (pentagonal vs. round roflumilast tablets) were equivalent with respect to systemic exposure to roflumilast as represented by AUC. However, C_{max} and t_{max} were different for the two tablet formulations. For the mean maximum plasma concentration C_{max}, the point estimate and the calculated 90% confidence interval (1.09 to 1.50) for the corresponding Test/Reference ratio were outside the equivalence range. Therefore, the two tablets have to be considered as not bioequivalent. The dissolution rate of the pentagonal tablet is obviously faster in the in vivo situation, resulting in a shorter time to reach the maximum plasma concentration. Subsequently, C_{max} is increased and elimination half-life decreased in comparison to the round tablet.

The two different galenical formulations had no influence on the systemic exposure to the N-oxide metabolite and its maximum plasma concentration. Bioequivalence of the two roflumilast tablet formulations was demonstrated with regard to roflumilast N-oxide.

Conclusions:

The pharmacokinetic data indicate that the two administered galenical tablet formulations (pentagonal vs. round roflumilast tablets) were equivalent with respect to systemic exposure to roflumilast as represented by AUC. However, for roflumilast, the two formulations differed with respect to C_{max} and t_{max}. The two tablet formulations were bioequivalent with regard to roflumilast N-oxide. Data on adverse events, vital signs, ECG parameters, and laboratory values indicate that Treatment A (test: **pentagonal** tablet of 500 µg roflumilast) and Treatment B (reference: **round** tablet of 500 µg roflumilast), administered as single morning dose at Study Day 1, were both safe and well tolerated in all subjects aged 21 to 42 years.