Synopsis of study report: 214/2001
Location in Module 5:

Study Code:
BY217/CP-043

Report Version:
1.0 (dated 10 January 2003)

Title of the study:

Investigation of pharmacokinetics of roflumilast and roflumilast N-oxide after single morning or evening oral administration of 500 µg roflumilast in healthy subjects - an open, randomized, two-period crossover study

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

Publication (reference): Not applicable

Studied period (years):
11 July 2001 – 12 August 2001

Clinical phase:
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Objectives:
The main aim of the present study was to compare, in healthy volunteers, the "morning" and "evening" pharmacokinetics of roflumilast and roflumilast N-oxide after a single oral administration of 500 µg roflumilast in the morning or in the evening. 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 either Treatment A (500 µg roflumilast s.i.d. at Study Day 1 in the **morning)** or the Treatment B (500 µg roflumilast s.i.d. at Study Day 1 in the **evening**). The treatment periods were separated by a washout period of at least 10 days. Blood samplings for

pharmacokinetic purposes were performed at pre-dose, and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 30h, 48h, 72h and 96h after morning or evening oral administration.

No. of subjects (total and for each treatment): 16 subjects participated in the study (PP and ITT population).

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:

Roflumilast

Dose:

500 µg

Mode of administration:

Oral administration with 240 ml water, s.i.d., in the morning (Treatment A) or in the evening (Treatment B)

Batch No.:

499130

Duration of treatment:

Single dose on Study Day 1

Reference product:

None.

Criteria for evaluation:

Primary variables: $AUC_{(0\text{-}inf)}$ and C_{max} of roflumilast and roflumilast-N-oxide

Secondary variables: $t_{1/2}$ and t_{max} of roflumilast and roflumilast-N-oxide, safety measurements and adverse events.

Statistical methods:

Pharmacokinetic characteristics were evaluated using the validated 'KINTPC' program (Version 2.0). $AUC_{(0\text{-inf})}$ was calculated based on the trapezoidal formula up to the last sampling time with a concentration above the limit of quantitation and was extrapolated to infinity using standard techniques. C_{max} and t_{max} were directly obtained from the plasma concentration-time profiles.

The biostatistical analysis was performed employing the 'BIOQPC' program (Version 1.2.2). Point estimates and 90%-confidence limits for the geometric means of $AUC_{(0\text{-inf})}$ and C_{max} values of roflumilast were evaluated for the ratio of the population medians for Treatment A (Reference, administration in the morning) and Treatment B (Test, administration in the evening) using a multiplicative model and a parametric analysis. A similar analysis was used for roflumilast N-oxide.

The secondary pharmacokinetic variables $t_{1/2}$ and t_{max} were analyzed for roflumilast and roflumilast N-oxide in an exploratory manner. A multiplicative model was applied for the variable $t_{1/2}$, whereas an additive model was used for t_{max}. 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 the parent compound roflumilast, the primary variable $AUC_{(0\text{-inf})}$ representing the systemic exposure as well as the secondary variable $t_{1/2}$ were not affected by morning or evening administration of roflumilast. However, the roflumilast mean maximum plasma concentration C_{max} after roflumilast intake in the evening was lowered in comparison to C_{max} after morning administration of roflumilast, whereas t_{max} was slightly increased, an effect that may relate to differences between stomach or intestinal content of the study volunteers. For roflumilast N-oxide, the pharmacokinetic characteristics of the primary and secondary variables were equivalent.

Conclusions:

The pharmacokinetic data indicate that morning or evening administration of roflumilast had no influence on the systemic exposure of the metabolite. Treatment A (500 µg roflumilast s.i.d. at study day 1 in the **morning)** and Treatment B (500 µg roflumilast s.i.d. at study day 1 in the **evening**) were both safe and well tolerated in subjects of both sexes, aged 18-45 years with respect to adverse events, vital signs, ECG parameters, and laboratory values.