Synopsis of study report: 177/2002
Location in Module 5:

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BY217/CP-051

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Title of the study:

Bioequivalence of two tablet formulations (pink vs. white) of 250 µg roflumilast – an open, randomized, two-period crossover study

Study center(s): Applied Analytical Industries Deutschland GmbH & Co KG (AAI), Wegenerstr. 13, 89231 Neu-Ulm, Germany

Publication (reference): Not applicable.

Studied period (years): 18 July 2002 – 23 August 2002

Clinical phase: I

Objectives:

The main aim of the present study was to compare, in healthy volunteers, the pharmacokinetics of two galenic tablet formulations (**pink** tablet serving as test and **white** tablet serving as reference) containing 250 µg roflumilast each. Further, the study provided information on the safety and tolerability of roflumilast.

Methodology:

The monocenter study was conducted according to an open, randomized, two-period crossover design. Subjects received either Treatment A (pink tablet as morning dose on Study Day 1) or Treatment B (white tablet as morning dose on Study Day 1). The study consisted of a screening examination including serology tests, drug screening and alcohol breath test (within 4 weeks before the first administration of study medication), two treatment periods of

5 days each, separated by a washout period of 10-14 days. A post-study examination was performed within 2 weeks after the end of treatment.

For pharmacokinetics blood samples were drawn at pre-dose, and at 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 10h, 12h, 14h, 24h, 30h, 48h, 72h and 96h after the single oral administration of 250 µg roflumilast.

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

In total, 36 healthy volunteers (18 men and 18 women) were randomized and included in the ITT-analysis. The PP-analysis consisted of 35 subjects.

Diagnosis and criteria for inclusion and randomization:

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: 250 µg

Mode of administration: oral administration with 200 ml water, s.i.d., in the morning

Batch No.: 220150 (pink tablet in Treatment A);
220170 (white tablet in Treatment B)

Duration of treatment:

Single dose on Study Day 1

Reference product:

None

Criteria for evaluation:

- **Primary pharmacokinetic variables:** Area under the curve [$AUC_{(0\text{-inf.})}$] and maximum plasma concentration [C_{max}] of roflumilast and roflumilast N-oxide
- **Secondary pharmacokinetic variables:** Terminal elimination half life [$t_{1/2}$] and time to reach maximum plasma concentration [t_{max}] of roflumilast and roflumilast N-oxide
- **Secondary safety variables:** Adverse events (AEs), laboratory work-up (blood chemistry, PTT, hematology, urinalysis), physical examination, blood pressure (BP),

pulse rate, body temperature, and 12-lead ECG including heart rate (HR), PR-, QRS-, RR-, QT-, and QTc-interval

Statistical methods:

The pharmacokinetic characteristics were evaluated using the validated 'KINTPC' program (Version 2.1). $AUC_{(0\text{-inf.})}$ 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 were evaluated for the Test/Reference ratio of the population medians (where Treatment A [pink tablet] is the Test and Treatment B [white tablet] is the Reference) using a multiplicative model and a parametric analysis.

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 in a descriptive manner, including summary statistics where appropriate.

SUMMARY - CONCLUSIONS

Pharmacokinetic results:

For both primary pharmacokinetic variables $AUC_{(0\text{-inf.})}$ and C_{max} of roflumilast and roflumilast N-oxide, the point estimate for the Test/Reference ratios of the geometric means and the respective 90% confidence interval were entirely within the conventional equivalence range used (0.80 to 1.25). Based on these results of the biostatistical analysis, the two administered galenical formulations of 250 µg roflumilast (pink vs. white tablets) were thus considered bioequivalent in the present study.

Pharmacokinetic Variable	Roflumilast		Roflumilast N-oxide	
	Point estimate	90% conf. limit	Point estimate	90% conf. limit
$AUC_{(0\text{-inf.})}$ [µg/lxh]	**0.96**	**0.90 – 1.02**	**1.01**	**0.97 – 1.05**
Cmax [µg/l]	**0.98**	**0.92 – 1.05**	**0.96**	**0.92 – 1.00**

Safety results:

During treatment, a total of 37 AEs were reported by 22 subjects. Comparing the two galenical formulations of 250 µg roflumilast, 17 of these AEs were experienced after the

intake of a pink tablet and 20 were experienced after the intake of a white tablet. Most AEs reported by the subjects were mild or moderate in intensity, and were assessed by the investigator as "unrelated" or "unlikely related" to the study medication. None of the reported AEs were assessed by the investigator as definitely related to the intake of roflumilast.

The most frequent AE was headache (n=26), which corresponded to 70% of the AEs reported by subjects in each group. There were no deaths or other SAEs in this study.

Laboratory values (including blood chemistry, hematology, urinalysis) and measurements of ECG parameters, BP, pulse rate, and body temperature did not reveal any clinically relevant alterations after administration of the study medication. With regard to safety, both galenical formulations (pink or white tablet) administrated as a single oral dose of 250 µg roflumilast were well tolerated and safe.

Conclusions:

In the present study, the two galenical formulations of 250 µg roflumilast (pink vs. white tablets) were found bioequivalent based on the biostatistical analysis of the primary pharmacokinetic variables $AUC_{(0\text{-inf.})}$ and C_{max} for roflumilast and roflumilast N-oxide.

The safety data showed a good tolerability of both galenical formulations (pink and white tablet) and did not raise concern regarding the intake of these tablets as single oral doses of 250 µg roflumilast.