Synopsis of study report: 58/2002
Location in Module 5:

Study Code:
BY217/FHP039

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Title of the study: Pharmacokinetics of roflumilast and roflumilast-N-oxide after single and repeated oral administration of 250 µg or 500 µg roflumilast - an open, randomized, two-period crossover study (Study No. BY217/FHP 039)

Study center: Clinical Pharmacology Dept. of the University of Tübingen, Germany

Publication (reference): not applicable

Studied period (years): 25 July 2001 – 23 November 2001

Clinical phase: I

Objectives:

The main aim of the present study was to investigate, in healthy volunteers, the intra-individual dose proportionality of single and repeated oral administration of 250 µg and 500 µg roflumilast as demonstrated by pharmacokinetics of roflumilast and its metabolites roflumilast-N-oxide, ADCP and ADCP N-oxide. Further, the study also provided information on the safety and tolerability of this roflumilast treatment.

Methodology:

The trial was conducted as an open, randomized, two-period crossover monocenter study. It consisted of a screening examination (within 4 weeks before the first administration of study medication), two treatment periods of 12 days each, separated by a washout period of 10-14 days. A post-study examination was performed within 2 weeks after the end of the treatment. For pharmacokinetics blood samples were drawn at the following time points following single

or repeated oral doses of 250 and 500 µg of roflumilast:

- Study Day 1: at pre-dose, and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 30h, 48h, 72h, 96h after morning administration of study medication;
- Study Day 12: at pre-dose, and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 30h, 48h, 72h after morning administration of study medication.

No. of subjects: Nineteen healthy subjects (14 men, 5 women).

Diagnosis and criteria for inclusion: Healthy subjects, Caucasian, aged 18-45 years.

Test product: Roflumilast
Dose: 250 µg (Treatment A) and 500 µg (Treatment B)
Mode of administration: oral administration with 240 ml water, once daily, in the morning
Batch No.: 199130 (tablets of 250 µg) and 499130 (tablets of 500 µg)

Duration of treatment: Two treatment periods, each lasting 12 days. Within each treatment period, one tablet of roflumilast (250 µg/day in Treatment A and 500 µg/day in Treatment B) was administered as a single dose on Study Day 1 and as repeated dose from Study Day 5 to Study Day 12.

Reference product: none

Criteria for evaluation:

- Pharmacokinetics: Primary variables were the **AUC** and $\mathbf{t_{1/2}}$ of roflumilast (B9302-107) and roflumilast-N-oxide (B9502-044) measured in plasma samples after single and repeated oral administration of 250 µg or 500 µg roflumilast. Secondary variables were the C_{max} and t_{max} for roflumilast and roflumilast N-oxide.
- Safety and tolerability: Physical examination including vital signs (blood pressure, pulse rate) as well as a 12-lead-ECG, and clinical laboratory investigations (clinical chemistry, hematology, urinalysis) were used as safety variables. In addition, adverse events were monitored during the entire study.

Statistical methods:

The biostatistical analysis was performed employing the 'BIOQPC' program (Version 1.2.2). $AUC_{(0-\infty)}$ and $t_{1/2}$ values were evaluated using a multiplicative model, i.e. by the corresponding analysis of variance model after logarithmic transformation, yielding point estimates and 90% confidence intervals for the respective Test/Reference ratios. The test dose (500 µg single or repeated oral doses of roflumilast) were referenced to the reference dose

(250 µg single or repeated oral doses of roflumilast). The secondary pharmacokinetic variables C_{max} and t_{max} were analyzed for roflumilast and roflumilast N-oxide in an exploratory manner. A multiplicative model was applied for the variable C_{max}; for the variable t_{max}, an additive model was used.

The safety variables were analyzed in a descriptive manner using summary statistics (e.g. median, 68%-range, mean, SD) where appropriate.

SUMMARY - CONCLUSIONS

Pharmacokinetic results

Primarily, dose proportionality (AUC) between the 250 µg and 500 µg dose was evaluated. Dose proportionality was found for roflumilast and roflumilast N-oxide, after the single dose (Study Day 1) and in steady state (Study Day 12), when referenced to the 250 µg dose. For the evaluation, the conventional equivalence range from 0.8 to 1.25 was used.

AUC for	Roflumilast on Study Day 1		Roflumilast on Study Day 12	
	Point estimate	90% conf. limit	Point estimate	90% conf. limit
Roflumilast	0.96	0.89 – 1.04	1.04	0.99 – 1.10
Roflumilast N-oxide	1.01	0.95 – 1.08	1.07	1.01 – 1.13

Concerning further PK-characteristics, the terminal half-life of the 250 µg and 500 µg dose was evaluated. For roflumilast, a difference was found in steady state between the 250 µg and 500 µg dose (point estimate of 1.11 with a 90%-confidence interval of 0.95 to 1.30), but there were no differences after the single dose. For roflumilast N-oxide, no difference was found between the 250 µg and 500 µg dose, after the single dose and in steady state, when referenced to the 250 µg dose.

t 1/2 for	Roflumilast on Study Day 1		Roflumilast on Study Day 12	
	Point estimate	90% conf. limit	Point estimate	90% conf. limit
Roflumilast	1.09	0.94 – 1.25	1.11	0.95 – 1.30
Roflumilast N-oxide	1.04	0.98 – 1.10	0.95	0.84 – 1.07

Steady state levels for the 250 and 500 µg dose were reached at Study Day 12, since no difference with respect to AUC of roflumilast and roflumilast N-oxide after the single dose

(Study Day 1) and in steady state (Study Day 12) was detected, when referenced to the respective single dose.

AUC for	250 µg roflumilast		500 µg roflumilast	
	Point estimate	90% conf. limit	Point estimate	90% conf. limit
Roflumilast	**0.94**	**0.88 – 1.00**	**1.00**	**0.93 – 1.06**
Roflumilast N-oxide	**0.98**	**0.93 – 1.04**	**1.04**	**0.98 – 1.10**

Safety results: During treatment, a total of 79 AEs were reported by 18 subjects. Most AEs reported by the subjects were mild or moderate in intensity. Furthermore, 70% of the AEs reported during treatment with 250 µg roflumilast and 51% of those reported during treatment with 500 µg roflumilast were considered by the investigator as "unrelated" or "unlikely related" to the study drug. None of the symptoms experienced by the subjects were definitely related to the intake of roflumilast. The most frequently reported AE was headache which occurred in 47% of the subjects.

Conclusions: In the present study, a dose proportionality of roflumilast and roflumilast N-oxide was demonstrated after oral administration of a single dose and repeated once-daily doses of 250 µg and 500 µg roflumilast.

In addition, laboratory values (including blood chemistry, hematology, urinalysis) and measurements of blood pressure, pulse rate, and ECG parameters did not reveal any clinically relevant alterations after administration of the study medication. Treatment with 250 µg or 500 µg once-daily doses of roflumilast was well tolerated and safe.