# Synopsis of study report: 213/2000
# Location in Module 5:

**Study Code:**
BY217/FHP021

**Report Date:**
09-Apr-2002

**Title of the study:**

Comparison of pharmacokinetics of a single dose of 500 µg roflumilast p.o. in healthy non-smokers and smokers

**Study center(s):**

Department of Clinical Pharmacology (FHP)/Phase I Unit, Byk Gulden, Byk-Gulden-Str. 2, 78467 Konstanz, Germany

**Publication (reference):**

Not applicable

**Studied period (years):**

06/2000 – 08/2000

**Clinical phase:**

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**Objectives:**

Primary: pharmacokinetics of a single oral dose of 500 µg roflumilast in healthy subjects, smokers compared to non-smokers
Secondary: safety and tolerability of roflumilast

**Methodology:**

The study was conducted according to an open, single-dose, one-period, parallel-group design. To each smoking subject, a non-smoking subject of the same sex, and comparable in age, height and weight was allocated (matched pairs).
Blood samples for the determination of roflumilast and the active metabolite B9502-044 (roflumilast-N-oxide) were taken at pre-dose and at 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 24 h, 30 h, 48 h, 54 h and 72 h post-dose.
Roflumilast and metabolite B9502-044 plasma concentrations were determined by a validated assay using reversed-phase HPLC with fluorescence detection after post-column photochemical derivatisation. Sample clean-up was performed using liquid/liquid extraction. The lower limit of quantitation (LLOQ) was 0.085 µg/l for roflumilast and 0.5 µg/l for metabolite B9502-044.
The safety and tolerability assessment was based on 12-lead resting ECG, blood pressure and pulse rate measurements at pre-dose, 1 h, 2 h and 4 h post-dose, at screening and post-study examination, on clinical laboratory (clinical chemistry, haematology, urinalysis) at screening and post-study examination, and on adverse events (continuously monitored).

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

24 subjects, 12 smokers and 12 non-smokers

**Diagnosis and criteria for inclusion:**

Healthy, Caucasian, male or female, aged ≥ 18 to < 65 years; body weight according to Broca ≥ 0.8 to ≤ 1.25; matching criteria: same sex, age within ± 5 years, height within ± 10%, weight within ± 10%.

**Test product:**

Roflumilast, 0.5-mg tablet

**Dose:**

500 µg (1 tablet)

**Mode of administration:**

Oral

**Batch No.:**

010200

**Duration of treatment:**

Single dose

**Reference product:**

Not applicable

**Dose:**

Not applicable

**Mode of administration:**

Not applicable

**Batch No.:**

Not applicable

**Criteria for evaluation:**

Pharmacokinetics: $AUC_{0-\infty}$ and $C_{max}$ of roflumilast; AUC of the active metabolite B9502-044; $t_{½}$ of roflumilast and the active metabolite B9502-044; $t_{max}$ of roflumilast.
Safety and tolerability: 12-lead resting ECG, blood pressure and pulse rate; clinical laboratory (clinical chemistry, hematology, urinalysis); adverse events.

**Statistical methods:**

Primary variables were $AUC_{0-\infty}$ and $C_{max}$ as respective extent and rate characteristics of roflumilast and AUC of the active metabolite B9502-044. $AUC_{0-\infty}$ was calculated by the trapezoidal formula up to the least sampling time with a concentration above the limit of quantitation, and was extrapolated to infinity using standard techniques. $C_{max}$ of roflumilast was directly obtained from the measured concentrations.
$t_{½}$ of roflumilast and its metabolite and $t_{max}$ of roflumilast were analysed with an explorative intention. $t_{½}$ was analysed analogously to AUC assuming a multiplicative model. For $t_{max}$, an additive model was used.
Point estimate and 90%-confidence limits were given for the ratio of the population medians (smokers/non-smokers) of the two study groups. The 90%-confidence interval for the between-groups-comparison (smokers/non-smokers) was based on the two-sample (independent) t-test after logarithmic transformation.

Secondary variables were the results of safety measurements (ECG, blood pressure, pulse rate), determined during the study, and at the screening and post-study examination.

These secondary variables were analysed in a merely descriptive manner including summary statistics such as median, 68%-range, mean, SD, or SEM, geometric mean and geometric 68%-range, where appropriate. Relevant values of the ECG print-out were: PQ, QRS, QTc and heart rate.

**SUMMARY - CONCLUSIONS**

**Summary:**

Pharmacokinetics:

**Pharmacokinetic characteristics (geometric means/68%-range) of roflumilast and the metabolite B9502-044 following a single oral dose of 500 µg roflumilast to healthy smokers (n=12):**

| | Roflumilast | B9502-044 |
|---|---|---|
| $AUC_{0-\infty}$ [µg*h/l] | 37.33 (26.03, 53.54) | 459.10 (344.03, 612.67) |
| $C_{max}$ [µg/l] | 7.829 (6.435, 9.523) | 10.234 (8.538, 12.268) |
| $t_{½}$ [h] | 12.93 (8.78, 19.04) | 26.13 (18.65, 36.59) |
| $t_{max}$ [h][1)] | 0.90 (± 0.17) | 8.38 (± 1.30) |

[1)] $t_{max}$: mean (± SEM)

**Pharmacokinetic characteristics (geometric means/68%-range) of roflumilast and the metabolite B9502-044 following a single oral dose of 500 µg roflumilast to healthy non-smokers (n=12):**

| | Roflumilast | B9502-044 |
|---|---|---|
| $AUC_{0-\infty}$ [µg*h/l] | 42.56 (25.57, 70.85) | 391.02 (294.38, 519.37) |
| $C_{max}$ [µg/l] | 7.460 (5.611, 9.920) | 8.958 (7.753, 10.350) |
| $t_{½}$ [h] | 14.46 (7.67, 27.26) | 24.84 (16.80, 36.72) |
| $t_{max}$ [h][1)] | 0.94 (± 0.17) | 12.50 (± 2.18) |

[1)] $t_{max}$: mean (± SEM)

**Point estimates (90%-confidence intervals) of pharmacokinetic characteristics of roflumilast and its metabolite B9502-044 following a single oral administration of 500 µg roflumilast to healthy smokers (Test) and to healthy non-smokers (Reference):**

| Pharmacokinetic characteristics | Point estimates (90%-CI) Roflumilast | B9502-044 |
|---|---|---|
| $AUC_{0-\infty}$ | 0.877 (0.644, 1.196) | 1.174 (0.950, 1.451) |
| $C_{max}$ | 1.049 (0.884, 1.246) | – |
| $t_{½}$ | 0.894 (0.619, 1.292) | 1.052 (0.810, 1.366) |
| $t_{max}$ | -0.042 (-0.446, 0.363) | – |

Safety and tolerability:
A total of 23 adverse events were documented in 13 subjects. No deaths, no other serious adverse events and no withdrawals due to an adverse event occurred. Smokers suffered from more adverse events than non-smokers (17 adverse events in seven smokers versus six adverse events in six non-smokers). Most adverse events had an 'unlikely relation' to the study medication (no adverse events with a 'likely' or 'definite relation'), and were of 'mild' intensity (no adverse event of 'severe' intensity). 'Headache' was the most frequently reported adverse event in smokers and non-smokers. Results of haematology, clinical chemistry and urinalysis examinations as well as values of blood pressure, pulse rate and ECG parameters did not show any relevant changes over time. No conspicuous differences between smokers and non-smokers were discernible.

**Conclusions:**

Pharmacokinetics:
Following single oral administration of 500 µg roflumilast to 12 healthy smokers, the pharmacokinetic characteristics were found to be comparable to the corresponding values of a control group of healthy non-smokers. The smoking habit did not affect the pharmacokinetics of roflumilast in healthy subjects.

Safety and tolerability:
With regard to safety a single oral dose of 500 µg roflumilast was safe and well tolerated. 'Headache' was the most frequently reported adverse event in both, smokers and non-smokers.