Synopsis of study report: 143/2001
Location in Module 5:

Study Code:
BY217/FHP026

Report Version:
Final

Title of the study:
Investigation of a possible pharmacokinetic interaction between roflumilast and theophylline in healthy subjects - an open, randomized, two-period crossover study.

Study center(s):
AAI Deutschland GmbH & Co KG, 89231 Neu-Ulm, Germany

Publication (reference):

Studied period (years):
2001

Clinical phase:
I

Objectives:
Primary: Pharmacokinetic interaction between theophylline and roflumilast
Secondary: Pharmacokinetics of roflumilast and roflumilast N-oxide; safety and tolerability of both, theophylline and roflumilast

Methodology:
The study was conducted according to an open, randomized two-period crossover design.

- Blood samples for determination of the **pharmacokinetics of theophylline** were taken on study days 5 and 10 at predose and at 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 22h, 24h after morning oral administration.
- Blood samples for determination of the **pharmacokinetics of roflumilast and roflumilast N-oxide** were taken on study days 5 and 10 at predose and at 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 24h after morning oral administration.
- **12-lead resting ECG, blood pressure and pulse rate** were measured at the following time points: Screening and post-study examination.

  Theophylline-roflumilast period: on study days 1 to 10 at pre-dose; on study days 1, 6 and 10 at 1h, 2h, 4h, 6h, 8h and 10h after morning oral administration; additionally on study day 11 at 24h.

  Roflumilast period: on study days 1 to 5 at pre-dose; on study days 1 and 5 1h, 2h, 4h, 6h, 8h and 10h after morning oral administration; additionally on study day 6 at 24h.
- **Body temperature** was determined at the following time points: Screening and post-study examination.

  Theophylline-roflumilast period: on study days 1, 6 and 10 at pre-dose, additionally on study day 11 at 24h.

  Roflumilast period: on study days 1 and 5 at pre-dose; additionally on study day 6 at 24h.
- **Clinical laboratory** (clinical chemistry, hematology, urinalysis) was determined during the screening examination and the post-study examination, on study days 1, 6 and 10 at pre-dose and on study day 11 at 24 h in the theophylline-roflumilast period and on study days 1 and 5 at pre-dose, and on study day 6 at 24 h in the roflumilast period.
- **Adverse events** were monitored continuously during the study.
- **Troponin I levels** were measured at the following time points: Screening and post-study examination.

  Theophylline-roflumilast period: on study days 6 and 10 at pre-dose.

  Roflumilast period: on study days 1 and 5 at pre-dose.

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

Number of subjects planned: 24 Number of subjects analyzed: male 14 / female 15

Diagnosis and criteria for inclusion:

Healthy subjects of either sex, aged between 18 and 64 years

Test product:

Treatment A:	theophylline-roflumilast period:
Dose:	750 mg theophylline capsules (1 capsule of 375 mg extended-release formulation each at 7 a.m. and 7 p.m) on study days 1 to 10 *together with* 500 µg roflumilast tablets (1 tablet of 500 µg at 7 a.m.) on study days 6 to 10

Mode of administration:

p.o.

Batch No.:

roflumilast: 499110, theophylline: 200971

Duration of treatment:

10 days

Reference product:

Treatment B: Roflumilast period:

Dose:

500 µg roflumilast tablets (1 tablet of 500 µg at 7 a.m.) on study days 1 to 5

Mode of administration:

p.o.

Batch No.:

Roflumilast: 499110

Criteria for evaluation:

Pharmacokinetics: The primary variables of the study were the pharmacokinetic characteristics area under the curve ($AUC_{(0-24h)}$) and percent peak-trough fluctuation [%PTF = difference of maximum and minimum plasma concentration, divided by the average steady-state plasma concentration, in percent; = 100 * (C_{max} - C_{min})/C_{av}) with C_{av} = $AUC_{(0-24\ h)}$ / 24] for theophylline (theophylline-roflumilast period). The secondary variables of the study were the pharmacokinetic characteristics area under the curve ($AUC_{(0-24h)}$) and maximum plasma concentration (C_{max}) as the respective extent and rate characteristics of roflumilast and roflumilast N-

oxide. In addition, the time of maximum plasma concentration (t_{max}) and the terminal elimination half-life ($t_{1/2}$) were determined for roflumilast and roflumilast N-oxide (roflumilast period and theophylline-roflumilast period). Other secondary variables were possible gender differences regarding $AUC_{(0-24h)}$, C_{max} and $t_{1/2}$ of roflumilast and roflumilast N-oxide (roflumilast period). Pharmacokinetics of theophylline were calculated for study days 5 (reference) and 10 (test).

Statistical methods:

Descriptive

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics:

For theophylline, the primary variables $AUC_{(0-24h)}$ representing the systemic exposure as well as the peak trough fluctuation (%PTF) and the secondary variables (C_{max}, t_{max} and $t_{1/2}$) were not influenced by concomitant treatment of roflumilast. For roflumilast and its metabolite roflumilast N-oxide an influence on the systemic exposure and on the peak trough fluctuation was found during concomitant theophylline treatment. The metabolite roflumilast N-oxide was not significantly influenced by concomitant theophylline treatment. Increased systemic exposure and increased C_{max} levels in females found for roflumilast and roflumilast N-oxide could only partially be explained by the lower body weights of the female subjects and therefore higher dose/kg ratios. After adjustment to body weight, point estimates of the male/female ratio of AUC and C_{max} were within the reference range, however, 90% confidence intervals were still outside that range.

Safety and tolerability:

Despite higher systemic exposure and higher C_{max} of roflumilast, the combination of theophylline and roflumilast, especially in female subjects, was better tolerated with regard to adverse events than roflumilast alone. The tolerability of roflumilast appears to be dependent upon the peak-trough fluctuation, more than upon absolute C_{max} or AUC. Other safety parameters, i.e. vital signs, laboratory findings and ECG parameters, remained nearly unchanged, irrespective of the treatment. With regard to these safety parameters, no clinically relevant interaction could be observed.