Synopsis of study report: 121/2002
Location in Module 5:

Study Code:
BY217/CP-047

Report Version:
Version 1.0 (dated 16 June 2003)

Title of the study:

Investigation of a possible pharmacokinetic interaction between roflumilast and erythromycin in healthy male subjects - An open, two-period study -

Study center(s):

AAI Applied Analytical Industries Deutschland GmbH & Co KG, Wegenerstr. 13, 89231 Neu-Ulm, Germany

Publication (reference):

Not applicable

Studied period (years):

25-April-2002 – 28-May-2002

Clinical phase:

Phase I

Objectives:

The main objective was to investigate a possible pharmacokinetic interaction between roflumilast and erythromycin (Erythrocin 500® Neo film coated tablets).

The primary objective was to investigate a possible pharmacokinetic influence of a single dose of erythromycin (Erythrocin 500® Neo film coated tablets) on roflumilast and roflumilast N-oxide at steady state. The secondary objective was to investigate a possible pharmacokinetic influence of roflumilast and roflumilast-N-oxide at steady state on the single-dose pharmacokinetics of erythromycin. Further, safety and tolerability of roflumilast was evaluated after co-administration of erythromycin.

Methodology:

The trial was conducted as an open, monocenter two-period Phase I study. It consisted of a screening examination, two treatment periods and a post-study examination. During treatment period 1, a single dose of 1 tablet Erythrocin 500® Neo film coated tablet was administered (= Treatment A). During treatment period 2, repeated oral doses of 1 tablet (500 µg) roflumilast were administered for 11 days and a single oral dose of 1 tablet Erythrocin 500® Neo film coated tablet (588.0 mg erythromycin ethylsuccinate) was concomitantly administered on Study Day 11 (= Treatment B).

To investigate the pharmacokinetics of erythromycin, roflumilast and roflumilast-N-oxide, blood samples were taken on Study Day 1 of period 1 as well as on Study Days 10 and 11 of period 2 at the time points: pre-dose, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 16 h and 24 h.

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

Eighteen healthy male subjects.

Diagnosis and criteria for inclusion:.

Caucasian males of an age between 18 to 45 years; Normal weight acc. to Broca index ($0.8 \leq$ weight [kg]/(height [cm] - 100) ≤ 1.25); assessed as healthy, based on a screening examination including medical history, physical examination, blood pressure, pulse rate, ECG, and clinical laboratory results; written informed consent

Test product:

Roflumilast 500 µg tablets

Batch No.:

101160

Concomitant product:
Erythrocin 500® Neo film coated tablets (containing 588.0 mg erythromycin ethylsuccinate, corresponding to 500 mg erythromycin)

Batch No.:
83387VA

Doses:
Period 1 (Treatment A): A single dose of 1 tablet Erythrocin 500® Neo film coated tablet containing 588.0 mg erythromycin ethylsuccinate (corresponding to 500 mg erythromycin)

Period 2 (Treatment B): Repeated doses of 500 µg roflumilast (11 doses of 500 µg roflumilast/day) and concomitant administration of 1 tablet of Erythrocin 500® Neo film coated tablet on Study Day 11.

Mode of administration:
Administration following an overnight fasting. Study medication taken together with 200 ml tap water.

Duration of treatment:
Period 1 (Treatment A) lasted 1 day. Following single administration of 1 tablet Erythrocin 500® Neo film coated tablet blood samples were collected at predetermined time points up to 24 h post dose.
Period 2 (Treatment B) lasted 12 days. One tablet of roflumilast 500 µg was administered for 11 days and 1 tablet Erythrocin 500® Neo film coated tablet was concomitantly administered on day 11. On Study Days 10 and 11, blood samples were collected at predetermined time points up to 24 h post-dose.

Reference product:
None

Criteria for evaluation:
- Pharmacokinetics: Primary variables were $AUC_{(0\text{-}24h)}$ and C_{max} of the serum concentrations of roflumilast and its active metabolite roflumilast-N-oxide at steady state following repeated daily administration of 500 µg roflumilast without concomitant drug administration and following concomitant administration of 1 tablet Erythrocin 500® Neo film coated tablet. Secondary variables were $AUC_{(0\text{-}inf.)}$, C_{max} and $t_{1/2}$ of erythromycin following single administration of 1 tablet of Erythrocin 500® Neo film coated tablet without concomitant drug administration and during steady state of roflumilast.

- Safety and tolerability: Physical examination including vital signs (blood pressure, pulse rate, body temperature), 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 program BIOQPC (Version 1.2.2) was used for statistical evaluations.
Primary variables were the pharmacokinetic characteristics of roflumilast and its N-oxide metabolite at steady state. $AUC_{(0\text{-}24h)}$ and C_{max} were investigated as the respective extent and rate characteristics of roflumilast and its N-oxide metabolite at steady state. Point estimates for roflumilast and roflumilast-N-oxide AUC and C_{max} ratios of Treatment B (Study Day 11)/ Treatment B (Study Day 10) were given together with the respective 90% confidence intervals using a multiplicative model and a parametric analysis.
Lack of interaction was concluded if the 90% confidence interval was entirely within the equivalence range of 0.80 to 1.25 for $AUC_{(0\text{-}24h)}$ and 0.7 to 1.43 for C_{max}.

Secondary pharmacokinetic variables were further pharmacokinetic characteristics as $AUC_{(0\text{-}inf.)}$, C_{max}, and elimination half-life of erythromycin, which was analyzed in analogy to the corresponding characteristics of roflumilast and its N-oxide metabolite

Further secondary variables were the safety and tolerability assessments such as blood pressure, heart rate, ECG, and clinical laboratory at screening and post-study examination as well as adverse events. These secondary variables were analyzed in a descriptive manner.

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetic results: The geometric mean values of $AUC_{(0\text{-}24h)}$ and C_{max} reflect a similar systemic exposure of subjects to both roflumilast and roflumilast N-oxide on Study Day 10 (roflumilast alone) and Study Day 11 (roflumilast + erythromycin). Point estimates for the Test/Reference ratios for $AUC_{(0\text{-}24h)}$ and C_{max} and their 90% confidence intervals were within their equivalence ranges (0.80 – 1.25 for $AUC_{(0\text{-}24h)}$ and 0.70 to 1.43 for C_{max}). For C_{max} of roflumilast, no influence was observed even if the strict equivalence range of 0.8 to 1.25 was applied.

For erythromycin, a significant influence on the pharmacokinetic parameters $AUC_{(0\text{-}inf.)}$ and C_{max} was observed. For $AUC_{(0\text{-}inf.)}$, the point estimate for the Test/Reference ratio (0.79) and the lower limit of the 90% confidence interval (0.70 – 0.90) were outside the equivalence range (0.80 – 1.25). For C_{max}, the point estimate for the Test/Reference ratio (0.81) was inside, the lower limit of the 90% confidence interval (0.64 – 1.01) was outside the equivalence range (0.70 – 1.43).

The terminal elimination half-life of erythromycin remained unchanged during concomitant roflumilast administration (the point estimate for the Test/Reference ratio of $t_{1/2}$ and the upper and lower limits of the 90% confidence interval were inside the equivalence range of 0.80 to 1.25).

Safety results: During the study, a total of 21 AEs were reported by 10 subjects. Most of the AEs were mild or moderate in intensity. No serious adverse events occurred.

The AEs assessed "likely related" by the investigator and the sponsor included the following symptoms: headache, diarrhea, nausea, dizziness, twitching, and vomiting. The most frequently reported AE was headache.

Laboratory values (including blood chemistry, hematology, urinalysis), measurements of blood pressure, pulse rate, as well as ECG parameters did not reveal any clinically relevant alterations after concomitant administration of roflumilast and erythromycin. A single dose of 500 mg erythromycin (588.0 mg erythromycin ethylsuccinate) and repeated once daily doses of 500 µg roflumilast were safe and well tolerated. The administration of a single dose of 500 mg erythromycin during repeated administration of 500 µg roflumilast was also safe and well tolerated.

Conclusions: No influence on the pharmacokinetic parameters $AUC_{(0\text{-}24h)}$ and C_{max} was found for roflumilast and its metabolite roflumilast N-oxide by concomitant erythromycin treatment. Statistical analysis of pharmacokinetic parameters and the derived 90% confidence intervals confirmed the absence of an interaction of erythromycin on the steady-state pharmacokinetics of roflumilast and roflumilast N-oxide.

For erythromycin, a significant influence on the pharmacokinetic parameters $AUC_{(0\text{-}inf.)}$ and C_{max} was observed. These indicate a reduced rate and extent of oral bioavailability of erythromycin when 500 mg erythromycin (588.0 mg erythromycin ethylsuccinate) was administered following repeated oral once daily doses of 500 µg roflumilast.

The terminal elimination half-life of erythromycin remained unchanged during concomitant roflumilast administration. It can be concluded that the influence on the systemic exposure of erythromycin and on the maximum plasma concentration are not related to erythromycin eliminating processes. Therefore, the decrease of $AUC_{(0\text{-}inf.)}$ and C_{max} could be related to a decreased resorption of erythromycin under concomitant roflumilast administration.

During the study, a total of 21 AEs were reported by 10 subjects. Most of the AEs were mild or moderate in intensity. No serious adverse events occurred.

Overall, the safety data obtained in the present study indicate that a single dose of 500 mg erythromycin (588.0 mg erythromycin ethylsuccinate) and repeated, once daily doses of 500 µg roflumilast were safe and well tolerated. The administration of a single dose of 500 mg erythromycin during repeated administration of 500 µg roflumilast was also safe and well tolerated.