2 Synopsis

Title of the study:

Cardiovascular pharmacodynamic and pharmacokinetic drug-drug interaction study between single oral doses of 500 µg roflumilast and 100 mg sildenafil in healthy male volunteers.

Study center:

Dept of Clinical Pharmacology, Institute of Pharmacology and Toxicology, University Hospital of Tübingen, Otfried-Mueller-Str. 10, 72076 Tübingen, Germany

Publication (reference):

Not applicable

Studied period (years):

15-Sep-2006 to 23-Nov-2006

Clinical phase:

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Objectives:

The aim of the study was to assess the cardiovascular pharmacodynamic (blood pressure [BP] and pulse rate, electrocardiogram [ECG] and impedance cardiography [ZCG]) interaction between single oral doses of 500 µg roflumilast and 100 mg sildenafil relative to placebo.

Further objectives were to assess the pharmacokinetic (PK) interaction between single oral doses of 500 µg roflumilast and 100 mg sildenafil relative to placebo. In addition, safety and tolerability of single and combined oral doses of 500 µg roflumilast and 100 mg sildenafil relative to placebo in healthy male volunteers were assessed.

Methodology:

The study was conducted according to a single-center, single-dose, double-blind, placebo- and active-controlled double-dummy, within-subject, 4-period change-over design with randomly assigned, period-balanced treatment sequences. The study consisted of a screening

examination including laboratory tests, drug screening, and alcohol blood test (within 21 to 2 days before Day 1), 4 study periods of 7 days each with a washout interval between periods of at least 7 days (with administration of study medication on Day 1 of each period), and a post-study examination performed within 6 to 14 days after the last intake of study medication.

Healthy male subjects were randomly assigned to a treatment sequence and received the following treatments:

- Treatment A: 500 µg roflumilast and 100 mg sildenafil once daily (s.i.d.);
- Treatment B: 500 µg roflumilast and placebo s.i.d.;
- Treatment C: placebo and 100 mg sildenafil s.i.d.;
- Treatment D: placebo and placebo s.i.d.

Supine BP and pulse rate were measured on baseline (Day -1) and treatment (Day 1) days at pre-dose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h after dosing as well as on screening and post-study examination. In addition, BP and pulse rate after 1 min relaxed upright standing were taken on baseline (Day -1) and treatment (Day 1) days at pre-dose, 1.0, 2.0, 4.0, 6.0 and 8.0 h after dosing, on screening and post-study examination. Eight-hour profiles of supine ZCG were performed on Day –1 and Day 1 of each treatment. Signals were recorded at the following 12 time points: pre-dose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h after morning administration on the profile days and on screening and post-study examination. Supine ECG on baseline (Day –1) and treatment (Day 1) days was recorded at pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h after dosing and on screening and post-study examination. The assessment of the ZCG and ECG profiles was performed by an external center (ACPS – Applied Clinical Pharmacology Services).

Blood samplings for PK measurements were performed on Test Day 1 at pre-dose, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0 and 96.0 h after dosing. The plasma concentrations of roflumilast, roflumilast N-oxide, sildenafil and N-desmethyl sildenafil were determined using high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS). The lower limits of quantification were 0.1 µg/L for roflumilast and roflumilast N-oxide and 1 µg/L for sildenafil and N-desmethyl sildenafil.

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

In total, 12 healthy male subjects were included in the study.

Diagnosis and criteria for inclusion:

Healthy Caucasian male subjects, who had given their written informed consent and who fulfilled the following criteria, were included in the study:

- age between 18 and 45 years;
- normal body weight as indicated by a Body Mass Index between 18 and 28 kg/m^2 and a body weight >50 kg;
- assessed as healthy, based on a screening examination including medical history, physical examination, BP, pulse rate, ECG, and clinical laboratory results.

Study medication, dose, mode of administration, and batch No.:

- roflumilast 500 µg: 500 µg once daily as tablet per os; batch no. 440270;
- roflumilast placebo: once daily as tablet per os; batch no. 130290;
- sildenafil 50 mg: 100 mg once daily as encapsulated tablets per os; batch no. 5172705D;
- pantoprazole placebo 40 mg: 80 mg once daily as encapsulated tablets per os; batch no. 015165 (used as placebo capsules with regard to sildenafil capsules).

Duration of treatment:

All subjects were hospitalized from the evening of Day –2 to the morning of Day 2 (24 h after the administration of the double-blind trial medication if medically appropriate). The duration of each treatment was 1 day.

Criteria for evaluation:

Primary pharmacodynamic variables:

- recumbent and standing systolic BP (SBP), diastolic BP (DBP) and pulse rate;
- recumbent transthoracic ZCG: ZCG-estimated cardiac output (CO), total peripheral resistance (TPR), pre-ejection period (PEP), electromechanical systole (QS2), ventricular ejection time (VET), and maximum velocity of the transthoracic impedance changes (dZ/dt_{max});
- 12-lead digital ECG: heart rate (HR), PQ-interval, QRS-duration, QT-interval, uncorrected and corrected according to Bazett (QTc[B]), Fridericia (QTc[F]) and Framingham (QTc[Fra]).

Primary PK variables:

- area under the plasma concentration versus time curve extrapolated from time zero to infinity (AUC_{inf}) and maximum plasma concentration (C_{max}) of roflumilast and roflumilast N-oxide.

Secondary pharmacodynamic variables:

- all other variables resulting from transthoracic ZCG were treated as secondary variables.

Secondary pharmacokinetic variables:

- AUC from time zero to last quantifiable concentration (AUC_{last}), time to reach maximum concentration (t_{max}), terminal elimination half-life ($t_{1/2}$), apparent plasma clearance (CL/F; roflumilast) and average plasma concentration (C_{ave}) of roflumilast and roflumilast N-oxide;
- AUC_{inf}, C_{max}, AUC_{last}, t_{max}, $t_{1/2}$, CL/F (sildenafil) and C_{ave} of sildenafil and N-desmethyl sildenafil;
    - plasma protein binding of roflumilast and roflumilast N-oxide, expressed as free plama concentrations.

Secondary safety variables:

- non-invasive BP, pulse rate, clinical laboratory and adverse events (AEs).

Statistical methods:

All pharmacodynamic values entering the analyses were adjusted for time of day and for Day -1. All analyses were carried out calculating different summary measures that summarized the values of one subject and one treatment over clock-time of treatment day. The most prominent summary measure was the excess area under the curve (eAUC). Furthermore, minimum and maximum and AUC were calculated.

The primary PK variables were analyzed using an analysis of variance (ANOVA). Point estimates expressed as percentage (%) of the reference and their 90% confidence interval (CI) were computed for the test/reference ratio. The secondary pharmacodynamic and PK variables were analyzed descriptively, including summary statistics (e.g. geometric mean, arithmetic mean, standard deviation, minimum, median, maximum).

Incidences of AEs by preferred term and body system were presented in a descriptive manner. The clinical laboratory data were presented on an individual basis and were marked according to the normal ranges.

SUMMARY - CONCLUSIONS

Summary:

Demography

A total of 12 male Caucasian subjects were included in this study. Their median (range) age was 27 years (22, 40); median body height was 180 cm (174, 202); median body weight was 79 kg (65, 114); median body mass index was 25 kg/m^2 (19, 28). Two of the subjects were current smokers while the other 10 subjects were non-smokers.

Pharmacodynamic variables

Roflumilast

Roflumilast mono-therapy had little – if any – cardiovascular effect, the observed trend of smaller time-averaged changes in HR and smaller time-averaged changes in CO were noteworthy but of little relevance since they were quite small. Roflumilast treatment tended to shorten the electrocardiographic PR-interval, but had no effect on the QT and QTc-intervals. These results are in line with a thorough QT/QTc study which was conducted according to Food and Drug Administration (FDA) guideline and indicated no effect on QTc interval when roflumilast was administered at doses up to 1000 µg.

Sildenafil:

Sildenafil mono-therapy tended to lower the time-averaged BP changes from baseline, without reflectory tachycardia; instead, there was a trend towards smaller minimum and average HR changes from baseline relative to placebo. Sildenafil was associated with a larger maximum change and a smaller minimum change in QTc than roflumilast, with little effect on the average time-matched QTc-change from baseline.

Roflumilast & sildenafil combination treatment:

The combination of 500 µg roflumilast & 100 mg sildenafil showed its own distinct cardiovascular HR, BP, ZCG/STI and QT/QTc response pattern, which is not explained by mere additivity of the effects of the mono-therapies (500 µg roflumilast or 100 mg sildenafil). Although there were no relevant differences in the summary measures of the time-matched changes from baseline for the uncorrected QT of the combination treatment relative to placebo, the maximum and average change from baseline of the HR-corrected QT-intervals tended to be larger for the combination treatment, also relative to the mono-therapies roflumilast and sildenafil.

Pharmacokinetic parameter estimates

Roflumilast and roflumilast N-oxide

Similar systemic exposures (90% CIs entirely included in the equivalence range of 80 to 125%) were seen for roflumilast and roflumilast N-oxide after the application of roflumilast & sildenafil and roflumilast alone. A 24% lower peak concentration was seen for roflumilast, and a similar peak concentration (90% CIs entirely included in the equivalence range of 80 to 125%) was seen for roflumilast N-oxide after the application of roflumilast & sildenafil, when compared with roflumilast alone.

Sildenafil and N-desmethyl sildenafil

Similar systemic exposures (90% CIs entirely included in the equivalence range of 80 to 125%) were seen for sildenafil and for N-desmethyl sildenafil after the application of roflumilast & sildenafil and sildenafil alone. A 13% lower peak concentration was seen for sildenafil and a 25% lower peak concentration was seen for N-desmethyl sildenafil after the application of roflumilast & sildenafil, when compared with sildenafil alone.

Free Roflumilast and roflumilast N-oxide

The mean free plasma concentrations for roflumilast and roflumilast N-oxide were similar at 1.5 and 12 h after the application of roflumilast & sildenafil when compared with roflumilast alone.

Free Sildenafil and N-desmethyl sildenafil

The mean free plasma concentrations for sildenafil and N-desmethyl sildenafil at 1 h after the application of roflumilast & sildenafil were higher compared with sildenafil alone, and similar at 8 h after the application of roflumilast & sildenafil when compared with sildenafil alone. The mean free plasma concentrations for sildenafil and N-desmethyl sildenafil were higher at 1 h after the application of study medication when compared with those at 8 h.

Adverse events

During combination treatment, 11 subjects reported 69 AEs while 9 subjects reported 32 AEs during roflumilast mono-treatment. A total of 9 subjects reported 42 AEs when taking sildenafil alone, and 9 subjects reported 19 AEs when taking placebo. Most AEs were mild or moderate in intensity. AEs resolved completely in all cases. There were no SAEs or deaths reported and no AE led to premature study discontinuation.

Laboratory investigations, physical findings, and vital signs

Laboratory values did not show any relevant changes between the screening and post-study examination. Further, no relevant alterations were observed during physical examination. Fluctuations in HR and BP were seen frequently; however, these observations did not constitute a safety concern.

Conclusions:

Overall, safety data indicated that single co-administration of 500 µg roflumilast and 100 mg sildenafil was safe and well tolerated. None of the cardiovascular changes or effects observed for the experimental treatments is likely to be of clinical relevance. None of the observations raised safety concerns with regard to the combined administration of 500 µg roflumilast and 100 mg sildenafil.

Date of report: 13-Oct-2008