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Title of the study:
Investigation on the cardiovascular and pharmacokinetic interaction between oral roflumilast and inhaled formoterol in healthy subjects

Investigators:
Six investigators at IKP GmbH (Richard-Wagner-Str. 20, 67269 Grünstadt, Germany)

Principal investigator:
[redacted] (IKP GmbH, Richard-Wagner-Str. 20, 67269 Grünstadt, Germany)

Study center:
Institut für Klinische Pharmakologie Bobenheim, Prof. Dr. Lücker GmbH (IKP GmbH), Richard-Wagner-Str. 20, 67269 Grünstadt, Germany

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Objectives:
The aim of the study was to investigate a potential cardiovascular interaction between multiple doses of oral roflumilast and inhaled formoterol in healthy subjects, specifically assessed by ZCG.

Further objectives were potential pharmacokinetic interactions between both substances and potential pharmacodynamic interactions with regard to alterations of serum potassium and glucose concentrations (metabolic profile), blood eosinophils, and heart rate (HR) and QTc interval from electrocardiogram (ECG). In addition, safety and tolerability of the mono-treatments and the combination treatment were assessed.

Methodology:

This single center study had an open, randomized, controlled, multiple-dose, parallel-group design. Healthy male subjects were assigned to Treatment A or Treatment B. Subjects in Treatment A received 500 µg/d roflumilast from Day 2 to Day 18 and 48 µg/d formoterol from Day 12 to Day 18. Subjects in Treatment B received 48 µg/d formoterol from Day 2 to Day 18 and 500 µg/d roflumilast from Day 9 to Day 18. The study consisted of a screening examination including serology tests, drug screening, and ethanol breath test (within 21 d before Day 1), a treatment period of 18 days (with administration of study medication from Day 2 to Day 18), and a post-study examination performed within one week after the last intake of study medication.

Impedance cardiography (ZCG) and ECG recordings were performed on Days 1, 11, and 18 in Treatment A and on Days 1, 8, and 18 in Treatment B. For the time profile, signals were recorded at the following time points: pre-dose, 10 min, 20 min, 40 min, 60 min, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, and 8 h after morning administration of study medication. For ECG profiles, one additional measurement at +12 h was performed.

The ZCG analysis was carried out by one analyst at ACPS who was blinded with regard to subject, day, and time within day. The ECG tracings were evaluated by the investigator. In addition, electronically recorded tracings of the ECG measurements were sent to an external ECG reader center (ExCard Research, Berlin, Germany) for a subsequent centralized and treatment-blinded analysis, as prospectively planned for this study. For details, see ALTANA Pharma Expert Report 389/2004 (Report on Electrocardiographic Findings), a separately compiled external expert report. This analysis was the primary analysis of ECG variables.

Metabolic profiles of glucose and potassium were determined on Days 1, 11, and 18 (Treatment A) and on Days 1, 8, and 18 (Treatment B) at each time point of ZCG plus one additional measurement +12 h and +24 h after the morning dose of study medication.

Blood samplings for pharmacokinetic measurements were performed for Treatment A on Days 9 and 10 (trough levels), Day 11, and Day 18 and for Treatment B on Days 6 and 7 (trough levels), Day 8, and Day 18. Blood samples were taken at pre-dose, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, and 24 h after administration of study medication (the two last sampling times refer to roflumilast only).

For the pharmacokinetic analysis, plasma concentrations of roflumilast, roflumilast N-oxide, and formoterol were determined using high performance liquid chromatography coupled with tandem mass spectrometry. The lower limits of quantification were 0.01 ng/mL for roflumilast and roflumilast N-oxide and 0.04 pg/mL for formoterol.

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

In total, 27 healthy young male subjects were included in the study. Twelve subjects were assigned to Treatment A and 15 subjects to Treatment B.

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 30 kg/m^2 and a body weight > 50 kg;
- assessed as healthy, based on a screening examination including medical history, physical examination, blood pressure (BP), pulse rate (PuR), ECG, and clinical laboratory results.

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

- roflumilast: 500 µg once daily in the morning as tablet per os; batch no. 320200;
- formoterol: 24 µg twice daily (i.e. 48 µg/d) in the morning and in the evening administered by dry powder inhaler; batch nos. U0015 (subjects 001 – 024) and U0044 (subjects 118, 121, and 122).

Duration of treatment:

All subjects were hospitalized from Day –1 to Day 19. In Treatment A, subjects received roflumilast for 17 d (Day 2 to Day 18) and formoterol for 7 d (Day 12 to Day 18). In Treatment B, subjects received formoterol for 17 d (Day 2 to Day 18) and roflumilast for 10 d (Day 9 to Day 18).

Criteria for evaluation:

- **Primary variables:** heart rate (HR), PEP, QS2, dZ/dt_{max}, CO, and TPR from ZCG/STI (systolic time intervals);
- **Secondary variables:**
  Secondary variables from ZCG/STI: RR interval, PQ duration, QT interval, VET (ventricular ejection time), Z0, systolic BP, diastolic BP, mean BP, WI (Weissler Index), QS2/QT-ratio, and SV;

  Secondary pharmacodynamic variables: serum glucose, potassium levels, peripheral blood eosinophils, HR, and QTc interval from 12-lead standard ECG;

  Secondary safety variables: ECG variables PR, QRS, RR, and QT, noninvasive BP, pulse rate, clinical laboratory, adverse events;

  Secondary pharmacokinetic parameter estimates: apparent clearance (steady state) (CLssF), $AUC_{(0\text{-tlast}),}$ and C_{max} as respective extent and rate characteristics of roflumilast and its N-oxide (alone and with formoterol at steady state), and of formoterol (alone and with roflumilast at steady state).

Statistical methods:

The primary variables of the ZCG were analyzed descriptively, including summary statistics (e.g. median, minimum and maximum, 68% range, mean, SD). To assess overall effects of the study medication at steady state, comparisons of the pre-dose morning values were performed. Further, maximum and minimum differences in the within-day variability were assessed for the change from baseline to mono-treatment (sensitivity analysis). Two different approaches were taken: Firstly, the maximum (minimum) values during mono-treatment were directly compared with the maximum (minimum) value at baseline, untransformed and as change from pre-dose. Secondly, maximum (minimum) values after time-adjustment (untransformed or as change from pre-dose) during mono-treatment were compared with the value at the corresponding baseline time point. The description of the results is focused on the time-adjusted analysis. To assess the differences between mono-treatment and combination treatment, the time-adjusted maximum and minimum values untransformed and as change from pre-dose were compared between the respective profile days. All comparisons between treatment days as well as treatment days and baseline are presented as differences. For the comparisons, a non-parametric analysis of dependent samples (Wilcoxon signed rank test) with corresponding Hodges-Lehmann point estimate and 95% confidence interval were calculated.

The secondary pharmacodynamic variables and the safety variables were analyzed descriptively, including summary statistics (e.g. median, min and max, 68% range, mean, SD) where appropriate.

Pharmacokinetic parameter estimates were obtained with a non-compartmental analysis approach using WinNonLin professional, version 4.01. Pharmacokinetic parameter estimates for formoterol, roflumilast, and roflumilast N-oxide were determined using an extravascular model. No statistical analyses of pharmacokinetic parameter estimates were performed.

SUMMARY - CONCLUSIONS

Summary:

Demography

In this study a total of 27 male Caucasian subjects were included (12 in Treatment A and 15 in Treatment B [including three protocol violators in Treatment B]). Their median (range) age was 33 years (25, 44) in Treatment A and 33 years (21, 44) in Treatment B; body height was 184 cm (169, 192) in Treatment A and 180 cm (168, 185) in Treatment B; body weight was 83 kg (66, 95) in Treatment A and 75 kg (61, 97) in Treatment B; body mass index was 25 kg/m^2 (23, 28) in Treatment A and 24 kg/m^2 (21, 30) in Treatment B.

Primary pharmacodynamic variables from impedance cardiography

In both, Treatment A and Treatment B, the effects observed were real formoterol effects. Most likely, vasodilation was the primary effect of formoterol, leading to compensatory inotropic effects (with an increase in HR, CO, dZ/dt_{max} and a decrease in QS2). Roflumilast as mono-treatment (Treatment A) and added on to formoterol treatment (Treatment B) had no relevant effect on cardiovascular function.

Overall, the effects observed during formoterol treatment were expected for treatment with a β_2-adrenoceptor agonist. They were consistent but small and within the normal physiological range. Based on the data, roflumilast does not appear to potentiate these effects.

Secondary pharmacodynamic variables

Effects on pharmacodynamic variables observed during mono-treatment or combined treatment were consistent with the changes observed by ZCG/STI in both treatment groups. Well-known effects of β_2-adrenoceptor agonists and PDE inhibitors occurred, but were not amplified to a relevant degree by the add-on treatment with the second drug. Further, there was no evidence of a relevant pharmacodynamic interaction between roflumilast and formoterol in healthy subjects with regard to a potential influence on myocardial repolarization (i.e. QTc prolongation).

Pharmacokinetic parameter estimates for roflumilast, roflumilast N-oxide, and formoterol

The geometric means and the 68% ranges of the steady state pharmacokinetic parameter estimates of formoterol, roflumilast, and roflumilast N-oxide did not differ, regardless

whether formoterol and roflumilast were administered alone or in combination with each other.

Comparisons of the pharmacokinetic parameter estimates between treatments may suggest a trend in pharmacokinetic parameter estimates, depending on treatment sequence. For example, AUC and C_{max} of roflumilast had slightly lower values (by 10 to 15%) if roflumilast was added to formoterol treatment (i.e. Treatment B, Day 18) than during roflumilast treatment alone (Treatment A, Day 11) and if formoterol was added to roflumilast treatment (Treatment A, Day 18). Similarly, a 10% lower AUC of roflumilast N-oxide was observed in Treatment B during combined treatment with formoterol and roflumilast on Day 18, compared with Treatment A on Day 18. However, considering the parallel-group design of the study, these slight differences have to be interpreted with caution, since they are most likely reflecting the inter-subject variability across two parallel groups rather than a sequence effect.

Adverse events
In Treatment A, 7 subjects reported 17 AEs during roflumilast mono-treatment and 8 subjects reported 22 AEs during combination treatment with roflumilast and formoterol. In Treatment B, 6 subjects reported 17 AEs during combination treatment with formoterol and roflumilast. Notably, no AE was reported during formoterol mono-treatment. All AEs were mild or moderate in intensity. There were no deaths or other SAEs reported and no AE led to premature study discontinuation. Given the limitation by the restricted number of subjects treated, it appears that the combination treatment in both treatment groups reflects the shared acknowledged AE profile of both drugs with regard to ‘headache’ and ‘tremor’.

Laboratory investigations and physical findings
Laboratory values did not show any clinically relevant changes between the screening and post-study examination. Further, no clinically relevant alterations were observed during physical examination (including BP and body temperature).

Pulse rate (PuR) was increased in both treatments during administration of formoterol. Also, in Treatment A an increase from baseline was observed during roflumilast mono-treatment, while in Treatment B the additional treatment with roflumilast did not further increase PuR.

Conclusions:
The study results demonstrate that the combination of orally administered roflumilast and inhaled formoterol under steady-state conditions did not increase the pharmacodynamic effects of each other, particularly on the cardiovascular system. Further, they did not negatively influence the AE profile of each other.