2 Synopsis

Title of the study:

A study of the effects of steady state enoxacin on the single dose pharmacokinetics of roflumilast and roflumilast N-oxide.

Study center(s):

CRS Mannheim GmbH, Grenadierstrasse 1, 68167 Mannheim, Germany

Publication (reference):

Not applicable

Studied period:

06-Nov-2006 to 14-Dec-2006

Clinical phase: I

Objectives:

Primary objective:

- To evaluate the effects of steady state enoxacin on the single dose pharmacokinetics of roflumilast and roflumilast N-oxide.

Secondary objectives:

- To evaluate the safety and tolerability of roflumilast and co-administration of roflumilast and enoxacin.
- To evaluate the effects of steady state enoxacin on the total phosphodiesterases type 4 inhibitory capacity (tPDE4i).
- To evaluate the individual metabolic activities of CYP1A2 and CYP3A4 of all participating study subjects at baseline and their potential alteration by steady-state enoxacin treatment as assessed by caffeine and midazolam phenotyping, respectively.

Methodology:

The study was conducted as a phase I, open-label, non-randomized, fixed sequence, two-period, single-center, drug-drug interaction study in healthy male and female subjects. The study consisted of:

- One screening visit within three weeks prior to baseline (Study Days -21 to -3).
- Two treatment periods of eight days (Period 1, Study Days -2 to 6) and 14 days (Period 2, Study Days 7 to 20).
- A post-study examination on Study Day 21 or later.

No. of subjects (total and for each treatment): A total of 20 subjects were included in this study. Of these, 19 subjects were included in the analysis of pharmacokinetic variables.

Diagnosis and criteria for inclusion:

To be eligible, a subject had to comply with all of the following criteria:

- Subject had been informed both verbally and in writing about the objectives of the clinical study, the methods, the anticipated benefits and potential risks and the discomfort to which he/she could be exposed, and had given written consent to participation in the study prior to study start and any study-related procedure.
- Healthy, non-smoking, male and female, white (Caucasian origin) subjects, aged between 18 and 45 years (inclusive) and assessed as healthy based on a screening examination including medical history, physical examination, vital signs, electrocardiogram (ECG) assessment, and clinical laboratory results.
- Normal body weight as evidenced by a body mass index (BMI) between ≥18 and ≤28 kg/m², and a body weight ≥50 kg (female) and ≥60 kg (male).
- For females of child bearing potential (without using hormonal contraceptives for at least two months prior to start of screening) a double contraception method was requested during the whole study meeting the criteria for a highly effective method of birth control. That meant at least two effective birth control methods such as condoms, diaphragms or intra-uterine devices had to be used.

Duration of treatment:

The subjects received oral applications of

- 500 µg roflumilast once daily on Study Days 1 and 12;
- 400 (2 x 200) mg enoxacin twice daily on Study Days 7 to 18;
- 2 mg midazolam once daily on Study Days -1 and 11;
- 150 (3 x 50) mg caffeine once daily on Study Days -1 and 11.

Reference product, doses, modes of administration, batch number:

As this was a drug-drug interaction study, this was not applicable.

Test products, doses, modes of administration, batch numbers:

Treatment	Formulation	Dose/posology	Mode of administration	Manufacturer	Batch no.	Expiry date
Roflumilast 500 µg	tablet	500 µg once daily	oral	ALTANA Oranienburg	440270	09/2008
Enoxacin Enoxor® 200 mg	tablet	400 (2x200) mg twice daily	oral	Pierre Fabre Pharma	G00118	09/2008
Caffeine Percoffedrinol® N 50 mg	tablet	150 (3x50) mg once daily	oral	Lindopharm	0502	09/2008
Midazolam 5 mg/5 mL Dormicum® V	solution	2 mg once daily	oral	Hoffmann La Roche	F015711	09/2008

Criteria for evaluation:

Pharmacokinetics

Primary variables:

- AUC_{inf}, AUC_{tlast}, C_{max} of roflumilast and roflumilast N-oxide

Secondary variables:

- $t_{1/2}$, t_{max} and CL/F (apparent oral plasma clearance) of roflumilast
- $t_{1/2}$ and t_{max} of roflumilast N-oxide
- tPDE4i
- Metabolic ratio of caffeine (5-acetylamino-6-formylamino-3-methyluracil [AFMU] + 1-methylxanthine [1X] + 1-methyluric acid [1U]/ 1,7-dimethyluric acid [17U])
- Single midazolam concentration at 4 hours (h) after the application of midazolam (SMC_4).

Safety and tolerability (secondary variables)

- Adverse events, vital signs (blood pressure [BP], pulse rate [PR]), ECG, safety laboratory

Demographics (secondary variables)

- Age, weight, BMI

Statistical methods:

Pharmacokinetic parameters including log-transformed C_{max} and AUC values of roflumilast and roflumilast N-oxide were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals (CI) for Test (roflumilast with enoxacin) as a percentage of Reference (roflumilast alone) were generated. A clinically meaningful interaction could be excluded, if the upper bound of the two-sided 90% CIs of the primary variables were all below 200%. An interim analysis was not planned and not performed. Demographics were analyzed descriptively.

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics:

For **roflumilast**, a 56% (CI 90%: 19% to 104%) higher mean systemic exposure (AUC_{inf}), a 20% (CI 90%: 6% to 37%) higher mean peak concentration and a 36% (CI 90%: -51% to -16%) lower mean apparent oral clearance was seen after roflumilast & enoxacin when compared with roflumilast alone. For **roflumilast N-oxide**, a 23% (CI 90%: -3% to 54%) higher mean systemic exposure (AUC_{inf}) and a 14% (CI 90%: -24% to -2%) lower mean peak concentration was seen after roflumilast & enoxacin when compared with roflumilast alone. The **mean tPDE4i** was 25% (CI 90%: 0% to 58%) higher after roflumilast & enoxacin when compared with roflumilast alone.

For the **CMR**, at predose, a 59% lower mean value was seen after caffeine & enoxacin when compared with caffeine alone. At 8 h after the application of caffeine, a 55% lower mean value was seen after caffeine & enoxacin when compared with caffeine alone. On Day -1, a 36% lower mean value was seen at 8 h after the application of caffeine when compared with that at predose. On Day 11, a 30% lower mean value was seen at 8 h after the application of caffeine when compared with the value at predose. With respect to systemic exposure of roflumilast and roflumilast N-oxide, no correlation was seen between CMRs and the respective AUCs, neither after the application of caffeine or roflumilast alone, or after caffeine & enoxacin or roflumilast & enoxacin. With respect to apparent oral clearance of roflumilast, no correlation was seen with CMRs after caffeine alone and roflumilast alone. However, a weak correlation was observed between CMRs after caffeine & enoxacin and CL/F of roflumilast after roflumilast & enoxacin. This trend seemed to be mainly driven by Subject 17.

For **SMCs**, a 32% higher mean value was seen after midazolam & enoxacin when compared with midazolam alone. SMCs correlated weakly with the extent of exposure values of roflumilast and roflumilast N-oxide, after roflumilast alone. This correlation became stronger when midazolam & enoxacin and roflumilast & enoxacin were applied. For **enoxacin trough concentrations**, an 18% (CI 90%: 1% to 38%) higher mean value on Day 12 was seen when compared with that on Day 11.

Safety:

No serious AE occurred during the course of the study. A total of 55 adverse events (AE) were observed in 18 of 20 subjects included in the study.

Most AEs were of mild (51) and moderate (3) intensity. Twenty-five (25) AEs were assessed by the Investigator as likely related to the study medication; all other AEs (30) were assessed as unlikely or not related to the study medication.

The reported AEs with likely relation to the investigational medicinal product (IMP) roflumilast were nervous system disorders (headache, dizziness) and gastrointestinal disorders (nausea, diarrhea). These AEs are common adverse events which have also been observed in other clinical trials with roflumilast. One incident of headache was of severe intensity and was considered as likely related, due to the previous administration of the IMP. For treatment of the AE paracetamol was given to the subject. Under treatment with roflumilast 15 of the 20 subjects (75%) reported 18 AEs of which 14 AEs were assessed as likely related to the IMP. Under treatment with roflumilast & enoxacin 11 of the 20 subjects (55%) reported 12 AEs of which 10 were assessed as likely related to the IMP. So the co-administration of roflumilast and enoxacin did not increase the number of AEs.

All safety laboratory values, vital signs, and ECG evaluations remained within the ranges normally observed in clinical phase-I studies. No influence of the IMP was noted.

Conclusions:

A weak interaction between roflumilast and enoxacin was observed. Since the mean tPDE4i activity was only increase by 25%, this interaction is most likely not to be clinically relevant. Safety data indicate that treatment with roflumilast was safe and well tolerated, irrespective of whether administered alone or in combination with enoxacin. Any additional risks of the combined intake did not become apparent.

Date of report: 05-Nov-2007