2 Synopsis

Title of the study:

Effects of repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinylestradiol on the pharmacokinetics of roflumilast and roflumilast N-oxide.

This study was conducted at a single center

AAIPharma, Wegenerstr. 13, 89231 Neu-Ulm, Germany

Publication (reference): Not applicable.

Studied period:

28-Feb-2007 (first subject in) to 16-Jan-2008 (database lock)

Clinical phase:

Phase I

Objectives:

Primary objectives:

- to assess the single dose PK (pharmacokinetics) of roflumilast and roflumilast N-oxide in female subjects with and without OCs (oral contraceptives).

Secondary objectives:

- to assess safety and tolerability;
- to assess further PK characteristics;
- to evaluate the OCs effects on tPDE4i (total phosphodiesterase-4 inhibitory activity).

Methodology:

This was a Phase I, single center, open-label, non-randomized, fixed sequence, PK study after a single oral dose of 500 µg roflumilast in healthy adult female subjects. The eligibility of the subjects was evaluated during the screening visit (Day -28 to -2) and related procedures prior to study enrolment. Eligible subjects entered into the study treatment period which consisted of two treatment periods that were ordered in a fixed sequence:

Treatment Period I (Day –1 to Day 6):

A single dose of roflumilast was administered on one of the first 3 days of the individual female subject's menstrual cycle. The first day of the menstrual cycle was the day on which the menstruation (bleeding) began before 10.00 am. Study Day 1 was defined as the day of the roflumilast administration. Following the administration of roflumilast, blood samples for the analysis of roflumilast and its N-oxide metabolite were taken up to 120 h (Day 6) after roflumilast dosing.

Treatment Period II (Day 6 to Day 26):

In the subsequent Treatment Period II, a daily fixed combination of 0.075 mg gestodene and 0.03 mg ethinylestradiol (Minulet®) was administered over 3 weeks (21 days, Day 6 to 26 of the study). On Day 21, a single dose of roflumilast 500 µg was concomitantly administered.

Blood samples for the PK of roflumilast and its N-oxide metabolite were then taken over the subsequent 120 h (corresponding to Day 21 to 26 of the study).

The study was completed by an end of study examination which occurred on Day 27 or later. At least 5.5 mL of blood/sample was taken, using lithium-heparinized monovettes, for the sampling for roflumilast and roflumilast N-oxide. On Days 1 to 6 and Days 21 to 26 blood samples were taken at the following times: pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 h (36 samples) after roflumilast dosing on Day 1 and Day 21, respectively.

Bioanalytics of roflumilast and roflumilast N-oxide in the collected plasma samples was performed by the Department of Bioanalytics, Nycomed GmbH, Konstanz (former ALTANA Pharma AG) using a validated HPLC-MS/MS method (High Performance Liquid Chromatography with tandem mass spectrometry). The LLOQ (Lower Limit of Quantification) in plasma was 100 pg/mL using a sample volume of 0.2 mL.

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

It was planned to enroll 20 healthy pre-menopausal female subjects (without any hormonal OC intake for at least 2 preceding menstrual cycles prior to study entry) in order to achieve 16 subjects who would have completed the study according to protocol.

During the course of the study, 21 subjects were enrolled, of which 20 took study medication and completed the study.

Diagnosis and main criteria for inclusion:

To be eligible, females of Caucasian origin who had given their written consent to participate in the study, were aged between 18 and 40 years (inclusive) and assessed as healthy in a screening examination. They had a body weight >50 kg and a body mass index (BMI) ≥18 and ≤28 kg/m². In addition, they met the following criteria regarding safe contraception:

- safe contraception (females with child bearing potential) prior to study entry (without using hormonal contraceptives for at least 2 months prior to start of first study medication) which meant the use of effective birth-control methods such as condoms, diaphragms, intra-uterine devices or sexual abstinence, which were thought to be medically acceptable forms of birth control. Females with tubal ligation or females with vasectomized partners were to be included, too;
- safe contraception during the entire study using hormonal contraceptive containing 0.075 mg gestodene and 0.03 mg ethinylestradiol (study medication) plus other effective birth-control methods such as condoms, diaphragms or intra-uterine devices without hormone (with the exception of females with tubal ligation).

Test product, dose, mode of administration, batch no.:

Roflumilast, 500 µg tablet, once daily, administered orally on Day 1 (Period I) and on Day 21 (Period II) in the morning (between 06.00 and 09.00 am, after an overnight fast of at least 10 h).

Batch number: 440270 (roflumilast AP Oranienburg)
Expiry date: 30-Sep-2008

Reference product, dose, mode of administration, batch no.:

Minulet®, 0.075 mg gestodene and 0.03 mg ethinylestradiol (tablet), once daily, administered orally from study Day 6 to Day 26 (Period II) in the morning (between 06.00 and 09.00 am).

Batch number: N0416G (Minulet®, Wyeth Pharma GmbH)
Expiry date: 30-Sep-2008

Duration of treatment:

The total study duration for one subject was a minimum of 27 days: Day -1 to Day 6 (Period I) and Day 6 to Day 26 (Period II), plus an end of study examination on Day 27 or later.

Criteria for evaluation:

Primary Variables

- AUC_{tlast} (area under the plasma concentration vs. time curve until the last measured plasma concentration above or equal to the lower limit of quantification), AUC_{inf} (area under the plasma concentration vs. time curve extrapolated to until infinity), and C_{max} (maximum plasma concentration) of roflumilast and roflumilast N-oxide.

Secondary Variables

- $t_{1/2}$ (elimination half-life), t_{max} (time to reach maximum plasma concentration) and CL/F (apparent oral clearance) of roflumilast;
- $t_{1/2}$ and t_{max} of roflumilast N-oxide;
- tPDE4i.

Safety and tolerability:

- AEs (adverse events), vital signs (blood pressure, pulse rate), ECG, safety laboratory.

Demographics:

- Age, weight, BMI.

Statistical methods:

Roflumilast

PK parameters, including log-transformed C_{max} and AUC (area under the plasma concentration vs. time curve) values (primary variables) and CL/F values (secondary variable) of roflumilast and roflumilast N-oxide, were analyzed with an ANOVA (analysis of variance) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (roflumilast with OCs) 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% confidence intervals of all primary variables were all below 200%.

Since this analysis was only descriptive, no confirmatory statement was concluded from the results. The PK variables were presented descriptively by treatment, providing geometric mean, 68%-range, arithmetic mean, SD (standard deviation), SE (standard error of the mean), minimum, median, maximum.

tPDE4i

Total PDE4 inhibitory activity was analyzed descriptively by treatment providing geometric mean, 68%-range, arithmetic mean, SD (standard deviation), SE (standard error of the mean), minimum, median, maximum.

General

All other variables were analyzed descriptively.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Overall, 21 subjects were enrolled and 1 subject withdrew consent prior to treatment. The 20 subjects who received study medication each completed both treatment periods.

The median age of the subjects was 28.5 years (range: 19 to 37 years). All subjects were white females.

Demographic and other baseline characteristics

		Roflumilast 500 µg (N=20)
Age [years]	Median (range)	28.5 (19, 37)
Age group [n (%)]	18 to ≤25 [years]	5 (25.0)
	>25 to ≤35 [years]	13 (65.0)
	>35 [years]	2 (10.0)
Weight [kg]	Mean ± SD	60 ± 7
Height [cm]	Mean ± SD	166 ± 6
BMI [kg/m^2]	Mean ± SD	22 ± 2
Sex [n (%)][a]	Female	20 (100.0)
Race [n (%)][a]	Caucasian	20 (100.0)
Smoking status [n (%)]	Non-smokers	15 (75.0)
	Ex-smokers	5 (25.0)
Systolic BP [mmHg][a]	Mean ± SD	112 ± 11
Diastolic BP [mmHg][a]	Mean ± SD	70 ± 8
Pulse rate [bpm][a]	Mean ± SD	68 ± 10
Body temperature [C][a]	Mean ± SD	37 ± 0

[a] At screening.
BMI = Body mass index, BP = blood pressure, bpm = beats per minute, N = number of subjects, n = number of observations, SD = standard deviation.

Pharmacokinetic results

For roflumilast, mean ratios of AUC_{tlast} and AUC_{inf} indicated a 49% and 51% higher systemic exposure after roflumilast and OC (ie Period II) when compared with roflumilast alone (Period I). The mean ratio of C_{max}, indicated a 38% higher peak concentration after

roflumilast and OC when compared with roflumilast alone. For roflumilast N-oxide, mean ratios of AUC_{tlast} indicated a similar systemic exposure after roflumilast and OC when compared with roflumilast alone. The mean ratio of AUC_{inf} indicated a 14% higher systemic exposure after roflumilast and OC when compared with roflumilast alone. The mean ratio of C_{max} indicated a 12% lower peak concentration after roflumilast and OC when compared with roflumilast alone. Mean ratios of $tPDE4i_{last}$ (total PDE4 inhibitory activity using area under the plasma concentration vs. time curves until the last measured plasma concentration above or equal to the lower limit of quantification) and $tPDE4i_{inf}$ (total PDE4 inhibitory activity using area under the plasma concentration vs. time curves extrapolated to infinity) indicated a higher total PDE4 inhibition after roflumilast and OC when compared with roflumilast alone (11% and 17%, respectively). However, according to the predefined criterion in the protocol, a clinically meaningful interaction was not seen, since the upper bound of the two-sided 90% confidence intervals of AUC and C_{max} of roflumilast and roflumilast N-oxide were below 200%.

Safety results

Two baseline AEs were reported in this study. During Period I, 12 subjects (60.0%) experienced 27 AEs while 13 subjects (65.0%) experienced 48 AEs during Period II. One of these AEs in Period I was nausea for which 2 episodes were reported on one day by one subject (ie 28 AEs if both episodes are counted). The only severe AEs were vomiting in one subject and headache in three subjects for Period I, and vomiting in three subjects for Period II. All AEs were reported as recovered without sequelae.

No deaths, SAEs, or discontinuations due to AE occurred during either treatment period.

The most frequently reported AEs were classed as nervous system disorders (10 subjects [50.0%] during Period I and 12 subjects [60%] during Period II) and gastrointestinal disorders (7 subjects [35.0%] during Period I and 9 subjects [45.0%] during Period II). The most frequent AEs were headache (9 subjects [45.0%] during Period I and 12 subjects [60%] during Period II) and nausea (6 subjects [30.0%] during Period I and 7 subjects [35.0%] during Period II).

There were no safety concerns with respect to laboratory values, vital signs, ECG, and physical examination. The most notable treatment related AEs were headache and nausea. The only remarkable difference between the treatment periods was an increase in the number of reported AEs, which is probably explained by the relative length of the treatment periods (ie 1 week vs 3 weeks).

Conclusions:

A clinically relevant interaction between roflumilast and the oral contraceptive containing 0,075 mg gestodene + 0,03 mg ethinylestradiol was not seen.

Assessments of AEs, laboratory investigations, vital sign and ECG measurements, and physical examination examinations did not reveal any safety concerns. This study indicated that a single dose of 500 µg roflumilast was well tolerated when administered following 3 weeks daily administration of OCs.

Date of report: 21-Jul-2008