2 Synopsis

Title of the study:

Effects of cimetidine repeated oral dose 400 mg twice-daily co-administration on the pharmacokinetics of roflumilast and roflumilast-N-oxide

study center:

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Publication (reference):

Not applicable

Studied period (years):

02 March 2006 – 09 May 2006

Clinical phase: I

Objectives:

Primary objective:

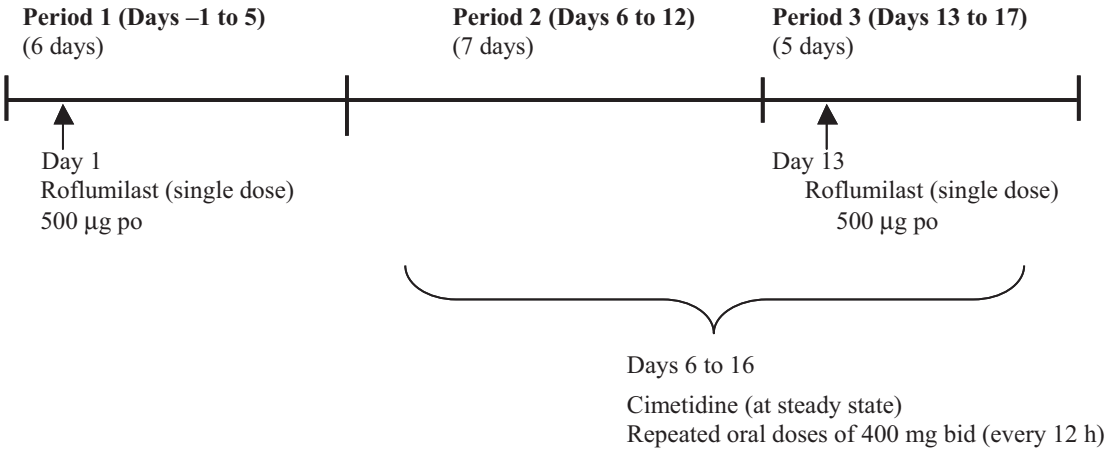
- To characterize the effects of repeated dose cimetidine 400 mg bid co-administration on the 500 µg single-dose pharmacokinetics of roflumilast and roflumilast N-oxide in healthy male and female adults.

Secondary objectives:

- To assess further pharmacokinetic parameters.
- To assess safety and tolerability throughout all treatment periods.

Methodology:

This study was conducted according to an open, single-center, non-randomized, three period, one fixed sequence design. It consisted of a screening examination, Period 1 (6 days) with single-dose roflumilast (500 µg per os [po] on Day 1), Period 2 (7 days) with repeated twice-daily (every 12 hours [h] = bid) doses of cimetidine (400 mg po on Days 6 to 12), Period 3 (5 days) with continued dosing of 400 mg cimetidine bid on Day 13 to Day 16 and roflumilast 500 µg po single dose co-administration on Day 13, and an end-of-study examination (on Day 18 or later).



Pharmacokinetic sampling for determination of roflumilast and its N-oxide metabolite plasma concentration-time profiles was done at the following times post-dose on Day 1 and Day 13, respectively: pre-dose, and 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 16 h, 24 h, 36 h, 48 h, 72 h, and 96 h post-administration.

Analytical method:

The plasma concentrations of roflumilast and roflumilast N-oxide were determined by a validated high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) detection method. The lower limit of quantitation (LLOQ) was 0.1 µg/L using a sample volume of 0.2 mL.

No. of subjects:

In total, 16 healthy subjects (8 males, 8 females) were included in this study performed in a single center.

Diagnosis and criteria for inclusion:

Eligible subjects were healthy male and female Caucasians, aged 18 to 45 years, with a normal body weight (i.e. a body mass index [BMI] between ≥18 and ≤28 kg/m^2 and a

minimum body weight of ≥50 kg), who gave their written informed consent. Women had to practice safe contraception (with the exception of hormonal contraceptives) which meant the use of effective birth control methods such as condoms, diaphragms, or intra-uterine devices which were thought to be medically acceptable forms of birth control in combination with spermicides.

Study medication, dose, mode of administration, batch no.:

- **Roflumilast**: 500 µg tablets, oral administration with 200 mL of water in the morning; batch No. 130230, manufactured by ALTANA Pharma Oranienburg GmbH
- **Cimetidine:** 400 mg tablets, oral administration with 200 mL of water in the morning and about 12 h after the morning administration; Tagamet®, manufactured by GlaxoSmithKline

Duration of treatment:

- **Roflumilast:** a single dose of 500 µg po administered in the morning on Day 1 (Period 1) and on Day 13 (Period 3)
- **Cimetidine:** 400 mg twice-daily (dosing interval of 12 h) po for 11 days (from Day 6 in Period 2 to Day 16 in Period 3)

Criteria for evaluation:

- **Primary pharmacokinetic parameter estimates:** area under the plasma concentration-time curve from time zero to last observed concentration (AUC_{last}),[1] maximum drug concentration in plasma (C_{max}) of roflumilast and roflumilast N-oxide, and apparent oral clearance (CL/F) of roflumilast after a single oral dose of 500 µg roflumilast administered alone (Period 1) or together with steady-state cimetidine (twice-daily doses of 400 mg po, Period 3)
- **Secondary pharmacokinetic parameter estimates:** time to reach maximum plasma concentration (t_{max}) and terminal half-life ($t_{1/2}$) of roflumilast and roflumilast N-oxide after a single oral dose of 500 µg roflumilast administered alone (Period 1) or together with steady-state cimetidine (twice-daily doses of 400 mg po, Period 3)
- **Safety variables:** Adverse events (AEs), laboratory work-up (including blood chemistry, hematology, urinalysis), physical examination, blood pressure (BP), pulse rate, body temperature, body weight, and 12-lead electrocardiogram (ECG, including heart rate, PQ [=PR], QRS, QT, and QTc parameters).

[1] The originally defined primary variable AUC extrapolated to infinity ($AUC_{0-\infty}$) needed to be changed to AUC_{last} as $AUC_{0-\infty}$ could not be determined in some of the subjects because the extrapolated area exceeded 20% of total AUC.

Statistical methods:

To compare the primary pharmacokinetic parameter estimates of roflumilast (AUC_{last}, C_{max}, and CL/F) and roflumilast N-oxide (AUC_{last}, C_{max}) between Period 1 (Reference) and Period 3 (Test), an analysis of variance (ANOVA) was performed where appropriate using the 90% confidence interval (CI). Geometric means were calculated as the antilogs of least-squares mean (LSM) log-transformed values (analogous to the geometric mean). Each primary pharmacokinetic parameter estimate was log-transformed prior to analysis. CIs of 90% for the ratio of the LSMs were performed. For each log-transformed parameter, a 90% CI was computed for the difference (Test-Reference) between the LSMs. The point estimates and confidence limits of the intervals were then exponentiated resulting in approximate 90% CI in the natural scale for the ratios of the geometric means. For AUC_{last} and C_{max} interaction was concluded if the corresponding two-sided 90% CIs were entirely above 1. As the Test/Reference ratio for CL is inversely proportional to the AUC ratio, interaction was concluded for CL if the corresponding two-sided 90% CIs were entirely below 1.

The secondary pharmacokinetic parameter estimate t_{max} was analyzed with a non-parametric analysis based on the untransformed data. The point estimate and the two-sided 90% confidence limits are given for the difference of the population medians for Test (single oral administration of roflumilast and co-administration of repeated oral dose of cimetidine) and Reference (single oral administration of roflumilast).

The safety variables were analyzed descriptively, including summary statistics (e.g. median, min and max, 68%-range, mean, standard deviation [SD]) where appropriate.

SUMMARY – CONCLUSIONS

Demographic data:

All 16 healthy subjects (8 males, 8 females) who entered the study were included and used for the evaluation of pharmacokinetic parameter estimates. All subjects were of Caucasian origin. Median [min, max] value for age was 25 [20 - 39] years, for body weight was 69 [53 - 110] kg, for BMI was 23 [20 – 28] kg/m^2, and for height was 174 [163 - 202] cm.

Pharmacokinetic results:

The pharmacokinetic parameter estimates AUC_{last}, C_{max}, CL/F and half-life indicate that inhibition of CYP 3A4 and CYP 1A2 enzymes with multiple administration of 400 mg bid cimetidine alters the single-dose pharmacokinetics of roflumilast (500 µg); it also increases the exposure and half-life of roflumilast N-oxide. The estimated tPDE4i activity was increased following the administration of roflumilast at steady-state cimetidine.

The AUC_{last} and C_{max} of roflumilast increased about 1.85-fold and 1.46-fold, respectively. The CL/F was decreased to 54%. The estimated half-life of roflumilast increased by approximately 32% following the administration of roflumilast with cimetidine.

Ratio percentage of roflumilast parameter estimates (ANOVA), geometric means and their respective 90% confidence intervals in healthy adults following single oral dose of 500 µg roflumilast administered alone (Reference) and together with twice-daily 400 mg cimetidine at steady state (Test)

Analyte	Dependent	N	Ref Geom. mean	Test Geom. mean	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast	C_{max} (µg/L)	16	6.84	9.99	146.12	125.78	169.75
	AUC_{last} (h•µg/L)	16	43.35	80.06	184.66	146.95	232.04
	$t_{1/2}$ (h)	16	22.00	29.08	132.20	114.78	152.28
	CL/F (L/h)	16	10.38	5.58	53.72	42.45	67.99

ANOVA = analysis of variance; CI 90 = 90% confidence interval; Ref = single oral dose of 500 µg roflumilast in Period 1; Test = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3. Ratio = (Test/Ref) x 100.

In contrast, AUC_{last} of roflumilast N-oxide showed a 1.27-fold increase. There was no alteration in $C_{max.}$ The estimated half-life of roflumilast N-oxide increased by approximately 42% when roflumilast was administered with cimetidine.

Ratio percentage of roflumilast N-oxide parameter estimates (ANOVA), geometric means and their respective 90% confidence intervals in healthy adults following single oral dose of 500 µg roflumilast administered alone (Reference) and together with twice-daily 400 mg cimetidine at steady state (Test)

Analyte	Dependent	N	Ref Geom. mean	Test Geom. mean	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast N-oxide	C_{max} (µg/L)	16	9.48	9.13	96.29	82.60	112.25
	AUC_{last} (h•µg/L)	16	448.43	570.69	127.27	103.60	156.34
	$t_{1/2}$ (h)	16	26.53	37.79	142.44	128.44	157.97

ANOVA = analysis of variance; CI 90 = 90% confidence interval; Ref = single oral dose of 500 µg roflumilast in Period 1; Test = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3. Ratio = (Test/Ref) x 100.

The estimated tPDE4i activity was approximately 48% higher when roflumilast was administered with cimetidine.

Ratio percentage of tPDE4i estimate (ANOVA), geometric mean and 90% confidence interval in healthy adults following single oral dose of 500 µg roflumilast administered alone (Reference) and together with twice-daily 400 mg cimetidine at steady state (Test)

Dependent	N	Ref Geom. mean	Test Geom. mean	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
tPDE4i	16	0.98	1.44	147.70	133.61	163.26

ANOVA = analysis of variance; CI 90 = 90% confidence interval; Ref = single oral dose of 500 µg roflumilast in Period 1; Test = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3. Ratio = (Test/Ref) x 100.

Safety results:

There were no deaths, SAEs, or unexpected AEs during this study. During treatment, a total of 43 AEs were reported by 15 subjects (93.8% of all subjects). The reported AEs were either mild or moderate in intensity with the exception of one episode of severe headache under cimetidine treatment. The AEs resolved completely in all cases and none of the AEs led to study discontinuation. The most frequently reported AE was headache which occurred in 11 (68.8%) of the 16 subjects.

Laboratory values did not show any clinically relevant changes between the screening and post-study examination. After intake of the study medication, no clinically relevant alterations were observed during physical examination (including ECG and vital signs).

Conclusions:

The outcome of the present study conducted in 16 healthy subjects (8 males, 8 females) demonstrates the effects of metabolic enzyme inhibition of the CYP 3A4 and CYP 1A2 pathway with cimetidine on the PDE4 inhibitor roflumilast and its pharmacodynamically active N-oxide metabolite.

The pharmacokinetic parameter estimates AUC_{last}, C_{max}, CL/F and half-life indicate that multiple administration of cimetidine 400 mg bid alters the single-dose pharmacokinetics of roflumilast (500 µg); it also increases the exposure (AUC_{last}) and half-life of roflumilast N-oxide. The estimated tPDE4i activity was increased following the administration of roflumilast at steady-state cimetidine.

Overall, safety data indicated that administration of a single oral dose of roflumilast (500 µg) with twice-daily oral doses of cimetidine (400 mg) was safe and well tolerated in this study.

Date of report: **28-Feb-2007**