Synopsis of study report: 8/2005
Location in Module 5:

Title of the study:

Effects of rifampicin (600 mg repeated oral dose) co-administration on the pharmacokinetics of roflumilast (500 µg single oral dose) and roflumilast N-oxide.
A CYP3A4 inducer study in healthy male subjects.

Study center(s):

AAI Applied Analytical Industries Deutschland GmbH and Co. KG, Neu-Ulm, Germany

Publication (reference):

Not applicable

Studied period (years):

16 September 2004 till 16 October 2004

Clinical phase:

Phase I

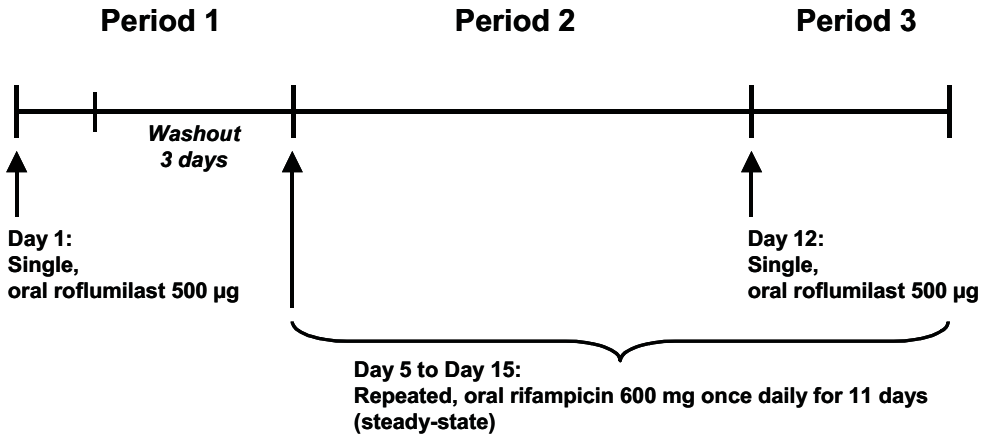
Objectives:

The primary objective of this study was to investigate the effects of steady-state rifampicin (600 mg repeated oral dose) co-administration on the pharmacokinetics of roflumilast and roflumilast N-oxide after a single oral dose of 500 µg roflumilast. The secondary objectives were to assess safety and tolerability throughout all treatment periods.

Furthermore, plasma concentrations of the metabolites ADCP and ADCP N-oxide were assessed.

Methodology:

This study was conducted according to an open-label, three-period, fixed-sequence design. It consisted of a screening examination, Period 1 (1 day), a washout period (3 days), Period 2 (7 days), Period 3 (4 days), and a post-study examination. The study design did not involve any washout phase between Period 2 and Period 3. A schematic depiction of the study design is shown below:



Period 1: Administration of a single, oral dose of roflumilast 500 µg once daily in the morning of study Day 1

Period 2: Repeated administration of oral rifampicin 600 mg once daily in the morning of study Day 5 to Day 11

Period 3: Continued (repeated) once-daily, oral administration of rifampicin 600 mg in the morning of Day 12 to Day 15 and co-administration of a single oral dose of roflumilast 500 µg in the morning of study Day 12.

Blood samples for measuring plasma concentrations of roflumilast and roflumilast N-oxide over time for pharmacokinetic analyses were taken at:

Period 1: pre-dose, and 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 30 h, 48 h, 54 h, 72 h and 96 h after administration. Period 1 is regarded as the pre-induction phase and will be referred to accordingly hereafter.

Period 3: pre-dose, and 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 30 h, 48 h, 54 h, 72 h and 96 h after administration. Period 3 is regarded as the induced phase and will be referred to accordingly hereafter.

Blood samples collected in Period 3 and used to assess roflumilast and roflumilast N-oxide in plasma were also used to measure plasma concentrations of ADCP and ADCP N-oxide.

Blood samples to determine plasma concentrations of rifampicin and to check for adequate exposure were collected pre-dose on Day 5, Day 10, and Day 11 during Period 2. On Day 12 (Period 3), blood samples were taken pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, and 3 h after administration.

The plasma concentrations of roflumilast, roflumilast N-oxide, ADCP, and ADCP N-oxide were determined using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay. The plasma concentrations of rifampicin were determined by using a validated liquid chromatography method with ultraviolet detection.

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

16 healthy male subjects

Diagnosis and criteria for inclusion:

Eligible subjects were healthy male Caucasians, aged 18 to 45 years, with a normal body weight (> 60 kg) and BMI > 18 and < 30 kg/m², and who gave their written informed consent.

Test product:

Roflumilast

Dose:

Roflumilast 500 µg once daily

Mode of administration:

Oral

Batch No.:

Roflumilast: 055203

Reference product:

Rifampicin

Dose:

Rifampicin 600 mg once daily

Mode of administration:

Oral

Batch No.:

Rifampicin: 003014

Duration of treatment:

Single oral roflumilast 500 µg was administered once daily on Study Day 1 and Day 12; Repeated, oral rifampicin 600 mg was administered once daily for 11 days (Day 5 to Day 15).

Criteria for evaluation:

The primary variables were the area under the plasma concentration-time curve extrapolated to infinity ($AUC_{(0-\infty)}$), and the maximum plasma concentration (C_{max}) of roflumilast and roflumilast N-oxide on Day 1 to Day 5 during pre-induction phase and Day 12 to Day 16 during induced phase.

The secondary variables were the ratio of $C_{max}/AUC_{(0-\infty)}$, the apparent oral clearance (CL/F), the terminal half-life ($t_{1/2}$), and the time to reach the maximum plasma concentration (t_{max}) of roflumilast, and $C_{max}/AUC_{(0-\infty)}$, $t_{1/2,}$ and t_{max} of roflumilast N-oxide metabolite on Day 1 to Day 5 (without concomitant administration of rifampicin = pre-induction phase) and Day 12 to Day 16 (under steady state condition of rifampicin = induced phase).

Plasma concentrations of rifampicin, ADCP, and ADCP N-oxide were assessed descriptively. Furthermore, safety and tolerability parameters were assessed throughout the study.

Statistical methods:

Pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide following oral administration were obtained by standard non-compartmental analysis using the program WinNonlin Professional, Version 4.1. Calculation of pharmacokinetic parameter estimates for rifampicin was not performed, as this was not the objective of this study. Exposure comparison for roflumilast and roflumilast N-oxide at pre-induction phase and during induced phase was based on the comparison of $AUC_{(0-\infty)}$, and AUC_{last} which denotes the AUC up to the last measured time point.

SUMMARY - CONCLUSIONS

Pharmacokinetic Summary:

The results of this study indicate that potent induction of CYP3A4 enzymes with rifampicin significantly influences the primary pharmacokinetic parameter estimates ($AUC_{(0-\infty)}$ and C_{max}) of roflumilast and roflumilast N-oxide in healthy male subjects.

Following the induction of CYP3A4 with rifampicin, the extent ($AUC_{(0-\infty)}$) and rate (C_{max}) of systemic exposure to roflumilast decreased by about 79% and 68%, respectively when compared with the respective values of roflumilast under non-induced conditions. In contrast, roflumilast N-oxide showed only a decrease in $AUC_{(0-\infty)}$ of 56% whereas C_{max} was increased by 30%. The increase of C_{max} of roflumilast N-oxide in the induced phase is consistent with the observed increase in CL/F of roflumilast, i.e. the rate of conversion of roflumilast to its N-oxide metabolite was considerably higher when compared to the non-induced phase. Statistical comparison of the key inferential parameter CL/F in Period 1 and Period 3 confirmed this observation: CL/F of roflumilast was almost five-fold higher in Period 3 and which may explain the decrease in $AUC_{(0-\infty)}$ and C_{max} of roflumilast.

Notably, under CYP3A4 induction, the decrease of $AUC_{(0-\infty)}$ of roflumilast N-oxide (56%) was less pronounced when compared with the decrease of roflumilast $AUC_{(0-\infty)}$ (79%), which suggests that the relative contribution of CYP3A4 on the clearance of the N-oxide metabolite may be lower than for the parent compound roflumilast.

Percent ratios of Test/Reference[a] of roflumilast pharmacokinetic parameter estimates based on least-squares geometric mean and the respective lower and upper limits of the 90% confidence interval (ANOVA). Calculations were performed with observations from N = 15 subjects in Period 1 (Reference) and Period 3 (Test).

Pharmacokinetic parameter estimate	RefGeo LSMean	TestGeo LSMean	Difference	Ratio (% Ref)	CI 90 Lower	CI 90 Upper
$AUC_{(0-\infty)}$ (h*µg/L)	37.77	7.80	-1.577	20.66	15.81	27.01
AUC_{last} (h*µg/L)	34.29	6.50	-1.663	18.95	14.50	24.77
CL/F (L/h)	13.24	64.06	1.577	483.92	370.24	632.49
C_{max} (h)	6.78	2.17	-1.139	32.02	26.37	38.87

[a] Percent rations = (Period 3 'roflumilast+rifampicin'/Period 1 'roflumilast alone') x 100.

Percent ratios of Test/Reference[a] of roflumilast N-oxide pharmacokinetic parameter estimates based on least-squares geometric mean and the respective lower and upper limits of the 90% confidence interval (ANOVA). Calculations were performed with observations from N = 15 subjects in Period 1 (Reference) and Period 3 (Test).

Pharmacokinetic parameter estimate	RefGeo LSMean	TestGeo LSMean	Difference	Ratio (% Ref)	CI 90 Lower	CI 90 Upper
$AUC_{(0-\infty)}$ (h*µg/L)	407.15	180.19	-0.815	44.26	35.80	54.71
AUC_{last} (h*µg/L)	363.06	177.00	-0.718	48.75	41.41	57.40
C_{max} (h)	9.38	12.23	0.265	130.40	114.79	148.13

[a] Percent rations = (Period 3 'roflumilast+rifampicin'/Period 1 'roflumilast alone') x 100.

T_{max} of roflumilast N-oxide also reflected the increased formation rate. In the same subject population, median t_{max} values showed tendencies towards shorter t_{max} for roflumilast N-oxide after induction and longer t_{max} without induction. Elimination $t_{1/2}$ was also decreased about three-fold.

Rifampicin plasma concentrations as determined on Study Day 12 showed that all subjects had expected and adequate exposure to rifampicin.

In all blood samples taken during Period 3, ADCP and ADCP N-oxide plasma concentrations were below the lower limit of quantitation. Thus, co-administration of roflumilast and rifampicin did not affect the formation of ADCP and ADCP N-oxide.

Safety and Tolerability Summary:

During the three study periods, 14 (88%) of the 16 subjects included in the study reported a total of 40 AEs. The intensities of almost all (39 AEs) of the reported AEs were mild or moderate. In most cases, symptoms subsided spontaneously after short duration. All AEs resolved completely. Overall, the most frequently reported AE (irrespective of causal relationship to study medication) was headache, which occurred in 8 (50%) subjects. None of the AEs led to study discontinuation and no serious or unexpected AEs or deaths were reported.

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 from physical examination (including ECG and vital signs).

Conclusions:

The outcome of the present study demonstrates the effects of metabolic enzyme induction of the CYP3A4 pathway with the potent inducing agent rifampicin on the PDE4 inhibitor roflumilast and its pharmacodynamically active N-oxide metabolite. Roflumilast and roflumilast N-oxide are low hepatic extraction entities, which are predominantly metabolized in the liver (and with regard to CYP3A4 activity, there is an ancillary contribution of the gut wall). From previous studies it is known that only very small amounts of roflumilast and roflumilast N-oxide are excreted unchanged via the renal route. As such, the disposition of roflumilast and roflumilast N-oxide may be altered by the induction of their principal/key metabolizing enzymes.

In this study, a substantial decrease in AUC (by 79%) and C_{max} (68%) of roflumilast was observed following the induction with rifampicin as compared to non-induced conditions. These findings were consistent with the observed increase in roflumilast CL/F, which was about five-fold higher following the induction with rifampicin. In contrast, roflumilast N-oxide showed a decrease in AUC by 56% and an increase in C_{max} by 30%.

Notably, ADCP and ADCP N-oxide were not affected by the induction of metabolizing enzymes investigated in this study.

The safety data obtained in the present study indicate that co-administration of roflumilast 500 µg and rifampicin 600 mg was well tolerated. With regard to roflumilast, no new safety and tolerability signals emerged from this study.