Synopsis of study report: 225/2004
Location in Module 5:

Study Protocol No.:
BY217/CP-060

Report Version:
Version 1.0

Title of the study:

Pharmacokinetic and clinical safety drug-drug interaction study between roflumilast 500 µg repeated oral dose and montelukast 10 mg single oral dose alone and repeated dose with roflumilast in healthy male subjects. Open, three fixed period study

Study center:

University Hospital Tübingen, Clinical Pharmacology Department, Otfried-Müller-Str. 45, 72076 Tübingen (Germany)

Publication (reference):

Not applicable

Studied period (years):

03 May 2004 – 15 July 2004

Clinical phase: I

Objectives:

Primary objectives:

- To investigate the effects of steady-state roflumilast (500 µg p.o.) co-administration on the single-dose pharmacokinetics of montelukast (10 mg p.o.)
- To investigate the effects of steady-state montelukast (10 mg p.o.) co-administration on the steady-state pharmacokinetics of roflumilast (500 µg p.o.)

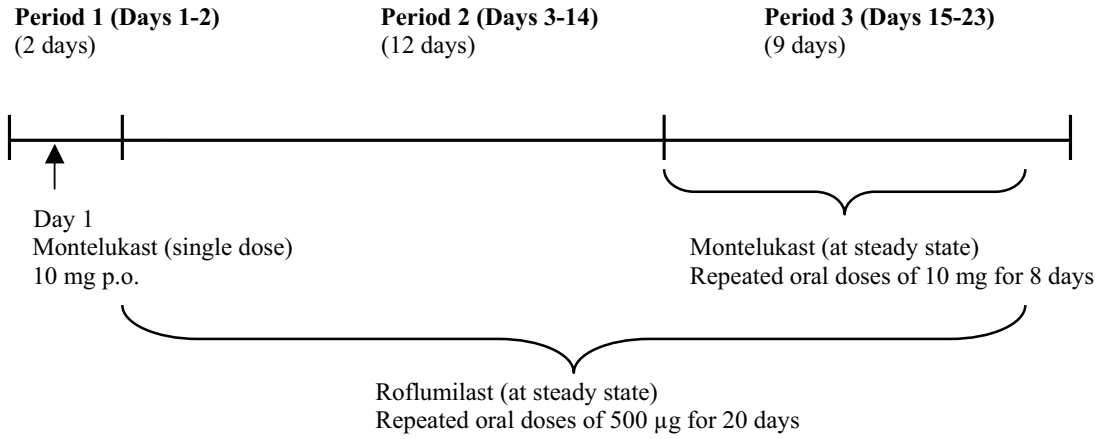
Secondary objectives:

- To assess the effects of steady-state roflumilast (500 µg p.o.) co-administration on the safety and tolerability of montelukast following a single oral dose of montelukast (10 mg)
- To assess the effects of steady-state montelukast (10 mg p.o.) co-administration on the safety and tolerability of steady-state roflumilast (500 µg p.o.)

Methodology:

This study was conducted according to an open, non-randomized, three period, one sequence design. It consisted of a screening examination, Period 1 (2 days) with single-dose montelukast (10 mg p.o. on Day 1), Period 2 (12 days) with repeated once-daily doses of roflumilast (500 µg p.o. on Days 3-14), Period 3 (9 days) with repeated doses of montelukast (10 mg p.o.) co-administered once-daily with roflumilast (500 µg p.o. on Days 15-22), and a post-study examination (on Day 23).

Repeated once-daily doses of 500 µg roflumilast were administered for a total of 20 days within Periods 2 and 3 (on Days 3-22), while repeated once-daily doses of 10 mg montelukast were administered for a total of 8 days in Period 3 (on Days 15-22).



The evaluation of the pharmacokinetic parameter estimates of montelukast, roflumilast and roflumilast N-oxide were based on their plasma levels determined at the following time points: at pre-dose, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 16 h and 24 h after oral administration of study medication.

The 24 h pharmacokinetic measurements were made on the days indicated below:

- **Study Day 1:** after a single oral dose of 10 mg montelukast administered alone
- **Study Day 14**: after daily oral doses of 500 µg roflumilast administered alone for 12 days (steady-state)
- **Study Day 15:** after oral co-administration of single-dose montelukast (10 mg) and steady-state roflumilast (500 µg)
- **Study Day 22:** after 8 days oral co-administration of 10 mg montelukast (steady-state) and 500 µg roflumilast (steady-state)

Trough values were determined on Study Days 12, 13, 14 (Period 2) for roflumilast and roflumilast N-oxide as well as on Study Days 20, 21, 22 (Period 3) for montelukast, roflumilast, and roflumilast N-oxide.

Analytical Method:
Plasma concentrations of montelukast were determined by using a validated High Performance Liquid Chromatography (HPLC) assay with fluorescence detection. The limit of quantitation in plasma (LLOQ) was 5 ng/mL for montelukast using a sample volume of 0.2 mL. The plasma concentrations of roflumilast and roflumilast N-oxide were determined by using a validated High Performance Liquid Chromatography with tandem Mass Spectrometry (HPLC-MS/MS) assay. The LLOQ was 0.10 ng/mL using a sample volume of 0.4 mL.

No. of subjects:

In total, 24 healthy male subjects were included in this study performed in a single center.

Diagnosis and criteria for inclusion:

Eligible subjects were healthy male Caucasians, aged 18 to 45 years, with a normal body weight, who gave their written informed consent.

Study medication, Dose, Mode of administration, Batch No.:

- **Roflumilast**: 500 µg tablets, oral administration with 240 mL of water in the morning; batch No. 130220, manufactured by ALTANA Pharma Oranienburg GmbH
- **Montelukast:** 10 mg tablets, oral administration with 240 mL of water in the morning; batch No. 235532, Singulair® 10 mg, commercially available from Dieckmann Arzneimittel GmbH

Duration of treatment:

- **Roflumilast:** once-daily doses of 500 µg p.o. administered in the morning for 20 days (Study Day 3-22, steady-state)
- **Montelukast:** single oral dose of 10 mg on Study Day 1, and once-daily doses of 10 mg p.o. administered for 8 days (Study Days 15-22, steady-state)

Criteria for evaluation:

- **Primary pharmacokinetic parameter estimates:** apparent oral clearance (CL/F), area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of montelukast (alone [single-dose] and with roflumilast at steady state), roflumilast and roflumilast N-oxide (alone at steady state and with co-administration of montelukast)
- **Secondary pharmacokinetic parameter estimates:** time to reach maximum plasma concentration (t_{max},) and terminal half-life ($t_{1/2}$) of montelukast, roflumilast and roflumilast N-oxide on Study Days 1, 14, 15 and 22

  Safety variables: Adverse events (AEs), laboratory work-up (including blood chemistry, hematology, urinalysis), physical examination, blood pressure (BP), pulse rate, body temperature, and 12-lead ECG (including heart rate, PR, QRS, QT, and QTc parameters).

Statistical methods:

The primary pharmacokinetic parameter estimates (AUC, C_{max}, and CL/F) of analytes were compared between treatments with the WinNonLin linear mixed effects modeling (bioequivalence wizard) to perform an analysis of variance (ANOVA) using the 90% confidence interval (CI) for the least-squares means (LSM). Each pharmacokinetic parameter estimate was log-transformed prior to analysis and a 90% CI was computed for the difference (Test-Reference) between the LSMs. Point estimates and confidence limits were then exponentiated resulting in approximate 90% CIs in the original scale for the ratios of geometric means.

Percentage ratios of geometric means for AUC, C_{max}, and CL/F of montelukast, roflumilast, and roflumilast N-oxide of the respective Test/Reference were calculated as stated above. Lack of interaction was concluded if the 90% confidence interval was entirely within the equivalence range of 0.80 to 1.25 for AUC and CL/F, and within the equivalence range of 0.70 to 1.43 for C_{max}.

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

SUMMARY – CONCLUSIONS

Demographic data:

All 24 healthy male subjects who entered the study were analyzed and used for the evaluation of pharmacokinetic parameter estimates. All subjects were of Caucasian origin. Median [min, max] value for age was 26 [18-44] years, for body weight was 78 [62-97] kg, and for height was 182 [170-192] cm.

Pharmacokinetic results:

Montelukast

Statistical comparison of primary pharmacokinetic parameter estimates of montelukast following single oral dose administered alone and together with steady-state roflumilast indicated a 9% increase in exposure (AUC) when single dose of montelukast was co-administered with roflumilast at steady state. Single-dose montelukast co-administration with roflumilast at steady state showed 9% decrease in apparent clearance (CL/F) when compared with single dose of montelukast administered alone.

Pharmacokinetic parameter estimates of montelukast after single oral dose of 10 mg administered alone (montelukast Reference) and together with 500 µg roflumilast at steady state (montelukast Test); geometric means, 68%-range

Parameter	Montelukast (N=24)	
	SD alone (Day 1)	SD with steady-state roflumilast (Day 15)
AUC	**2499.721***	**2733.523***
(hr*µg/L)	1800.707, 3470.085	1971.099, 3790.854
CL/F	**4.000**	**3.658**
(L/hr)	2.881, 5.553	2.638, 5.073
C_{max}	**347.481**	**376.202**
(µg/L)	233.857, 516.311	257.013, 550.665

*$AUC_{(0-\infty)}$; ** AUC_{tau}
SD = single dose; SS = steady state

Point estimates and 90%-confidence interval for the Test/Reference ratios of the primary pharmacokinetic parameter estimates for montelukast after single oral dose of 10 mg montelukast alone (Reference) and together with once-daily doses of 500 µg roflumilast (Test)

Montelukast SD alone (Reference, N=24)	Montelukast SD, Roflumilast SS (Test, N=24)	
	Ratio (% Ref)	90% CI
AUC	**109.353**	94.598, 126.410
CL/F	**91.447**	79.108, 105.711
C_{max}	**108.266**	91.401, 128.242

SD = single dose; SS = steady state

Roflumilast and roflumilast N-oxide

There was no change in primary pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide after steady-state montelukast co-administration (repeated oral doses of 10 mg/day).

Pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide after steady-state administration of 500 µg roflumilast alone (roflumilast/roflumilast N-oxide Reference) and with concomitant steady-state montelukast treatment (10 mg/day, Test)
geometric means, 68%-range

	Roflumilast (N=24)		Roflumilast N-oxide (N=24)	
	Roflu SS alone	Roflu SS with montelukast SS	Roflu SS alone	Roflu SS with montelukast SS
AUC_{last}	**35.216**	**34.524**	**417.205**	**412.004**
(hr*µg/L)	26.037, 47.632	25.448, 46.836	328.513, 529.841	324.418, 523.236
CLss_F	**14.198**	**14.483**	NA	NA
(L/hr)	10.502, 19.194	10.675, 19.650	NA	NA
C_{max}	**7.29**	**6.973**	**23.767**	**23.463**
(µg/L)	5.336, 9.959	5.223, 9.310	19.420, 29.087	18.624, 29.560

CLss_F: apparent oral clearance at steady state; Roflu SS = roflumilast at steady state
NA = not applicable

The pharmacokinetic results for the parent drug and metabolite met the predefined equivalence criteria. For C_{max}, not only the equivalence range of 0.7 to 1.43 postulated in the study protocol was met but also the standard equivalence range of 0.80 to 1.25.

Point estimates and 90%-confidence interval for the Test/Reference ratios of the primary pharmacokinetic parameter estimates for roflumilast and roflumilast N-oxide after steady-state administration of 500 µg roflumilast alone (Reference) and together with steady-state montelukast treatment (10 mg/day, Test)

	Roflumilast (N=24)		Roflumilast N-oxide (N=24)	
	Ratio (% Ref)	**90% CI**	**Ratio (% Ref)**	**90% CI**
Test: montelukast SS, roflumilast SS; Reference: roflumilast SS alone				
AUC_{last}	**98.035**	84.632, 113.560	**98.753**	87.952, 110.881
CLss_F	**102.005**	88.059, 118.159	NA	NA
C_{max}	**95.646**	82.681, 110.644	**98.720**	88.875, 109.654

SS = steady state; CLss_F: apparent oral clearance at steady state; NA = not applicable

Safety results:

During treatment, a total of 81 AEs were reported by 21 subjects (88% of all subjects). The reported AEs were either mild or moderate in intensity, and they resolved completely in all cases. The most frequently reported AE was headache which occurred in 14 (58%) of the 24 subjects. None of the events were classified as serious AEs and none of them led to study discontinuation. No 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 during physical examination (including ECG and vital signs).

Conclusions:

The pharmacokinetic parameter estimates CL/F, AUC, and C_{max} indicate that multiple oral administration of 10 mg montelukast do not alter the steady-state pharmacokinetics of roflumilast (500 µg) and roflumilast N-oxide.

In contrast, steady-state roflumilast co-administration results in a clinically insignificant increase (9%) in the single dose AUC of montelukast. This is reflected by a 9% decrease in montelukast apparent clearance.

Overall, the safety data obtained in the present study indicate that co-administration of daily oral doses of 500 µg roflumilast and 10 mg montelukast were safe and well tolerated. Therefore, no roflumilast or montelukast dose adjustment is warranted when both drugs are administered together.