Synopsis of study report: 163/2003
Location in Module 5:

Study Protocol No.:
BY217/CP-055

Report Version:
1.0

Title of the study:
Investigation of a possible pharmacokinetic interaction between once daily 500 µg roflumilast and a single dose of 200 mg ketoconazole in healthy subjects – an open study

Study center(s):
FARMOVS-PAREXEL Clinical Research Organization, Bloemfontein, South Africa

Publication (reference):
None

Studied period (years):
July until August 2003

Clinical phase:
I

Objectives:
Primary
Influence of a single oral dose of ketoconazole on the pharmacokinetics of roflumilast and roflumilast N-oxide at steady-state

Secondary
Safety and tolerability

Methodology:

The following procedures were performed during the study:

Safety

Medical history, physical examination, core body temperature, blood pressure and pulse rate, 12-lead ECG, adverse events, clinical laboratory parameters, urinalysis, drug screening and ethanol breath test, pregnancy test (in females of child-bearing potential).

Pharmacokinetics

Determination of roflumilast and roflumilast N-oxide concentrations in plasma.

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

Twenty-six healthy subjects of either sex were enrolled in this study. The total population could be less, but had not to exceed more than 50% of females. All subjects received both study drugs, roflumilast and ketoconazole.

Diagnosis and criteria for inclusion:

This was a phase I study conducted in healthy subjects. Therefore, the main criteria for inclusion were age restrictions and a body weight according to the Broca index.

Test product:

Roflumilast with ketoconazole (on Day 11)

Dose:

A single oral dose of 500 µg roflumilast on Days 1 to 11, co-administered with a single oral tablet of 200 mg ketoconazole on Day 11

Mode of administration:

Oral tablets

Batch No.:

320190 (roflumilast)
02CL475 (ketoconazole)

Duration of treatment:

Eleven days of dosing

Reference product:

Roflumilast (on Day 10)

Dose:

A single oral dose of 500 µg roflumilast on Days 1 to 11

Mode of administration:

Oral tablets

Batch No.:

320190

Criteria for evaluation:

Primary Variables

AUC(0-24h) and Cmax,ss of roflumilast and of roflumilast N-oxide on Day 10 (reference treatment: roflumilast alone) and on Day 11 (test treatment: roflumilast+ketoconazole). Blood samplings for pharmacokinetic purposes (roflumilast and roflumilast N-oxide) were drawn on Days 10 and 11 at pre-dose, and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h and 24h after morning administration of study medication. To confirm that steady state conditions had been reached, pre-dose blood sampling was also performed on Days 8 and 9, immediately prior to intake of the tablet. A baseline blood sample was collected on Day 1, before the first administration of study medication.

Secondary Variables

tmax, t½ and body weight normalized apparent clearance at steady state (CLss/ FBW) for roflumilast. Results of safety measurements and adverse events.

Statistical methods:

The test treatment [Day 11 (roflumilast+ketoconazole)] was compared with the reference treatment [Day 10 (roflumilast alone)] with respect to the pharmacokinetic variables AUC(0-24h) and Cmax,ss for roflumilast and roflumilast N-oxide, using an analysis of variance accounting for subject and treatment effects, after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the 'roflumilast+ketoconazole / roflumilast alone' mean ratios of those variables were calculated.

Based on this analysis of variance point estimates and 90% confidence intervals for the ratio 'roflumilast+ketoconazole' / 'roflumilast alone', it could be concluded that there was no relevant interaction of ketoconazole on roflumilast, if the calculated (confirmatory) 90% confidence intervals for AUC(0-24h) and Cmax,ss were completely contained in the

conventional equivalence range of 80% to 125%. Pharmacokinetic characteristics tmax, t½ and body weight normalized apparent clearance at steady state (CLss/ FBW) for roflumilast, as well as the results of safety and tolerability assessments were presented descriptively.

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics

A summary of pharmacokinetic characteristics [geometric mean (68% range); tmax: median (min/ max)] of roflumilast and roflumilast N-oxide at Day 10 (roflumilast alone) and Day 11 (roflumilast+ketoconazole) is displayed below:

Pharmacokinetic Characteristic	Roflumilast		Roflumilast N-oxide	
	Roflumilast – Day 10 – n=25	**Roflumilast +Ketoconazole – Day 11 – n=24**	**Roflumilast – Day 10 – n=25**	**Roflumilast +Ketoconazole – Day 11 – n=24**
$AUC_{(0-24h)}$ [µg/l*h]	50.1	69.9	641.3	575.9
	(33.1, 75.9)	(48.9, 99.8)	(454.8, 904.4)	(417.1, 795.3)
$C_{max,ss}$ [µg/l]	8.48	9.24	38.13	31.09
	(6.61, 10.89)	(6.88, 12.41)	(27.03, 53.78)	(22.32, 43.29)
t_{max} [h]	1.00	1.50	4.00	4.00
	(0.50, 3.00)	(0.50, 3.00)	(1.50, 4.00)	(2.00, 6.00)
$t_{1/2}$ [h]	13.44	14.46	n.a.	n.a.
	(10.04, 17.98)	(10.07, 20.77)		
CLss/FBW [l/h/kg]	0.1424	0.1024	n.a.	n.a.
	(0.0985, 0.2059)	(0.0726, 0.1444)		

The effect of concomitant ketoconazole administration on roflumilast and roflumilast N-oxide pharmacokinetics, based on point estimates and 90% confidence intervals for the Test/Reference ratios of roflumilast and roflumilast N-oxide, is given in the following table:

Pharmacokinetic Characteristic	Roflumilast n=24		Roflumilast N-oxide n=24	
	Point estimate	90% confidence interval	Point estimate	90% confidence interval
$AUC_{(0-24h)}$	1.34	1.29 – 1.39	0.88	0.86 – 0.89
$C_{max,ss}$	1.06	0.98 – 1.16	0.80	0.77 – 0.83
CLss/FBW	0.75	0.72 – 0.77	n.a.	n.a.

Based on AUC values, a single dose of ketoconazole increased roflumilast steady-state exposure approximately 34%, but had no effect on roflumilast N-oxide exposure. Steady-state Cmax values of roflumilast were similar with ketoconazole administration while Cmax values of roflumilast N-oxide decreased about 20%. Increased systemic exposure of roflumilast was related to the significant reduction of roflumilast apparent clearance and can be attributed to concomitant ketoconazole administration.

Safety

One serious adverse event occurred (tracheitis that led to hospitalization). The subject recovered without sequelae, and the adverse event was considered to be not related to the study medication. Two subjects experienced adverse events that lead to premature discontinuation. Both subjects recovered without sequelae. A total of 57 adverse events were reported in 21 subjects, 51 adverse events in 20 subjects during the roflumilast treatment period, and 6 adverse events in 3 subjects during the roflumilast+ketoconazole treatment period. Headache was the most frequently reported adverse event in both treatment groups. No clinically relevant hematology, clinical chemistry or urinalysis results were seen. Changes from baseline for vital signs and ECG parameters were comparable between the roflumilast and the roflumilast+ketoconazole treatment period.

Conclusions:

Concomitant ketoconazole administration generated a significant increase (34%) in the systemic exposure of roflumilast. Roflumilast N-oxide systemic exposure was not significantly decreased under concomitant ketoconazole administration. Overall, the administration of roflumilast together with ketoconazole was safe and well tolerated.