Synopsis of study report: 162/2003
Location in Module 5:

Study Protocol No.:
BY217/CP-050

Report Version:
1.0

Title of the study:

Steady state pharmacokinetics of 500 µg roflumilast of healthy elderly (≥ 65 years) subjects compared with healthy young (18 to 45 years) and healthy middle aged (46 to 64 years) subjects. An open, three parallel group comparison.

Study center:

FARMOVS-PAREXEL Clinical Research Organization, Bloemfontein, South Africa.

Publication (reference):

None

Studied period (years):

May to June 2003

Clinical phase:

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Objectives:

Primary: Pharmacokinetics of roflumilast and roflumilast N-oxide under steady state conditions in healthy elderly subjects (aged ≥ 65 years), compared to healthy young subjects (aged 18 to 45 years), and to healthy middle aged subjects (aged 46 to 64 years).
Secondary: Safety and tolerability.

Methodology:

The following procedures were performed during the study:

Pharmacokinetics: Determination of roflumilast and roflumilast N-oxide in plasma.
Safety: Medical history, physical examination, core body temperature, blood pressure and pulse rate, 12-lead ECG, adverse events, clinical laboratory parameters.

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

Young: 22 healthy subjects, 19 to 44 years of age (11 male, 11 female)
Middle aged: 22 healthy subjects, 46 to 64 years of age (11 male, 11 female)
Elderly: 22 healthy subjects, 65 to 76 years of age (12 male, 10 female)

Diagnosis and criteria for inclusion:

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

Test product:

Roflumilast

Dose:

500 µg (tablet) roflumilast once daily at Days 1 to 15

Mode of administration:

Oral tablet

Batch No.:

320 190

Duration of treatment:

Fifteen days of dosing

Reference product:

None

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

Primary Variables: AUCT and $t_{½}$ of roflumilast and of roflumilast N-oxide on Day 15. Blood samplings for pharmacokinetic purposes were performed on Day 15 at pre-dose, and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 26h, 48h, 72h, 96h, 120h and 144h after morning administration of study medication.
To confirm that steady state conditions had been reached, pre-dose blood sampling was also performed on Days 13 and 14 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: $C_{max,ss}$ and t_{max} of roflumilast and of roflumilast N-oxide. Results of safety measurements and adverse events.

Statistical methods:

Pharmacokinetic parameter estimates were calculated using a traditional, non compartmental approach with WinNonLin (Version 4.01). For the comparison of pharmacokinetic parameters between the 3 populations, an analysis of variance (ANOVA) using the 90% CI for the ratio of the least-squares means (LSM) were performed using WinNonLin (Version 4.01) bioequivalence wizard. Each pharmacokinetic parameter estimate was log-transformed prior to analysis. For each log-transformed parameter a 90% CI was computed for the difference (test-reference) between the means. The endpoints of the intervals were then exponentiated resulting in approximate 90% CIs in the natural scale for the ratios of geometric means.
Pharmacokinetic characteristics Cmax,ss and tmax of roflumilast and roflumilast N-oxide, safety and tolerability assessments were presented descriptively.

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics/ Pharmacodynamics

Summary of pharmacokinetic characteristics of **roflumilast** in healthy male and female subjects after 15 days of once-daily oral doses of 500 µg roflumilast [geometric mean, (68% range); t_{max}: median (min/max)]:

Roflumilast		**C_{max} [ug/L]**	**AUCT [h*ug/L]**	**CLss/FBW [L/h/kg]**	**$t_{1/2}$ [h]**	**t_{max} [h]**
Elderly	Value	10.17	67.20	0.1016	30.98	1
(n=22)	Range	12.29 - 8.42	93.11 - 48.50	0.1397 - 0.0739	41.93 - 22.88	1.5 - 0.5
Middle aged	Value	8.17	52.48	0.1260	28.78	1.00
(n=22)	Range	10.97 - 6.09	76.48 - 36.01	0.1814 - 0.0875	39.80 - 20.81	0.5 - 2
Young	Value	8.74	53.10	0.1264	30.29	1.00
(n=19)	Range	11.54 - 6.62	76.49 - 36.86	0.1844 - 0.0866	46.40 - 19.77	4 - 0.5

Summary of pharmacokinetic characteristics of **roflumilast N-oxide** in healthy male and female subjects after 15 days of once-daily oral doses of 500 µg roflumilast [geometric mean, (68% range); t_{max}: median (min/max)]:

Roflumilast N-oxide		**C_{max} [ug/L]**	**AUCT [h*ug/L]**	**$t_{1/2}$ [h]**	**t_{max} [h]**
Elderly	Value	42.75	717.47	34.903	2
(n=22)	Range	56.89 - 32.12	991.32 - 519.27	47.89 - 25.44	10 - 1.5
Middle aged	Value	34.88	593.11	31.64	3
(n=22)	Range	47.88 - 25.41	820.88 - 428.54	44.64 - 22.43	8 - 1.5
Young	Value	37.73	605.39	29.72	3
(n=19)	Range	53.14 - 26.79	871.81 - 420.38	44.34 - 19.92	8 - 1.5

Percentage ratio of geometric means for test (male and female elderly, n = 22; male and female middle aged, n = 22) / reference (male and female young, n = 19) and 90 % CI of roflumilast and roflumilast N-oxide after 15 days of once-daily oral doses of 500 µg roflumilast:

		Ref	**Test**	**Ratio [%Ref]**	**CI 90 Lower**	**CI 90 Upper**
Roflumilast	AUCT	Young	Elderly	126.56	105.04	152.5
		Young	Middle aged	98.84	82.03	119.09
	CLss/FBW	Young	Elderly	80.37	66.8	96.7
		Young	Middle aged	99.64	82.81	119.88
	$t_{1/2}$	Young	Elderly	102.28	85.1	122.93
		Young	Middle aged	95.04	79.07	114.23
Roflumilast N-oxide	AUCT	Young	Elderly	118.51	99.36	141.36
		Young	Middle aged	97.97	82.14	116.86
	$t_{1/2}$	Young	Elderly	117.45	97.65	141.27
		Young	Middle aged	106.47	88.52	128.06

Comparison of pharmacokinetic parameter estimates between the young, middle aged and elderly indicated that there was a low margin difference between these populations.

Comparison of pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide in the elderly vs. young population: Data analyzed suggests that roflumilast exposure in the elderly was 27 % higher then in the young population. This difference reflected the 20 % lower CLss/FBW in the elderly. There was no difference in the $t_{½}$. Similar differences between these two populations were observed for roflumilast N-oxide. Exposure in the elderly was 19 % higher than in the young population. Elderly had also 17 % longer $t_{1/2}$.

Comparison of pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide in the middle aged vs. young population: In contrast to the elderly, comparison of roflumilast exposure and CLss/FBW between the middle aged and the young population showed no difference. However, estimated $t_{1/2}$ in the middle aged population was 5 % shorter than in the young population. The same pattern of similarities and differences, as observed for roflumilast, was also observed for roflumilast N-oxide exposure. Comparison of the exposure between these populations showed no difference. However, a 6 % prolongation of $t_{½}$ in the middle aged population was observed.

Exploratory investigations regarding the gender differences within the population showed an age-dependent gender related trend. However, any conclusion is equivocal especially considering that the study was not designed to investigate the gender difference. There were no major differences in formation disposition of ratio between these populations as indicated by the disposition formation ratios of $AUC_{Roflumilast\ N\text{-}oxide}$/ $AUC_{Roflumilast}$, although an age related trend is observed. Overall the study suggests that differences in pharmacokinetic parameter estimates between these three populations were less then 30 %.

Exploratory measurements of urine 6ß-hydroxycortisol and cortisol were performed to assess the potential induction of cytochrome P450 isoenzyme CYP3A4. Although an increase in the urine 6ß-hydroxycortisol/ cortisol ratio can be observed in all age groups, the results are not conclusive with respect to an induction of cytochrome P450 isoenzyme CYP3A4 due to overlapping standard deviations.

Safety

Overview of subjects with treatment emergent adverse events

	Young n=22			Middle-aged n=22			Elderly n=22		
	E*	n**	%***	E*	n**	%***	E*	n**	%***
Adverse events	79	19	86	92	22	100	135	21	95
Male subjects	23	9	82	36	11	100	65	11	92
Female subjects	56	10	91	56	11	100	70	10	100
Causality (definite or likely related)	63	19	86	71	22	100	123	21	95
Intensity (severe or moderate)	25	13	59	24	16	73	29	17	77
Discontinuations (due to adverse events)	2	1	5	0			0		
Serious adverse events	0			0			0		

* number of adverse events ** number of subjects with adverse events *** % of subjects with adverse events

Three-hundred-and-six adverse events were reported by 62 of the 66 subjects during the study period: 19 of the young subjects reported 79 events, 22 of the middle-aged subjects reported 92 events and 21 of the elderly subjects experienced 135 events. 124 adverse events were

reported by 31 male, and 182 adverse events by 31 female subjects. One young female subject withdrew from the study due to adverse events (pharyngitis and sinusitis). No serious adverse events occurred during the study.

'Headache' was most frequently reported in all age groups. The number of subjects with 'headache', 'musculoskeletal pain', 'back pain', and 'loose stools' showed an age-dependent trend with the highest frequencies in the elderly group. 'Insomnia' was only reported in the elderly group, 'diarrhoea NOS' only in the young. With respect to laboratory-, vital signs- and ECG values, only physiological differences were found between the different age groups. Also, no clear age-dependent trend was discernable. Single out-of-range values were observed, however, all were considered to be without clinical relevance.

Conclusions:

Comparison of pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide in the elderly vs. young population suggests that roflumilast exposure in the elderly was 27 % higher then in the young population. This difference reflected the 20 % lower CLss/FBW in the elderly. There was no difference in the $t_{½}$. Similar differences between these two populations were observed for roflumilast N-oxide. Exposure in the elderly was 19 % higher than in the young population. Elderly had also 17 % longer $t_{1/2}$.

Comparison of pharmacokinitic parameter estimates of roflumilast and roflumilast N-oxide in the middle aged vs. young population suggests that, in contrast to the elderly, comparison of roflumilast exposure and CLss/FBW between the middle aged and the young population is not different. However, estimated $t_{1/2}$ in the middle aged population was 5 % shorter than in the young population. For roflumilast N-oxide exposure, there was no difference between these populations. However, a 6 % prolongation of $t_{½}$ in the middle aged population was observed.

With respect to tolerability in healthy subjects, an age-depended gender related increase in adverse events cannot be excluded. Overall however, the application of 500 µg roflumilast for 15 days was safe in young, middle aged and elderly healthy subjects.