Synopsis of study report: 37/2000K1
Location in Module 5:

Study Code:
BY217/FHP023

Report Date:
15-Nov-2000

Title of the study:
Investigation of the safety, tolerability and pharmacokinetics of gradually increasing repeated oral doses (500 µg/d, 750 µg/d, 1000 µg/d) of roflumilast in healthy male and female subjects. A double blind randomized placebo controlled study.

Study center(s):
AAI Applied Analytical Industries Deutschland GmbH & Co KG, 89231 Neu-Ulm, Germany

Publication (reference):
Not available

Studied period (years):
09 September 1999 - 14 October 1999

Clinical phase:
I

Objectives:
Primary:
- Safety and tolerability

Secondary:
- Pharmacokinetics of roflumilast (B9302-107) and metabolite B9502-044

Methodology:

The study was conducted according to a double-blind, parallel-group design with 2:1 randomization of gradually increasing roflumilast doses (N=12) and placebo (N=6):

Group I: roflumilast treatment for 21 consecutive days (N=12):
days 1-7: 500 µg/d roflumilast (2 tablets of 250 µg each per day)
days 8-14: 750 µg/d roflumilast (3 tablets of 250 µg each per day)
days 15-21: 1000 µg/d roflumilast (4 tablets of 250 µg each per day)

Group II: placebo treatment for 21 consecutive days (N=6):
days 1-7: 2 placebo tablets per day
days 8-14: 3 placebo tablets per day
days 15-21: 4 placebo tablets per day

12-lead resting ECG, blood pressure and heart rate were measured predose and 1 h, 2 h, 4 h, 8 h and 12 h post dose on days 1, 7, 8, 14, 15 and 21. Clinical laboratory was determined predose on days 1, 8, 15, and in the morning of day 22 (Additional safety measurements were performed at pre and final check.). Adverse events were monitored continuously during the study.
Repeated blood samples for pharmacokinetic purposes were taken on days 7 and 14 (up to 24 h each) as well as on day 21 (up to 54 h).

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

Total: 18 (17 male, 1 female)
Roflumilast at increasing doses: 12 (11male, 1 female)
Placebo: 6 (all male)

Diagnosis and criteria for inclusion:

Healthy subjects of either sex.

Duration of treatment:

21 days

Test product:

Roflumilast

Dose:

500 µg/d on days 1-7
750 µg/d on days 8-14

1000 µg/d on days 15-21

Mode of administration:

p.o. (tablets containing 250 µg each)

Batch No.:

007399 (BY217-93)
008399 (BY217-93)
009399 (BY217-93)

Reference product:

Placebo

Dose:

Not applicable

Mode of administration:

p.o. (2 tablets on days 1-7; 3 tablets on days 8-14; 4 tablets on days 15-21)

Batch No.:

010399 (BY217-93)
011399 (BY217-93)
012399 (BY217-93)

Criteria for evaluation:

Safety and tolerability:

12-lead resting ECG, blood pressure and heart rate were measured predose and 1 h, 2 h, 4 h, 8 h, and 12 h post-dose on days 1, 7, 8, 14, 15, and 21. Clinical laboratory (clinical chemistry, hematology, urinalysis) was determined predose on days 1, 8, 15, and in the morning of day 22. Adverse events were monitored continuously during the study.

Pharmacokinetics:

$AUC_{(0\text{-}24\ h)}$ and C_{max} in steady state as respective extent and rate characteristics of roflumilast (B9302-107) and metabolite B9502-044 based on plasma levels determined at the following time points: predose, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h and 24 h after administration of 500 µg, 750 µg and 1000 µg roflumilast on study days 7, 14 and 21. Terminal half-life $t_{½}$ was calculated additionally for the highest roflumilast dose level of 1000 µg in steady state. Therefore, additional blood samples were taken at 30 h, 48 h and 54 h following administration of 1000 µg roflumilast on day 21.

Statistical methods:

Descriptive

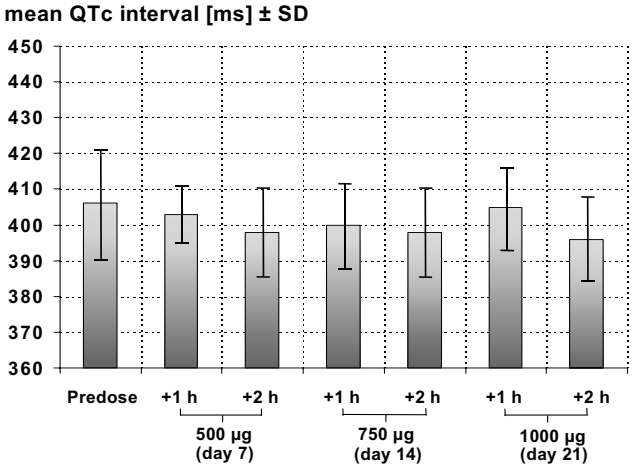
SUMMARY – CONCLUSIONS

Summary:

Safety and tolerability:

With regard to safety, it can be stated that repeated doses of 1000 µg/d roflumilast were safe and well-tolerated when the daily dose was gradually increased in steps of 250 µg after one week of treatment each. There was no increase in the frequency and severity of adverse events when the roflumilast dosage was increased step by step from 500 µg/d to 1000 µg/d.

In particular, serial recordings of 12-lead resting ECG revealed normal findings. Duration of QT_c interval was not prolonged by roflumilast treatment (see figure below). All individual values of QT_c interval were within the normal range of up to 450 ms.



Pharmacokinetics:

The plasma samples were assayed for parent compound roflumilast (B9302-107) and the metabolite B9502-044. Roflumilast and metabolite B9502-044 plasma concentrations were determined by a validated assay using reversed-phase HPLC with fluorescence detection after post-column photo-chemical derivatization. Sample clean-up was performed using liquid/liquid extraction. The lower limit of quantitation (LLOQ) was 0.085 µg/l for roflumilast and 0.5 µg/l for metabolite B9502-044.

Pharmacokinetic characteristics (geometric means / 68%-range) of roflumilast (B9302-107) and the metabolite B9502-044 following a gradually increasing repeated oral dose of 500 µg/d (Days 1-7), 750 µg/d (Days 8-14) and 1000 µg/d (Days 15-21) roflumilast to healthy subjects (N=12)

Study day	PK characteristics		Roflumilast (B9302-107)		Metabolite B9502-044	
Day 7	AUC	(µg x h/l)	32.61	(23.96, 44.37)	347.17	(284.71, 423.33)
	C_{max}	(µg/l)	4.740	(3.714, 6.050)	20.681	(17.234, 24.818)
	$t_{½}$	(h)	14.33	(9.00, 22.82)	not ascertainable	
	t_{max}	(h)	2.25 ± 0.56		4.08 ± 0.40	
Day 14	AUC	(µg x h/l)	50.82	(36.90, 70.00)	587.34	(462.32, 746.17)
	C_{max}	(µg/l)	8.153	(6.042, 11.002)	33.720	(27.281, 41.677)
	$t_{½}$	(h)	13.70	(8.67, 21.67)	not ascertainable	
	t_{max}	(h)	1.71 ± 0.28		5.33 ± 0.43	
Day 21	AUC	(µg x h/l)	65.92	(49.49, 87.81)	799.93	(638.52, 1002.15)
	C_{max}	(µg/l)	11.135	(8.289, 14.958)	50.618	(43.766, 58.541)
	$t_{½}$	(h)	14.66	(10.39, 20.67)	19.64	(15.08, 25.59)
	t_{max}	(h)	1.60 ± 0.39		5.17 ± 0.30	

Pharmacokinetic characteristics (geometric means / 68%-range) of roflumilast (B9302-107) and the metabolite B9502-044 following a gradually increasing repeated oral dose of 500 µg/d (Days 1-7), 750 µg/d (Days 8-14) and 1000 µg/d (Days 15-21) roflumilast to healthy subjects (N=12)

		Point estimates (90%-confidence intervals)			
Pharmacokinetic characteristics		***) 500 µg/day (Test 1)**		****) 1000 µg/day (Test 2)**	
		Roflumilast	**B9502-044**	**Roflumilast**	**B9502-044**
$AUC_{(0-24\,h)}$	(µg x h/l)	0.96 (0.93, 1.00)	0.89 (0.84, 0.94)	1.00 (0.95, 1.04)	1.02 (0.97, 1.08)
C_{max}	(µg/l)	0.87 (0.78, 0.98)	0.92 (0.86, 0.98)	1.02 (0.87, 1.19)	1.07 (0.96, 1.20)

*) N=12 **) N=11

Conclusions:

Safety and tolerability:

Repeated doses of 500 µg/d, 750 µg/d, and 1000 µg/d roflumilast were safe and well-tolerated when the dosage was gradually increased.

Pharmacokinetics:

With respect to AUC and C_{max}, a dose-proportional increase was observed with gradual increase of the dose from 500 µg/d to 1000 µg/d. The terminal half-life was not influenced by increasing the dose. After administration of the last dose, the terminal half-life was 14.7 h and 19.6 h for roflumilast and metabolite B9502-044, respectively.