Synopsis of study report: 11/98K
Location in Module 5:

Study Code:
BY217/FHP010

Report Date:
15-Sep-1998

Title of the study:

Study on the effect of food intake on the pharmacokinetics of the new phosphodiesterase inhibitor B9302-107 after single oral dose administration of 0.5 mg to healthy volunteers

Study center(s):

Dept. of Clinical Pharmacology (FHP)/Phase I Unit, Byk Gulden Pharmaceuticals, Byk-Gulden-Str. 2, 78467 Konstanz, Germany

Publication (reference):

Not available

Studied period (years):

October 1997 – December 1997

Clinical phase:

I

Objectives:

Primary:

- Investigation of a possible food interaction of roflumilast (B9302-107)

Secondary:

- Safety and tolerability of roflumilast (B9302-107)
- Pharmacokinetics of metabolites B9202-045 and B9502-044 in plasma

- Pharmacokinetics of B9302-107, B9202-045 and B9502-044 in urine

Methodology:

Randomized, open, 2-period crossover design

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

12 healthy subjects (10 m and 2 f; median age: 27.0 years, median body weight: 80.0 kg).

Diagnosis and criteria for inclusion:

Healthy subjects

Duration of treatment:

Single-dose

Test product:

Roflumilast

Dose:

0.5 mg (2 tablets of 0.25 mg each)

Mode of administration:

Treatment A: 0.5 mg roflumilast p.o. (2 tablets of 0.25 mg roflumilast each) after intake of an American breakfast.

Batch No.:

072496

Reference product:

Roflumilast

Dose:

0.5 mg (2 tablets of 0.25 mg each)

Mode of administration:

Treatment B: 0.5 mg roflumilast p.o. (2 tablets of 0.25 mg roflumilast each) in fasted state.

Batch No.:

072496

Criteria for evaluation:

Pharmacokinetics:

Blood samples for determination of the pharmacokinetic profiles of parent compound B9302-107 and metabolites B9202-045 and B9502-044 were taken up to 54 h after administration in both study periods. Urine fractions of Subjects No. 07-12 were collected following administration under fasted conditions.

B9302-107 and B9502-044 plasma concentrations were determined by the Dept. of Drug Metabolism and Pharmacokinetics (FKM), Byk Gulden, Konstanz, by means of a validated assay using reversed-phase HPLC with fluorescence detection after post-column photochemical derivatization. Sample clean-up was performed using liquid/liquid-extraction. The lower limit of quantitation (LLOQ) was 0.1 and 0.5 µg/l for B9302-107 and B9502-044, respectively.

Analysis of B9202-045 was conducted by pharm-analyt Labor GmbH, 2500 Baden bei Wien, Austria. B9202-045 plasma concentrations were determined by a GC-MS method. The LLOQ was 0.04 µg/l.

The assays used for urine analysis were equal to those used for the plasma samples.

Safety and tolerability:

Blood pressure, heart rate, ECG, clinical laboratory, urinalysis, physical examination at predefined time points and continuous recording of adverse events.

Statistical methods:

Pharmacokinetics:

Primary characteristics were $AUC_{0-\infty}$ and C_{max} of roflumilast (B9302-107) in plasma as extent and rate characteristics. Point estimate and 90%-confidence limits were given for the ratio of the population medians for Test (with breakfast) and Reference (without breakfast) in plasma, using a multiplicative model and a parametric analysis. A similar ratio analysis was performed for the pharmacodynamically active metabolite B9502-044. Moreover, a ratio analysis of AUC values was performed for B9502-044/B9302-107 under both fed and fasted conditions. Urine pharmacokinetics were presented descriptively.

Safety and tolerability:

Descriptively

SUMMARY - CONCLUSIONS

Summary:

Results:

Pharmacokinetics:

Pharmacokinetic characteristics under fed conditions (Treatment A):

Results are given as geom. means with 68%-range except for t_{max} which is given as mean ± SEM

	B9302-107	B9502-044	B9202-045
$AUC_{0-\infty}$ [µg/l*h]	34.88 [1)]	304.56 [2)]	n.a.
	(29.60-41.09)	(255.75-362.69)	
C_{max} [µg/l]	3.845	8.401	0.065 [3)]
	(3.013-4.907)	(7.021-10.053)	(0.045-0.093)
$t_{½}$ [h]	11.1	20.6	n.a.
	(7.3-17.0)	(13.5-31.5)	
t_{max} [h]	1.96 ± 0.35	12.08 ± 0.82	19.18 ± 5.72 [3)]
C_{max}/AUC [1/h]	0.111 [1)]	0.027 [2)]	n.a.
	(0.080-0.155)	(0.021-0.036)	

n.a. = not ascertained; [1)] N=11; [2)] N=9; [3)] N=7

Pharmacokinetic characteristics under fasted conditions (Treatment B):

Results are given as geom. means with 68%-range except for t_{max} which is given as mean ± SEM

	B9302-107	B9502-044	B9202-045
AUC0-∞ [µg/l*h]	31.25	350.85 [1)]	n.a.
	(24.69-39.54)	(283.09-434.83)	
Cmax [µg/l]	6.517	8.813	0.075 [2)]
	(4.979-8.531)	(7.072-10.983)	(0.066-0.084)
t½ [h]	10.3	19.6	n.a.
	(6.4-16.4)	(13.7-28.1)	
tmax [h]	0.96 ± 0.19	12.25 ± 0.76	26.60 ± 10.68
Cmax/AUC [1/h]	0.209	0.025 [1)]	n.a.
	(0.143-0.304)	(0.020-0.031)	

n.a. = not ascertained; [1)] N=11; [2)] N=5

Ratio analysis of AUC and C_{max} values of B9302-107 and B9502-044 under fed (Test) and fasted (Reference) conditions:

Values are given as point estimates with 90%-confidence limits

	B9302-107	B9502-044		
AUC	1.12 (1.00-1.25) [1)]	0.91 (0.79-1.04) [2)]	[1)] N=11	[2)] N=8
C_{max}	0.59 (0.49-0.70)	0.95 (0.90-1.01)		

Ratio analysis of AUC values of B9502-044 (Test) and B9302-107 (Reference) under fed and fasted conditions:

Values are given as point estimates with 90%-confidence limits

	AUC ratio B9502-044/B9302-107
Fed conditions	9.11 (8.02-10.34) [N=8]
Fasted conditions	11.11 (10.24-12.06) [N=11]

Renal excretion of B9302-107 and B9502-044:

Cumulative values in % of the dose; mean ± SD; N=6

Time interval	B9302-107	B9502-044
0 h - 4 h	0.030 ± 0.009	0.011 ± 0.016
4 h - 8 h	0.043 ± 0.014	0.011 ± 0.016
8 h - 12 h	0.055 ± 0.021	0.011 ± 0.016
12 h - 24 h	0.083 ± 0.024	0.084 ± 0.053

Safety and tolerability:

Repeated implementation of safety measurements (blood pressure, heart rate, ECG, clinical laboratory investigation, urinalysis, physical examination, continuous recording of adverse events) did not reveal clinically relevant findings.

Conclusions:

Pharmacokinetics:

For parent compound roflumilast (B9302-107), lack of food interaction can be concluded only for the extent and not for the rate of absorption.

For the pharmacodynamically active metabolite B9502-044, however, lack of food interaction can be concluded for both rate and extent of absorption. Statistical comparison of AUCs of metabolite B9502-044 referenced to those of the parent compound showed a value higher by a factor of about 10 under both fed and fasted conditions.

Plasma concentrations of B9202-045 could be detected at low levels only, reflecting low formation of this metabolite following a single oral dose.

Parent compound B9302-107 and metabolite B9502-044 were excreted in the urine in traces only. Metabolites B9502-054 and B9202-045 could not be detected in urine.

Safety and tolerability:

Safety and tolerability of the two single oral doses of 0.5 mg roflumilast was very good, regardless whether the drug was taken after breakfast or in fasted state.