Synopsis of study report: 152/2000
Location in Module 5:

Study Code:
BY217/FHP024

Report Date:
25 January 2002

Title of the study:
Investigation of the pharmacokinetics of a single oral dose of 500 µg roflumilast in healthy middle-aged subjects (>45 and <65 years)

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

Publication (reference):
none

Studied period (years):
2000

Clinical phase:
I

Objectives:
Primary: Pharmacokinetics of roflumilast (B9302-107) and metabolite B9502-044
Secondary: Safety and tolerability

Methodology:

The study was conducted according to an open, one period design. Each subject received 500 µg roflumilast as a single dose (2 tablets of 250 µg roflumilast each) after a standard breakfast. Blood samples for determination of the pharmacokinetics of roflumilast (B9302-107) and metabolite B9502-044 were taken predose and at 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, 24 h, 30 h, 48 h, 54 h and 72 h post dose. 12-lead resting ECG, blood pressure and pulse rate were measured predose and 1 h, 2 h, 4 h, 8 h and 12 h post dose as well as during the screening examination and the post-study examination. Clinical laboratory (clinical chemistry, hematology, urinalysis) was determined during the screening examination and the post-study examination. Adverse events were monitored continuously during the study. Renal creatinine clearance was determined during the study.

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

12 (10 male, 2 female); all subjects received the same treatment.

Diagnosis and criteria for inclusion:

Healthy subjects of either sex, aged >45 years and <65 years.

Test product:

Roflumilast

Dose:

500 µg/d on day 1

Mode of administration:

p.o. (two tablets containing 250 µg each)

Batch No.:

BY217-124

Duration of treatment:

1 day (single dose)

Reference product:

n.a.

Dose:

n.a.

Mode of administration:

n.a.

Batch No.:

n.a.

Criteria for evaluation:

Pharmacokinetics: AUC0-inf. and Cmax were estimated as extent and rate characteristics of roflumilast, respectively, and AUC and Cmax of the active metabolite B9502-044. Additionally, t½ and tmax of roflumilast, and t½ and tmax of the active metabolite B9502-044 were calculated. The renal creatinine clearance was determined during the study in order to evaluate whether or to what extent the pharmacokinetic characteristics of roflumilast were dependent on renal clearance

Safety and tolerability: 12-lead resting ECG, blood pressure and heart rate were obtained at predefined time point, clinical laboratory (clinical chemistry, hematology, urinalysis) during the screening examination and the post-study examination. Adverse events were monitored continuously during the study.

Statistical methods:

Descriptive

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics:

The plasma samples were assayed for the 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 liq-uid/liquid extraction. The lower limit of quantita-tion (LLOQ) was 0.085 µg/l for roflumilast and 0.5 µg/l for metabolite B9502-044.

The following tables show the pharmacokinetics of roflumilast in middle-aged healthy sub-jects and the statistical comparison to historical data of elderly or young healthy subjects

Pharmacokinetic characteristics (geometric means / 68%-range) of roflumilast (B9302-107) and the metabolite B9502-044 after a single dose of 500 µg in healthy subjects aged >45 years and <65 years (N=12)

Pharmacokinetic characteristics	**Roflumilast Geometric mean (68%-Range)**	**B9502-044 Geometric mean (68%-Range)**
AUC(0-inf) (µgxh/l)	40.41 (27.44, 59.50)	383.96 (291.27, 506.15)*
Cmax (µg/l)	5.427 (3.752, 7.851)	8.526 (6.664, 10.907)
t1/2 (h)	16.64 (10.89, 25.43)	30.87 (20.65, 46.14)
tmax (h)	1.23 + 0.13	10.08 + 2.47

tmax: mean ± SEM, *N = 8

Point estimates (90%-confidence intervals) of pharmacokinetic characteristics of roflumilast (B9302-107) and its metabolite B9502-044 following a single oral administration of 500 µg roflumilast to middle-aged healthy subjects (Test, BY217/FHP024) and to elderly healthy subjects (Reference, BY217/FHP018), aged ≥ 65 years

	Ratios of middle-aged versus elderly	
Pharmacokinetic characteristics	**Roflumilast Point estimate (90%-CI)**	**B9502-044 Point estimate (90%-CI)**
AUC(0-inf)	0.759 (0.593, 0.972)	0.911 (0.748, 1.108)
Cmax	1.159 (0.905, 1.485)	0.996 (0.859, 1.154)
t1/2	0.739 (0.578, 0.944)	1.037 (0.807, 1.332)
tmax (difference, h)	-0.938 (-1.660, -0.215)	0.417 (-4.526, 5.359)

Point estimates (90%-confidence intervals) of pharmacokinetic characteristics of roflumilast (B9302-107) and its metabolite B9502-044 following a single oral administration of 500 µg roflumilast to middle-aged healthy subjects (Test, BY217/FHP024) and to young healthy subjects (Reference, BY217/FHP010)

	Ratios of middle-aged versus young	
Pharmacokinetic characteristics	**Roflumilast** **Point estimate (90%-CI)**	**B9502-044** **Point estimate (90%-CI)**
AUC(0-inf)	1.159 (0.935, 1.435)	1.261 (1.038, 1.531)
Cmax	1.412 (1.134, 1.758)	1.015 (0.873, 1.180)
t1/2	1.499 (1.113, 2.017)	1.497 (1.121, 2.000)
tmax (difference, h)	-0.729 (-1.389, -0.069)	-2.000 (-6.614, 2.614)

Safety:

A single dose of 500 µg roflumilast was well tolerated in subjects aged >45 years and <65 years. There was only one subject, who reported 3 adverse events, which occurred not earlier than 11 days after dosing. All these events were considered to be unrelated to the treatment. In particular, serial recordings of 12-lead resting ECG revealed normal findings. Duration of QTc interval was not prolonged by roflumilast treatment. All individual values of QTc interval were similar to the respective predose values and only exceptionally exceeded the normal range of up to 450 ms in two subjects (one of each gender), who a priori exhibited comparatively high QTc values. Laboratory parameters remained unaffected by the treatment.

Conclusions:

Pharmacokinetics:

Compared to historical data obtained from studies with elderly healthy subjects or young healthy subjects who received the same dose of 500 µg roflumilast as a single oral dose, AUCs of roflumilast and metabolite B9502-044 of middle-aged subjects were lower than the corresponding AUCs of elderly subjects and higher than the corresponding AUCs of young healthy subjects. With respect to Cmax of roflumilast, changes observed in the middle-aged were moderate in comparison to the elderly (about 16%) and more pronounced in comparison to the young (about 41%). Cmax of metabolite B9502-044 remained virtually unchanged. The elimination half-life of roflumilast and the metabolite B9502-044 increased by about 50% in the middle aged as compared to the young. Although these findings suggest a pharmacoki-

netic age dependency of roflumilast and its major metabolite B9502-044, their clinical relevance should be studied in prolonged treatment and larger patient populations.

Safety and tolerability:

A single dose of 500 µg roflumilast was well tolerated in subjects aged >45 years and <65 years with regard to adverse events, vital signs, ECG parameters and laboratory values.