Synopsis of study report: 181E/99
Location in Module 5:

Study Code:
BY217/FHP018

Report Date:
03-May-2000

Title of the study:

Pharmacokinetics of roflumilast after single dose oral administration of 0.5 mg to healthy elderly subjects.

Study center(s):

QUINTILES Innovex (Biodesign) GmbH, Obere Hardtstrasse 8-16, D-79114 Freiburg

Publication (reference):

Not available

Studied period (years):

16 November 1998 –26 March 1999

Clinical phase:

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Objectives:

Primary:

- Pharmacokinetics of a single oral dose of 0.5 mg roflumilast (B9302-107) in healthy male and female subjects aged ≥ 65 years.

Secondary:

- Safety and tolerability; pharmacokinetics of the metabolite B9502-044.

Methodology:

The study was conducted according to an open, single-dose, one-period design.
Blood samples for pharmacokinetic purposes were taken predose, and at 0.25 h, 0.5 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 at 72 h after oral administration.

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

N=12 (10 male, 2 female).

Diagnosis and criteria for inclusion:

Healthy male or female subjects aged ≥ 65 years.

Duration of treatment:

1 day (single dose)

Test product:

Roflumilast

Dose:

0.5 mg (2 tablets of 0.25 mg each)

Mode of administration:

p.o.

Batch No.:

094398

Reference product:

Not applicable

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

Pharmacokinetics:

Primary variable: $AUC_{(0, inf)}$ and C_{max} as respective extent and rate characteristics of roflumilast. Secondary pharmacokinetic variables: $t_{½}$ and t_{max} of roflumilast and pharmacokinetic characteristics of the metabolite B9502-044.

Safety and tolerability:

Measurements of ECG, blood pressure and pulse rate, physical examination and clinical laboratory investigations (clinical chemistry, hematology, urinalysis) during the screening visit and the post study examination; additional measurements of ECG, blood pressure and pulse rate at predose, and at 1 h and 2 h after dosing; adverse events.

Statistical methods:

Point estimates and 90%-confidence limits for the ratio of the population medians for Test (elderly) and Reference (young volunteers from Study BY217/FHP010) using a multiplicative model and a parametric analysis; otherwise descriptive.

SUMMARY – CONCLUSIONS

Summary:

Pharmacokinetics:

The following table shows a summary of the pharmacokinetic characteristics of roflumilast (B9302-107) and metabolite B9502-044 after single oral administration of 0.5 mg roflumilast. Values are given as geometric means with 68%-range except for t_{max} which is given as mean ± SEM (N=12):

Pharmacokinetic characteristics (geometric means / 68%-range) of roflumilast (B9302-107) and metabolite B9502-044 following a single oral dose of 0.5 mg roflumilast to elderly subjects (N=12)

Study BY217/FHP018	Roflumilast (B9302-107)	B9502-044
$AUC_{(0-\infty)}$ [µgxh/l]	53.23 (38.81, 73.01)	421.64 (351.96, 505.11)
C_{max} [µg/l]	4.681 (3.345, 6.551)	8.561 (7.239, 10.126)
$t_{½}$ [h]	22.53 (17.71, 28.67)	29.78 (21.93, 40.44)
t_{max} [h] [1)]	2.17 ± 0.39	9.67 ± 1.47

[1)] t_{max}: mean ± SEM

Following oral administration of 0.5 mg roflumilast to elderly subjects, the geometric mean of the maximum plasma concentrations C_{max} of roflumilast was 4.681 µg/l (68%-range: 3.345, 6.551 µg/l) and was attained at a mean value of 2.17 h. Following the individual maxima, roflumilast was eliminated biphasically with a terminal half-life of 22.53 h (68%-range:

17.71, 28.67 h). The geometric mean of the $AUC_{(0-\infty)}$ was 53.23 µgxh/l (68%-range: 38.81, 73.01 µgxh/l). The geometric mean of the maximum plasma concentrations C_{max} of metabolite B9502-044 was 8.561 µg/l (68%-range: 7.239, 10.126 µg/l) and was attained at a mean value of 9.67 h. Following the individual maxima, B9502-044 was eliminated with a geometric mean terminal half-life of 29.78 h (68%-range: 21.93, 40.44 h). The geometric mean of the $AUC_{(0-\infty)}$ was 421.64 µgxh/l (68%-range: 351.96, 505.11 µgxh/l).
The pharmacokinetic data obtained in the present study with healthy elderly subjects were compared with the results of the previous study BY217/FHP010 [Study Report No. 11/98] with healthy young and middle-aged subjects ≤ 45 years.

After logarithmic transformation, the point estimates and the corresponding 90%-confidence limits were given for the ratios of the population means for the in pairs comparisons of both subject groups with elderly subjects and young healthy subjects.
Comparison of the two subject groups for roflumilast was assessed by using AUC (extent of absorption) and C_{max} (rate of absorption) as primary criteria. The point estimates (90%-CI) for these characteristics were as follows: AUC: 1.526 (1.271, 1.833) and C_{max}: 1.218 (0.991, 1.496). The point estimate (90%-CI) of $t_{½}$ as a secondary criterion (explorative evaluation) was 2.029 (1.593, 2.584).
The secondary characteristics AUC and $t_{½}$ of B9502-044 were also analyzed in an explorative intention, yielding the following point estimates and 90%-confidence intervals: AUC: 1.384 (1.196, 1.602) and $t_{½}$: 1.445 (1.115, 1.871).

Point estimates (90%-confidence intervals) of pharmacokinetic characteristics of roflumilast (B9302-107) and its metabolite B9502-044 following a single oral administration of 0.5 mg roflumilast to healthy young subjects (Reference, BY217/FHP010) and to elderly healthy subjects (Test, BY217/FHP018)

	Point estimate (90%-CI)	
Parameter	**Roflumilast (B9302-107)**	**B9502-044**
$AUC_{(0-\infty)}$ [µgxh/l]	1.526 (1.271, 1.833)	1.384 (1.196, 1.602)
C_{max} [µg/l]	1.218 (0.991, 1.496)	1.019 (0.902, 1.151)
$t_{½}$ [h]	2.029 (1.593, 2.584)	1.445 (1.115, 1.871)
t_{max} [h]	0.208 (-0.687, 1.104)	-2.417 (-5.313, 0.480)

The point estimate (90%-CI) of t_{max} was 0.208 (-0.687, 1.104) for roflumilast and -2.417 (-5.313, 0.480) for the metabolite B9502-044.

Safety and tolerability:
The results of the safety measurements at screening, during the study day and during the post study examination did not reveal any pathological findings. The following adverse events

were reported during the study: headache (3 cases in 3 subjects), vomiting (2 cases in 2 subjects), nausea (1 case), pain in the legs (1 case), common cold (1 case), pasty stool (1 case), loss of appetite (1 case).

Conclusions:

Pharmacokinetics:

The primary aim of this study was to evaluate the pharmacokinetics of roflumilast (B9302-107) after single oral administration of 0.5 mg roflumilast to elderly healthy subjects. These data have been compared to historical data obtained from study BY217/FHP010, where healthy young volunteers had also received 0.5 mg roflumilast as a single oral dose. With respect to AUC, a distinct increase was observed in elderly subjects as compared to young subjects. This increase was more pronounced for roflumilast than for the metabolite B9502-044. This increase of AUC was the result of a prolongation of the half-life, being 22.5 h and 29.8 h in elderly subjects and 11.1 h and 20.6 h in young volunteers for roflumilast and metabolite B9502-044, respectively. Only minor changes were observed in C_{max} in the elderly subjects when compared to young subjects.

These findings suggested that the prolongation of the half-life in elderly subjects was the result of a reduction in clearance.

Safety and tolerability:

Single administrations of 0.5 mg roflumilast were safe and tolerable in healthy elderly subjects.