Synopsis of study report: 23/2001
Location in Module 5:

Study Code:
BY217/FHP020

Report Date:
06-Sep-2001

Title of the study:

Pharmacokinetics of roflumilast after single oral dose administration of 0.5 mg to patients suffering from severe renal impairment

Study center(s):

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Publication (reference):

Not applicable

Studied period (years):

14 September 1999 – 07 December 1999

Clinical phase:

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Objectives:

Primary:

- The investigation of the pharmacokinetics of roflumilast (B9302-107) in patients with severe renal impairment in comparison to a matched control group of healthy subjects.

Secondary:

- To assess the safety, tolerability and pharmacokinetics of the pharmacologically active metabolite B9502-044.

Methodology:

Open label parallel group comparison

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

Total: 24
12 patients with severe renal impairment
12 healthy control subjects

Diagnosis and criteria for inclusion:

For each patient with severe renal impairment one healthy subject was included according to the following matching criteria: Same sex, age within ± 5 years, weight within ± 10%, height within ± 10%

Duration of treatment:

Single dose

Test product:

Roflumilast

Dose:

0.5 mg

Mode of administration:

p.o.

Batch No.:

023498

Reference product:

Not applicable

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

Pharmacokinetics:

$AUC_{(0-\infty)}$ and C_{max} of roflumilast

$t_{½}$ and t_{max} of roflumilast

$AUC_{(0-\infty)}$, and $t_{½}$ of the metabolite B9502-044

Safety and tolerability:

Clinical laboratory, urinalysis, ECG, blood pressure, heart rate and adverse events

Statistical methods:

Point estimates and 90%-confidence limits for the ratio of the population medians of $AUC_{(0-\infty)}$ and C_{max} of Test (patients with renal impairment) and Reference (healthy subjects).
Safety data were evaluated descriptively.

SUMMARY – CONCLUSIONS

Summary:

Pharmacokinetic evaluation:

The following tables show a summary of the pharmacokinetic characteristics of roflumilast (B9302-107) and the metabolite B9502-044 after single oral administration of 0.5 mg roflumilast to patients with renal impairment (n=12) and healthy control subjects (n=12). Values are given as geometric means with 68%-range except for t_{max} which is given as mean ± SEM (n=12).

Patients with renal impairment:

		B9302-107	B9502-044
$AUC_{(0-\infty)}$	(µg x h/l)	35.48 (23.73, 53.04)	428.93 (334.19, 550.54)
C_{max}	(µg/l)	4.266 (2.744, 6.633)	6.840 (5.350, 8.745)
$t_{½}$	(h)	22.08 (14.18, 34.41)	37.40 (21.88, 63.94)
t_{max}	(h)	1.38 ± 0.16	19.82 ± 4.41

Healthy control subjects:

		B9302-107	B9502-044
$AUC_{(0-\infty)}$	(µg x h/l)	44.69 (33.47, 59.68)	461.18 (366.23, 580.74)
C_{max}	(µg/l)	5.072 (3.625, 7.097)	7.780 (6.350, 9.534)
$t_{½}$	(h)	18.52 (11.43, 30.00)	28.70 (21.97, 37.49)
t_{max}	(h)	1.79 ± 0.18	16.92 ± 2.88

Comparison of the two groups for roflumilast was assessed by using AUC (extent of absorption) and C_{max} (rate of absorption) as primary criteria. The point estimates (90%-Cl) for these characteristics were as follows: AUC: 0.794 (0.618, 1.019) and C_{max}: 0.841 (0.639, 1.107). The point estimate (90%-Cl) of $t_{½}$ as a secondary criterion (explorative intention) was 1.193 (0.862, 1.650). The point estimate (90%-Cl) of t_{max} was –0.417 (-0.834, 0.001) for roflumilast. The secondary characteristics AUC and $t_{½}$ of metabolite B9502-044 were also analyzed in an explorative intention, yielding the following point estimates and 90%-confidence intervals: AUC: 0.930 (0.775, 1.116) and $t_{½}$: 1.303 (0.951, 1.787).

Safety and tolerability:

Two adverse events (atrial arrhythmia and back pain) which were considered to be unrelated to test drug were reported by two healthy controls. There were no individual subjects with adverse events that were reason for discontinuation.

None of the hematology, biochemistry, urinalysis, vital signs and ECG assessments showed any relevant changes from baseline. No trends could be discerned, neither within subjects nor over subject groups.

Conclusions:

Pharmacokinetic evaluation:

Following single oral administration of 0.5 mg roflumilast to 12 patients with severe renal impairment, the pharmacokinetic characteristics were found to be comparable to the corresponding values of a control group of healthy volunteers.

A dose adjustment was not considered to be necessary in the investigated population subgroup.

Safety and tolerability:

A single dose of 0.5 mg of roflumilast was well tolerated both in patients with renal impairment and in healthy control subjects. No drug related changes were observed in any of the safety parameters studied. The study did not reveal any new safety aspects with regard to the study medication.