Synopsis of study report: <153/2000>
Location in Module 5:

Study Code:
BY217/FHP025

Report Date:
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Title of the study:
Investigation of the pharmacokinetics of 250 µg roflumilast in healthy elderly subjects (≥ 65 years) after single dosing and in steady state

Study center(s):
AAI Applied Analytical Industries Deutschland GmbH & Co KG, Wegenerstr. 13, 89231 Neu-Ulm, Germany

Publication (reference):
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Studied period (years):
2000

Clinical phase:
Phase I - Study

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

Methodology:

The study was conducted in an open, one period design. 18 healthy subjects of either sex were included in the study and completed the study according to protocol. Each subject received 250 µg roflumilast as a single dose (Day 1) and for 8 consecutive days (Days 4-11). Repeated blood samples were taken for pharmacokinetics. For safety reasons, ECG, blood pressure and heart rate were measured repeatedly. Clinical laboratory parameters were determined during screening examination and at post-study examination. Adverse events were monitored continuously during the study.

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

18 (14 male, 4 female)

Diagnosis and criteria for inclusion:

Healthy subjects of either sex, aged ≥ 65 years

Test product:

Roflumilast

Dose:

250 µg/d on day 1, 250 µg/d on days 4-11

Mode of administration:

p.o. (tablets containing 250 µg each)

Batch No.:

089100

Duration of treatment:

9 days (day 1: single dose; days 4-11: continuous treatment)

Reference product:

n.a.

Dose:

n.a.

Mode of administration:

n.a.

Batch No.:

n.a.

Criteria for evaluation:

Pharmacokinetics: AUC and C_{max} were estimated as extent and rate characteristics of roflumilast, respectively, and AUC and C_{max} of the active metabolite B9502-044. Additionally, $t_{1/2}$ and t_{max} of roflumilast and 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. All pharmacokinetic parameters were estimated for single and multiple dosing.

Safety and tolerability: 12-lead resting ECG, blood pressure and heart rate were obtained at pre-defined time points, clinical laboratory during screening examination and post-study examination. Adverse events were monitored continuously during the study.

Statistical methods:

descriptive

SUMMARY - CONCLUSIONS

Summary:

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 photochemical 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.

Following oral administration of 250 µg roflumilast on Day 1, the geometric mean of the maximum plasma concentrations Cmax of roflumilast was 2.900 µg/l (68%-range: 2.146, 3.918 µg/l) and was attained at a mean value of 1.64h. Following the individual maxima, roflumilast was eliminated biphasically with a terminal half-life of 21.00h (68%-range:

15.31, 28.81h). The geometric mean of the $AUC_{(0-\infty)}$ was 27.20 µgxh/l (68%-range: 20.94, 35.35 µgxh/l).

Following oral administration of 250 µg roflumilast on Day 1, the geometric mean of the maximum plasma concentrations C_{max} of metabolite B9502-044 was 3.596 µg/l (68%-range: 2.857, 4.525 µg/l) and was attained at a mean value of 15.65h. Following the individual maxima, B9502-044 was eliminated with a geometric mean terminal half-life of 38.66h (68%-range: 24.88, 60.08h). The geometric mean of the $AUC_{(0-\infty)}$ was 210.60 µgxh/l (68%-range: 195.20, 227.30 µgxh/l).

After oral administration of 250 µg roflumilast on Day 11, the geometric mean of the maximum plasma concentrations C_{max} of roflumilast was 3.538 µg/l (68%-range: 2.628, 4.763 µg/l) and was attained at a mean value of 2.43h. Having reached the individual maxima, roflumilast was eliminated biphasically with a terminal half-life of 18.86h (68%-range: 13.15, 27.06h). The geometric mean of the $AUC_{(0-24)}$ was 28.71 µgxh/l (68%-range: 19.69, 41.85 µgxh/l).

After oral administration of 250 µg roflumilast on Day 11, the geometric mean of the maximum plasma concentrations C_{max} of metabolite B9502-044 was 13.612 µg/ (68%-range: 10.473, 17.692 µg/l) and was attained at a mean value of 6.44h. As blood samples on Day 11 were only in the 24 hour dosing interval, the terminal half-life for elimination of metabolite B9502-044 could not be calculated. The geometric mean of the $AUC_{(0-24h)}$ was 254.93 µgxh/l (68%-range: 196.21, 331.24 µgxh/l).

Safety and tolerability:

Single and repeated doses of 250 µg roflumilast were well tolerated in healthy elderlies. There was no increase in the frequency of adverse events under repeated doses of roflumilast in comparison to single dosing. The adverse event reported most often was headache, which occurred 3 times after single dosing.

There were no systematic effects of roflumilast upon blood pressure and laboratory findings. Mean heart rate mildly increased within the first hour after dosing and was slightly higher in steady-state. Serial recordings of 12-lead resting ECG always revealed findings, which were comparable to the respective pre-dose ECGs. Duration of QTc interval in mean was not prolonged by roflumilast treatment. All individual values of QTc interval were similar to the respective pre-dose values. There were only few subjects, who sometimes exhibited comparatively high QTc values without apparent relation to roflumilast intake.

Conclusions:

Pharmacokinetics:

Equivalence was demonstrated for roflumilast and metabolite B9502-044 with respect to primary characteristic AUC. With respect to C_{max}, equivalence could formally not be demonstrated for roflumilast. In addition, equivalence could not be demonstrated for C_{max} of metabolite B9502-044. However, explorative evaluation of $t_{1/2}$ for roflumilast showed confidence limits for this characteristic within the equivalence range.

Safety and tolerability:

Single and repeated oral doses of 250 µg roflumilast were well tolerated when given to healthy subjects aged ≥ 65 years.