Synopsis of study report: 67/99
Location in Module 5:

Study Code:
BY217/FHP015

Report Date:
14-Sep-1999

Title of the study:
Study on the bioequivalence of three tablet strengths (0.1 mg, 0.25 mg, 0.5 mg) of roflumilast

Study center(s):
Dept. of Clinical Pharmacology (FHP)/ Phase I Unit, Byk Gulden GmbH, Byk-Gulden-Str. 2, 78467 Konstanz, Germany

Publication (reference):
Not available

Studied period (years):
05 October 1998 – 08 December 1998

Clinical phase:
I

Objectives:
Primary:
- Investigation of the bioequivalence of three strengths of roflumilast (B93207-107) tablets: 0.1 mg, 0.25 mg, 0.5 mg each.

Secondary:
- Safety and tolerability; pharmacokinetics of the pharmacologically active metabolite B9502-044.

Methodology:

The study was conducted according to a randomized, open, three-period, change-over design. Repeated blood samples for pharmacokinetic purposes were taken in the study periods up to 72 h after oral administration. Safety measurements were performed at pre and final check.

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

18 (male)

Diagnosis and criteria for inclusion:

Healthy subjects.

Duration of treatment:

1 day (single dose)

Test product:

Roflumilast

Dose:

Test product 1: Total dose: 0.5 mg (five tablets of 0.1 mg each)
Test product 2: Total dose: 0.5 mg (one tablet of 0.5 mg)

Mode of administration:

Oral administration

Batch No.:

Test product 1: 088398
Test product 2: 086398

Reference product:

Roflumilast

Dose:

Total dose: 0.5 mg (two tablets of 0.25 mg each)

Mode of administration:

Oral administration

Batch No.:

087398

Criteria for evaluation:

Pharmacokinetics:

Primary variables were $AUC_{(0-\infty)}$ and C_{max} as respective extent and rate characteristics of roflumilast. Secondary pharmacokinetic variables were $t_{1/2}$ and t_{max} of roflumilast and pharmacokinetic characteristics ($AUC_{(0-\infty)}$, $t_{1/2}$) of the metabolite B9502-044.

Safety and tolerability:

Safety measurements (12-lead resting ECG, blood pressure, heart rate, clinical laboratory physical examination) at pre and final check; adverse events.

Statistical methods:

Point estimate and 90%-confidence limits for the ratio of the population medians for Test and Reference using a multiplicative model and a parametric analysis; otherwise descriptive.

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics:

Pharmacokinetic characteristics of roflumilast (B93207-107) in plasma following a single oral dose of 0.5 mg (five tablets of 0.1 mg, two tablets of 0.25 mg or one tablet of 0.5 mg):

Table 1:

	Test 1 (Treatment A) (5 tablets à 0.1 mg)	**Test 2 (Treatment C) (1 tablet à 0.5 mg)**	**Reference (Treatment B) (2 tablets à 0.25 mg)**
$AUC_{(0-\infty)}$	33.9[1]	33.8	33.5[2]
[µg/l*h]	(25.4–45.4)	(25.8–44.2)	(26.8–41.8)
C_{max}	8.182	7.754	7.817
[µg/l]	(6.713–9.971)	(5.814–10.341)	(6.322–9.666)
$t_{½}$	11.46[1]	9.70	10.82[2]
[h]	(7.47–17.56)	(6.67–14.11)	(7.79–15.03)
t_{max}	0.53 ± 0.03	0.61 ± 0.06	0.64 ± 0.09
[h]			

[1]: n=17, [2]: n=16

Point estimates and 90%-confidence intervals for the ratio "Test 1/Reference" are 1.03 (0.97 - 1.09) for AUC and 1.05 (0.94 - 1.16) for C_{max}. Point estimates and 90%-confidence intervals for the ratio "Test 2/Reference" are 1.03 (0.98 - 1.10) for AUC and 0.99 (0.90 - 1.10) for C_{max}.

Pharmacokinetic characteristics of metabolite B9502-044 in plasma following a single oral dose (0.5 mg) of the three tablet formulations of B9302-107:

Table 2:

	Test 1 (Treatment A) (5 tablets à 0.1 mg)	**Test 2 (Treatment C) (1 tablet à 0.5 mg)**	**Reference (Treatment B) (2 tablets à 0.25 mg)**
$AUC_{(0-\infty)}$ [µg/l*h]	368.7[1] (284.7–477.5)	382.4 (301.8–484.6)	374.0 (300.0–466.2)
C_{max} [µg/l]	9.708 (8.052–11.705)	9.795 (8.059–11.904)	9.841 (8.180–11.840)
$t_{½}$ [h]	20.16[1] (16.31–24.92)	22.31 (18.23–27.32)	19.69 (16.47–23.53)
t_{max} [h]	8.56 ± 0.97	8.81 ± 1.00	6.39 ± 1.00

[1]: n=17

Point estimates and 90%-confidence intervals for the ratio "Test 1/Reference" are 0.97 (0.93 - 1.01) for AUC and 1.01 (0.94 - 1.09) for $t_{½}$. Point estimates and 90%-confidence intervals for the ratio "Test 2/Reference" are 1.02 (0.97 - 1.06) for AUC and 1.13 (1.05 - 1.21) for $t_{½}$.
Therefore, bioequivalence of the three strengths could be demonstrated for all pharmacokinetic variables using the predefined equivalence acceptance limits of 0.80 to 1.25 concerning $AUC_{(0-\infty)}$ and of 0.70 to 1.43 concerning C_{max}.

Safety and tolerability:
Safety measurements did not reveal any clinically relevant findings. No adverse events arose that were assessed as definitely related to the study medication. No differences were seen between the three tablet strengths with regard to symptoms or quantity of adverse events, respectively.

Conclusions:

Pharmacokinetics:
The results of this study revealed bioequivalence of the three strengths of roflumilast (B9302-107) tablets: 0.1 mg, 0.25 mg, 0.5 mg each.
A total (single) dose of 0.5 mg (five tablets of 0.1 mg, two tablets of 0.25 mg or one tablet of 0.5 mg, respectively) was administered in this study.

Safety and tolerability:
Single oral administrations of 0.5 mg roflumilast were safe and well tolerated, regardless whether administered as five tablets of 0.1 mg, two tablets of 0.25 mg or one tablet of 0.5 mg.