Synopsis of study report: 242E/98
Location in Module 5:

Study Code:
BY217/FHP006

Report Date:
28-Jun-1999

Title of the study:

Randomized study to investigate the absolute bioavailability of Roflumilast in healthy volunteers

Study center(s):

QUINTILES Innovex (Biodesign) GmbH, Obere Hardtstr. 8-16, 79114 Freiburg, Germany

Publication (reference):

Not available

Studied period (years):

03 July 1998 – 03 August 1998

Clinical phase:

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Objectives:

- Absolute bioavailability of Roflumilast derived from plasma concentrations after oral and intravenous administration; safety and tolerability.

Methodology:

Open, randomized two-period cross-over design (latin square) in healthy male Caucasian subjects. Treatments: 2 tablets Roflumilast, each containing 0.25 mg (oral administration);

0.15 mg Roflumilast i.v. (short-term infusion over 15 minutes). Treatments were separated by a wash-out period of at least one week. Pre-study examination within one month prior to study start including medical examinations and clinical laboratory examination. Pharmacokinetic determination of Roflumilast deriving from blood samples, collected at prescheduled times up to +54 hours after administration in each study period. For safety and tolerability determination, blood pressure and pulse rate were measured and electrocardiograms were evaluated at prescheduled times. At the i.v. study period, a continuous ECG (2 lead) and heart rate monitoring (from ECG) was recorded. All adverse events were documented in detail. Post-study examination was performed 48 to 54 h after the last administration.

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

Total: 13 (p.o.: 13, i.v.: 12)
Analyzed per protocol analysis: 12; analyzed per intention-to-treat analysis: 13
One drop-out (not related to study medication) after the first study period.

Diagnosis and criteria for inclusion:

Healthy male and female subjects, aged between 18 to 45 years; body weight according to Broca ≥ 0.8 to ≤ 1.25.

Duration of treatment:

Test product: 1 day (single dose)
Reference product: 1 day (single dose) short-term infusion over 15 minutes

Test product:

Roflumilast, tablets

Dose:

2 tablets, each containing 0.25 mg; (dose: 0.5 mg)

Mode of administration:

per oral (p.o.)

Batch No.:

165197

Reference product:

Roflumilast, vials

Dose:

Containing 8 mg/10 mg (concentration 0.8 mg/ml) for dilution with lipid emulsion Lipofundin MCT 10% (B. Braun, Melsungen AG, Melsungen, Germany)

Mode of administration:

intravenous (i.v.)

Batch No.:

049198

Criteria for evaluation:

Absolute bioavailability:

Derived from plasma concentrations after oral and i.v. administration. Sampling times: **oral administration:** 0 h (predose), and then +0.25 h, +0.5 h, +0.75 h, +1.00 h, +1.50 h, +2.00 h, +2.50 h, +3.00 h, +4.00 h, +5.00 h, +6.00 h, +8.00 h, +10.00 h, +12.00 h, +14.00 h, +24.00 h, +30.00 h, +48.00 h, +54.00 h; **intravenous administration:** -15 min (predose), -10 min, -5 min, 0 h (end of infusion), and then +0.25 h, +0.5 h, +0.75 h, +1.00 h, +1.50 h, +2.00 h, +2.50 h, +3.00 h, +4.00 h, +5.00 h, +6.00 h, +8.00 h, +10.00 h, +12.00 h, +14.00 h, +24.00 h, +30.00 h, +48.00 h, +54.00 h.

Pharmacokinetics:

$AUC_{(0-\infty)}$ was chosen as primary variable for confirmative statistical analysis. $AUC_{(0-\infty)}$ was calculated by the trapezoidal formula up to the last blood sampling time with a concentration above the limit of quantitation and then extrapolated to infinity using standard techniques.

Safety and tolerability:

Pre-study: demographic data, medical history, physical examination, body weight and temperature, clinical laboratory parameters incl. drug screening, HbsAG and HIV-test 1 and 2. Blood pressure, pulse rate: pre-study, 0 h (predose), 0.50, 1, 4, 8 h, post-study. ECG (12 leads): pre-study, 0 h, 1, 8 h (oral administration); -15, -10, -5 min, 0 h, 1, 8 h (i.v. administration), post-study; ECG monitoring (continuous ECG 2-lead and heart rate): prior to start of infusion up to at least 15 min thereafter. Documentation of adverse events. Post-study: physical examination, body weight and temperature, clinical laboratory parameters excluding drug screening, HbsAG and HIV-test 1 and 2.

Statistical methods:

As primary variable for confirmative statistical analysis $AUC_{(0-\infty)}$ as respective extent characteristics was chosen. $AUC_{(0-\infty)}$ was calculated by the trapezoidal formula up to the last sampling time with a concentration above the limit of quantitation, and then extrapolated to infinity using standard techniques.

As secondary variable, the results of blood pressure, heart rate and ECG measurements, determinations of clinical laboratory parameters, and adverse events occurred throughout the study were analyzed in a merely descriptive manner including summary statistics such as median, 68%-range, mean, SD and geometric mean.

SUMMARY – CONCLUSIONS

Summary:

Pharmacokinetics:

Plasma concentrations of roflumilast (B9302-107) and metabolite B9502-044 were determined by the Dept. of Drug Metabolism and Pharmacokinetics (FKM), Byk Gulden, Konstanz, 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 and 0.5 µg/l for roflumilast (B9302-107) and B9502-044, respectively.

The following tables show a summary of the pharmacokinetic characteristics (geom. mean and 68%-range) of roflumilast (B9302-107) and metabolite B9502-044 after single oral (0.5 mg) and intravenous (0.15 mg) administration of roflumilast:

Single oral administration of 0.5 mg roflumilast:

	B9302-107	**B9502-044**
$AUC_{(0-\infty)}$ [µg*h/l]	37.22 (25.20 - 54.98)	400.47 (291.09 - 550.97) (N=6)
C_{max} [µg/l]	8.328 (5.793 - 11.973)	13.107 (9.883 - 17.382)
$t_{½}$ [h]	15.70 (12.38 - 19.90)	20.60 (15.40 - 27.56) (N=8)
t_{max} [h]	0.98 ± 0.12	8.83 ± 3.96

Single intravenous short-term infusion over 15 minutes of 0.15 mg roflumilast:

	B9302-107	**B9502-044**
$AUC_{(0-\infty)}$ [µg*h/l]	14.06 (9.71 – 20.36)	99.22 (80.07 - 122.96) (N=8)
C_{max} [µg/l]	6.364 (5.035 – 8.044)	2.875 (2.307 – 3.582)
$t_{½}$ [h]	14.79 (10.05 - 21.76)	22.73 (14.81 - 34.90) (N=11)
t_{max} [h]	0.22 ± 0.01	6.92 ± 0.95
Cl [l/h/kg]	0.137 (0.097 – 0.194)	not ascertained
Vd_{area} [l/kg]	2.924 (2.389 – 3.580)	not ascertained

Absolute bioavailability of roflumilast (B9302-107) and ratio analysis of AUC values of B9502-044 (Test) and B9302-107 (Reference) following single oral and intravenous administration of roflumilast:

Values are given as point estimates with 90%-confidence limits.

	0.15 mg i.v.	**0.5 mg p.o.**
Roflumilast bioavailability	reference	0.79 (0.69 - 0.92)
AUC ratio B9502-044/B9302-107	7.44 (5.97 - 9.27) (N=8)	12.41 (10.01 - 15.38) (N=6)

Safety and tolerability:
Repeated implementation of safety measurements did not reveal clinically relevant findings. No adverse events arose that were assessed as likely or definitely related to the study medication.

Conclusions:

Pharmacokinetics:
The primary aim of this study was to determine the absolute bioavailability of roflumilast (B9302-107) following single oral and intravenous administration. The absolute bioavailability was calculated to be 79% with 90%-confidence limits of 69 - 92%.
In addition to parent compound roflumilast, the N-oxide metabolite B9502-044 was determined. Statistical comparison of AUCs referenced to those of the parent compound showed values higher by factor 7.44 following intravenous administration and by factor 12.41 following oral administration.

Safety and tolerability:
Both, oral administration of 0.5 mg roflumilast and intravenous administration of 0.15 mg roflumilast were safe and well tolerated.