Synopsis of study report: 180E/99
Location in Module 5:

Study Code:
BY217/FHP016

Report Date:
9-Mar-2000

Title of the study:
Study on the bioequivalence of three tablet formulations (0.25 mg each) of roflumilast

Study center(s):
QUINTILES Innovex (Biodesign) GmbH, Obere Hardtstr. 8–16, D-79114 Freiburg

Publication (reference):
Not available

Studied period (years):
09 June 1999 – 14 July 1999

Clinical phase:
I

Objectives:
- Investigation of bioequivalence of 3 formulations of Roflumilast (B9302-107) tablets (0.25 mg). Determination of safety and tolerability; pharmacokinetics of the pharmacologically active metabolite B9502-044.

Methodology:
Open, randomized three-period change-over design with random allocation of eligible healthy subjects to six treatment sequences of a balanced Latin Square design and its mirror image. Between each study period, a washout interval of at least 7 days (but not more than 3 weeks)

was maintained. Treatments: Treatment A: Reference (present phase I/II formulation), 2 tablets each containing 0.25 mg Roflumilast p.o. Treatment B: Test 1 (present formulation manufactured by Oranienburger Pharmawerk), 2 tablets each containing 0.25 mg Roflumilast p.o. Treatment C: Test 2 (planned market formulation), 2 tablets each containing 0.25 mg Roflumilast p.o. Pre-study examination within one month prior to study start including medical examinations and clinical laboratory examination. Pharmacokinetic determinations of Roflumilast deriving from blood samples, collected at prescheduled times up to +72 hours after administration in each study period. For safety and tolerability determination, blood pressure and pulse rate were measured and electrocardiograms (12 leads) were recorded at prescheduled times. All adverse events were documented in detail. Post-study examination was performed within 2 weeks after termination of the study.

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

Total: 24
Analyzed per protocol analysis: 24; analyzed per intention-to-treat analysis: 24.
There was no drop-out.

Diagnosis and criteria for inclusion:

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

Duration of treatment:

Test 1: one single dose; **Test 2:** one single dose
Reference: one single dose

Test product:

Test 1: Roflumilast, tablets (present formulation manufactured by Oranienburger Pharmawerk, galenical formula B-OPW) = **treatment B**
Test 2: Roflumilast, tablets (planned market formulation, galenical formula C-OPW) = **treatment C**

Dose:

Test 1: 2 tablets, each containing 0.25 mg; (total dose: 0.5 mg)
Test 2: 2 tablets, each containing 0.25 mg; (total dose: 0.5 mg)

Mode of administration:

Test 1 and 2: per oral (p.o.)

Batch No.:

Test 1: 128299
Test 2: 129299

Reference product:

Roflumilast tablets (present phase I/II formulation, galenical formula B-FG1) = **treatment A**
Dose:
2 tablets, each containing 0.25 mg; (total dose: 0.5 mg)

Mode of administration:

Per oral (p.o.)

Batch No.:

127299

Criteria for evaluation:

Bioequivalence of Roflumilast (B9302-107) and pharmacokinetics of the metabolite B9502-044 derived from plasma concentrations after oral administration. Sampling times**:** 0 h (predose), and then +0.25 h, +0.5 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, +24.00 h, +30.00 h, +48.00 h, +54.00 h and, +72.00 h p.a.

Pharmacokinetics: $AUC_{(0-\infty)}$ and C_{max} were chosen as primary variables for confirmative statistical analysis.

Safety and tolerability: Pre-study: demographic data, medical history, physical examination, body weight and body temperature, clinical laboratory parameters including drug screening, Hb_sAg, anti HCV (IgG), HIV-test I and II. Blood pressure, pulse rate: pre-study, 0 h (predose), 1.00, 2.00 h p.a., post-study. ECG (12 leads): pre-study, 0 h, 1.00 h, 2.00 h p.a., post-study. Documentation of adverse events. Post-study: physical examination, body weight and temperature, clinical laboratory parameters excluding drug screening, Hb_sAg, anti HCV (IgG), HIV-test I and II.

Statistical methods:

As primary variables for confirmative statistical analysis $AUC_{(0-\infty)}$ and C_{max} were chosen as respective extent and rate characteristics for Roflumilast. $AUC_{(0-\infty)}$ 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. C_{max} was obtained directly from the measured concentrations. Point estimates and 90%-confidence limits were given for the ratio of the population medians for Test treatment C (Test 2) and Treatment A (Reference) using a multiplicative model and a parametric analysis unless substantial deviations from this model called for a nonparametric analysis. In the parametric approach, the residual variance was calculated by means of corresponding ANOVA model after a log-transformation. Equivalence between Test and Reference was concluded if the 90%-confidence interval was entirely within the equivalence range of 0.80 to 1.25 concerning

$AUC_{(0-\infty)}$ and 0.70 to 1.43 concerning C_{max}. If the bioequivalence of A and C could not be concluded, the bioequivalence of Treatment B (Test 1) and Treatment A (Reference) was of interest and should have been analyzed as described above.
The following secondary pharmacokinetic characteristics were analyzed with an explorative intention: terminal half life $t_{1/2}$ of Roflumilast; time of maximum concentration t_{max} of Roflumilast, pharmacokinetic characteristics ($AUC_{(0-\infty)}$ and $t_{1/2}$) of the metabolite B9502-044. If extrapolation of AUC up to infinity was not feasible, AUC up to the last sampling time (t_{last}) was calculated. Further secondary variables were the results of safety measurements: blood pressure, pulse rate, body temperature and ECG 12 leads (PQ, QRS, QTc and heart rate). These parameters were analysed in a merely descriptive manner including summary statistics such as median, 68%-range, mean, SD and geometric mean and geometric 68%-range, where appropriate.
Clinical laboratory data were presented on an individual basis and marked according to the normal ranges provided by QUINTILES Innovex (Biodesign) GmbH. For each adverse event the following items were reported: nature, incidence, duration, intensity and Investigator's and Sponsor's causality assessment.

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics:

Ratio analysis of $AUC_{(0-\infty)}$ and C_{max} for Roflumilast demonstrated bioequivalence within the given equivalence ranges for treatment B and A (Test 1 and Reference) with respect to $AUC_{(0-\infty)}$ as well as $C_{max.}$

Ratio analysis of $AUC_{(0-\infty)}$ and C_{max} demonstrated bioequivalence for treatment C (Test 2, planned market formulation) and treatment A (Reference, present FG1 formulation) with respect to $AUC_{(0-\infty)}$, but not with respect to C_{max}. The lower confidence limits for C_{max} (0.67) were out of the equivalence range of 0.70 to 1.43. Therefore, in the overall assessment, treatment C was not bioequivalent to treatment A (Reference).

Parameters	Test 1 (Treatment B)	Test 2 (Treatment C)	Reference (Treatment A)
$AUC_{(0-\infty)}$	35.36	33.03	33.45
[µg/l·h]	(24.01, 52.06)	(21.76, 50.13)	(23.08, 48.50)
C_{max}	6.482	5.534	7.591
[µg/l]	(5.266, 7.978)	(4.502, 6.803)	(6.264, 9.200)
$t_{½}$	14.84	13.91	13.09
[h]	(9.08, 24.25)	(7.91, 24.43)	(8.16, 21.00)
t_{max}	1.06 ± 0.08	1.54 ± 0.10	0.86 ± 0.12
[h]			

The pharmacokinetic evaluation of the pharmacologically active metabolite B9502-044 was not performed.

Safety and tolerability:
Roflumilast was safe and tolerated when administered orally as single dose (0.5 mg) to healthy male and female subjects in three different formulations: Treatment A: Reference (present phase I/II formulation); Treatment B: Test 1 (present formulation manufactured by OPW) and Treatment C: Test 2 (planned market formulation), as well.
No serious adverse events occurred during the study. Most frequent adverse events were nervous system disorders, predominantly headache of mild to moderate intensity. No adverse events arose that were judged as definitely related to the study medication in the investigator's causality assessment.
Safety measurements did not reveal any clinically relevant findings. In particular, there were no significant deviations of cardiovascular parameters or clinical laboratory results.

Conclusions:

Pharmacokinetics:
Ratio analysis of $AUC_{(0-\infty)}$ and C_{max} for Roflumilast demonstrated bioequivalence for treatment B and A (Test 1 and Reference).
Ratio analysis of $AUC_{(0-\infty)}$ and C_{max} demonstrated bioequivalence for treatment C (Test 2, planned market formulation) and treatment A (Reference, present FG1 formulation) with respect to $AUC_{(0-\infty)}$, but not with respect to C_{max}. Therefore, in the overall assessment, treatment C was not bioequivalent to treatment A (Reference).

Safety and tolerability:
Roflumilast was investigated to be safe and tolerated when administered orally (dose: 0.5 mg) to healthy male and female subjects in three different formulations. Regarding the adverse events, mostly headache (mild to moderate intensity) was reported.
Hence, it can be stated that all three Roflumilast formulations investigated in this study were safe and tolerated.