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

Study Code:
BY217/FHP012

Report Date:
21-Mar-2000

Title of the study:

Study to investigate the effect of roflumilast on vigilance and traffic safety in healthy volunteers – A randomized, placebo-controlled, double-blind crossover study.

Study center(s):

conTest – Zentrum für Psychometrie und Klinische Prüfung, TÜV Kraftfahrt GmbH, Am Grauen Stein, 51105 Köln, Germany

Publication (reference):

Not available

Studied period (years):

28 October 1998 – 28 April 1999

Clinical phase:

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Objectives:

Primary:

- Investigation of the possible influence of roflumilast on vigilance and traffic safety in healthy volunteers.

Secondary:

- Safety and tolerability.

Methodology:

The study was conducted according to a randomized, placebo-controlled, double-blind, two-period crossover design. Series of tests (5 individual procedures) to describe vigilance and performance were carried out on study day 0 (baseline), study day 1 (after 1st dosing), and study day 7 (after 7th dosing) in each study period.

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

Intention-to-treat (ITT):	n = 19 (9 male, 10 female)
Roflumilast:	n = 19
Placebo:	n = 18
Per-protocol (PP):	n = 18 (9 male, 9 female)
Roflumilast:	n = 18
Placebo:	n = 18

Diagnosis and criteria for inclusion:

Healthy subjects.

Duration of treatment:

7 days

Test product:

Roflumilast

Dose:

500 µg (2 tablets of 250 µg each))

Mode of administration:

p.o.

Batch No.:

069398

Reference product:

Placebo

Dose:

2 tablets of identical appearance to the roflumilast tablets

Mode of administration:

p.o.

Batch No.:

070398

Criteria for evaluation:

Evaluation of vigilance and traffic safety:

Series of tests (5 individual procedures: signal detection, measuring motor response coordination, measuring reaction under stress, measuring vigilance, measuring the precision of visual orientation) to describe vigilance and performance were carried out on study day 0 (baseline), study day 1 (after 1st dosing), and study day 7 (after 7th dosing) in each study period.

Safety and tolerability:

Safety measurements (physical examination, clinical laboratory, urinalysis, ECG, blood pressure and pulse rate performed at pre and final check, and clinical laboratory, blood pressure and pulse rate in the morning of day 7 in the first period).

Statistical methods:

A confirmatory test was carried out to show that roflumilast was at least equivalent to placebo with respect to safety-relevant performance (i.e., total score of the five performance test values obtained on study day 7 of both periods). All other comparisons were intended to be explorative.

Primary endpoints: Safety-relevant performance

Statistical model: The tests performed on study day 0 of both periods represent the test baseline, subsequent data were expressed as changes from baseline. An analysis of covariance model was used for the psychometric tests.

The statistical hypotheses to be tested were:

H0: roflumilast 0.5 mg $\geq$ placebo + δ

versus

H1: roflumilast 0.5 mg < placebo + δ

in which $\delta = 0.9\sigma$ and σ: standard deviation of safety-relevant performance. Based on previous results with this test setting under BAC-levels in the range of approx. 0.05%, $\delta = 0.9\sigma$ appeared to be a reasonable choice for the equivalence region.

Safety data were evaluated descriptively.

SUMMARY – CONCLUSIONS

Summary:

Vigilance and traffic safety:

For efficacy data evaluation an analysis of covariance was to be performed with baseline results as covariates in order to control possible differences in baseline performance levels of subjects. Carry-over effects as consequence of the chosen cross-over fashion were at first

checked by t-test (p=0.1). Compared with this p-level there were no indications for significant differences effected by carry-over phenomena. As to the general statistical evaluation (sum-score of the z-transformed and summed-up results of the five performance tests applied) safety-relevant performance had been tested before treatment and after having reached steady state of roflumilast (7th dose). This comparison was regarded as being of confirmatory nature. The results of this did not show any inferiority according to the analysis of the upper limits of 90%-confidence intervals (using LS MEANS and StdERR). Descriptively corresponding analyses were performed to evaluate the results of the comparisons baseline/1st dose and baseline /steady state concerning the five single performance tests.
The interval-inclusion method led at first to the general decision that equivalence of roflumilast to placebo (baseline/steady state comparison) is to be concluded. Furthermore, with respect to the results of the five single performance tests during treatment period in comparison to placebo there was no statistically significant inferiority of roflumilast.

Safety and tolerability:
The results of the safety measurements at screening, in the morning of day 7 of the first period, and during the post study examination did not reveal any pathological findings. During the roflumilast treatment period and the placebo treatment period, 3 adverse events were reported each. One subject dropped out due to inter current illness which was not drug-related.

Conclusions:

Vigilance and traffic safety:
All performance tests applied did not show any disadvantage of roflumilast relatively to placebo neither with the global sum scores nor with the single test procedures at any test run during the treatment periods. Roflumilast and placebo were equivalent to each other with respect to safety-relevant performance both at beginning of intake and at steady state.

Safety and tolerability:
The 7-day treatment with 500 µg/d roflumilast was safe and well-tolerated.