Synopsis of study report: 201E/97
Location in Module 5:

Study Code:
BY217/FHP009

Report Date:
04-Feb-1998

Title of the study:

Safety and tolerability of the new phosphodiesterase inhibitor B9302-107 administered to healthy male volunteers as repeated oral doses over 3 weeks. A double-blind randomized placebo-controlled crossover study

Study center(s):

Quintiles Innovex (Biodesign) GmbH, Obere Hardtstr. 8–16, 79114 Freiburg, Germany

Publication (reference):

Not available

Studied period (years):

March 1997 – May 1997

Clinical phase:

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Objectives:

Primary:

- Safety and tolerability

Secondary:

- Orientative data on pharmacokinetics and pharmacodynamics

Methodology:

Placebo-controlled, randomized, double-blind, 2-period crossover investigation

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

Intention-to-treat analysis: 16 healthy male subjects (median age: 32 years; median body weight: 79 kg)

Per-protocol analysis: 14 healthy male subjects (median age: 34 years; median body weight: 77 kg)

Diagnosis and criteria for inclusion:

Healthy male subjects

Duration of treatment:

21 days

Test product:

Roflumilast

Dose:

0.5 mg (2 tablets of 0.25 mg each) s.i.d.

Mode of administration:

p.o.

Batch No.:

0611977

Reference product:

Placebo

Dose:

2 tablets s.i.d.

Mode of administration:

p.o.

Batch No.:

062197

Criteria for evaluation:

Safety and tolerability:

Repeated implementation of blood pressure, heart rate, ECG, clinical laboratory investigation, olfactometry, and continuous recording of adverse events.

Pharmacokinetics:
Blood samples were taken at 2 h after administration on study days 1, 7, 14 and 21, and the plasma was assayed for parent compound B9302-107 (roflumilast) and metabolite B9202-045. Analysis of the parent compound was conducted by the Department of Drug Metabolism and Pharmacokinetics (FKM), Byk Gulden. B9302-107 plasma concentrations were determined by 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 0.1 µg/l.
Analysis of metabolite B9202-045 was performed by pharm-analyt Labor GmbH, A-2500 Baden bei Wien, Austria. B9202-045 plasma concentrations were determined by GC-MS analysis. LLOQ varied from 0.08 to 0.320 µg/l depending on the volume of plasma available for extraction.

Pharmacodynamics:
Blood samples for the determination of TNFα in whole blood were taken predose and at 2 h after administration on study days 1 and 21 each. Analysis was performed by the Dept. of Biochemistry (FB1), Byk Gulden, by ELISA.

Statistical methods:

Safety and tolerability: Descriptive
Pharmacokinetics: Descriptive
Pharmacodynamics: Descriptive

SUMMARY - CONCLUSIONS

Summary:

Safety and tolerability:
The adverse events reported most frequently under treatment with roflumilast were: back pain/lumboischialgia/lumbalgia (8 of 16 subjects), headache (3 of 16 subjects), loose stools/diarrhea (2 of 16 subjects) and common cold (2 of 16 subjects). The frequency of the above-mentioned symptoms under treatment with placebo was as follows: lumbalgia was reported by 2 of 16 subjects, gastrointestinal complaints and headache were reported by 1 of 16 subjects each. Apart from these complaints some single events were reported under both treatments.
In most of the cases with back pain/lumboischialgia/lumbalgia the symptoms subsided spontaneously under continued treatment with the study medication. Neurological examinations were performed by a nerve specialist and revealed normal findings. It should be noted that lumbalgia was also reported by two subjects under placebo treatment.
Repeated implementation of safety measurements (i.e. physical examination, blood pressure, heart rate, ECG, clinical laboratory, and olfactometry) did not reveal clinically relevant findings.

Pharmacokinetics:
Geometric means with geometric 68% range of plasma concentrations [µg/l] of parent compound B9302-107 (roflumilast) and metabolite B9202-045 in the 2 h-samples on study days 1, 7, 14 and 21 following single or repeated oral administration of 0.5 mg B9302-107:

	Study day 1	**Study day 7**	**Study day 14**	**Study day 21**
parent compound B9302-107 (roflumilast):	**(N=15)**	**(N=15)**	**(N=14)**	**(N=15)**
geom. means	3.208	3.934	3.907	3.765
geom. 68% range	1.870-5.502	2.783-5.561	2.788-5.475	2.220-6.387
metabolite B9202-045:	**(N=15)**	**(N=7)**	**(N=10)**	**(N=10)**
geom. means	all values < D.L.	0.145	0.181	0.244
geom. 68% range		0.100-0.209	0.138-0.238	0.167-0.356

D.L.: detection limit

Pharmacodynamics:
On day 1, the blood levels of TNFα determined at 2 h after roflumilast and placebo administration did not differ significantly. There is a relative high variability of individual TNFα concentrations. From day 1 to day 21, the median blood levels of TNFα (determined at 2 h after dosing) increased significantly under placebo treatment and decreased slightly under roflumilast treatment. On day 21, the median TNFα concentration in whole blood determined at 2 h after roflumilast administration (4833 pg/ml) was clearly lower than the median TNFα concentration obtained at 2 h after placebo administration (6265 pg/ml). The difference did not reach statistical significance at the 5%-level, two-sided, as the nonparametric 95%-confidence interval - calculated for the respective Test/Reference ratios after logarithmic transformation - ranged from 0.65 to 1.01 (parametric: 0.66 to 1.002); point estimate: 0.79 (parametric: 0.81).

Conclusions:

Safety and tolerability:
Adverse events seemed to be more frequent under treatment with roflumilast as compared to placebo. Nevertheless, repeated dosing of 0.5 mg/d roflumilast was safe and well tolerated. None of the adverse events was considered to be definitely related to the study medication. The etiology of some rather uncommon adverse events such as lumbalgia cannot be finally assessed yet, however, neurological examinations revealed normal findings, so that a risk for the subjects could be excluded. This assessment is confirmed by the fact that most of these symptoms subsided spontaneously under continued treatment with the study medication.

Pharmacokinetics:
Measurement of B9302-107 (roflumilast) and B9202-045 concentrations in the 2h plasma samples resulted in values which demonstrate compliance with the study protocol for all subjects throughout the study. All concentration values were in the expected range. Comparison of the mean concentrations of B9302-107 showed approximately constant values throughout the study. When mean concentrations of metabolite B9202-045 on study days 7, 14 and 21 were compared, a continuous increase in concentration throughout the duration of the study period (i.e. about 50% between days 7 and 21) could be observed. On study day 1, no metabolite B9202-045 was detectable in the 2h plasma samples of all subjects.

Pharmacodynamics:
Determination of TNFα in whole blood did not lead to final conclusions in this study, however, 2 h after administration on day 21, the median blood level of TNFα was clearly lower under roflumilast treatment than under placebo treatment. The difference on day 21 is mainly related to an increase of median TNFα concentration under placebo treatment. Nevertheless, the results give hints that roflumilast may cause a suppression of TNFα, taking into account that under both treatments the median TNFα concentration may be on a higher level on day 21 as compared to day 1 due to interfering variables.