Synopsis of study report: 128E/97
Location in Module 5:

Study Code:
BY217/FHP004

Report Date:
23-Jan-1998

Title of the study:

Safety and tolerability of the new phosphodiesterase inhibitor (B9302-107) administered to healthy male volunteers as ascending repeated oral doses over 7 days

Study center(s):

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

Publication (reference):

Not available

Studied period (years):

April 1996 – October 1996

Clinical phase:

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Objectives:

Primary:

- Safety and tolerability

Secondary:

- Preliminary data on pharmacokinetics and pharmacodynamics

Methodology:

Placebo-controlled, single-blind, 3-period ascending dose investigation with a randomly interspersed placebo period and a subsequent 4th period in which all subjects received b.i.d. treat-

ment of roflumilast (The daily dose of roflumilast in the fourth period depended on the results of the preceding periods).

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

11 healthy male subjects (median age: 32 years; median body weight: 67.4 kg)

Diagnosis and criteria for inclusion:

Healthy male subjects

Duration of treatment:

7 days

Test product:

Roflumilast

Dose:

D1: 0.5 mg/d (2 placebo tablets and 2 tablets of 0.25 mg in the morning)
D2: 1.0 mg/d (4 tablets of 0.25 mg in the morning)
D3: 1.0 mg/d (2 tablets of 0.25 mg in the morning and 2 tablets of 0.25 mg in the evening)

Mode of administration:

p.o.

Batch No.:

113196

Reference product:

Placebo

Dose:

D0: 4 tablets in the morning

Mode of administration:

p.o.

Batch No.:

114196

Criteria for evaluation:

Safety and tolerability:

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

Pharmacokinetics:
Repeated blood sampling for determination of the pharmacokinetic profiles of roflumilast (B9302-107) and metabolite B9202-045 on day 7.
Analysis of parent compound B9302-107 was conducted by the Dept. of Pharmacokinetics and Drug Metabolism, Byk Gulden, by reversed-phase HPLC with fluorescence detection after post-column photochemical derivatization (LLOQ: 0.1 µg/L).
Analysis of metabolite B9202-045 was performed by pharm-analyt Labor GmbH, A-2500 Baden bei Wien, by GC-MS analysis (LLOQ: 0.04 µg/L).

Pharmacodynamics:
Repeated implementation of impedance cardiography and repeated blood sampling for the determination of TNFα in whole blood.

Statistical methods:

Safety and tolerability:
Descriptive

Pharmacokinetics:
Calculated parameters were $t_{½}$ (B9302-107 only), t_{max} (B9302-107 only), C_{max}, and AUC using the KINT program (Version 2.1).
Statistical ratio analysis of AUCs was calculated using the BioQPC program (Vers. 1.1.2). Results were given as point estimates with upper and lower 90% confidence limits.

Pharmacodynamics:
Descriptive

SUMMARY - CONCLUSIONS

Summary:

Results:
Safety and tolerability:
Adverse events reported most frequently under treatment with 0.5 mg/d roflumilast were: diarrhea, increased frequency of defecation, loose stool (5/11 subjects), headache (5/11 subjects), sleep disturbances (2/11 subjects), lumboischialgia, lumbalgia (2/11 subjects). Adverse events were more frequent and pronounced under treatment with 1.0 mg/d roflumilast. The adverse events reported most frequently were: nausea, anorexia (1.0 mg s.i.d.: 5/9 subjects; 0.5 mg b.i.d.: 8/8 subjects), headache (1.0 mg s.i.d.: 5/9 subjects; 0.5 mg b.i.d.: 6/8 subjects), gastrointestinal complaints such as diarrhea and abdominal pain

(1.0 mg s.i.d.: 5/9 subjects; 0.5 mg b.i.d.: 2/8 subjects), lumboischialgia, lumbalgia (1.0 mg s.i.d.: 4/9 subjects; 0.5 mg b.i.d.: 3/8 subjects).
Altogether 6 of 11 subjects dropped out during the study due to adverse events. Subject No. 05 dropped out after day 4 of period 3 (1.0 mg s.i.d.) due to various adverse events (headache, dizziness, gastrointestinal pain, nausea, sleep disturbance, tinnitus, and hot flushes). Subject No. 06 dropped out after day 4 of period 4 due to lumbalgia, nausea and lack of appetite. Subject No. 07 discontinued study participation after the first administration of day 5 of period 4 due to lumboischialgia. Subject No. 08 dropped out after morning administration of day 4 of period 4 due to lack of appetite and tiredness. Subject No. 103 was only administered the trial drug on day 1 of period 4, then dropped out due to paresthesia and dizziness. Subject No. 03 dropped out after period 1 (0.5 mg s.i.d.) due to an intercurrent pneumonia which was assessed as unlikely drug-related.
Repeated implementation of safety measurements (i.e. clinical laboratory, physical examination, vital signs, ECG, spermiogram, olfactometry) did not reveal clinically relevant findings.

Pharmacokinetics:

Pharmacokinetic characteristics: geometric means (68% range); mean ± SEM for t_{max}

Dose	**0.5 mg s.i.d. (N=10)**	**1.0 mg s.i.d. (N=8)**	**0.5 mg b.i.d. (N=4)**
Parent compound B9302-107 (roflumilast)			
$t_{1/2}$ [h]	8.2 (6.7 - 10.0)	8.1 (6.1 - 10.6)	6.3 (4.1 - 9.7)
t_{max} [h]	2.60 ± 0.36	1.94 ± 0.33	1.13 ± 0.24
C_{max} [µg/l]	5.47 (3.98 - 7.53)	10.93 (7.36 - 16.22)	7.43 (4.74 - 11.64)
AUC [µg/l*h]	32.86 (20.63 - 52.37) [1]	61.46 (39.14 - 96.50) [1]	27.43 (18.96-39.70) [2]
Point estimate (90% conf. limits)	reference	0.98 (0.87 - 1.11)	0.99 (0.88 - 1.12)
Metabolite B9202-045			
$t_{1/2}$ [h]	n.a.	n.a.	n.a.
t_{max} [h]	n.a.	n.a.	n.a.
C_{max} [µg/l]	0.24 (0.14 - 0.43)	0.56 (0.35 - 0.91)	0.52 (0.29 - 0.96)
AUC [µg/l*h]	4.14 (2.22 - 7.70) [1]	10.15 (6.03 - 17.06) [1]	4.87 (2.69 - 8.81) [2]
Point estimate (90% conf. limits)	reference	1.14 (0.95 - 1.35)	1.13 (1.08 - 1.18)
Point estimate (90% conf. limits) of the AUC ratio metabolite/parent compound	0.13 (0.10 - 0.16)	0.17 (0.14 - 0.20)	0.18 (0.13 - 0.24)

n.a.= not ascertained; [1] = AUC(0-24h); [2] = AUC(0-12h)

Pharmacodynamics:
As to impedance cardiography, repeated measurements of global flow, cardiac output, preload, contractility, cardiac work, pump efficiency, thoracic fluids and mean arterial pressure did not exceed the physiological degree of variation.
The mean TNF_{α} concentration in whole blood tended to decrease during roflumilast treatment in contrast to placebo. However, there was a high intra- and interindividual variability of the measured values.

Conclusions:

Safety and tolerability:
The results suggested that the maximum tolerable dose for repeated dosing is reached with 0.5 mg/d roflumilast. Repeated administration of 0.5 mg/d roflumilast over 7 days was sufficiently tolerated in this study. Hence, it was concluded that 0.5 mg/d is the dosage of interest that would be investigated in further phase I studies and in phase II studies.

Pharmacokinetics:
AUC and C_{max} of parent compound B9302-107 and metabolite B9202-045 increased in proportion to the dose when B9302-107 was administered at dose levels of 0.5 mg s.i.d. and 1.0 mg s.i.d.. Comparable values for AUC and C_{max} of parent compound in the dosing interval were determined following administration of 0.5 mg B9302-107 s.i.d. and 0.5 mg B9302-107 b.i.d.. Comparison of AUCs of metabolite B9202-045 following administration of 0.5 mg B9302-107 s.i.d. and 0.5 mg B9302-107 b.i.d. showed an increase in AUC of 14% and 13%, respectively. No relevant differences in the AUC ratio of metabolite/parent compound at all three dose levels were calculated.

Pharmacodynamics:
Results of impedance cardiography and of TNFα determination in whole blood did not lead to final conclusions.