Synopsis of study report: 259E/97
Location in Module 5:

Study Code:
BY217/FHP005

Report Date:
24-Apr-1998

Title of the study:

Safety, tolerability and orientative pharmacokinetics of roflumilast after increasing i.v. single doses

Study center(s):

Institut für Medizinforschung Allensbach (IMA), Konstanzer Str. 7A, D-78476 Allensbach

Publication (reference):

Not available

Studied period (years):

November 1997 – December 1997

Clinical phase:

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Objectives:

Primary:

- Safety and systemic and local tolerability of the roflumilast infusion solution

Secondary:

- Orientative pharmacokinetics for selection of the roflumilast dosage suitable for a planned bioavailability study

Methodology:

Single blind, 5-period ascending dose design with randomly interspersed placebo.

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

4 subjects (2 male, 2 female); median age: 28 years; median body weight: 70.0 kg

Diagnosis and criteria for inclusion:

Healthy subjects

Duration of treatment:

Intravenous infusion over 15 minutes

Test product:

Vials containing 8 mg/10 ml roflumilast for dilution with the lipid emulsion Lipofundin® MCT 10% (Braun Melsungen)

Dose:

0.01 mg roflumilast diluted in Lipofundin® MCT 10% emulsion
0.03 mg roflumilast diluted in Lipofundin® MCT 10% emulsion
0.07 mg roflumilast diluted in Lipofundin® MCT 10% emulsion
0.15 mg roflumilast diluted in Lipofundin® MCT 10% emulsion

Mode of administration:

Intravenous infusion

Batch No.:

037497

Reference product:

Placebo (Lipofundin® MCT 10% emulsion)

Dose:

Lipofundin® MCT 10% emulsion

Mode of administration:

Intravenous infusion

Batch No.:

039497

Criteria for evaluation:

Safety and tolerability were assessed by repeated measurements of 12-lead ECG, blood pressure and heart rate as well as by safety measurements at pre and final check and continuous recording of adverse events.
Repeated blood samplings were taken up to 8 h after each dosing for pharmacokinetic purposes.

Statistical methods:

Safety and tolerability were evaluated descriptively.
The following pharmacokinetic characteristics were determined: $AUC_{(0\text{-}8h)}$, C_{max}, t_{max}, $t_{½}$, Cl/kg, Vd_{area}/kg.

SUMMARY - CONCLUSIONS

Summary:

Results:

Local tolerability was very good. The mean and median values of blood pressure (BP) and heart rate (HR) were comparable under placebo and roflumilast treatment up to the dose level of 0.07 mg. The diastolic blood pressure tended to decline from 7.5 min until 30 min after start of infusion of 0.15 mg roflumilast, however, means and medians of diastolic blood pressure were still within the normal range. Subject No. 03 showed a remarkable decrease in diastolic blood pressure at 7.5 min after start of infusion with 0.15 mg roflumilast (BP: 117/37 mmHg, HR: 59 b/min; predose value: BP 115/78 mmHg, HR 48 b/min), but at 15 min after start of infusion (= t_{max}), the value had normalized (BP: 104/61; HR: 49 b/min).

Pharmacokinetic characteristics:

Geom. means with 68%-range

	0.01 mg	**0.03 mg**	**0.07 mg**	**0.15 mg**
$AUC_{(0-\infty)}$ [µg/lxh]	n.a.	n.a.	n.a.	15.00 [2)]
C_{max} [µg/l]	0.426 [3)] (0.346–0.526)	1.144 (0.903–1.450)	3.123 (2.148–4.541)	5.178 (4.069–6.590)
$t_{½}$ [h]	n.a.	n.a.	11.4 [1)]	13.7 [2)]
Cl/kg [l/h]	n.a.	n.a.	n.a.	0.1578 [2)]
Vd_{area}/kg [l]	n.a.	n.a.	n.a.	3.112 [2)]

n.a.: not ascertainable; [1)] n=1, [2)] n=2, [3)] n=3

Conclusions:

Safety and tolerability was good. An influence of 0.15 mg roflumilast i.v. on diastolic blood pressure cannot be excluded and should be of interest in the subsequent bioavailability study.

C_{max} values after intravenous administration of 0.01, 0.03, 0.07 and 0.15 mg roflumilast increased in proportion to the dose. Derived from the orientative pharmacokinetic data of this study, the required intravenous dose for the planned bioavailability study is 0.15 mg.