Synopsis of study report: 134/99K1
Location in Module 5:

Study Code:
BY217/FHP014

Report Date:
29-Nov-1999

Title of the study:

Investigation of a possible pharmacokinetic interaction between roflumilast and salbutamol in healthy male subjects

Study center(s):

Institute of Pharmacology, University of Greifswald, Friedrich-Loeffler-Str. 23d, D 17487 Greifswald

Publication (reference):

Not available

Studied period (years):

17 November 1998 – 05 March 1999

Clinical phase:

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Objectives:

Primary:

- Investigation of a possible pharmacokinetic interaction of salbutamol (Sultanol® N, MDI 100 µg) on roflumilast in fasted state

Secondary:

- Investigation of a possible pharmacokinetic interaction of roflumilast on salbutamol (Sultanol® N, MDI 100 µg) in fasted state
- Investigation of a possible pharmacokinetic interaction of salbutamol (Sultanol® N, MDI 100 µg) on the pharmacological active metabolite of roflumilast (B9502-044) in fasted state
- Safety and tolerability

Methodology:

The study was conducted according to a randomized, open, three-period, change-over design with random allocation of the eligible subjects to the 6 treatment sequences of a Latin Square and its mirror image. In one study period the subjects received roflumilast alone (Test 1), in another study period they received salbutamol alone (Test 2), and in a third study period both drugs were given together (Reference).
Repeated blood samples for pharmacokinetic purposes were taken up to 72 h after roflumilast administration and up to 24 h after salbutamol inhalation, beginning each after the morning administration on day 7. Safety measurements were performed on day 7 of each study period and at pre and final check.

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

13; for each treatment:

roflumilast + salbutamol:	12
roflumilast alone:	13, one drop-out
salbutamol alone:	13

Diagnosis and criteria for inclusion:

Healthy male subjects (median age: 24 years; median weight: 85 kg)

Duration of treatment:

7 days

Test product:

Roflumilast

Dose:

0.5 mg/d (2 tablets of 0.25 mg each)

Mode of administration:

p.o., dosing at 8.00 a.m. on days 1-7

Batch No.:

030498

Reference product:

Salbutamol (Sultanol® N, MDI 100 µg)

Dose:

200 µg (2 puffs of 100 µg each)

Mode of administration:

Aerosol inhalations by means of metered dose inhaler, 200 µg at 8.00 a.m., 2.00 p.m. and at 8.00 p.m. on days 1-7

Batch No.:

031498

Criteria for evaluation:

Pharmacokinetics:

Plasma levels of roflumilast and metabolite B9502-044 determined up to 72 h after roflumilast administration. Plasma levels of salbutamol determined up to 24 h after salbutamol morning inhalation on day 7.

Safety and tolerability:

12-lead resting ECG, blood pressure and heart rate determined predose, 1 h and 2 h after roflumilast administration on day 7; safety measurements at pre and final check; continuous monitoring of adverse events.

Statistical methods:

For each of the drugs assayed geometric means and 90%-confidence limits were given for the respective Test/Reference ratios.

Roflumilast:

Equivalence of the pharmacokinetic characteristics of roflumilast was concluded if the 90%-confidence interval was entirely within the equivalence range of 0.80 to 1.25 concerning $AUC_{(0\text{-}24h)}$ and 0.70 to 1.43 concerning C_{max}.

Metabolite B9502-044:

$AUC_{(0\text{-}24h)}$ and C_{max} of the pharmacologically active metabolite B9502-044 were analysed in analogy to the corresponding characteristics of roflumilast. An extended equivalence range of 0.67 to 1.50 for the pharmacokinetic characteristics of the active metabolite B9502-044 was chosen because of the in-vivo formation of the metabolite.

Salbutamol:

$AUC_{(0\text{-}6h)}$, C_{max} and elimination half-life of salbutamol were analysed in analogy to the corresponding characteristics of roflumilast. An extended equivalence range of 0.67 to 1.50 for the pharmacokinetic characteristics of salbutamol was chosen recognizing that inhalation technique plays a major part in determining lung deposition.

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics:

The summary statistics of the pharmacokinetic characteristics for parent compound roflumilast, its active metabolite B9502-044 and salbutamol are summarized in the following table (see next page):

	Roflumilast		**Metabolite B9502-044**		**Salbutamol**	
	Reference (Rofl. + Salb.)	**Test 1** (Rofl. alone)	**Reference** (Rofl. + Salb.)	**Test 1** (Rofl. alone)	**Reference** (Rofl. + Salb.)	**Test 2** (Salb. alone)
AUC[1] [µgxh/l]	**32.82** (24.64, 43.72)	**30.85** (22.17, 42.93)	**393.88** (306.45, 506.26)	**400.62** (315.16, 509.26)	**2.407** (1.883, 3.075)	**2.188** (1.504, 3.183)
C_{max} [µg/l]	**6.976** (5.289, 9.202)	**7.232** (5.580, 9.372)	**23.836** (19.697, 28.844)	**24.408** (19.934, 29.887)	**0.619** (0.465, 0.823)	**0.578** (0.442, 0.755)
t_{max}[2] [h]	**0.75** (0.50, 1.00)	**0.75** (0.50, 1.00)	**3.00** (1.50, 4.00)	**3.00** (2.00, 4.00)	**0.75** (0.25, 4.00)	**0.63** (0.25, 3.00)
$t_{½}$ [h]	**14.25** (9.61, 21.13)	**16.65** (11.87, 23.36)	**21.07** (16.66, 26.64)	**20.54** (14.88, 28.35)	**3.32** (2.52, 4.38)	**4.03** (2.97, 5.47)

[1]: $AUC_{(0–24h)}$ for roflumilast and B9502-044; $AUC_{(0–6h)}$ for salbutamol; [2]: t_{max}: median (min, max)

Point estimates and 90%-confidence intervals for the ratios of the respective population medians for roflumilast (Test 1: roflumilast alone; Reference: roflumilast and salbutamol), its active metabolite B9502-044 (Test 1: roflumilast alone; Reference: roflumilast and salbutamol), and salbutamol (Test 2: salbutamol alone; Reference: roflumilast and salbutamol) are given in the following table:

	AUC*	C_{max}	$t_{½}$
Roflumilast	**0.94**	**1.04**	**1.16**
	(0.83, 1.05)	(0.91, 1.19)	(1.00, 1.34)
Metabolite B9502-044	**1.02**	**1.02**	**0.97**
	(0.94, 1.10)	(0.97, 1.08)	(0.82, 1.16)
Salbutamol	**0.91**	**0.93**	**1.12**
	(0.81, 1.03)	(0.79, 1.11)	(1.02, 1.45)

*: $AUC_{(0–24h)}$ for roflumilast and B9502-044; $AUC_{(0–6h)}$ for salbutamol

Safety and tolerability:
Repeated implementation of safety measurements did not reveal clinically relevant findings. The 7-day treatment with 0.5 mg per day roflumilast p.o. was safe and tolerated, regardless whether administered alone or in combination with salbutamol (2 x 100 µg per inhalation three times daily). Regarding evaluations by the clinical investigator or sponsor's assessments (CIOMS forms) no adverse event described was assessed as definitely related to the study medication.

Conclusions:

Pharmacokinetics:
Lack of interaction was demonstrated for roflumilast with respect to the primary characteristics AUC and C_{max} since the 90%-confidence intervals are entirely in the clinically stipulated equivalence range. Lack of interaction was also shown for the secondary characteristics AUC and C_{max} of B9502-044 and salbutamol. Explorative evaluation of $t_{1/2}$ of roflumilast, B9502-44, and salbutamol also showed 90%-confidence intervals for this characteristic within the equivalence range.

Safety and tolerability:
7-day treatment with 0.5 mg/d roflumilast was safe and tolerated, regardless whether administered alone or in combination with salbutamol.