Synopsis of study report: 46/99
Location in Module 5:

Study Code:
BY217/FHP017

Report Date:
24-Nov-1999

Title of the study:

Investigation of a possible pharmacokinetic interaction between roflumilast and budesonide 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):

01 September 1998 – 11 November 1998

Clinical phase:

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Objectives:

Primary:

- Investigation of a possible pharmacokinetic interaction of budesonide (Pulmicort® Turbohaler® 400 µg) on roflumilast in fasted state

Secondary:

- Investigation of a possible pharmacokinetic interaction of roflumilast on budesonide (Pulmicort® Turbohaler® 400 µg) in fasted state
- Investigation of a possible pharmacokinetic interaction of budesonide (Pulmicort® Turbohaler® 400 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 budesonide 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 54 h after roflumilast administration and up to 12 h after budesonide inhalation. 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):

12 (total: 12; for each treatment: 12)

Diagnosis and criteria for inclusion:

Healthy male subjects (median age: 26 years; median weight: 79.5 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.:

076398

Reference product:

Budesonide (Pulmicort® Turbohaler® 400 µg)

Dose:

800 µg (2 puffs of 400 µg each)

Mode of administration:

Powder inhalations by means of a dry powder inhaler;
800 µg at 8.00 a.m. and at 8.00 p.m. on days 1-6, and at 8.00 a.m. on day 7

Batch No.:

074398

Criteria for evaluation:

Pharmacokinetics:
Plasma levels of roflumilast and metabolite B9502-044 determined up to 54 h after roflumilast administration. Serum levels of budesonide determined up to 12 h after budesonide inhalation.

Safety and tolerability:
12-lead resting ECG, blood pressure and heart rate determined predose, 1 h and 2 h after 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 $AUC_{(0-24h)}$ and 0.70 to 1.43 concerning C_{max}.

Metabolite B9502-044:
$AUC_{(0-24h)}$ and C_{max} of the pharmacologically active metabolite B9502-044 were analyzed 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.

Budesonide:
$AUC_{(0-12h)}$, C_{max} and elimination half-life of budesonide were analyzed in analogy to the corresponding characteristics of roflumilast. An extended equivalence range of 0.67 to 1.50 for the

pharmacokinetic characteristics of budesonide 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 budesonide are summarized in the following table:

	Roflumilast		**Metabolite B9502-044**		**Budesonide**	
	Reference (Rofl. + Bud.)	**Test 1** (Rofl. alone)	**Reference** (Rofl. + Bud.)	**Test 1** (Rofl. alone)	**Reference** (Rofl. + Bud.)	**Test 2** (Bud. alone)
AUC[1] [µg*h/l]	**32.40** (21.42, 49.01)	**32.47** (21.97, 47.98)	**358.69** (285.40, 450.81)	**389.32** (304.98, 496.98)	**2.48** (1.51, 4.07)	**2.92** (1.82, 4.69)
C_{max} [µg/l]	**7.961** (6.475, 9.787)	**7.391** (6.297, 8.676)	**20.866** (16.731, 26.024)	**23.782** (19.709, 28.696)	**0.754** (0.418, 1.362)	**0.874** (0.537, 1.420)
C_{max}/AUC [1/h]	**0.2457** (0.1664, 0.3627)	**0.2276** (0.1539, 0.3366)	**0.0582** (0.0534, 0.0634)	**0.0611** (0.0540, 0.0691)	**0.3041** (0.2549, 0.3628)	**0.2995** (0.2545, 0.3524)
t_{max}[2] [h]	**0.50** (0.50, 1.50)	**0.50** (0.50, 1.50)	**2.75** (1.50, 4.00)	**3.50** (2.00, 4.00)	**0.50** (0.25, 1.00)	**0.25** (0.25, 0.75)
$t_{½}$ [h]	**12.49** (8.29, 18.81)	**14.71** (11.26, 19.23)	**22.56** (18.19, 27.98)	**19.89** (15.96, 24.78)	**2.83** (2.00, 4.00)	**3.26** (2.66, 4.00)

[1]: $AUC_{(0–24h)}$ for roflumilast and B9502-044; $AUC_{(0–12h)}$ for budesonide
[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 budesonide), its active metabolite B9502-044 (Test 1: roflumilast alone; Reference: roflumilast and budesonide), and budesonide (Test 2: budesonide alone; Reference: roflumilast and budesonide) are given in the following table:

	AUC	C_{max}	$t_{½}$
Roflumilast	1.00 (0.92, 1.09)	0.93 (0.84, 1.03)	1.18 (0.99, 1.41)
Metabolite B9502-044	1.09 (1.01, 1.17)	1.14 (1.07, 1.22)	0.92 (0.81, 1.04)
Budesonide	1.18 (0.96, 1.44)	1.16 (0.91, 1.48)	1.15 (0.93, 1.43)

Safety and tolerability:

Repeated implementation of safety measurements did not reveal clinically relevant findings. The subjective tolerability of roflumilast and budesonide was good. Additional risks caused by the concomitant administration did not become evident. No adverse events arose that were 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 for AUC, C_{max}, and $t_{1/2}$ of budesonide. Explorative evaluation of $t_{1/2}$ of roflumilast and B9502-044 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 well-tolerated, regardless whether administered alone or in combination with budesonide.