Synopsis of study report: <120/2002>
Location in Module 5:

Study Code:
BY217/CP-028

Report Version:
1.0

Title of the study:

Investigation of the pharmacokinetic drug-drug interaction between oral formoterol and oral roflumilast
-A randomized, open, 2-period- study-

Study center(s):

AAI Applied Analytical Industries, Deutschland GmbH & Co KG, Wegener Str. 13, Neu-Ulm, Germany

Publication (reference):

none

Studied period (years):

January 2002 – March 2002

Clinical phase:

I

Objectives:

The aim of the study was the investigation of possible pharmacokinetic drug-drug interactions of oral formoterol and roflumilast.

Further objectives were safety and tolerability of the substances when given separately or in combination. In addition also in the light of safety possible pharmacodynamic interactions were investigated.

Methodology:

This was an open, randomized, 2-period-crossover study in 24 healthy subjects.
The study consisted of a screening examination, two study periods and a post study visit. The study periods were separated by a wash-out period of 2 –4 weeks.
In one study period subjects received 40 µg oral formoterol (as formoterol fumarate) as a single dose (on Study Day 1). This period was called "Treatment Period I".
In the other study period the subjects received roflumilast 250 µg once daily for nine days (Study Days 1-9) and roflumilast 250 µg plus formoterol 40 µg (as fumarate) on the tenth study day (Study Day 10). This period was called "Treatment Period II".
The sequence of Treatment Periods was randomly assigned, i. e. subjects started with Treatment Period II and continued with Treatment Period I or vice versa.
Pharmacokinetic assessments:
Blood samplings for pharmacokinetic purposes (analysis of roflumilast and its N-oxide metabolite) were performed on Study Days 9 and 10 of Treatment Period II at pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h and 24 h.
Urine samples for pharmacokinetic purposes (analysis of formoterol) were performed on the Study Days 1-3 of Treatment Period I and on the Study Days 10-12 of Treatment Period II, and all urine of a subject of the following periods had to be sampled: predose, 0 – 2 h, 2 h – 4 h, 4 h – 8 h, 8 h – 12 h, 12 h – 24 h, 24 h – 36 h, 36 h – 48 h.
Pharmacodynamic assessments:
Blood for clinical laboratory examinations (i. e. serum potassium, blood eosinophiles), vital signs (blood pressure and pulse rate) and the 12-lead ECG had to be obtained at predose, 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h and 24 h after dosing on Study Day 1 of Treatment Period I and on Study Day 10 of Treatment Period II.
On Study Day 9 of Treatment Period II vital signs and 12-lead ECG were obtained at the times given above but no additional clinical laboratory assessments were made.
Safety assessments:
In addition to the mentioned pharmacodynamic assessments which contain aspects of safety, adverse events were recorded continuously during the study, and a screening and a post-study examination was performed including clinical safety laboratory, ECG, physical examination and assessment of vital signs.

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

24 total and for each treatment

Diagnosis and criteria for inclusion:

The following inclusion criteria were defined:

- Males or females of an age between 18 - 45 years
- Normal weight acc. to Broca index (0.8 ≤ weight [kg]/(height [cm] - 100) ≤ 1.25)
- Assessed as healthy, based on a screening examination including medical history, physical examination, blood pressure, pulse rate, ECG, and clinical laboratory results
- Caucasian
- Written informed consent

Test products:

Treatment C:

Roflumilast	dose:	250 µg (in one tablet)
	plus	
Formoterol (as fumarate)	dose:	40 µg (in one tablet, trade-mark ATOCK 40)

Dose:

Cf. test products

Mode of administration:

Oral

Batch No.:

The clinical trial medication received the batch number BY217-178. This number was printed on the labels of the study medication.
Identification of bulk products:
Formoterol 40 µg tablets where manufactured by Yamanouchi Pharma, Japan and had the bulk product batch number K001R01.
Roflumilast 250 µg tablets where manufactured by Oranienburger Pharmawerke, Germany and had the bulk product batch number 101180.

Duration of treatment:

One day

Reference products:

Treatment B: Roflumilast dose: 250 µg (in one tablet)

Treatment A: Formoterol (as fumarate) dose: 40 µg (in one tablet, trademark ATOCK 40)

Doses:

Cf. Reference products

Mode of administration:

oral

Batch No.:

Identical to test products

Criteria for evaluation:

Primary Pharmacokinetic Variables:

Primary variables were the steady state $AUC_{(0-24h)}$ of roflumilast and its N-oxide metabolite and the cumulative urinary excretion of formoterol up to 48 h after administration $A_{e(0-48h)}$.

Secondary Pharmacokinetic Variables:

Secondary pharmacokinetic variables were further pharmacokinetic characteristics of roflumilast and its N-oxide metabolite as C_{max}, elimination half life $t_{½}$, time of maximum concentration t_{max} and the renal elimination half-life $t^{e}_{½}$ of formoterol.

Secondary Pharmacodynamic Variables:

The pharmacodynamic parameters heart rate, QTc, serum potassium and peripheral blood eosinophiles were analyzed as secondary variables.

Safety and Tolerability:

Adverse events were recorded continuously throughout the study. Further safety variables were clinical safety laboratory, ECG, physical examination and vital sign measurements.

Statistical methods:

For each primary variable and separately for roflumilast, its N-oxide metabolite, and formoterol, point estimate and 90%-confidence limits were given for the ratio of the population

medians for Test and the respective Reference using a multiplicative model and a parametric analysis.

Equivalence between Test and the respective reference, i.e. lack of interaction for the respective chemical entity, was concluded if the 90%-confidence interval was entirely within the equivalence range of 0.80 to 1.25 for the pharmacokinetic parameters cumulative urinary excretion of formoterol and $AUC_{(0-24)}$ of roflumilast. For the $AUC_{(0-24)}$ of the N-oxide metabolite of roflumilast an extended equivalence range of 0.67- 1.50 was chosen because of the in vivo formation of the metabolite. The secondary pharmacokinetic variables were analyzed in analogy to the primary pharmacokinetic variables, however for t_{max} an additive statistical model was chosen.
The pharmacodynamic parameters (mean values of assessments up to 24 h after dosing) heart rate, QTc, serum potassium and blood eosinophiles were analyzed by providing point estimate and 90%-confidence limits for the ratio of the population medians for Test and the respective Reference using a multiplicative model and a parametric analysis.
The safety variables were analyzed in a merely descriptive manner including summary statistics such as median, 68%-range, mean, SD or SEM and geometric mean and geometric 68%-range, where appropriate.

SUMMARY - CONCLUSIONS

Summary Pharmacokinetics:

In the table below point estimates and 90%-confidence limits for the Test (steady state roflumilast plus single dose formoterol) /Reference (steady state roflumilast alone) ratios of roflumilast and roflumilast N-oxide $AUC_{(0-24h)}$, $t_{1/2}$, C_{max} and t_{max} values are provided.

Pharmacokinetic Characteristic	Roflumilast Point estimate	Roflumilast 90% confidence limit	Roflumilast N-oxide Point estimate	Roflumilast N-oxide 90% confidence limit
$AUC_{(0-24h)}$	0.96	0.93 – 0.99	0.94***)	0.92 – 0.97***)
C_{max}	0.97	0.91 – 1.03	0.96	0.92 – 1.00
$t_{1/2}$	0.90*)	0.76 – 1.08*)	0.92**)	0.73 – 1.16**)
t_{max}	0.00	-0.25 – 0.00	0.00	-0.25 – 0.50

* = n = 18 (terminal rate constant could not be estimated by log-linear regression in 6 subjects)

** = n = 8 (terminal rate constant could not be estimated by log-linear regression in 16 subjects)

*** = n = 22 (extrapolated part of the AUC did exceed 30% of the total AUC, consequently AUC value was not included in analysis in 2 subjects)

No significant influence on the primary pharmacokinetic parameter $AUC_{(0-24h)}$ by concomitant formoterol treatment were found for roflumilast and its metabolite roflumilast N-oxide. Point estimates of the Test/Reference ratios of 0.96 for roflumilast and 0.94 for roflumilast N-oxide, as well as their 90% confidence intervals were entirely in the respective equivalence ranges. Equivalence for roflumilast N-oxide was still found if the more strictly equivalence range of 0.80 to 1.25 was applied instead of the extended equivalence range of 0.67 to 1.50. As already found for the primary variables, no significant influence on the secondary parameters C_{max}, $t_{1/2}$ and t_{max} were found for roflumilast and roflumilast N-oxide.
Point estimates and 90%-confidence limits for the Test/Reference ratios of formoterol $A_{e(0-48h)}$ and $t^e_{1/2}$ values following one single oral administration of formoterol and one single oral administration of formoterol under roflumilast steady state conditions are shown in the following table.

Pharmacokinetic Characteristic	**Formoterol Point estimate**	**Formoterol 90% confidence limit**
$A_{e(0-48h)}$	0.94	0.87 – 1.01
$t^e_{1/2}$	1.00*)	0.85 – 1.17*)

*) The number of subjects was N=18 (terminal rate constant could not be estimated by log-linear regression in 6 subjects)

The point estimates for the Test/Reference ratio of the geom. mean $A_{e(0-48h)}$ found for formoterol as well as the respective 90% confidence limits were within the equivalence range of 0.80 – 1.25. For the Test/Reference ratio of the urinary elimination half-life, a point estimate of 1.00 was found, the 90% confidence interval was entirely included in the equivalence range. For the urinary elimination half-life of formoterol also no significant influence was observed under concomitant roflumilast administration.

Therefore, as the major result of this study, no drug – drug interaction was found for all three compounds subjected to this study, namely roflumilast, its major metabolite roflumilast N-oxide and formoterol.

Summary Pharmacodynamics:
The table below summarizes the comparative statistics for the PD-variables heart rate, QTc (Bazett), serum potassium and blood eosinophiles: Point estimates (90% -confidence intervals) for the ratios of the treatment comparisons roflumilast/formoterol vs. formoterol alone and roflumilast /formoterol vs. roflumilast alone are provided.

Mean values up to 24 h after dosing	Roflumilast 250 µg/ Formoterol 40 µg vs. Formoterol 40 µg alone	Roflumilast 250 µg/ Formoterol 40 µg vs. Roflumilast 250 µg alone
	Point estimates (90 % -confidence intervals)	
QTc-interval (Bazett)	1.00 (0.99 – 1.00)	1.02 (1.01 – 1.02)
Heart rate	1.02 (1.00 – 1.04)	1.07 (1.05 – 1.09)
Serum potassium	1.01 (0.99 – 1.02)	n. a.
Blood eosinophiles	0.85 (0.74 – 0.96)	n. a.

Roflumilast plus formoterol did not lead to an additional increase of QTc as compared to formoterol alone, and the increase in heart rate was not significant.
However the addition of formoterol to roflumilast led to a statistically significant increase of heart rate and QTc as compared to roflumilast alone.
The addition of roflumilast to formoterol did not lead to a further decrease in serum potassium as compared to formoterol alone.

A decrease of blood eosinophiles (% of Total White Blood Cell Count, TWCC) under the combination of roflumilast plus formoterol as compared to formoterol alone was observed. This can be an indicator of the systemic anti-inflammatory potency of roflumilast.

Safety Summary:
The most frequent adverse event was headache under all treatments. Headache is a common finding in Phase I studies in healthy volunteers but is also known to occur more frequently under roflumilast treatment.
Tremor occurred only when formoterol was administered alone or in combination with roflumilast. However under roflumilast plus formoterol tremor occurred more often then under formoterol alone. Tremor is a known side-effect of beta-2 agonists.
Adverse events in the gastrointestinal tract were found under roflumilast alone (six events of nausea, one adverse event of gastrointestinal pain, three adverse events of diarrhea where diarrhea and gastrointestinal pain occurred in subjects experiencing nausea).
Under formoterol alone one female subject (No. 22) experienced extrasystoles (repeated ventricular extrasystoles including ventricular bigemini and ventricular couplets). This adverse event was not observed under formoterol plus roflumilast.

Apart from the above described pharmacodynamic results and the ECG-finding of ventricular extrasystoles in one subject under formoterol alone the assessment of the other clinical safety laboratory variables, ECG and assessments of vital signs did not show clinically relevant changes.

Conclusions:

No drug – drug interaction was found for all three compounds subjected to this study, namely roflumilast, its major metabolite roflumilast N-oxide and formoterol.
The safety profile of both compounds should be observed when they are given in combination.