Synopsis of study report: **97/2002**
Location in Module 5:

Study Code:
By217/CP-029

Report Date:
05 August 2002

Title of the study:

Potential influence of roflumilast on pharmacodynamics and pharmacokinetics of R- and S-warfarin and vice versa in healthy male subjects – a double-blind, placebo controlled, randomized, crossover study

Study center:

FARMOVS-PAREXEL Clinical Research Organisation, Bloemfontein, 9300, South Africa

Publication (reference):

Not applicable

Studied period (years):

0.25 years

Clinical phase:

Phase I

Objectives:

Primary:	Influence of steady-state roflumilast on the pharmacodynamics of warfarin [Prothrombin Time (PT) and coagulation factor VII clotting activity].
Secondary:	Influence of steady-state roflumilast on the pharmacokinetics of R- and S-warfarin.

Influence of single-dose warfarin on the pharmacokinetics of roflumilast and roflumilast-N-oxide at steady state.
Safety and tolerability.

Methodology:

Methods and procedures that were performed during the course of the study, were: Medical history, physical examination, core body temperature, blood pressure and pulse rate, 12-lead ECG parameters (PR, QRS, QT, QTc and heart rate), adverse events (monitored continuously during the course of the study), clinical laboratory parameters (clinical chemistry, haematology and urinalysis), coagulation status, drug screen for abuse of substances and ethanol breath test. Determination of pharmacodynamics (PT, Factor VII) and pharmacokinetics (R- and S-warfarin determinations and determinations of roflumilast and roflumilast-N-oxide at steady state).

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

Twenty-four (24) healthy male subjects in order to be able to complete the study with at least 21 evaluable subjects.

Diagnosis and criteria for inclusion:

Healthy males, aged between 18 and 45 years and of normal weight according to the Broca index.

Test product:

Roflumilast

Dose:

1 tablet (500µg) daily

Mode of administration:

Oral administration

Batch No.:

101160

Duration of treatment:

12 days

Test product:

Warfarin

Dose:

Single oral dose of 25 mg warfarin sodium (5 x 5 mg tablets) on Day -14 and Day 8 in Phase 2 or 3

Mode of administration:

Oral administration

Batch No.:

1517D

Reference product:

Placebo

Dose:

1 tablet daily for 12 days

Mode of administration:

Oral administration

Batch No.:

101160

Criteria for evaluation:

Pharmacodynamics:	PT and Factor VII.
Pharmacokinetics:	R- and S-warfarin concentrations and roflumilast and roflumilast-N-oxide concentrations at steady state.
Safety and tolerability:	Safety measures and adverse events.

Statistical methods:

Statistical methods: To compare pharmacodynamics and pharmacokinetics between treatments, the logarithms of the applicable characteristics were analyzed using an analysis of variance (ANOVA) including sequence, subject (sequence), period and treatment effects. Based on these analyses, point estimates (LS-Means) and confirmatory two-sided 90% confidence intervals for the ratio "roflumilast + warfarin" / "placebo + warfarin" were calculated by re-transformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

SUMMARY - CONCLUSIONS

Summary:

Pharmacodynamic evaluation:
The point estimate and 90% confidence interval for the mean ratio "(warfarin + roflumilast) / (warfarin + placebo)", based on ln-transformed excess AUC(0-120h) data analysis was 99.3% and 92.3% to 106.9% for PT. The point estimate and 90% confidence interval for the mean ratio "(warfarin + roflumilast) / (warfarin + placebo)", based on ln-transformed AUC(0-120h) data analysis, was 102.1% and 99.7% to 104.7% for Factor VII.

Pharmacokinetic evaluation:

R-warfarin S-warfarin

PK variable	Unit	Point estimate	90% CI	Point estimate	90% CI
AUC(0-tlast)	(mg*h/l)	1.031	101.4% - 104.9%	1.033	101.5% - 105.1%
AUC(0-inf)	(mg*h/l)	1.024	99.9% - 105.0%	1.030	100.9% - 105.1%
Cmax	(ng/ml)	1.012	97.1% - 105.5%	1.001	94.9% - 105.6%

Safety and tolerability:
No serious adverse events were reported during the study. No subject withdrew due to adverse events. The combination roflumilast and warfarin was tolerated well in healthy male volunteers.

Conclusions:

Pharmacodynamic evaluation:
No pharmacodynamic interaction of roflumilast with racemic warfarin was observed in the healthy volunteers in this study.

Pharmacokinetic evaluation:
No pharmacokinetic interaction of roflumilast with racemic warfarin was observed in the healthy volunteers in this study. No significant influence on the pharmacokinetic parameters was found for roflumilast and its metabolite roflumilast N-oxide by concomitant warfarin treatment.

Safety and tolerability:
No serious adverse events or deaths occurred. No new safety signals, compared to previous studies were detected.