2 Synopsis

Title of the study:

Supplement to Clinical Study Report 318/ 2003: **Urine** and **plasma** pharmacokinetics of roflumilast and roflumilast N-oxide and their metabolites after single and repeated oral administration of 250 µg and 500 µg roflumilast in Japanese and Caucasian subjects – a double blind, randomized, dose escalating, two-period, two parallel group comparison

Study center:

Richmond Pharmacology Ltd., Atkinson Morley's Hospital, Copse Hill, Wimbledon, London SW20 0NE

Publication (reference):

None

Studied period (years):

2003

Clinical phase:

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Objectives:

Primary (from clinical study report 318/2003)

The pharmacokinetics of repeated oral administration of 250 µg and 500 µg roflumilast were compared between Japanese and Caucasian subjects (steady state pharmacokinetics).

Secondary (from clinical study report 318/2003)

The pharmacokinetics of a single oral administration of 250 µg and 500 µg roflumilast were compared between Japanese and Caucasian subjects (single dose pharmacokinetics).

The safety, tolerability and metabolic activity were compared between Japanese and Caucasian subjects.

*In CSR 318/2003 of study BY217/CP-048, contrary to the original intention, only **plasma** pharmacokinetic data of roflumilast and roflumilast N-oxide were presented.*

*In this report, **urine** pharmacokinetic data of roflumilast and roflumilast N-oxide, generated during the course of the study, but not presented in CSR 318/2003, are documented.*

In addition to the original intention, the following investigations were performed and are presented in this report:

- *Descyclopropyl roflumilast and descyclopropyl roflumilast N-oxide concentrations in plasma and urine were measured and pharmacokinetic parameters generated.*
- *ADCP and ADCP N-oxide concentrations in plasma and urine were measured and pharmacokinetic parameters generated.*

Methodology:

This study was conducted as a double blind, randomized, dose escalating, two-period, two parallel group comparison. During the first period, subjects received either 250 µg roflumilast or placebo on Day 1 and then on Days 5 to 15. During the second period, after a washout period of at least 15 days, subjects received 500 µg roflumilast or placebo on Day 1, and then Days 5 to 15. Subjects remained resident in the Unit from admission on Day -2 until the morning of Day 4, then returned every day until Day 13, and were re-admitted on Day 14 until the morning of Day 18. A post-study examination was conducted within two weeks of Day 19 of Period 2.

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

A total of 30 healthy male subjects (15 Japanese with an age range of 20-34 years and a weight range of 51-71 kg and 15 Caucasian with an age range of 19-28 years and a weight range of 63-90 kg) were included in this study.

Diagnosis and criteria for inclusion:

Male volunteers between 18 and 45 years of age, with a normal bodyweight according to the Broca Index ($0.72 \leq$ weight / (height-100) ≤ 1.08), were assessed as healthy on the basis of a pre-study screening examination including medical history, physical examination, blood pressure, pulse rate, 12-lead ECG and clinical laboratory analysis.

Test product:

Treatment A

250 µg roflumilast or interspersed placebo (tablet)

Treatment B
500 µg roflumilast or interspersed placebo (tablet)

Dose:

Treatment A (250 µg roflumilast or placebo) and Treatment B (500 µg roflumilast or placebo) were administered as a single dose on Day 1, and then repeated doses on Days 5 to 15, during Periods 1 and 2, respectively.

Mode of administration:

Roflumilast tablets were orally administered with 150 mL water. Subjects were instructed to swallow a mouthful of water before taking the tablet with the remaining water.

Batch No.:

250 µg roflumilast
Batch Number: 120190; Retest Date: 31 January 2006

500 µg roflumilast
Batch Number: 320190; Retest Date: 31 January 2006

Duration of treatment:

Each study period (Days 1 to 15) consisted of 5 nights and 4 full days' residence, then ten daily outpatient visits followed by another 5 nights and 4 full days' residence. The entire study was approximately 12 weeks from pre-study screening to the post-study examination.

Reference product:

Placebo

Dose:

Not applicable

Mode of administration:

Placebo tablets were orally administered with 150 mL water. Subjects were instructed to swallow a mouthful of water before taking the tablet with the remaining water.

Batch No.:

Placebo
Batch Number: 130290; Retest Date: 31 January 2006.

Criteria for evaluation:

Primary Variables (from clinical study report 318/2003)

AUC_{tau} ($AUC_{(0-24h)}$) of roflumilast and roflumilast N-oxide and C_{max} of roflumilast on Day 15, following the repeated oral administration of 250 µg and 500 µg roflumilast. Blood samples for pharmacokinetic purposes were collected at pre-dose, and 0.5hr, 1hr, 1.5hr, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr, 14hr, 24hr, 30hr, 48hr, 60hr, 72hr and 96hr after morning administration of study medication on Day 15.

Secondary Variables (from clinical study report 318/2003)

C_{max} of roflumilast N-oxide and C_{min}, HL ($t_{1/2}$), t_{max}, $CL_{ss}FB$, $V_{ss}FB$, urinary excretion ratio, renal elimination half-life, CL_r of roflumilast and roflumilast N-oxide on Day 15, after the repeated oral administration of 250 µg and 500 µg roflumilast. Blood sample for pharmacokinetic purposes were collected as for primary variables.

Trough values of roflumilast and roflumilast N-oxide were collected on Days 6 to 14, to demonstrate the achievement of steady state.

AUC_{inf} ($AUC_{(0-inf)}$) and AUC_{tau} ($AUC_{(0-24h)}$), C_{max}, HL ($t_{1/2}$), t_{max}, CLFB and V_dFB of roflumilast and roflumilast N-oxide on Day 1, after the single oral administration of 250 µg and 500 µg roflumilast. Blood samples for pharmacokinetic purposes were collected at pre-dose, and 0.5hr, 1hr, 1.5hr, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr, 14hr, 24hr, 30hr, 48hr, 60hr, 72hr and 96hr after morning administration of study medication on Day 1.

Urine samples for pharmacokinetic purposes were collected during the intervals 0-4hr, 4-8hr, 8-12hr and 12-24hr after the administration of study medication on Day 15, to evaluate the cumulative excretion rate as well as the renal elimination half-life of roflumilast and roflumilast N-oxide.

Results of physical examination, blood pressure and heart rate, 12-lead ECG variables (PR, QRS, QT, QTc and heart rate), laboratory measurements (clinical chemistry, hematology, coagulation, urinalysis), and adverse events.

Cortisol and 6ß-hydroxycortisol in 24-hour urine, as well as cortisol in serum at the corresponding time point of ‘pre-dose’ and ‘24h’ (according to the PK sample schedule) on Day –1, and at pre-dose and 24hr after the administration of study medication on Day 15, to determine the CYP 450 3A4 activity.

Plasma *data of descyclopropyl roflumilast and descyclopropyl roflumilast N-oxide as well as ADCP and ADCP N-oxide were only analyzed when the dose of 500 µg of roflumilast was applied.* ***Urine*** *data for roflumilast and roflumilast N-oxide, descyclopropyl roflumilast and*

descyclopropyl roflumilast N-oxide as well as ADCP and ADCP N-oxide were analyzed for both doses, i.e. 250 and 500 µg of roflumilast.

Statistical methods:

Primary Variables (from clinical study report 318/2003)

AUC_{tau} ($AUC_{(0-24h)}$) of roflumilast and roflumilast N-oxide and C_{max} of roflumilast (steady state pharmacokinetics). Analyses via ANOVA, point estimates and 90%-confidence intervals.

Secondary Variables (from clinical study report 318/2003)

Steady state pharmacokinetics, after repeated oral administration of 250 µg and 500 µg roflumilast: C_{max} of roflumilast N-oxide, and C_{min}, HL ($t_{1/2}$), t_{max}, $CL_{ss}FB$, $V_{ss}FB$, urinary excretion ratio, renal elimination half life, CL_r of roflumilast and roflumilast N-oxide and trough values of roflumilast and roflumilast N-oxide. Analyses via ANOVA, point estimates and 90%-confidence intervals.

Single dose pharmacokinetics, after single oral administration of 250 µg and 500 µg roflumilast: AUC_{inf} ($AUC_{(0-inf)}$) and AUC_{tau} ($AUC_{(0-24h)}$), C_{max}, HL ($t_{1/2}$), t_{max}, CLFB and V_dFB of roflumilast and roflumilast N-oxide. Analyses via ANOVA, point estimates and 90%-confidence intervals.

Secondary (other) variables of safety, tolerability, and metabolic activity. Analyses via descriptive statistics.

*For **Plasma** data of descyclopropyl roflumilast and descyclopropyl roflumilast N-oxide as well as ADCP and ADCP N-oxide, and for **urine** data of roflumilast and roflumilast N-oxide, descyclopropyl roflumilast and descyclopropyl roflumilast N-oxide as well as ADCP and ADCP N-oxide, no statistical analysis of the pharmacokinetic parameter estimates were performed due to insufficient data. The sole purpose of this report is to present the results of the examinations in a descriptive manner.*

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetics

Data analyzed suggest that the difference and similarities reported (CSR 318/2003 of study BY217/CP-048) for roflumilast and roflumilast plasma pharmacokinetic parameter estimates were also observed in the analysis of metabolites and clearly follow the pharmacokinetics of the two active components. Any difference and similarity between the populations in terms of different rates of metabolism deducted from these data would carry a large uncertainty. Overall, as indicated in the discussion, a clear conclusion cannot be made due to limited

information. However, similar trends observed in the roflumilast and roflumilast plasma pharmacokinetics, can also be observed in urine.

Safety (from clinical study report 318/2003)

Throughout the study (Day 1 of Period 1 to the post study examination), a total of 25 subjects (12 Japanese and 13 Caucasian) reported a total of 93 adverse events. No noteworthy differences were found between the number of Japanese and the Caucasian subjects with adverse events (80% vs. 86.7%). The overall number of adverse events was similar between the two groups [49 events (or 52.7%) in the Japanese group vs. 44 events (or 47.3%) in the Caucasian group]. However, the percentage of adverse events, assessed by the investigator as 'likely' related to the study medication was notably lower in the Japanese group [13 events (or 26.5%) vs. 23 events (or 52.3%) in the Caucasian group]. No adverse events during the course of this study were considered to have a 'definite' relationship with treatment administration. No serious adverse events or deaths occurred during the course of this study. Overall, no clinical relevant differences between the Japanese and the Caucasian group were seen with respect to incidence and nature of adverse events.

A number of transient, out-of-range results were reported with respect to hematology, clinical chemistry and urinalysis variables, as well as vital signs and ECG parameters. However, no clinically relevant differences were seen between the Japanese and the Caucasian group. Within each group, no dose-dependent trends were evident.

Conclusions:

Pharmacokinetics

Due to limitations of the additional evaluation of human roflumilast metabolites in plasma and urine (short urine collection period, possible lack of assay sensitivity for ADCP and ADCP N-oxide) and the explorative nature of this evaluation, no conclusions should be drawn.

Safety (from clinical study report 318/2003)

No clinically relevant differences were seen between both ethnic groups. Single and repeated doses of 250 µg and 500 µg roflumilast were safe and well tolerated in healthy male Japanese and Caucasian subjects.

Date of report: 26-Oct-2006