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**CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A5821023**

**Protocol Title:** An Evaluation of the Effects of Roflumilast on Cardiac Repolarization, Pharmacokinetics, Safety, and Tolerability in Healthy Volunteers

**Study Center(s):** PPD Development, LP; 706 Ben White Boulevard West; Austin, TX 78704

**Publications Based on the Study:** None

**Study Initiation and Completion Dates:** 15 December 2004 to 11 April 2005

**Phase of Development:** Phase 1

**Study Objective(s):**

- To assess the effects of multiple-dose orally administered roflumilast on cardiac repolarization as measured by electrocardiogram (ECG) parameters in healthy subjects
- To assess the pharmacokinetics (PK) of roflumilast and roflumilast N-oxide following multiple daily doses of 500 and 1000 µg
- To assess the safety and tolerability of roflumilast 500, 750, and 1000 µg once daily (QD) multiple doses when gradually titrated in healthy subjects

## METHODS

**Study Design:** This was a single center, randomized, placebo- and active-controlled, parallel group study in 2 cohorts of healthy subjects. A total of 80 subjects were to be enrolled into the study, with 40 subjects randomly allocated to Group A and 40 subjects randomly allocated to Group B.

**Table S1. Study Treatment (Protocol A5821023)**

| Group | Day 1 | Days 3 to 16 | Days 17 to 23 | Days 24 to 37 |
|---|---|---|---|---|
| A | Placebo | Placebo QD | Placebo QD | Placebo QD |
| | | Roflumilast 500 µg QD | Roflumilast 750 µg QD | Roflumilast 1000 µg QD |
| B | Moxifloxacin 400 mg | Placebo QD | Placebo QD | Placebo QD |
| | | Roflumilast 500 µg QD | Roflumilast 750 µg QD | Roflumilast 1000 µg QD |

The trial was open label on Day 1 when the subjects were taking either placebo or moxifloxacin. The trial was subject- and investigator-blinded on Days 3 to 37 when the subjects were taking either placebo or roflumilast 500, 750, and 1000 µg.

**Diagnosis and Main Criteria for Inclusion:** Healthy subjects of any race and either gender; age 18 to 55 (inclusive), with a body weight of >50 kg, and a body mass index (BMI) 18 to 30 kg/$m^2$ (weight [kg]/height [meters]$^2$)

**Study Treatment:**

**Table S2. Lot and Formulation Numbers (Protocol A5821023)**

| Study Drug | Strength and Dosage Form | Lot Number | Formulation Number |
|---|---|---|---|
| Roflumilast | 250-µg tablet | Altana: 006104<br>Clinicopia: 04-011828 | Altana: 5217097 |
| Roflumilast | 500-µg tablet | Altana: 106302<br>Skokie: SP21825<br>Clinicopia: 03-00444 | Altana: 5217098 |
| Moxifloxacin | 400-mg tablet | Vendor (Bayer): 5400737<br>Clinicopia: 04-018910 | D0300248 |
| Placebo | NA | Altana: 047203<br>Skokie: SP21824<br>Clinicopia: 03-003886 | Altana: 5217099 |
| Placebo | NA | Altana: 005103<br>Skokie:SP21809<br>Clinicopia: 03-03911 | Altana: 5217099 |

NA = Not Applicable.

All subjects were confined from the evening of Day -2 to the morning of Day 2, and from the evening of Day 15 to the morning of Day 38. For convenience, subjects could remain in confinement from the evening of Day -2 through the morning of Day 42. Subjects ingested trial medication at approximately 0800 hours with 240 mL of ambient temperature water. Subjects swallowed the trial medication whole and did not chew the medication prior to swallowing. All study drug doses were administered and witnessed by clinic staff.

Roflumilast 250 µg, roflumilast 500 µg, and matching placebo tablets were packaged in blister cards containing 10 tablets each. Moxifloxacin 400-mg tablets were supplied in their commercially packaged 30-count bottles.

**Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:**

**Pharmacokinetic Evaluations:** Serial PK blood samples were collected on Days 16 and 37. PK parameter values for roflumilast and roflumilast N-oxide on Days 16 and 37 were calculated by noncompartmental analysis of plasma concentration-time data. Parameters estimated include area under the curve (AUC), maximum concentration (Cmax), time to maximum concentration (tmax), and terminal elimination half-life (t½).

**Pharmacodynamic Evaluations:** Standard 12-lead ECGs were evaluated using machine-generated assessments (GE Medical MUSE, Mac 1200) on Days -1, 1, 16, and 37 at the following time points, prior to drawing PK samples: Predose (prior to breakfast), 1, 2, 4 (prior to

lunch), 6, 8, 12, and 24 hours postdose. Since no drug was given on Day -1, the ECG measurement schedule for Day -1 matched the schedule that was used on Days 16 and 37.

**Safety Evaluations:** All subjects were evaluated for safety. Safety evaluations included physical examinations, vital signs (heart rate, blood pressure), 12-lead ECGs, adverse events and safety laboratory tests.

**Statistical Methods:**

**Pharmacokinetic Evaluations:** PK parameter values were summarized by descriptive statistics by study day (500 µg or 1000 µg QD) for all subjects, and for each treatment group (placebo or moxifloxacin on Day 1).

**Pharmacodynamic Evaluations:** The primary endpoint was time-matched change from baseline in QTcF (Fridericia's correction of the QT interval), calculated for each subject by subtracting the QTcF at each nominal time on the baseline day (Day -1) from the QTcF at the same nominal time on Days 1, 16, and 37. The primary comparison for clinical interpretation was the largest difference between roflumilast and placebo at any nominal time postdose. The primary comparison between moxifloxacin and placebo for clinical interpretation was at the moxifloxacin anticipated tmax, about 2 hours postdose on Day 1.

The comparisons were made using a repeated measures analysis of variance (ANOVA) consisting of treatment, subject within treatment, time, time by treatment effects, and baseline (Day -1) as covariate. The covariance structure was specified as compound symmetry. Least squares (LS) means and 90% confidence intervals (CIs) for the time-matched changes from baseline were reported for each treatment at each time. Least squares means and 90% CIs were reported for the differences from placebo, also 90% CIs for the difference between moxifloxacin and placebo were reported, as specified in the analysis plan.

The primary treatment-placebo comparisons were: Roflumilast 500 µg QD with placebo on Day 16, and roflumilast 1000 µg QD with placebo on Day 37.

## RESULTS

**Subject Disposition and Demography:** Eighty healthy volunteers (54 males and 26 females) entered the study. Sixty-five subjects completed the study. Seven subjects withdrew consent, 4 subjects were withdrawn due to adverse events, 2 subjects were lost to follow up, 1 subject was withdrawn due to lack of compliance, and 1 subject was withdrawn for other reasons.

**Pharmacokinetic, Pharmacodynamic, and/or Other Results:**

**Pharmacokinetic Results:** PK parameter values for roflumilast and roflumilast N-oxide are summarized in Table S3. Values on Day 16 following 500-µg QD dosing in this study are consistent with those observed previously in healthy volunteers. Increases in Cmax, Cmin, and AUC on Day 37 following 1000-µg QD dosing are proportional with the 2-fold increase in dose. Mean values by treatment group (placebo or moxifloxacin on Day 1) are similar to the overall means presented here.

**Table S3. Summary of Pharmacokinetic Parameter Values Following Administration of Roflumilast Oral QD Doses to Healthy Volunteers, Study A5821023**

| | Parameter | Arithmetic Mean (%CV) Parameter Values | |
|---|---|---|---|
| | | Day 16 (500 µg) N = 38 | Day 37 (1000 µg) N = 30 |
| Roflumilast | Cmax, ng/mL | 5.14 (26.2) | 10.6 (33.7) |
| | tmax, hr | 2.69 (40.0) | 2.97 (52.8) |
| | Cmin, ng/mL | 0.86 (63.3) | 1.55 (59.3) |
| | AUC(0-24), ng*hr/mL | 45.6 (34.3) | 90.2 (32.3) |
| | CL/F, mL/min | 203 (32.9) | 205 (34.9) |
| | t½, hr | ND | 21.7 (36.6) |
| Roflumilast N-Oxide | Cmax, ng/mL | 27.4 (32.8) | 53.8 (36.5) |
| | tmax, hr | 5.98 (32.9) | 8.69 (72.9) |
| | Cmin, ng/mL | 17.3 (42.5) | 33.4 (45.4) |
| | AUC(0-24), ng*hr/mL | 530 (33.2) | 1060 (37.8) |
| | t½, hr | ND | 26.0 (26.7) |

ND = Not determined.

**Pharmacodynamic Results:**

**Statistical Analyses of QTc Intervals:**

The largest mean time-matched change from baseline difference from placebo in the moxifloxacin 400 mg group on Day 1 in QTcF was 6.79 msec and 6.97 msec in QTcP (population correction of the QT interval). These differences were statistically significant from zero. Thus, the study was judged to have adequate sensitivity to detect QTc prolongation.

The estimated population heart rate correction factor was 0.4413. The statistical analyses were performed with both QTcF and QTcP.

The primary comparison for clinical interpretation between active drug and placebo was the largest difference from placebo in time-matched change from baseline in QTcF and QTcP at any nominal time postdose. The largest mean differences from placebo for Days 16 and 37 are displayed in Table S4 below.

**Table S4. QTcF and QTcP: Largest Time-Matched Mean Differences from Placebo (Protocol A5821023)**

| Treatment Group | Hour | Difference^ | 90% CI |
|---|---|---|---|
| | **QTcF** | | |
| Day 1<br>Moxifloxacin Day 1 | 6 | 6.79 | (4.15, 9.43)* |
| Day 16<br>Roflumilast 500 µg QD | 4 | -3.23 | (-6.77, 0.31) |
| Day 37<br>Roflumilast 1000 µg QD | 2 | -4.81 | (-8.61, -1.00)* |
| | **QTcP** | | |
| Day 1 | | | |
| Moxifloxacin Day 1 | 6 | 6.97 | (4.47, 9.46)* |
| Day 16 | | | |
| Roflumilast 500 µg QD | 1 | 2.39 | (-0.82, 5.60) |
| Day 37 | | | |
| Roflumilast 1000 µg QD | 1 | 0.77 | (-2.58, 4.12) |

* Statistically significant
^ Difference = Active treatment – placebo.

**Pharmacokinetic/Pharmacodynamic Results:**
The estimated correction factor for heart rate was 0.4413 which indicated that neither Fridericia nor Bazett correction would properly correct QT for heart rate. Thus, population corrected QT (QTcP) was used for the PK/PD analysis.

Both QTcB and QTcF showed significant dependency on RR ($p < 0.05$).

When the QTcP and plasma concentration data (both roflumilast and roflumilast N-oxide, simultaneously) were modeled to determine the relationship between time-matched change from baseline in dQTcP and exposure using a linear mixed effect model, the slope parameters were not statistically significantly different from zero. The population mean estimates (95% CI) for the slope parameters for roflumilast and roflumilast N-oxide were -0.0282 (-0.0756, 0.0192) ms/(ng/mL) and -0.145 (-0.498, 0.208) ms/(ng/mL), respectively. The modeling result suggested that dQTcP is best described as a linear combination of roflumilast and the N-oxide such as -0.0282*roflumilast conc – 0.145*N-oxide conc, but dQTcP was not statistically different from zero in the observed roflumilast and roflumilast N-oxide concentration ranges.

**Safety Results:** There were no deaths or other serious adverse events during the study. There were 4 subject withdrawals due to adverse events. Each of the subjects was withdrawn after receiving moxifloxacin and/or placebo. Twenty-eight of 40 subjects receiving multiple dose roflumilast 500 µg, 26 of 38 subjects receiving multiple dose roflumilast 750 µg, and 28 of 37 subjects receiving multiple dose roflumilast 1000 µg reported adverse events. Thirty-three of 59 subjects receiving placebo and 9 of 40 subjects receiving moxifloxacin reported adverse events. All adverse events were mild or moderate. One subject had a serum creatinine value on Study Day 49 (Closeout) of 2.7 mg/dL. The serum creatinine on the last day (Day 37) of multiple-dose roflumilast was within normal limits (1.1 mg/dL) and values were within normal limits throughout the entire dosing period. Unscheduled follow-up serum creatinine values were 1.4 mg/dL on Day 58 and 1.5 mg/dL on Day 62. On Day 77, the subject returned for a repeat

serum creatinine assessment, and the value had returned to within normal limits (1.1 mg/dL). The Principal Investigator (PI) considered the serum creatinine value of 2.7 mg/dL on Day 49 to be a laboratory error, based both upon the subject's pattern of creatinine values, ranging from 1.1 to 1.3, throughout the study and information gathered while interviewing the subject. The test was not repeated immediately due to the subject's unavailability. In the opinion of the PI, creatinine is not considered to be a test that changes rapidly so it is very unlikely that a shift from 1.1 to 2.7 over 12 days or a shift from 2.7 to 1.4 over 9 days is real. Furthermore, the repeat values of 1.4 and 1.5 values were considered possibly part of the subject's normal fluctuation, especially considering his lean body type and his serum creatinine values during the study.

All other clinical laboratory abnormalities were sporadic, transient, and appeared to be unrelated to study drug administration. There were no clinically important physical examination findings, and there were no clinically important changes in vital signs measurements.

**Conclusion(s):**

These results indicate that when roflumilast is administered at doses up to 1000 µg, there is no effect on the QTc interval. No apparent differences were observed between treatment groups with regard to subject characteristics or subject withdrawal rates. Multiple oral daily doses of roflumilast, at 500, 750, and 1000 µg were overall safe and well-tolerated.