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CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A5821013

Protocol Title: A Study of the Effect of Fluvoxamine on the Pharmacokinetics of Roflumilast and Roflumilast-N-Oxide

Study Center(s): One study center – United States

Publications Based on the Study: None

Study Initiation and Completion Dates: 12 May 2004 to 03 Aug 2004

Phase of Development: Phase 1

Study Objective(s):

1. To evaluate the effect of fluvoxamine on the pharmacokinetics (PKs) of roflumilast
2. To evaluate the effect of fluvoxamine on the PKs of roflumilast-N-oxide
3. To investigate the safety and tolerability of roflumilast and coadministration of roflumilast and fluvoxamine

Study Design: This was an open-label, nonrandomized, 1-sequence, 2-period, 2-treatment study in 16 healthy volunteers.

Table S1. Study Treatments (Protocol A5821013)

Study Day 1	Study Days 8-14	Study Day 15	Study Days 16-21
Roflumilast 500 µg PO	Fluvoxamine 50 mg PO QD	Roflumilast 500 µg PO Fluvoxamine 50 mg PO	Fluvoxamine 50 mg PO QD

Number of Subjects: A total of 16 subjects were enrolled into the study to help ensure the collection of a complete data set for at least 12 subjects.

Diagnosis and Main Criteria for Inclusion: Healthy subjects of any race and either gender; age 18 to 65 (inclusive), with a body weight of 50 kg or greater, and a body mass index (BMI) $\leq$35 kg/m^2 (weight [kg]/height [meters]^2); with females required to be of nonchildbearing potential (prior hysterectomy, postmenopausal [ie, 2 years since last menstrual period], or tubal ligation).

Study Treatment:

Table S2. Lot and Formulation Numbers (Protocol A5821013)

Study Drug	Strength and Dosage Form	Lot Number	Formulation Number
Roflumilast	500 µg tablet	Altana - 091102 Skokie - SP21036 Clinicopia - 04-008598	Altana - 5217098 Skokie - R101189 Clinicopia - PS0300560
Fluvoxamine	50 mg tablet	W030199 Clinicopia - 04-010053	D0400780

Sixteen subjects received a single dose of roflumilast 500 µg on Days 1 and 15. Fluvoxamine 50 mg daily was taken from Study Days 8 to 21. On Study Day 15, roflumilast and fluvoxamine were taken at the same time. Each roflumilast dose was administered with 8 oz of room-temperature water. For Study Days 1 and 15, subjects began fasting 8 hours prior to the roflumilast dose and continued fasting for 4 hours after dosing.

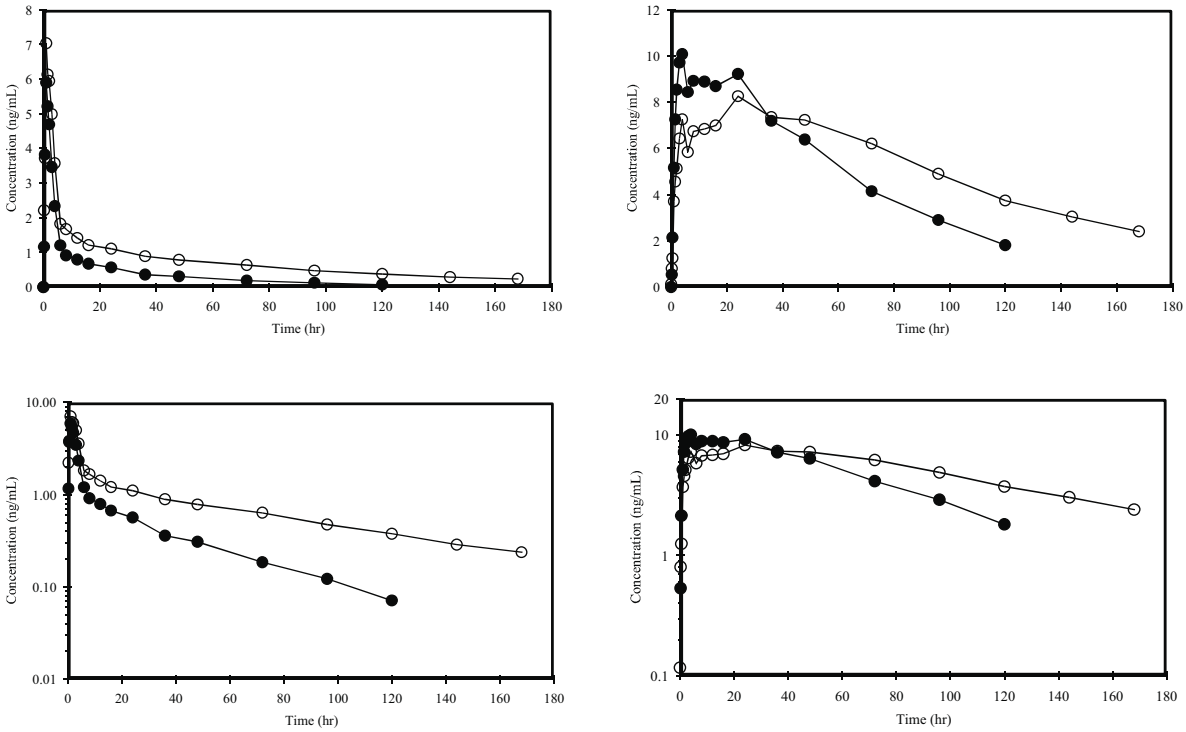
Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

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

Statistical Methods: PK parameters including log-transformed maximum observed plasma concentration (Cmax), area uner the plasma concentration-time profile (AUC), and oral clearance (CL/F) values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (roflumilast with fluvoxamine) as a percentage of reference (roflumilast alone) were generated.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: PK results for roflumilast and roflumilast-N-oxide are summarized in the following figure and tables.

Figure S1. Mean Roflumilast (Left Panels) and Roflumilast-N-Oxide (Right Panels) Plasma ConcentrationTime Profiles Following Single Oral 500-µg Roflumilast Doses Alone (Filled Symbols) and With Steady-State Fluvoxamine (Open Symbols) (Study A5821013)



Upper and lower panels are linear and semilogarithmic plots, respectively.

Table S3. Summary of Roflumilast Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Fluvoxamine (Protocol A5821013)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Fluvoxamine (Test, N = 14)	Roflumilast Alone (Reference, N = 16)		
Cmax, ng/mL	7.94	7.12	112	100 to 124.53
$AUC_{(0\text{-}tlqc)}$, ng·hr/mL	119	50.8	234	207 to 265
$AUC_{(0\text{-}\infty)}$, ng·hr/mL	141	55.2	256	218 to 301
CL/F, L/hr	3.53	9.06	39.0	33.2 to 45.9
Tmax, hr	1.16	1.28	Not Applicable	
t½, hr	64.8	33.1	Not Applicable	

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Table S4. Summary of Roflumilast-N-Oxide Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Fluvoxamine (Protocol A5821013)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Fluvoxamine (Test, N = 14)	Roflumilast Alone (Reference, N = 16)		
Cmax, ng/mL	8.42	10.5	80.3	73.6 to 87.7
$AUC_{(0\text{-}tlqc)}$, ng·hr/mL	868	635	137	126 to 148
$AUC_{(0\text{-}\infty)}$, ng·hr/mL	1190	780	152	132 to 175
Tmax, hr	29.5	10.4	Not Applicable	
t½, hr	78.5	44.0	Not Applicable	

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

In the presence of steady-state fluvoxamine, roflumilast time to maximum observed plasma concentration (Tmax) and Cmax values were similar to those observed when roflumilast was administered alone. Mean Tmax was less than 10 minutes earlier and mean Cmax was 12% higher with steady-state fluvoxamine. In contrast, mean roflumilast AUC values with steady-state fluvoxamine were more than double those observed when roflumilast was administered alone, and mean CL/F decreased by approximately 60%. Mean roflumilast terminal half-life (t½) with steady-state fluvoxamine was nearly twice as long as that for roflumilast administered alone.

In the presence of steady-state fluvoxamine, mean Tmax for roflumilast-N-oxide was almost 3 times later and Cmax was 20% lower than when roflumilast was administered alone. Mean roflumilast-N-oxide $AUC_{(0\text{-}tlqc)}$ and $AUC_{(0\text{-}\infty)}$ values with steady-state fluvoxamine increased by 37% and 52%, respectively, relative to those observed when roflumilast was administered alone. Mean roflumilast-N-oxide t½ increased by about 80% with steady-state fluvoxamine.

Nine of the 14 subjects had quantifiable concentrations of roflumilast-N-oxide at predose on Day 15, and the predose concentration for 1 subject exceeded 5% of Cmax. Corrected Cmax and AUC values (both $AUC_{[0\text{-}tlqc]}$ and $AUC_{[0\text{-}\infty]}$) were determined for roflumilast-N-oxide on Day 15.

Corrected Cmax and AUC values are summarized in Table S5; results are comparable to those for the uncorrected values.

Table S5. Summary of Roflumilast-N-Oxide AUC and Cmax Values Corrected for Observed Day 11 Predose Concentrations, Protocol A5821013

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Fluvoxamine (Test, N = 14)	Roflumilast Alone (Reference, N = 16)		
Corrected Cmax	8.30	10.5	79.1	72.2 to 86.8
Corrected $AUC_{(0\text{-}tlqc)}$	848	635	134	122 to 146
Corrected $AUC_{(0\text{-}\infty)}$	1170	780	150	130 to 173

Safety Results: There were no deaths, other serious adverse events, or withdrawals due to adverse events during the study. Five of 16 subjects receiving single dose roflumilast 500 µg, 2 of 14 subjects receiving single dose roflumilast 500 µg + fluvoxamine 50 mg once daily (QD), and 3 of 16 subjects receiving fluvoxamine 50 mg QD reported adverse events. One of 14 subjects receiving single dose roflumilast 500 µg + fluvoxamine 50 mg QD and 2 of 16 subjects receiving fluvoxamine 50 mg QD reported adverse events that were considered treatment associated. All adverse events were mild or moderate.

One subject had leukocytosis (mild elevation in white blood count [WBC]) considered definitely not related to study drug administration, and creatinine increased (mild elevation in serum creatinine) considered of unknown relationship to study drug administration on Day 29 (Closeout). These findings, as well as sinusitis also considered definitely not related to study drug administration, were recorded as adverse events. The subject's WBC count elevated from 9.50 thousand/mcL (Screening) to 12.40 thousand/mcL (Day 29) before returning to 10.40 thousand/mcL (normal limits 3.8-10.8 thousand/mcL) by Day 35. Serum creatinine elevated from 1.30 mg/dL (Screening) to 1.5 mg/dL on Day 29, then rose to 1.70 mg/dL on Day 55, before returning to 1.40 mg/dL (normal limits 0.5-1.4 mg/dL) by Day 64. On Day 63, the subject was confined to the clinical research unit where he received aggressive oral (PO) hydration, and underwent additional safety assessments. Urine studies (including urinalysis, urine microalbumin, urine eosinophils, 24 hour urine protein, and kidney ultrasound), and glomerular filtration rate were normal. Urine electrolytes were consistent with being hydrated. This subject's study data were evaluated by a nephrologist, and the rise in serum creatinine was determined to be due to dehydration. All other clinical laboratory abnormalities were sporadic, transient, and appeared to be unrelated to study drug administration. There were no clinically important changes in physical examination, ECG, or vital sign measurements.

Conclusion(s): Based on AUC values, steady-state fluvoxamine administration increases roflumilast exposure more than 2-fold, and increases roflumilast-N-oxide exposure by approximately 50%. Steady-state fluvoxamine administration had little effect on roflumilast Cmax, but roflumilast-N-oxide Cmax decreased by about 20% and occurred about 3 times later.

Single oral 500-µg roflumilast doses were safe and well-tolerated, with and without coadministration with fluvoxamine.