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CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A5821014

Protocol Title: A Study of the Effect of Erythromycin on the Pharmacokinetics of Roflumilast and Roflumilast-N-Oxide (Protocol A5821014)

Study Center(s): Comprehensive Phase One; 108 Northeast First Street; Fort Lauderdale, FL 33301

Publications Based on the Study: None

Study Initiation and Completion Dates: 27 Jul 2004 to 30 Aug 2004

Phase of Development: Phase 1

Study Objective(s):

- To evaluate the effect of erythromycin on the pharmacokinetics of roflumilast;
- To evaluate the effect of erythromycin on the pharmacokinetics of roflumilast-N-oxide; and
- To investigate the safety and tolerability of coadministration of roflumilast and erythromycin.

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

Table S1. Study Treatment (Protocol A5821014)

Study Day 1	Study Days 9-14	Study Day 15	Study Days 16-21
Roflumilast 500 µg PO	Erythromycin 500 mg TID w/meals	Roflumilast 500 µg PO Erythromycin 500 mg TID w/meals	Erythromycin 500 mg TID w/meals

Number of Subjects: Sixteen healthy volunteers (8 males and 8 females) entered the study. Fifteen subjects completed the study. One subject was withdrawn due to an adverse event following 1 dose of 500 µg roflumilast.

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, and a body mass index (BMI) 18 to 35 kg/m^2 (weight [kg]/height [meters]^2.

Study Treatment:

Table S2. Lot and Formulation Numbers (Protocol A5821014)

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
Erythromycin	500 mg tablet	12297AF21 Clinicopia - 04-010054	D0400779

On Day 1, 16 subjects received a single dose of roflumilast 500 µg between 0700 and 0900 hours on an empty stomach. Erythromycin 500 mg was taken 3 times a day (TID) with meals from Study Days 9 to 21. On Study Day 15, roflumilast and the morning dose of erythromycin were taken at the same time on an empty stomach. Each roflumilast dose was administered with 8 oz of room-temperature water. For Study Days 1 and 15, subjects began fasting approximately 8 hours prior to the roflumilast dose and continued fasting for at least 4 hours after dosing.

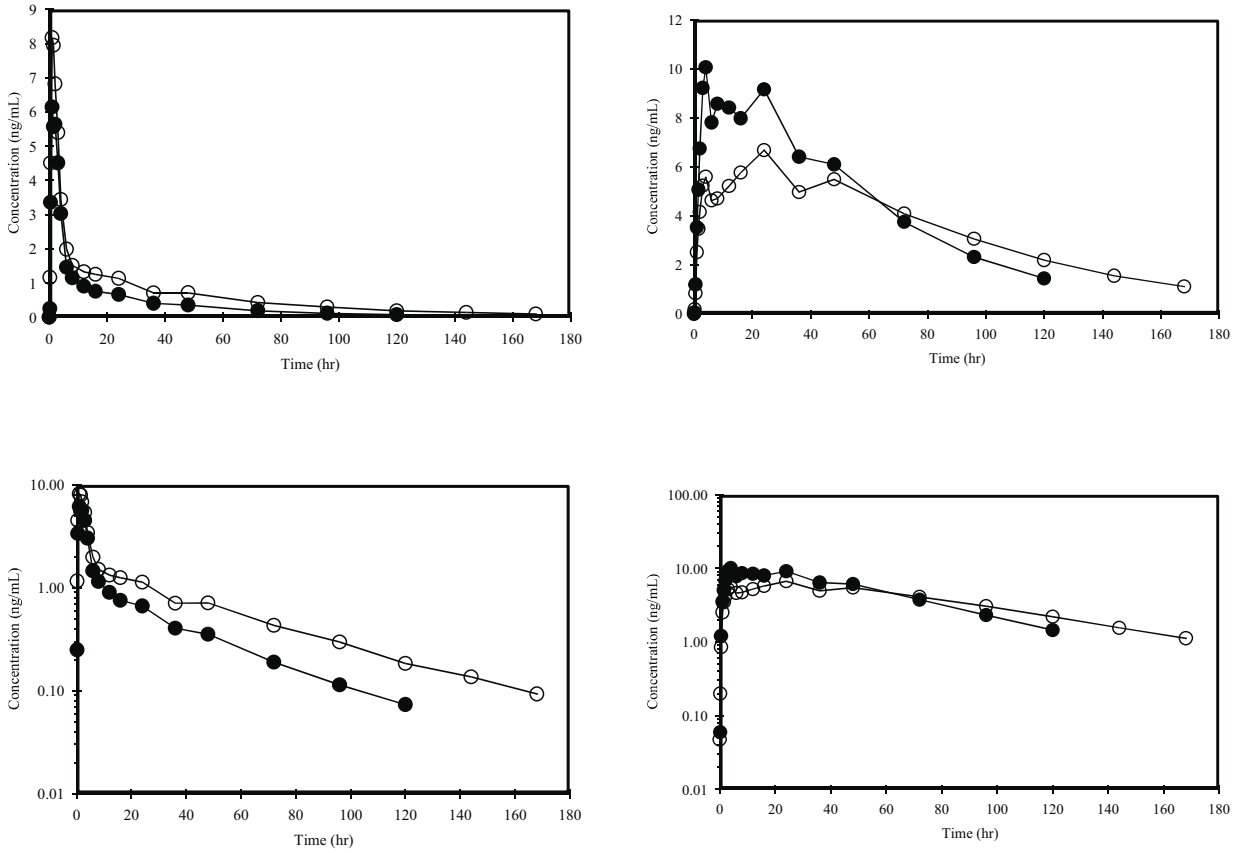
Pharmacokinetic Evaluations: Pharmacokinetic blood samples were collected serially for 120 hours following the Day 1 roflumilast dose, and for 168 hours following the Day 15 roflumilast dose. Plasma concentrations of roflumilast and roflumilast-N-oxide were measured using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method. Pharmacokinetic parameter values for plasma roflumilast and roflumilast-N-oxide were calculated by noncompartmental analysis using WinNonlin Version 4.0.1.

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: Pharmacokinetic parameters including log-transformed maximum observed plasma concentration (Cmax,) area under 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 erythromycin) as a percentage of reference (roflumilast alone) were generated. Lack of an effect of erythromycin on roflumilast would be concluded if the 90% confidence intervals for both Cmax and AUC, based on log-transformed data, were entirely contained within the interval of 80% to 125%.

Pharmacokinetic Results: Pharmacokinetic 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 Concentration-Time Profiles Following Single Oral 500-µg Roflumilast Doses Alone (Filled Symbols) and With Steady-State Erythromycin (Open Symbols) (Study A5821014)



Left panel – roflumilast Right panel – roflumilast-N-oxide
Upper and lower panel are linear and semi-logarithmic plots, respectively.

Table S3. Summary of Roflumilast Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Erythromycin 500 mg TID (Protocol A5821014)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Erythromycin (Test)	Roflumilast Alone (Reference)		
N	15	16		
Cmax, ng/mL	9.79	6.97	140	125 to 158
$AUC_{(0\text{-}tlqc)}$, ng·hr/mL	97.6	57.2	171	152 to 191
$AUC_{(0\text{-}\infty)}$, ng·hr/mL	104	61.0	170	150 to 192
CL/F (L/hr)	4.83	8.20	58.9	52.1 to 66.5
tmax	1.62	1.59	Not Applicable	
t½	38.0	28.0	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.

Table S4. Summary of Roflumilast-N-Oxide Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Erythromycin 500 mg TID (Protocol A5821014)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Erythromycin (Test)	Roflumilast Alone (Reference)		
N	15	16		
Cmax, ng/mL	6.90	10.4	66.4	61.02 to 72.30
$AUC_{(0\text{-}tlqc)}$, ng·hr/mL	589	574	103	94.33 to 111.77
$AUC_{(0\text{-}\infty)}$, ng·hr/mL	669	646	104	91.63 to 117.04
tmax	24.5	8.69	Not Applicable	
t½	48.0	32.4	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 erythromycin, mean roflumilast AUC values were approximately 70% higher than those observed when roflumilast was administered alone and mean CL/F decreased by 41%. Mean roflumilast time to maximum observed plasma concentration (tmax) did not change, but Cmax increased by 40% with erythromycin co-administration. Mean roflumilast terminal half-life (t½) was about 10 hours (36%) longer with erythromycin.

In the presence of steady-state erythromycin, mean roflumilast-N-oxide AUC values were similar to those observed when roflumilast was administered alone. The 90% confidence intervals for the treatment ratios of $AUC_{(0\text{-}\infty)}$ and $AUC_{(0\text{-}tlqc)}$ values, based on log-transformed

data, were both within the 80% to 125% range. However, with erythromycin co-administration mean roflumilast-N-oxide Cmax was about 34% lower, and mean tmax nearly tripled, occurring almost 16 hours later. Mean roflumilast-N-oxide t½ increased by about 48% with erythromycin.

Quantifiable predose plasma concentrations of roflumilast-N-oxide were observed in 5 of the 15 subjects on Day 15, when roflumilast was administered with erythromycin. However, the highest observed predose concentration (0.221 ng/mL for Subject 10021030) was less than 5% of the lowest Cmax value observed for any subject (4.80 ng/mL for Subject 10021044) for this treatment. Therefore no correction for carryover concentrations was necessary.

Safety Results: There were no deaths, or other serious adverse events during the study. One subject was withdrawn on Study Day 6 due to the adverse event nausea experienced on Study Day 1 and considered definitely related to study drug administration. The nausea was resolved on Study Day 2. Additional adverse events for this subject were vomiting on Study Day 1 considered probably related and headache on Study Day 1 considered possibly related to study drug administration. These additional adverse events resolved on Study Day 1.

Eight of 16 subjects receiving single dose roflumilast 500 µg, 3 of 15 subjects receiving single dose roflumilast 500 µg + erythromycin 500 mg TID, and 5 of 15 subjects receiving erythromycin 500 mg TID reported adverse events. Seven subjects receiving single dose roflumilast 500 µg, 3 subjects receiving roflumilast 500 µg + erythromycin 500 mg TID, and 2 subjects receiving erythromycin 500 mg TID reported adverse events that were considered treatment associated. All adverse events were mild or moderate.

One subject had elevated alanine aminotransferase (ALT) values beginning on Day 14 (46, 44, and 44 IU/L on Days 14, 15, and 17, respectively) that decreased to a value of 37 IU/L (normal limits 0-40 IU/L) on Day 20. One subject had elevated ALT values beginning on Day 14 (75, 69, 63, 52, 48, and 61 IU/L on Days 14, 15, 17, 20, 22, and 36, respectively) that decreased to a value of 43 IU/L on Day 44. These ALT elevations were not considered clinically relevant. All other clinical laboratory abnormalities were sporadic, transient, and appeared to be unrelated to study drug administration. There were no clinically relevant changes in physical examination, ECG, or vitals sign measurements.

Conclusion(s):

Based on AUC values, steady-state erythromycin administration (500 mg TID) increases roflumilast exposure approximately 70% but has no effect on roflumilast-N-oxide exposure. Cmax values of roflumilast increased with steady-state erythromycin administration (40%) while Cmax values of roflumilast-N-oxide decreased about 34%.

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