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Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A5821012

Protocol Title: A Study of the Effect of Ketoconazole 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: 05 May 2004 to 21 Jun 2004

Phase of Development: Phase 1

Study Objective(s):

- To evaluate the effect of ketoconazole on the pharmacokinetics of roflumilast;
- To evaluate the effect of ketoconazole on the pharmacokinetics of roflumilast-N-oxide; and
- To investigate the safety and tolerability of roflumilast and co-administration of roflumilast and ketoconazole.

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

Table S1. Study Treatments (Protocol A5821012)

Study Day 1	Study Days 8-10	Study Day 11	Study Days 12-20
Roflumilast 500 µg PO	Ketoconazole 200 mg PO BID	Roflumilast 500 µg PO + Ketoconazole 200 mg PO BID	Ketoconazole 200 mg PO BID

Number of Subjects: A total of 16 subjects were enrolled into the study to help insure the collection of a complete data set for at least 12 subjects. One subject was withdrawn due to an adverse event.

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) ≤35 kg/m2 (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 A5821012)

Study Drug	Strength and Dosage Form	Lot Number	Formulation Number
Roflumilast	500 µg tablet	Altana — 091102	Altana — 5217098
		Skokie — SP21036	Skokie — R101189
		Clinicopia — 04-008598	Clinicopia — PS0300560
Ketoconazole	200 mg tablet	1L1820	D0400566
		Clinicopia — 04-011205	

Sixteen subjects received a single dose of roflumilast 500 µg on Days 1 and 11. Ketoconazole 400 mg daily (200 mg twice daily [BID]) was taken from Study Days 8 to 20. On Study Day 11, roflumilast and the morning dose of ketoconazole were taken at the same time. Each roflumilast dose was administered with 8 oz of room-temperature water. For Study Days 1 and 11, subjects began fasting 8 hours prior to the roflumilast dose and continued fasting for 4 hours after dosing.

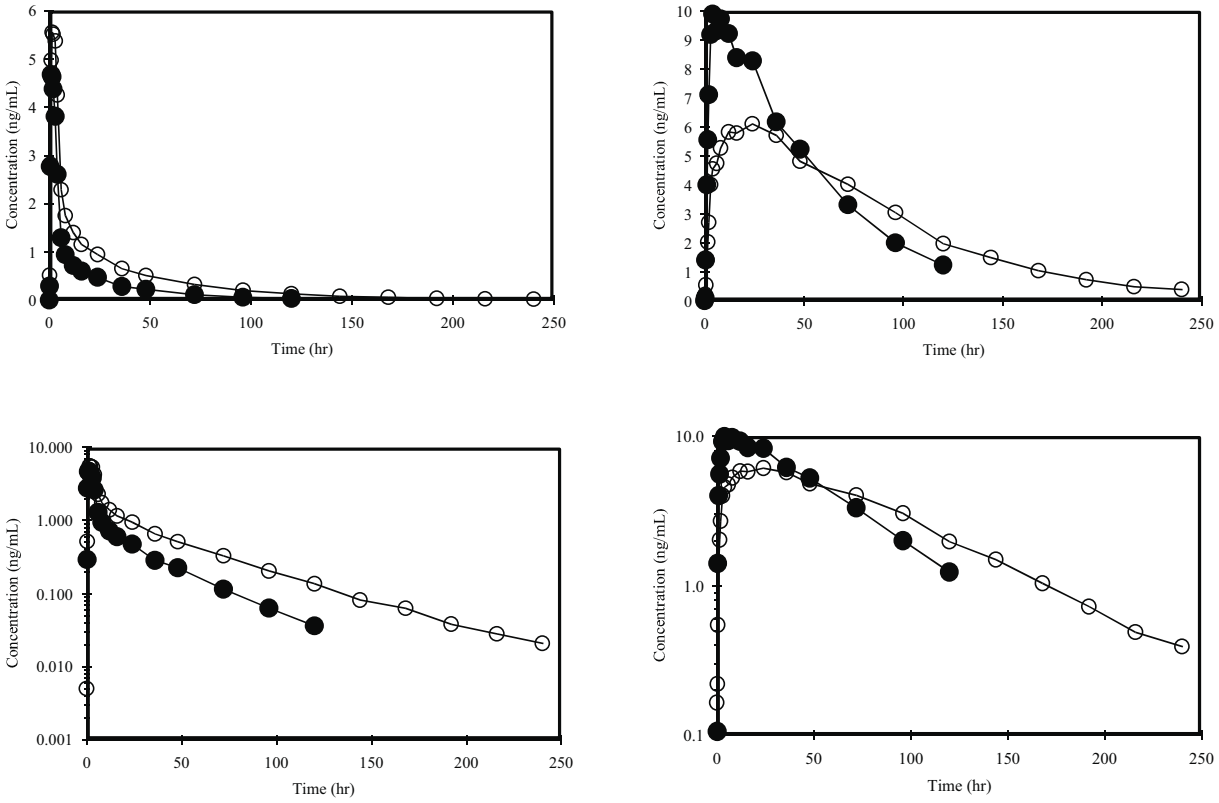
Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Pharmacokinetic blood samples were collected serially for 120 hours following the roflumilast dose on Day 1, and for 240 hours following the roflumilast dose on Day 11. Plasma concentrations of roflumilast and roflumilast N-oxide were measured using a validated liquid chromatography/ mass spectrometry/ mass spectrometry (LC/MS/MS) method. Pharmacokinetic parameters were determined from plasma concentration-time data using standard noncompartmental methods.

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) and area under the plasma concentration-time profile (AUC) values were analyzed with an analysis of variance (ANOVA) model. Model-based 90% confidence intervals for test (roflumilast with ketoconazole) as a percentage of reference (roflumilast alone) were generated.

Pharmacokinetic, Pharmacodynamic, and/or Other 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 Ketoconazole (Open Symbols) (Study A5821012)



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 Ketoconazole (Study A5821012)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Ketoconazole (Test)	Roflumilast Alone (Reference)		
Cmax, ng/mL	6.94	5.63	123	106 to 143
AUC(0-tlqc), ng·hr/mL	83.7	41.6	201	175 to 232
AUC(0-∞), ng·hr/mL	88.2	44.3	199	171 to 231
CL/F (L/hr)	5.67	11.3	50.2	43.3 to 58.4
tmax	2.16	1.69	Not Applicable	
t½	39.7	23.7	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 Ketoconazole (Study A5821012)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Ketoconazole (Test)	Roflumilast Alone (Reference)		
Cmax, ng/mL	6.69	10.7	62.3	56.8 to 68.3
AUC(0-tlqc), ng·hr/mL	586	540	109	97.8 to 121
AUC(0-∞), ng·hr/mL	611	595	103	91.5 to 115
tmax	21.5	9.56	Not Applicable	
t½	43.5	31.5	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 ketoconazole, mean roflumilast AUC values were approximately double those observed when roflumilast was administered alone and mean CL/F decreased by 50%. Mean roflumilast Cmax increased by 23% and mean t½ increased by about 68% with ketoconazole co-administration. One subject had a quantifiable roflumilast concentration at predose on Day 11 but the value was less than 2% of the Day 11 Cmax for this subject and was not considered to be of concern.

In the presence of steady-state ketoconazole, mean roflumilast N-oxide AUC values were similar to those observed when roflumilast was administered alone. However, mean roflumilast N-oxide Cmax was about 37% lower than that observed without ketoconazole and mean tmax was more

than double that observed without ketoconazole. Mean roflumilast N-oxide t½ increased by about 38% with ketoconazole.

Eleven of the 16 subjects had quantifiable concentrations of roflumilast N-oxide at predose on Day 11, and the predose concentrations exceeded 5% of Cmax for 2 subjects. Corrected Cmax and AUC values (both AUC(0-tlqc) and AUC(0-∞)) were determined for roflumilast N-oxide on Day 11.

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 A5821012

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Ketoconazole, Corrected (Test)	Roflumilast Alone (Reference)		
Cmax	6.57	10.7	61.2	55.7 to 67.3
AUC(0-tlqc)	575	540	106	95.5 to 119
AUC(0-∞)	600	595	101	89.4 to 114

Safety Results: There were no deaths or serious adverse events during the study. One subject was withdrawn due to the adverse event abnormal liver function tests on Study Day 14. This adverse event was considered related to study drug administration. On Study Day 14, ALT was 190 (reference range 2-60 U/L), exceeding the protocol-specified withdrawal criterion of ALT >2 times the upper limit of normal (ULN) and the subject was withdrawn from the study. ALT then ranged between 196 and 273 between Days 16 to 21 before starting a decline to a normal value of 51 on Day 35. This subject's AST levels was also elevated beginning on Study Day 14 and increased to about 1.5 to 2 times the ULN before returning to within normal limits by Study Day 28. In addition, one subject had a decreased hematocrit level on Day 28. Anemia was recorded as an adverse event, which was considered unrelated to study drug administration but was considered related to blood collection. 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 vitals sign measurements.

Two of 16 subjects receiving single dose roflumilast 500 µg, 7 of 16 subjects receiving single dose roflumilast 500 µg + ketoconazole 200 mg BID, and 7 of 16 subjects receiving ketoconazole 200 mg BID reported adverse events. Four of 16 subjects receiving single dose roflumilast 500 µg + ketoconazole 200 mg BID and 6 of 16 subjects receiving ketoconazole 200 mg BID reported adverse events that were considered treatment associated. One adverse event was severe, all others were mild or moderate.

Conclusion(s): Based on AUC values, steady-state ketoconazole administration (200 mg BID) increases roflumilast exposure approximately 2-fold but has no effect on roflumilast N-oxide

exposure. Cmax values of roflumilast increased with steady state ketoconazole administration (23%) while Cmax values of roflumilast-N-oxide decreased about 38%.

Single oral 500-µg roflumilast doses were safe and well-tolerated. Elevated liver enzymes occurred in 1 subject, and were attributed to ketoconazole administration.

Addendum for Public Disclosure

Please note the age range is incorrect in this synopsis. The correct age range of this study was from 18 to 55 years.

Date of Addendum: 27 August 2014