The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

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 A5821015

Protocol Title: A Study of the Effect of Maalox Administration on the Single-Dose Pharmacokinetics of Roflumilast and Roflumilast-N-Oxide (Protocol A5821015)

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: 09 September 2004 to 03 November 2004

Phase of Development: Phase 1

- **Study Objective(s):** To evaluate the effect of Maalox administration on the pharmacokinetics of roflumilast;
- To evaluate the effect of Maalox administration on the pharmacokinetics of roflumilast-N-oxide; and
- To investigate the safety and tolerability of coadministration of roflumilast and Maalox.

Study Design: This was an open-label, randomized, 6-sequence, 3-period, 3-treatment, 3-way crossover study in 30 healthy volunteers. Subjects received treatment according to the following schedule (Table S1).

Table S1. Study Treatment (Protocol A5821015)

Group (Sequence)	**Day 1**	**Day 15**	**Day 29**
A	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg Maalox 30 mL
B	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL after 2 hours
C	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg
D	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg
E	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL
F	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg Maalox 30 mL after 2 hours

Number of Subjects: Thirty healthy volunteers (14 males and 16 females) entered the study. Twenty-seven subjects completed the study. There were two subject withdrawals due to adverse events, and one subject who withdrew consent.

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 35 kg/m^2 (weight [kg]/height [meters]^2)

Study Treatment:

Table S2. Lot and Formulation Numbers (Protocol A5821015)

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: PS0401623
Maalox	Max Fast Relief (355 mL)	Commercial: 325007 Clinicopia: 04-015140	Clinicopia: A040051

NA = Not Applicable.

The subjects began fasting at least 8 hours prior to each dose. Each roflumilast dose was taken at approximately 08:00 with 240 mL of ambient temperature water. Subjects swallowed the trial medication whole, and did not chew the medication prior to swallowing. For the period where Maalox and roflumilast were taken together, Maalox was taken first and was immediately followed by the roflumilast dose. For the period where Maalox was taken 2 hours post the roflumilast dose, Maalox was not taken with additional water. All subjects were required to refrain from lying down, eating and drinking beverages, including water, during the first 4 hours of dosing.

Roflumilast was supplied as 500-µg tablets for oral administration presented in blister packs. Maalox Extra Strength was supplied as a cherry-flavored liquid in bulk bottles for oral administration. Study drugs were dispensed by qualified site personnel.

Pharmacokinetic Evaluations: Pharmacokinetic blood samples were collected serially for 120 hours following the Day 1, 15, and 29 roflumilast doses. Plasma concentrations of roflumilast and roflumilast N-oxide were measured using a validated liquid chromatography/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:

Table S3. Pharmacokinetic Parameters Determined in Study A5821015

Parameter	Definition
Cmax	Maximum plasma concentration
tmax	Time for Cmax
AUC(0-tlqc)	Area under plasma concentration-time profile from time zero to time of last quantifiable concentration (lqc)
λz	Terminal rate constant
t½	Terminal half-life
AUC(0-∞)	Area under plasma concentration-time profile extrapolated to infinite time
AUCextrap	Percent of AUC(0-∞) due to extrapolation
CL/F	Oral clearance

Pharmacokinetic parameters including log-transformed Cmax, AUC, and 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 the test treatments (roflumilast with Maalox, and roflumilast with Maalox after 2 hours) as a percentage of reference (roflumilast alone) were generated. Lack of an effect of Maalox on roflumilast would be concluded if the 90% confidence intervals for both Cmax and AUC(0-∞), 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 Circles), With Maalox (Open Circles), and With Maalox After 2 Hours (Open Squares) (Protocol A5821015)

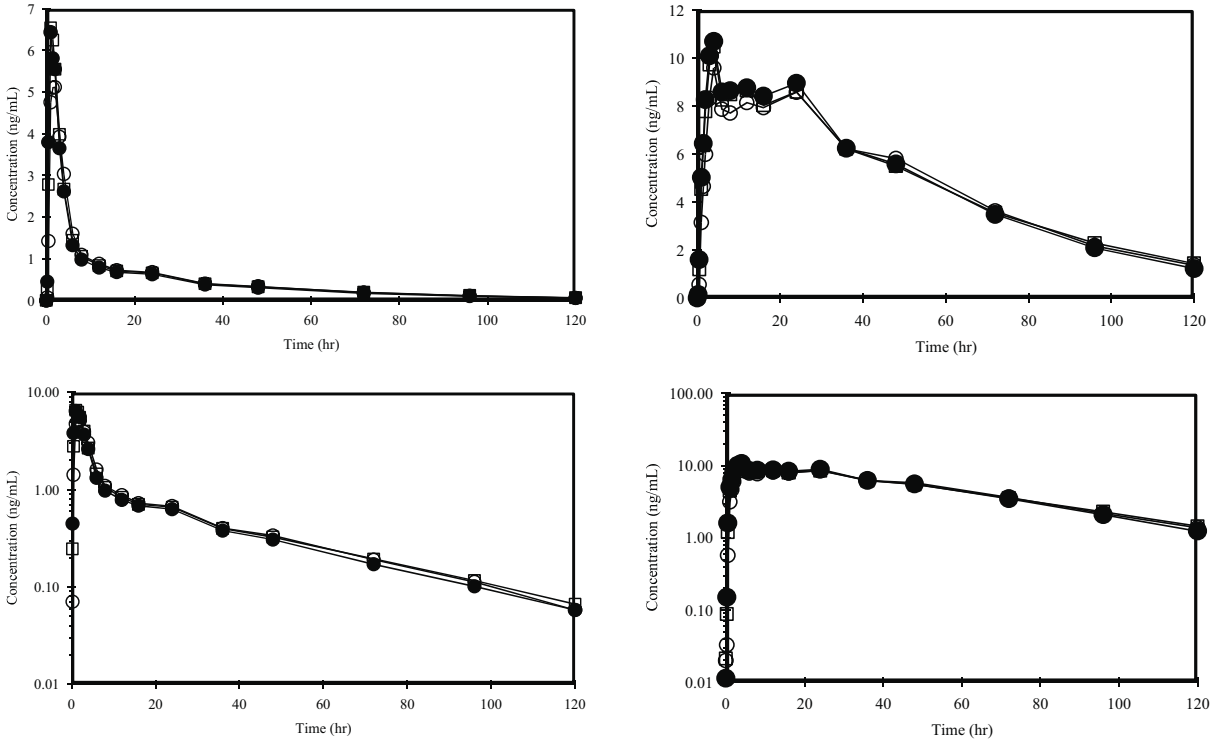

Table S4. Summary of Roflumilast Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference), With Maalox, and With Maalox After 2 Hours (Protocol A5821015)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Maalox (Test)	Roflumilast Alone (Reference)		
N	30	28		
Cmax, ng/mL	6.55	7.37	88.8	80.4 to 98.1
AUC(0-tlqc), ng*hr/mL	54.5[a]	52.4	104	100 to 108
AUC(0-∞), ng*hr/mL	58.0[a]	55.6	104	100 to 109
CL/F (L/hr)	8.62[a]	8.98	95.9	92.2 to 99.9
tmax	1.84	1.56	Not Applicable	
t½	28.5[a]	28.4	Not Applicable	
	Roflumilast With Maalox After 2 hr (Test)	Roflumilast Alone (Reference)		
N	29	28		
Cmax, ng/mL	7.21	7.37	97.8	88.5 to 108
AUC(0-tlqc), ng*hr/mL	54.6	52.4	104	100 to 108
AUC(0-∞), ng*hr/mL	58.2	55.6	105	100 to 109
CL/F (L/hr)	8.59	8.98	95.6	91.9 to 99.5
tmax	1.62	1.56	Not Applicable	
t½	30.3	28.4	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.
a N = 29.

Table S5. Summary of Roflumilast N-Oxide Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference), With Maalox, and With Maalox After 2 Hours (Protocol A5821015)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Maalox (Test)	Roflumilast Alone (Reference)		
N	30	28		
Cmax, ng/mL	9.70	10.6	91.6	86.9 to 96.6
AUC(0-tlqc), ng*hr/mL	550[a]	558	98.5	95.2 to 102
AUC(0-∞), ng*hr/mL	616[a]	617	99.8	96.1 to 104
tmax	9.03	5.92	Not Applicable	
t½	33.2[a]	31.7	Not Applicable	
	Roflumilast With Maalox After 2 hr (Test)	Roflumilast Alone (Reference)		
N	29	28		
Cmax, ng/mL	10.7	10.6	101	95.4 to 106
AUC(0-tlqc), ng*hr/mL	556	558	99.6	96.3 to 103
AUC(0-∞), ng*hr/mL	629	617	102	98.1 to 106
tmax	6.83	5.92	Not Applicable	
t½	35.3	31.7	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.
a N = 29.

Roflumilast: Based on AUC(0-∞) values, extent of roflumilast absorption with Maalox administered either concurrently or 2 hours after roflumilast was similar to that for roflumilast alone. Based on Cmax and tmax values, rate of roflumilast absorption with Maalox administered either concurrently or 2 hours after roflumilast was similar to that for roflumilast administered alone. The 90% confidence intervals for treatment ratios of mean AUC(0-∞) and Cmax values, based on log-transformed data, were all within the 80% to 125% range. Mean tmax values for the 3 treatments were between 1.5 and 2.0 hours. Mean roflumilast t½ was similar across all treatments, averaging about 29 hours.

N-Oxide: Results for roflumilast N-oxide were similar to those for the parent compound. Based on AUC(0-∞) values, total exposure for roflumilast N-oxide with Maalox administered either concurrently or 2 hr after roflumilast was similar to that for roflumilast administered alone. The 90% confidence intervals for treatment ratios of mean AUC(0-∞) and Cmax values, based on log-transformed data, were all within the 80% to 125% range. Mean roflumilast N-oxide tmax was about 3 hr (53%) later when roflumilast was administered with Maalox, and about 1 hour (15%) later when Maalox was administered after 2 hours, compared to that for roflumilast alone. Mean roflumilast N-oxide t½ was similar across all treatments, averaging about 33 hours.

Safety Results: There were no deaths, or other serious adverse events during the study. There were 2 subject withdrawals due to adverse events. On Study Day 22, 1 subject began experiencing multiple episodes of chest pain which was considered resolved by the investigator on Study Day 30. The subject was withdrawn on Study Day 29. The subject received roflumilast 500 µg + Maalox 30 mL on Study Day 1, and roflumilast 500 µg + Maalox 30 mL after 2 hours on Study Day 15. This adverse event was moderate in intensity and considered unlikely related to study drug administration. The subject also experienced headache beginning on Study Day 15 and continuing to Study Day 17 which was considered mild and possibly related to study drug administration. On Study Day 22, another subject developed a urinary tract infection which was considered resolved by the investigator on Study Day 36. The subject was withdrawn on Study Day 36 after receiving all scheduled doses of study drug. This adverse event was moderate in intensity and considered unlikely related to study drug administration. Other adverse events reported by this subject include: Headache beginning on Study Day 4 and resolving on Study Day 5, considered moderate and unlikely related to study drug administration; dizziness on beginning on Study Day 24 and resolving on Day 28, considered mild and unlikely related to study drug administration; and dizziness beginning and resolving on Study Day 29 considered mild and possibly related to study drug administration.

Nine of 28 subjects receiving single dose roflumilast 500 µg, 9 of 30 subjects receiving single dose roflumilast 500 µg + Maalox 30 mL, and 9 of 29 subjects receiving single dose roflumilast 500 µg + Maalox 30 mL after 2 hours reported adverse events. Eight subjects receiving single dose roflumilast 500 µg, 9 subjects receiving roflumilast 500 µg + Maalox 30 mL, and 7 subjects receiving single dose roflumilast 500 µg + Maalox 30 mL after 2 hours reported adverse events that were considered treatment associated. All adverse events were mild or moderate. All 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.

Conclusion(s): Administration of 30 mL Maalox either concurrently with, or 2 hr after, a single 500-µg roflumilast oral tablet dose has no clinically important effect on the pharmacokinetics of roflumilast or roflumilast N-oxide. The pharmacokinetic results for the parent drug and metabolite meet the usual bioequivalence criterion.

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