1. Title page

Title of study:	A Clinical Pharmacological (Phase I) Study of APTA-2217 in Healthy Adult Male Volunteers (Single oral dose)
Study drug name	APTA-2217 (Roflumilast)
Study Design/ Reference product / Objectives/Dosage and Administration/ Study population:	Design: A placebo controlled, double blind, 4-period ascending dose, alternative panel
	Reference product: placebo
	Objective: To evaluate the pharmacokinetics (PK) and safety of APTA-2217 after administration of single oral dose of 125, 250, 500 or 1000 mcg to healthy adult male Japanese volunteers under fasting conditions.
	Dosage and administration: single dose of APTA-2217 125, 250, 500, 1000 mcg or placebo were administered orally under fasting conditions.
	Study population; Japanese healthy male adult subjects
Study Sponsor	Tanabe Seiyaku Co., LTD.
Study protocol No.:	APTA-2217-HP-01
Study Development Phase	Phase I
Study Initiation date:	April 25th, 2003 (Date when the informed consent of the first subject was obtained)
Premature termination	Not applicable.
Study Completion date:	June 29th, 2003 (Date of the post-study examination of the last subject)
[redacted]	[redacted]
Statements of GCP compliance	This study was conducted in compliance with the study protocol, the Pharmaceutical Affairs Law Articles 14-3 and 80-2, “Guidelines for Good Clinical Practice (GCP)” (MHW Ordinance No. 28 dated March 27, 1997). All documentations pertaining to this study is appropriately retained in Osaka Pharmacology Research Clinic and Tanabe Seiyaku Co., LTD.
Date of the report:	June, 27, 2005

2. Synopsis

Outline-1-

Sponsor: Tanabe Seiyaku Co., LTD. Product name: undecided Drug Substance: APTA-2217 (Roflumilast)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*

Study Title:	A Clinical Pharmacological (Phase I) Study of APTA-2217 in healthy male volunteers. Single oral dose.
Study site:	Osaka Pharmacology Research Clinic 12-11, Kasuga 4-chome, Suita city, Osaka 565-0853, JAPAN Tel. 06-6330-8721, Fax. 06-6330-8725
Publication:	None
Study period:	About 2months. (From date of consent of first subject to date of last subject completing the post-study examination) April 25, 2003 until June 29, 2003
Phase of development:	Phase I
Objective:	To evaluate the pharmacokinetics (PK) and safety of APTA-2217 after single oral dose administration of 125, 250, 500 or 1000 mcg to healthy adult male Japanese volunteers under fasting conditions.
Methodology:	1) Screening examination: After obtaining written informed consent from subjects, screening examinations were performed to determine the subjects' eligibility according to the inclusion/exclusion criteria. 2) Treatment period: The subjects that were admitted to enter the study as a result of the screening examinations, were assigned to Groups A and B. Each group consisted of 12 subjects and 2 substitutes. Active drug was allocated to 9 subjects and placebo was allocated to 3 subjects in each period, and specified observations and tests were performed. The minimum-dosing interval of the study drug between Period 1 and Period 2, Period 2 and Period 3, and Period 3 and Period 4 was 7 days. 3) Post-study examination: Post-study examination was conducted on Day 15 (±2) after the last administration.

	Period 1	Period 2	Period 3	Period 4
Group A (n=12) (+2 substitutes)	125 mcg: n=9 placebo: n=3		500 mcg: n=9 placebo: n=3	
Group B (n=12) (+2 substitutes)		250 mcg: n=9 placebo: n=3		1000 mcg: n=9 placebo: n=3
During each study period subjects were hospitalized from 2 days before administration of roflumilast up to Day 5 for 7 days (7 days and 6 nights).				

Outline -2-

Sponsor: Tanabe Seiyaku Co., LTD. Product name: undecided Drug Substance: APTA-2217 (Roflumilast)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*

Summary (continued):

Number of subjects (planned and analyzed):

Number of subjects planned: 12 in Group A, 12 in Group B (24 total)

Number of subjects administered: 12 in Group A, 12 in Group B (24 total)

Number of subjects analyzed for pharmacokinetics: 12 in Group A, 12 in Group B (24 total)

Number of subjects analyzed for safety: 12 in Group A, 12 in Group B (24 total)

Inclusion and exclusion criteria

<Inclusion criteria>

Subjects who fulfilled all of the following criteria and were capable to give their signatures of consent to participate in this study.

(1) Healthy adult male subjects who were between 20 and 45 years old at the time of informed consent and provided a written informed consent.

(2) Subjects who were determined appropriate to participate in the study by the investigator (subinvestigator) based on the result of the screening examination.

<Exclusion criteria>

Subjects who met any of the following criteria were excluded from participation in this study.

(1) History of allergy to any drug or food.

(2) Body weight exceeding ± 20% of the standard weight ([height (cm) − 100] × 0.9) or less than 50 kg at screening examination.

(3) Subjects who participated in another study within 6 months prior to the informed consent.

(4) History of more than 400 mL blood donated or drawn within 12 weeks or 200mL blood donated or drawn within 4 weeks prior to the informed consent.

(5) History of more than 800 mL blood donated or drawn within 1 year prior to the informed consent.

(6) Subjects who had any surgery known to alter the gastrointestinal absorption of drugs (excluding appendectomy or hernioplasty/herniotomy).

(7) Any signs of cardiac disease at screening examination (e.g. QTc >430msec, PR >220msec) or history of cardiac disease.

(8) A positive result of HBs antigen, serological syphilitic reaction, HCV antibody, or HIV antibody at screening examination.

(9) Subjects who are taking any medication.

(10) Subjects who were judged by the investigator (subinvestigator) to be ineligible to enter the study based on medical reasons.

Outline-3-

Sponsor: Tanabe Seiyaku Co., LTD. Product name: undecided Drug Substance: APTA-2217 (Roflumilast)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*

Study medication, reference product, dosage, method of administration and lot number:

<Study medication, reference product, and lot number>
APTA-2217, Tablet 125, 250, 500 mcg and indistinguishable placebo

	Batch number	Dosage
Study medication		
APTA-2217 Tablet 125 mcg	30005	125 mcg of APTA-2217 contained in each tablet
APTA-2217 Tablet 250 mcg	30006	250 mcg of APTA-2217 contained in each tablet
APTA-2217 Tablet 500 mcg	30007	500 mcg of APTA-2217 contained in each tablet
Reference product		
APTA-2217 Tablet 125 mcg placebo	30008	
APTA-2217 Tablet 250 mcg placebo	30009	
APTA-2217 Tablet 500 mcg placebo	30010	

< Dosage, method of administration >
Single doses of 125, 250, 500, 1000 (500 mcg tablet x 2) mcg of APTA-2217 or placebo were administered orally under fasting conditions.

Administration period: Group A: Single administration during Periods 1 and 3
Group B: Single administration during Periods 2 and 4

Criteria for evaluation:
Pharmacokinetic variables
(1) Plasma concentration [roflumilast and the major metabolite (roflumilast N-oxide)]
(2) Urine excretion [roflumilast and the major metabolite (roflumilast N-oxide)]
(3) Pharmacokinetic parameters [roflumilast and the major metabolite (roflumilast N-oxide)]
C_{max}, AUC, T_{max} and $t_{1/2}$ of roflumilast and the major metabolite (roflumilast N-oxide), and CLt, Vd/F, Rate of urine excretion and CLr as reference data, were calculated.
(4) Metabolic activity index [cortisol levels in plasma and urine, 6β-hydroxycortisol in urine]
Safety variables
(1) Adverse events
(2) Adverse events suspected to be causally related to the investigational drug.

Outline-4-

Sponsor: Tanabe Seiyaku Co., LTD.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*
Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)		

Statistical method:

(1) Pharmacokinetics

Plasma and urinary concentration of roflumilast and its active metabolite (roflumilast N-oxide) were measured after administration of each dose. The summary statistics of pharmacokinetic parameters ($AUC_{(0\text{-inf})}$, t_{max}, C_{max}, $t_{1/2}$, CLt, Vd/F) was calculated and dose-proportionality of C_{max} and $AUC_{(0\text{-inf.})}$ was evaluated.

(2) Safety

The incidence of all adverse events and adverse events suspected to be causally related to the investigational drug was calculated for each dose.

Discussion/Conclusions

Pharmacokinetic results:

(1) Plasma and urinary concentrations of roflumilast and the metabolite (roflumilast N-oxide)

Roflumilast in plasma reached the maximum concentration 1 hour after the administration of APTA-2217. The plasma levels of roflumilast gradually decreased bi-exponentially. On the other hand, plasma concentrations of roflumilast N-oxide were higher than that of roflumilast and reached the maximum concentrations 4 hours after the administration of APTA-2217. Subsequently, plasma concentrations of roflumilast N-oxide decreased gradually.

The pharmacokinetic parameters of plasma concentrations of roflumilast and roflumilast N-oxide after oral administrations of single doses of 125, 250, 500 or 1000 mcg of APTA-2217 to healthy adult males under fasting conditions were evaluated.

Dose	125 mcg	250 mcg	500 mcg	1000 mcg
Roflumilast				
$AUC_{(0\text{-inf.})}$ [mcg·h/L]	9.7 (6.1, 15.3)	20.0 (16.4, 24.4)	38.3 (26.0, 56.4)	80.8 (64.2, 101.8)
C_{max} [mcg/L]	2.059 (1.666, 2.545)	3.924 (3.164, 4.867)	7.242 (5.622, 9.330)	12.637 (10.416, 15.332)
t_{max} [h]	1.00 (0.50, 2.00)	1.00 (1.00, 1.50)	1.00 (0.50, 3.00)	1.00 (0.50, 3.00)
$t_{1/2}$ [h]	9.33 (4.71, 18.49)	9.80 (7.83, 12.26)	14.58 (10.56, 20.13)	17.27 (10.66, 27.98)
CLt [L/h]	12.94 (8.16, 20.52)	12.51 (10.26, 15.25)	13.06 (8.86, 19.24)	12.37 (9.82, 15.59)
Vd/F [L]	174.23 (123.91, 244.99)	176.93 (146.14, 214.19)	274.65 (216.61, 348.24)	308.35 (209.34, 454.19)

Geometric mean (68 % range); Median (min, max) for t_{max}.

Outline-5-

Sponsor: Tanabe Seiyaku Co., LTD.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*
Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)		

Summary – Discussion/Conclusions Pharmacokinetic results: (continued):

Dose	125 mcg	250 mcg	500 mcg	1000 mcg
Roflumilast N-oxide				
$AUC_{(0\text{-inf.})}$ [mcg·h /L]	128.9 (90.1, 184.6)	222.7 (179.4, 276.3)	494.3 (353.0, 692.1)	925.6 (733.3, 1168.4)
C_{max} [mcg/L]	3.189 (2.787, 3.649)	5.760 (4.927, 6.734)	11.344 (9.663, 13.317)	23.188 (20.056, 26.810)
t_{max} [h]	4.00 (3.00, 4.00)	4.00 (4.00, 10.00)	4.00 (4.00, 10.00)	4.00 (4.00, 4.00)
$t_{1/2}$ [h]	22.65 (15.85, 32.36)	18.70 (15.03, 23.26)	23.03 (17.19, 30.85)	20.57 (16.68, 25.38)
CLmet [L/h]	1.01 (0.70, 1.44)	1.17 (0.94, 1.45)	1.05 (0.75, 1.47)	1.12 (0.89, 1.42)
Vd/F [L]	32.93 (26.63, 40.72)	31.49 (28.76, 34.49)	34.94 (28.24, 43.24)	33.34 (29.61, 37.54)

Geometric mean (68 % range); Median (min, max) for t_{max}.

The 95 % confidence interval of the regression coefficient for C_{max} of both roflumilast and roflumilast N-oxide did not include 1. However, it was considered that dose-proportionality for C_{max} of roflumilast and roflumilast N-oxide was almost obtained because both the point estimates of ratios of C_{max} and the 95 % confidence interval were approximately 2 (1.83 [95 % CI: 1.72 ~ 1.95] for roflumilast, 1.94 [95 % CI: 1.89 ~ 2.00] for roflumilast N-oxide), when the dose was doubled.

For $AUC_{(0\text{-inf})}$ of roflumilast and roflumilast N-oxide, the 95% confidence interval of the regression coefficient included 1, thus it was considered that there was dose-proportionality.

$t_{1/2}$ of roflumilast was prolonged with dose increases, and significant differences were found between doses in statistical analyses. A possible cause is as follows: the terminal elimination phase could not be evaluated in 125 mcg and 250 mcg, and as a result, $t_{1/2}$ of roflumilast of those doses was shortened. For $t_{1/2}$ of roflumilast N-oxide, statistically significant differences between doses were noted, however, the respective geometric means were close, and it was considered that there were no marked differences between doses.

For CLt of roflumilast and Clmet of roflumilast N-oxide, it was considered that there were no marked differences between doses.

For Vd/F of roflumilast and roflumilast N-oxide, the result of the comparison among doses was similar to the result of $t_{1/2}$.

Outline-6-

Sponsor: Tanabe Seiyaku Co., LTD.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*
Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)		

Summary – Discussion/Conclusions Pharmacokinetic results: (continued):

Cumulative urinary excretion rates of roflumilast and roflumilast N-oxide were small. The geometric means of the cumulative urinary excretion rates up to 96 hours for roflumilast at the doses of 125, 250, 500, and 1000 mcg were 0.056, 0.066, 0.060 and 0.051%, respectively. The geometric means of the cumulative urinary excretion rates up to 96 hours for roflumilast N-oxide were 0.503, 0.542, 0.559 and 0.547%, respectively. The geometric means of renal clearances of roflumilast at the doses of 125, 250, 500, and 1000 mcg were 0.008, 0.009, 0.008 and 0.006 L/h, respectively. The geometric means of renal clearances of rofulmilast N-oxide were 0.005, 0.006, 0.006 and 0.006 L/h, respectively.

(2) Cortisol levels in plasma and urine, 6β-hydroxycortisol in urine

Plasma and urinary cortisol concentration and urine 6β-hydroxycortisol concentration were measured in healthy adult male volunteers who received a single oral dose of APTA-2217 at 125, 250, 500 or 1000 mcg under fasting condition. APTA-2217 is metabolized by hepatic CYP3A4 and CYP1A2. Cortisol is metabolized to 6β-hydroxycortisol by CYP3A4, therefore, the metabolic clearance (CLm) of cortisol was measured to determine the inter-individual difference of CYP3A4 activity in the study subjects.

The correlation coefficient between the extra renal clearance of rofulmilast and CLm of cortisol at each dose was 0.3101~0.6862 (positive correlation). Thus, it was considered that the CLm of cortisol partially correlated to the extra renal clearance of roflumilast. The individual differences of the metabolic activity (CYP3A4) among the subjects were considered to be partially responsible for the inter-individual difference of the pharmacokinetics of APTA-2217.

Safety results:

The following safety results were obtained after single oral administration of 125, 250, 500 or 1000 mcg APTA-2217 to healthy Japanese adult males. All 24 subjects who received the study medication were included in the safety analysis. One subject (subject number 101) of Group A in the placebo treatment group was withdrawn from the study between the time period after the hospital discharge in Period 1 and prior to the administration in Period 3.

Outline-7-

Sponsor: Tanabe Seiyaku Co., LTD.	Individual Study Table Referring to Part of the Dossier	*(For Reviewing Authority Use only)*
Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)	Volume: Page:	

Summary – Discussion/Conclusions Safety results: (continued):

(1) Adverse events (AEs)

The summary of adverse events reported from the administration to hospital discharge in each period was as follows.

	Period 1 (Dose: 125 mcg)		Period 2 (Dose: 250 mcg)		Period 3 (Dose: 500 mcg)		Period 4 (Dose: 1000 mcg)	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
Number of subjects included in the safety evaluation	9	3	9	3	9	2	9	3
Number of subjects reported at least one AE (%)	0 (0.0)	0 (0.0)	2 (22.2)	1 (33.3)	3 (33.3)	0 (0.0)	5 (55.6)	0 (0.0)
Number of AEs	0	0	2	1	4	0	9	0
Gastrointestinal disorders								
Queasy							3 (33.3)	
Nervous system disorders								
Headache			1 (11.1)				2 (22.2)	
Light headedness							1 (11.1)	
Hematology(include blood groups)								
APTT prolonged					2 (22.2)			
Prothrombin time prolonged					1 (11.1)			
White blood cell count increased			1 (11.1)				1 (11.1)	
Neutrophil percentage increased							1 (11.1)	
Lymphocyte percentage decreased							1 (11.1)	
Lipid analyses								
Cholesterol total decreased				1 (33.3)				
Renal and urinary tract tests and urinalyses								
Urinary sediment present					1 (11.1)			

No AEs were reported for patients who received 125 mcg. There were two subjects (22.2%) with at least one AE at a dose of 250 mcg, 3 subjects (33.3%) at a dose of 500 mcg and 5 subjects (55.6%) at a dose of 1000 mcg.

None of the subjects who received 125 mcg reported any AEs suspected to be causally related to the investigational drug (0.0%). There was one subject (11.1%) at 250 mcg, 2 subjects (22.2%) at 500 mcg and 4 subjects (44.4%) at 1000mcg.

In this study, queasy (3 subjects), headache (3 subjects - reported twice in one subject), light headedness (1subject), APTT prolonged (2 subjects), prothrombin time prolonged (1 subject), white blood cell count increased (2 subjects), neutrophil percentage increased (1 subject), lymphocyte percentage decreased (1 subject), cholesterol total decreased (1 subject), urinary sediment present (1 subject) were reported as AEs

Of the AEs, queasy, headache and light headedness were judged as “Probably related” to the investigational drug based on the Adverse Drug Reaction information confirmed in the overseas studies.

Outline-8-

Sponsor: Tanabe Seiyaku Co., LTD.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*
Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)		

Summary – Discussion/Conclusions Safety results: (continued):

Prothrombin time prolonged, APTT prolonged (1 subject out of 2 subjects) and urinary sediment present were judged as "Possibly related" although the changes were small, because the causal relation to the investigational drug could not be ruled out with certainty in these cases. Other AEs reported in this study were determined as "not related" to the investigational drug. Headache reported in one subject administered 1000 mcg was moderate in intensity and the subject was treated with an ice pillow. Other AEs resolved without any treatments.

(2) Deaths, Other Serious AEs, and Other significant AEs

No deaths or other serious AEs were reported in this study.

One subject (subject number 101) in Group A was withdrawn from this study after the hospital discharge in Period 1 (treated with placebo) and prior to the administration in Period 3 due to AEs, "acute upper respiratory tract infection" and "body temperature increased" of moderate intensity, "pulse rate increased" and "heart rate increased" of mild intensity, and "white blood cell increased", "neutrophil percentage increased", "lymphocyte percentage decreased" and "urine ketone body present". In this case, these AEs were judged as "not related" to the investigational drug. Drug therapy (PL®, Cefzon and Voltaren) was given to this subject, when "acute upper respiratory tract infection" and "body temperature increased" occurred. Other AEs in this subject resolved spontaneously, as confirmed at the follow-up visit.

(3) Clinical laboratory variables (numerical or qualitative data)

Clinical laboratory values outside of the reference range were occasionally noticed in several variables, however the changes were small and not considered to be of clinical concern. Additionally statistically significant changes between pre- and post-dose measurements were occasionally noticed in several variables, however these changes were not considered to be of clinical concern except for the laboratory abnormalities reported as AEs.

Outline-9-

Sponsor: Tanabe Seiyaku Co., LTD.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For Reviewing Authority Use only)*
Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)		

Summary – Discussion/Conclusions Safety results: (continued):

(4) Vital Signs and Other Physical Findings Related to Safety

For the vital sighs [blood pressure (supine), pulse rate (supine) and body temperature], the time-couse showed similar values in the post-dose in all treatments. There were no significant changes. For the mean values of 12-lead ECG at rest (HR, QRS, QT, QTc and PR), statistically significant increases or decreases were occasionally noted in comparison between values on Day –1 and Day 1 and between values at pre-dose and up to 96 hr after administration. However, all of the changes were small and clinically insignificant.

Based on the above results, the single dose oral administration of APTA-2217 at 125, 250, 500 or 1000 mcg was safe and well tolerated in healthy adult male volunteers.

Conclusions:

Pharmacokinetic profiles

The C_{max} and $AUC_{0\text{-}inf}$ of roflumilast and roflumilast N-oxide after administration of single oral doses of 125 mcg up to 1000 mcg APTA-2217 to healthy adult male volunteers increased in proportion to the dose.

The $t_{1/2}$ and Vd/F of roflumilast were prolonged and increased with dose increases, and significant differences were found between doses in statistical analyses. The fact that the terminal elimination phase could not be evaluated in 125 mcg and 250 mcg was considered to be the cause for this. For $t_{1/2}$ and Vd/F of roflumilast N-oxide, significant differences were noted, however, the respective geometric means were close, and it was considered that there were no marked differences between doses.

Apparent total clearance (CLt and CLmet) and renal clearance of both roflumilast and roflumilast N-oxide were almost constant for all doses.

Cumulative urinary excretion rates of roflumilast and roflumilast N-oxide were small and the dose-proportional increase was not observed.

As CLm of cortisol was an indicator for the metabolic activities of CYP3A4 in each subject and the CLm was partially correlated to the extra renal clearance of APTA-2217, the individual differences of the metabolic activity (CYP3A4) among the subjects were considered to be partially responsible for the inter-subject difference of the pharmacokinetics of APTA-2217.

Safety profiles

Single oral dose administration of 125, 250, 500 and 1000 mcg of APTA-2217 to healthy adult male volunteers was safe and well tolerated.