1. Title Page

Title of study:	A clinical Pharmacological (Phase I) Study of APTA-2217 in healthy adult volunteers (Gender factor, Single oral dose)
Study drug name:	APTA-2217 (Roflumilast)
Study Design/ Reference product / Objectives/Dosage and Administration/ Study population:	Design: Placebo controlled, randomized, double-blind
	Reference product: Placebo
	Objective: To compare the pharmacokinetics between males and females, and evaluate the safety of APTA-2217 after single oral administration of 500 mcg under fasting condition in healthy adult volunteers.
	Dosage and Administration: The investigational drug was administered orally as a single dose of APTA-2217 500 mcg or placebo under fasting condition.
	Study population: Japanese healthy adult volunteers (males and females)
Study sponsor:	Tanabe Seiyaku Co., LTD.
Study protocol No.:	APTA-2217-HP-03
Phase of development:	Phase I
Study initiation date:	September 22, 2003 (Date when the informed consent of the first subject was obtained)
Premature termination:	None
Study completion date:	October 22, 2003 (Date of the post-study examination of the last subject)
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), and “Revised Guidelines for Good Clinical Practice (Revised GCP)” (MHLW Ordinance No. 106, June 12, 2003). All documentation pertaining to this study was appropriately retained in Osaka Pharmacology Research Clinic and Tanabe Seiyaku Co., LTD.
Date of the report:	April, 25, 2005

2. Synopsis

Report Summary -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 AuthorityUse only)*

Study title:

A clinical Pharmacological (Phase I) Study of APTA-2217 in healthy adult volunteers (Gender factor, Single oral dose)

Study site:

Osaka Pharmacology Research Clinic
12-11, Kasuga 4-chome, Suita city, Osaka, 565-0853, Japan
Tel. +81-6-6330-8721, Fax. +81-6-6330-8725

Publication: None

Study period: Approximately one month September 22, 2003 (Date when the informed consent of the first subject was obtained) to October 22, 2003 (Date of the post-study examination of the last subject)	Phase of development: Phase I

Objective:

To compare the pharmacokinetics between males and females, and evaluate the safety of APTA-2217 after single oral administration of 500 mcg under fasting condition in healthy adult volunteers.

Methodology:

1) Screening examination

After obtaining written informed consent from subjects, screening examinations were performed to confirm the eligibility to participate in the study.

2) Administration period

Of subjects who were eligible, based on the results of screening examination, ten subjects and 2 substitutes were selected for each gender. Study medication was randomly allocated and administered to subjects in the male and female groups (8 subjects for the active drug, and 2 subjects for placebo), and specified observations and tests were performed. Subjects were hospitalized for 8 days and 7 nights.

3) Post-study examination

Specified observations and tests were performed on Day 15 ± 2 days after administration.

	Male group: 10 subjects (+ 2 substitutes)	Female group: 10 subjects (+ 2 substitutes)
Administration period	500 mcg: 8 subjects Placebo: 2 subjects	500 mcg: 8 subjects Placebo: 2 subjects
Subjects were hospitalized from 2 days before administration to Day 6 for 8 days (8 days and 7 nights).		

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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 AuthorityUse only)*

Number of subjects (planned and evaluated):
Number of subjects planned; 10 males and 10 females (20 subjects in total)
Number of subjects administered; 10 males and 10 females (20 subjects in total)
Number of subjects evaluated for pharmacokinetics; 10 males and 10 females (20 subjects in total)
Number of subjects analyzed for safety; 10 males and 10 females (20 subjects in total)

Subjects and main criteria for inclusion:
<Inclusion criteria>
Subjects who met all of the following criteria and had the ability of informed consent were included in the study.

1) Healthy adult 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 principal investigator (subinvestigator) based on the result of screening examination.

<Exclusion criteria>
Subjects who fulfilled any of the following criteria were excluded from the study.

1) A 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 for males and 45 kg for females at screening examination.
3) Subjects who participated in any clinical study and received investigational drug within 4 months prior to informed consent.
4) A history of blood donation or blood collection of 400 mL or more within 12 weeks for males and within 16 weeks for females (prior to informed consent).
5) A history of blood donation or blood collection of 200 mL or more within 4 weeks prior to informed consent.
6) A history of blood donation or blood collection of a total of 800 mL or more for males and 400 mL or more for females within one year prior to informed consent.
7) A history of any surgery known to alter gastrointestinal absorption of drugs (excluding appendectomy or hernioplasty/herniotomy).
8) Any clinical signs of cardiac diseases at screening examination (e.g., a QTc interval of ≥ 430 msec for males and ≥ 450 msec for females, or a PR interval of ≥ 220 msec), or a history of those diseases.
9) A positive result of HBs antigen, serological syphilitic reaction , HCV antibody, or HIV antibody at screening examination.

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Drug Substance: APTA-2217 (Roflumilast)		

10) Subjects of childbearing potential, who stated at the time of informed consent that a reliable contraceptive measure (e.g., no sexual intercourse, IUD, bilateral tubal ligation) could not be taken during the period from the menstrual cycle including the date of informed consent to the menstrual cycle including the day of the post-study examination.
11) Subjects who were pregnant or lactating at the time of informed consent.
12) Subjects who had positive pregnancy test or had no pregnancy test at screening examination.
13) Subjects currently taking any medication.
14) Subjects who were not suitable to participate in the study for medical reason(s) by judgement of the principal investigator (subinvestigator).

Study drug, reference product, dosage, method of administration and lot number:
<Study drug, reference product, and lot number>
APTA-2217 500 mcg tablets, and APTA-2217 placebo tablets identical in appearance toAPTA-2217 500 mcg tablets

1) Study drug

	Active ingredient/Content	Lot No.	Expiration date
APTA-2217 500 mcg tablets	500 mcg of APTA-2217 contained in each tablet	30007	January 2005

2) Reference product

	Active ingredient/Content	Lot No.	Expiration date
APTA-2217 500 mcg placebo tables	Not applicable	30010	August 2005

<Dosage and method of administration>
The investigational drug was administered orally as a single dose of APTA-2217 500 mcg or placebo under fasting condition.

Administration period:
Single administration

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<table>
<tr><td>Sponsor:
Tanabe Seiyaku Co., LTD.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

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Page:</td><td rowspan="3">(For Reviewing AuthorityUse only)</td></tr>
<tr><td>Product name: undecided</td></tr>
<tr><td>Drug Substance:
APTA-2217 (Roflumilast)</td></tr>
<tr><td colspan="3">Criteria for evaluation:
1) Pharmacokinetic variables
(1) Plasma concentration: Roflumilast, and the main metabolite (roflumilast N-oxide)
(2) Pharmacokinetic parameters: C_{max}, AUC, T_{max} and $t_{1/2}$ of roflumilast and roflumilast N-oxide. As reference data, apparent total body clearance (CLt for roflumilast, Clmet for roflumilast N-oxide), and apparent distribution volume in the terminal elimination phase (Vd/F).
(3) Protein binding rate: roflumilast, and roflumilast N-oxide
(4) Metabolic activity index: cortisol levels in plasma and urine, and 6beta-hydroxycortisol in urine
2) Safety variables
(1) Adverse events
(2) Adverse events suspected to be causally related to the investigational drug</td></tr>
</table>

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

Statistical methods:

1) Pharmacokinetics

(1) Plasma drug concentration

For subjects receiving the study drug, the geometric mean and 68% range of plasma concentrations of roflumilast and roflumilast N-oxide were calculated by gender at each time point.

The pharmacokinetic parameters for roflumilast and roflumilast N-oxide in plasma were calculated for each subject by a non-compartment model analysis. The C_{max} and T_{max} were determined based on peak plasma concentrations, whereas $t_{1/2}$ was calculated with the elimination rate constant (Ke), which was obtained by linear regression between logarithmic transformed plasma concentrations in the terminal elimination phase versus time. The $AUC_{(0\text{-inf.})}$ was calculated with the trapezoidal method and extrapolation to infinity with the Ke.

The geometric mean and 68% range of each parameter (median, and min to max for T_{max}) were calculated by gender.

The point estimates and the 90% confidence interval of the gender differences (male minus female) were calculated using log-transformed $AUC_{(0\text{-inf.})}$, C_{max}, $t_{1/2}$, CLt, CLmet and Vd/F; these estimates were inversely transformed to estimate the ratio of male to female.

(2) Plasma protein binding rate

For subjects receiving the study drug, the geometric mean and 68% range of plasma protein binding rate of roflumilast N-oxide were calculated by gender.

(3) Metabolic activity index

The ratio (X_{6beta}/X_{col}) of cumulative urinary excretion amount of 6beta-hydroxycortisol (X_{6beta}) to that of cortisol (X_{col}) up to 24 hr after administration of the study drug or placebo was calculated. The cortisol AUC (AUC_{col}) from time 0 to 24 hr after administration was determined, and the metabolic clearance (CLm) of cortisol to 6beta-hydroxycortisol was calculated by the following formula:

$CLm = X_{6beta}/AUC_{col}$

The geometric mean and 68% range of X_{6beta}/X_{col} and CLm of cortisol were calculated by gender.

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Drug Substance: APTA-2217 (Roflumilast)		

Statistical methods (continued):

2) Safety

The occurrence rates of all adverse events and adverse events related to the investigational drug that occurred during the period from administration to hospital discharge was calculated by gender and drug (APTA-2217 and placebo), and the number of each individual event was presented.

For quantitative parameters of general clinical laboratory tests for subjects receiving APTA-2217, the mean and standard deviation (SD) were calculated by gender at each test time point, and pre- and post-dose comparisons were made using the paired t-test. For qualitative parameters for subjects receiving APTA-2217, the distribution of data and the shift from pre-dose to post-dose (pre-dose > post-dose, pre-dose = post-dose and pre-dose < post-dose) was presented by gender at each test time point.

For blood pressure (systolic and diastolic), pulse rate, and body temperature for subjects receiving APTA-2217, the mean and SD were calculated by gender at each measurement time point.

For 12-lead ECG (HR, QRS, QT, QTc, and PR) at resting conditions for subjects receiving APTA-2217, the mean and SD were presented by gender at each measurement time point. Also, the mean and standard error (SE) of the difference of matched time points' values between one day before administration and on Day 1 at corresponding time points were calculated and compared using the paired t-test. For subjects receiving APTA-2217, the mean and SE of the difference between pre- and post-dose measurements obtained up to 120 hr after administration (every 24 hr) were also calculated by gender, and compared using the paired t-test.

The test was two-sided at the significance level of 5%.

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

Summary – Conclusions:

Pharmacokinetic results:

In this study, there were no missing data since all of 20 subjects [10 subjects each of the male and female groups (8 subjects receiving APTA-2217 500 mcg, and 2 subjects receiving placebo in each group)] completed the study,. However, in the female group, there were two subjects who received concomitant medication. The handling of the measurements for these subjects was discussed for each variable. As the result, it was decided that the two subjects would be included in the evaluations of plasma protein binding rate and metabolic activity index but be excluded in the tabulation of plasma drug concentrations.

	Roflumilast		Roflumilast N-oxide	
Gender	Male	Female	Male	Female
$AUC_{(0\text{-inf.})}$ [mcg·h/L]	43.0 (31.3, 59.2)	46.6 (36.4, 59.8)	513.6 (452.7, 582.8)	581.5 (457.8, 738.6)
C_{max} [mcg/L]	7.240 (5.126, 10.224)	6.049 (3.670, 9.971)	12.130 (10.594, 13.889)	13.324 (11.590, 15.319)
T_{max} [h]	1.00 (0.50, 3.00)	1.00 (0.50, 3.00)	4.00 (4.00, 4.00)	4.00 (4.00, 4.00)
$t_{1/2}$ [h]	20.87 (10.28, 42.37)	19.42 (12.90, 29.24)	22.78 (19.61, 26.45)	25.72 (19.68, 33.62)
CLt or CLmet [L/h]	11.61 (8.45, 15.96)	10.72 (8.36, 13.74)	1.01 (0.89, 1.15)	0.89 (0.70, 1.14)
Vd/F [L]	349.68 (180.85, 676.12)	300.35 (243.46, 370.53)	33.25 (27.69, 39.94)	33.17 (29.07, 37.86)

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

1) After administration of APTA-2217, the plasma concentration of roflumilast was elevated rapidly and subsequently exhibited a biphasic elimination profile in both males and females. Plasma concentrations of roflumilast N-oxide was elevated more moderately than roflumilast, peaked in 4h after administration for the both males and females. No marked differences, depending on gender, were found in the geometric means of plasma concentration profiles.

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

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

2) No marked differences in any pharmacokinetic parameters of roflumilast and roflumilast N-oxide between genders were observed.
3) The actual value of the protein binding rate of roflumilast at 1 h after administration in males and females was >97.5% except 91.0% for one female. The protein binding rate of roflumilast N-oxide was 98.0% (geometric mean), for both male and female subjects and no differences were noted between genders in the protein binding rate in 4 h after administration.
4) The X_{6beta}/Xcol (geometric mean) after administration of APTA-2217 in male and female subjects was 7.32 and 10.58, and the CLm was 0.046 and 0.026 L/h, respectively.

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Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)		

Summary – Conclusions (continued):
Safety results:

The summary of adverse events reported from administration of APTA-2217 to hospital discharge was as follows.

	Male		Female	
	APTA-2217	Placebo	APTA-2217	Placebo
Number of subjects included in the safety evaluation	8	2	8	2
Number of subjects reported with at least one AE (%)	0 (0.0)	0 (0.0)	7 (87.5)	0 (0.0)
Number of AEs	0	0	12	0
Gastrointestinal disorders				
Diarrhea	-	-	1*(12.5)	-
Queasy	-	-	2*(25.0)	-
Vomiting	-	-	1*(12.5)	-
Nervous system disorders				
Headache	-	-	1*(12.5)	-
Reproductive system and breast disorders				
Menses painful	-	-	3(37.5)	-
Renal and urinary tract investigations and urinalyses				
Urinary sediment present	-	-	1(12.5)	-
Urinary occult blood positive	-	-	3(37.5)	-

* Adverse events suspected to be causally related to the investigational drug by investigator (definitely related or probably (likely) related or possibly (unlikely) related)

1) No adverse events occurred in the male group after administration of APTA-2217 and placebo during the period from administration to hospital discharge.
2) No adverse events developed in the female group after administration of placebo during the period from administration to hospital discharge. In contrast, after administration of APTA-2217, 7 of 8 subjects (87%) experienced a total of 12 adverse events, and those that occurred in at least 2 subjects included “menstrual pain,” “positive urinary occult blood,” and “queasy.” 4 of 8 subjects (50%) developed a total of 5 adverse events suspected to be causally related to the investigational drug, consisting of 2 episodes of “queasy,” and one episode each of “diarrhea,” “vomiting,” and “headache.” All of the adverse events were mild or moderate in intensity and resolved without any therapy or with symptomatic therapy.

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Product name: undecided		
Drug Substance: APTA-2217 (Roflumilast)		

Safety result (continued):

3) Concerning adverse events that occurred during the period from administration of the investigational drug to hospital discharge, the incidence of all adverse events that occurred in subjects receiving APTA-2217 was significantly higher in the female group (87%, 7/8 subjects) than in the male group (0%, 0/8 subjects) (P=0.001). Although the incidence of adverse events suspected to be causally related to the investigational drug was 0 subject (0%) in male and 4subjects (50%) in females, indicating a higher incidence in the female group, there was no significant difference between the genders (P=0.077).

4) After hospital discharge, 3 of 8 subjects (37.5%) experienced a total of 6 adverse events in both the male and female groups. The type of adverse events were primarily abnormal laboratory values observed at the post-study examination, and the causal relationship of all events to the investigational drug was assessed as “unrelated” by the investigator (subinvestigator).

5) There were no deaths or other serious adverse events in this study.

6) After administration of APTA-2217, 2 of 8 subjects (25.0%) in the female group experienced one adverse event each requiring therapy, which include “menstrual pain” and “headache.” The relationship of “menstrual pain” to the investigational drug was assessed as “unrelated”, “Headache” resolved promptly after symptomatic therapy.

7) For hematology, blood coagulation, and blood chemistry, some changes were noted for certain test parameters after administration of APTA-2217 in both males and females. However, all such changes were considered to be clinically insignificant

8) For urine analysis, abnormal occult blood and sediment were observed in the female group after administration of APTA-2217; however, such observations were considered to be due to menstruation.

9) No clinically significant findings were found in either male or female subjects in vital signs (blood pressure, pulse rate, and body temperature).

10) For 12-lead ECG parameters at resting conditions, statistically significant increases or decreases (P<0.05) were occasionally noted in comparison between values on Day –1 and Day 1 (intra-day variation) and between pre-dose and up to 120 hr after administration (inter-day variation) in both the male and female groups after administration of APTA-2217; however, all of the changes were considered to be clinically insignificant.

Report Summary –11-

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Drug Substance: APTA-2217 (Roflumilast)		

Summary – Conclusions (continued):

Conclusion:

After a single oral administration of APTA-2217 500 mcg to healthy adult subjects (male and female) under fasting condition, no significant differences were noted in the pharmacokinetics of roflumilast and roflumilast N-oxide between male and female subjects. Adverse events were reported only in the females during the period from administration of study medication to hospital discharge, half of which were considered to be gender specific (menstrual pain, urinary occult blood positive). There were no other adverse events with characteristics largely different from those observed so far in the investigational drug. The results of this study indicate that a single oral administration of APTA-2217 at 500 mcg is safe and tolerable in both male and female subjects.