1. Title Page

Title of study:	A clinical pharmacological (Phase I) study of APTA-2217 in healthy adult male volunteers (Effect of food intake, single oral dose)
Study drug name:	APTA-2217 (Roflumilast)
Study Design/ Reference product / Objectives/Dosage and Administration/ Study population:	Design: A randomized, open-label, 2-period crossover study
	Reference product: None
	Objective: To compare the pharmacokinetics and evaluate the safety of APTA-2217 after single oral administration of 500 mcg under fasting and fed (low fat diet) conditions in healthy adult male volunteers.
	Dosage and Administration: The investigational drug was administered orally as a single dose of 500 mcg under fasting condition or within 30 minutes after a meal.
	Study population: Japanese healthy adult male subjects
Study sponsor:	Tanabe Seiyaku Co., LTD.
Study protocol No.:	APTA-2217-HP-04
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 31, 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 documentations pertaining to this study is appropriately retained in Osaka Pharmacology Research Clinic and Tanabe Seiyaku Co., LTD.
Date of the report:	April, 25, 2005

2. Synopsis

Report Summary -1-

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

Volume:

Page:</td><td rowspan="3">(For Reviewing Authority Use only)</td></tr>
<tr><td>Product name: undecided</td></tr>
<tr><td>Drug Substance:
APTA-2217 (Roflumilast)</td></tr>
<tr><td colspan="3">Study title:
A clinical pharmacological (Phase I) study of APTA-2217 in healthy adult male volunteers (Effect of food intake, single oral dose)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td colspan="3">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</td></tr>
<tr><td colspan="3">Publication: None</td></tr>
<tr><td colspan="2">Study period: Approximately one month
September 22, 2003 (Date when the informed consent of the first subject was obtained) to October 31, 2003 (Date of the post-study examination of the last subject)</td><td>Phase of development:
Phase I</td></tr>
<tr><td colspan="3">Objective:
To compare the pharmacokinetics and to evaluate the safety of APTA-2217 after single oral administration of 500 mcg under fasting and fed (low fat diet) conditions in healthy adult male volunteers.</td></tr>
<tr><td colspan="3">Methodology:
1) Screening examination
After the obtaining written informed consent from subjects, screening examinations were performed to confirm the eligibility for study participation.
2) Administration period
Of the subjects who were determined eligible based on the screening examination results, 10 subjects and 2 substitutes were selected; 5 subjects were randomized to either Group A (the initial administration was given under fasting) or Group B (the initial administration was given after ingestion of standardized food). Study medication was administered in Periods 1 and 2 according to the allocated food condition, and specified observations and tests were performed. During each study period, subjects were hospitalized for 8 days and 7 nights, and the minimum-dosing interval of the study drug between Period 1 and Period 2 was 10 days.</td></tr>
</table>

Report Summary -2-

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	Period 1	Period 2
Group A (5 subjects)	Administration of APTA-2217 500 mcg tablets under the fasting condition	Administration of APTA-2217 500 mcg tablets under the fed condition
Group B (5 subjects)	Administration of APTA-2217 500 mcg tablets under the fed condition	Administration of APTA-2217 500 mcg tablets under the fasting condition
During each study period subjects were hospitalized from 2 days before administration of roflumilast up to Day 6 for 8 days (8 days and 7 nights). The minimum-dosing interval of the study drug between Period 1 and Period 2 was 10 days.		

3) Post-study examination

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

Number of subjects (planned and analyzed):

Number of subjects planned: 10 subjects (5 subjects for each Group A and B)
Number of subjects: 10 subjects (5 subjects for each GroupA and B)
Number of subjects evaluated for pharmacokinetics: 10 subjects (5 subjects for each Group A and B)
Number of subjects evaluated for safety: 10 subjects (5 subjects for each Group A and B)

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

<Exclusion criteria>

Subjects who had any of the following criteria were excluded from the 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 any clinical study and received investigational drug within 4 months prior to informed consent.
4) History of blood donation or blood collection of 400 mL or more within 12 weeks or 200 mL or more within 4 weeks prior to informed consent.

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Summary – Subjects and main criteria for inclusion (continued):

5) History of blood donation or blood collection of a total of 800 mL or more within 1 year prior to informed consent.
6) History of any surgery known to alter gastrointestinal absorption of drugs (excluding appendectomy or hernioplasty/herniotomy).
7) Any clinical signs of cardiac diseases at screening examination (e.g. QTc interval of ≥ 430 msec, or PR interval of ≥220 msec), or a history of those diseases.
8) A positive result for HBs antigen, serological syphilitic reaction, HCV antibody, or HIV antibody at screening examination.
9) Subjects currently taking any medication.
10) Subjects who were determined inadequate to participate in the study by the investigator (subinvestigator) for medical reason(s).

Study drug, reference product, dosage, method of administration and lot number:
<Study drug, reference product, and lot number>
1) Study drug

	Active ingredient/Content	Lot No.	Expiration date
APTA-2217 500 mcg tables	500 mcg of APTA-2217 contained in each tablet	30026	January 2005

2) Reference product
None

<Dosage and method of administration>
The investigational drug was administered orally as a single dose of 500 mcg under fasting condition or within 30 minutes after a meal.

Administration period:
Single administration in each of Study periods 1 and 2

Criteria for evaluation:
1) Pharmacokinetic variables
(1) Plasma concentration: roflumilast and the major 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 and CLmet for roflumilast N-oxide), and apparent distribution volume in the terminal elimination phase (Vd/F).
2) Safety variables
(1) Adverse events
(2) Adverse events suspected to be causally related to the investigational drug

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Statistical methods:

1) Pharmacokinetics

The pharmacokinetic parameters for roflumilast and roflumilast N-oxide in plasma were calculated for each subject by non-compartment model analysis. 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. $AUC_{(0\text{-inf.})}$ was calculated with the trapezoidal method and extrapolation to infinity with the Ke.

The geometric mean and 68% range for each parameter (for T_{max}, median and min to max) were calculated for each food condition (under fasting or fed condition).

To compare pharmacokinetic parameters of roflumilast and roflumilast N-oxide between fasting and fed conditions, an analysis of variance (ANOVA) (the significant level set at 5%) was performed in terms of untransformed T_{max} and logarithmic transformed other parameters for roflumilast and roflumilast N-oxide with food condition, subjects, and administration period as factors.

Statistical methods

2) Safety

For all adverse events and adverse events suspected to be causally related to the investigational drug, occurrence rates s were calculated for each food condition (under fasting or fed condition) regardless of onset period, and the number of individual events was presented.

For quantitative parameters of general clinical laboratory tests, the mean and standard deviation (SD) were calculated for each food condition (under fasting or fed condition) at each time point, and pre- and post-dose comparisons were made with a paired t test. For qualitative parameters, the distribution of data and a shift from pre-dose to post-dose data (pre-dose>post-dose, pre-dose=post-dose, and pre-dose<post-dose) were presented for each food condition (under fasting or fed condition) at each time point.

For blood pressure (systolic and diastolic levels), pulse rate, and body temperature, the mean and SD were calculated for each study period (under fasting or fed condition) at each time point.

For 12-lead ECG data (HR, QRS, QT, QTc, and PR) at rest, the mean and SD were presented for each food condition (under fasting or fed condition) at each time point. The mean and standard error (SE) of the difference between matched time points' value on Day –1 and Day 1 were calculated and compared with a paired t test. 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 for each food condition (under fasting or fed condition), and compared using a paired t test.

The significance level for tests was set at two-sided 5%.

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Summary – Conclusions:

Pharmacokinetic results:

1) After administration of APTA-2217, plasma concentrations of roflumilast were elevated more rapidly than that of roflumilast N-oxide. No marked differences depending on food condition were found for the geometric means of plasma concentration in the elimination phase.

	Roflumilast		Roflumilast N-oxide	
Condition	Fasting	Fed	Fasting	Fed
$AUC_{(0\text{-inf.})}$ [mcg·h/L]	37.9 (26.6, 54.0)	39.3 (27.7, 55.9)	474.3 (345.5,651.1)	448.2 (332.4,604.4)
	log(1.038) [1)] log(1.008) – log(1.069) [2)]		log(0.945) [1)] log(0.925) – log(0.965) [2)]	
C_{max} [mcg/L]	7.651 (4.964, 11.793)	6.643 (5.003,8.820)	12.558 (10.367,15.212)	10.496 (8.590, 12.824)
	log(0.868) [1)] log(0.726) – log(1.038) [2)]		log(0.836) [1)] log(0.815) – log(0.857) [2)]	
T_{max} [h]	1.00 (0.50, 4.00)	1.75 (1.00, 3.00)	4.00 (4.00, 10.00)	6.00 (4.00, 10.00)
$t_{1/2}$ [h]	11.87 (7.22,19.52)	11.44 (7.96, 16.43)	19.86 (15.48, 25.48)	20.18 (16.59, 24.56)
CLt or CLmet [L/h]	13.20 (9.26, 18.80)	12.70 (8.94, 18.05)	1.10 (0.80, 1.50)	1.16 (0.86, 1.57)
Vd/F [L]	225.95 (172.46, 296.03)	209.65 (173.13, 253.88)	31.40 (26.53, 37.16)	33.78 (27.90, 40.90)

Geometric mean (68 % range); Median (min, max) for T_{max}.
1) Difference of logarithmic transformed mean value. 2) 90% confidence intervals.

2) The C_{max} values under fed condition were lowered by 13.2% for roflumilast and by 16.4% for roflumilast N-oxide compared to the values under fasting condition. Although in the difference of the log transformed mean (90% confidence interval), the lower limit of the confidence interval for C_{max} of roflumilast deviated from the acceptable range between log(0.8) and log(1.25), as the deviation was relatively small, it was concluded that food has only an insignificant effect on C_{max}. .
3) Regarding AUC, the difference of the log transformed mean (90% confidence interval) for roflumilast and roflumilast N-oxide fell into the range between log(0.8) and log(1.25); thus, it was concluded that there was no food effect on this variable (AUC).

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Summary – Conclusions (continued):
Pharmacokinetic results:

4) Based on the results of C_{max} and $AUC_{(0\text{-inf})}$, it was concluded that there was little or no effect of food on the pharmacokinetics of roflumilast and roflumilast N-oxide.
5) The T_{max} under fed condition was slightly longer than that under fasting condition. The ratio of mean value (90% confidence interval) was 1.25 (0.675 to 1.825) for roflumilast and 1.32 (0.919 to 1.721) for roflumilast N-oxide.
6) For $t_{1/2}$, and CLt, CLmet and Vd/F calculated as reference data, the 90% confidence interval for the difference in logarithmic transformed mean values for both roflumilast and roflumilast N-oxide fell into the range between log(0.8) and log(1.25); thus, it was concluded that food has no effect on these variables.

Safety results:

1) The summary of adverse event reported after the administration of the investigational drug and prior to the hospital discharge was as follows:

	Fasting condition	Fed condition
Number of subjects included in the safety evaluation	10	10
Number of subjects reported at least one AE(%)	0(0.0)	2(20.0)
Number of AEs	0	2
Nervous system disorders		
Light headedness	-	1*(10.0)
Hematology investigations (incl. blood groups)		
aPTT prolonged**	-	1(10.0)

* Adverse events suspected to be causally related to the investigational drug by investigator (Definitely related or Probably (likely) related or Possibly (unlikely) related)
** aPTT: activated partial thromboplastin time

During the period from administration to hospital discharge, no adverse events were noted after administration of roflumilast under fasting condition. After administration under the fed condition, 2 of 10 subjects (20.0%) experienced 1 event each 'light headedness' and 'aPTT prolonged.' Adverse events suspected to be causally related to the investigational drug include only 1 event of 'light headedness' in 1 subject (10.0%). The event was mild in intensity and resolved without any treatment.

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2) After hospital discharge (during the period from hospital discharge in Period 1 to the time immediately before administration in Period 2, and from hospital discharge in Period 2 to completion of the post-study examination), 1 adverse event of "CK increased" was observed in one subject (10.0%) receiving administration under fasting condition; however, the causal relationship to the investigational drug was assessed as "not related".
3) There were no deaths, other serious adverse events or other significant adverse events in this study.
4) For clinical laboratory tests, significant increases or decreases were occasionally noted in pre- and post-dose comparisons for parameters of hematology, blood coagulation and blood chemistry both under fasting as well as under fed conditions; however, all of such changes were slight and within the reference ranges. No abnormalities were observed for the urine analysis (qualitative).
5) No clinically significant findings were noted in vital signs (blood pressure, pulse rate and body temperature) after administration of study medication under either fasting or fed conditions.
6) For 12-lead ECG parameters at resting conditions under both fasting and fed condition, 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 values pre-dose and up to 120 hr after administration (inter-day variation). However, all of the changes were small and clinically insignificant. No marked differences were found in the time-course of respective parameters between fasting and fed conditions.

Summary – Conclusions (continued):
Conclusion:

After single oral administration of APTA-2217 at 500 mcg to healthy adult male subjects under fasting or fed condition, the C_{max} decreased and the T_{max} was slightly delayed in the fed condition for roflumilast and roflumilast N-oxide; no change was noted in the $AUC_{(0\text{-inf})}$. It was concluded that food has no relevant effect on the systemic absorption of APTA-2217. The above results were almost consistent with results from overseas clinical studies. One adverse event suspected to be causally related to the investigational drug included a mild episode of 'light headedness'. Thus, the safety and tolerability of APTA-2217 were considered to be favorable under both fasting as well as under fed conditions.