1. Title Page

Title of Study:	A clinical pharmacological (Phase I) study of APTA-2217 in healthy elderly male volunteers (single oral dose)
Study medication name	APTA-2217 (Roflumilast)
Study Design/ Reference Product/ Objectives/Dosage and Administration/ Study population:	Design: Placebo controlled, randomized double blind study, 2-period ascending dose, alternative panel
	Reference Product: Placebo
	Objective: To evaluate the pharmacokinetics and safety of APTA-2217 after a single oral administration of 250 mcg or 500 mcg under the fasting condition in healthy elderly male volunteers.
	Dosage and Administration: The investigational drug was administered orally as a single dose of APTA-2217 250 mcg or 500 mcg, or placebo under fasting condition.
	Study population: Japanese healthy male subjects aged between 65 and 80 years of age
Study sponsor:	Tanabe Seiyaku Co., LTD.
Study protocol No.:	APTA-2217-HP-02
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 30, 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 is appropriately retained in CPC 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 elderly male volunteers (single oral dose)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td colspan="3">Study site:
Medical Corporation Kouryokai, CPC Clinic
18-38, Toso 4-chome, Kagoshima city, Kagoshima, 890-0081, Japan
Tel: +81-99-259-5243, Fax: +81-99-259-8372</td></tr>
<tr><td colspan="3">Publication: None</td></tr>
<tr><td colspan="2">Study period: Approximately one month
September 22, 2003 (Informed consent of the first subject was obtained) to October 30, 2003 (Post-study examination of the last subject)</td><td>Phase of development:
Phase I</td></tr>
<tr><td colspan="3">Objective:
To evaluate the pharmacokinetics and safety of APTA-2217 after single oral administration of 250 mcg or 500 mcg under the fasting condition in healthy elderly male volunteers.</td></tr>
<tr><td colspan="3">Methodology:
1) Screening examination
After obtaining the written informed consent from subjects, screening examinations were performed to confirm the eligibility to participate in the study.
2) Administration period
Of the subjects who were eligible, based on the results of screening examination, 12 subjects and at least 1 substitute were selected for each Group A and B. The randomized investigational drug was administered to subjects in Group A during Period 1 and those in Group B during Period 2 (9 subjects for the study medication and 3 subjects for placebo), and specified observations and tests were performed. Subjects were hospitalized for 10 days and 9 nights in each study period; the minimum-dosing interval between study periods 1 and 2 was at least 14 days.</td></tr>
</table>

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3) Post-study examination

Specified observations and tests were to be performed on Day 15 ± 2 days after administration (the post-study examination in Period 1 was actually performed on Day 15 + 3 days).

	Period 1	Period 2
Group A (12 subjects) (+ at least one substitute)	250 mcg: 9 subjects Placebo: 3 subjects	Not applicable
Group B (12 subjects) (+ at least one substitute)	Not applicable	500 mcg: 9 subjects Placebo: 3 subjects
Subjects were hospitalized from 2 days before administration to Day 8 for 10 days (10 days and 9 nights) in each period.		

Number of subjects (planned and analyzed):

Number of subjects planned: 12 subjects in each study Group A and B (24 subjects in total)

Number of subjects receiving the investigational drug: 12 subjects in each Group A and B (24 subjects in total)

Number of subjects evaluated for pharmacokinetics: 12 subjects in each Group A and B (24 subjects in total)

Number of subjects evaluated for safety: 12 subjects in each Group A and B (24 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 male subjects who were between 65 and 80 years old at the time of receiving informed consent and provided written informed consent.
2) Subjects who were suitable to participate in the study by the principal investigator (subinvestigator) based on the results of the screening examination.

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Subjects and main criteria for inclusion (continued):

<Exclusion criteria>

Subjects who had any of the following criteria were excluded from the study.

1) A history of any allergy to 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) A 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.
5) A history of blood donation or blood collection of a total of 800 mL or more within one year prior to informed consent.
6) Anemic condition (hemoglobin < 12.5 g/dL at screening examination).
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 ≥ 440 msec, or a PR interval of ≥ 220 msec) or a history of those diseases.
9) A positive result for HBs antigen, serological syphilitic reaction , HCV antibody, or HIV antibody at screening examination.
10) Subjects currently taking any medication.
11) Subjects who were not suitable to participate in the study by the principal investigator (subinvestigator) for medical reason(s).

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Drug Substance: APTA-2217 (Roflumilast)		

Study medication, reference product, dosage, mode of administration and lot number:
<Study medication, reference product, and lot number>
APTA-2217 250 mcg and 500 mcg tablets, and matched placebo tablets indistinguishable from these tablets

1) Study medication

	Active ingredient/Content	Lot No.	Expiration date
APTA-2217 250 mcg tablets	250 mcg of APTA-2217 contained in each tablet	30006	January 2005
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 250 mcg placebo tablets	Not applicable	30009	April 2005
APTA-2217 500 mcg placebo tablets		30010	April 2005

<Dosage and mode of administration>
The investigational drug was administered orally as a single dose of APTA-2217

Administration period:
Group A: Single administration in study Period 1
Group B: Single administration in study Period 2

Criteria for evaluation:
1) Pharmacokinetic variables
(1) Plasma concentration: roflumilast and the main metabolite (roflumilast N-oxide)
(2) Pharmacokinetic parameters: C_{max}, T_{max}, $t_{1/2}$, and estimated $AUC_{(0\text{-inf.})}$, apparent total body clearance (CLt for roflumilast and CLmet for roflumilast N-oxide) and apparent distribution volume in the terminal elimination phase (Vd/F) of roflumilast and roflumilast N-oxide. As reference data, $AUC_{0\text{-}72h}$.
(3) Metabolic activity index: Cortisol levels in plasma and urine, and 6beta-hydroxycortisol in urine

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

2) Safety variables
(1) Adverse events
(2) Adverse events suspected to be causally related to the investigational drug

Statistical methods:

1) Pharmacokinetics

(1) Plasma drug concentration

The geometric mean and 68% range for plasma concentrations of roflumilast and roflumilast N-oxide after administration of the study medication were calculated by each dose at each time point.

The pharmacokinetic parameters of roflumilast and roflumilast N-oxide were calculated for each subject by 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 $AUC_{0\text{-}72h}$ and $AUC_{(0\text{-}inf.)}$ were calculated with the trapezoidal method and extrapolation to infinity with Ke.

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

Statistical analyses were performed to compare pharmacokinetic parameters between the doses, and between elderly and young subjects. As data for young subjects, the results obtained from “A clinical pharmacological (Phase 1) study of APTA-2217 in healthy male volunteers (single oral dose)” (Study protocol No.: APTA-2217-HP-01) were used.

For the analysis of differences of pharmacokinetic parameters between doses, t test was performed after logarithmic transformation and point estimates and 95% confidence intervals for the ratios of the parameters between doses were constructed. For the comparison with non-elderly, two-way ANOVA was performed after logarithmic transformation and point estimates and 90% confidence intervals for the ratios of the parameters of elderly to non-elderly were constructed.

(2) Metabolic activity index

The ratio ($X_{6\ beta}/X_{col}$) of cumulative urinary excretion amount of 6beta-hydroxycortisol ($X_{6\ beta}$) to that of cortisol (X_{col}) up to 24 hours after administration of the study medication or placebo was calculated. The cortisol AUC (AUCcol) from time 0 to 24 hours after administration was determined, and the metabolic clearance (CLm) of cortisol to 6β-hydroxycortisol was calculated using the following formula.

$CLm = X_{6\beta}/AUCcol$

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

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Statistical methods (continued):

2) Safety

The incidence of all adverse events and those related to the investigational drug that occurred during the period from administration of study medication to hospital discharge was calculated for each dose (250 mcg, 500 mcg and placebo), and the number of individual events was presented.

For quantitative parameters of clinical laboratory tests, the mean and standard deviation (SD) were calculated by each dose 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 the shift from pre-dose to post-dose data (pre-dose > post-dose, pre-dose = post-dose, and pre-dose < post-dose) were presented by each dose at each time point.

For blood pressure (systolic and diastolic levels), pulse rate and body temperature, the mean and SD were calculated by each dose at each time point.

For 12-lead ECG data (HR, QRS, QT, QTc, and PR) at resting conditions, the mean and SD were presented by each dose at each time point. Also, the mean and standard error (SE) for the difference between values on Day –1 and Day 1 matched for time points were calculated and compared with a paired t test. The mean and SE for the difference between pre-dose and post-dose measurements obtained up to 168 hours after administration (every 24 hours) were also calculated by each dose and compared with a paired t test.

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

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Drug Substance: APTA-2217 (Roflumilast)		

Summary – Conclusions:
Pharmacokinetic results:

	Roflumilast		Roflumilast N-oxide	
Dose	250 mcg	500 mcg	250 mcg	500 mcg
$AUC_{(0\text{-inf.})}$ [mcg·h/L]	33.4 (23.9, 46.8)	60.4 (49.2, 74.1)	376.4 (277.9, 509.7)	709.3 (599.2, 839.7)
C_{max} [mcg/L]	4.708 (3.278, 6.763)	6.177 (4.478, 8.522)	6.188 (5.121, 7.477)	12.393 (10.801, 14.220)
T_{max} [h]	0.50 (0.50, 3.00)	0.50 (0.50, 3.00)	4.00 (3.00, 24.00)	4.00 (4.00, 24.00)
$t_{1/2}$ [h]	33.19 (19.16, 57.49)	29.34 (24.05, 35.80)	32.90 (23.60, 45.88)	32.19 (27.21, 38.08)
CLt or CLmet [L/h]	7.48 (5.35, 10.46)	8.27 (6.74, 10.15)	0.69 (0.51, 0.93)	0.73 (0.62, 0.87)
Vd/F [L]	357.95 (238.69, 536.80)	350.23 (281.49, 435.75)	32.78 (26.35, 40.77)	34.04 (27.83, 41.62)

Geometric mean (68% range); Median (min, max) for T_{max}
250 mcg: 9 subjects, 500 mcg: 9 subjects

1) After administration of APTA-2217, plasma concentrations of roflumilast was elevated rapidly and showing a biphasic elimination profile. Plasma concentrations of roflumilast N-oxide were elevated more moderately than roflumilast, peaking at 4 h after administration for both doses of 250 and 500 mcg. Those concentrations remained relatively constant up to 24 h after administration and subsequently showed a monophasic elimination profile.
2) Significant differences were noted in the $AUC_{(0\text{-inf})}$ of roflumilast, and $AUC_{(0\text{-inf})}$ and C_{max} of roflumilast N-oxide between the doses, and 95% confidence interval of the inter-dose ratio (500/250 mcg) for each parameter included the dose ratio of 2; however, no significant difference was found in the C_{max} of roflumilast between the doses. There were no significant differences in $t_{1/2}$, CLt, CLmet or Vd/F for either roflumilast or roflumilast N-oxide between the doses.
3) Compared with young subjects (data from study APTA-2217-HP-01), the $AUC_{(0\text{-inf})}$ and $t_{1/2}$ were higher, and CLt and CLmet were lower in elderly subjects for both roflumilast and roflumilast N-oxide. No difference was noted in C_{max}, and no obvious difference was found in Vd/F.

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Drug Substance: APTA-2217 (Roflumilast)		

Summary – Conclusions:
Pharmacokinetic results: (continued)

The ratio of pharmacokinetic parameters between ages

Pharmacokinetic parameter		Roflumilast	Roflumilast N-oxide
$AUC_{(0\text{-inf})}$		1.626 (1.378, 1.918)	1.558 (1.341, 1.809)
C_{max}		1.012 (0.857, 1.194)	1.083 (0.989, 1.187)
$t_{1/2}$	250 mcg	3.386 (2.556, 4.484)	1.568 (1.354, 1.817)
	500 mcg	2.012 (1.519, 2.665)	
CLt or CLmet		0.615 (0.521, 0.726)	0.642 (0.552, 0.746)
Vd/F	250 mcg	2.023 (1.623, 2.522)	1.007 (0.905, 1.120)
	500 mcg	1.275 (1.023, 1.590)	

The point estimate of the ratio (95% confidence interval)
Elderly subjects (250 mcg: 9 subjects and 500 mcg: 9 subjects)
Non-elderly subjects (250 mcg: 9 subjects and 500 mcg: 9 subjects)

4) After administration of APTA-2217 250 and 500 mcg and placebo, the X_{6beta}/X_{col} ratio (geometric means) was 9.9 (7.3, 13.6), 7.4 (4.9, 11.0) and 7.0 (4.7, 10.3), respectively, and CLm of cortisol was 0.081 (0.062, 0.104), 0.074 (0.041, 0.132) and 0.059 (0.047, 0.075) L/h, respectively. No marked differences were noted in any parameters between the doses or between placebo and the active drug.

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Drug Substance: APTA-2217 (Roflumilast)		

Summary – Conclusions (continued):
Safety results:

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

Dose	250mcg (GroupA)	500mcg (GroupB)	Placebo (A+B)
Number of subjects included in the safety evaluation	9	9	6
Number of subjects reported at least one AE (%)	2 (22.2)	0 (0.0)	2 (33.3)
Number of AEs	2	0	3
Gastrointestinal disorders			
Constipation			1* (16.7)
Loose stools	1* (11.1)		
Haematology investigations (include blood groups)			
White blood cell count decreased	1 (11.1)		
Renal and urinary tract investigations and urinalyses			
Urinary sediment present			1* (16.7)
Urinary occult blood positive			1* (16.7)

* Adverse events suspected to be causally related to the investigational drug by investigator (Definitely related or Probably (likely) related or Possibly (unlikely) related)

1) During the period from the administration of the investigational drug to hospital discharge, 2 of 9 subjects (22.2%) receiving 250 mcg of APTA-2217 experienced 2 adverse events, each 1 event of “loose stools” and “white blood cell count decreased.” No adverse events occurred after administration of APTA-2217 500 mcg. After administration of placebo, 2 of 6 subjects (33.3%) developed 3 adverse events (“loose stools”, “urinary sediment present,” and “urinary occult blood positive”).
2) The incidence of adverse events suspected to be causally related to the investigational drug (from the administration of the investigational drug to hospital discharge) was 1 event in 1 subject (11.1%) after administration of APTA-2217 250 mcg, no adverse events after administration of APTA-2217 500 mcg, and 3 events in 2 subjects (33.3%) after administration of placebo.

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Summary – Conclusions:
Safety results (continued):

3) There was only 1 adverse event related to the investigational drug, "loose stools" that occurred after administration of APTA-2217 250 mcg. It was mild in intensity and resolved without any treatment.
4) During the period after hospital discharge, 1 of 9 subjects (11.1%) receiving APTA-2217 at 250 mcg developed 1 event ("total bilirubin increased"), and 1 of 6 subjects (16.7%) receiving placebo experienced 2 events ("GPT increased" and "GGTP increase"). The causal relationship of all the events to the investigational drug was assessed as "unrelated".
5) There were no deaths, other serious adverse events or other significant adverse events in this study.
6) For hematology, blood coagulation and blood chemistry, significant increases or decreases from the pre-dose levels were occasionally noted in some test parameters after administration of APTA-2217 at both 250 and 500 mcg; however, all of such changes were slight and not considered to be of clinical concern.
7) There were subjects who presented a shift from "-" to "±" for occult blood in urine after administration of APTA-2217 at both 250 and 500 mcg. A similar change was noted after administration of placebo.
8) No clinically significant findings were found at any dose level in vital signs (blood pressure, pulse rate, and body temperature).
9) For 12-lead ECG parameters at resting conditions, statistically significant increases or decreases ($P<0.05$) were occasionally noted in comparisons between values on Day –1 and Day 1 (intra-day variation) and between pre-dose and up to 168 hours (inter-day variation) after administration of APTA-2217. A similar change was observed after administration of placebo.

Conclusion:

Compared with young subjects, the $AUC_{(0\text{-inf.})}$ and $t_{1/2}$ were higher, and CLt and CLmet were lower in elderly subjects for both roflumilast and roflumilast N-oxide. These results were consistent with those obtained from overseas clinical studies. There was only 1 adverse event related to APTA-2217, mild "loose stools" that developed after administration of APTA-2217 at 250 mcg. It was thus concluded that the safety and tolerability of APTA-2217 were no concern in healthy elderly males.