2. Synopsis

Sponsor: Mitsubishi Tanabe Pharma Corporation	
Product name: Undecided	
Compound: APTA-2217 (Roflumilast)	

Title of Study:

A verification study of APTA-2217 in patients with chronic obstructive pulmonary disease (A placebo-controlled double-blind, parallel group study)

Investigators: see 16.1.4 (a total of 199 investigators)

Study centres: see 16.1.4 (a total of 183 centers, 184 departments)

Publication: Not applicable

Studied period:	Phase of development:
20 months (19 January 2005 to 11 September 2006)	II/III

Objectives:

- to investigate the efficacy and safety after 24-week treatment of APTA-2217 at doses of 500 mcg and 250 mcg in patients with COPD using placebo as a control
- to investigate the pharmacokinetics of roflumilast and roflumilast N-oxide after repeated administration of APTA-2217 at doses of 500 mcg and 250 mcg

Methodology:

Multi-center, randomized, placebo-controlled, double-blind, parallel-group study

Number of patients:

Planed Number.: 570 (190 subjects per group)

Registered at baseline: 706

Randomized: 600 (500 mcg: 204, 250 mcg: 205, Placebo: 191)

Full analysis set: 600, Per protocol set: 522

Safety analysis set for the screening period: 703

Safety analysis set for the treatment period: 600

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Diagnosis and main criteria for inclusion:

- FEV_1/FVC ratio (post-bronchodilator) <70%
- FEV_1 (post-bronchodilator) ≥30% and < 80% predicted
- FEV_1 increase of <12% and/or <0.2 L after receiving 200 mcg salbutamol
- In a stable clinical state with no change in the contents of COPD therapy within 4 weeks before the registration day (including the registration day)
- Current smoker or ex-smoker (smoking cessation at least one year ago) with a smoking history of at least 10 pack years
- At least 40 years of age when written consent is obtained.

Test product

APTA-2217 tablets 500 mcg: One tablet contains 500 mcg of APTA-2217.

APTA-2217 tablets 250 mcg: One tablet contains 250 mcg of APTA-2217.

Reference product

APTA-2217 placebo tablets: Tablets indistinguishable from APTA-2217 tablets 500 mcg and 250 mcg.

Dose and mode of administration

Screening period: APTA-2217 placebo tablets, one tablet once daily per os after breakfast.

Treatment period: APTA-2217 tablets 500 mcg, 250 mcg or placebo tablet, one tablet once daily per os after breakfast.

Batch Number

APTA-2217 placebo tablets (screening period): 40114.

APTA-2217 tablets 500 mcg (treatment period): 40117.

APTA-2217 tablets 250 mcg (treatment period): 40116.

APTA-2217 placebo tablets (treatment period): 40115.

Duration of treatment:

Screening period 4 weeks, treatment period 24 weeks.

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Criteria for evaluation

Efficacy:

(1) Primary endpoint:

Pulmonary function test: Mean change from baseline to the last evaluation visit in

- post-bronchodilator: FEV_1

(2) Secondary endpoints:

Pulmonary function test: Mean change from baseline to each evaluation visit in

- pre-bronchodilator: FEV_1, FVC, MMEF, $\dot{V}_{50}/\dot{V}_{25}$, PEF
- post-bronchodilator: FEV_1 (excluding the last evaluation visit), FVC, MMEF, $\dot{V}_{50}/\dot{V}_{25}$, PEF

2) Evaluation of the diary: Mean change from baseline to weekly mean at each evaluation week in

- COPD symptom score: cough score, sputum score, dyspnea score, and score sum
- The puff number of the short-acting inhaled β_2-stimulator (Sultanol® Inhaler)

3) Evaluation of QOL: Mean change from baseline to each evaluation visit in

- SGRQ: symptoms score, activity score, impacts score, and total score

4) COPD exacerbation

- Number of day to the first COPD exacerbation
- Number of the COPD exacerbations

Safety:

(1) Incidence of adverse events

(2) Incidence of adverse events for which relationship with the study product cannot be excluded

Pharmacokinetics:

Plasma concentrations (roflumilast, roflumilast N-oxide)

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Statistical methods:

Efficacy

(1) Primary endpoint

For the change from the base value in FEV_1 (post-bronchodilator) as the primary endpoint, assuming that the means in the drug groups satisfy $\mu_{Placebo} \leq \mu_{250\ mcg} \leq \mu_{500\ mcg}$, a comparison between placebo and each dosage of APTA-2217 was made using the closed testing procedure. The comparison in each step was made by the analysis of covariance using a model including the changes in FEV_1 as the dependent variable and the followings as the factors and covariates: treatment group, baseline values, smoking status, gender, and age.

(2) Secondary endpoint

1) Pulmonary function tests: Regarding the changes from the baseline at each evaluation visit after the allocation, comparisons between the treatment groups were conducted by the analysis of covariance using the same statistical model to primary endpoint.

2) COPD symptom score: Regarding the changes in the weekly means of each score at each week after the allocation, comparisons between the treatment groups were made using the Willcoxon rank sum test.

3) The puff number of the short-acting inhaled β_2-stimulator: Regarding the changes in the weekly means of score at each week after the allocation, comparisons between the treatment groups were made using the Willcoxon rank sum test.

4) SGRQ: Regarding the changes from the baseline at each evaluation visit after the allocation, comparisons between the treatment groups were conducted by the analysis of covariance using the similar statistical model to primary endpoint.

5) COPD exacerbations: Regarding the number of COPD exacerbation per 24 weeks, comparisons between the treatment groups were conducted using the Willcoxon rank sum test. For the initial COPD exacerbation as the event, the cumulative exacerbation-free rate was calculated using the Kaplan-Meier method. Regarding the time to the initial COPD exacerbation from the allocation day, comparisons between the treatment groups were conducted using the logrank test.

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Safety

Adverse events and adverse events with a suspected causal relationship to the study drug will be tabulated separately for each dosage and the incidence for each dosage was calculated.

Pharmacokinetics

After treatment at the respective doses, plasma concentrations of roflumilast and its active metabolite roflumilast N-oxide were measured, and based on the obtained results, the pharmacokinetic analysis will be conducted by the technique of population pharmacokinetics. The results of pharmacokinetic analysis are reported in a separate report.

Summary

Efficacy results:

(1) Primary endpoint

Between-treatment comparisons in post-bronchodilator FEV_1 for the endpoint analyses revealed a statistically significant difference between 500 mcg and placebo groups and between 250 mcg and placebo groups (ANCOVA, difference in LSmean: 0.078 L (500 mcg–placebo), 0.074 L (250 mcg–placebo), $p<.001$ for both). The repeated measurement analysis and PPS analysis performed as robustness analyses also produced results similar to those in the FAS.

(2) Secondary endpoint

1) Pulmonary function test

Between-treatment comparisons by ANCOVA in pulmonary function measurements at all evaluation visits from the baseline were performed (excluding post-bronchodilator FEV_1 at the last evaluation visit, as this was already evaluated as primary endpoint). Statistically significant differences in favor of active drug groups were observed for comparisons of 500 mcg group with placebo group and 250 mcg group with placebo group in changes in pulmonary function measurements at the last evaluation from the baseline, except for post-bronchodilator $\dot{V}_{50}/\dot{V}_{25}$ Although post-bronchodilator $\dot{V}_{50}/\dot{V}_{25}$ did not show statistically significant deference in favor of active drug group, the actual values of post-bronchodilator $\dot{V}_{50}/\dot{V}_{25}$ did not show worsening trend throughout the study in the active drug groups, which was seen in placebo group.

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2) COPD symptom score

Weekly means of dyspnea and cough scores and score sums showed no marked change throughout the study in all groups. A statistically significant difference in favor of placebo was observed for comparisons of 500 mcg group with placebo group in changes in sputum score from the baseline to last evaluation week (Wilcoxon rank sum test, p=0.029). For other scores, no statistically significant differences between any pair of the groups were observed.

3) Puff number of short-acting inhaled β_2-stimulator

Weekly means of puff numbers of short-acting inhaled β_2-stimulator showed no marked change throughout the study in all groups. Statistically significant between-treatment differences were not observed between any pair of the groups for changes in the numbers from the baseline.

4) SGRQ score

The LSmean difference of changes in impacts score at last evaluation visit from baseline was 2.46±1.18 between the 500 mcg and placebo groups, showing statistically significant difference in favor of placebo (ANCOVA, p=0.037). No statistically significant difference was seen in the scores between 250 mcg and placebo groups. No statistically significant differences were observed between any pair of the groups in the LSmean differences of changes in symptoms score, activity score, or total score at last evaluation visit from baseline; however, actual values of these scores in 250 mcg groups were superior to those in 500 mcg and placebo groups.

5) COPD exacerbations

The number of COPD exacerbations did not differ significantly between any pair of the groups. For “moderate or severe exacerbation” and “moderate exacerbation”, the number of days to the first COPD exacerbation was significantly longer in 500 mcg group than in placebo group (logrank test, p=0.040 for both).

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Safety results:

The total incidence of adverse events reported during the treatment period was 91.7% in 500 mcg group, 86.3% in 250 mcg group, and 84.3% in placebo group. A statistically significant difference was found in the total incidence between 500 mcg and placebo groups (Fisher's exact test, p=0.029). Adverse events which occurred 4% of patients or more in either active drug group and of which incidence was higher in the active drug groups than in placebo group were diarrhoea NOS, anorexia, weight decreased, loose stools, insomnia, headache and dizziness. Most adverse events reported during the treatment period were classified as mild or moderate in all groups.

The incidence of drug-related adverse events reported during the treatment period was 57.8% in 500 mcg group, 37.1% in 250 mcg group, and 27.2% in placebo group. The incidence of adverse events resulting in study discontinuation during the treatment period was 23.5% in 500 mcg group, 13.2% in 250 mcg group, and 6.3% in placebo group. For both, the incidence was higher in 500 mcg, 250 mcg, and placebo groups in this order, and the gastrointestinal symptoms were the most common events.

The incidence of serious adverse events reported during the treatment period did not differ among the groups (9.8% in 500 mcg group, 9.8% in 250 mcg group, and 6.3% in placebo group). Throughout the study, one patient died of cardiopulmonary arrest during the screening period. No death occurred during the treatment period.

No noteworthy changes were detected during the treatment period in laboratory tests, vital signs measurements, or 12-lead ECG findings in any group.

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Conclusion:

This study demonstrated the efficacy of APTA-2217 at doses of 500 mcg and 250 mcg once daily for 24 weeks based on post-bronchodilator FEV_1 of patients with moderate or severe COPD. APTA-2217 was shown to improve pulmonary function.

On the other hand, the study did not show the efficacy of APTA-2217 for most secondary endpoints based on COPD symptoms scores, the puff number of short-acting inhaled β_2-stimulator, SGRQ, and COPD exacerbations.

The incidence of adverse events was higher for APTA-2217 than for placebo. Common adverse events were gastrointestinal symptoms. The incidence of individual adverse events tended to be higher in 500 mcg group than in 250 mcg group. No meaningful changes were detected in laboratory tests, vital signs measurements, or 12-lead ECG findings.

These results indicate that APTA-2217 can improve the pulmonary function of COPD patients at doses of 500mcg and 250 mcg once daily. For the safety, 250 mcg of APTA-2217 was shown to be more tolerable than 500 mcg of the study drug.