2. Synopsis

Sponsor: Mitsubishi Tanabe Pharma Corporation	
Product name: Undecided	
Compound: APTA-2217 (Roflumilast)	
Title of Study: A long-term study of APTA-2217 in patients with chronic obstructive pulmonary disease	
Investigators: see 16.1.4 (a total of 72 investigators)	
Study centres: see 16.1.4 (a total of 70 centers, 70 departments)	
Publication: Not applicable	
Studied period: 18 months (13 July 2005 to 16 January 2007)	Phase of development: III
To investigate the safety after 52-week treatment of APTA-2217 at doses of 500 mcg and 250 mcg in patients with COPD. The efficacy will be investigated secondarily.	
Methodology: An extension study of APTA-2217-06 study (Multi-center, placebo-controlled, randomized, double-blind, parallel-group study). After the key-open of APTA-2217-06 study, administration to placebo group would be terminated.	
Number of patients: Planned Number: 150 Enrolled: 152 (500 mcg: 40, 250 mcg: 54, Placebo: 58) Full analysis set: 152 Safety analysis set: 152	
Diagnosis and main criteria for inclusion: Patients with COPD who have completed the study APTA-2217-06 24-week evaluation and have submitted the informed consent in writing.	

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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

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

Batch Number

APTA-2217 tablets 500 mcg: 50041.

APTA-2217 tablets 250 mcg: 50040.

APTA-2217 placebo tablets: 50042.

Duration of treatment:

52 weeks, APTA-2217-06 study included (28 weeks for APTA-2217-08 study)

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Criteria for evaluation

Safety:

Incidence of adverse events and incidence of adverse events for which relationship with the study product cannot be excluded.

Efficacy:

(1) Pulmonary function test: Mean change from baseline of APTA-2217-06 study to each evaluation visit.
- post-bronchodilator FEV_1, FVC, MMEF, $\dot{V}_{50}/\dot{V}_{25}$ and PEF

(2) Diary: Mean change from baseline of APTA-2217-06 study to weekly mean at each evaluation week.
- COPD symptom score: cough score, sputum score, dyspnea score, and score sum
- The puff number of the short-acting inhaled β_2-stimulator

(3) QOL: Mean change from baseline of APTA-2217-06 study to each evaluation visit.
- 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

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Statistical methods:

Safety

Adverse events that occurred from treatment period of ATPA-2217-06 study were tabulated separately for each dosage and the incidence rate for each dosage was calculated. The same analysis was performed for adverse events with a suspected causal relationship to the study drug.

Efficacy

(1) Pulmonary function tests

With respect to each parameter at each evaluation time point, mean values, standard deviation (SD), mean of the amount of change of each parameter from initial treatment period of APTA-2217-06 and standard error (SE) were calculated separately for each dosage.

(2) Diary

With respect to the changes in the weekly means of COPD symptom score and the puff number of the short-acting inhaled β_2-stimulator at each week, mean values, SD, mean of the amount of change of each parameter from initial treatment period of APTA-2217-06 and SE were calculated separately for each dosage.

(3) SGRQ

With respect to each score at each evaluation time point, mean values, SD, mean of the amount of change of each parameter from initial treatment period of APTA-2217-06 and SE were calculated separately for each dosage.

(4) COPD exacerbations

Cumulative exacerbation rate after the allocation day of APTA-2217-06 study was calculated using the Kaplan-Meier method based on the FAS for APTA-2217-06 study. The summary statistics for the number of COPD exacerbation per 52 weeks were presented by treatment group.

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Summary

This study was intended to evaluate long term safety of APTA-2217 500 mcg and 250 mcg. Efficacy was evaluated secondary.

Efficacy results:

Pulmonary function test

Changes in pre- and post-bronchodilator values of FEV_1, FVC, MMEF, $\dot{V}_{50}/\dot{V}_{25}$ and PEF at each evaluation visit from T0 were evaluated. Both pre- and post-bronchodilator values of FEV_1 and FVC improved after allocation in the active drug groups, followed by natural decline of lung function. In the placebo group, the worsening of these values started after allocation. Both pre- and post-bronchodilator MMEF improved after allocation in all the treatment groups, but declined thereafter in the active drug groups. The values at T_{last} were similar to those obtained at T0. The pre- bronchodilator $\dot{V}_{50}/\dot{V}_{25}$ improved after allocation in the 250 mcg group, but showed a tendency to decline in other treatment groups. The post-bronchodilator $\dot{V}_{50}/\dot{V}_{25}$ showed a tendency to decline after allocation in the placebo group, but improved in the active drug groups. Both pre- and post-bronchodilator PEF showed a tendency to decline in all the treatment groups. The degree of decline was the smallest in the 250 mcg group, and was similar between the 500 mcg group and the placebo group.

COPD symptom score

The changes in dyspnea score, sputum score, cough score, and score sum from W0 to each evaluation visit were evaluated. In cough score and score sum, the degree of improvement was greater in the active drug groups. In other scores, there were no major differences among the treatment groups.

Puff number of short-acting inhaled β_2-stimulator

The changes in the weekly means of the puff number of short-acting inhaled β_2-stimulator from W0 to each evaluation visit were evaluated. The change from W0 to W_{last} was small, and there were no major differences among the treatment groups.

SGRQ score

The changes in symptoms score, activity score, impacts score, and total score from T0 to each evaluation visit were evaluated. In all the scores, the degree of improvement at T_{last} was the largest in the 250 mcg group.

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COPD exacerbation

The number of COPD exacerbations and the number of days to the first COPD exacerbation per 52 weeks were evaluated in the FAS of Study APTA-2217-06. The numbers seen in the long term part of the study should be cautiously interpreted due to the small sample size and event rates. In the number of COPD exacerbations per 52 weeks, the number of moderate or severe exacerbations was higher in the active drug groups than in the placebo group. In the number of days to the first COPD exacerbation, the mean number of days to moderate or severe COPD exacerbation was shorter in the active drug groups than in the placebo group.

Safety results:

The total incidence of adverse events reported during the treatment period (52 weeks, APTA-2217-06 study period included) was 97.5% (39/40 patients) in the 500 mcg group, 98.1% (53/54 patients) in the 250 mcg group, 96.6% (56/58 patients) in the placebo group. Adverse events that occurred at high incidences in the 500 or 250 mcg group were diarrhea NOS, loose stools, anorexia, headache, insomnia, glucose urine present and weight decreased. Most of these events (gastrointestinal symptoms, headache, insomnia and weight decreased) were the same as common adverse events already reported in foreign clinical studies and Study APTA-2217-06.

The incidence of drug-related adverse events reported during the treatment period was 55.0% (22/40 patients) in the 500 mcg group, 38.9% (21/54 patients) in the 250 mcg group, 37.9% (22/58 patients) in the placebo group, and was higher in the 500 mcg group than in the 250 mcg and placebo groups. Drug-related adverse events that occurred at high incidences in the 500 or 250 mcg group were diarrhea NOS, loose stools, weight decreased. These events were the same as common drug-related adverse events already reported in foreign clinical studies and Study APTA-2217-06.

Most adverse events were classified as mild or moderate in all groups. Among all adverse events reported during the treatment period, the incidence of those classified as severe was 5.0% (2/40 patients) in the 500 mcg group, 5.6% (3/54 patients) in the 250 mcg group, 5.2% (3/58 patients) in the placebo group. In the incidence of adverse events classified as severe, there were no differences among the treatment groups, and a causal relationship to the study drug was denied for any of these events.

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The incidence of adverse events that occurred during the extension study period (28 weeks, APTA-2217-08 study period) was 90.0% (36/40 patients) in the 500 mcg group, 92.6% (50/54 patients) in the 250 mcg group, 82.8% (48/58 patients) in the placebo group. Adverse events that occurred in at high incidences in the 500 mcg or 250 mcg group were nasopharyngitis, weight decreased, insomnia, and upper respiratory tract inflammation. The incidence of all these events was high also in the data tabulated for the entire treatment period, and therefore did not indicate an increase in the incidence due to the long-term use of APTA-2217.

Regarding diarrhea NOS or loose stools, nausea, weight decreased, anorexia or appetite decreased NOS, headache, insomnia, and dizziness, the number of days to the onset of these events was assessed by Kaplan-Meier method. As a result, the incidences of these adverse events were increased in dose-dependent manner and it was found that the number of patients with the first onset of diarrhea NOS or loose stools, nausea, headache, and dizziness in the early phase of the treatment with the study drug was the highest in the 500 mcg group, followed by the 250 mcg group and the placebo group in this order.

The incidence of serious adverse events reported during the treatment period was 27.5% (11/40 patients) in the 500 mcg group, 13.0% (7/54 patients) in the 250 mcg group, 10.3% (6/58 patients) in the placebo group. A causal relationship to the study drug was denied for most of these events.

As results of the between-treatment comparison of body weight (B0 and T_{last}) by paired t test, mean ± SD of the change in body weight were −3.4 ± 3.0 kg in the 500 mcg group, −1.7 ± 2.9 kg in the 250 mcg group, and −0.6 ± 2.3 kg in the placebo group, showing a dose-dependent decrease in body weight. Statistically significant decreases were observed in all the groups ($p=<0.001$, $p<0.001$, $p=0.048$, respectively).

Throughout the study, no noteworthy changes were detected in laboratory test data, vital signs measurements, or ECG findings in any treatment group.

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Conclusions:

In this study, the effects of APTA-2217 250 mcg or 500 mcg on pulmonary function measurements, evaluation of patient diary (evaluation of symptoms, puff number of short-acting inhaled β_2-stimulator), and SGRQ were evaluated in moderate to severe COPD patients. In pulmonary function measurements and SGRQ, an initial improvement followed by a decline was observed. The decline during the evaluation period of 52 weeks was considered to be attributable to the fact that a higher number subjects showing insufficient improvement in the active drug groups proceeded to the long-term study, and also attributable to the progressive nature of COPD. In the evaluation of patient diary, since the changes in the endpoints were small, no distinct efficacy of APTA-2217 was observed. Since this study was conducted in a limited sample size, further studies need to be conducted on the efficacy of long-term treatment with APTA-2217.

Regarding the long-term safety of APTA-2217, adverse events, such as headache, gastrointestinal symptoms, and weight decreased, have been reported frequently in the use of APTA-2217. The incidence of each adverse event tended to be higher in the 500 mcg group than in the 250 mcg group. However, this result matched the previous Japanese and foreign clinical study results, and long-term treatment did not alter the safety profile of APTA-2217.

These findings suggest that in these type of patients, regarding safety, once daily dosing of APTA-2217 for 52 weeks is more tolerable at 250 mcg than at 500 mcg. No conclusion can be drawn from this study concerning long term efficacy of APTA 2217.