## External Clinical Study Report No. 398/2008

Version (1.0)

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| Title | A verification study of APTA-2217 in adult patients with bronchial asthma (A placebo-controlled double-blind, parallel group study) |
| INN | Roflumilast |
| Nycomed Project No. | BY217 |
| Tanabe Study Protocol No. | APTA-2217-05 |
| Tanabe Study Report No. | APTA-2217-05 |
| Tanabe Version No. [1)] | 1.0 |

[1)] Please note that the Tanabe versioning system differs from that at Nycomed

**A verification study of APTA-2217 in adult patients with bronchial asthma**
**(A placebo-controlled double-blind, parallel group study)**

# Clinical Study Report

Sponsor
Mitsubishi Tanabe Pharma Corporation

Co-development Company
Nycomed GmbH

APTA-2217 is a drug licensed by Nycomed GmbH

Protocol No.: APTA-2217-05
Version: 1.0

# 1. Title page

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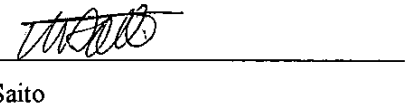
|---|---|
| Title | A verification study of APTA-2217 in adult patients with bronchial asthma (A placebo-controlled double-blind, parallel group study) |
| Compound | APTA-2217 (Roflumilast) |
| Indication studied | Bronchial asthma |
| Study design<br>Reference product<br>Studied period<br>Dose<br><br>Study population | · Multi-center, randomized, double-blind, parallel group study<br>· Placebo-controlled<br>· 24 weeks<br>· 500 mcg, 250 mcg, or placebo, one tablet once daily per os after breakfast<br>· Adult patients with bronchial asthma |
| Sponsor | Mitsubishi Tanabe Pharma Corporation |
| Protocol No. | APTA-2217-05 |
| Clinical phase | II/III |
| Study initiation date | 22 June 2004 |
| Date of early termination | Not applicable |
| Study completion date | 1 September 2006 |
| Name of sponsor's responsible medical officer | Prof. Mitsuru Adachi<br>Department of Internal Medicine I, Showa University Hospital |
| Person responsible for study/ Sponsor's contact person |  <br>Makoto Saito<br>General manager, Clinical research II department, Development division, Mitsubishi Tanabe Pharma Corporation<br>2-2-6 Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan<br>TEL : 03-3241-4737 FAX : 03-3241-4749 |
| Statement of GCP compliance | This study was conducted by following GCP (Ordinance No.28 of the Ministry of Health and Welfare dated March 27, 1997) and amendment GCP (Ordinance No.106 of the Ministry of Health, Labour and Welfare dated June 12, 2003). Related documents are stored at study sites or at sponsor based on GCP. |
| Version date | Dec 17 2008 |

## 2. Synopsis

<table>
<tr><td>Sponsor: Mitsubishi Tanabe Pharma Corporation</td><td rowspan="3"></td></tr>
<tr><td>Product name:<br>Undecided</td></tr>
<tr><td>Compound:<br>APTA-2217 (Roflumilast)</td></tr>
<tr><td colspan="2">Title of Study:<br>A verification study of APTA-2217 in adult patients with bronchial asthma (A placebo-controlled double-blind, parallel group study)</td></tr>
<tr><td colspan="2">Investigators: see 16.1.4 (a total of 161 investigators)</td></tr>
<tr><td colspan="2">Study centres: see 16.1.4 (a total of 145 centers, 146 departments)</td></tr>
<tr><td colspan="2">Publication: Not applicable</td></tr>
<tr><td>Studied period:<br>27 months (22 June 2004 to 1 September 2006)</td><td>Phase of development:<br>II/III</td></tr>
<tr><td colspan="2">Objectives:<br>· to investigate the efficacy and safety after 24-week treatment of APTA-2217 at doses of 500 mcg and 250 mcg in adult patients with bronchial asthma using placebo as a control<br>· to investigate the pharmacokinetics of roflumilast and roflumilast N-oxide after repeated administration of APTA-2217 at doses of 500 mcg and 250 mcg</td></tr>
<tr><td colspan="2">Methodology:<br>Multi-center, randomized, placebo-controlled, double-blind, parallel-group study</td></tr>
<tr><td colspan="2">Number of patients:<br>Planed Number.: 450 (150 subjects per group)<br>Registered at baseline: 993<br>Randomized: 472 (500 mcg: 153, 250 mcg: 165, Placebo: 154)<br>Full analysis set: 471, Per protocol set: 425<br>Safety analysis set for the screening period: 986<br>Safety analysis set for the treatment period: 472</td></tr>
</table>

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Diagnosis and main criteria for inclusion:

- %$FEV_1$ ranging between 60 and 80%
- $FEV_1$ increase of >12% and >0.2 L after receiving 200 mcg salbutamol
- Patients with no change in the contents of asthmatic therapy within 4 weeks before the registration day (including the registration day)
- Non-smokers or patients who quit smoking for at least 12 months
- At least 20 years and up to 70 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): 40011.

APTA-2217 tablets 500 mcg (treatment period): 40015.

APTA-2217 tablets 250 mcg (treatment period): 40014.

APTA-2217 placebo tablets (treatment period): 40012.

Duration of treatment:

Screening period 2-4 weeks, treatment period 24 weeks.

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Criteria for evaluation

Efficacy:

(1) Primary endpoint:

Pulmonary function test ($FEV_1$): Mean change from baseline to the last evaluation visit.

(2) Secondary endpoints:

1) Pulmonary function test ($FEV_1$ (excluding the final evaluation), FVC, $FEF_{25-75}$, and PEF): Mean change from baseline to each evaluation visit.
2) Diary (PEF, asthma symptoms, the puff number of short-acting inhaled $\beta_2$-stimulator): Mean change from baseline to weekly mean at each evaluation week.
3) QOL (AQLQ(S)): Mean change from baseline to each evaluation visit.
4) Severe asthma exacerbation: Number of days to the asthma exacerbation.

Safety:

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

Pharmacokinetics:

Plasma concentrations (roflumilast, roflumilast N-oxide). The results of pharmacokinetic analysis will be reported in a separate report.

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Statistical methods:

Efficacy

(1) Primary endpoint

For the change from the base value in $FEV_1$ 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 from baseline to the last evaluation visit in $FEV_1$ as the dependent variable and the following as the factors and covariates: treatment group, baseline $FEV_1$ values, gender, age and smoking history.

(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) Diary

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. For the change in the weekly mean of morning PEF and evening PEF, comparisons between the treatment groups were conducted by the analysis of covariance using the same statistical model to primary endpoint.

3) AQLQ(S)

Comparisons between the treatment groups were conducted by the analysis of covariance using the same statistical model to primary endpoint.

4) Severe asthma exacerbation

Regarding the time to the exacerbation from the randomized day, comparison between the treatment groups will be conducted using the Cox's proportional hazard model.

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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 will be reported in a separate report.

Summary

Efficacy results

(1) Primary endpoint

The changes in $FEV_1$ from allocation to the final evaluation were compared between treatment groups by analysis of covariance (ANCOVA), and the 500 mcg group showed significantly superior results to the placebo group (difference in LS mean: 0.086 L, p=0.011). There was no significant difference between the 250 mcg and placebo groups. Repeated measurement analysis performed to confirm robustness and analysis of the PPS showed the same results as those in the FAS.

(2) Secondary endpoints

1) Pulmonary function test

ANCOVA was performed for the changes in each pulmonary function test besides $FEV_1$ at each evaluation visit after allocation. At the time of the final evaluation, the 500 mcg group was significantly superior in FVC to the placebo and 250 mcg groups (500 mcg group – placebo group: difference in LS mean: 0.094 L, p=0.020; 500 mcg group - 250 mcg group: difference in LS mean: 0.080 L, p=0.043). For $FEF_{25-75}$, the 500 mcg group was significantly superior to the placebo group (difference in LS mean: 0.141 L/sec, p=0.018). While there were no significant differences in PEF between any of the groups, the degree of improvement in time-course changes was greater in the 500 mcg group than the 250 mcg and placebo groups.

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2) Asthmatic symptom score

The Wilcoxon rank sum test was performed for the asthmatic symptom score (daytime asthmatic symptom score, nighttime asthmatic symptom score, asthma summary symptom score) to compare the changes from allocation to the final evaluation between treatment groups. The 500 mcg and 250 mcg groups were significantly superior to the placebo group (daytime: p=0.014 and p=0.027, respectively; nighttime: p=0.038 and p=0.029, respectively; and summary symptom score: p=0.008 and p=0.020, respectively).

Symptom-free days (days when the daytime and nighttime asthmatic symptom scores are both 0) was compared between treatment groups by the Wilcoxon rank sum test, and the rates of symptom-free days in the 500 mcg, 250 mcg, and placebo groups were 61.69%, 63.49%, and 50.86%, respectively, so the 500 mcg and 250 mcg groups showed significantly superior results to the placebo group (p=0.014 and p=0.003, respectively).

3) Puff number of the short-acting inhaled $\beta_2$-stimulator

The changes in the puff number from the allocation to the final evaluation were compared between treatment groups by the Wilcoxon rank sum test, and the 500 mcg and 250 mcg groups were significantly superior to the placebo group (p=0.002 and p=0.005, respectively).

Rescue medication-free days (days when the puff number of the short-acting inhaled $\beta_2$-stimulator during the daytime and nighttime is 0) were compared between treatment groups by the Wilcoxon rank sum test. Rescue medication-free days in the 500 mcg, 250 mcg, and placebo groups were 72.83%, 71.06%, and 63.27%, respectively, and it was statistically significantly superior in the 500 mcg group compared to the placebo group (p=0.019).

4) Patient diary, PEF

For the weekly average of morning and evening PEF, the LS mean of the changes from allocation to the final evaluation was compared by ANCOVA, and there were no significant differences between any of the treatment groups. For the weekly average of diurnal changes in PEF, the LS mean of the changes from allocation to the final evaluation was compared by the Wilcoxon rank sum test, and there were no significant differences between any of the treatment groups.

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5) AQLQ score

ANCOVA was performed on the changes in the scores for symptoms, activity limitation, emotional function, exposure to environmental stimuli, and the overall score from allocation to the final evaluation, and there were no significant differences between treatment groups. On the other hand, the time course changes in all of the scores showed improving tendencies during the treatment period in all treatment groups, and the changes at the final evaluation showed numerically superior results in the active drug groups compared to the placebo group.

6) Severe asthma exacerbation

The number of days to severe asthma exacerbation was compared between treatment groups by the Cox proportional-hazards regression. The hazard ratios in the 500 mcg and 250 mcg groups to the placebo group were 0.35 and 0.48, respectively, and the 500 mcg and 250 mcg groups were significantly superior to the placebo group ($p<0.001$ and $p=0.008$, respectively).

Safety results

The incidence of adverse events during the treatment period was 82.4% in the 500 mcg group, 77.0% in the 250 mcg group, and 72.1% in the placebo group, respectively, so it was higher in the order of the 500 mcg, 250 mcg and placebo groups. Adverse events that were observed at ≥3% in 500 mcg group or in 250 mcg group and that had higher incidence in 500 mcg group than in 250 mcg and placebo group included headache, diarrhoea NOS, nausea, dizziness and anorexia. The severity of the adverse events was mostly mild or moderate in all of the treatment groups.

The incidence of adverse events for which relationship with the investigational product could not be excluded (drug-related adverse events) reported during the treatment period was 28.8% in the 500 mcg group, 22.4% in the 250 mcg group, and 11.0% in the placebo group. The incidence of adverse events resulting in study discontinuation during the treatment period was 13.7% in the 500 mcg group, 8.5% in the 250 mcg group, and 5.8% in the placebo group, showing a dose-dependent increase.

The incidence of serious adverse events was 3.9% in the 500 mcg group, 2.4% in the 250 mcg group, and 3.2% in the placebo group, which was similar in all the groups. There were no deaths during the treatment period.

There were no specific changes in laboratory tests, vital signs, or 12-lead ECG.

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Conclusion:

As the result of this study, the efficacy on $FEV_1$ when APTA-2217 500 mcg was administered once daily for 24 weeks in adult patients with moderate bronchial asthma was verified.

In addition, it was shown that APTA-2217 500 mcg improved pulmonary function test values (FVC, $FEF_{25-75}$) more than placebo. Also, for the asthmatic symptom score, puff number of the short-acting inhaled $\beta_2$-stimulator and days to severe asthma exacerbation as the secondary endpoints, it was shown that APTA-2217 possessed improvement effects compared to placebo. On the other hand, the effects of APTA-2217 on the morning and evening PEF and the AQLQ(S) could not be confirmed in this study.

The incidence of adverse events was higher in active drug groups than in the placebo group. Common adverse events were gastrointestinal symptoms, headache and dizziness. The incidence of adverse events resulting in discontinuation of the study was higher compared to placebo and there is a trend for dose-dependency. The rate of discontinuation of the study was the highest in patients receiving placebo, and the primary reason was worsening of the underlying disease. No clinically significant changes were detected in laboratory tests, vital sign measurements, or 12-lead ECG findings.

These results indicate that APTA-2217 can improve the pulmonary function of adult patients with bronchial asthma at a dose of 500 mcg once daily, and safety and tolerability were also shown.