External Clinical Study Report No. 404/2008

Version (1.0)

Title	A long-term study of APTA-2217 in adult patients with bronchial asthma
INN	Roflumilast
Nycomed Project No.	BY217
Tanabe Study Protocol No.	APTA-2217-07
Tanabe Study Report No.	APTA-2217-07
Tanabe Version No. [1)]	1.1

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

A long-term study of APTA-2217 in adult patients with bronchial asthma

Clinical Study Report

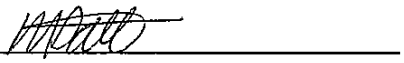
Sponsor
Mitsubishi Tanabe Pharma Corporation

Co-development Company
Nycomed GmbH

APTA-2217 is a drug licensed by Nycomed GmbH

Protocol No.: APTA-2217-07
Version: 1.1

1. Title page

Title	A long-term study of APTA-2217 in adult patients with bronchial asthma
Compound	APTA-2217 (Roflumilast)
Indication studied	Bronchial asthma
Study design	・ An extension study of "A verification study of APTA-2217 in adult patients with bronchial asthma (APTA-2217-05*)". Same dosage as APTA-2217-05 study was administrated for 28 weeks. Note; unblind after key-open of APTA-2217-05 study. * Multi-center, placebo-controlled, randomized, double-blind, parallel group study
Reference product	・ To maintain the blindness in Study APTA-2217-05, the patients were continuously treated with the same drug as that given in Study APTA-2217-05 (500 mcg, 250 mcg, or placebo); however, this study did not intend to confirm the inter-drug efficacy.
Studied period	・ 28 weeks (total 52 weeks, APTA-2217-05 study inluded)
Dose	・ 500 mcg, 250 mcg, or placebo, one tablet once daily per os after breakfast
Study population	・ Adult patients with bronchial asthma
Sponsor	Mitsubishi Tanabe Pharma Corporation
Protocol No.	APTA-2217-07
Clinical phase	Phase III
Study initiation date	20 Dec 2004
Date of early termination	Not applicable
Study completion date	11 Jan 2007
Name of sponsor's responsible medical officer	Prof. Mitsuru Adachi Department of Internal Medicine I, Showa University Hospital
Person responsible for study/ Sponsor's contact person	 Makoto Saito General manager, Clinical research II department, Development division, Mitsubishi Tanabe Pharma Corporation 2-2-6 Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan 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	Jan 16 2009

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 adult patients with bronchial asthma	
Investigators: see 16.1.4 (a total of 69 investigators)	
Study centres: see 16.1.4 (a total of 65 centers, 65 departments)	
Publication: Not applicable	
Studied period: 25 months (20 Dec 2004 to 1 Jan 2007)	Phase of development: III
Objectives: To investigate the safety after 52-week treatment of APTA-2217 at doses of 500 mcg and 250 mcg in adult patients with bronchial asthma. The efficacy will be investigated secondarily.	
Methodology: An extension study of APTA-2217-05 study (Multi-center, placebo-controlled, randomized, double-blind, parallel-group study). After the key-open of APTA-2217-05 study, administration to placebo group would be terminated.	
Number of patients: Planed Number.: 150 Enrolled: 151 (500 mcg: 44, 250 mcg: 59, Placebo: 48) Full analysis set: 151 Safety analysis set: 151	
Diagnosis and main criteria for inclusion: Patients with asthma disease who meet all of the following inclusion criteria and have submitted the informed consent in writing. (1) Patients who have completed the study APTA-2217-05 24-week evaluation (2) $\%FEV_1 \geq 60\%$ at 18-week and/or at 24-week measurements of APTA-2217-05.	

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

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: 40122.

APTA-2217 tablets 250 mcg: 40121.

APTA-2217 placebo tablets: 40120.

Duration of treatment:

52 weeks, APTA-2217-05 study included (28 weeks for APTA-2217-07 study)

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 (FEV_1, FVC, FEF_{25-75}, and PEF): Mean change from baseline of APTA-2217-05 study to each evaluation visit.

(2) Diary (PEF, asthma symptoms): Mean change from baseline of APTA-2217-05 study to weekly mean at each evaluation week.

(3) QOL (AQLQ(S)): Mean change from baseline of APTA-2217-05 study to each evaluation visit.

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

Statistical methods:

Safety

Adverse events that occurred from treatment period of ATPA-2217-05 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, summary statistics (mean, standard deviation (SD), standard error (SE), median, Min, Max) were presented separately for each dosage.

(2) Diary

With respect to the changes in the weekly means of PEF and each score at each week, summary statistics (mean, SD, SE, median, Min, Max) were presented separately for each dosage.

(3) AQLQ(S)

With respect to each score, summary statistics (mean, SD, SE, median, Min, Max) were presented separately for each dosage.

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

Summary

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

Efficacy results:

(1) Pulmonary function test

The changes in pulmonary function measurements such as FEV_1, FVC, FEF_{25-75}, and PEF from T0 to each evaluation visit were evaluated. The time course changes in all pulmonary function measurements showed improving tendencies in all the treatment groups, and all the measurements improved at T_{last} compared with T0. The 500 mcg group achieved the greatest improvements in all pulmonary function measurements at T_{last}.

(2) Patient diary (asthmatic symptom score)

The changes in the daytime and nighttime asthmatic symptom scores and the asthma summary symptom score from W0 to each evaluation visit were evaluated. The time course changes in all of the scores showed improving tendencies in all the treatment groups, and all the scores improved at W_{last} compared with W0. The 250 mcg group achieved the greatest improvements in all the scores at W_{last}.

(3) Patient diary (PEF)

The changes in the morning and evening PEF values, and diurnal changes of PEF from W0 to each evaluation visit were evaluated. The time course changes in all of the values showed improving tendencies in all the treatment groups, and the values improved at W_{last} compared with W0. The degree of improvement at W_{last} was greater for all the values in the 250 mcg group than in the 500 mcg group.

(4) AQLQ(S) score

The changes in AQLQ(S) scores such as scores of symptoms, activity limitation, emotional function, and exposure to environmental stimuli, and the overall score from T0 to each evaluation visit were evaluated. The time course changes in all of the scores showed improving tendencies in all the treatment groups, and all the scores improved at T_{last} compared with T0. The 250 mcg group achieved the greatest improvements in all the scores at T_{last}, except the score of exposure to environmental stimuli. For the score of exposure to environmental stimuli, the degree of improvement was greater in the order of the 500 mcg, 250 mcg, and placebo groups.

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

Safety results:

The total incidence of adverse events reported during the treatment period (52 weeks, APTA-2217-05 study period included) was 86.4% in the 500 mcg group, 88.1% in the 250 mcg group, and 91.7% in the placebo group. Among the adverse events that occurred at high incidences in the 500 mcg or 250 mcg group (≥8%), those that were more frequent in the active drug groups than in the placebo group were headache, diarrhea NOS and loose stools. Adverse events that occurred in at least 3% of patients in both active drug groups, and were more frequent than in the placebo group were glucose urine present (500 mcg group: 4.5%, 250 mcg group: 5.1%, placebo group 0.0%) and weight decreased (500 mcg group: 4.5%, 250 mcg group: 5.1%, placebo group: 0.0%). Most adverse events were classified as mild or moderate in all groups.

The incidence of adverse events resulting in study discontinuation during the treatment period was 4.5% in the 500 mcg group, 3.4% in the 250 mcg group, and 0.0% in the placebo group.

The incidence of drug-related adverse events during the treatment period was 31.8% in the 500 mcg group, 39.0% in the 250 mcg group, and 14.6% in the placebo group, and higher in the active drug groups than in the placebo group. Drug-related adverse events that occurred in at least 8% of patients in the 500 mcg or 250 mcg group, and were more frequent than in the placebo group were loose stools. Drug-related adverse events that occurred in at least 3% of patients in both active drug groups, and were more frequent than in the placebo group were weight decreased.

Among all adverse events reported during the treatment period, the incidence of adverse events that occurred during the extension period (28 weeks, APTA-2217-07 study period) was 65.9% in the 500 mcg group, 76.3% in the 250 mcg group, and 75.0% in the placebo group, and comparable among the treatment groups. There were no adverse events that occurred in at least 8% of patients in the 500 mcg or 250 mcg group, or were more frequent than in the placebo group in extension study. There were also no adverse events that resulted in increased incidences associated with long-term treatment with APTA-2217.

As results of the assessment of headache, diarrhea NOS/loose stools, and nausea in terms of the number of days to onset by Kaplan-Meier analysis, the number of days to onset was longer for all of these events in the order of the placebo, 250 mcg, and 500 mcg group.

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

The incidence of serious adverse events reported during the treatment period was 4.5% (2 case) in the 500 mcg group, 0.0% in the 250 mcg group, 0.0% in the placebo group. All serious adverse events had resolved at the outcome assessment, and were assessed to be not related to the investigational product.

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

Conclusions:

The results of this study suggested that APTA-2217 given at a dose of 500 mcg or 250 mcg could improve pulmonary function measurements, patient diary-based assessments (asthmatic symptom scores and PEF), and AQLQ(S) in adult patients with moderate bronchial asthma, and further maintain the improvements over a 52-week period.

As for the safety of long-term treatment with APTA-2217, adverse events such as headache and gastrointestinal symptoms were reported at high frequencies; however, this result matched the Japanese and foreign clinical study results and long-term treatment did not alter the safety profile of APTA-2217.

The above results suggest that APTA-2217 given at 500 mcg or 250 mcg once daily can improve the pulmonary function, and maintain the improvement over a long period of time in adult patients with bronchial asthma. The results also showed that APTA-2217 is safe and well tolerated in long-term treatment.