Janssen Pharmaceutical K.K *

Abbreviated Clinical Study Report

A Prospective, Multicenter, Open-label, Single Arm, Phase III Study to Assess the Efficacy and Safety of Macitentan (ACT-064992) in Subjects With Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Protocol AC-055E301; Phase 3

ACT-064992 (Macitentan)

* This report was created by Janssen Pharmaceutical K.K while the study was conducted by Actelion Pharmaceuticals Japan Ltd. The term "sponsor" is used throughout the protocol to represent Actelion Pharmaceuticals Japan Ltd and/or Janssen Pharmaceutical K.K.

NCT Number: NCT03809650

PRINCIPAL INVESTIGATOR: Takeshi Ogo, MD, PhD - Division of Pulmonary Circulation, Department of Cardiovascular Medicine, Department of Advanced Medicine for Pulmonary Hypertension, National Cerebral and Cardiovascular Center, PPD ; Japan

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Tadahiro Fujino, MD, PhD

DATE STUDY INITIATED: 13 May 2019 (Date first subject signed informed consent)

DATE STUDY COMPLETED: 30 March 2020 (Date of last observation for last subject recorded as part of the database)

Status: Approved
Date: 13 August 2020
Prepared by: Janssen Pharmaceutical K.K
EDMS number: EDMS-RIM-46355, 1.0

GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

SYNOPSIS

Name of Sponsor/Company	Actelion Pharmaceuticals Japan Ltd*
Name of Investigational Product	ACT-064992 (Macitentan)

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Protocol No.: AC-055E301

Title of Study: A Prospective, Multicenter, Open-label, Single Arm, Phase III Study to Assess the Efficacy and Safety of Macitentan (ACT-064992) in Subjects With Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

NCT No.: NCT03809650

Principal Investigator: Takeshi Ogo, MD, PhD - Division of Pulmonary Circulation, Department of Cardiovascular Medicine, Department of Advanced Medicine for Pulmonary Hypertension, National Cerebral and Cardiovascular Center, PPD ; Japan.

Study Centers: 32 sites in Japan

Publication (Reference): None

Study Period: 13 May 2019 (Date first subject signed informed consent) to 30 March 2020 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 3

Objectives:

Primary Objective:

The primary objective was to evaluate the change ratio of pulmonary vascular resistance (PVR) at rest from baseline at Week 16 administration of macitentan in subjects with chronic thromboembolic pulmonary hypertension (CTEPH) who were not indicated for pulmonary endarterectomy (PEA) and/or subjects who had postoperative persistent or recurrent pulmonary hypertension (PH) after PEA and/or balloon pulmonary angioplasty (BPA).

Secondary Objectives:

The secondary objectives were as follows:

- To evaluate the change from baseline to Week 16 of administration in the following items:
  - PVR at rest
  - Pulmonary vascular resistance index (PVRI) at rest
- To evaluate change from baseline to Week 24 of administration in the following items:
  - Six-minute walk distance (6MWD)
  - Borg dyspnea index

  - World Health Organization functional class (WHO FC)

- To evaluate the safety of macitentan

Exploratory Objectives:

The exploratory objectives were as follows:

- To evaluate change from baseline to Week 16 in pulmonary hemodynamic parameters other than PVR
- To evaluate changes from baseline to each observation time point from baseline to Week 24 in 6MWD, WHO FC, and N-terminal pro-B type natriuretic peptide (NT-proBNP) concentration
- To evaluate changes from baseline to each observation time point every 24 weeks during the extension period and at the end/discontinuation of study treatment in 6MWD, WHO FC, and NT-proBNP concentration
- Time to first PH-related disease progression during the efficacy evaluation period until the end of treatment (EOT) (during the efficacy evaluation period plus safety follow-up period for death), defined as:
  - All causes death
  - Lung transplantation
  - Hospitalization due to PH-related disease progression
  - Initiation of intravenous or subcutaneous prostanoid therapy due to PH-related disease progression
  - Other PH-related disease progression, defined by the combined occurrence of all of the following 3 events in a subject:
    - When a decrease in 6MWD of at least 15% from baseline was observed at 2 consecutive visits
    - The WHO FC had deteriorated, or the investigator judged that there was no chance for improvement in a subject whose WHO FC was IV at the time of starting study agent administration
    - Need for additional PH therapy due to PH deterioration

Methodology:

This was a prospective, multicenter, open-label, single arm, Phase 3 study to evaluate the efficacy and safety of macitentan in subjects with CTEPH.

The study included the following consecutive periods:

- Screening period: within 30 days before the first macitentan administration
- Efficacy evaluation period: 24 weeks
- Extension period: from 1 day after the efficacy evaluation period until obtainment of approval or discontinuation of the development
- Safety follow-up period: up to 30 days after the EOT. If macitentan was switched to a commercially available form of macitentan, until 1 day after the last dose of macitentan.

Any subject who prematurely discontinued macitentan was required to undergo an assessment at the time of macitentan discontinuation as soon as possible but no later than 7 days after the last dose of macitentan. The safety follow-up period was up to 30 days after the last dose of macitentan administration. The end of

study per subject was defined as the last observation day of the study. The number of days for which a subject was considered to participate in the study was until the obtainment of marketing approval or discontinuation of the development of macitentan. However, if macitentan was switched to a commercially available form of macitentan in a subject, the number of days was to be until the day following the last dose of macitentan.

Number of Subjects (planned and analyzed):

Planned: A total of 27 subjects were planned to be enrolled in the study.

Analyzed: A total of 9 subjects were enrolled and treated macitentan 10 mg. All enrolled subjects prematurely discontinued macitentan due to the AC-055E201 (MERIT-1) study circumstances and not due to any safety concerns. A total of 9 subjects were included in the efficacy and safety analyses.

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria	**Description**
Age and sex	Japanese man or women, between 18 and 89 years of age
Subjects diagnosed with CTEPH meeting any of the criteria	Subjects who had not undergone BPA and for whom the investigator determined not to implement PEA at the time of the acquisition of informed consent due to the organized thrombosis localized in the peripheral regions, high risk (complications, old age, etc) or for any other reasons Subjects who had postoperative persistent or recurrent PH after undergoing PEA and/or BPA
WHO FC	PH subjects whose WHO FC was I to IV
6MWD	6MWD measured during the screening period ranged from 150 m to 450 m
Right heart catheterization (RHC)	Subjects who met the following conditions according to the RHC performed during the screening period or within 8 weeks before signing the informed consent form: - Resting mean pulmonary artery pressure (mPAP) ≥25 mm Hg - Pulmonary artery wedge pressure (PAWP) ≤15 mm Hg (if PAWP could not be measured or the value of PAWP was not reliable, left ventricular end-diastolic pressure ≤13 mm Hg) - PVR at rest ≥400 dyn·sec/cm^5
Anticoagulation agents	Subjects treated with anticoagulation agents, unfractionated heparin, or low molecular weight heparin at least 90 days prior to RHC at baseline
Key Exclusion Criteria	**Description**
Recurrent thromboembolism	Subjects undergoing treatment with oral anticoagulation agents only, but not showing treatment effect of those agents
Prior history	Symptomatic acute pulmonary embolism within 180 days prior to the start of macitentan administration Known moderate-to-severe restrictive lung disease or obstructive lung disease, or known significant chronic lung disease Acute or chronic conditions (other than respiratory impairment) that could hamper the treatment assessment (in particular with 6MWD) (eg, angina, intermittent claudication) Symptomatic coronary artery disease requiring nitrate use or intervention (eg, percutaneous coronary intervention, coronary artery bypass graft) Acute myocardial infarction during the screening period Systolic blood pressure (BP) <90 mm Hg at the screening

Key Inclusion Criteria	Description
Invasive procedures	BPA within 90 days prior to undergoing baseline RHC PEA within 180 days prior to undergoing baseline RHC
Prior and concomitant medications	Subjects previously treated with macitentan Subjects treated with intravenous or subcutaneous administration of endothelin receptor antagonist, selective prostacyclin receptor agonist, L-arginine, prostanoid, or other study agents within 30 days prior to RHC at baseline (excluding the acute administration for vascular reactivity test during RHC) WHO FC I or II: Subjects who received any of the following medications within 30 days prior to RHC at baseline (excluding the acute administration for vascular reactivity test during RHC): - soluble guanylate cyclase (sGC) stimulator - phosphodiesterase-5 inhibitors (PDE-5i) - oral/inhaled prostanoid WHO FC III or IV: Subjects who newly started or had not maintained a stable dose of the following medications within 30 days prior to RHC at baseline (excluding the acute administration for vascular reactivity test during RHC): - sGC stimulator - PDE-5i - oral/inhaled prostanoid More than 2 medications among sGC stimulator, PDE-5i, and oral/inhaled prostanoid were concomitantly used within 30 days prior to RHC at baseline
Key laboratory values	Hemoglobin <75% of lower limit of normal at screening Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN) at screening

Test Product, Dose, and Mode of Administration, Batch No.:

Macitentan 10 mg was administered orally once daily. Macitentan batch number used in the study was ZE011, expiration date: April 2021.

Duration of Treatment:

Subjects were to receive macitentan until approval was obtained or the development was discontinued.

Criteria for Evaluation:

Efficacy was evaluated by using RHC, 6MWD/Borg dyspnea index, and WHO FC. Safety assessment was based on reported adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, vital sign measurements, physical examinations, and pregnancy.

Statistical Methods:

Sample Size Determination:

Analysis of Primary Endpoint: The analysis was planned to be performed on the full analysis set (FAS) (subjects who received macitentan at least once and who were evaluable for postdosing PVR. It was permitted to evaluate the missing PVR data due to worsening PH symptoms by imputing the value with the worst one). The primary endpoint, ratio of PVR at Week 16/PVR at baseline, was tested by Wilcoxon's rank sum test. A 2-sided Type I error of 0.05 was used.

Sample Size Required: For patients not indicated for surgery and those with persistent or recurrent PH after surgery, it was considered that their medical conditions differed but that the expected effect size did not vary in terms of the site of action of macitentan. Although there was no previous study evaluating the efficacy of macitentan in Japanese patients, no ethnic difference was likely to exist. Thus, based on data from a foreign Phase 2 study (MERIT-1) evaluating the efficacy of macitentan in foreign inoperable CTEPH patients who were unable to undergo PEA, by assuming a log-normal distribution as 0.8 (mean) of treatment effect size (subjects undergoing PH treatment at baseline) in the active macitentan group and 0.82 (all subjects), the data randomly extracted from the distribution were simulated for evaluation.

For 1 subject (placebo group) in whom PVR could not be measured due to death or worsening of PH symptoms in the MERIT-1 study and in whom the value was imputed by the worst one, it was considered as an incidental case. Based on the probability in the AC-055E201 (MERIT-1) study, the sample size required in the current study was determined between 21 and 34 in case that 0, 1, or 2 cases of missing data in whom PVR was imputed by the worst value due to death or worsening of PH symptoms occurred. The probability of imputing by the worst value was estimated as 69%, 95%, and 99% in 0, ≤1, and ≤2, respectively (in case of 30 subjects). By anticipating that the treatment effect of riociguat as prior therapy (continued) was comparable to that of PDE-5i or prostanoid, a total of 27 subjects were required to ensure 70% power taking the feasibility of the subjects into account.

Analysis Sets:

Screening Analysis Set (SCR): All subjects screened among those who gave their consent to participate in the study.

Full Analysis Set (FAS): All subjects who received at least 1 dose of macitentan and who were evaluable for at least 1 efficacy assessment item among those who gave their consent to participate in the study. Efficacy analysis was performed on the FAS.

Per Protocol Set (PPS): All subjects from the FAS excluding the following subjects:

- Subjects with any event including protocol deviations, which could affect the main analysis of the primary variable
- Subjects who were not evaluable for the primary variable

Safety Analysis Set: All subjects who received at least 1 dose of macitentan and who were evaluable for safety after dosing.

As the study was prematurely discontinued, which led to the limited sample size, the PPS was not used for analysis.

Efficacy:

Level of Significance: The primary endpoint, ratio of PVR at Week 16/PVR at baseline was tested by nonparametric Wilcoxon's rank sum test. Significance level was controlled at the 2-sided α=0.05 level, and all other tests including tests for secondary endpoints had no formal statistical hypotheses. Thus, multiplicity was not necessary to consider.

Primary Endpoint: The primary endpoint was defined as ratio of PVR from baseline at Week 16 (PVR at Week 16/PVR at baseline). The primary estimand, the main clinical quantity of interest to be estimated in the study was defined by the following 4 components:

- Population: Japanese subjects with CTEPH who were not indicated for PEA and/or subjects who had postoperative persistent or recurrent PH after PEA and/or BPA
- Variable: ratio of PVR at Week 16/PVR at baseline

- Intercurrent event: no intercurrent events were to be taken into account
- Population-level summary: ratio in pre- and postdosing PVR at Week 16

Analysis Methods: Since the study was discontinued prematurely, no formal statistical testing was performed, and no imputation rules were applied for missing data. The sensitivity analysis was not performed. Only descriptive statistics were provided. In addition to the ratio in PVR, descriptive statistics with PVR at rest at baseline and Week 16 were provided. In this analysis, no intercurrent events were taken into account because the crude descriptive analysis without intercurrent events was considered to be the first approach.

Secondary Endpoints:

- Change from baseline to Week 16 in resting PVR and PVRI
- Change from baseline to Week 24 in 6MWD
- Change from baseline to Week 24 in Borg dyspnea index checked after undergoing 6MWD test
- Change from baseline to Week 24 in WHO FC

Analysis Methods: Since the study was discontinued prematurely, no formal statistical testing was performed, and no imputation rules were applied for missing data. The sensitivity analysis was not performed. Descriptive statistics were provided with the change from baseline and value at each timepoint. With regards to WHO FC, categorical analysis was also applied with each timepoint.

Other Efficacy Endpoints:

- Change from baseline to Week 16 in pulmonary hemodynamic parameters mean right atrial pressure, mPAP, cardiac output (CO), cardiac index (CI), total pulmonary resistance (TPR), and mixed venous oxygen saturation (SVO2)
- Change in 6MWD from baseline to each time point in the efficacy evaluation period and every 24 weeks in the extension period up to the EOT
- Change in Borg dyspnea index from baseline to each time point in the efficacy evaluation period and every 24 weeks in the extension period up to the EOT
- Change in WHO FC from baseline to each time point in the efficacy evaluation period and every 24 weeks in the extension period up to the EOT
- Change in NT-proBNP from baseline to each time point in the efficacy evaluation period and every 24 weeks in the extension period up to the EOT
- Time to first PH-related disease progression during the efficacy evaluation period until the EOT (during the efficacy evaluation period plus safety follow-up period for death), defined as:
  - All causes death
  - Lung transplantation
  - Hospitalization due to PH-related disease progression
  - Initiation of intravenous or subcutaneous prostanoid therapy due to PH-related disease progression
  - Other PH-related disease progression, defined by the combined occurrence of all of the following 3 events in a subject:
    - When a decrease in 6MWD of at least 15% from baseline was observed at 2 consecutive visits

- The WHO FC had deteriorated, or the investigator judged that there was no chance for improvement in a subject whose WHO FC was IV at the time of starting macitentan administration
- Need for additional PH therapy

Analysis Methods: Since the study was discontinued prematurely, no formal statistical testing was performed, and no imputation rules were applied for missing data. The sensitivity analysis was not performed. Descriptive statistics were provided with change from the baseline and value at each timepoint. With regards to WHO FC, categorical analysis was also applied with each timepoint. For the time to first PH-related disease progression up to the EOT, listing of the time to first PH-related disease progression was provided.

Safety:

Treatment-emergent adverse events, laboratory analyte values, vital sign measurements, and physical examination findings reported during the study were summarized.

RESULTS:

This study was prematurely discontinued due to MERIT-1 study circumstances and not due to any safety concerns. In November 2019, the sponsor decided to voluntarily withdraw the health authority filings that were still under review globally for macitentan 10 mg for the treatment of inoperable CTEPH. This decision was not driven by any safety concerns but due to feedback from health authorities that additional clinical data would be required for approval. Due to the discontinuation of the study, this CSR was prepared as an abbreviated report in accordance with the FDA guidance.

STUDY POPULATION:

Of the 11 subjects screened, 9 (81.8%) were enrolled and treated with macitentan 10 mg. All enrolled subjects were withdrawn from the study: 7 subjects due to sponsor's decision; 1 subject met a withdrawal criterion (was unable to write the medication diary appropriately); 1 subject withdrew consent. All enrolled subjects prematurely discontinued macitentan: 8/9 (88.9%) subjects due to the physician's decision (7 subjects were withdrawn due to sponsor's decision* and 1 subject met a withdrawal criterion) and 1/9 (11.1%) subjects withdrew consent. (*Note: As the electronic case report form [eCRF] design did not have "sponsor decision" as an option, therefore, "physician decision" was selected instead of "sponsor decision"). None of the subject prematurely discontinued macitentan due to any safety concerns. Overall, there was a higher proportion of women (8/9 [88.9%] subjects) than men (1/9 [11.1%] subjects). The median age was 70.0 (range: 51 to 80) years, with the majority of subjects aged ≥65 years (7/9 [77.8%]). The median time from CTEPH diagnosis to screening was 0.10 (range: 0.0 to 14.2) years. At baseline, the mean (SD) PVR, 6MWD, and Borg dyspnea index score were 796.8 (421.87) dyn.sec/cm^5, 341.8 (84.89) m, and 5.4 (2.19), respectively. A total of 5/9 (55.6%) subjects were WHO FC III and 4/9 (44.4%) subjects were WHO FC II at baseline. A total of 6/9 (66.7%) subjects were not receiving any concomitant pulmonary arterial hypertension (PAH) medication at baseline. Riociguat (3/9 [33.3%] subjects), spironolactone (2/9 [22.2%] subjects), azosemide, furosemide, and cilnidipine (1/9 [11.1%] subjects each) were taken for PH at baseline. The mean (SD) percentage of macitentan compliance was 99.211% (2.1715%). The median duration of exposure to macitentan was 22.6 (range: 9 to 34) weeks. The median number of macitentan tablets received was 158 (range: 57 to 240).

EFFICACY RESULTS:

Primary Efficacy Endpoint:

In the FAS (n=9), the mean (SD) ratio of PVR at Week 16/PVR at baseline was 71.9% (34.31%).

Secondary Efficacy Endpoints:

- The mean (SD) decrease in PVR from baseline to Week 16 was 181.4 (243.90) dyn.sec/cm^5. Similarly, the mean (SD) decrease in PVRI from baseline to Week 16 was 280.58 (366.014) dyn.sec.m^2/cm^5.
- The mean (SD) baseline 6MWD was 341.8 (84.89) m, and after 24 weeks of treatment, the mean (SD) total distance walked in 6 minutes increased by 44.3 (46.75) m.
- There was no clinically meaningful change observed in the Borg dyspnea index score from baseline to Week 24.
- One/9 (11.1%) subjects showed an improvement from WHO FC III to WHO FC II at Week 8 during the study; however, no change was observed in other subjects.

Other Efficacy Endpoints:

- The pulmonary hemodynamic parameters showed a mean (SD) increase of 0.30% (11.843%), 0.57 (0.914) L/min/m^2, and 0.822 (1.4492) L/min from baseline for SVO2, CI, and CO, respectively at Week 16. A mean (SD) decrease (ie, improvement) of 4.0 (7.35) mm Hg, 0.1 (2.67) mm Hg, and 180.111 (251.0574) dyn.sec.cm^5 from baseline was observed for mPAP, mRAP, and TPR, respectively at Week 16.
- A mean (SD) increase of 20.7 (55.11) m, 33.4 (46.31) m, and 44.3 (46.75) m at Week 8, Week 16, Week 24 was observed in 6MWD from baseline.
- There was no clinically meaningful change observed in the Borg dyspnea index score from baseline over time until Week 24.
- One/9 (11.1%) subjects showed an improvement from WHO FC III to WHO FC II at Week 8 during the study; however, no change was observed in other subjects.
- A mean (SD) decrease in NT-proBNP levels was observed from Week 4 to Week 20 (range: 12.9 [178.22] pg/mL to 164.1 [498.80] pg/mL) compared to baseline. At Week 24, a mean (SD) increase of 22.2 (182.61) pg/mL from baseline was observed.

SAFETY RESULTS:

All treated subjects experienced 1 or more treatment-emergent adverse events (TEAEs) during the study. The most frequently reported TEAEs (reported by ≥20% of subjects) were nasopharyngitis (4/9 [44.4%] subjects), angioplasty (4/9 [44.4%] subjects), and fatigue (2/9 [22.2%] subjects). Angioplasty was the only severe TEAE that was reported in 1/9 (11.1%) subjects, which was considered as not related to macitentan by the investigator. One-third of the subjects experienced mild or moderate TEAEs that were related to macitentan. The TEAEs that were considered as related to macitentan and reported in at least 1 subject were anemia, fatigue, edema, BP decreased, nasal congestion, and hypotension.

There were no TEAEs that led to death or TEAEs that led to dose interruption or discontinuation of treatment during the study. A total of 4/9 (44.4%) subjects experienced 5 serious TEAEs during the study. All serious TEAEs reported were angioplasty (hospitalization for BPA), performed on the same day or later than the date of macitentan discontinuation and were considered as not related to macitentan by the investigator. The outcome of all events was reported as resolved.

A total of 4/9 (44.4%) subjects experienced 1 or more TEAEs of special interest: joint swelling (1/9 [11.1%] subjects); anemia and liver function test abnormal (1/9 [11.1%] subjects); hypotension and edema (1/9 [11.1%] subjects); and BP decreased (1/9 [11.1%] subjects). All TEAEs of special interest were mild or moderate in severity. The investigator considered the events of anemia, edema, hypotension, and BP decreased as related to macitentan and the events of liver function abnormal and joint swelling as not related to macitentan. The outcome of all events was reported as resolved except the events of anemia and BP decreased, which were not resolved at the time of this report.

In general, mean changes from baseline in laboratory values were not clinically meaningful. One subject was reported with a marked abnormal hemoglobin decrease during the safety follow-up period, which was mild in intensity. The investigator considered the event as related to macitentan.

STUDY LIMITATIONS: This study was prematurely discontinued due to MERIT-1 study circumstances and not due to any safety concerns. The actual number of subjects enrolled was smaller than the planned number of subjects.

CONCLUSIONS:

- The premature study discontinuation and small number of subjects who were evaluated for efficacy precluded a definite conclusion from being drawn about the efficacy of macitentan 10 mg.
- No serious safety concern was observed with macitentan 10 mg in Japanese subjects with CTEPH.

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