Non-Interventional Study (NIS) Protocol

Document Number:	c37302912-04
BI Study Number:	1245.286
BI Investigational Product(s):	Empagliflozin
Title:	Post Marketing Surveillance on Long Term Drug Use of JARDIANCE® Tablets in Patients with chronic heart failure in Japan.
Brief lay title:	PMS of JARDIANCE in CHF
Protocol version identifier:	Version 4.0
Date of last version of protocol:	5 October 2023
PASS:	Yes
EU PAS register number:	EUPAS44340
Active substance:	Empagliflozin
Medicinal product:	JARDIANCE® Tablets
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	Study objective is to investigate the safety and effectiveness of long-term daily use of JARDIANCE® Tablets in patients with chronic heart failure under real-world use.
Country(-ies) of study:	Japan
Author:	[redacted]

Marketing authorisation holder(s):	[redacted]
MAH contact person:	
EU-QPPV:	
Signature of EU-QPPV:	e-signature is on BIRDS
Date:	1 April 2024

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1. TABLE OF CONTENTS

[redacted]

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BIcMQ	Boehringer Ingelheim
CHF	Chronic Heart Failure
CI	Confidence Interval
CRF	Case Report Form
eCRF	Electronic Case Report Form
CV	CardioVascular
EDC	Electronic Data Capture
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
GPSP	Good Post- marketing Study Practice
HF	Heart Failure
HFrEF	Heart Failure with reduced Ejection Fraction
J-PMD Act	Japanese pharmaceuticals and Medical Devices Act
J-RMP	Japan Risk Management Plan
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHLW	Ministry of health, Labour and Welfare
[redacted]	
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
T2DM	Type 2 Diabetes mellitus

3. RESPONSIBLE PARTIES

[redacted]

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the Post Marketing Surveillance (PMS) tracking system which manage the contracts with site and investigators name.

Co-sponsor

[redacted]

Medical advisor

[redacted]

Task:

1. Providing medical advice and comments on the study results
2. Providing medical advice on risk minimisation
3. Reviewing the contents of publication for the study results

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: JARDIANCE® Tablets			
Name of active ingredient: Empagliflozin			
Protocol date: 1 November 2021	**Study number:** 1245.286	**Version/Revision:** Version 4.0	**Version/Revision date:** 1 April 2024
Title of study:	Post Marketing Surveillance on Long Term Drug Use of JARDIANCE® Tablets in Patients with chronic heart failure (CHF) in Japan.		
Rationale and background:	In Japan, post-approval execution of Post Marketing Surveillance is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and effectiveness data for re-examination. Re-examination period is defined by J-PMD Act. Four years after approval of additional indication, results of PMS need to be submitted as a part of re-examination dossier to the Japanese regulatory authority, the Ministry of Health, Labour and Welfare (MHLW). Collected data from PMS will be included in the Japanese periodic safety reports and submitted to MHLW on designated dates until the end of re-examination period.		
Research question and objectives:	Study objective is to investigate the safety and effectiveness of long-term daily use of JARDIANCE® Tablets in patients with CHF under real-world use.		
Study design:	Cohort study Non-interventional, single arm study based on newly collected data Patients will be observed for up to 52 weeks after start of the treatment with JARDIANCE® Tablets or until discontinuation of administration.		
Population:	<u>Inclusion criteria</u> - Patients with chronic heart failure who are prescribed with JARDIANCE® Tablets in Japan. - Patients who have never been treated with Empagliflozin (including treatment for T2DM) before enrolment. <u>Exclusion criteria</u> None		

Variables:	Outcomes: Primary outcome: - Incidence of adverse drug reactions (ADR) (focus on hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis, renal impairment) Secondary outcomes: - Incidence of all-cause death - Incidence of CV death - Incidence of hospitalizations for heart failure [redacted]
Data sources:	Patients' data will be collected by electronic Case Report Form on Electronic Data Capture system
Study size:	1000 (safety set)
Data analysis:	Descriptive statistics will be summarised for safety and effectiveness.
Milestones:	Planned start of data collection: 1 APR 2022 Planned end of data collection: 30 JUN 2024 Study Report planned to be archived in 1-2Q 2025

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	16 December 2021	3	Updated Medical adviser	Administrative update
		6	Added registration in the EU PAS register	Registration to EU PAS
		9.3.1	Added the rationale for observation period	Directions from PMDA
		9.3.3, Annex 2	Added covariate items (patient status, hospitalization history, device usage, underlying disease, exercise, diet therapy, water intake management, BNP)	Directions from PMDA
2	5 October 2023	[redacted]		
3	1 April 2024	9.6	Amendment (non-substantial)	Contract 2 of 9.6 DATA MANAGEMENT was changed from 1 April 2024. This amendment is non-substantial and categorized as unnecessary to submit to PMDA

6. MILESTONES

Milestone	**Planned Date**
Start of data collection	1 April 2022
End of data collection	30 June 2024
Registration in the EU PAS register	22 November 2021
Final report of study results:	1-2Q 2025

7. RATIONALE AND BACKGROUND

Heart failure (HF) is a progressive and potentially fatal condition that is affecting over 60 million people worldwide and expected to increase as the population ages. HF is a major and growing public health problem in the developed countries. In Japan, approximately 1.2 million individuals have HF with an estimated prevalence of 1% (R20-3363, R20-0158). Empagliflozin outcome trial in patients with CHF with reduced ejection fraction (EMPEROR-Reduced; BI trial number 1245.121 (P20-07681)) 3 compared empagliflozin 10 mg once daily treatment with placebo as add-on to standard of care treatment in patients with HFrEF (left ventricular ejection fraction (LVEF) ≤40%), regardless of baseline diabetes status. The risk of cardiovascular death or hospitalisation for heart failure (primary endpoint) was significantly reduced with empagliflozin treatment. As shown in the testing hierarchy for the two key secondary endpoints, empagliflozin was also superior to placebo in reducing the risk of recurrent hospitalisation for heart failure and in slowing renal function decline as assessed by eGFR slope of change, the latter accompanied by less frequent renal outcome events. These benefits were consistent for patients with and without type 2 diabetes mellitus. The results from the adverse events and safety laboratory analyses were similar to the known safety profile of empagliflozin. Of the 3730 patients enrolled in EMPEROR-Reduced, 144 patients in the empagliflozin group were enrolled from Japan. As there is limited number of Japanese patients with NYHA III (15 patients) or IV (0 patient), eGFR <45 mL/min/1.73m^2 (37 patients) and without type 2 diabetes (74 patients) in EMPEROR-Reduced, PMDA requested to collect more safety information of those patients.
This Post Marketing Surveillance (PMS) with 1,000 patients has been planned to collect the safety data (especially hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis, renal impairment) according to the Safety Specification on the J-RMP and PMDA's request. PMDA also required to collect information on effectiveness related survey items (all-cause death, CV death, hospitalizations for heart failure) in this study. They asked us to confirm the occurrence of all-cause death and CV death in real world because the number of all-cause death in the empagliflozin group was higher than in placebo group in Japanese patients in 1245.121. However, they thought the effectiveness related survey items were not considered to be serious issue and control group (comparator) was not necessary. We estimate that the study will collect the safety data from patients with NYHA III-IV (50 patients), eGFR <45 mL/min/1.73m^2 (more than 100 patients) and without type 2 diabetes (500 patients) referring to the epidemiological surveys in Japan (R20-3363, R21-3494, R20-3355, R21-3495, R21-3496) and Japanese patients of EMPEROR-Reduced (P20-07681).

In Japan, post-approval execution of Post Marketing Surveillance (PMS) is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and efficacy data for re-examination. Re-examination period is defined by J-PMD Act. Four years after approval of combination drugs, results of PMS need to be submitted as a part of re-examination dossier to the Japanese regulatory authority, the Ministry of Health, Labour and Welfare (MHLW).

Collected data from PMS will be included in the Japanese periodic safety reports and submitted to MHLW on designated dates until the end of re-examination period.

The protocol may be revised because of new information or knowledge obtained in the course of conducting PMS. When a change of the approved label such as in dosage and administration or indications is made during the re-examination period of JARDIANCE® Tablets (except that for this change a re-examination period is newly designated by MHLW) and [redacted] finds it necessary to revise this protocol, handling each matter should be discussed and the protocol may be revised. If any issue or concern arises (e.g. suggestion of a potential for clinically significant adverse reaction, remarkable increase in incidence of an adverse reaction, or any issue or concern on safety or efficacy assessment made prior to the approval of JARDIANCE® Tablets) in the course of PMS, implementation of additional special surveillance or post-marketing clinical trial should be discussed to identify or confirm a cause or estimated cause of such issue. Special surveillance is defined by J-PMD Act. It means surveillance for long-term use or special patient population (elderly, renal/hepatic dysfunction etc.).

8. RESEARCH QUESTION AND OBJECTIVES

Study objective is to investigate the safety and effectiveness of long-term daily use of JARDIANCE® Tablets in patients with CHF under real-world use.
The primary outcome of this study is the incidence of any adverse drug reactions (ADRs) (focus on hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis, renal impairment) (see section 9.3.2).

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study based on newly collect data of patients under routine care to confirm safety and effectiveness of JARDIANCE® Tablets in real-world setting in Japanese patients with CHF.

9.2 SETTING

9.2.1 Study sites

Sites throughout entire country will be equally listed according the size of the hospitals or general clinics at which JARDIANCE® Tablets are available for prescription.

Planned number of site: Approximately 200 Sites (including CV internal medicine)

A medical representative will explain the objective and design of this study to investigators at each study site and conclude a written contract with the head of the study site (e.g., hospital director).

9.2.2 Study population

As this is a non-interventional study, no specific treatment is mandated or withheld from the patients. No limitations are set up on background factors and their concomitant drugs in use of actual medical practice.

Inclusion criteria
- Patients with CHF failure who are prescribed with JARDIANCE® Tablets in Japan.
- Patients who have never been treated with Empagliflozin (including treatment for T2DM) before enrolment.

Exclusion criteria
None

Registration period
From April 2022 to March 2023

9.2.2.1 Patient registration method

The registration method will be a central registration system. Patients who begin treatment with JARDIANCE® Tablets after the conclusion of the contract will be registered by entering necessary information in the Electronic Data Capture (EDC) system within 14 days from the day of treatment initiation (inclusive).
Patient registration will be stopped when the overall target number of patients for the study is reached.

9.2.3 Study visits

The study will consist of a baseline visit and further visits in a 52-week follow-up for patients who have initiated JARDIANCE® Tablets treatment. The follow-up data (safety and administration of JADRIANCE®) from patients who change hospital and continue taking JADRIANCE® will be collected by participating investigators if possible.

9.2.4 Study discontinuation

[redacted] reserves the right to discontinue the PMS overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment overall goals or goals at a particular study site.
2. Emergence of any effectiveness/safety information that could significantly affect continuation of the PMS or any other administrative reasons.
3. Violation of Good Post- marketing Study Practice (GPSP), the Non-interventional Study protocol, or the contract by study site or investigator, disturbing the appropriate conduct of the PMS.

The study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Exposures

Exposure to JARDIANCE® Tablets is estimated as time from the day JARDIANCE® Tablets is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient during the regular observation period).

Patients newly initiating JARDIANCE® Tablets will be followed up to 52 weeks.

For the Japanese population of Study 1245.121, the estimated cumulative incidence functions (all-cause death being taken into consideration as competing risk) at approximately

one year (360 days) and last assessment or censored after treatment were approximately 0.7% and 2.0% for hypoglycemic events and approximately 8% and 14% for volume depletion in the empagliflozin group. No estimated cumulative incidence function was calculated for the effect of increased ketone body/ketoacidosis or acute renal failure (For acute renal failure, the estimated cumulative incidence functions [all-cause death being taken into consideration as competing risk] at approximately one year [360 days] and last assessment or censored after treatment were approximately 7% and 16% in the empagliflozin group for the entire population of Study 1245.121. In addition, in empagliflozin group for Japanese population, 13 patients occurred acute renal failure). For these events, there was no tendency for an increase in the estimated cumulative incidence function between at approximately one year [360 days] after treatment and at last assessment or censored from approximately one year [360 days] after treatment. In the empagliflozin group of the Japanese population of Study 1245.121, the incidences of adverse events of hypoglycemia, volume depletion and acute renal failure were 1.54, 9.35, and 6.95 (/100 patient-years), respectively. The incidences of all-cause death, CV death, and hospitalizations for heart failure at Year 1 was 3.1%, 2.3%, and 6.2%, respectively. Assuming that the proportions of these events for this study are the same as in 1245.121 described above, the estimated incidences of events of hypoglycemia, volume depletion, acute renal failure, all-cause death, CV death, and hospitalizations for heart failure at 1 year are 10, 94, 70, 30, 23,62 patients, respectively in this study. The incidence of ketoacidosis is very low so that collected cases will be individually examined.
If the number of events for the analysis is sufficient, a subpopulation analysis will be performed and considered as much as possible. For events in which the number of collected patients is small, the patients with events will be examined individually.
Based on these considerations, setting the observation period to one year in this study is found to be appropriate because the applicant assumes that the one-year observation period enables to sufficiently collect adverse drug reactions requiring additional pharmacovigilance activities in the Japanese population.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary endpoint of this study is the incidence of ADRs (focus on hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis, renal impairment).
ADRs definition and reporting is described in section 11.

There is no primary outcome for effectiveness as the primary objective of a PMS is evaluating safety.

9.3.2.2 Secondary outcomes

- Incidence of all-cause death
- Incidence of CV death
- Incidence of hospitalizations for heart failure

[redacted]

9.3.3 Covariates

The following variables based on physician's report will be considered important baseline characteristics and potential risk factors for the outcomes of interest.

Demographics:
Patient status (inpatient/outpatient), Gender, year of birth, indication, pregnancy status, height, body weight, Body Mass Index (derived), hypersensitivity factor (pick up from medical history and concomitant disease data), diagnosed date of HF, NYHA classification, NT-proBNP, LVEF, alcohol habit, smoking history, degree of renal/hepatic functions at baseline, T2DM (diagnosed date) , dates of previous hospitalisations for heart failure, device usage (cardiac pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy, other)

Medical history / Concomitant disease:
Underlying disease (ischemic heart disease (angina pectoris, myocardial infarction, other) / non-ischemic heart disease (hypertensive, valvular, idiopathic cardiomyopathy, other), hypertension, stroke, atrial fibrillation, hyperlipidemia, hyperuricemia, malignancy, hypersensitivity factor, others

Previous / Concomitant drugs and therapies:
Previous drugs (in the 3 months before newly starting JARDIANCE® Tablets):
HF, T2DM, others
Dose, daily frequency, start and end date

Concomitant drugs and therapies:
HF, T2DM, others
Dose, daily frequency, start and end date, reason for use, route of administration
Exercise, diet therapy and water intake management
Start and end date, compliance

Administration of JARDIANCE® Tablets:
Dose, daily frequency, start and end date, primary reason of discontinuation, reason for changing hospital, compliance

Echocardiography:

Left ventricular ejection rate, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial dimension, early diastolic left ventricular filling velocity (E peak), peak atrial filling velocity (A peak), Early-diastolic mitral annular velocity (e')

Blood pressure and pulse rate (if applicable):
Systolic / diastolic blood pressure, pulse rate

Physical examination:
Body weight, grip strength

Laboratory tests (blood biochemistry and urinalysis) (if applicable):

Haematology: Erythrocyte count (RBC), haemoglobin (Hb), haematocrit (Hct), leukocyte counts (WBC), leukocyte fraction (Neutrophil count, lymphocyte count), platelet count

Blood chemistry: HbA1c (NGSP), fasted blood glucose, creatinine (CRE), aspartate transaminase (AST, SGOT), alanine transaminase (ALT, SGPT), alkaline phosphatase (ALP), gamma-glutamyl-transferase (γ-GTP), albumin, total bilirubin (T-BIL), blood urea nitrogen (BUN), total cholesterol (T-CHO), HDL cholesterol (HDL), LDL cholesterol (LDL), Triglycerides (TG), uric acid (UA), ketone, BNP, NT-proBNP

Urinalysis: Glucose, protein, albumin, ketone, creatinine.

Body Mass Index (BMI):
BMI（kg/m^2）= weight(kg) / height^2 (m^2)

Grades for renal dysfunction are as follows. eGFR will be derived from serum creatinine.

Normal:	eGFR ≥90 mL/min/1.73m^2
Mild:	eGFR ≥60 mL/min/1.73m^2 and <90 mL/min/1.73m^2
Moderate:	eGFR ≥30 mL/min/1.73m^2 and <60 mL/min/1.73m^2
Severe:	eGFR <30 mL/min/1.73m^2

Investigator should judge the grade for hepatic dysfunction by using lab data category as described below and symptoms/concomitant diagnoses.

Normal:	Normal AST/ALT
Mild:	AST/ALT >ULN and <3x ULN
Moderate:	AST/ALT≥3xULN and <5x ULN + total Bil<= 2xULN
Severe:	AST/ALT≥5 xULN, or AST/ALT≥3xULN and <5x ULN + total Bil> 2xULN

ULN is taken from the corporate standard reference range [redacted]).

Enzymatic method:
eGFR（mL/min/1.73 m^2）= 194 × Creatinine (mg/dL) $^{-1.094}$ × $Age^{-0.287}$
For female, ×0.739
Jaffe rate assay:
eGFR（mL/min/1.73 m^2）= 175 × Creatinine (mg/dL) $^{-1.154}$ × $Age^{-0.203}$
For female, ×0.742

See ANNEX 2 for more details.

9.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via the EDC system.

In EDC system, two casebooks will be set:
Book 1 includes baseline, 12 weeks and 26 weeks.
Book 2 includes 40 weeks and 52 weeks.

The data are to be transmitted immediately after being entered into EDC at 26 weeks (Book 1) and 52 weeks (Book 2) after the start of treatment or at discontinuation.
For any adverse events, the data should be immediately entered into EDC and transmitted.

9.5 STUDY SIZE

1000 patients will be included in the study. 1200 patients will be enrolled.

Because there is no hypothesis for this study, no sample size calculation is conducted based on the statistical test. The observed proportions of confirmed hypoglycaemia, ketoacidosis (narrow BIcMQ), fluid volume depletion (narrow BIcMQ), and acute renal failure (narrow SMQ) in the empagliflozin group in the Japanese population of the EMPEROR-Reduced study were 1.4% (2/144), 0% (0/144), 11.8% (17/144), and 9% (13/144), respectively. Also, the proportions of patients with heart failure in the empagliflozin group in the Japanese population in the EMPEROR-Reduced study who had NYHA III or IV and eGFR <45 mL/min/1.73m^2, and no type 2 diabetes were 10.4% (15/144), 25.7% (37/144), and 51.4%, respectively. The proportions of adverse events in the empagliflozin group observed in the Japanese population in the EMPEROR-Reduced study described above are assumed to be the true proportions of adverse events, while to be conservative, the proportions of risk factors (NYHA III or IV, eGFR <45 mL/min/1.73m^2, no type 2 diabetes) of 5% (50/1000), 10% (100/1000), and 50% (500/1000) based on the epidemiological surveys in Japan (R20-3363, R21-3494, R20-3355, R21-3495, R21-3496) are assumed to be the true proportions of risk factors in this study.

Assuming that the odds ratio of "yes" to "no" is 2, the power to detect a difference in a specific risk factor at a two-sided significance level of 5% when 1000 Japanese patients are included in the study is given by the values in Table 1. In calculating the power, we used the normal approximation formula of the two-sample binomial test for the difference in the proportions of the risk factors "yes" and "no" considered as two independent samples.

Table 1 Power to detect a difference in a specific risk factor at a two-sided significance level of 5% when 1000 Japanese patients are included in the study is given by the values

		The true proportions of adverse events		
		1.4% (hypoglycaemia)	9% (acute renal failure)	11.8% (fluid volume depletion)
The true proportions of risk factor "yes"	5%	0.190	0.442	0.499
	10%	0.242	0.641	0.717
	50%	0.325	0.946	0.979

In addition, the upper limits of the 95% confidence intervals (CI) for confirmed hypoglycaemia, fluid volume loss, and acute renal failure in the empagliflozin group observed in the Japanese population of the EMPEROR-Reduced study were calculated by normal approximation to be 0.033, 0.137, and 0.171, respectively (since ketoacidosis are not observed in the EMPEROR-Reduced study, the upper limits of the 95% for the ketoacidosis was not calculated). In this study, the upper limits of the 95%CI will be less than 0.033, 0.137, and 0.171, respectively, when the number of patients with each adverse event was 23, 116, and 148 for the total of 1000 cases in this study, indicating that it can be explained that incidence rates are not much higher than those observed in the EMPEROR-Reduced study with a certain accuracy. Furthermore, in EMPEROR-Reduced study, since limited number of patients were exposed by treatment drug, it was difficult to find signal of risk regarding to rare adverse events. Therefore, it is meaningful to show probabilities observing at least one adverse event. Table 2 shows the probabilities that one or more cases of confirmed hypoglycaemia, fluid volume depletion, or acute renal failure will occur, assuming that the number of cases with risk factors "Yes" is 50, 100, and 500, respectively, in addition to the total of 1000 cases in this study (since ketoacidosis are not observed in the EMPEROR-Reduced study, the probability for the ketoacidosis was not calculated). For example, if true proportion of an AE is 1.4% (hypoglycaemia) and 500 patients who have a specific risk factor "Yes" are enrolled into study, probability observing such AE in this study is 99.9%, that is almost certainly it can be observed such AE in this study.

Table 2 Probabilities that one or more cases of confirmed hypoglycaemia, fluid volume depletion, or acute renal failure will occur, assuming that the number of cases with risk factors "Yes" is 50, 100, and 500, respectively, in addition to the total of 1000 cases in this study

		The true proportions of adverse events		
		1.4% (hypoglycaemia)	9% (acute renal failure)	11.8% (fluid volume depletion)
Sample size	50	0.506	0.991	0.998
	100	0.756	1	1
	500	0.999	1	1
	1000	1	1	1

9.6 DATA MANAGEMENT

The data management plan is summarized below. Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

Patients' data will be gathered by EDC system provided by external vendor below.

	Contract 1	Contract 2
Company Name	[redacted]	
Outsourced work	EDC system setting Patient registration Clinical Data Management	Document management of contract with site.

9.7 DATA ANALYSIS

This is a non-interventional study to collect data on patients under routine medical practice on safety, effectiveness and appropriate use of JARDIANCE® Tablets treatment. The analyses in this PMS are descriptive and exploratory by nature. No formal hypotheses tests will be made.

All analyses will be performed on the "safety set" that will include all patients who have received treatment of JARDIANCE® Tablet at least one time except those who are found to have no observation after registration, invalid registration, or invalid contract with the site.

Subgroup analyses will be performed if sample size allows.

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the separate statistical analysis plan, which will be finalized before the end of data collection.

9.7.1 Main analysis

In this PMS, since the primary endpoint is the incidence of ADRs (focus on hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis, renal impairment), the main analysis is to show frequency, proportion and its corresponding confidence interval (CI). The details are given in Section 9.7.3.

9.7.3 Safety analysis

The safety analysis will include all patients who registered in the study and receiving the JARDIANCE® Tablets treatment at least one time except those who are found to have no observation after enrolment, invalid registration, or invalid contract with the site (see section 9.7). In general, safety analyses will be descriptive, based on BI standards, and focus on AEs related to the JARDIANCE® Tablets treatment.

AEs will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between the initiation of JARDIANCE® Tablets prescribed at baseline visit and 7 days (inclusive) after the last administration will be considered ‘treatment emergent’. An AE is considered to be an ADR if either the physician/investigator who has reported the AE or the sponsor assesses its causal relationship as ‘related’.

The frequency of ADRs will be tabulated by system organ class and preferred term according to the current MedDRA version. The frequency of SAEs will also be tabulated likewise. The incidence of ADRs stratified based on patient demographics will also be displayed.

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.

9.8 QUALITY CONTROL

All processes are conducted according to GPSP Standard Operating Procedures (SOP). Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The general scientific objective of this non-interventional study is to obtain an estimate of the occurrence of the adverse events in the population under study. Due to the design which uses a single cohort in this observational safety study, a potential limitation is the absence of comparator groups, such as active treatments or natural progression of disease. Moreover, there are issues that may impose limitations in particular on the validity of the assessment based on the study data such as selection bias, loss to follow up and information and recall bias.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

This PMS study is to be conducted in accordance with both the in-house SOP and working instructions which are in compliance with GPSP.

9.10.2 Study records

CRFs for individual patients will be provided by the sponsor via EDC system.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the study site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

Direct access to source data and documents for PMS study is not allowed in Japan.

9.10.3 Completion of study

Completion of the PMS will be notified to PMDA when the re-examination document is applied to in accordance with J-PMD Act and GPSP.

10. PROTECTION OF HUMAN SUBJECTS

There is no regulation or requirement for ensuring the well-being and rights of participants in a non-interventional observational study.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the patient's treating physician.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

The review by Institutional Review Board is not mandatory for conducting PMS in Japanese GPSP. The sponsor will enter into a contract with a representative (e.g., head of hospital) in accordance with GPSP. Written informed consent prior to patient participation in the trial is not a regulatory or legal requirement in accordance with GPSP.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this PMS is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the PMS needs to be available for inspection on request by the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions (see [redacted] for collection requirements) and of
any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A SAE is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or

development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

An AE which possibly leads to disability will be reported as an SAE. Every new occurrence of cancer or an exacerbation of an existing cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF. When any adverse events occur, the data should be immediately entered into eCRF and transmitted. :

- all ADRs (serious and non-serious),
- all AEs with fatal outcome,

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken JARDIANCE® Tablets, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the Non-interventional Study AE form is to be completed and forwarded as well as soon as possible.

Priority survey items:

Hypoglycaemia, the events relevant volume depletion, influence of ketone body increased / ketoacidosis, renal impairment

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages.

Reporting of related Adverse Events associated with any other BI drug
The investigator is encouraged to report all AEs related to any BI drug other than JARDIANCE® Tablets, according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to the local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final reports will be submitted to PMDA in Japan Periodic safety report. And also the final report for this PMS is included in re-examination documents.
This study is planned for the publication based on the final report.

The rights of the physician and of the sponsor with regard to publication of the results of this PMS study are described in the contract. As a general rule, no PMS study results should be published prior to finalization of the Study Report.

In addition, further interim analysis might be performed for the scientific presentations and publications for the purposes of promoting appropriate use of JARDIANCE® Tablets.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R20-3363 Japan Circulation Society. Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure. 2017

R20-0158 Okura Y, Ramadan MM, Ohno Y, et al. Impending Epidemic: Future Projection of Heart Failure in Japan to the Year 2055. Circ J 2008; 72:489-491.

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R21-3494 Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, et al. and for the JCARE-CARD Investigators. Characteristics and Outcome of Hospitalized Patients With Heart Failure and Reduced vs Preserved Ejection Fraction - A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) -. Circ J 2009; 73: 1893-1900.

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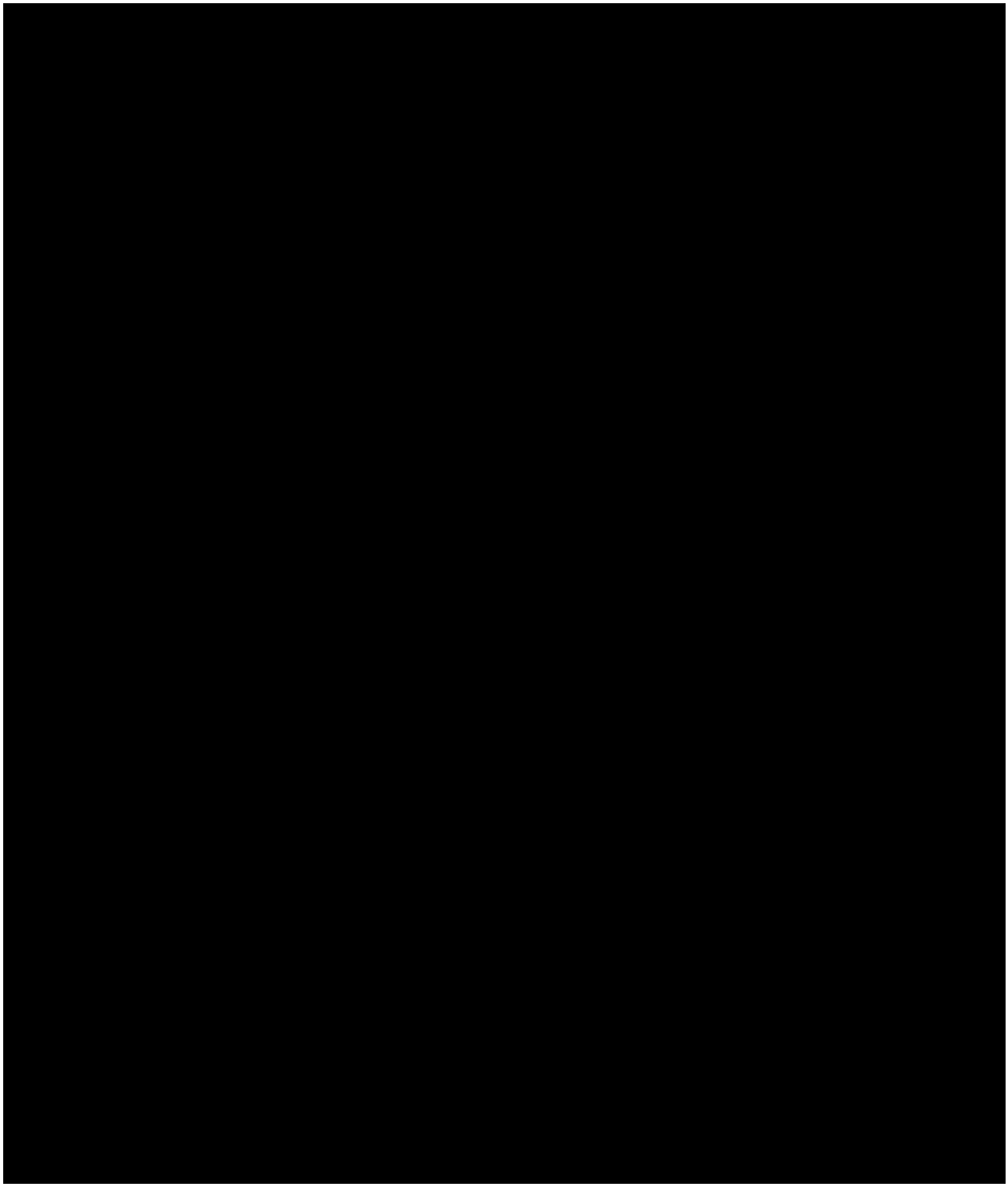
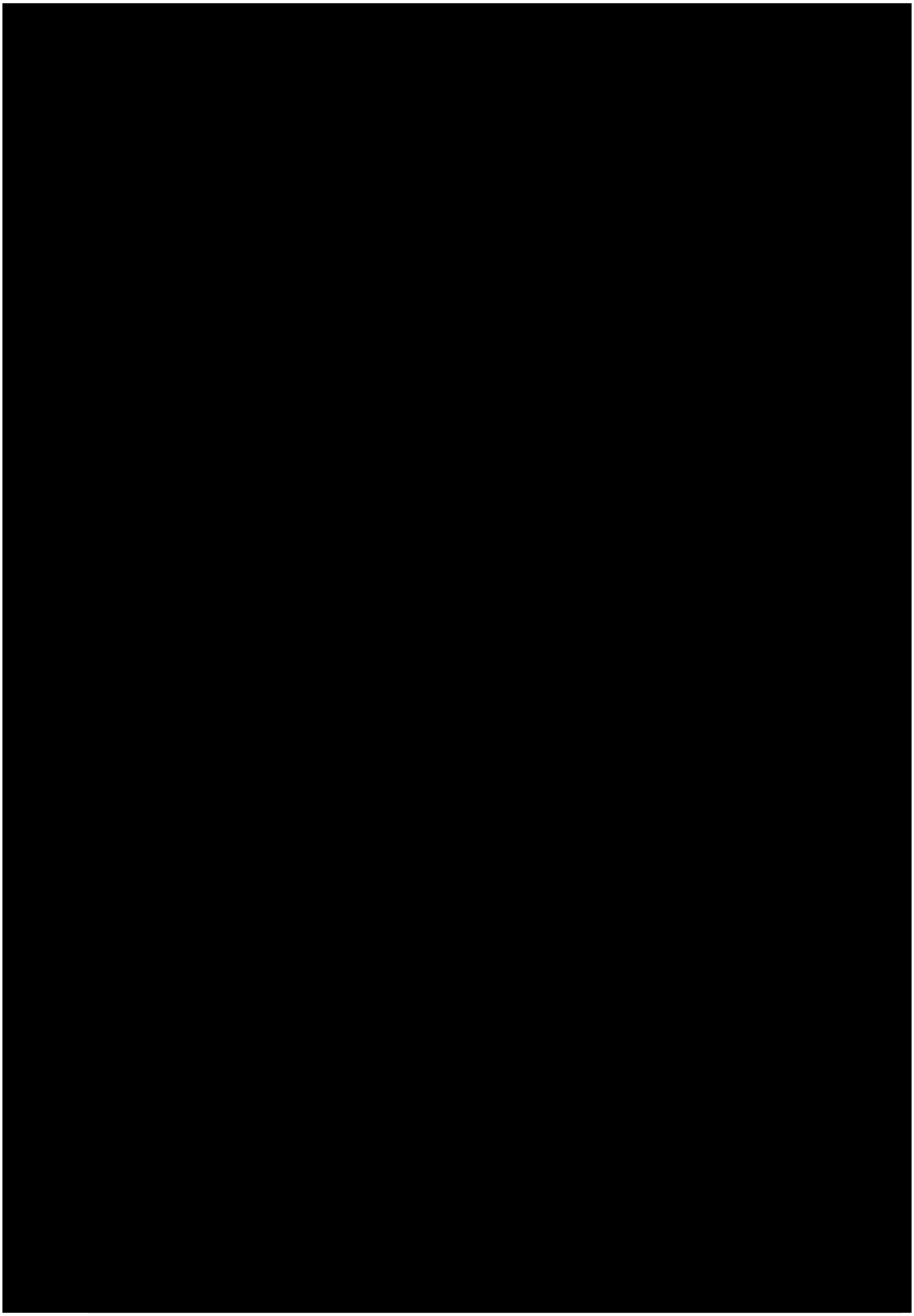
R21-3495 Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, et al. for the JCARE-CARD Investigators. Chronic Kidney Disease as an Independent Risk for Long-Term Adverse Outcomes in Patients Hospitalized With Heart Failure in Japan -Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD)-. Circ J 2009; 73: 1442-1447.

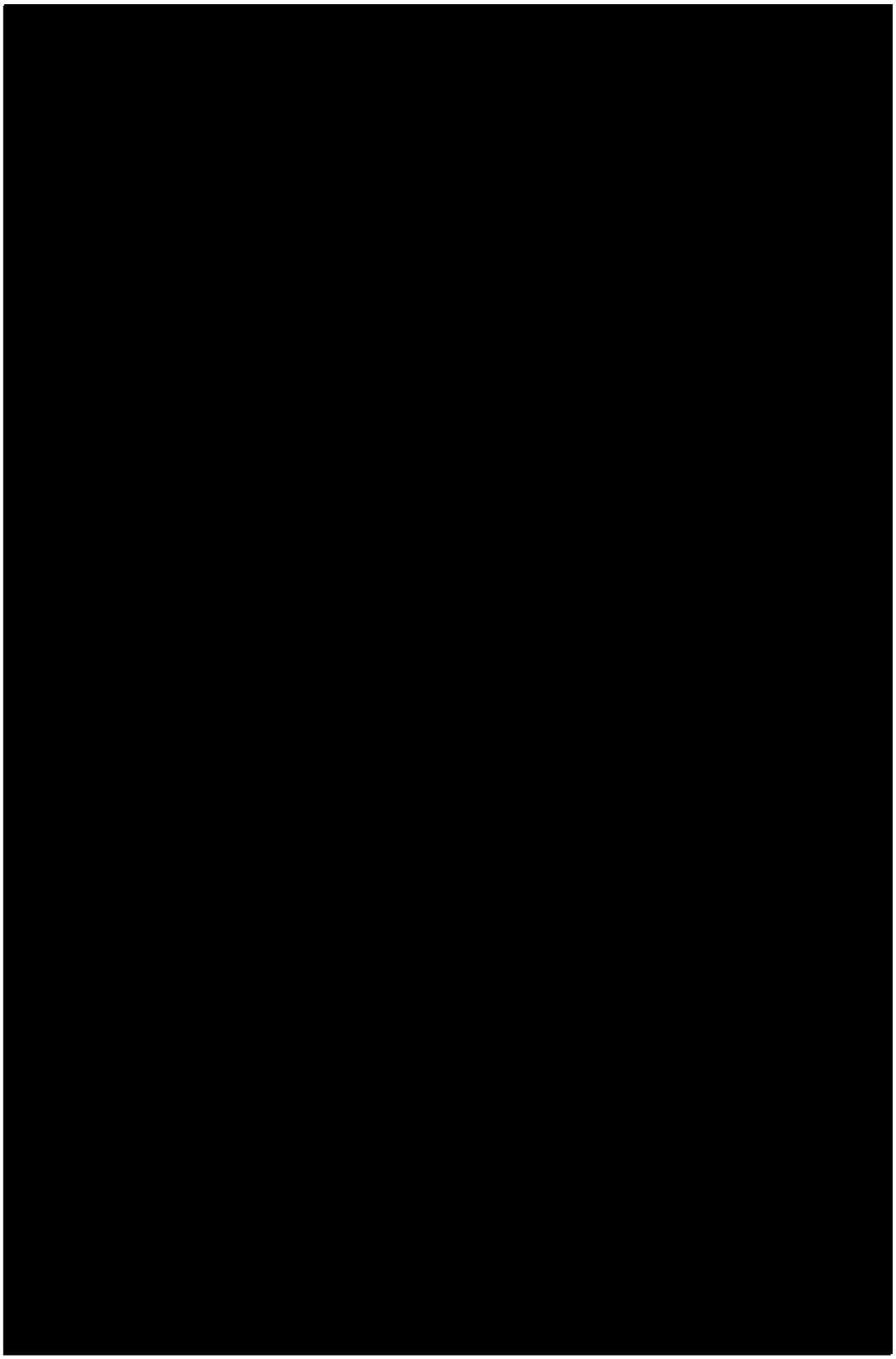
R21-3496 Shiba N, Matsuki M, Takahashi J, et al. Prognostic Importance of Chronic Kidney Disease in Japanese Patients With Chronic Heart Failure -Implications of the CHART Study-. Circ J 2008; 72: 173-178.

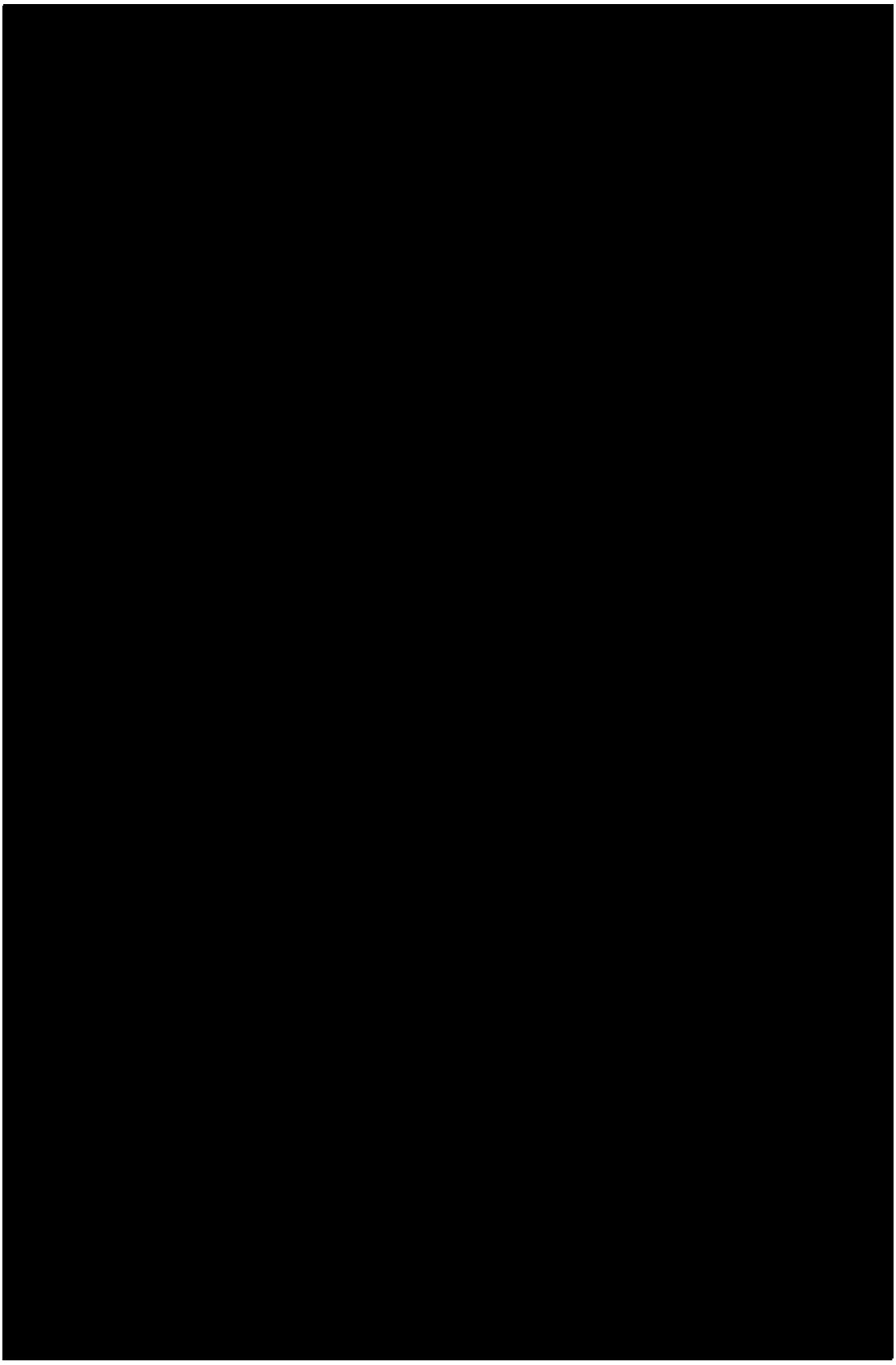
13.2 UNPUBLISHED REFERENCES

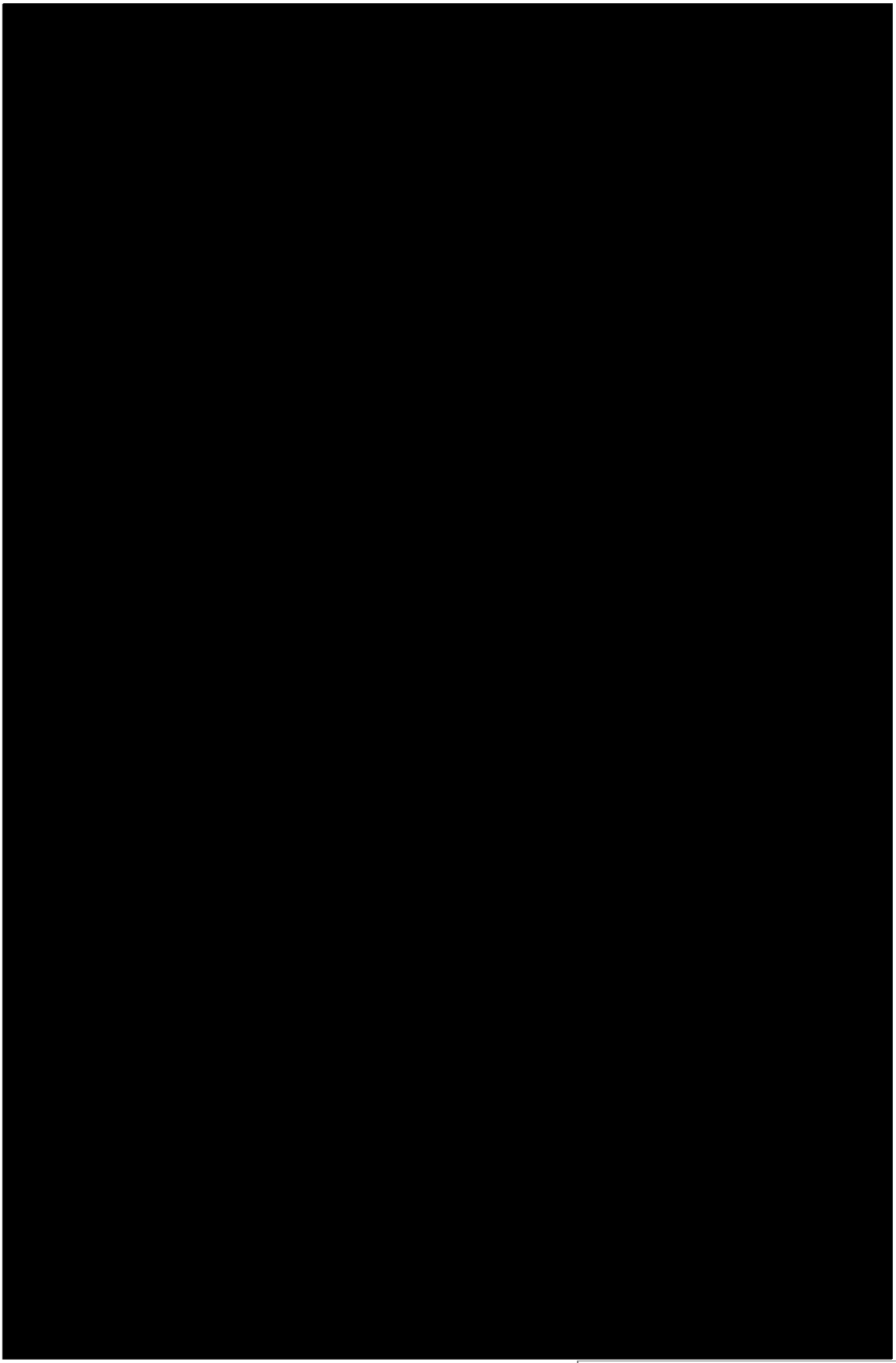
[redacted]

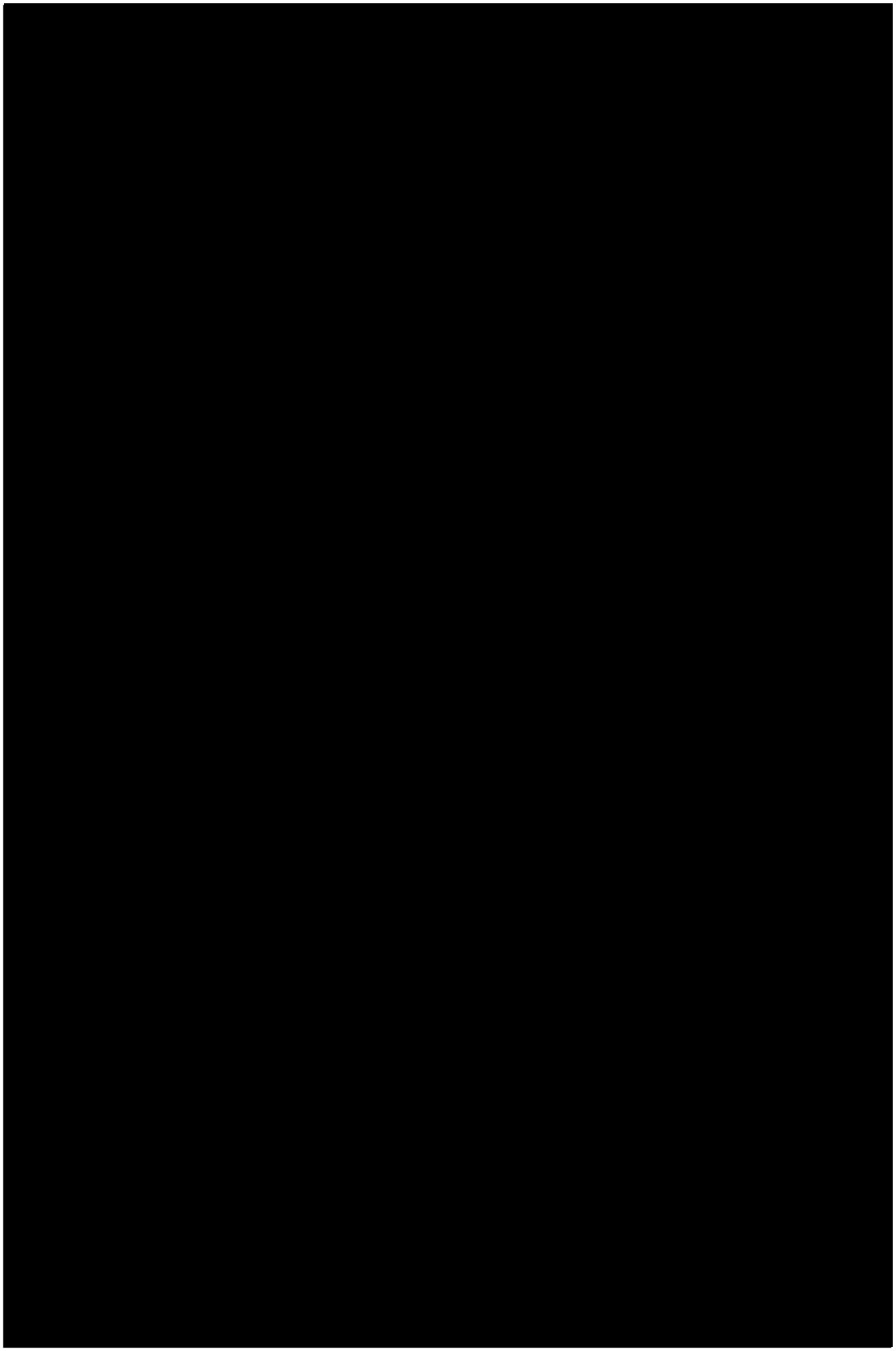


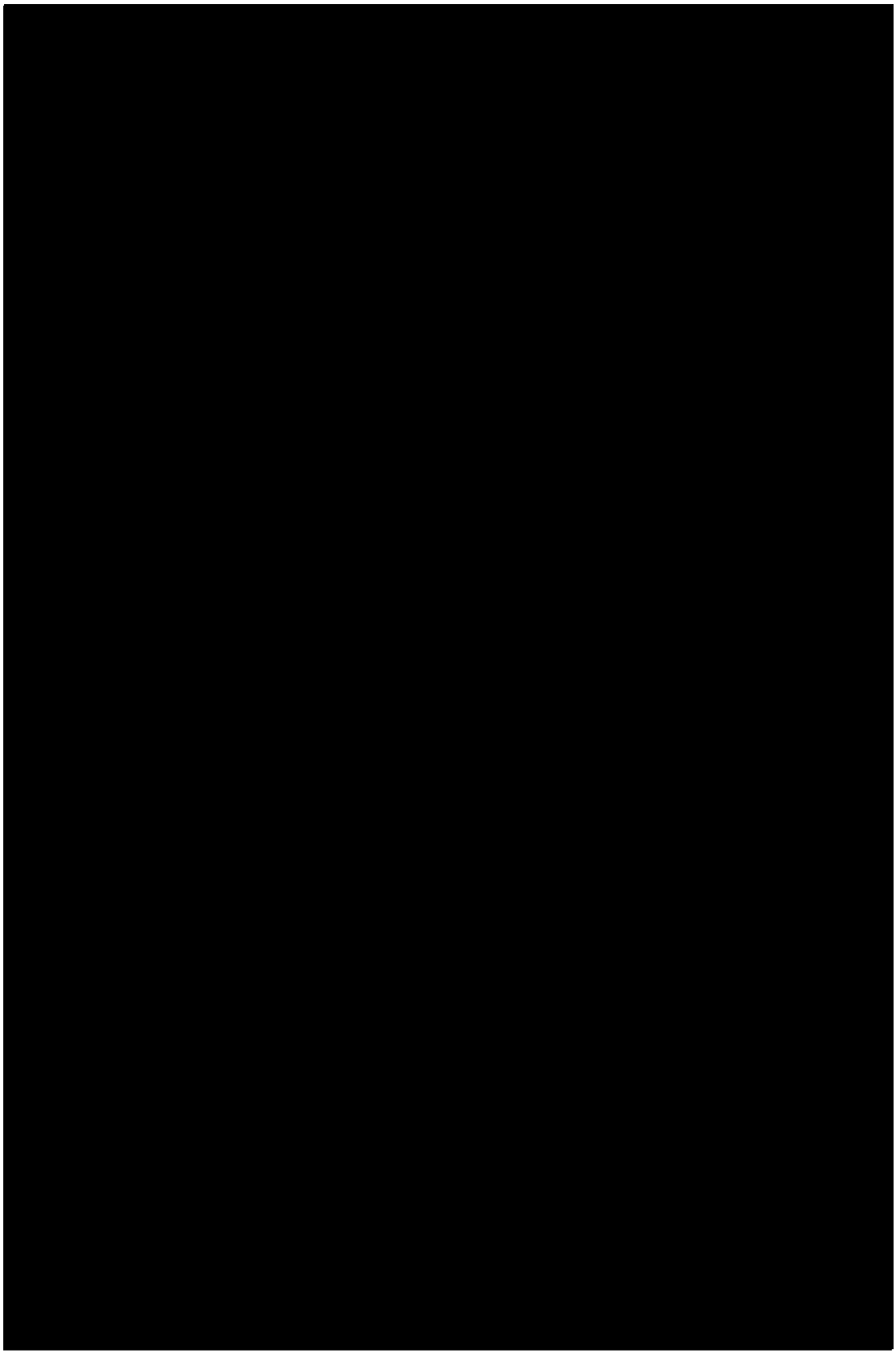












APPROVAL / SIGNATURE PAGE

Document Number: c37302912 **Technical Version Number:4.0**

Document Name: 1245-0286-non-interventional-study-protocol

Title: Post Marketing Surveillance on Long Term Drug Use of JARDIANCE® Tablets in Patients with chronic heart failure in Japan.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	04 Apr 2024 07:37 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**