Observational and Non-Interventional Study (ONIS)
New Data Collection Protocol

Document Number:	c43224154-01
BI Study Number:	1245-0340
BI Investigational Product(s):	Empagliflozin
Title:	Post Marketing Surveillance on Long Term Use of JARDIANCE® Tablets in Patients with Chronic Kidney Disease in Japan.
Brief lay title:	Post Marketing Surveillance of JARDIANCE in Chronic Kidney Disease
Protocol version identifier:	Version 1.0
Date of previous version of protocol:	Not applicable
PASS:	Yes
EU PAS register number:	TBD
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 kidney disease under real-world use.
Country(-ies) of study:	Japan

Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
In case of PASS, add: **MAH contact person:**	[redacted]
In case of PASS, add:	[redacted]
In case of PASS, add:	e-signature is on BIRDS
Date:	22 Apr 2024

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BI	Boehringer Ingelheim
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CHF	Chronic Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRE	Creatinine
CRF	Case Report Form
eCRF	Electronic Case Report Form
DMRP	Data Management and Review Plan
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESKD	End Stage Kidney Disease
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
γ-GTP	Gamma-Glutamyl Transferase
GPSP	Good Post- marketing Study Practice
Hb	Haemoglobin
Hct	Haematocrit
HDL	High Density Lipoprotein
IgA	Immunoglobulin A
IRB	Institutional Review Board
J-PMD Act	Japanese pharmaceuticals and Medical Devices Act
J-RMP	Japan Risk Management Plan
LDL	Low Density Lipoprotein
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHLW	Ministry of health, Labour and Welfare
[redacted]	
NGSP	National Glycohemoglobin Standardization Program
NISnd	Non-interventional Cohort Study with New Data Collection
NT-pro BNP	N-terminal pro-Brain Natriuretic Peptide
ONIS	Observational and Non-interventional Study
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance

RBC	Red Blood Cell
SAE	Serious Adverse Event
SEAP	Statistical and Epidemiological Analysis Plan
SGLT-2	Sodium-Glucose Co-transporter-2
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures
T1DM	Type 1 Diabetes
T2D	Type 2 Diabetes
T2DM	Type 2 Diabetes mellitus
T-BIL	Total Bilirubin
T-CHO	Total cholesterol
TG	Triglycerides
UA	Uric Acid
UACR	Urine Albumin-to-Creatinine Ratio
UPCR	Urine Protein-to-Creatinine Ratio
WBC	White Blood Cell Count

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.

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: 22 Apr 2024	**Study number:** 1245-0340	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable
Title of study:	Post Marketing Surveillance on Long Term Use of JARDIANCE® Tablets in Patients with Chronic Kidney Disease (CKD) 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 CKD 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 the start of the treatment with JARDIANCE® Tablets or until discontinuation of administration.		
Population:	<u>Inclusion criteria</u> - Patients with CKD who are prescribed JARDIANCE® Tablets for CKD according to the current Japanese package insert and who provided written informed consent prior to enrolment in this study. - Patients who have never been treated with JARDIANCE® Tablets (including treatment for T2DM and/or CHF) before enrolment. <u>Exclusion criteria</u> None		

Variables:	These outcomes are reported over the observational period. Outcomes: <u>Primary outcome:</u> - Incidence of adverse drug reactions (focus on the safety specification on Japan Risk Management Plan (J-RMP): The events relevant volume depletion) <u>Secondary outcomes:</u> - Kidney disease progression (defined as incidence of end-stage kidney disease, a sustained decline in eGFR to <10 mL/min/1.73m^2, renal death, or a sustained decline of ≥40% in eGFR from baseline) - Incidence of cardiovascular death - Incidence of all cause death - Incidence of hospitalization for heart failure - Change from baseline in eGFR to the last observation on treatment [redacted]
Data sources:	Patients' data will be collected by electronic Case Report Form on Electronic Data Capture system
Study size:	800 (safety set)
Data analysis:	Descriptive statistics will be summarised for safety and effectiveness.
Milestones:	Planned start of data collection: 1 SEP 2024 Planned end of data collection: 31 MAY 2027 Study Report planned to be archived in 30 APR 2028

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None				

6. MILESTONES

Milestone	Planned Date
Start of data collection	1 Sep 2024
End of data collection	31 May 2027
Registration in the EU PAS register	TBD
Final report of study results:	2Q 2028

7. RATIONALE AND BACKGROUND

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting kidney structure and function. In high-income countries, the prevalence of CKD is about 10% and is likely to increase as average population age rises and diabetes mellitus becomes more prevalent.(R19-0901, R13-2805)

Selective inhibition of sodium-glucose co-transporter-2 (SGLT-2) with empagliflozin causes urinary glucose excretion and reduces blood glucose, weight, plasma circulating volume and blood pressure. This has been shown to translate safely into reduced clinical risk from cardiovascular disease (particularly heart failure and cardiovascular death) in people with type 2 diabetes (T2D) and established cardiovascular disease. SGLT-2 inhibition with empagliflozin also reduces albuminuria and slows the annual decline in estimated glomerular filtration rate in people with T2D who still have preserved kidney function. The kidney effects may result from increased sodium delivery to the kidney's macula densa, which in turn causes glomerular afferent arteriolar vasoconstriction and reduced intraglomerular pressure. Raised intraglomerular pressure is believed to be central to the "final common pathway" of disease progression in CKD. Since SGLT-2 inhibition with empagliflozin also causes glycosuria and acute haemodynamic changes in kidney function in people without diabetes, empagliflozin may also be nephroprotective in conditions without ambient hyperglycaemia, which collectively account for 50 to 70% of patients with CKD worldwide. Patients with established CKD are at substantial risk of progressing to end-stage kidney disease despite the use of medical therapies, including renin-angiotensin system inhibition, so identifying new treatments to delay progression is a priority. Moreover, patients with CKD are at high risk of cardiovascular death and heart failure, which may also be reduced by empagliflozin.
The number of patients treated with empagliflozin in 1245-0137 trial was 3292, including 292 from Japan. Since the high incidence of the events relevant volume depletion have been observed in Japanese patients (5.1% in empagliflozin 10mg group, 1.7% in placebo group) and further study is needed for "patients with eGFR less than 20 mL/min/1.73 m^2 or greater than 90 mL/min/1.73 m^2, UACR less than 200 mg/g, polycystic," etc., PMDA requested to collect more safety information of those patients.

This Post Marketing Surveillance (PMS) with 800 patients has been planned to collect the safety data (especially the events relevant volume depletion) according to the Safety Specification on the J-RMP and PMDA's request.

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 chronic kidney disease in real-world clinical settings in Japan.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Non-interventional cohort study with new data collection (NISnd) (Observational)

9.2 SETTING

9.2.1 Study sites

Sites (hospital and general clinics) at which JARDIANCE® Tablets are available for prescription will be selected in Japan.

Planned number of sites: Approximately 250 Sites

A Good Post-marketing Study Practice (GPSP) personnel explains the objective and design of this study to investigators at study site and establishes a written contract with the head of the study site (e.g., hospital director).

9.2.1.1 Managing Site and Physician/Investigator Selection, Contracting and Training

See ANNEX 3.

9.2.2 Study population

As this is a real-world, observational, non-interventional study where 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 CKD who are prescribed JARDIANCE® Tablets for CKD according to the current Japanese package insert and who provided written informed consent prior to enrolment in this study.
- Patients who have never been treated with Empagliflozin (including treatment for T2DM and CHF) before enrolment.

Exclusion criteria
None

Registration period
From 01 September 2024 to 28 February 2026

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 patients will be observed for up to 52 weeks after the start of the treatment with JARDIANCE® Tablets or discontinuation of administration.

9.2.4 Study discontinuation

Boehringer Ingelheim (BI) reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any effectiveness / safety information that could significantly affect continuation of the study, or any other administrative reasons
3. Violation of GPSP, the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

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

9.2.5 Flow chart

Time point / Item	Observation period				
	Baseline	Week 12	Week 26	Week 40	Week 52 or at discontinuation
Registration	X*				
Demographics	X				
Medical history / Concomitant disease	X				
Previous medications	X				
Administration status of JARDIANCE® Tablets		X (Record throughout the observation period)			
Concomitant medications	X (Record throughout the observation period)				
Concomitant therapy	X (Record throughout the observation period)				
Blood pressure, pulse rate and body weight	(X)	(X)	(X)	(X)	(X)
Laboratory tests	(X)	(X)	(X)	(X)	(X)
Adverse events		X (Examine throughout the observation period)			
Pregnancy status	X	X	X	X	X
e-signature, eCRF transmit**			X		X

(X) : If applicable
* : Patients administered JARDIANCE® Tablets should be registered within 14 days from the day of first administration.
** : When an adverse event occurs or upon discontinuation, data should be entered into the eCRF and transmitted using the EDC system.

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).

9.3.2 Outcomes

These outcomes are reported over the observational period.

9.3.2.1 Primary outcomes

The primary outcome of this study is the incidence of ADRs (focus on the events relevant volume depletion).
The ADR 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

- Kidney disease progression (defined as incidence of ESKD, a sustained decline in eGFR to <10 mL/min/1.73m^2, renal death, or a sustained decline of ≥40% in eGFR from baseline)
- Cardiovascular death
- All cause death
- Hospitalization for heart failure
- Change from baseline in eGFR to the last observation on treatment

ESKD is defined as the initiation of maintenance dialysis or receipt of a kidney transplant

[redacted]

9.3.3 Covariates

The following variables based on physician's report will be considered important baseline (the start of the treatment with JARDIANCE® Tablets) characteristics and potential risk factors for the outcomes of interest.

Demographics:
Hospitalization/outpatients, gender, year of birth, indication, diagnosed date of CKD, cause of kidney disease (diabetic kidney disease, hypertensive nephrosclerosis, glomerulonephritis [the type of nephritis: IgA nephropathy, focal segmental gomerulosclerosis, etc], multiple pustular kidney, transplanted kidney, other), pregnancy status, height, body weight, body mass index (derived), waist circumferences, smoking histoy, alcohol habit, eGFR at baseline, eGFR at 12 months and 6 months before the baseline (derived)

Medical history / Concomitant disease:
T1DM/T2DM, hypertension, dyslipidemia, heart failure, ischemic heart disease, and hypersensitivity factor, others

Previous / Concomitant medications and therapies:
Previous medications (in the 3 months before starting JARDIANCE® Tablets):
Dose, frequency, start and end date, reason for use

Diet therapy, kinesitherapy
Start and end date

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

Physical measurements:
Pulse rate, blood pressure (systolic / diastolic), body weight

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-pro BNP
Urinalysis:	Glucose, protein, albumin, ketone, creatinine, Urine Protein-to-Creatinine Ratio (UPCR), Urine Albumin-to-Creatinine Ratio (UACR)

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

UACR will be derived from urinary albumin and creatinine.

Normal:	UACR <30 mg/g
Microalbuminuria	UACR ≥30 mg/g and <300 mg/g
Macroalbuminuria	UACR ≥300 mg/g

UPCR will be derived from urinary protein and creatinine.

Normal:	UPCR <0.15 g/g

Microalbuminuria UPCR ≥0.15 g/g and <0.50 g/g
Macroalbuminuria UPCR ≥0.50 g/g

Enzymatic method (R12-4182):
eGFR（mL/min/1.73 m^2）= 194×Creatinine (mg/dL) $^{-1.094}$×Age$^{-0.287}$
For female, ×0.739
Jaffe rate assay (R09-1573):
eGFR（mL/min/1.73 m^2）= 175×Creatinine (mg/dL) $^{-1.154}$×Age$^{-0.203}$
For female, ×0.742

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

800 patients (safety analysisset) will be included in the study. 1000 patients will be enrolled to attrition.

The proportion of patients with relevant volume depletion events in the empagliflozin group in the Japanese population of EMPA-KIDNEY trial was 5.1% (15/292). Assuming that proportion is the true proportion of patients that will experience relevant volume depletion events in this PMS study, the precision of the estimate of the proportion of the events relevant volume depletion would be approximately 1.5%, as one-sided width of the 95% confidence interval, if 800 Japanese patients are available as safety analysis population. Possible risk factor associated with the events relevant volume depletion is the concomitant diuretics, and the observed proportion of it was 19.5% (57/292) in the Japanese population of EMPA-KIDNEY trial. Assuming the true proportion of "yes" risk factor in the study is 19.5%, the true proportion of the events relevant volume depletion in the patient population with "yes" risk factor is 5.1%, and the true odds ratio of 2.5 for "yes" risk factors to "no" risk factor, the power to detect differences of the proportion of the events relevant volume depletion between "yes" risk factor and "no" risk factor at a two-sided significance level of 5% is 82% (which is more than 80%), when 800 Japanese patients are included in the PMS study.

9.6 DATA MANAGEMENT

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

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

9.7 DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the Statistical and Epidemiological Analysis Plan (SEAP), which will be finalized before the end of data collection.

This is a real-world, observational, 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. Additional information on planned subgroup analyses are provided in the SEAP.

9.7.1 Main analysis

In this PMS, since the primary outcome is the incidence of ADRs (with a focus on the events relevant to volume depletion), the main analysis is to estimate frequency and proportion (n,%) of patients experiencing events and its corresponding confidence interval (CI). The details are given in section 9.7.3.

[redacted]

[redacted]

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

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the ONIS-DMRP.
All processes are conducted according to GPSP Standard Operating Procedures (SOP) ([redacted]). 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 information bias caused by patients not visiting the sites and outcomes not captured in this study.

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

Case Report Forms (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 investigator's site.

Data reported on the Electronic Case Report Forms (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

When the study is completed, the investigator should inform the head of the study site of the completion in writing, and the head of the study site should promptly inform the IRB and sponsor of the completion in writing if needed.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, J-PMD Act, GPSP ordinance, and the relevant Boehringer Ingelheim Standard Operating Procedures (SOPs).

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.
In this study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) prior to enrolment in this study, according to the relevant BI Standard Operating Procedures (SOPs) in order for the participant to be eligible for study enrolment.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study 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 Adverse Event (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 unfavorable 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 Drug Reaction
An Adverse Drug Reaction (ADR) 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 authorization 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 Serious Adverse Event (SAE) is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- 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 hospitalization but might jeopardize 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 hospitalization 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 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 ONIS. Once a patient has been enrolled in the study and has taken JARDIANCE® Tablets, the investigator must discontinue the treatment with JARDIANCE® Tablets immediately and report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).
In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the Non-interventional Study eCRF is to be completed and forwarded as well as soon as possible.

All AE collection and reporting is required.

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.

Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Patient Safety and Pharmacovigilance

All AEs and Drug Exposure during Pregnancymust be reported immediately after the data entry by the investigator on the ONIS eCRF and / or Pregnancy Monitoring Form until the end of the study and provide BI unique entry point:

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and send eCRF.

Information required

For each reportable AE, the investigator should provide the information requested on the appropriate (e)CRF page.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse Event reporting to regulatory agencies will be done by the Marketing Authorisation Holder (MAH) according to 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 investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no 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.

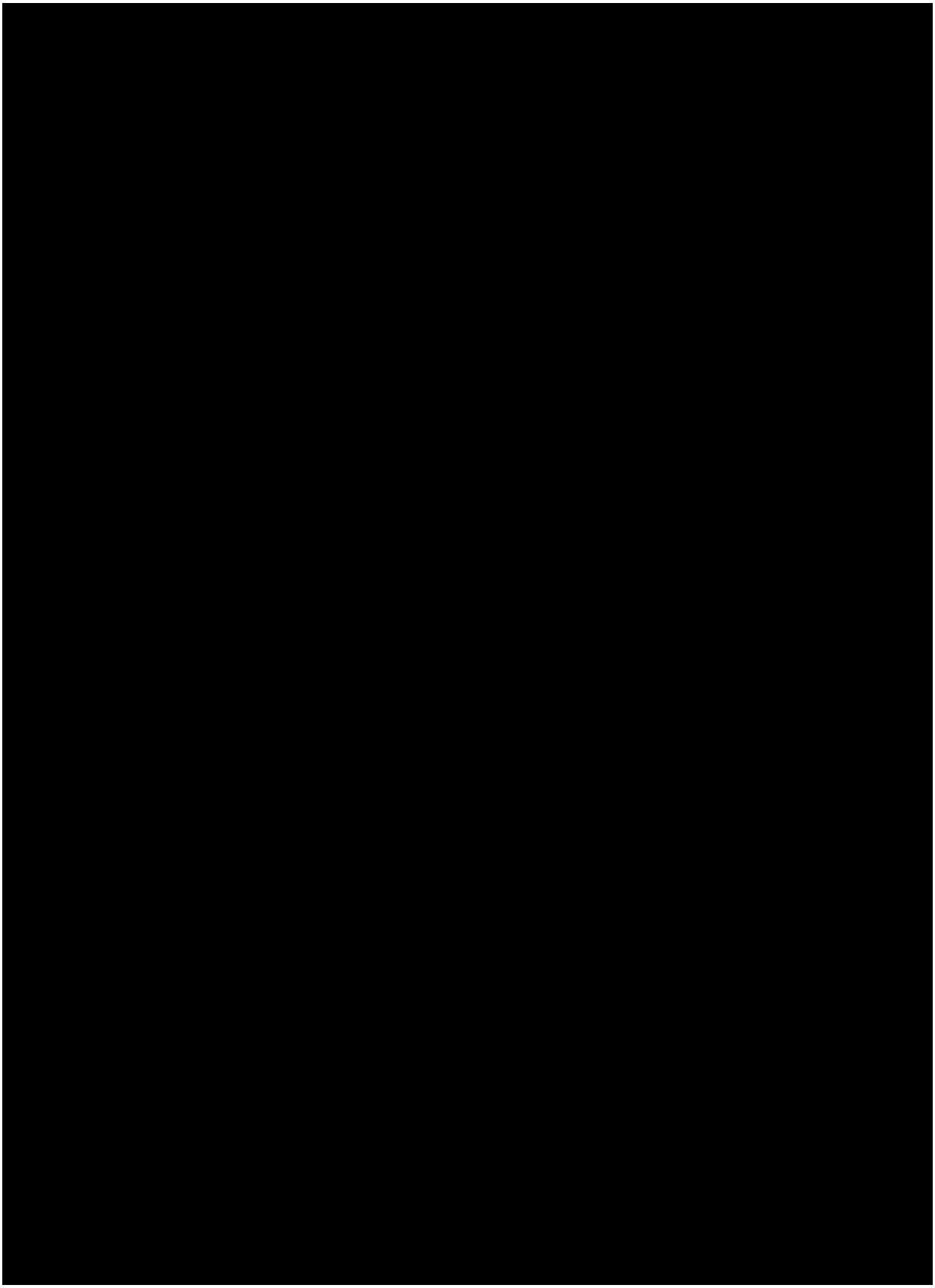
13. REFERENCES

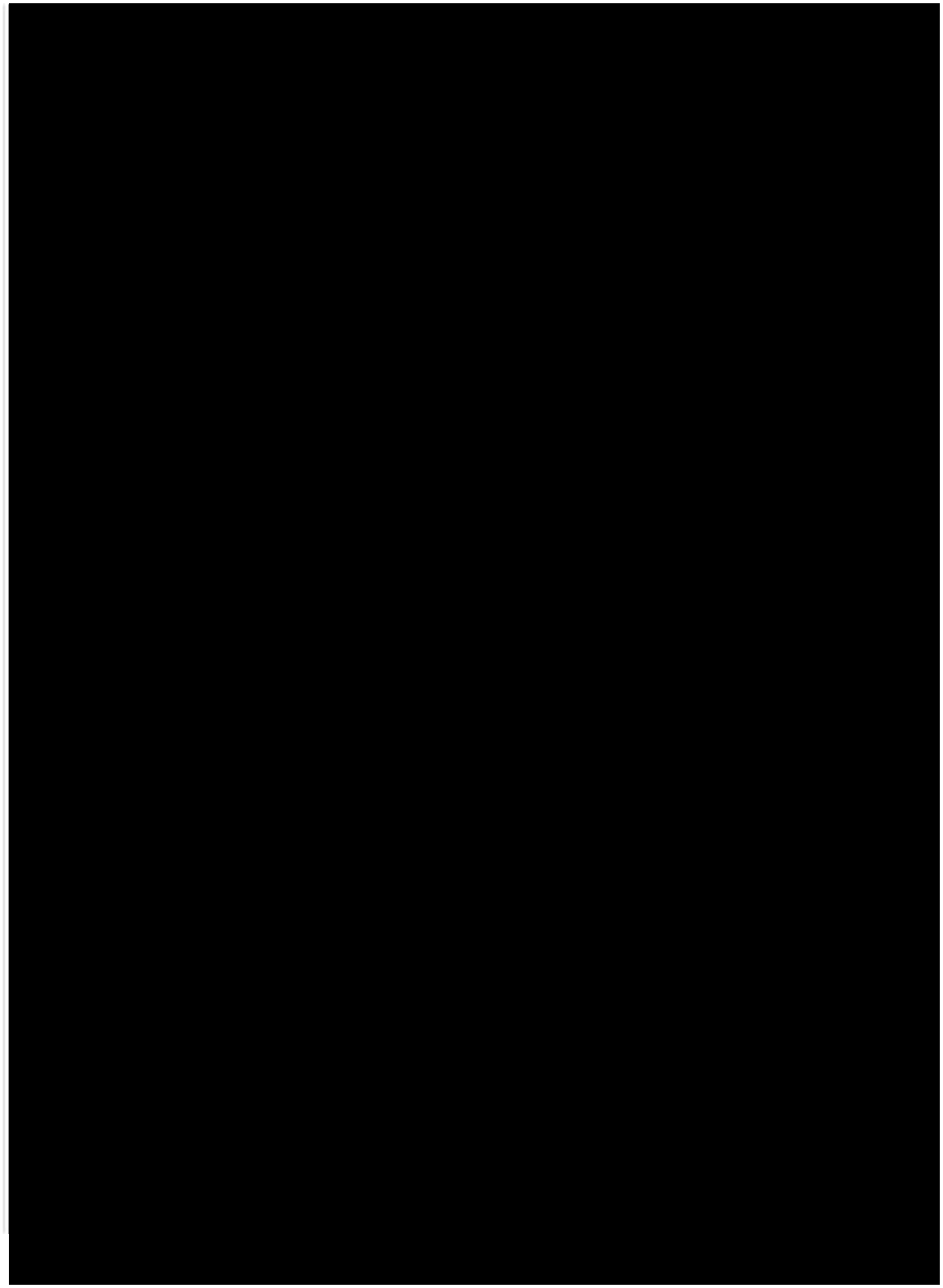
13.1 PUBLISHED REFERENCES

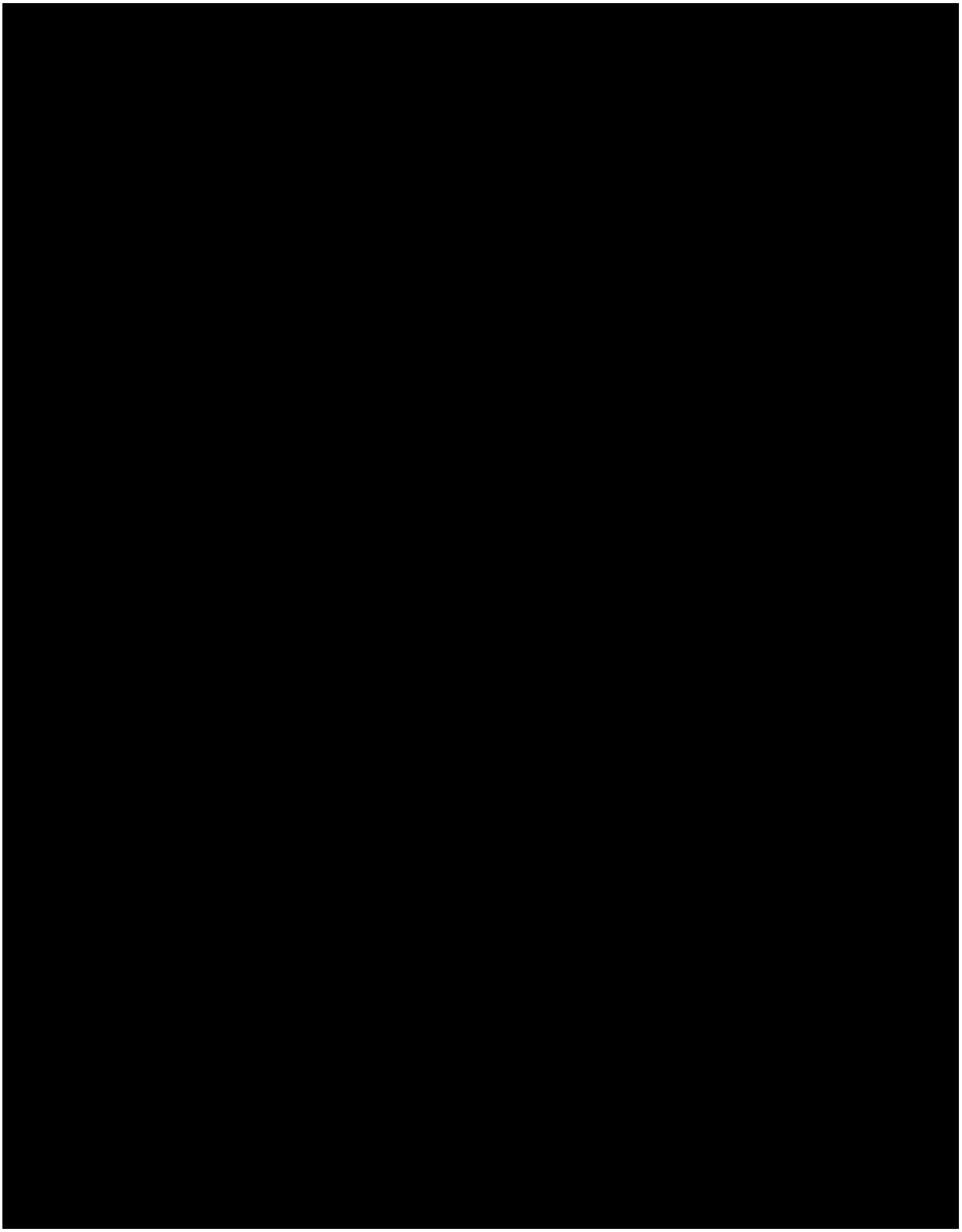
R19-0901 Levey AS, Coresh J. Chronic kidney disease. Lancet 2012; 379(9811): 165-80.
R13-2805 Stevens PE, O'Donoghue DJ, de Lusignan S, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int 2007; 72(1): 92-9.
R12-4182 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, Collaborators Developing the Japanese Equation for Estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis; 2009; 53(6); 982-992.
R09-1573 Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function - measured and estimated glomerular filtration rate. N Engl J Med; 2006; 354(23); 2473-2483.

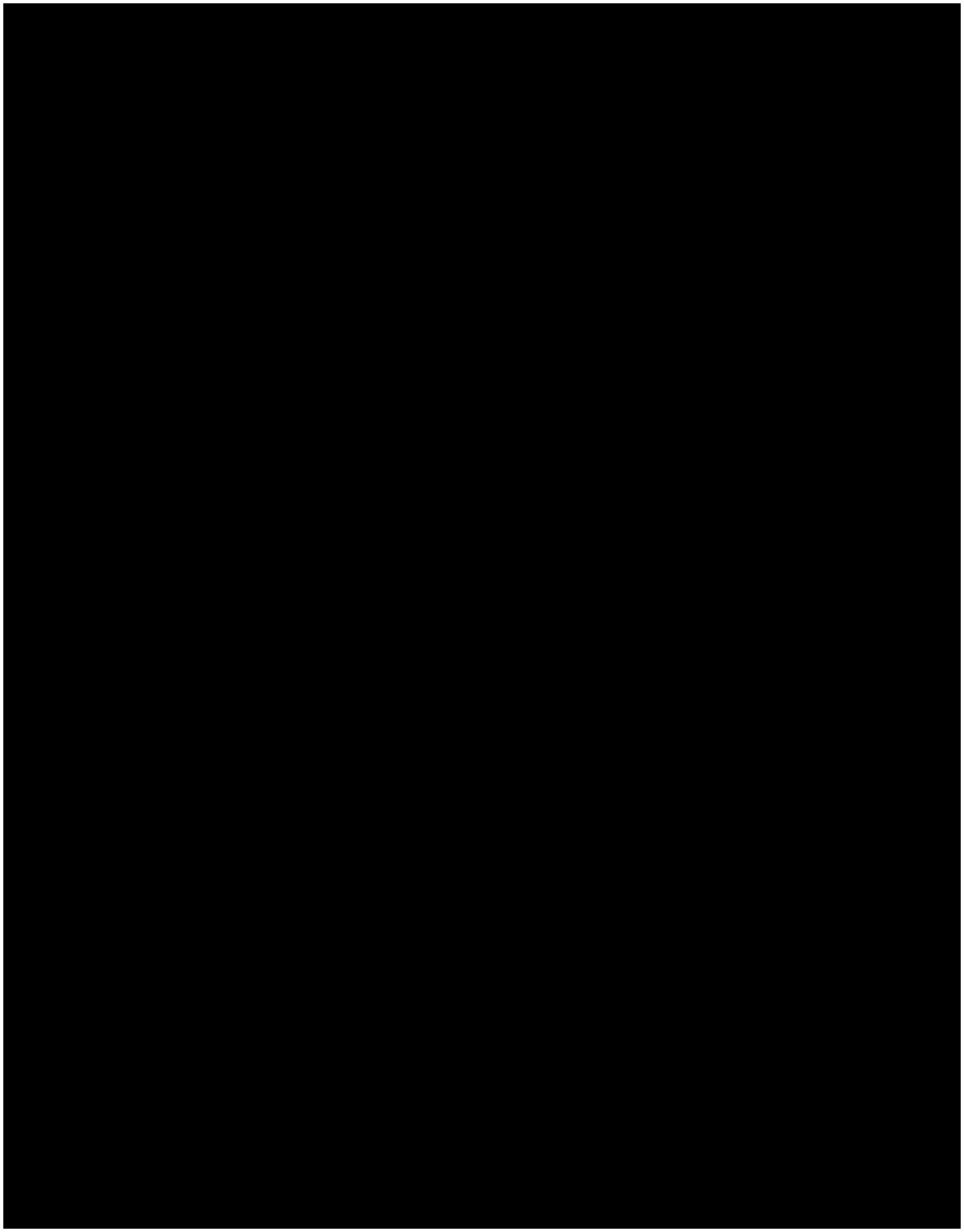
13.2 UNPUBLISHED REFERENCES

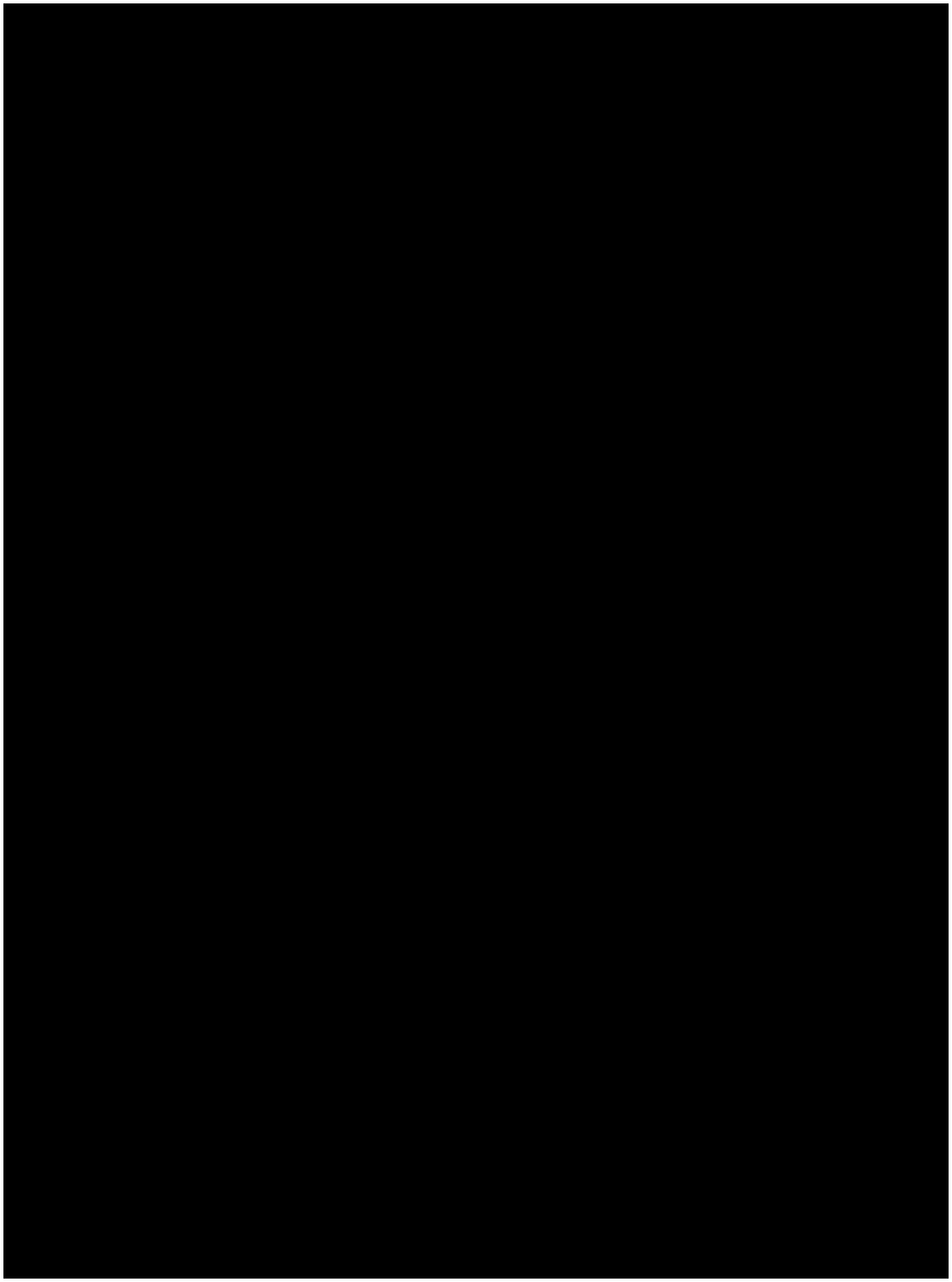
[redacted]

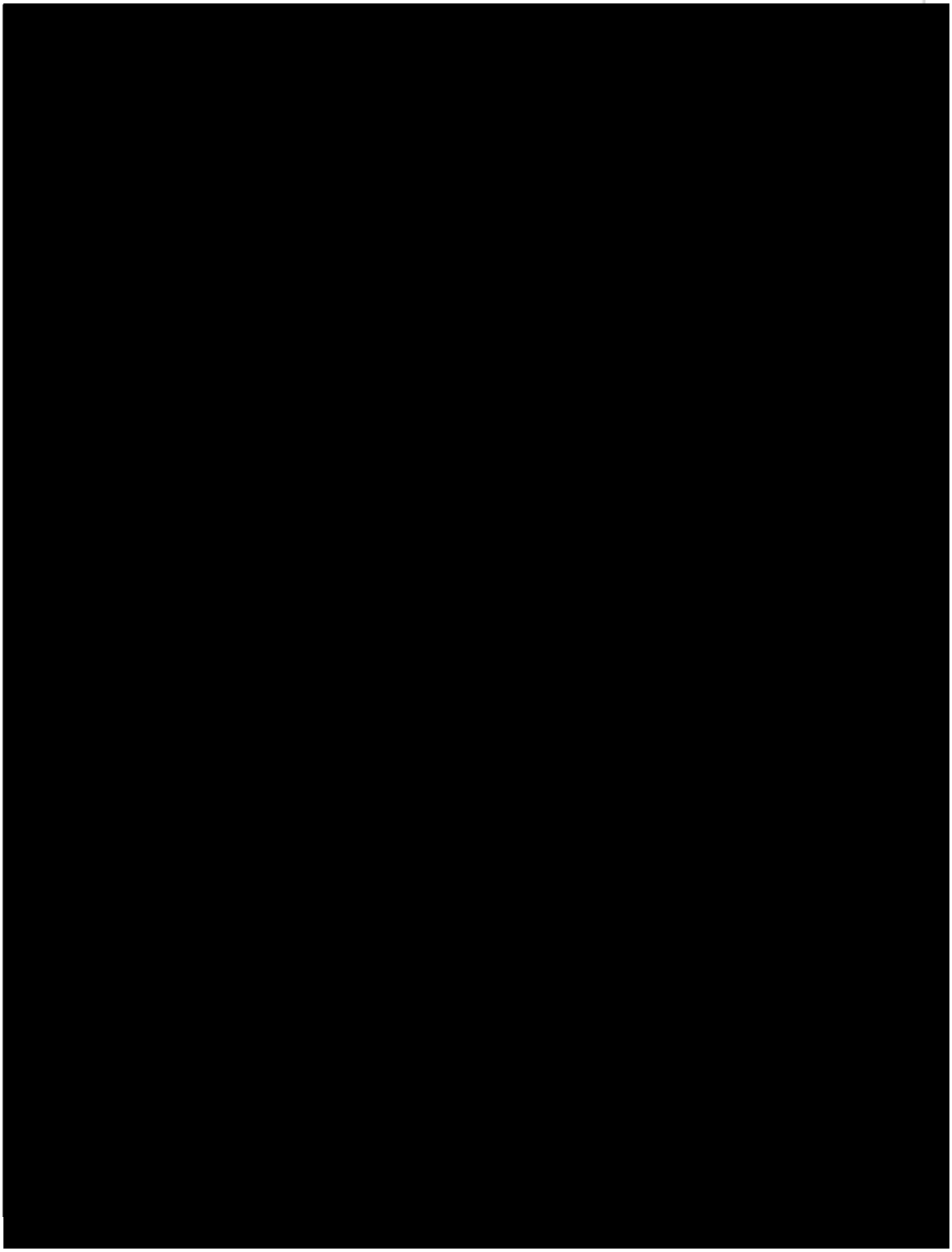












APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	25 Apr 2024 07:44 CEST
Approval-EU Qualified Person Pharmacovigilance		25 Apr 2024 08:26 CEST
Approval		25 Apr 2024 08:46 CEST
Approval-[redacted] Pharmacovigilance		25 Apr 2024 08:58 CEST
Approval		26 Apr 2024 02:22 CEST
Approval-[redacted] Pharmacovigilance		26 Apr 2024 08:24 CEST
Approval		01 May 2024 12:46 CEST
Approval		08 May 2024 23:33 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	09 May 2024 00:31 CEST