Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c27548067-06**
BI Study Number:	1199-0387
BI Investigational Product(s):	Nintedanib
Title:	Post-marketing Surveillance on long term use of Ofev Capsules in Systemic Scleroderma associated Interstitial Lung Disease (SSc-ILD) in Japan
Brief lay title	PMS of Ofev Capsules in SSc-ILD
Protocol version identifier:	Version 5.0
Date of last version of protocol:	6.Oct.2023
PASS:	Yes
EU PAS register number:	EU PAS32905
Active substance:	Nintedanib
Medicinal product:	Ofev Capsules 300 mg daily (150 mg b.i.d) or 200 mg (100 mg b.i.d)
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted].
Joint PASS:	No
Research question and objectives:	The primary objective is to confirm the incidence of adverse drug reactions (focus on gastrointestinal symptoms including diarrhoea and nausea) to Ofev Capsules seen in clinical trials with real world data generated in patients with SSc-ILD.
Country(-ies) of study:	Japan
Author:	[redacted]

Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	e-signature is on BIRDS
Date:	5.Apr.2024
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[redacted]

2. LIST OF ABBREVIATIONS

ACA	Anti-Centromere Antibodies
ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
APTT	Activated partial thromboplastin time
(anti-)RNA Pol III	Anti-RNA polymerase III antibodies
AST	Aspartate aminotransferase
ATA	Anti-topoisomerase antibodies
BI	Boehringer Ingelheim
BNP	Brain natriuretic peptide
CA	Competent Authority
CCDS	Company Core Data Sheet
CCL18	CC-Chemokine Ligand 18
CI	Confidence Interval
CK	Creatinine Kinase
Cr	Creatinine
CRF	Case Report Form
CRP	C-reactive protein
CTP	Clinical Trial Protocol
DLco	Carbon Monoxide diffusion capacity
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-5L	EuroQol 5-Dimensional quality of life Questionnaire (five-level version)
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GPSP	Good Post-marketing Study Practice
GVP	Good Pharmacovigilance Practices
Hb	Hemoglobin
Hct	Hematocrit
HRCT	High-Resolution Computed Tomography
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
KL-6	Krebs von den Lungen-6
LDH	Lactase Dehydrogenase
MAH	Marketing Authorisation Holder

MedDRA	Medical Dictionary for Drug Regulatory Activities
MHLW	Ministry of Health Labour and Welfare
MMRM	Mixed Model Repeated Measures
[redacted]	
NIS	Non-Interventional Study
NSIP	Non-specific Interstitial Pneumonia
NT-proBNP	N-terminal pro-brain natriuretic peptide
PASS	Post-Authorization Safety Study
PMD	Pharmaceutical and Medical Device
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
PH	Pulmonary Hypertension
PT	Prothrombin Time
RBC	Red Blood cell Count
RMP	Risk Management Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SP-D	Surfactant Protein D
SSc	Systemic Sclerosis
TSAP	Trial Statistical Analysis Plan
UIP	Usual Interstitial Pneumonia
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.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Ofev Capsules			
Name of active ingredient: Nintedanib			
Protocol date: 24 Sep.2019	**Study number:** 1199-0387	**Version/Revision:** Version 5.0	**Version/Revision date:** 5.Apr.2024
Title of study:	Post-marketing Surveillance (PMS) on long term use of Ofev Capsules in Systemic Scleroderma associated Interstitial Lung Disease (SSc-ILD) in Japan		
Rationale and background:	This PMS plan is proposed as additional pharmacovigilance plan of the Japanese RMP. In Japan, post-approval execution of PMS is one of the portions 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. Ten years after approval for new indication of orphan 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 SENSCIS trial evaluated the efficacy and safety of nintedanib in patients with SSc-ILD (NCT02597933). As the number of Japanese patients treated with nintednib in SENSCIS trial was few (34, total: 288), confirmation of the safety profile of nintedanib treatment for SSc-ILD patients in the real world clinical setting was required by PMDA.		
Research question and objectives:	In the SENSCIS trial, the incidence of gastrointestinal symptoms on the administration of Ofev tended to be higher compared to the clinical trial results for IPF. Real world data have already been collected over 3 years on IPF through post-marketing experience after 2015. Specifically, the safety data has been collected in over 5,000 patients in the ongoing all case survey of PMS on IPF (1199.202). However, the safety data/profile in the Japanese patients with IPF who had demographics characteristics often observed in SSc-ILD patients (female and≥30- <65 age range) is		

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	limited in 1199.202. This PMS (1199-0387) is conducted in order to accumulate the safety data under the real world setting in Japanese SSc-ILD patients to assess the safety profile, especially gastrointestinal symptoms including diarrhoea and nausea in this patient population. The primary objective is to confirm the incidence of adverse drug reactions (focus on gastrointestinal symptoms including diarrhoea and nausea) to Ofev seen in clinical trials with real world data generated in patients with SSc-ILD		
Study design:	Non-interventional cohort study with new data collection (NISnd) Patients newly initiated Ofev Capsules will be enrolled and followed up to 104 weeks (2 years) or until discontinuation of administration.		

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Name of active ingredient: Nintedanib			
Protocol date: 24 Sep.2019	**Study number:** 1199-0387	**Version/Revision:** Version 5.0	**Version/Revision date:** 5.Apr.2024
Population:	Inclusion criteria - Patients in Japan with SSc-ILD who are prescribed with Ofev Capsules and have never been treated with Ofev Capsules before enrolment will be included. Exclusion criteria None		
Variables:	Outcomes: Primary outcome: Incidences of adverse drug reactions (ADRs) (focus on gastrointestinal symptoms including diarrhoea and nausea) Secondary outcomes: None [redacted]		

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Data sources:	Patients' data will be collected by electronic Case Report Form on Electronic Data Capture system		
Study size:	500 (safety set)		
Data analysis:	Analyses are descriptive in nature, incidence rates and corresponding confidence intervals will be given, for safety specification item (gastrointestinal symptoms including diarrhoea and nausea and other ADRs which are identified (other than gastrointestinal symptoms including diarrhoea and nausea) on J-RMP in terms of Ofev for SSc-ILD.		
Milestones:	Planned start of data collection: 1 APR 2020 Planned end of data collection: 30 Sep 2026 Study Report planned to be archived in 3Q 2027		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1.	10.Jan.2020	6.	Added the register information from EU PAS register dated on 24.Dec.2019	Registration to EU PAS
2.	10.Jan.2020	7.,8.,11.	Changed descriptions about safety specification in align with J-RMP modification (PMS plan mapping was changed from hepatic disorders to gastrointestinal symptoms)	Directions from PMDA
3.	10.Jan.2020	9.	Added outcome and revised covariate settings and ANNEX 2. Updated the descriptions in align with safety specification modification	Directions from PMDA
4.	21.Jan.2022	6.	Changed Milestones	Period extension (Due to Covid19 impact, and rare patient existence)
5.	21.Jan.2022	9.2.2.2	Changed Registration period	Ensure the required number of patients
6.	6.Oct.2023	6., 9.2.2.2	Changed Milestones and	Period extension (Ensure the

			Changed Registration period	required number of patients) This amendment is non-substantial.
[redacted]				
8.	5.Apr.2024	9.6	Amendment (non-substantial)	Contract 2 of 9.6 DATA MANAGEMENT was changed from 1 Apr 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 2020
End of data collection	30 Sep 2026
Registration in the EU PAS register	24 December 2019
Final report of study results:	3Q 2027

7. RATIONALE AND BACKGROUND

Systemic sclerosis (SSc) is a devastating disease of unknown aetiology. It is a rare disease [R14-4918, R14-4927], characterised by systemic (multi-organ) immunological, vascular, and fibrotic abnormalities, with a heterogeneous clinical course. Fibrosis, the hallmark of the disease, can affect skin and internal organs [R18-2777]. The processes underlying fibrosis include activation of resident fibroblasts and differentiation of various other cell sources into activated myofibroblasts, which are the source of excessive extracellular matrix production and deposition in the lesion tissue. These processes are thought to be fundamentally similar, regardless of the specific organ involved [R18-2777, R18-3578].

Skin thickening and hardening is observed in the majority of patients with SSc [R17-0419]. The 2 major disease subsets, defined based on the extent of skin fibrosis, are limited cutaneous SSc, with skin involvement generally limited to the hands, face, and feet, and diffuse cutaneous SSc, with skin involvement also proximal to the elbows and knees [R17-0352].

Interstitial lung disease (ILD) is one of the most frequent disease manifestations, which progresses more rapidly in the first years after diagnosis of SSc [R16-0081, R17-0317, R15-2466, R15-6261, R17-0419] and is the main cause of SSc-related deaths.

Nintedanib is a small molecule that inhibits a distinct spectrum of receptor tyrosine kinases and non-receptor tyrosine kinases, including vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor receptors, Src family kinases (Src, Lck, and Lyn), and colony stimulating factor 1 receptor. These kinases and their down-stream signalling cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling.

In in vitro and animal studies in multiple models of SSc/SSc-ILD and other organ fibrosis, nintedanib has shown inhibitory effects on fibrosis in the lung, skin, heart, kidney, and liver. Nintedanib also ameliorated vascular manifestations in an animal model of SSc.

Nintedanib (Ofev®), at a recommended dose of 150 mg twice daily (bid), is an approved treatment for idiopathic pulmonary fibrosis (IPF) in more than 65 countries. Nintedanib was shown to reduce the annual rate of decline in forced vital capacity (FVC) in patients with IPF, consistent with slowing disease progression.

A statistically significant effect of nintedanib on the primary endpoint of the annual rate of decline in FVC was demonstrated in the 52-week phase III trials 1199.32 (INPULSIS®-1) and 1199.34 (INPULSIS®-2). In the pooled analysis of the INPULSIS® trials, the adjusted rate of decline in FVC was -114 mL/year in the nintedanib group and -224 mL/year in the placebo group. The adjusted difference between the treatment groups was 110 mL/year (95% CI 76, 144; $p<0.0001$), corresponding to a relative reduction of ~50%. In addition, in the pooled analysis, the proportion of FVC responders, defined as patients with no absolute decline in FVC% predicted >5% at 52 weeks, was higher for nintedanib (53.0%) than placebo (38.8%), resulting in an odds ratio of 1.84 (95% CI 1.43, 2.36). The proportion of FVC responders, using a 10% threshold, was also higher for nintedanib (70.1%) compared with placebo

(60.5%), with an odds ratio of 1.58 (95% CI 1.21, 2.05). Overall mortality over 52 weeks was numerically lower in the nintedanib group (5.5%) compared with the placebo group (7.8%) in the pooled analysis. The analysis of the time to death over 52 weeks resulted in a hazard ratio (HR) of 0.70 (95% CI 0.43, 1.12). Data on long-term treatment of patients with IPF with nintedanib are available from 2 open-label extension trials 1199.35 and 1199.33 (INPULSIS-ON®). The median exposure to nintedanib was 27.2 months in trial 1199.35 and 31.5 months in INPULSIS-ON®. Changes in FVC in both trials were generally consistent with those seen in the 52-week trials, suggesting a sustained effect of nintedanib on lung function in the long-term.

The safety profile of nintedanib has been investigated comprehensively in IPF and established in this indication in >60 000 patient-years exposure postmarketing. The risks of treatment with nintedanib are primarily related to the gastrointestinal tract (diarrhoea, nausea, vomiting, abdominal pain, pancreatitis) and increases in liver enzymes and bilirubin, including drug-induced liver injury (DILI). Based on data from clinical trials and post-marketing and supported by population pharmacokinetic models, patients with low body weight (<65 kg), Asian, and female patients have a higher risk of liver enzyme elevations with nintedanib treatment. Risks of nintedanib treatment also include hypertension, bleeding, thrombocytopenia, gastrointestinal perforation, thrombo-embolism, decreased appetite, decreased weight, rash, and pruritus.

The SENSCIS trial is a randomised, placebo-controlled Phase III trial that evaluated the efficacy and safety of nintedanib in patients with SSc-ILD (NCT02597933).

As the number of Japanese patients treated with nintednib in SENSCIS trial was few (34, total: 288), confirmation of the safety profile of nintedanib treatment for SSc-ILD patients in the real world clinical setting was required by PMDA.

[redacted]propose “PMS with 500 patients as safety analysis set” that will take into consideration the following points.

- Although the safety profile in Ofev was consistent between SSc-ILD patients and IPF patients in the clinical trials, the incidence of hepatic enzyme elevation tends to be high in Japanese patients in the clinical trial for IPF.
- The difference in demographics between SSc-ILD patients and IPF patients is gender and age. Characteristic demographics with SSc-ILD is female and ≥30- <65 age range. Female patients tend to have lower body weight.
- Real world data have already been collected over 3 years on IPF through post-marketing experience after 2015. Specifically, the safety data has been collected in over 5,000 patients in the ongoing all case survey of PMS on IPF (1199.202). However, the safety data/profile in the Japanese patients with IPF who had demographics characteristics often observed in SSc-ILD patients (female and≥30- <65 age range) is limited in 1199.202.
- This PMS (1199-0387) is conducted in order to accumulate the safety data under the real world setting in Japanese SSc-ILD patients who are expected to have lower body weight and to assess the safety profile, especially gastrointestinal symptoms including diarrhoea and nausea in this patient population.

In Japan, Ofev Capsiles for SSc-ILD indication has received marketing approval on 20.December 2019.

This PMS plan is proposed as additional pharmacovigilance plan of the Japanese RMP.
In Japan, post-approval execution of PMS is one of the portions 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. Ten years after approval for new indication of orphan 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.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to confirm the incidence of adverse drug reactions (focus on gastrointestinal symptoms including diarrhoea and nausea) to Ofev Capsules seen in clinical trials with real world data generated in patients with SSc-ILD.

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 of Ofev Capsules in real-world setting in Japanese patients with SSc-ILD.

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 Ofev Capsules are available for prescription.

Planned number of site: Approximately 200 Sites

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.

9.2.2.1 Inclusion/ exclusion criteria

Inclusion criteria
- Patients in Japan with SSc-ILD who are prescribed with Ofev Capsules and have never been treated with Ofev Capsules before enrolment will be included.

Exclusion criteria
None

9.2.2.2 Registration period

From April 2020 to June 2024

9.2.2.3 Patient registration method

The registration method will be a continuous investigation system. Patients who begin treatment with Ofev Capsules after the conclusion of the contract will be registered by entering necessary information in the Electronic Data Capture (EDC) system within 14 days as possible whenever from the day of treatment initiation (inclusive).

Patient registration will be stopped when the overall target number of patients for the study is reached. After the end of the registration period, investigators use a signed form to confirm

that patients have been registered continuously at the site. A log of all patients included in the study will be maintained at the site.

9.2.3 Study visits

The study will consist of a baseline visit and further visits in a 104-week follow-up for patients who have initiated Ofev Capsules treatment. See ANNEX 2 for more details.

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 goals overall or 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 Ofev Capsules is estimated as time from the day Ofev Capsules 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 Ofev Capsules will be followed up to 104 weeks.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary endpoint of this study is the incidence of adverse drug reactions (ADRs). 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

None

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. Additional characteristics may be included based on new information that could become available during the course of the study. For all events/interventions/measures dates will be recorded.

- Demographics
    - Gender (Pregnancy status, only for female)
    - Age (Year of birth)
    - Height (cm)
    - Weight (Kg)
    - Vital signs (Systolic/Diastolic blood pressure(mmHg) and pulse rate(bpm) in the sitting position)
    - Smoking status
    - Reason for Ofev prescription (SSc-ILD, Others)
    - Child-Pugh classification (A to C) (with any hepatic concomitant disease)
    - Serum creatinine (Creatinine clearance according to Cockcroft and Gault).
    - Immunological test (antinuclear antibodies (ANA), anti-topoisomerase antibodies (ATA), anti-RNA polymerase III antibodies ((anti-)RNA Pol III), anti-Centromere antibodies (ACA), anti-U1-RNP antibodies, Others)
    - Time [years] since SSc diagnosis (SSc First diagnosis)
    - SSc subtype (Diffuse, Limited)
    - Time [years] since first onset of non-Raynaud symptom
    - Digital ulcers (Number of ulcers)
    - Pulmonary hypertension
    - Time [years] since SSc-ILD diagnosis (SSc-ILD First diagnosis)
    - ILD lesion expansion (%)
    - Chest HRCT (UIP pattern, NSIP pattern, Others)
    - SSc-ILD severity
    - ILD symptoms (Dyspnea, Cough)
    - ILD progression

- Treatment states of Ofev (start date, reason for use, dosage and administration status)
- Medical history/Concomitant diagnosis
- Previous/Concomitant medications for SSc-ILD and except for SSc-ILD
- Pulmonary function test (FVC, FVC percent predicted, FEV1, FEV1 percent predicted, DLco percent predicted, SpO2 at rest)
- EQ-5D-5L
- Laboratory tests (if applicable):
    - Hematological (RBC, Hb, Hct, WBC, Platelet count)
    - Liver function (AST, ALT, GGT, ALP, Total bilirubin)
    - Other biochemical (CRP, CK, LDH, BNP, NT-proBNP, KL-6, SP-D)
    - Coagulation (INR, APTT, PT)
    - Others

See ANNEX 2 and ANNEX 3 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, three casebooks will be set:
- Book 1 includes baseline, 4 and 12 weeks.
- Book 2 includes 24, 36 and 52 weeks.
- Book 3 includes 68, 84, 100 and 104 weeks.

The data are to be transmitted immediately after being entered into EDC at 12 weeks (Book 1), 52 weeks (Book 2) and 104 weeks (Book 3) 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

500 patients as safety analysis will be included in the study. Although there may be cases of no visit after registration and/or unable to collect CRF, and those cases will be excluded as a safety analysis set, therefore planned number of registration will be approximately 550 patients.

Rationale for the study size setting is as follows.
The proportion of investigator defined drug-related serious “Gastrointestinal disorders” in 1199.214 which is phase III multi-national trial was 1.0% (3/288 pts) in Nintedanib group. There was no cases such AEs in Placebo group. And no cases was seen in Japanese patients also. To investigate the investigator defined drug-related serious “Gastrointestinal disorders” in Japanese patients, the sample size was calculated as below.
If the true proportion of patients with above AEs is assumed to be 3-fold (i.e., 3.0%), the sample size of 428 is required to have 90% power for rejecting the null hypothesis of incidence = 1.0% by using one sample chi-square test with a 0.05 two-sided significance level. Considering drop out patients, setting 500 patients as safety analysis set.

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

This is a non-interventional study to collect data on patients under routine medical practice on safety, effectiveness and appropriate use of Ofev Capsules treatment. Analyses are descriptive in nature, including confidence intervals. Subgroup analyses will be performed if sample size allows.

Per local regulation, any patient who meets one of the following criteria is treated as ineligible for all analyses:

- No safety observation was documented after registration.
- No required registration procedure was followed.
- No valid site contract was available.

9.7.1 Analysis of Safety

In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on any suspected ADRs, serious AEs, AEs leading to death, AEs leading to treatment discontinuation, Incidences of adverse events leading to dose decreasing and focused on safety specification item (gastrointestinal symptoms including diarrhoea and nausea).

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between first intake of Ofev Capsules prescribed at baseline visit and within 28 days (inclusive) after the last intake will be considered 'treatment emergent'. An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The frequency and incidence of AEs/ADRs will be tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics (see section 9.3.3).

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

9.7.3 Interim analyses

Several interim analyses will be performed for the purpose of submission of periodic safety reports to PMDA (Pharmaceuticals and Medical Devices Agency) in project (status update of using Ofev Capsules not only with this study but all usage, every 6 month in two years after approval and every 12 months afterward. The submission date is depending on the time from the approval).

Final results will be submitted in the re-examination dossier to PMDA by March 2030.

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 incidence of adverse drug reactions 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 group arising from the study sites for comparing the data to be obtained with active treatments. However, baseline data from a registry are expected to be available for use as a comparison group if feasible.

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

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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.

The review by IRB 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 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 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 serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalisation, 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 authorisation. 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 characterised 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 Ofev Capsules, 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 NIS AE form is to be completed and forwarded as well within the respective timelines.

Safety specification item:

Gastrointestinal symptoms including diarrhoea and nausea (one of important identified risks) stated in the Japan RMP

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF 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 Ofev Capsules, 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 Ofev Capsules.

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13.1 PUBLISHED REFERENCES

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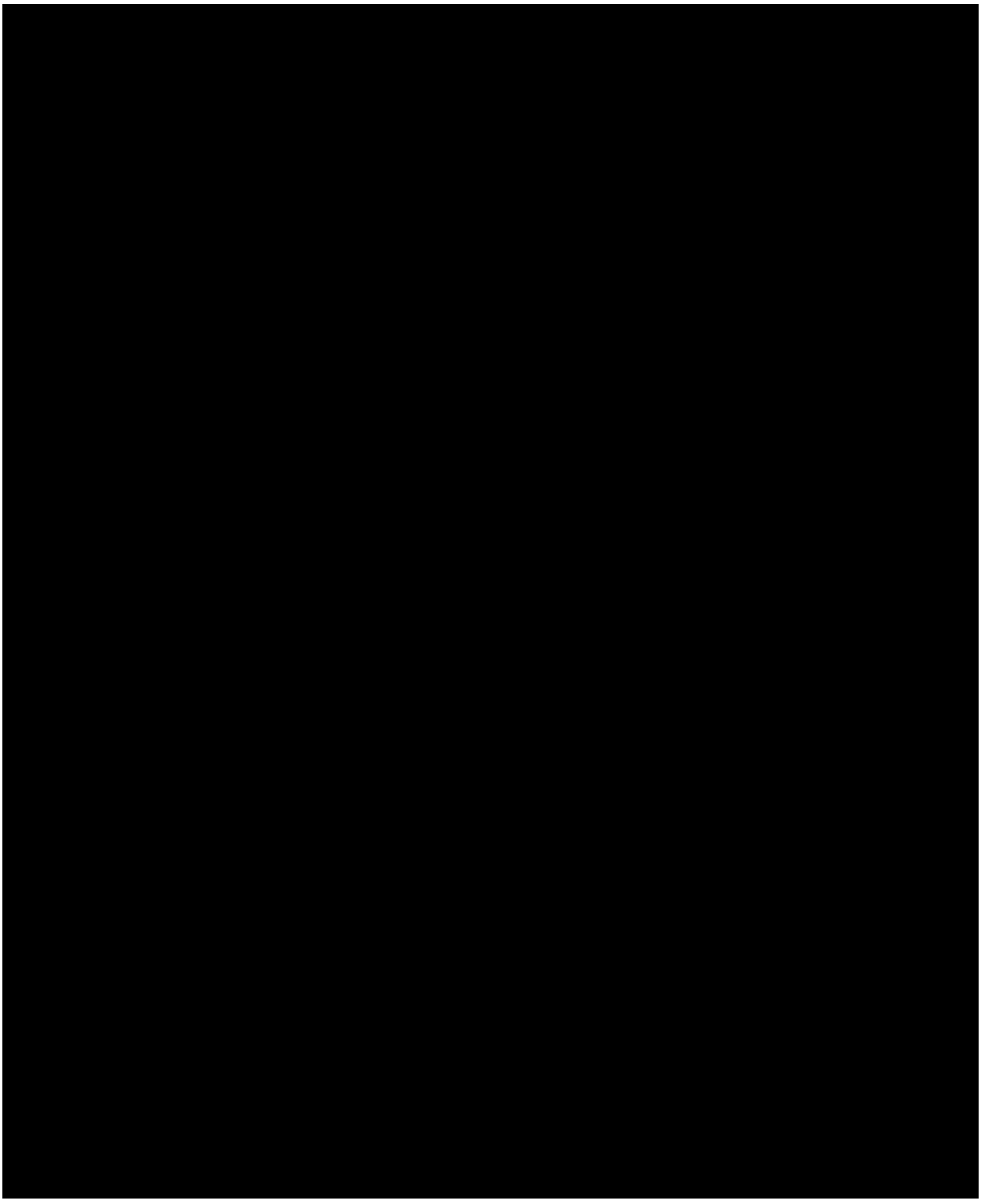

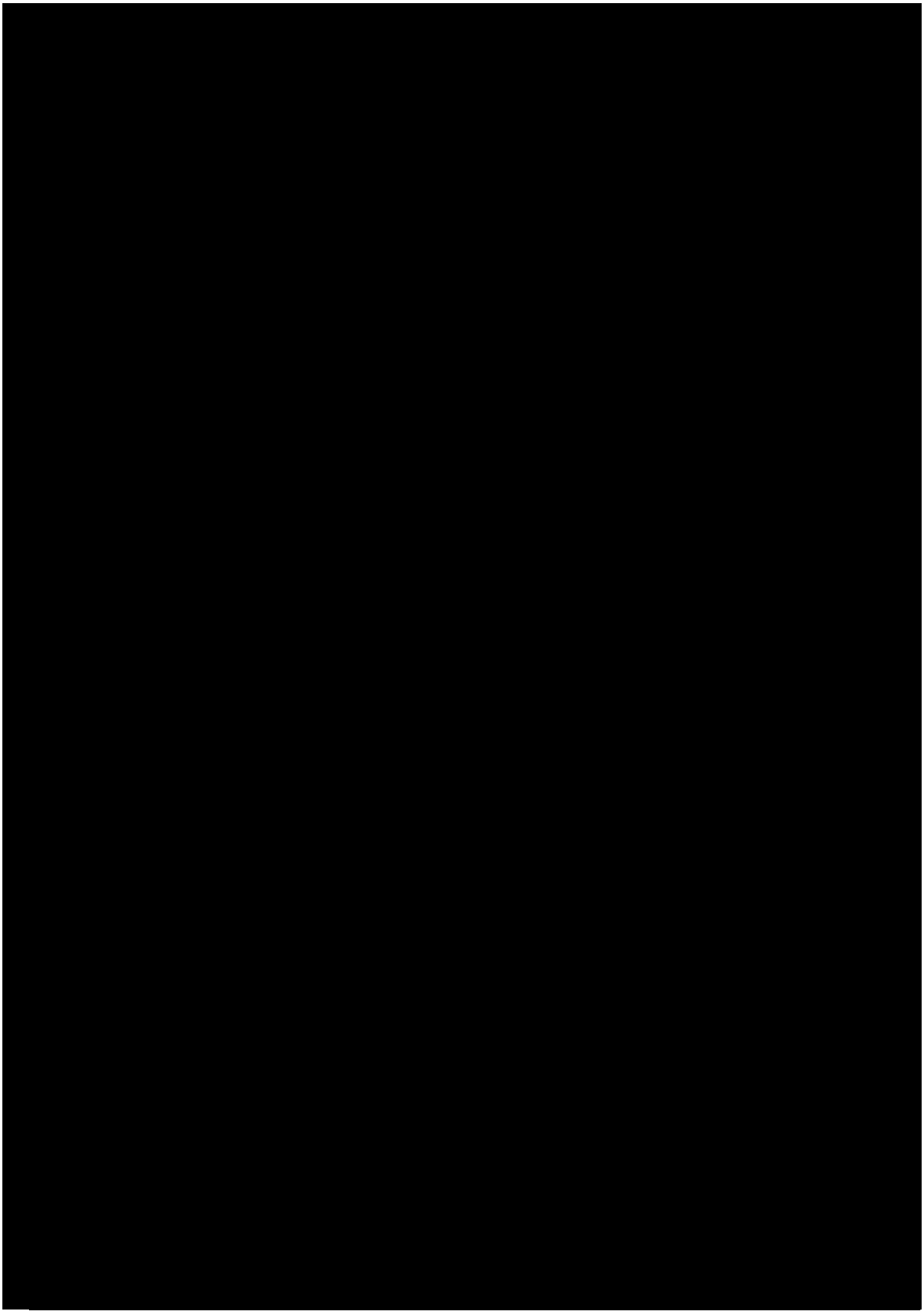

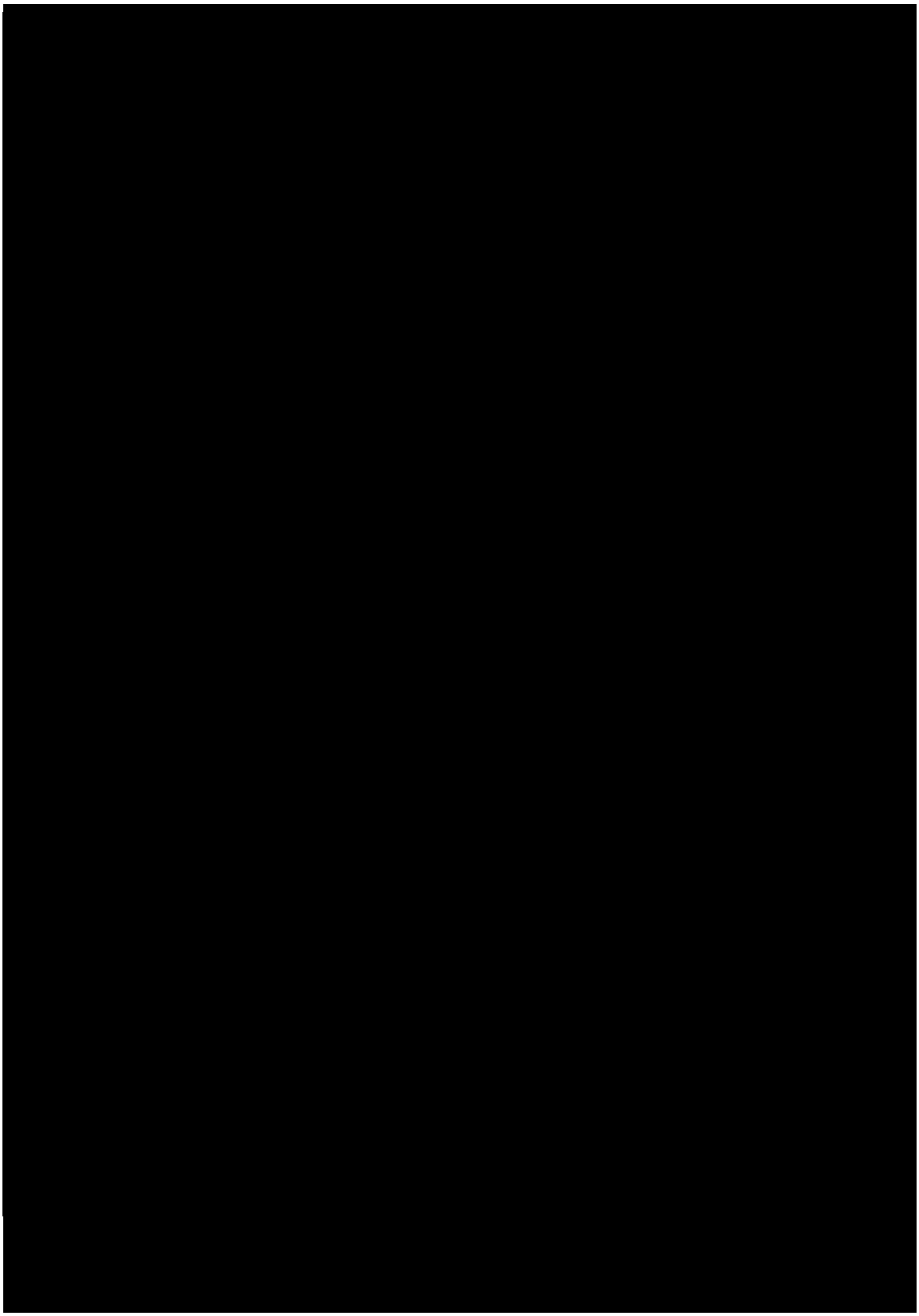

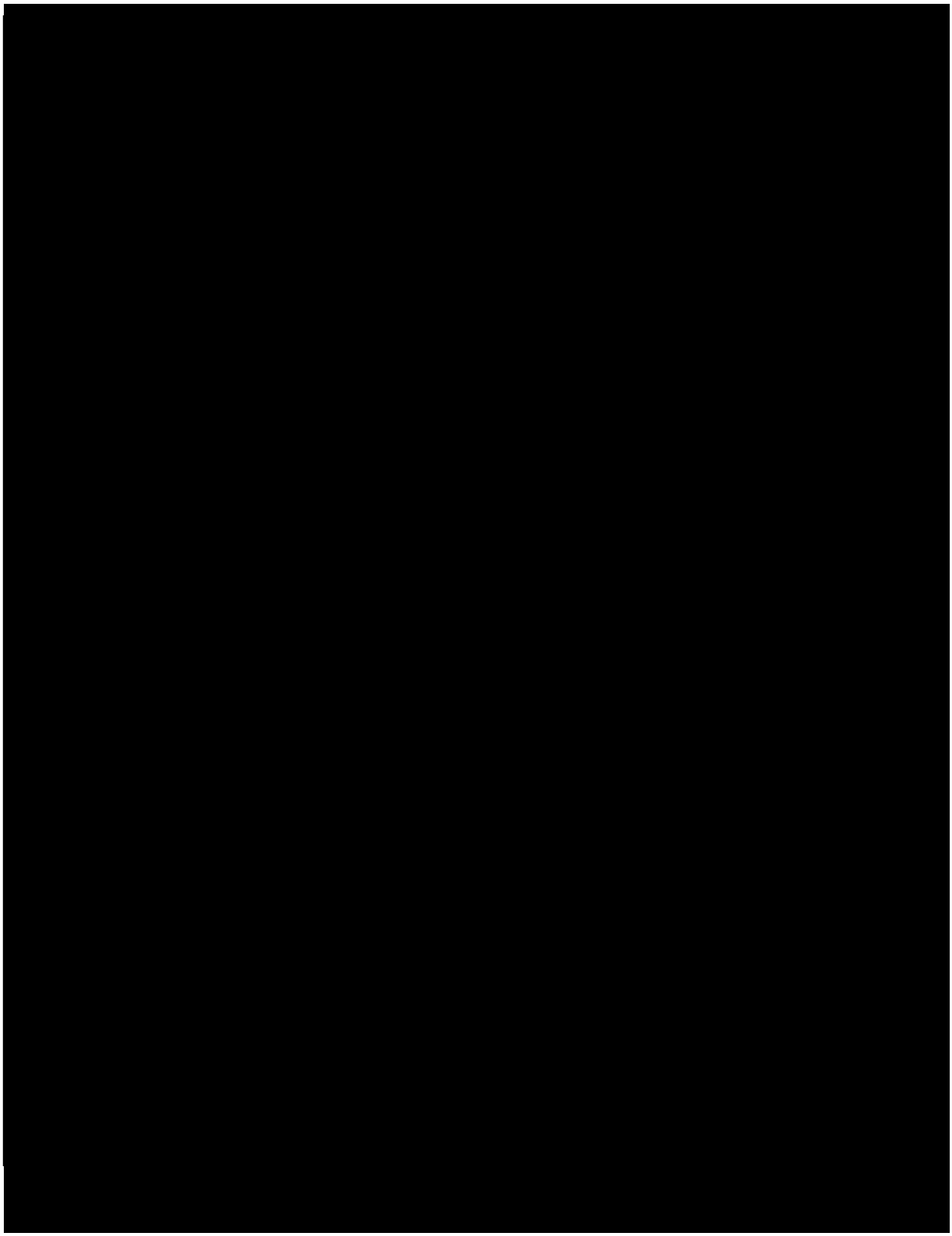

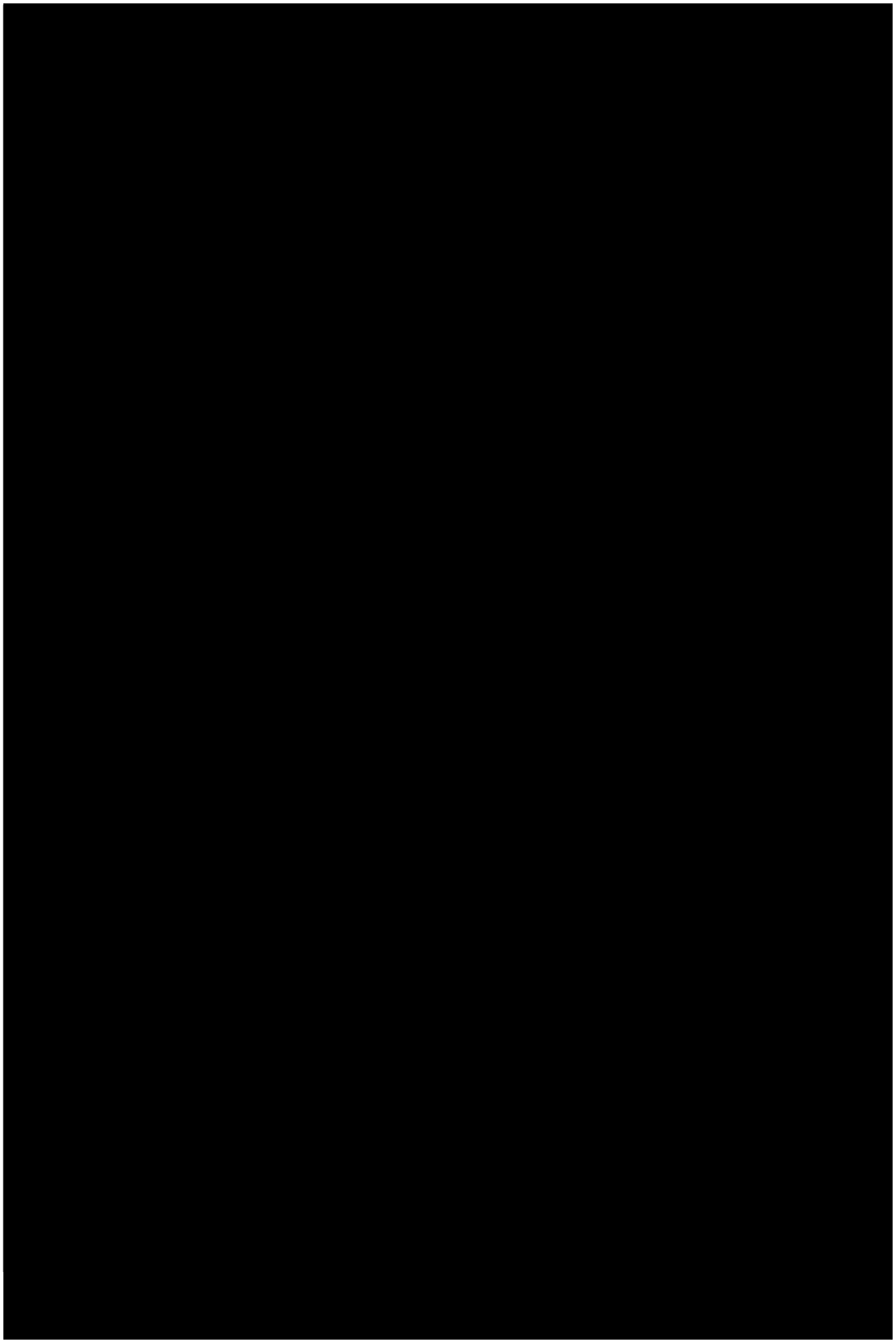

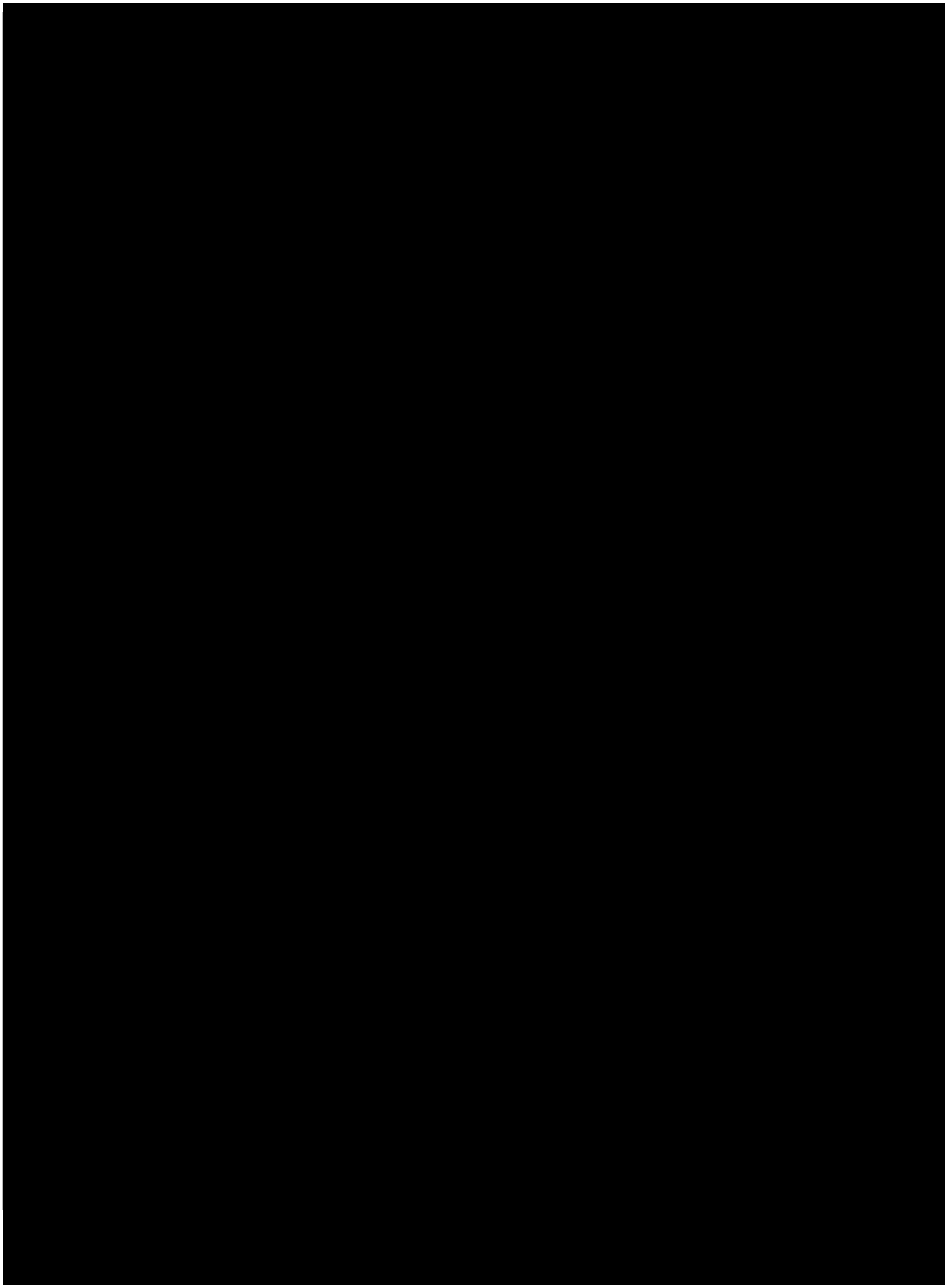

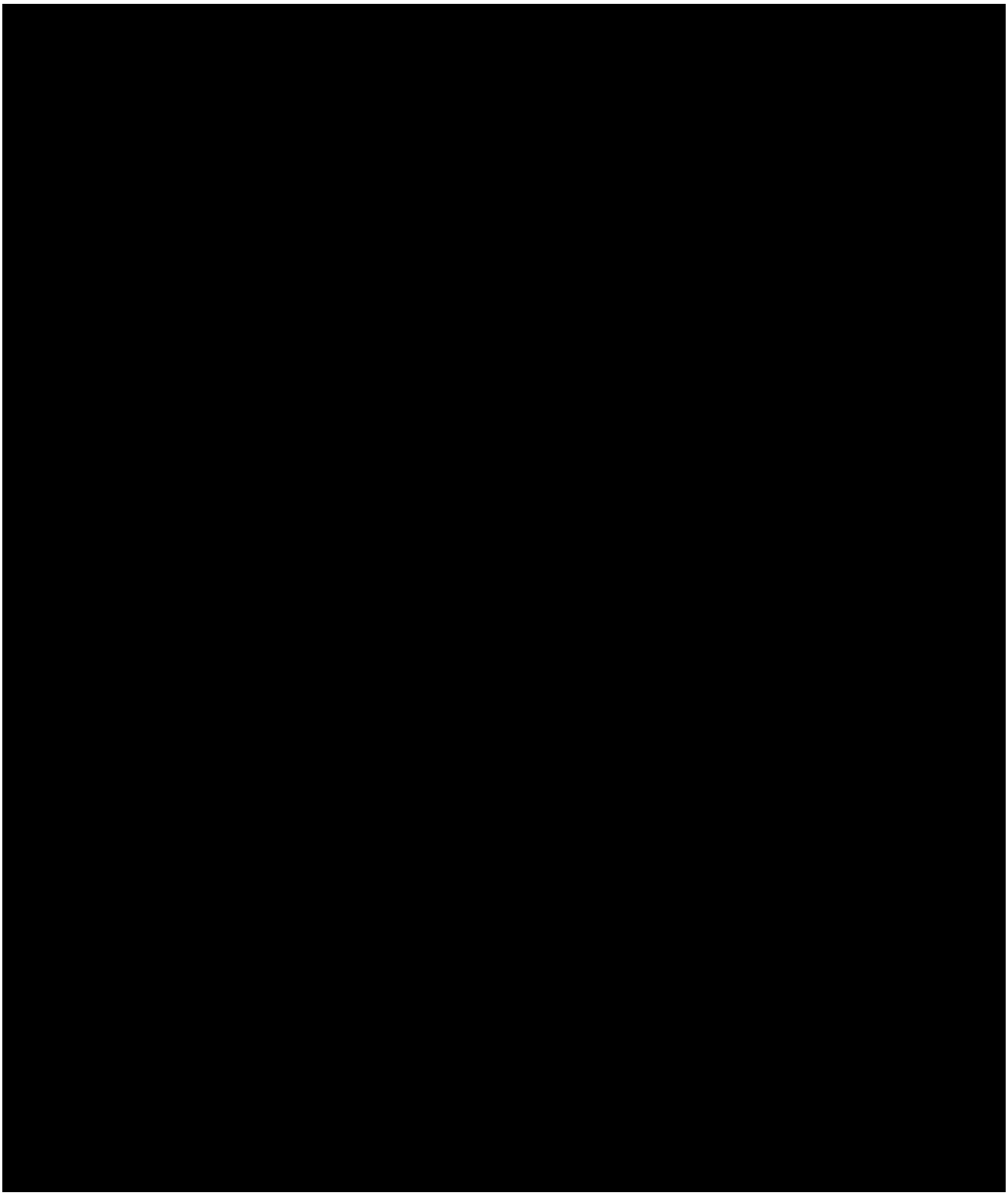

APPROVAL / SIGNATURE PAGE

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Title: Post-marketing Surveillance on long term use of Ofev Capsules in Systemic Scleroderma associated Interstitial Lung Disease (SSc-ILD) in Japan

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	10 Apr 2024 10:39 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed