Boehringer Ingelheim

Non-interventional Study Protocol

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BI Study Number:	1199.402
BI Investigational Product(s):	Nintedanib
Title:	Post-marketing Surveillance of Ofev Capsules in Chronic fibrosing Interstitial Lung Diseases with a progressive phenotype in Japan
Brief lay title	PMS of Ofev Capsules in PF-ILD
Protocol version identifier:	Version 4.0
Date of last version of protocol:	1 April, 2024
PASS:	Yes
EU PAS register number:	EUPAS36605
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 evaluate the incidence of adverse drug reactions (focus on hepatic function disorders) of Ofev Capsules under the real world setting in patients with PF-ILD
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: **<EU-QPPV:>**	[redacted]
In case of PASS, add: **<Signature of EU-QPPV:>**	e-signature is on BIRDS.
Date:	1 APR 2024

Page 1 of 39

1. TABLE OF CONTENTS

TITLE PAGE 1
1. TABLE OF CONTENTS 3
2. LIST OF ABBREVIATIONS 5
3. RESPONSIBLE PARTIES 7
4. ABSTRACT 8
5. AMENDMENTS AND UPDATES 11
6. MILESTONES 12
7. RATIONALE AND BACKGROUND 13
8. RESEARCH QUESTION AND OBJECTIVES 16
9. RESEARCH METHODS 17
9.1 STUDY DESIGN 17
9.2 SETTING 17
9.2.1 Study sites 17
9.2.2 Study population 17
9.2.2.1 Inclusion/ exclusion criteria 17
9.2.2.2 Registration period 17
9.2.2.3 Patient registration method 17
9.2.3 Study visits 18
9.2.4 Study discontinuation 18
9.3 VARIABLES 18
9.3.1 Exposures 18
9.3.2 Outcomes 18
9.3.2.1 Primary outcomes 18
9.3.2.2 Secondary outcomes 19
[redacted]
9.3.3 Survey items 19
9.4 DATA SOURCES 20
9.5 STUDY SIZE 21
9.6 DATA MANAGEMENT 21
9.7 DATA ANALYSIS 21
9.7.1 Main analysis 22
[redacted]
9.8 QUALITY CONTROL 23

9.9 LIMITATIONS OF THE RESEARCH METHODS 23
9.10 OTHER ASPECTS 23
9.10.1 Data quality assurance 23
9.10.2 Completion of study 23
10. PROTECTION OF HUMAN SUBJECTS 24
10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT 24
10.2 STATEMENT OF CONFIDENTIALITY 24
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 25
11.1 STUDY RECORDS 25
11.1.1 Source documents 25
11.1.2 Direct access to source data and documents 25
11.2 DEFINITIONS OF ADVERSE EVENTS 25
11.3 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING 26
11.4 REPORTING TO HEALTH AUTHORITIES 28
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 29
13. REFERENCES 30
13.1 PUBLISHED REFERENCES 30

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
ANCA	Anti-neutrophil cytoplasmic antibody
aPTT	Activated partial thromboplastin time
ARS	Amino acyl-tRNA synthetases
AST	Aspartate aminotransferase
ATA	Anti-topoisomerase antibodies
BI	Boehringer Ingelheim
BNP	Brain natriuretic peptide
CCP	Cyclic Citrullinated Peptid
CI	Confidence Interval
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
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GGT	Gamma-glutamyltransferase
GPSP	Good Post-marketing Study Practice
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
MPO	Myeloperoxidase
[redacted]	
NIS	Non-Interventional Study
NSIP	Non-specific Interstitial Pneumonia
ONIS	Observational Non-Interventional Study
PASS	Post-Authorization Safety Study

PF-ILD	Chronic fibrosing Interstitial Lung Diseases with a progressive phenotype
PMD	Pharmaceutical and Medical Device
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
PR3	Serine Proteinase3
PT	Prothrombin Time
RBC	Red Blood cell Count
RF	Rheumatoid Factor
RMP	Risk Management Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SP-D	Surfactant Protein D
SS	Sjögren's syndrome
SSc	Systemic Sclerosis
TSAP	Trial Statistical Analysis Plan
UIP	Usual Interstitial Pneumonia
ULN	Upper Limit of Normal
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 manages 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: List pharmacotherapeutic Nintedanib			
Protocol date: 13 March, 2020	**Study number:** 1199.402	**Version/Revision:** Version 4.0	**Version/Revision date:** 1 April, 2024
Title of study:	Post-marketing Surveillance of Ofev Capsules in Progressive Fibrosing Interstitial Lung Disease 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 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. Five years and ten months 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 PMDA on designated dates until the end of re-examination period. The INBUILD (1199.247) trial was completed and INBUILD-ON (1199.248) trial is conducted as Phase III trials that evaluated the efficacy and safety of nintedanib in patients with PF-ILD. IPF patients were excluded in these trials. As the number of Japanese patients treated with nintednib in INBUILD trial was few (52, total: 332), confirmation of the safety profile of nintedanib treatment for PF-ILD patients in the real world clinical setting is required.		
Research question and objectives:	To evaluate the incidence of adverse drug reactions (focus on hepatic function disorders including liver enzyme elevation) of Ofev Capsules under the real world setting in patients with PF-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.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Ofev capsules			
Name of active ingredient: List pharmacotherapeutic Nintedanib			
Protocol date: 13 March, 2020	**Study number:** 1199.402	**Version/Revision:** Version 4.0	**Version/Revision date:** 1 April, 2024
Population:	Inclusion criteria - Patients in Japan with PF-ILD who are prescribed with Ofev Capsules and have never been treated with Ofev Capsules before enrolment will be included. Exclusion criteria - Diagnosis of IPF - Patients with PF-ILD due to systemic scleroderma as the underlying disease		
Variables:	Outcomes: Primary outcome: Incidence of adverse drug reactions (ADRs) by overall, each individual (especially focus on the safety specification on J-RMP: hepatic function disorders) Secondary outcome: None [redacted]		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Ofev capsules			
Name of active ingredient: List pharmacotherapeutic Nintedanib			
Protocol date: 13 March, 2020	**Study number:** 1199.402	**Version/Revision:** Version 4.0	**Version/Revision date:** 1 April, 2024
	[redacted] Others: characteristics associated with ADRs Demographics, baseline characteristics, labs and vitals as baseline, concomitant therapy and medications etc.		
Data sources:	Patients' data will be collected by electronic Case Report Form on Electronic Data Capture system		
Study size:	Approximately 400 (for enrolment)		
Data analysis:	Analyses are descriptive in nature, incidence rates and corresponding confidence intervals will be given for all ADRs in terms of Ofev for PF-ILD.		
Milestones:	Planned start of data collection: 1 OCT 2020 Planned end of data collection: 31 DEC 2024 Study Report planned to be archived in 4Q 2025		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2.0	03 June, 2020	Study population	Amendment	Indication wording was changed
[redacted]				
4.0	1 April, 2024	9.6 DATA MANAGEMENT	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 October 2020
End of data collection	31 December 2024
Registration in the EU PAS register	EUPAS36605
Final report of study results:	4Q 2025

7. RATIONALE AND BACKGROUND

Based on clinical experience, there is a group of patients who, independent from the ILD classification, at some point in time, develop a progressive fibrosing phenotype. In this group of patients, the natural history appears to follow a course similar to IPF with worsening of respiratory symptoms, lung function, quality of life and functional status, as well as early mortality despite treatment with currently available non-approved immunomodulatory therapies. The proposed terminology for describing this group is Chronic fibrosing Interstitial Lung Diseases with a progressive phenotype (PF-ILD).

Based on expert consensus, the main fibrosing ILDs in which progressive behavior is present include:

- Idiopathic Interstitial Pneumonias (IIPs): mainly IPF, idiopathic non-specific interstitial pneumonia (iNSIP) and unclassifiable IIP
- Chronic fibrosing hypersensitivity pneumonitis (CHP)
- Autoimmune ILDs: connective tissue disease- ILD (CTD-ILD) (mainly RA-ILD and SSc-ILD) and interstitial pneumonia with autoimmune features
- Environmental/occupational fibrosing lung disease

The scientific working hypothesis is that the response to lung injury in these ILDs includes the development of fibrosis which becomes progressive, self-sustaining and independent of the original clinical association or trigger. It is postulated that, at this stage, targeted antifibrotic therapy is required to slow the progression of the disease. And, the efficacy of Nintedanib for PF-ILD was shown at INBUILD trial.

Based on the similarity in both, the biologic and clinical behaviours i.e. self-sustaining fibrosis and progressive decline in lung function and early mortality, it is considered justified to group patients with PF- ILDs together regardless of their original ILD diagnosis.

Nintedanib is a kinase inhibitor indicated for the treatment of IPF, which has been shown to slow the progression of IPF. Because of the similarity in both the underlying pathophysiology and clinical course of PF-ILD and IPF, it became clear that nintedanib elicit similar effects in PF-ILD as it demonstrated in IPF shown in the INBUILD trial. These clinical results confirm the pre-clinical data indicating that nintedanib impacts fundamental processes of lung fibrosis and that the anti-fibrotic activity of nintedanib is independent of the cause of the fibrosing lung disease (P14-02860, P14-17410, P15-02392, P15-06100).

The primary endpoint of the INBUILD trial was met in both co-primary populations. Treatment with nintedanib significantly reduced the annual rate of decline in FVC [mL/year] over 52 weeks compared with placebo in the overall population and in patients with HRCT with UIP-like fibrotic pattern. The results were shown to be robust and were consistent in the complementary population of patients with other HRCT fibrotic patterns.
Analyses of time-to-event endpoints indicated reductions in clinically meaningful outcome events and provided supportive evidence for a slowing of disease progression by nintedanib. The treatment benefit of nintedanib on lung function was accompanied by improvements in patient-reported outcomes such as dyspnoea and cough.
The observed safety profile of nintedanib in patients with progressive fibrosing ILD

comprised risks that were manageable or occurred at a low frequency. The most frequently reported AEs were gastrointestinal disorders, in particular diarrhoea, nausea, and vomiting. Common AEs were mostly mild or moderate in intensity. In addition, treatment with nintedanib was associated with elevations in liver enzymes. The large majority of liver enzyme elevations normalised upon treatment interruption, dose reduction, treatment discontinuation, or spontaneously with continued treatment. There were no new or unexpected safety concerns identified in the INBUILD trial.

The safety profile of nintedanib has been investigated comprehensively in IPF and stablished in this indication in > 80 000 patient-years exposure postmarketing as of May 2019. 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, pruritus, alopecia and headache.

The INBUILD trial is a randomized, placebo-controlled Phase III trial that evaluated the efficacy and safety of nintedanib in patients with PF-ILD.

As the number of Japanese patients treated with nintedanib in INBUILD trial was few (52, total 332), confirmation of the safety profile of nintedanib treatment for PF-ILD patients in the real world clinical setting is required.

This “PMS with 400 patients for enrolment” that will take into consideration the following points.

- The safety profile in Ofev was similar in ‘PF-ILD patients’ to that in IPF in the clinical trials. The incidence of hepatic enzyme elevation was higher in Japanese population than overall population in the INBUILD trial for PF-ILD other than IPF.
- Real world data in patients with IPF has already been collected over 3 years through post-marketing experience after 2015 in 1199.202 (the ongoing all case survey of PMS in IPF). The total number of patients registered in 1199.202 was over 5,000. PF-ILD patients may have different concomitant diseases and medications with IPF patients in 1199.202.
- As the IPF is also a progressive fibrosing ILD, the safety data collected in 1199.202 would be supportive for PF-ILD, however the number of patient with PF-ILD other than IPF is limited. Therefore, the PMS in patients with PF-ILD other than IPF will be required in order to accumulate the safety data under the real world setting in Japanese PF-ILD patients to assess the safety profile, especially hepatic function disorders including liver enzyme elevation.

In Japan, Ofev Capsules for PF-ILD indication has received marketing approval on May 2020 (Plan).
This PMS plan is proposed as additional pharmacovigilance plan of the Japanese RMP.

In Japan, post-approval execution of PMS 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. Five years and ten months after approval for additional indication on 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 PMDA on designated dates until the end of re-examination period.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to evaluate the incidence of adverse drug reactions (focus on hepatic function disorders) of Ofev Capsules under the real world setting in patients with PF-ILD.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study based on newly collected data of patients under routine care to confirm safety of Ofev Capsules in the real-world setting in Japanese patients with PF-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 sites: Approximately 100 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, treatment with Ofev for PF-ILD at the contracted site is for participation. 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 PF-ILD who are prescribed with Ofev Capsules and have never been treated with Ofev Capsules before enrolment will be included.

Exclusion criteria
- Diagnosis of IPF
- Patients with PF-ILD due to systemic scleroderma as the underlying disease

9.2.2.2 Registration period

From October 2020 to September 2022

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 whenever possible 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 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 Good Post-marketing Study Practice (GPSP) , the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / 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 outcome 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 Survey items

- Demographics
  - Gender (Pregnancy status, only for female)
  - Age (Year of birth)
  - Height (cm)
  - Weight (Kg)
  - Systolic/Diastolic blood pressure (mmHg) and pulse rate (bpm) in the sitting position
  - Smoking status
  - Reason for Ofev prescription
  - Underlying diagnosis (Idiopathic nonspecific interstitial pneumonia, Unclassifiable idiopathic interstitial pneumonia, Hypersensitivity pneumonitis, Rheumatoid Arthritis associated ILD, Mixed connective tissue disease, Exposure-related ILD, Sarcoidosis, Other ILD)
  - Child-Pugh classification (with any hepatic concomitant disease)
  - Serum creatinine (Creatinine clearance according to Cockcroft and Gault).
  - Immunological test (Rheumatoid Factor, Anti-cyclic citrullinated peptid antibody,

Antinuclear antibodies, Anti Sjögren's syndrome-A antibody, Anti-amino acyl-tRNA synthetases antibody, MPO-ANCA, PR3-ANCA, other)
- Time [years] since PF-ILD diagnosis (PF-ILD First diagnosis)
- Criteria for assessment of progression (images, symptoms, respiratory function examination)
- Chest HRCT criteria (UIP-like*, Others)
- ILD symptoms (Dyspnea, Cough)
- Criteria for PF-ILD**

*: The HRCT criteria for UIP pattern as the Phase III IPF trials for Nintedanib is used. UIP-like pattern includes A, B and C, or criteria A and C, or criteria B and C as described below:

A. Definite honeycomb lung destruction with basal and peripheral predominance

B. Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance

C. Atypical features are ABSENT, specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

**: The patients who fulfil at least one of the following criteria for PF-ILD within 24 months of the screening visit

- clinically significant decline in FVC % predicted (%pred) based on ≥10% relative

Decline

- marginal decline in FVC %pred based on ≥5 – <10% relative decline in FVC combined with worsening of respiratory symptoms

- marginal decline in FVC %pred based on ≥5 – <10% relative decline in FVC

combined with increasing extent of fibrotic changes on chest imaging

- worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging

- Treatment states of Ofev (start date, reason for use, dosage and administration status)
- Medical history/Concomitant diagnosis
- Previous/Concomitant medications for PF-ILD and except for PF-ILD
- Concomitant therapy
- Pulmonary function test (FVC, FVC percent predicted, FEV1, FEV1 percent predicted, DLco percent predicted, SpO2 at rest)
- Laboratory tests:
  Collect data which is needed for case. AST/ALT are collected from all cases as possible.
  - Hematological (RBC, Hb, Hct, Platelet count, WBC, differential count of leukocytes)
  - Liver function (AST, ALT, γ-GTP, ALP, Total bilirubin)
  - Other biochemical (CRP, CK, LDH, BNP, SP-D, KL-6)
  - Coagulation (PT, PT-INR, aPTT)
  - 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 72, 84, 96 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

As mentioned below, 354 patients will be needed as safety analysis set in the study. There may be cases that some patients are not eligible for analyses (see Section 9.7). Therefore planned number of registration will be approximately 400 patients.

The incidence of hepatic enzyme elevation tends to be higher in Japanese patients than in other ethnic groups. Hepatic functional disorder (AE) including hepatic enzyme elevation is an important factor for evaluating risk-benefit balance.
It is used as reference event for the sample size evaluation in PMS studies in Japan. The proportion of overall patients with maximum ALT and/or AST ≥ 5 Upper Limit of Normal was 3.8% (2/52) in Japanese nintedanib group of INBUILD trial.
If the true proportion of patients with hepatic enzymes elevation is assumed to be 2-fold (i.e., 7.6%), the sample size of 354 is required to have 90% power for rejecting the null hypothesis of incidence = 3.8% by using one sample chi-square test with a 0.05 two-sided significance level.

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 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 visit after registration.
- No required registration procedure was followed.
- No valid site contract was available.

9.7.1 Main analysis

In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on any ADRs, serious AEs, AEs leading to death, AEs leading to treatment discontinuation, acute ILD exacerbations and liver enzyme elevations (AST and/or ALT ≥3x to <5x ULN, ≥5x ULN).

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.

[redacted]

9.8 QUALITY CONTROL

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 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 Completion of study

Completion of the PMS will be notified to PMDA when the re-examination document and periodic safety reports are 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 STUDY RECORDS

eCRFs for individual patients will be provided by the sponsor via remote data capture.

11.1.1 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.

11.1.2 Direct access to source data and documents

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

11.2 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 adverse event 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 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 adverse event 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 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 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.

11.3 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 adverse events (AEs) (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 adverse event. An adverse reaction, in contrast to an adverse event, 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 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.

Focused safety specification on J-RMP:
Hepatic function disorders (important identified risks)

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 adverse events related to any BI drug other than the 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.

11.4 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the 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 Study 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.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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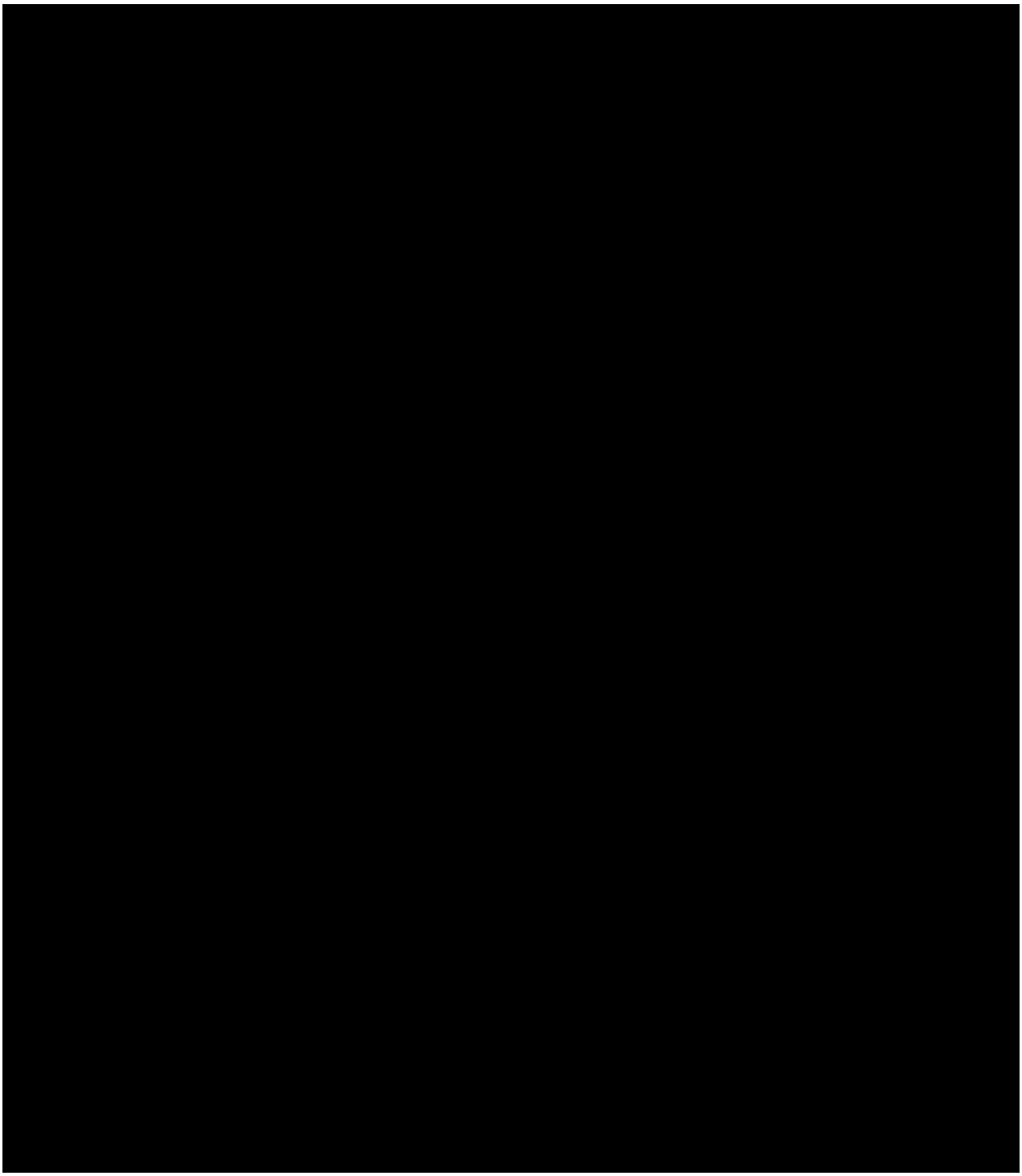

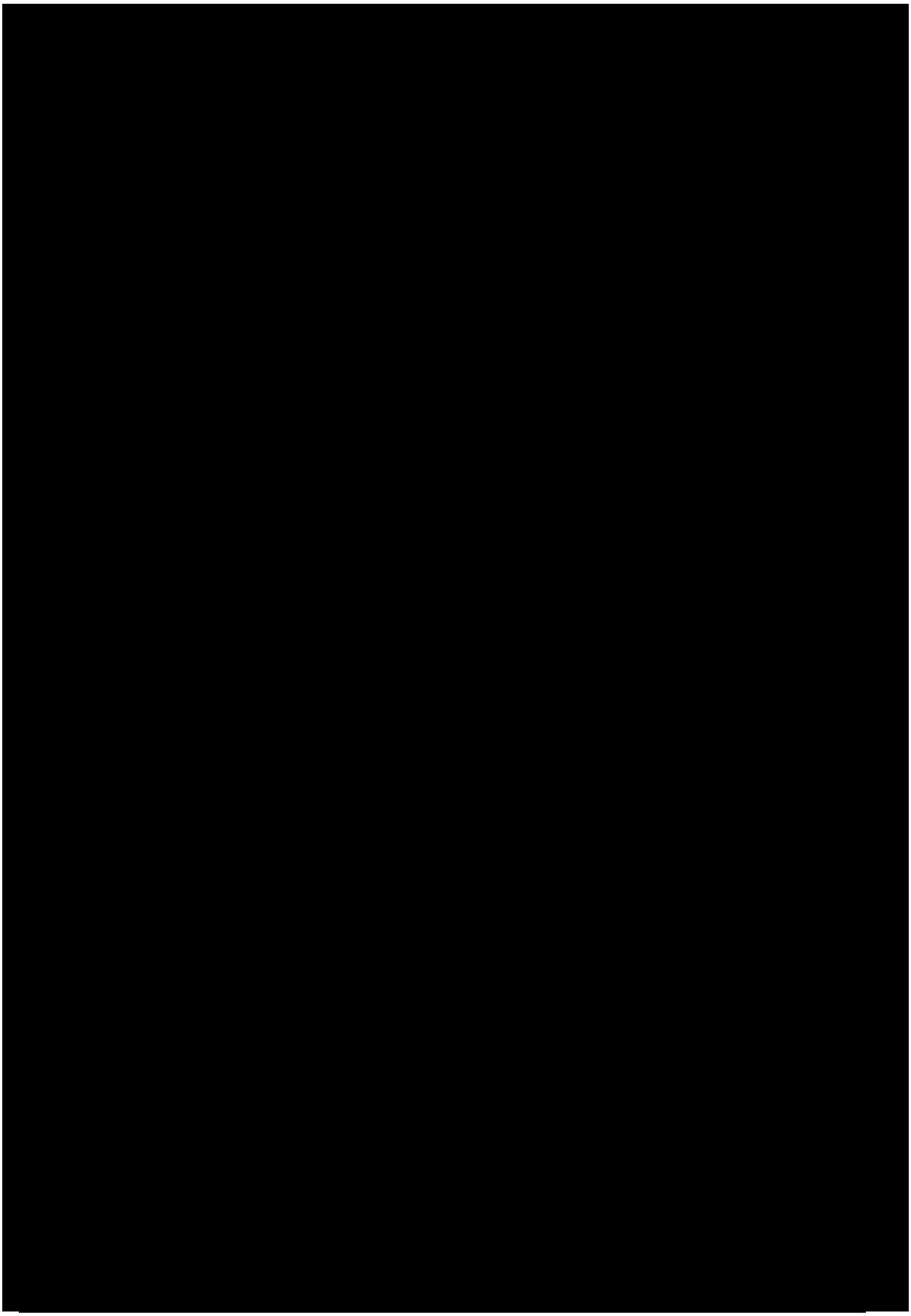

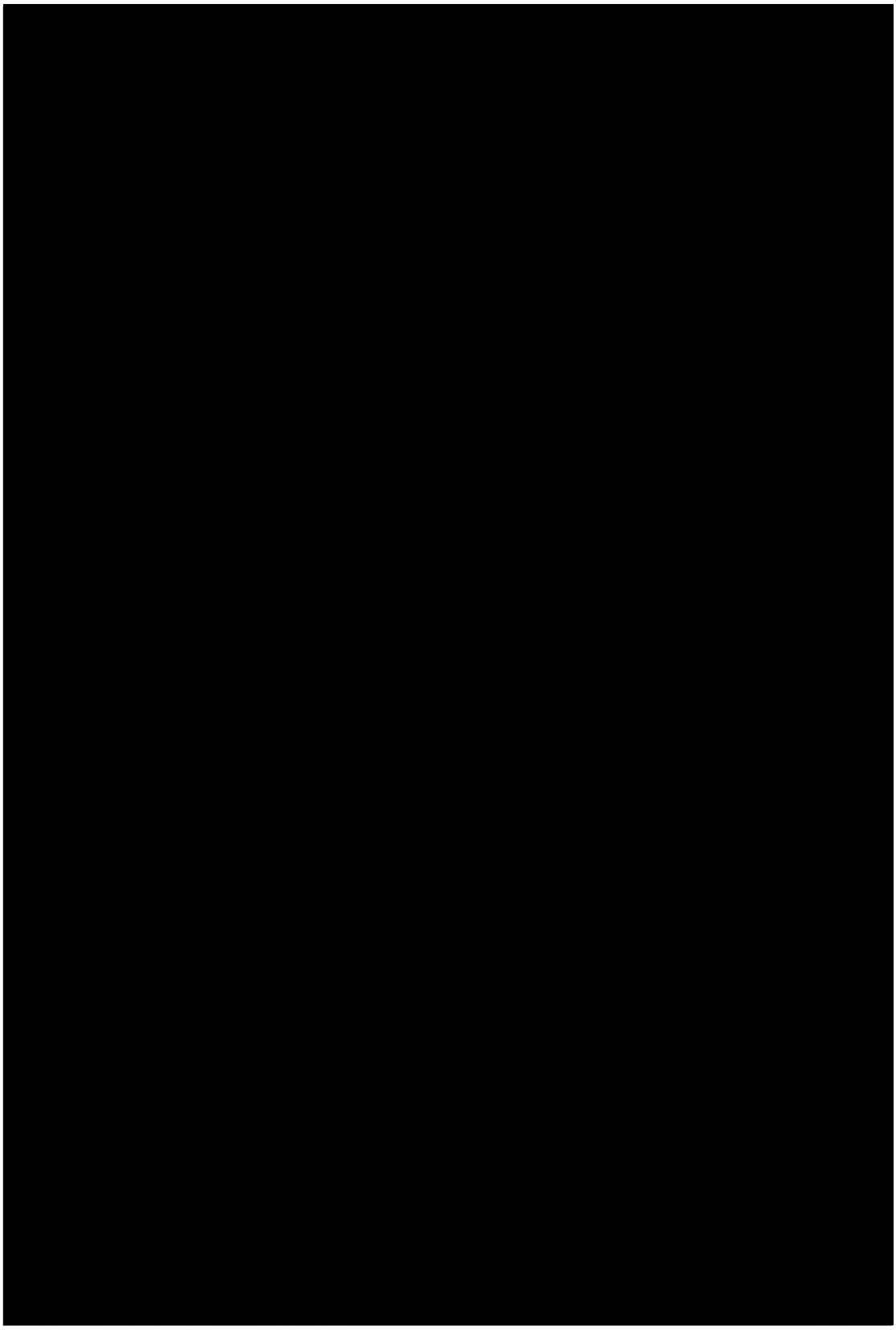

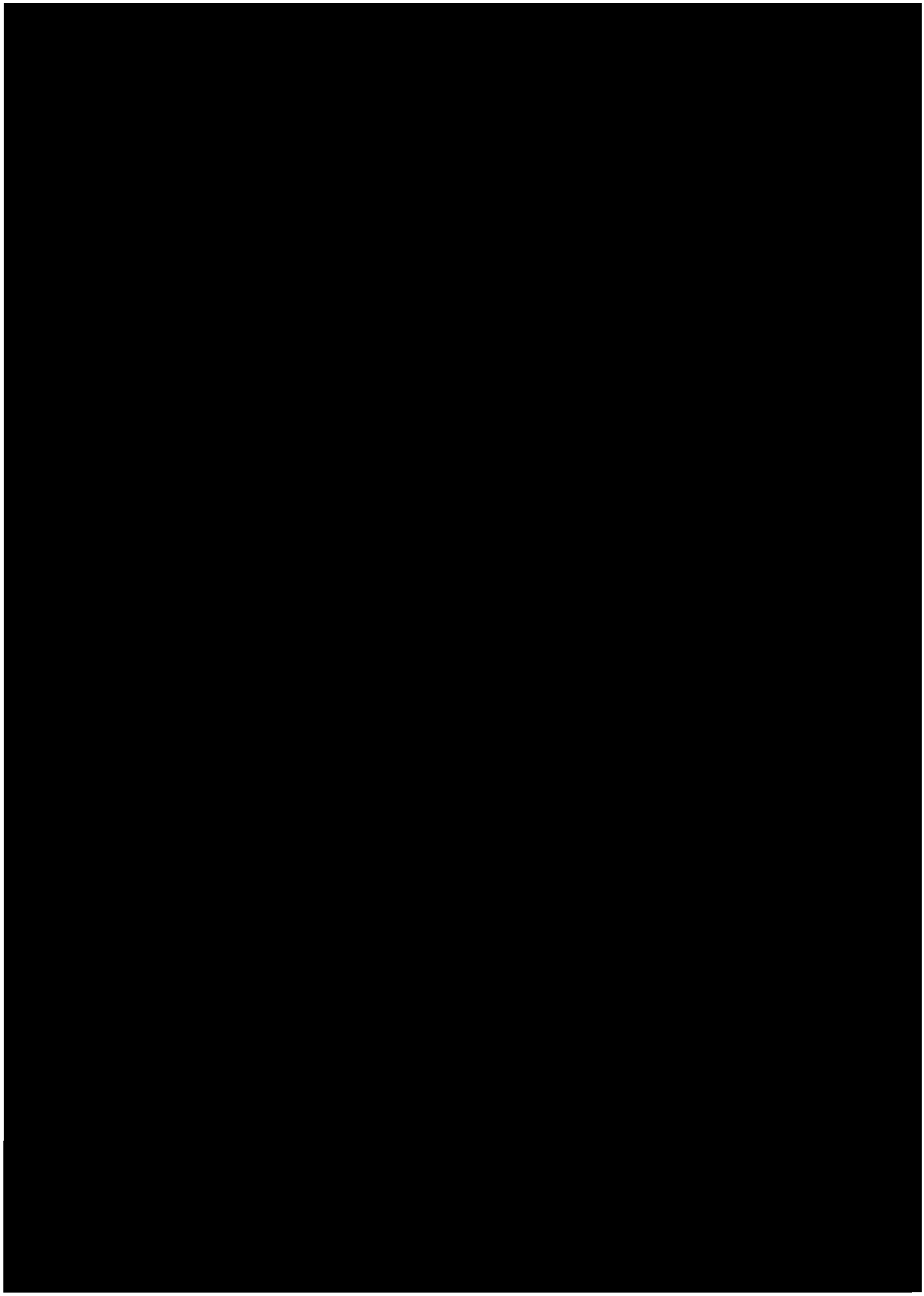

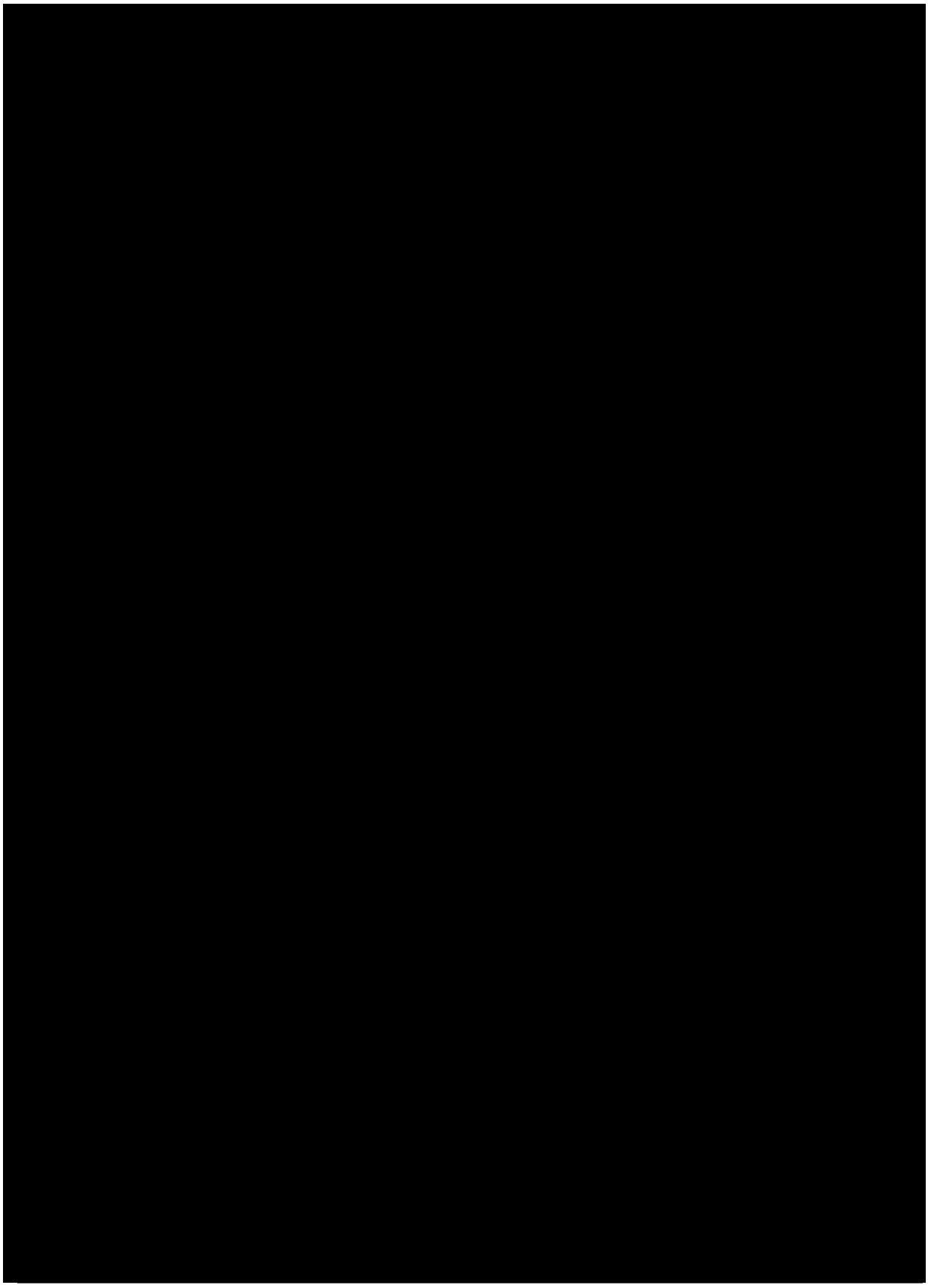

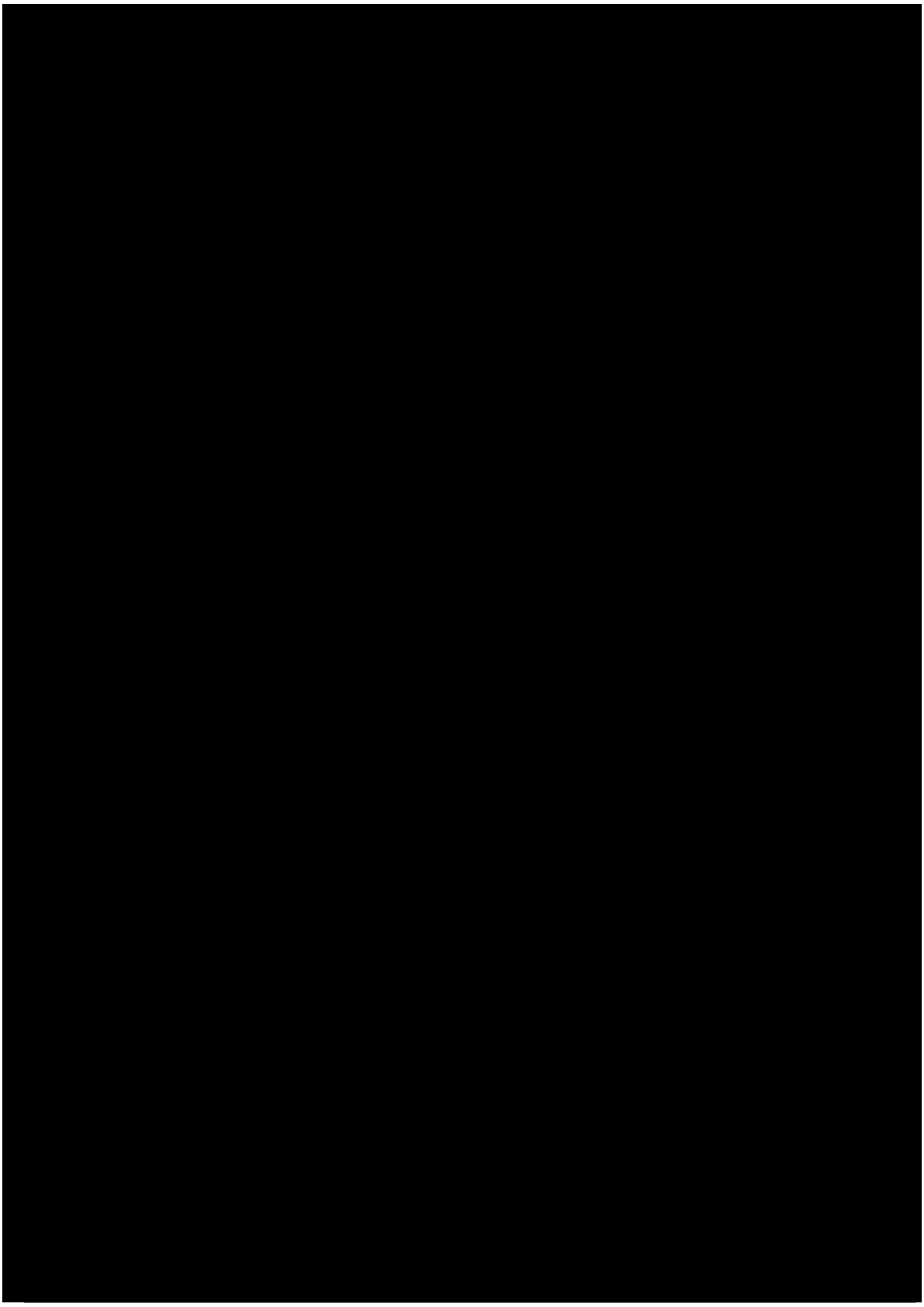

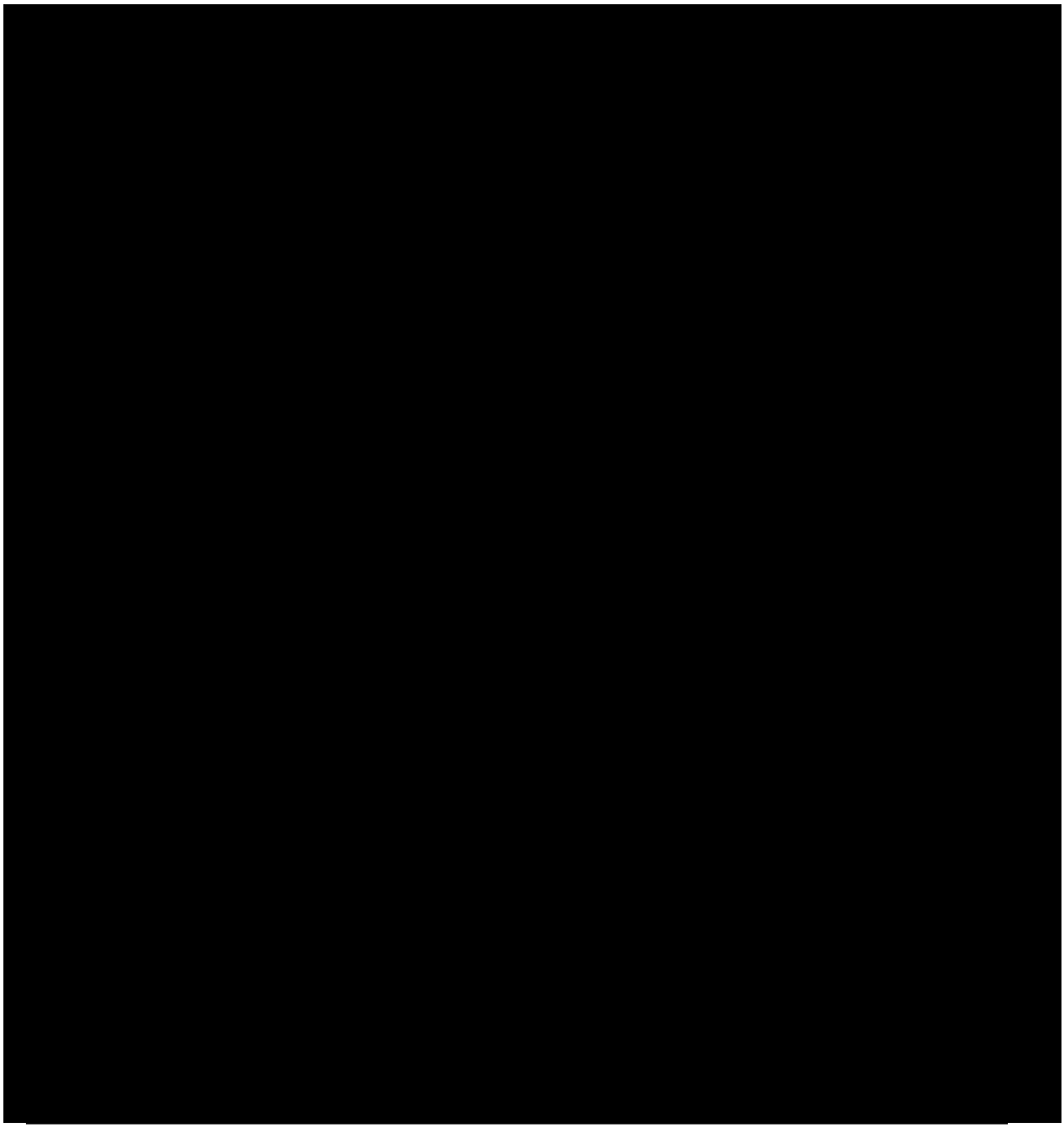

APPROVAL / SIGNATURE PAGE

Document Number: c29889733 **Technical Version Number:4.0**

Document Name: 1199-0402-non-interventional-study-protocol

Title: Post-marketing Surveillance of Ofev Capsules in Chronic fibrosing Interstitial Lung Diseases with a progressive phenotype in Japan

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	09 Apr 2024 01:38 CEST

(Continued) Signatures (obtained electronically)

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