Statistical and Epidemiological Analysis Plan (SEAP) for Observational and Non-Interventional Study (ONIS)

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Title:	Observational, multicentre, prospective, real-world post-authorization safety study describing the achievement of nintedanib-associated **DIA**rrhoea control after 12 weeks of follow-up in patients with idiopathic pu**L**monary **FIB**rosis (IPF) and progressive pulmonary fibrosis (other than IPF) in Spain: the DIALFIB study
Brief lay title:	A study based on medical records in Spain that looks at diarrhoea control in people with pulmonary fibrosis who are taking nintedanib
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADL	Activities of Daily Living
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
Bid	Twice per day
BSFS	Bristol Stool Form Scale
CA	Competent Authority
CDA	Confidentiality Agreement
CRA	Clinical Research Associate
CRO	Clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMRP	Data Management and Review Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group scale
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMR	Electronic Medical Records
EU	European Union
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
HTTPS	Hypertext Transfer Protocol Secure
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
ILDs	Interstitial Lung Diseases
iPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
ISF	Investigator Site File
MAH	Marketing Authorisation Holder
MSL	Medical Scientific Liaison
ONIS	Observational and Non-Interventional Study
OPU	Operative Project Unit
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PD	Protocol Deviation
PF-ILD	Progressive Fibrosing Interstitial Lung Diseases
PIS	Patient Information Sheet
PPF	Progressive Pulmonary Fibrosis
PS	Performance Status
PSP	Patient Support Programme
SAE	Serious Adverse Event

SEAP	Statistical and Epidemiological Analysis Plan
SFQ	Site Feasibility Questionnaire
SIV	Site Initiation Visit
SSc	Systemic Sclerosis
SSc-ILD	Systemic Sclerosis associated Interstitial Lung Diseases
SSL	Secure Sockets Layer
SOP	Standard Operating Procedure
TKI	Tyrosine Kinase Inhibitor

3. RESPONSIBLE PARTIES

BI:

Study role	**Contact**
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Market Access & Healthcare Affairs Team	[redacted]
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[redacted]

Study role	**Contact**
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Lead Epidemiologist	[redacted]
ONIS Statistician	[redacted]
ONIS Data Manager	[redacted]

4. PURPOSE AND SCOPE

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse parenchymal lung disorders characterized by inflammation and fibrosis, that have a prevalence estimated to be up to 76.0 cases per 100,000 people in Europe (10, 11). The archetypal and most common fibrotic ILD is the idiopathic pulmonary fibrosis (IPF), which is defined as a chronic fibrosing interstitial pneumonia of unknown cause, that affects around 8.2 per 100,000 people (11, 12). In recent years, the term progressive pulmonary fibrosis (PPF) (also referred as progressive fibrosing ILD [PF-ILD]) has emerged to identify patients with ILDs -other than IPF- who experience worsening respiratory symptoms due to progressive radiological and physiological changes (12). These patients account for 13 to 40% of non-IPF ILDs (11, 13) and for more than 21% of all ILDs (14). Patients with IPF and other PPF have poor prognosis, and are at increased risk of mortality, with most patients dying or requiring lung transplant within two years of diagnosis (14, 15). For this population, receiving prompt treatment is critical to delay disease progression.

In the last decade, the treatments of patients with IPF and other PPF have made substantial improvements, based on novel therapies. Nintedanib, one of the two treatments available for IPF and the only treatment available for other PPFs, is a tyrosine kinase inhibitor (TKI) that acts by blocking tyrosine kinase enzymes of lung cells receptors (such as fibroblast growth factor receptors), inhibiting the generation of fibrotic tissue and reducing lung function decline (1, 2). Its use has been approved since January 2015 in Europe for patients with IPF, and since August 2022, for patients with systemic sclerosis associated ILD (SSc-ILD) (3) -a disease in which immune system overactivity leads to progressive scarring of the lungs- and other chronic fibrosing ILDs with a progressive phenotype (4, 16). Despite its proven benefits, nintedanib is not exempt of adverse events (AE), with the most frequent being diarrhoea (1-5).

Diarrhoea, defined as the passage of three or more loose or liquid stools in a 24-hour period (17) [loose or liquid stools defined as stools with a Bristol Stool Form Scale (BSFS) of 6 or 7 points (18)], is reported by 66.9% to 75.7% of nintedanib-treated patients (2-5), most frequently in those with low body mass index (19). Although most (95%) of nintedanib AEs are categorized as not serious (6), the high prevalence of diarrhoea and its potential impact on patients' health status, often leads to dosage reduction or -in around 13%- to treatment discontinuation (5, 7-9), especially in female patients (5, 20). In this context and considering the limited treatment alternatives for IPF and other PPFs, it is essential to describe the real-world proportion and characteristics of patients who achieve control of nintedanib- associated diarrhoea.

In addition to dose adjustments and treatment interruptions, the management of nintedanib-associated diarrhoea is commonly based on the use of symptomatic therapies (e.g., loperamide, codeine, astringent diet, fluid, and electrolyte replacement) (5). However, to date, this AE continues to affect nintedanib adherence. In Spain, the recommendation of carob -the plant from the carob tree- to manage nintedanib-associated diarrhoea is increasing. This plant belongs to the Leguminosae family (or Fabaceae family), has been cultivated since ancient times, and has traditionally been used to treat gastrointestinal disorders (21-23). In the latest years, its primary

products (i.e., flour, powder, and syrup) have been incorporated in foods, beverages, and supplements and it is increasingly recommended due to its anti-inflammatory, antimicrobial, anti-diarrhoeal, antioxidant, antiulcer, anti-constipation, and glucose anti-absorption properties. However, there is limited evidence on the real-world use of this plant and of its association with diarrhoea outcomes in nintedanib-treated patients. In Spain, this was studied in a pilot observational study published by Alsina et al., where 87.7% of patients taking carob flour to treat nintedanib-associated diarrhoea had achieve diarrhoea control at 3-month follow-up (24). This study aims to describe the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up among patients with IPF and other PPF who suffer a first episode of nintedanib-associated diarrhoea in real world settings in Spain. It is expected that the study findings would suggest potential alternatives to address this problem and guide future studies aiming to prove the effectiveness of anti-diarrhoeal treatments in this population.

5. AMENDMENTS AND UPDATES

FVC collected in % predicted is collected and shown in Table 8.

In Table 12 and Table 17, relative change in body weight compared to weight at baseline visit will be also calculated.

Table 16 “To describe the nintedanib utilization pattern (occurrence of dose reductions from 150 mg bid to 100 mg bid, permanent withdrawal, and escalations from 100 mg bid to 150 mg bid) in the study population from diarrhoea initiation to 12-week follow-up due to diarrhoea” was added in order to extend the analysis of nintedanib utilization pattern due to diarrhoea.

Table 25 “To describe the type of treatment of nintedanib-associated diarrhoea for those patients that have a Dose reduction due to diarrhoea, and after that, the patient recovers the optimal dose of nintedanib (150 mg bid) from diarrhoea initiation to 12-week follow-up” was added in order to extend the analysis of type of treatment of nintedanib-associated diarrhoea, for those patients that have a Dose reduction due to diarrhoea, and after that, the patient recovers the optimal dose of nintedanib (150 mg bid).

Table 26 “To describe the first type of treatment of nintedanib-associated diarrhoea from diarrhoea initiation to 12-week follow-up.” was added to extend the analysis to describe the first type of treatment received for nintedanib-associated diarrhoea.

Table 27: “To compare changes in diarrhoea indicator BSFS with the type of treatment of nintedanib-associated diarrhoea at 3,6 and 12-week follow-up referent to diarrhoea initiation” was added for further analysis.

Non-substantial amendment

After 7 months of recruitment, only 9 patients had been included in the study. To facilitate patient recruitment, time period allowed between index date and baseline visit was increased from 5 days to 4 weeks.

As stated in the study protocol: Time period between Index Date and Baseline visit was extended from 5 days to 4 weeks. Baseline visit will be performed as close as possible to the index date and not later than 4 weeks after the index date.

This non-substantial amendment was included in protocol version 3 (29Oct2024). On October 29th, 2024, protocol v3.0 and the Patient Information Sheet and Informed Consent Form (v3.0 29Oct2024) were notified to the Ethics Committee. This non-substantial amendment was approved by the Ethics Committee in November 2024.

End of recruitment without reaching the planned N

As mentioned in section 10.4, the planned sample size of 100 patients was sufficient to estimate a proportion of 0.5 with a reference population of 6,337 patients, assuming a replacement rate of 10%.

However, due to difficulties in recruiting patients, the Sponsor decided to close the recruitment period on January 31st 2025, as planned, without reaching the expected N of 100 patients. On January 31st 18 patients had been included.

To address the study objectives, once all the 18 patients have completed the 12-weeks follow-up period, the database will be locked, and all statistical analyses will be performed with this new sample size.

6. RESEARCH QUESTION AND OBJECTIVE

This is an observational, non-interventional, and prospective post authorization safety study (PASS) that will describe the real-world proportion of patients that achieve nintedanib-associated diarrhoea control after 12 weeks of follow-up, in hospital settings in Spain. It will include outpatients (i.e., those attending ambulatory visits) with IPF and other PPF treated with nintedanib (150 mg bid) and having a first episode of diarrhoea after nintedanib initiation.

Main research question:
Among patients with IPF and PPF (other than IPF) treated with 150 mg bid of nintedanib suffering a first episode of nintedanib-associated diarrhoea in real-world settings in Spain, which is the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up?

Primary Objective:
To describe the proportion of patients who achieve diarrhoea control while taking a nintedanib dose of 150 mg bid at 12-week follow-up in patients with IPF and other PPF reporting a first episode of nintedanib-associated diarrhoea.

Secondary Objectives:

1. To describe the change in the proportion of patients taking the optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation.
2. To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 12-week follow-up referent to diarrhoea initiation.
3. To describe the proportion of patients using carob flour for the management of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up.
4. To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at diarrhoea initiation and 12-week follow-up.
5. To describe the nintedanib utilization pattern (occurrence of dose reductions from 150 mg bid to 100 mg bid, permanent withdrawal, and escalations from 100 mg bid to 150 mg bid) in the study population from diarrhoea initiation to 12-week follow-up.

Further objectives:

1. To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 6-week follow-up referent to diarrhoea initiation.
2. To describe the number of patients who do not receive treatment for nintedanib-associated diarrhoea in all the study period (i.e., from diarrhoea initiation to 12-week follow-up).
3. To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at 6-week follow-up referent to diarrhoea initiation.
4. To describe the counts of different treatment combinations (e.g., loperamide + carob flour) used at least once for the management of nintedanib-associated diarrhoea from diarrhoea initiation to 12-week follow-up.
5. To describe the occurrence of at least one episode of persistent diarrhoea (lasting ≥14 days) and the number of persistent diarrhoea episodes in the study population from diarrhoea initiation to 12-week follow-up.
6. To describe the duration of the first nintedanib-associated diarrhoea episode.
7. To describe the time from nintedanib initiation to the first nintedanib-associated diarrhoea episode.
8. To describe the occurrence of at least one nintedanib temporary interruption from diarrhoea initiation to 12-week follow-up.

7. RESEARCH METHODS

7.1 STUDY DESIGN

This is an observational, non-interventional, multicenter, and prospective, real-world PASS, that will describe the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up in patients with IPF and other PPF treated with nintedanib in hospital settings in

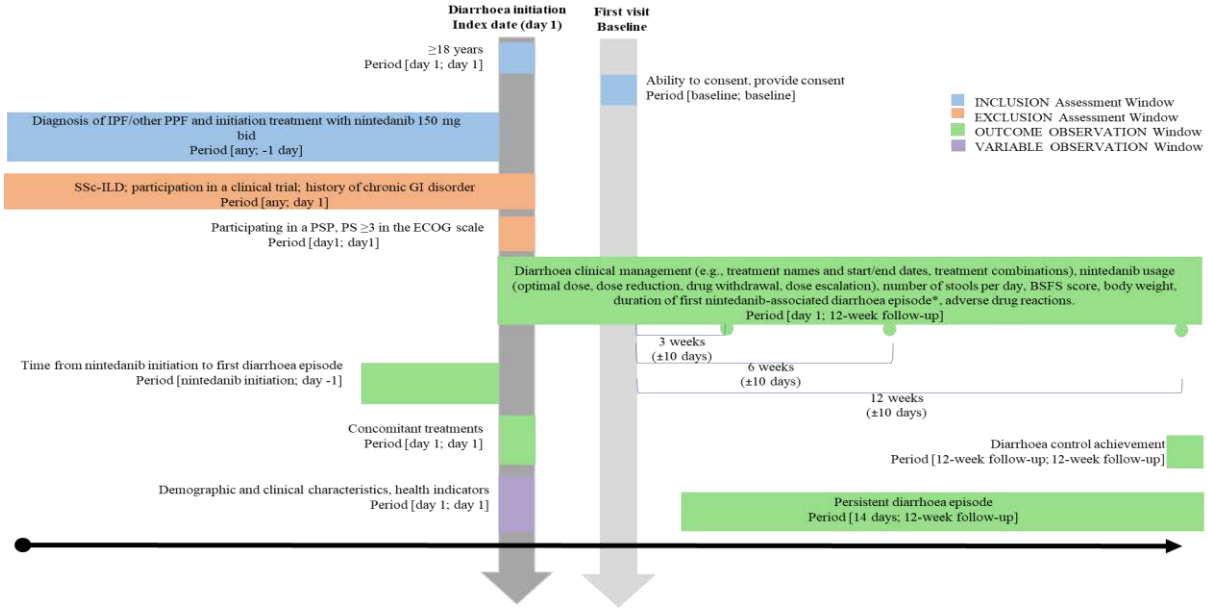
Spain. It will be conducted using primary data collected during routine medical contacts, which will be complemented with secondary data extracted from electronic medical records (EMR) and recorded by pulmonologists (or delegates) in an electronic case report form (eCRF). Patients will be competitively recruited during a first face-to-face consultation with their pulmonologists due to a first episode of diarrhoea after the initiation of nintedanib.

Study baseline, defined as the first face-to-face visit of patients with their pulmonologists due to a reported first episode of diarrhoea (when the pulmonologist will collect data related to the day of diarrhoea initiation), will be conducted as soon as possible, within the first 4 weeks after the diarrhoea initiation (index date) reported by the patient. Patients will be followed 3, 6, and 12 weeks after the baseline visit (Figure 1). These time points were selected based on a previous pilot study (24) in which patients were followed-up around 3 months to evaluate the association of nintedanib-associated diarrhoea treatment and diarrhoea outcomes.

The decision to conduct an observational study emerged due to the lack of evidence regarding the management of diarrhoea in patients treated with nintedanib in Spain. Considering that the clinical management of diarrhoea (which might include conventional antidiarrheic drugs, but also dietary interventions) and diarrhoea outcomes (e.g., diarrhoea duration and intensity) are not always registered as structured data (e.g., using ATC codes) or in detail to obtain conclusions, a prospective design was chosen to allow a more accurate, comprehensive, and homogenic registration of these variables.

This is a non-interventional study -as defined by the Clinical Trial Directive (DIR 2001/20/EC) of the European Parliament- that will be conducted following the guidelines of the International Council for Harmonization (ICH) Good Pharmacoepidemiology Practice (GPP). It is sponsored by Boehringer Ingelheim (BI) and managed by [redacted] clinical research organization (CRO). As this is a non-interventional study, the decision to prescribe nintedanib and any other intervention will be made under the sole responsibility of the healthcare professional independently from the decision to include the subject in the study. This decision should be made in accordance with routine/standard clinical practice at the investigational site. In addition, the strategy to manage nintedanib-associated diarrhoea will be decided according to the usual clinical practice in each participating site. In usual clinical practice, diarrhoea management might include diet modifications including the use of carob flour, hydration, treatment with loperamide or other anti-diarrhoeal medications, and nintedanib treatment modifications (e.g., dose reductions and/or temporary/permanent interruptions).

Figure 1: Study design



Abbreviations: ECOG= Eastern Cooperative Oncology Group scale; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis; PSP= Patient Support Programme; GI= gastrointestinal; PS= performance status; SSc-ILD= systemic sclerosis associated interstitial lung disease. Vertical arrow indicates patient timeline and horizontal arrow indicates dataset timeline. * The duration of the first nintedanib-associated diarrhoea episode will be evaluated from the first occurrence of diarrhoea until end of diarrhoea. Loss of follow-up is not included in the image.

7.2 SETTING

This study will include patients diagnosed with IPF and other PPF who have a first visit with their pulmonologist (study baseline) due to a first episode of diarrhoea while being treated with 150 mg bid of nintedanib in hospital settings in Spain. Recruitment will last approximately 6 months (depending on the initiation date in each site) and the study period will last approximately 9 months (from the inclusion of the first patient to the last follow-up visit of the last patient). The 6 months of recruitment could be extended if target sample size is not reached.

Index date will be defined as the date of diarrhoea initiation and study baseline will be defined as the first face-to-face patient visit with their pulmonologist due to a first episode of diarrhoea after the initiation of nintedanib (baseline will be performed as close as possible to index date and maximum 4 weeks after index date).
Patients will be assessed at study baseline and at 3-, 6-, and 12-week follow-up from baseline; and will be followed until death, loss of follow-up, or end of study follow-up (12 weeks), whichever comes first. Patients who withdraw nintedanib will be still followed until the 12-week follow-up.

7.3 STUDY POPULATION

This study will include patients diagnosed with IPF and other PPF, as registered in their EMR at least one day before the initiation of the first nintedanib-associated diarrhoea episode.

Eligible patients will be those being treated with nintedanib (having started treatment at least one day before diarrhoea initiation, at a dose of 150 mg twice per day [bid]) having a first face-to-face visit with their pulmonologists due to a first diarrhoea episode after nintedanib initiation, during the study recruitment period (Table 1). To ensure sample representativeness, participants will be recruited in multiple study centres across Spain and a maximum number of participants per hospital will be stablished.

Identification of potential participants:

Potential participants, who could eventually meet the study selection criteria, will be:

1. Patients receiving a first nintedanib prescription by pulmonologists or
2. Patients being treated with nintedanib and have not presented any diarrhoea episode since nintedanib initiation.

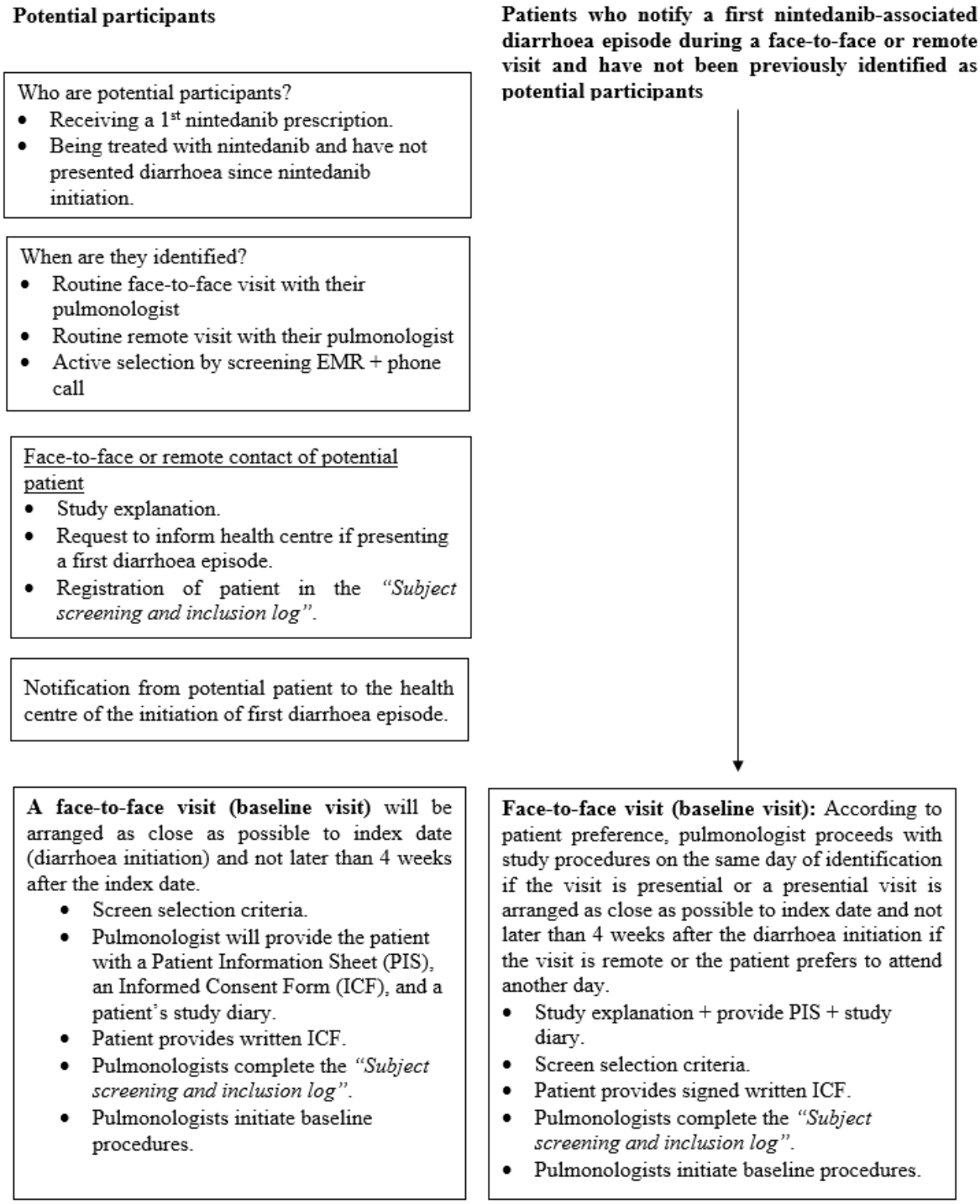
Potential participants will be identified through one of the following ways:

1. During a routine face-to-face visit with their pulmonologist.
2. During a routine remote visit with their pulmonologist
3. During an active selection and calling of potential participants, identified by screening EMR, by the pulmonologist.

Recruitment, providing informed consent, and initiation of baseline visit:

The pulmonologist will invite to participate in the study those patients previously identified as potential participants and those patients not previously identified as potential participants. In both cases, patients will be invited to participate after patients' report of a first diarrhoea episode while taking nintedanib (Figure 2).

Figure 2: Steps from participants recruitment to study baseline



The procedure for potential participants will be as follows:

1. During a face-to-face or remote contact with a potential participant, the pulmonologist will explain the study to them, and they will be asked to inform the health centre if presenting a first diarrhoea episode.

2. Once the study has been explained to potential participants, the pulmonologist will register potential participants in the *Screening section* of the *"Subject screening and inclusion log"*.

3. Potential participants will inform the health centre about the initiation of a first episode of diarrhoea during treatment with nintedanib. Health centre will inform the potential participants that the pulmonologist will perform a face-to face visit with them as close as possible to the date of diarrhoea initiation and no later than 4 weeks after diarrhoea initiation.

4. Pulmonologists will arrange a presential visit with the potential participants to confirm if the potential participant meets the study selection criteria, as close as possible to index date and within the next 4 weeks after the diarrhoea initiation.

5. If a potential participant meets the selection criteria and wants to participate in the study, the pulmonologist will provide the patient with a Patient Information Sheet (PIS), an Informed Consent Form (ICF) and a patient's study diary. The patients will be included in the study once they provide the signed written consent. The patient will receive a copy of the signed informed consent form. This visit, in which the consent is provided, will be considered as baseline visit and all data related to onset of diarrhoea will be collected (see Table 2). The pulmonologist will record in the patient's EMR the date when the patient has signed the informed consent form.

6. Pulmonologist will complete the inclusion section of the *"Subject screening and inclusion log"* confirming the participation of patient in the study.

The procedure for patients who notify a first diarrhoea episode associated with nintedanib during a face-to-face or remote visit with their pulmonologist and have not previously been identified as potential participants, will be as follows:

1. The pulmonologist will explain the study to the patient during this visit and will confirm if patient meets screening selection criteria.

2. If it is a face-to face visit and patient accepts to participate, the pulmonologist will give to the patient the PIS, the ICF and the paper patient's diary and depending on patient preferences, the ICF could be signed, and study baseline visit could be performed on the same day or a new presential visit can be scheduled as close as possible to the index date and no later than 4 weeks after diarrhoea initiation. The patient will receive a copy of the informed consent signed.

3. If it is a remote visit and the patient accepts to participate, the pulmonologist will arrange a presential visit as close as possible to index date and not later than 4 weeks after diarrhoea initiation. During this visit, considered as baseline visit, the pulmonologist will give to the patient the PIS, the ICF and the paper patient's diary. The patient will sign the ICF and will receive a copy of the signed ICF.

4. In both cases, pulmonologists will complete the inclusion section of the "*Subject screening and inclusion log*". In all cases, the physician will document in the patient's EMR the date of signing the paper consent.

Selection criteria:

The study will include patients diagnosed with IPF and other PPF. Idiopathic pulmonary fibrosis is defined as a chronic fibrosing interstitial pneumonia of unknown cause while the term PPF refers to patients with ILDs -other than IPF- who have at least two of the following three criteria: worsening of respiratory symptoms, radiological progression, and physiological progression occurring during the past year (12). In this study, these diagnoses will be defined as having an IPF or PPF diagnose confirmed by a physician, as registered in the EMR.
The study will exclude patients with SSc-ILD. This decision was based on the fact that nearly 90% of patients with Systemic Sclerosis (SSc) present gastrointestinal manifestations affecting the oesophagus, stomach, small and large bowels, liver, and pancreas (25), leading to symptoms such as dyspepsia, nausea, vomiting, abdominal bloating/distension, and faecal incontinence (26). Therefore, in these patients, the management of nintedanib-related diarrhoea and its association with diarrhoea outcomes likely differs from the rest of patients presenting PPF.

Table 1: Selection criteria

Inclusion criteria/definition
1. Adults (≥18 years old) at diarrhoea initiation.
2. Ability to consent and to conduct all procedures of the study, as judged by the study investigator, and agreeing to participate providing informed consent at baseline.
3. Diagnosis of IPF or PPF (other than IPF), as registered in EMR using free text or ICD codes (ICD-9 and/or ICD-10), at least 1 day before diarrhoea initiation.
4. Being treated with 150 mg bid of nintedanib when initiating diarrhoea symptoms, defined as having a nintedanib ATC code (L01EX09) or the molecule/commercial name registered in the EMR, for at least 1 day before diarrhoea initiation.
5. First pulmonologist consultation (face-to-face) at the time of recruitment due to a first diarrhoea episode as defined by the pulmonologist since nintedanib initiation. Diarrhoea defined as the passage of three or more loose or liquid stools in a 24-hour period (17) (loose or liquid stools defined as stools with a BSFS of 6 or 7 points (18)).
Exclusion criteria

1.	Patients diagnosed with systemic sclerosis associated interstitial lung disease (SSc-ILD) as registered in EMR using free text or ICD codes (ICD-9 and ICD-10). Referent to any time before or at diarrhoea initiation.
2.	Participation in any clinical trial including a drug or device at any time before or at diarrhoea initiation.
3.	Participation in any Patient Support Programme (PSP) at diarrhoea initiation.
4.	Having history of chronic gastrointestinal disorder (e.g., inflammatory bowel disease or the short gut syndrome), pancreatic dysfunction/insufficiency, or colon cancer; due to the likelihood of faecal incontinence. Referent to any time before or at diarrhoea initiation.
5.	Having a performance status (PS) ≥3 points on the ECOG scale at diarrhoea initiation, due to the likelihood of faecal incontinence.

Abbreviations: ATC= anatomical therapeutic chemical; ECOG= Eastern Cooperative Oncology Group scale; EMR= electronic medical record; ICD= International Statistical Classification of Diseases and Related Health Problems; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis; baseline: first pulmonologist visit (face-to-face) due to a first episode of diarrhoea after nintedanib initiation.

7.4 STUDY VISITS

Patients will be assessed at study baseline (date of the first face-to-face pulmonologist visit for study data collection) and at 3-, 6-, and 12-week follow-up after baseline visit during face-to-face or remote consultations (e.g., by phone). Due to the real-world variability in the timing of medical visits/contacts, flexible time windows will be stablished (±10 days).

Data collection schedule and method:

The variables/group of variables will be collected during the period of study (from baseline to 12-week follow-up) to meet the study objectives (Table 2).

Patient's diary will be provided to all included patients, in paper. This diary will serve as a support document, that patients can use to register the information that will be later collected at each follow-up visit and will not be considered a source document. This information will include, at least:

- Diarrhoea-related information.
- Information on diarrhoea treatment.
- Nintedanib pattern of use.

Table 2: Data collection schedule and data collection method

	Baseline (Presential)	Follow-up contacts (Presential or remote)			Method
		3-week (± 10 days)	6-week (± 10 days)	12-week (± 10 days)	
Obtaining Informed Consent	x				A signed ICF paper copy will be provided to all patients. Written informed consent date will be documented in the EMR.
Eligibility confirmation	x				Obtained from EMR and/or reported by patients during first study contact.
Demographic/clinical characteristics • Age, years • Sex • Race/ ethnicity • Body mass index (or weight and hight), kg/m^2 • Smoking status • Pulmonary disease: IPF/other PPF (type of PPF) and date of diagnosis • Time since diagnosis to 1st first episode of nintedanib-associated diarrhoea. • Comorbidities and date of diagnosis o Arterial hypertension o Diabetes o Gastroesophageal reflux o Coronary heart disease o Sleep apnoea-hypopnea syndrome o Heart disease o Asthma o Chronic bronchitis o Chronic Obstructive Pulmonary Disease o Emphysema o Lung cancer o Other relevant comorbidities: names and dates	x*				Obtained from EMR, reported by patients during study contact, and/or directly measured by the pulmonologist (e.g., weight).

	Baseline (Presential)	Follow-up contacts (Presential or remote)			Method
Health indicators • FVC, litres • Diffusing Capacity of Lung for Carbon Monoxide, (% predicted) • ECOG scale, score	x*				Obtained from EMR, reported by patients during study contact, and/or directly measured by the pulmonologist (e.g., FVC).
Diarrhoea control achievement, yes/no (<3 loose or liquid stools in a 24-hour period, while being treated with 150 mg bid of nintedanib)				x	Obtained from EMR and/or reported by patient (with support of his/her diary) during study contact
Diarrhoea indicators and body weight • Number of stools per day • BSFS score • Body weight, kilograms • Mean number of stools per day in the last 7 days. • Mean BSFS score in the last 7 days. • Mean number of loose or liquid stools in the last seven days	 x* x* x*	 x x x	 x x x	 x x x	Obtained from EMR, reported by patient (with support of his/her diary) during study contact, and/or directly measured by the pulmonologist.
Persistent diarrhoea episode (≥3 loose or liquid stools in a 24-hour period for a total duration ≥14 days) • Occurrence of at least one persistent diarrhoea episode, yes/no • Number of persistent diarrhoea episodes				x	Obtained from EMR and/or reported by patient (with support of his/her diary) during study contact.
Duration of first nintedanib-associated diarrhoea episode, days		x**	x**	x**	Obtained from EMR and/or reported by patient (with support of his/her diary, if available at baseline) during study contact.
Time from nintedanib initiation to the first diarrhoea episode, days	x				Obtained from EMR and/or reported by patient (with support of his/her diary, if available

	Baseline (Presential)	Follow-up contacts (Presential or remote)			Method
					at baseline) during study contact.
Nintedanib use • Optimal nintedanib dose • Dose reductions • Drug withdrawal (permanent/ temporal) • Dose escalation	x*	x	x	x	Obtained from EMR and/or reported by patient (with support of his/her diary) during study contacts.
Concomitant treatment to nintedanib (excluding treatment of nintedanib-associated diarrhoea) • Receiving concomitant treatment, yes/no • Drug name, start date	x*				Obtained from EMR and/or reported by patient during study contact.
Clinical management of nintedanib-associated diarrhoea • Receiving treatment nintedanib-associated diarrhoea, yes/no. • Type of pharmacological treatment (drug names and start and end dates) (e.g., loperamide). • Type of non-pharmacological treatment (treatment names and start and end dates) (e.g, carob flour, zinc, probiotics, other dietary interventions, hydration). • Treatment combinations.	x*	x	x	x	Obtained from EMR and/or reported by patient (with support of his/her diary). during study contact.
Loss of follow-up, yes/no.		x	x	x	Extracted from EMR and confirmed during study contacts.
Adverse Drug Reactions	x	x	x	x	Reported by patient (with or without support of his/her diary) during the study period.

Abbreviations: BSFS= Bristol Stool Form Scale; ECOG= Eastern Cooperative Oncology Group scale; EMR= electronic medical record; FVC= Forced vital capacity; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis. * Measured referent to the day of diarrhoea initiation. ** To collect only if not collected in previous visits.

8. VARIABLES

A summary of variables related to main objectives are described in Table 3.

Table 3: Main variables related to study objectives

Diarrhoea control achievement, yes/no (<3 loose or liquid stools in a 24-hour period while being treated with 150 mg bid of nintedanib)

Diarrhoea indicators and body weight

- Number of stools per day, mean number of stools per day in the last 7 days
- BSFS score, mean BSFS score in the last 7 days
- Number of loose or liquid stools, mean number of loose or liquid stools in the last 7 days
- Body weight, kilograms, last measure available

Nintedanib use

- Optimal nintedanib dose
- Dose reductions
- Drug withdrawal (permanent/ temporal)
- Dose escalation

Clinical management of nintedanib-associated diarrhoea

- Receiving treatment nintedanib-associated diarrhoea, yes/no.
- Type of pharmacological treatment (drug names and start and end dates) (e.g., loperamide).
- Type of non-pharmacological treatment (treatment names and start and end dates) (e.g, carob flour, zinc, probiotics, other dietary interventions, hydration).
- Treatment combinations.

Persistent diarrhoea (≥3 loose or liquid stools in a 24-hour period for a total duration of ≥14 days)

- Occurrence of at least one persistent diarrhoea episode, yes/no
- Number of persistent diarrhoea episodes

Time from nintedanib initiation to the first diarrhoea episode, days

Duration of first nintedanib-associated diarrhoea episode, days

8.1 EXPOSURES

Effect assessment of nintedanib and diarrhoea treatments is not an objective of this observational study. Patients will have been already treated with nintedanib before being included in the study. Prescription of nintedanib and diarrhoea treatments will have been done under the sole responsibility of the healthcare professional and independently of the present study. Nintedanib and diarrhoea treatments pattern of use will be collected (e.g., dose reduction, escalation, interruptions, withdrawals) with descriptive purposes. No intervention, either diagnostic or therapeutic, will be applied to patients other than that used for routine clinical practice.

8.2 OUTCOMES

The study outcomes are detailed in Table 4. Diarrhoea will be defined as the passage of three or more loose or liquid stools in a 24-hour period (18) (loose or liquid stools defined as stools with a BSFS of 6 or 7 points (17)); and a diarrhoea episode will be defined considering that two diarrhoea episodes are separated by at least 7 days without any diarrhoea.
The BSFS is a 7-point ordinal scale of stool types used in clinical practice and research (18, 27). It ranges from the hardest (1 point or type 1) to the softest stool form (7 points or type 7), with 6 and 7 points considered abnormally loose/liquid stools. Persistent diarrhoea will be defined as a diarrhoea episode lasting ≥14 days (17, 28, 30).

8.2.1 Primary outcomes

Table 4: Outcomes of study according to study objectives

	Primary objective	Primary Outcome name
1	To describe the proportion of patients who achieve diarrhoea control while taking a nintedanib dose of 150 mg bid at 12-week follow up in patients with IPF and other PPF reporting a first episode of nintedanib-associated diarrhoea.	1. Achievement of diarrhoea control (yes/no), defined as the passage of less than 3 loose or liquid stools in a 24-hour period (loose or liquid stools defined as stools with a BSFS of 6 or 7 points while being treated with 150 mg bid of nintedanib, at 12-week follow-up. Safety Issue: Yes
	Secondary objective	Secondary Outcome name
1	To describe the change in the proportion of patients taking the optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation.	1. Absolute change in the proportion of patients taking optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation. Safety Issue: No
2	To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 12-week follow-up referent to diarrhoea initiation.	2. Absolute change in BSFS score at week 12 follow-up referent to diarrhoea initiation. 3. Absolute change in number of stools per day at 12-week follow-up referent to diarrhoea initiation. 4. Absolute change in current body weight (in kilograms) at 12-week follow-up referent to diarrhoea initiation. Safety Issue: Yes
3	To describe the proportion of patients using carob flour for the management of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up.	5. Proportion of patients using carob flour for the treatment of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up. Safety Issue: No

	Secondary objective	Secondary Outcome name
4	To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at diarrhoea initiation and 12-week follow-up.	6. Number of patients per treatment category for nintedanib-associated diarrhoea at diarrhoea initiation. 7. Number of patients per treatment category for nintedanib-associated diarrhoea at 12-week follow-up. Treatment categories of nintedanib-associated diarrhoea could include pharmacological treatments (e.g., loperamide) or non-pharmacological treatment (e.g., carob flour, zinc, probiotics, other dietary interventions, hydration). Safety Issue: No.
5	To describe the nintedanib utilization pattern (occurrence of dose reductions from 150 mg bid to 100 mg bid, permanent withdrawal, and escalations from 100 mg bid to 150 mg bid) in the study population from diarrhoea initiation to 12-week follow-up.	8. Occurrence of at least one dose reduction (yes/no), defined as reduction of nintedanib dose from 150 mg bid to 100 mg bid, from diarrhoea initiation to 12-week follow-up. 9. Occurrence of permanent withdrawal, defined as discontinuing 150 mg bid or 100 mg bid of nintedanib and not reintroducing it before the 12-week follow-up). 10. Occurrence of at least one dose escalation (yes/no), defined as an increase of nintedanib dose from 100 mg bid to 150 mg bid from diarrhoea initiation to 12-week follow-up. Safety Issue: No.

8.2.2 Secondary outcomes

The secondary outcomes are detailed in Table 4.

[redacted]

[redacted]

8.3 COVARIATES

The covariates analysed in the study are described in Table 6.

Table 6: Covariates to describe the study population

Demographic and clinical characteristics of the study population at diarrhoea initiation.

- Age: continues variable, in years.
- Sex: categorized in male/ female.
- Race/ ethnicity: categorized in:
  - Asian
  - Black
  - Latino
  - White
  - Other
- Body mass index: calculated weight in kilograms divided by the square of body height in meters (kg/m^2).
- Smoking status: categorized in former smoker/ current smoker/ no smoker.
- Pulmonary disease: IPF/PPF (type of PPF) and date of diagnosis.
- Comorbidities and date of diagnosis
  - Arterial hypertension
  - Diabetes
  - Gastroesophageal reflux
  - Coronary heart disease
  - Sleep apnoea-hypopnea syndrome
  - Heart disease
  - Asthma
  - Chronic bronchitis
  - Chronic Obstructive Pulmonary Disease
  - Emphysema
  - Lung cancer
  - Other relevant comorbidities: names and dates
- Health indicators.
  - FVC in litres (last measure available).
  - FVC (% predicted) (last measure available).
  - Diffusing Capacity of Lung for Carbon Monoxide (% predicted) (last measure available).
  - ECOG scale, to assess PS.

Concomitant treatment at diarrhoea initiation (excluding treatment of nintedanib-associated diarrhoea)

- Receiving concomitant treatment, yes/no.
- Drug name, start date.

Loss of follow-up, yes/ no.

Adverse Drug Reactions

Abbreviations: ECOG= Eastern Cooperative Oncology Group scale; EMR= electronic medical record; FVC= Forced vital capacity; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis; PS: Performance Status.

9. DATA SOURCES

This study will use primary data collected by pulmonologists during presential or remote medical contacts, and secondary data obtained from hospital's EMR.

Primary data collection
The required study information will be recorded by pulmonologists (or delegates) in an eCRF. It is expected that the data collected in the eCRF will match the data in the patient medical charts maintained by the study sites.

The pulmonologist will provide the patient with a paper patient's diary as a support document to help the patients remembering the information collected at each follow-up. The patient's diary will not be considered a source document and therefore, it will not be collected nor kept by the study site.

An Investigator data collection supporting guide will be provided to investigators, summarizing the information to collect in each study time-point.

10. DATA MANAGEMENT AND SOFTWARE / TOOLS

The data management plan is summarized below. Full details of the data management plan will be included in a separate ONIS-Data Management and Review Plan (ONIS-DMRP). This ONIS-DMRP will be written by [redacted]. and approved by BI before the design of the study database is finalized.

During the study completion, data will be collected by study sites investigators (pulmonologists or delegates) during direct interviews with patients and through EMR review. Then, data will be entered to an eCRF. Investigators will be responsible for the integrity of the data reported.

Each participating site will have access exclusively to the data entered in its own site.

All sites will be fully trained on using the online data capture system, including eCRF completion, guidelines, and support files. Investigators and site personnel will be able to access their account with a username and a password. All eCRFs should be completed by designated trained personnel. The eCRF will be reviewed, electronically signed, and dated by the Principal

Investigator. All changes or corrections to eCRFs will be documented in an audit trail and an adequate explanation will be required.

All investigators will be required to follow local laws and regulations and institutional practices for document retention.

All information about this observational study and individual participant medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities, and as applicable by law. Publications may result from this study, but in no case patient confidentiality will be compromised.

Data in the eCRF system will be kept in a central location and all data will be transmitted to a central database. The eCRF is a web-based application accessible on any computer with an Internet connection. The Hypertext Transfer Protocol Secure (HTTPS) with a 128-bit Secure Sockets Layer (SSL) certificate will be used for web communication. This will ensure the confidentiality of the communications between the servers and the investigators' computers by encrypting all the transmitted data ("secure connection"). The SSL technology implemented ensures that all the data transferred to the server from the CRO database will be encoded and protected from external attacks. Audit trail follow-up will ensure monitoring of any movement of the saved data. The information recorded for each value stored in the database includes event date, responsible party, variable, old value, new value, and type of step taken (data creation, updating or deletion). This audit process provides an additional safety mechanism to ensure the security of the data stored and could also be useful for the site staff in answering questions regarding data entry.

BI will perform oversight of the data management of this study. [redacted] will produce eCRF specifications for the study, based on their templates, including quality checking to be performed on the data.

All the information entered in the eCRF must be traceable to the original documents in the patient's EMR.

The investigator must keep the original ICF (signed by the patient), and the patient will be given a signed copy.

10.1 SOFTWARE/TOOLS

All statistical analyses will be conducted using SAS Guide Enterprise (version 7.15 or higher).

10.2 HANDLING OF MISSING VALUES

Since the data collection will be made in the framework of standard clinical care, data entry completeness cannot be assured. Thus, missing information will be extensively described and will be considered during results interpretation.

10.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

Specifically, the potential limitations in this study are:

- Misclassification bias, it occurs when a participant is categorized incorrectly. The definition of cases with nintedanib-related diarrhoea might be subjected to bias (diarrhoea could be due to another reason). However, we reduced the risk of this bias by including only first cases of diarrhoea after nintedanib initiation.
- Other misclassification bias will be that the diagnosis of patients with IPF and other PPF, might have been made following different methods and criteria among study centres and clinicians. This is particularly likely in the case of PPF (other than IPF), a term that has been recently introduced in medicine.
- Sampling bias: As with most clinical diagnosis, it is possible that patients with less severe diarrhoea symptoms are misdiagnosed and incorrectly classified as non-diarrhoea cases. In addition, the classification of a diarrhoea episode as “first”, is based on self-reported information, which might be subjected to recall bias.
- Confounding: Confounding is a type of bias in which the confounding variable is associated with the exposure and outcome variables. In this study, the objective is descriptive, and no cause-effect associations or modelling that can be influenced by cofounding will be stablished. In this line, no control for confounding was stablished (e.g., adjusting models by cofounders, or matching of participants).
- Generalization: Since this is a national study, extrapolation of results to other countries should be taken with caution. Based on the inclusion of consecutive patients across multiple regions, it is expected that the results from this study will be representative of the Spanish population with IPF and other PPFs treated with nintedanib and may be generalizable to other Spanish regions with similar demographics and health care systems.
- The reporting of diarrhoea indicators, nintedanib pattern of use, and diarrhoea management by the patient may be subjected by recall bias. Also, the information to be collected by patient in the diary may not be complete or accurate. Patient may forget some information or commit some mistakes when filling it. However, the use of a patients’ diary as a support document and the information provided by the EMR would be used to decrease this bias.
- The reporting date of diarrhoea initiation to the health centre might not coincide with the actual diarrhoea initiation date. Ideally, both dates will coincide, thus baseline visit will be as close as possible to diarrhoea initiation. However, the time window between diarrhoea initiation and reporting to the health centre will be likely small, since most physicians in Spain inform the patients about this nintedanib adverse event and advise them to communicate it to the health centre.
- The presence or not of diarrhoea and its evolution may be related to adherence to treatment with nintedanib or to other factors (e.g., having preventive diarrhoea treatment), but these variables will not be collected since it is not an objective of the study.

10.4 STUDY SIZE

This study will be carried out in Spain, a country with a total population of 47.4 million people. Given that IPF affects around 8.2 per 100,000 people (11, 12), ILD affects up to 76.0 cases per 100,000 people in Europe (10, 11), and PPF affects up to 40% of non-IPF ILDs (11, 13), it is estimated that there is a total of 3,887 patients diagnosed with IPF and 12,855 diagnosed with PPF in Spain. Considering that approximately 50% of these patients are treated with nintedanib (9), and that up to 75.7% present diarrhoea as a result of the treatment (2-5), it is estimated that 6,337 patients in Spain are diagnosed with IPF or other PPF and present nintedanib-associated diarrhoea.

To describe the diarrhoea control in patients with IPF and other PPF treated with nintedanib, a proportion of 0.5 is supposed (maximum indeterminacy or maximum sample size possible). Given that the proportion of patients who control the diarrhoea caused by nintedanib is unknown, the best strategy is to take maximum indeterminacy. Using this approach, a sample size of 100 is sufficient to estimate -with a 95% confidence and a precision of +/- 10.3%- a proportion of 0.5 with a reference population of 6,337 patients, assuming a replacement rate of 10%.

Due to the difficulties faced in including patients in the study, and after performing a non-substantial protocol amendment (see section 5), and other actions to try to ease the recruitment, without success, the Sponsor decided to close the recruitment period on January 31st 2025, as planned, without reaching the expected N of 100 patients. On January 31st 18 patients had been included.

To address the study objectives, once all the 18 patients have completed the 12-weeks follow-up period, the database will be locked, and all statistical analyses will be performed with this new sample size.

11. DATA ANALYSIS

The statistical analysis plan for the study is summarized below.

11.1 MAIN ANALYSIS

Descriptive statistics will be presented as absolute (counts) and relative frequencies (proportions) for categorical variables; and mean, standard deviation, median, 25 and 75 quartiles, and minimum, and maximum values for continuous variables.

Descriptive statistics will be applied to the primary objective to describe the proportion of patients who achieve diarrhoea control, and to the secondary objectives.

[redacted]

11.3 SAFETY ANALYSIS

Adverse Drug Reactions (ADRs) will be notified to Pharmacovigilance according to the protocol and they will be described according to full details documented in the DMRP.

12. QUALITY CONTROL

Full details of quality control, data review, and monitoring plan are documented in the ONIS-DMRP.

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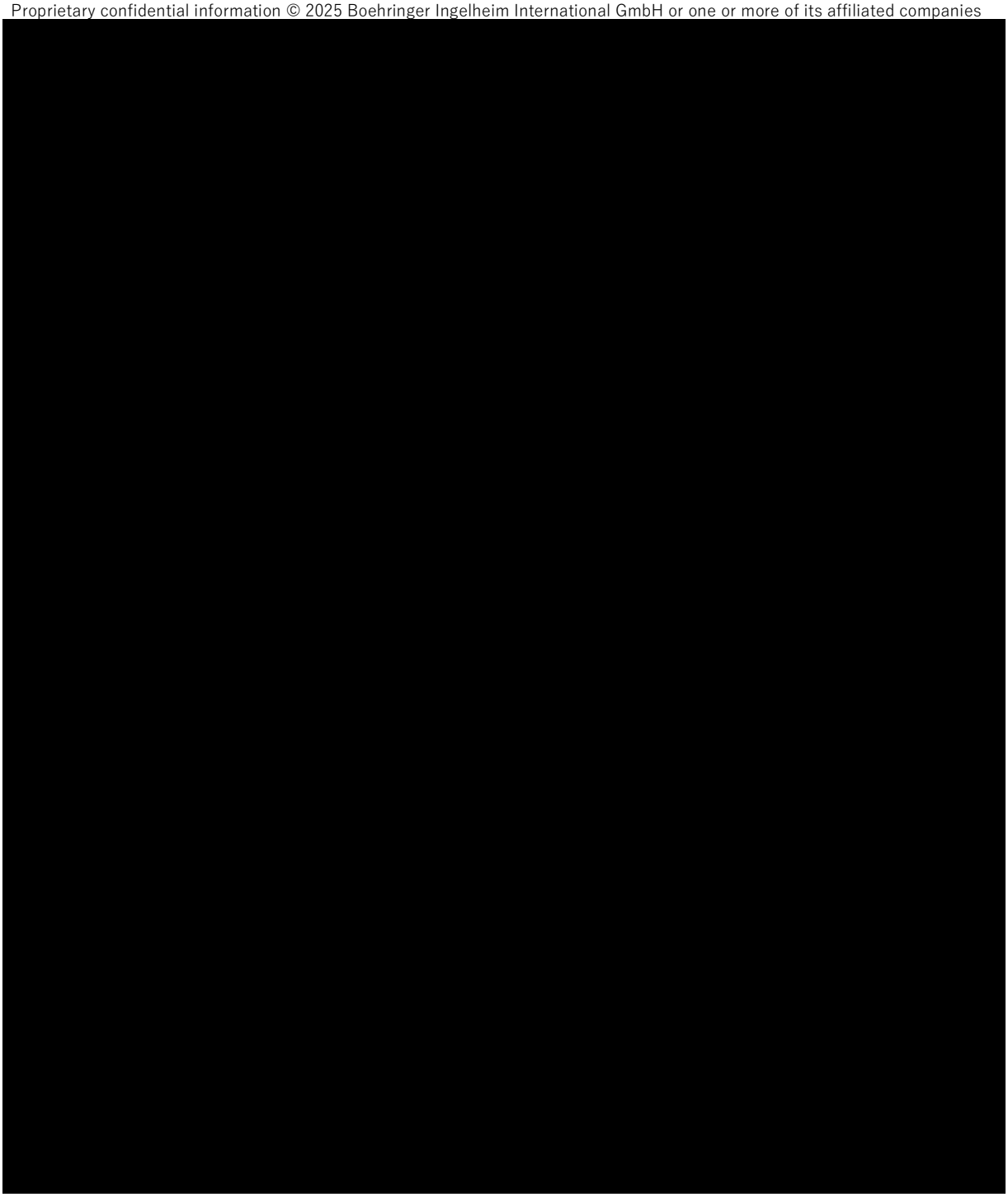

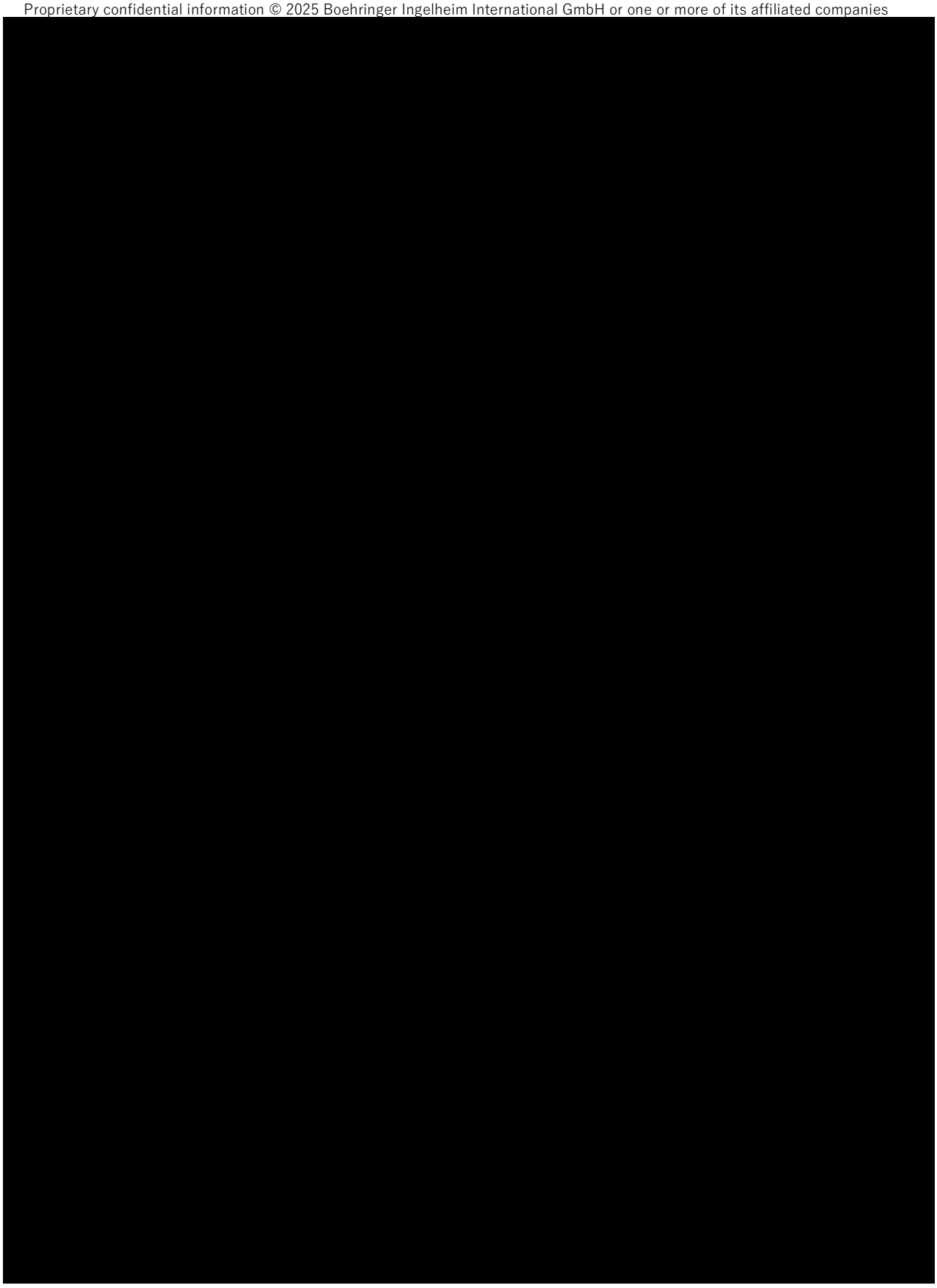

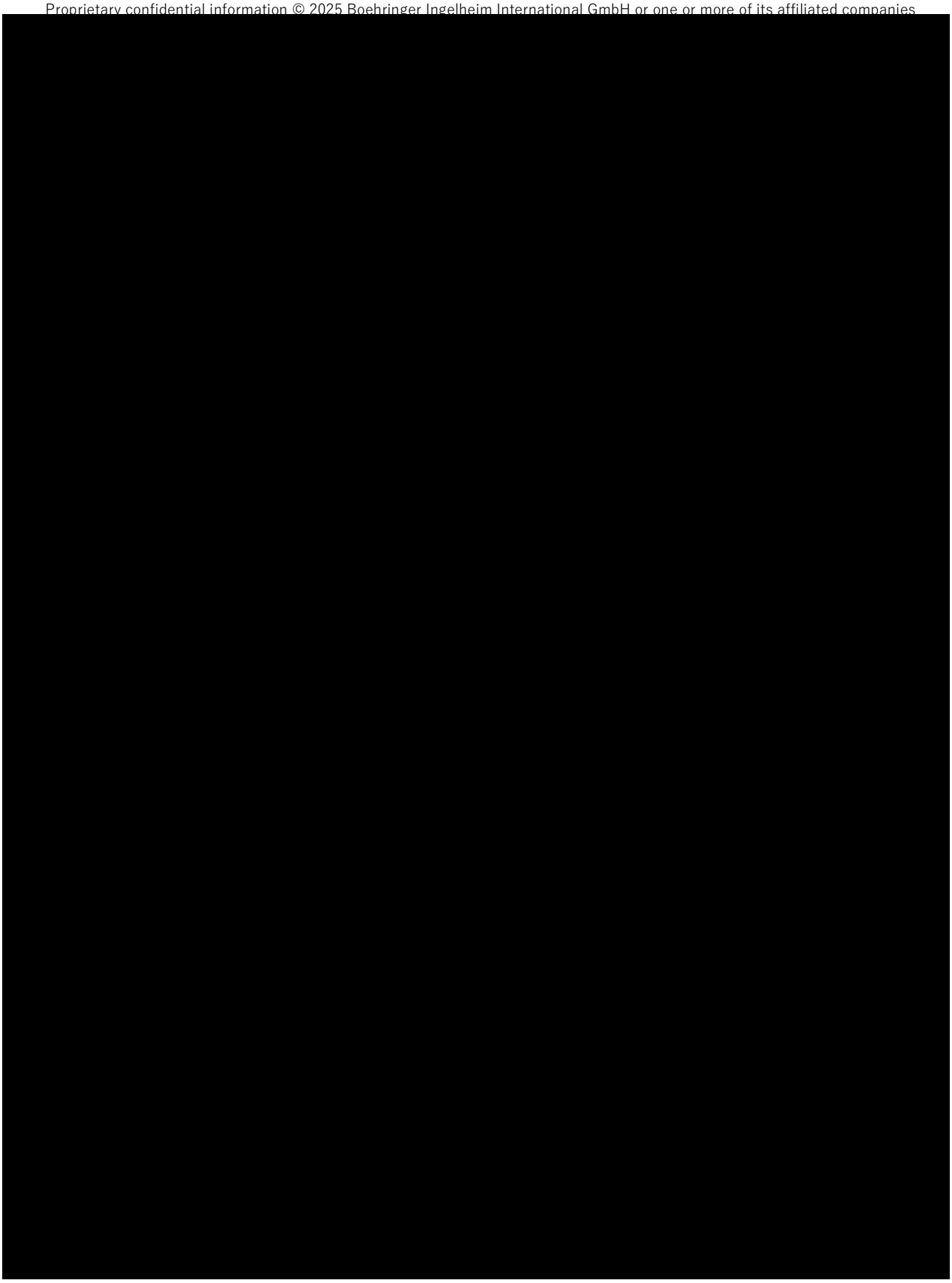

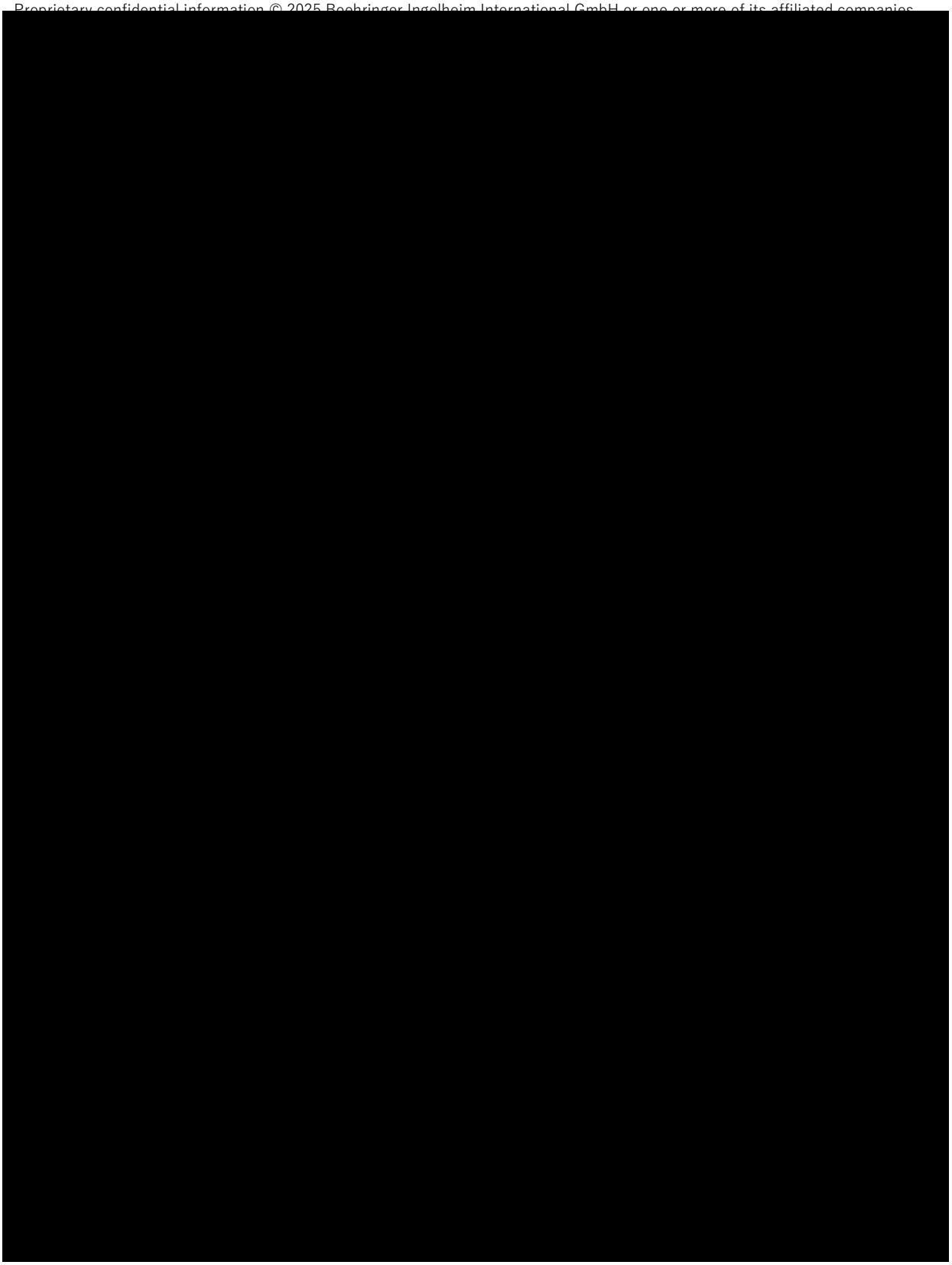

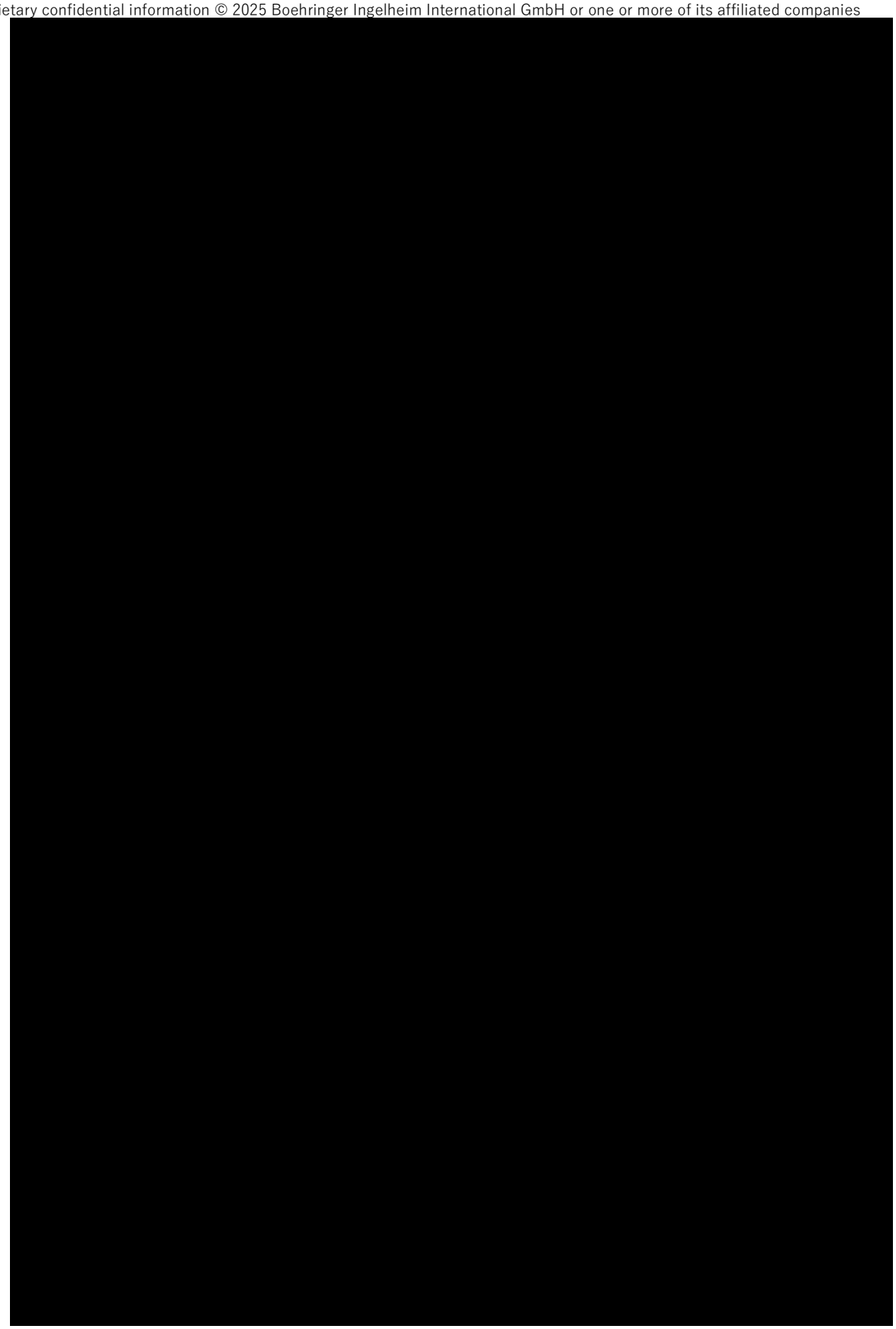

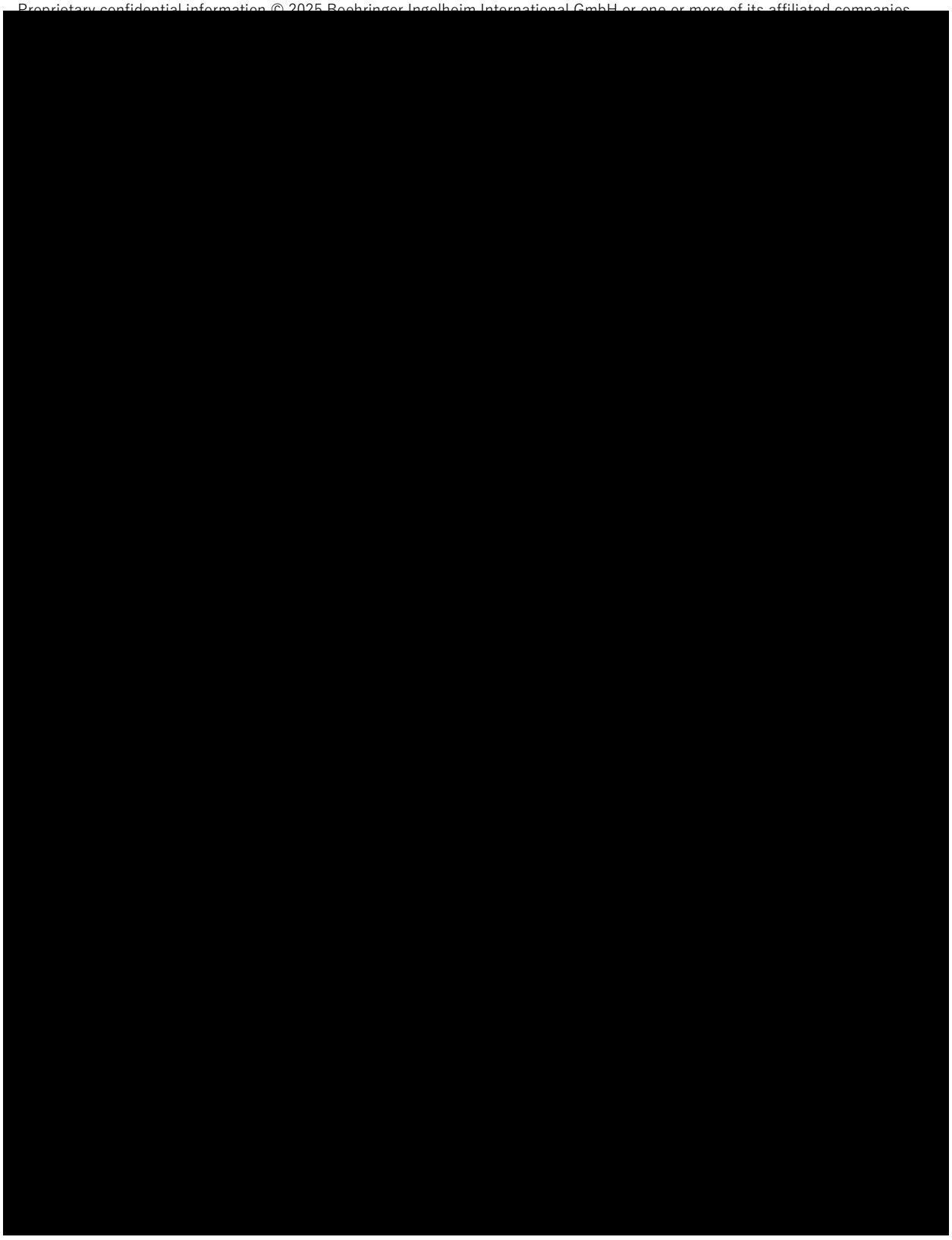

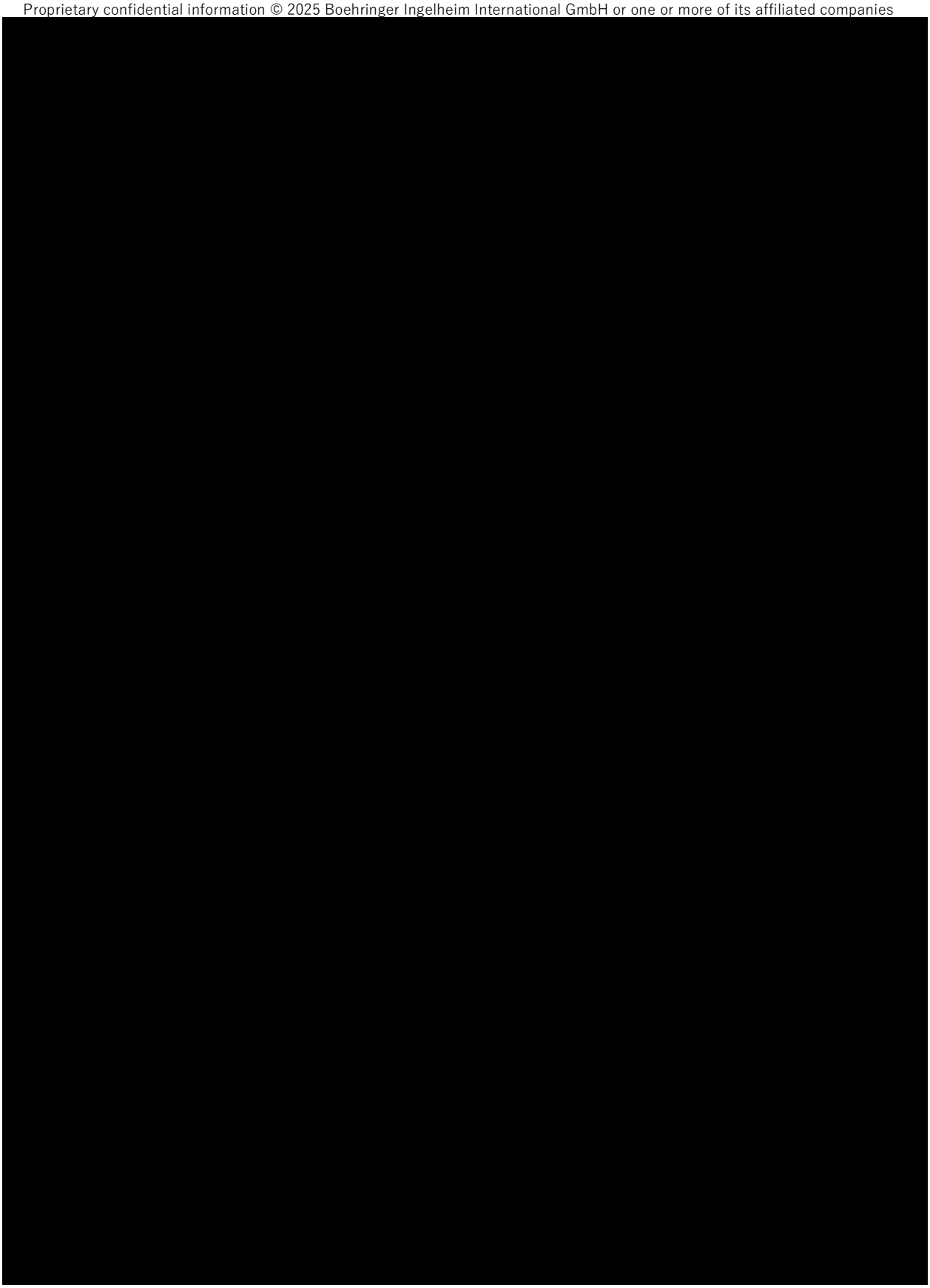

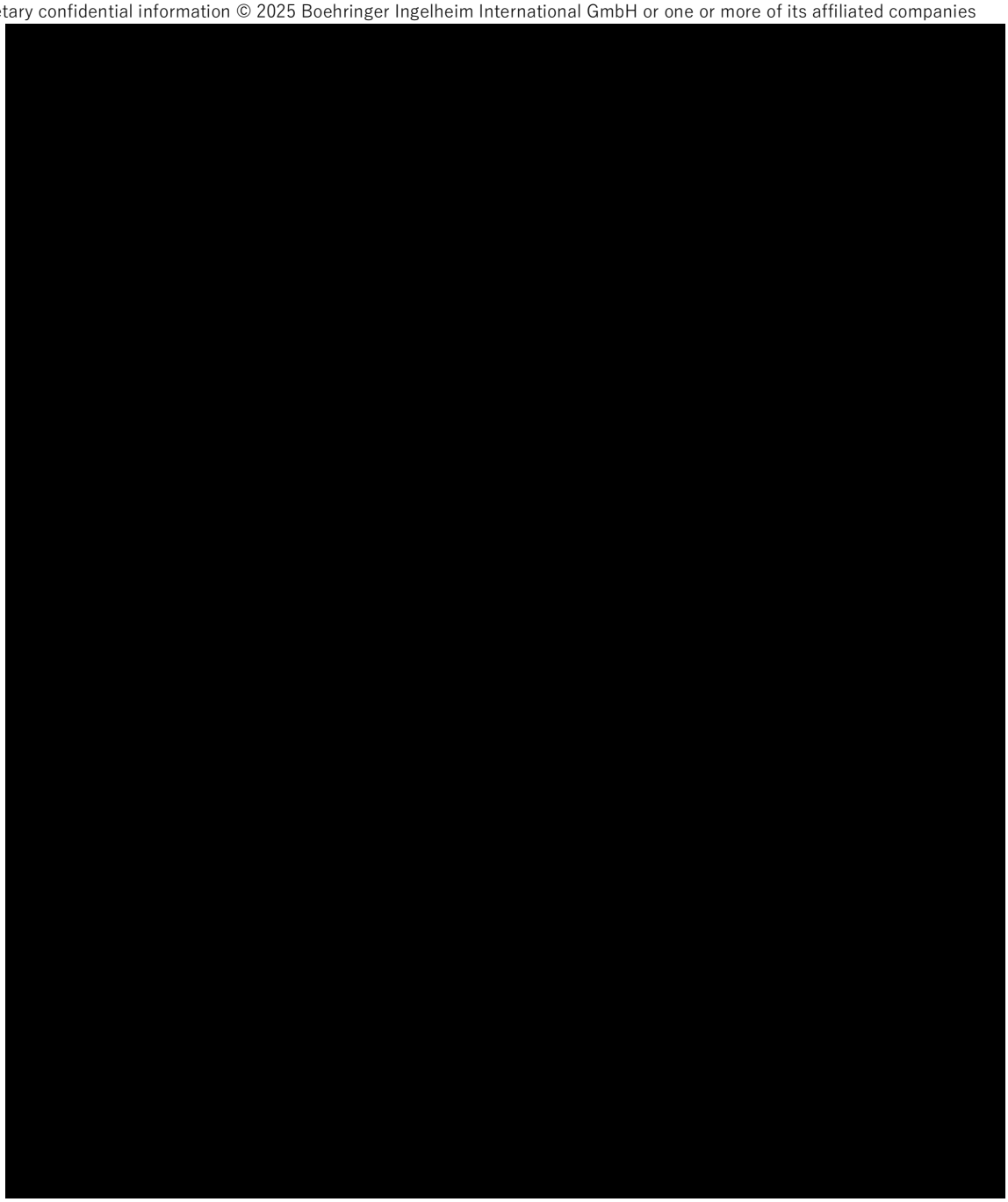

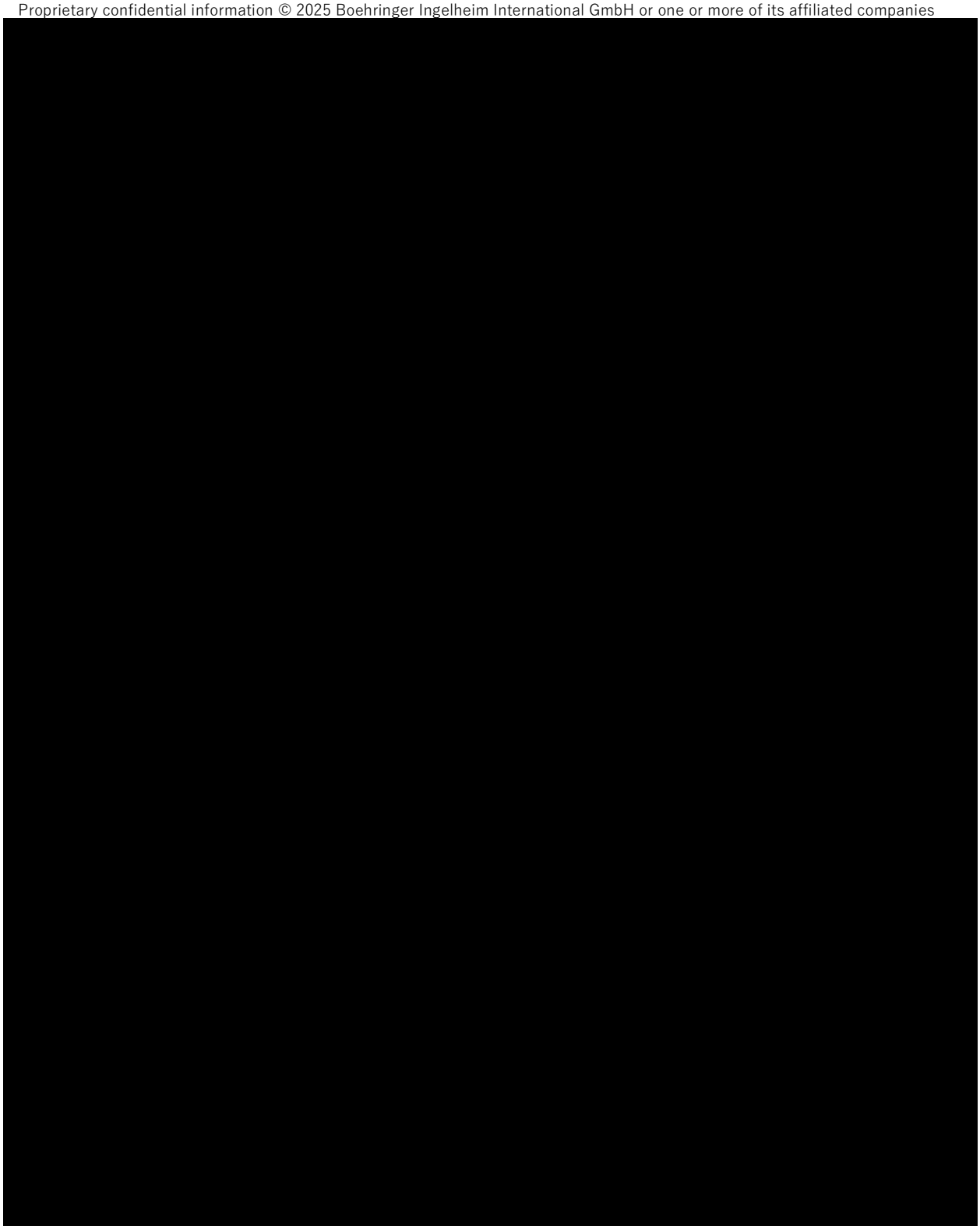

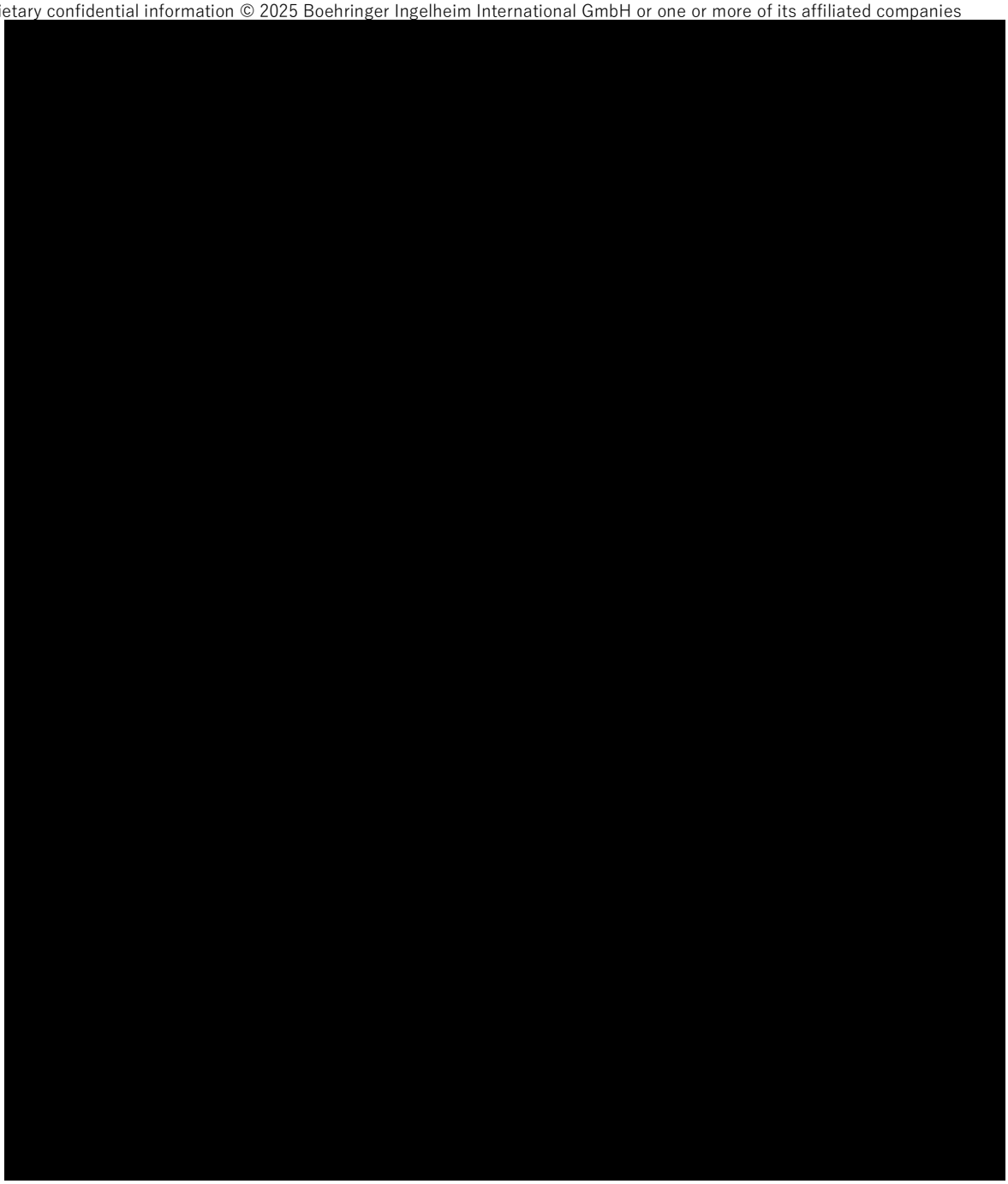

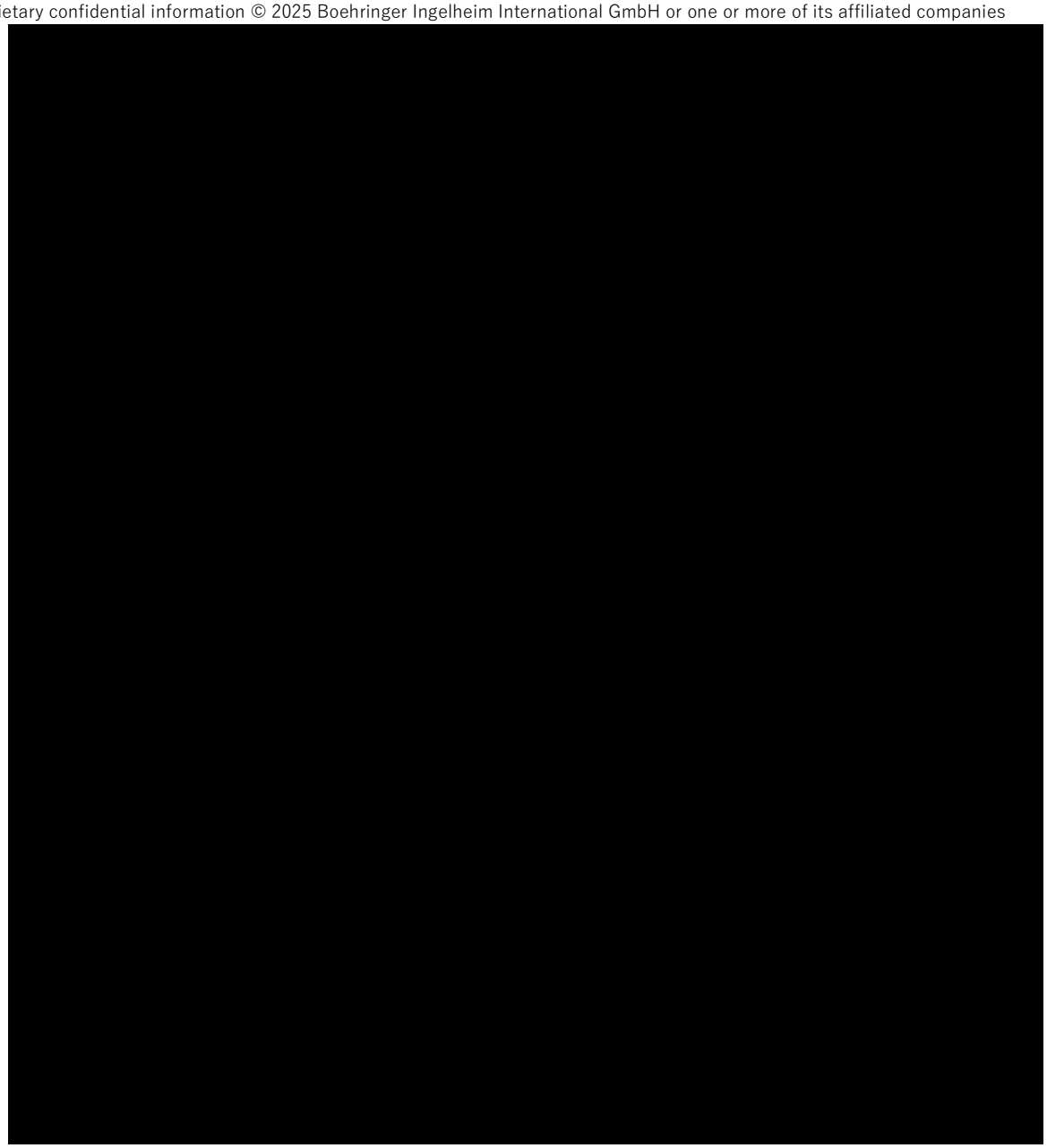

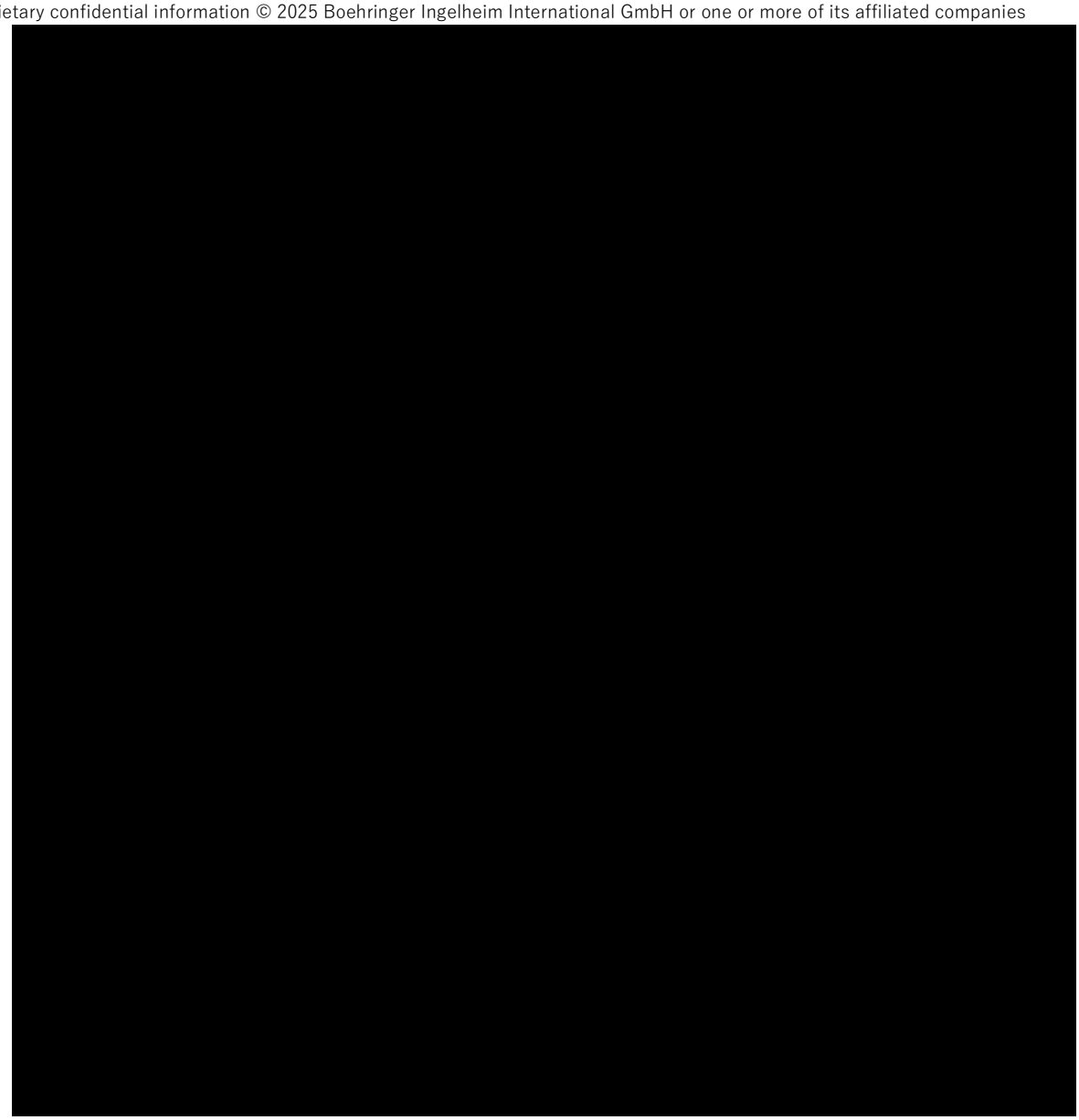

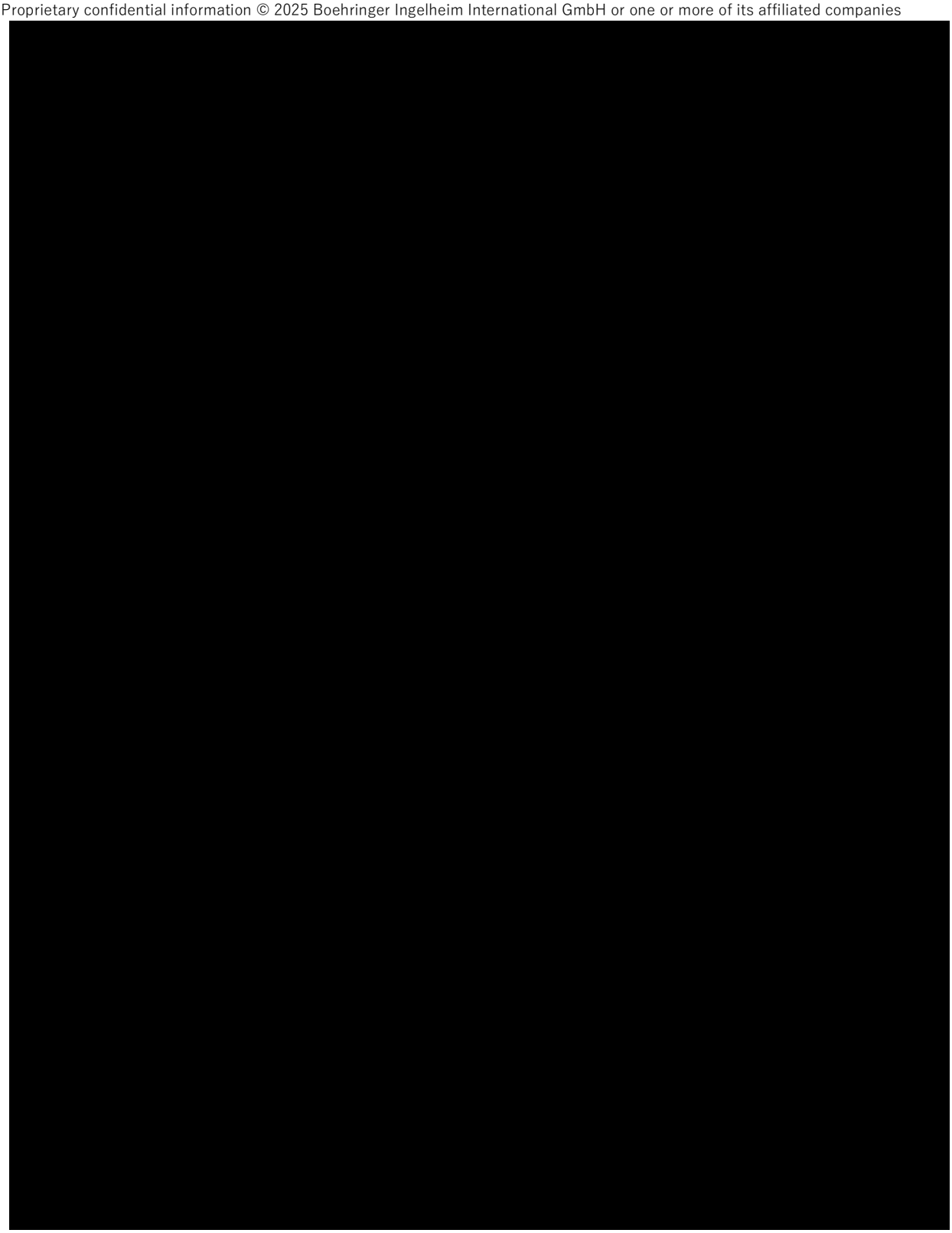

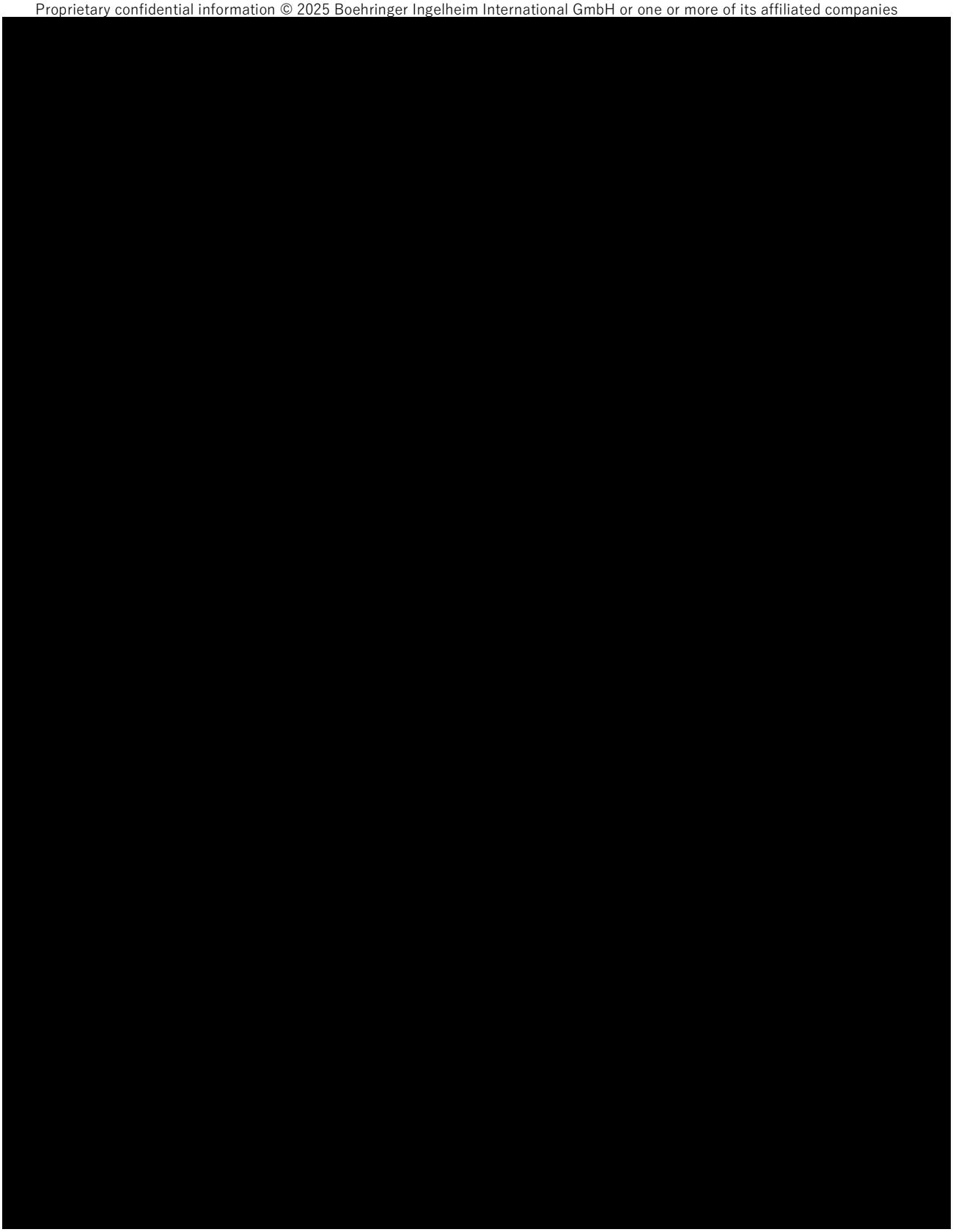

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Reason for signing: Approved	Name: [redacted] Role: Reviewer Date of signature: 27-Mar-2025 13:00:50 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Reviewer Date of signature: 27-Mar-2025 13:08:04 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 28-Mar-2025 11:18:34 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 01-Apr-2025 07:43:19 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 01-Apr-2025 07:45:41 GMT+0000

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