Boehringer Ingelheim

Clinical Trial Protocol

Document Number:		**c11787364-05**
EudraCT No.: **EU Trial No:**	2016-003403-66	
BI Trial No.:	1199.225 SENSCIS®- ON (Extension)	
BI Investigational Product(s):	Nintedanib	
Title:	An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)	
Lay Title:	A trial to evaluate the safety of long term treatment with nintedanib in patients with scleroderma related lung fibrosis.	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator:	[redacted] Phone : [redacted] Fax: [redacted]	
Status:	Final Protocol **(Revised Protocol (based on global amendment 3)**	
Version and Date:	**4.0**	**13 Aug 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		Nintedanib	
Protocol date: 30 May 2017	**Trial number:** 1199.225		**Revision date:** **13 Aug 2020**

Title of trial:	An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD) SENSCIS®- ON
Coordinating Investigator:	[redacted]
Trial site(s):	Multi-centre trial conducted in approximately 30 countries; identical to sites which enrolled patients into 1199.214 and into 1199-0340
Clinical phase:	III
Objective(s):	The primary objective of this trial is to assess the long-term safety of nintedanib treatment in patients with Systemic Sclerosis associated Interstitial Lung Disease who have completed (did not prematurely discontinue trial medication) the phase III parent trial SENSCIS® (1199.214) and to assess the safety of the ongoing nintedanib treatment in patients with Systemic Sclerosis associated Interstitial Lung Disease who have completed the phase I drug-drug interaction (DDI) trial 1199-0340.
Methodology:	Extension trial to evaluate the long term tolerability and safety of Nintedanib

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		Nintedanib	
Protocol date: 30 May 2017	**Trial number:** 1199.225		**Revision date:** **13 Aug 2020**

No. of patients:	
total entered:	Approximately 400 patients
each treatment:	Not applicable
Diagnosis:	Systemic Sclerosis associated Interstitial Lung Disease
Main criteria for inclusion:	Patients who have completed (did not prematurely discontinue trial medication) SENSCIS® (1199.214) or 1199-0340.
Test product(s):	Nintedanib
dose:	Nintedanib 150 mg bid (300 mg daily) or 100 mg bid (200 mg daily)
mode of administration:	p. o.
Comparator products:	Not applicable
dose:	
mode of administration:	
Duration of treatment:	Treatment duration for each patient will be variable. Treatment will be stopped if a reason for withdrawal is met. The trial is estimated to last approximately 34 months.

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		Nintedanib	
Protocol date: 30 May 2017	**Trial number:** 1199.225		**Revision date:** **13 Aug 2020**

Endpoints	The primary endpoint is the incidence of overall adverse events over the course of the extension trial.
Safety criteria:	Adverse events, physical examination including weight, vital signs, laboratory evaluations.
Statistical methods:	Descriptive statistics of adverse events and other safety parameters.

FLOWCHART

Visit*	1 [1,2]	2 [1,2]	2a	3	3a	4	4a	5	5a	6	6a	7	Xa [9]	X [9]	EOT [10]	FU [11]
	Screening	**Open Label Treatment Period**														**FU**
Week		**0**	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	**60 + every 16w**	**68 + every 16w**		
Day **Time window (days)**		**1**	**15** **±3**	**29** **±3**	**57** **±3**	**85** **±3**	**127** **±7**	**169** **±7**	**211** **±7**	**253** **±7**	**309** **±7**	**365** **±7**	**±7**	**±7**		**+7**
Informed consent	X [3]															
Demographics	X															
In-/Exclusion criteria		X														
Baseline Conditions	X	X														
Physical examination, vital signs	X	X		X		X		X		X		X		X	X	X
Adverse events, conc. therapy	X [4]	X [4]		X		X		X		X		X		X	X	X
12-lead ECG		X						X				X				
Safety Laboratory (blood and urine)	X	X	X [5]	X	X [5]	X	X [5]	X	X [5]	X	X [5]	X	X [5]	X	X	
Pregnancy test [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optional biobanking sample [7]		X										X				
[redacted]																
IRT call/notification		X		X		X		X		X		X		X	X	
Dispense trial medication		X		X		X		X		X		X		X		
Collect trial medication				X		X		X		X		X		X	X	
Compliance / drug accountability				X		X		X		X		X		X	X	
Termination of trial medication															X	
Conclusion of patient participation																X

Footnotes:

*In case of dose change (reduction or re-escalation) additional visits have to be included (refer to Section 6.2.4)

[1] Visit 1 should occur at least one day after trial completion of SENSCIS® (Follow up Visit) or 1199-0340 (End of Treatment/end of Study Visit). Visit 2 of this extension trial is to be scheduled:

- within a maximum of 12 weeks after last drug intake in SENSCIS® (please see also Section 6.2.1)
- within a maximum of 1 week after last drug intake in 1199.340

[2] Combining of Visit 1 and Visit 2:

- For patients who completed SENSCIS®, Visit 1 and Visit 2 may occur on the same day if the period between the last available laboratory test within SENSCIS® and Visit 2 of the extension trial (1199.225) is ≤ 6 weeks.
- For patients who completed 1199-0340, Visit 1 and Visit 2 are always scheduled on the same day.

If medical condition is not stable and new Adverse Events occurred, a new laboratory test has to be performed. For patients performing Visit 1 and Visit 2 on the same day, eligibility assessment will be based on laboratory data from last laboratory test available within SENSCIS® / 1199-0340. In case Visit 1 and Visit 2 takes place on the same day, laboratory tests, physical examination and vital signs are performed only once on that day and are recorded under Visit 2 in the eCRF

[3] The patient is required to sign informed consent prior to any trial related activities

[4] Only medical conditions that are occurring concomitantly at the time of screening will be recorded as baseline conditions in the eCRF, including any ongoing AEs from SENSCIS® or 1199-0340 respectively.

[5] Cautionary note: dependent on concomitant treatment additional safety monitoring should be considered at discretion of the investigator. Intermediate lab tests (a-Visits) do not necessarily need to be a site visit.

[6] ß-HCG will be performed at central lab at Visit 2 only. Urine dipstick pregnancy tests will be provided centrally and should be performed in all women of childbearing potential every 4-6 weeks: at least every visit and if necessary, additionally at home or at a local doctor / laboratory. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory. Woman of childbearing potential will be instructed accordingly

[7] Only after the dedicated biobanking Informed Consent has been received

[8] Self-reported outcome questionnaires must always be done by patients in a quiet place prior to any other visit procedure

[9] Same scheme should be repeated as often as needed: one complete visit every 16 weeks and one intermediate visit (a-visit) in between (every 16 weeks)

[10] End of Treatment Visit to be performed if a reason for withdrawal is met (refer to Section 3.3.4)

[11] A follow-up (FU) visit should be planned for 7 days after last drug intake in case trial medication had to be discontinued permanently due to adverse events

[12] At selected sites (if the locally required language version is available)

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[redacted]

ABBREVIATIONS

AE	Adverse Event
ACE	Angiotensin-Converting-Enzyme
ACR	American College of Rheumatology
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALK	Alkaline Phosphatase
ALT	Alanine Aminotransferase
(anti-)RNA Pol	Anti-RNA polymerase III Antibodies
AST	Aspartate Aminotransferase
ATS / ERS	American Thoracic Society / European Respiratory Society
AUC	Area Under the Curve
BI	Boehringer Ingelheim
bid	Bis in die (twice daily dosing)
BNP	Brain Natriuretic Peptide
CA	Competent Authority
CI	Confidence Interval
CK	Creatine Kinase
Cmax	Maximum measured concentration of the analyte in plasma
CML	Local Clinical Monitor
CNS	Central Nervous System
CO	Carbon Monoxide
COPD	Chronic Obstructive Pulmonary Disease
CRA(s)	Clinical Research Associate(s)
CRO	Clinical Research Organisation
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DEDP	Drug Exposure during Pregnancy
DILI	Drug-Induced Liver Injury
dL	Decilitre
DoH	Declaration of Helsinki
[redacted]	[redacted]
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e.g.	Example given
EMA	European Medicines Agency
EOT	End of Treatment
EudraCT	European Clinical Trials Database
EULAR	European League against Rheumatism
FDA	Food and Drug Administration

FEV_1	Forced Expiratory Volume in 1 second
FGFR	Fibroblast Growth Factor Receptor
FU	Follow-up
[redacted]	[redacted]
g	Gram
GAVE	Gastric antral vascular ectasia
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GIT	Gastrointestinal tract
GLI	Global Lung Initiative
GP	General Practitioner
h	Hour
[redacted]	[redacted]
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
Hct	Haematrocrit
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
i.e.	id est
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
I.U. s. c.	International Unit sub cutaneous
Lck	Lymphocyte-specific protein tyrosine kinase
LDH	Lactate Dehydrogenase
Lyn	Lymphocyte antigen receptor-associated tyrosine kinases
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
min	Minute
mL	Millilitre
mm	Millimetre
mmHg	Millimetres of mercury
mmol	Millimolar
[redacted]	[redacted]
nRTK	Non-Receptor Tyrosine Kinase
PAH	Pulmonary Arterial Hypertension
(p) PDGF / R	(polyclonal) Platelet Derived Growth Factor / Receptor
PFT	Pulmonary Function Test
P-gp	P-glycoproteine (MDR1)
PH	Pulmonary Hypertension
PI / IC	Patient Information / Informed Consent
p. o.	per os (oral)

PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QT	Interval in the electrocardiogram from the onset of the QRS complex to the end of the T wave
RBC	Red Blood Cells
RDC	Remote Data Capture
REP	Residual Effect Period
(m)RNA	(messenger) Ribonucleid Acid
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SENSCIS®	Safety and Efficacy of Nintedanib in Systemic Sclerosis
[redacted]	[redacted]
SOP	Standard Operating Procedure
SpO_2	Saturation of oxygen
Src	Rous sarcoma viral oncogene
SSc	Systemic Sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
UGT1A1	UDP-glucuronosyltransferase polypeptide A1
ULN	Upper Limit of Normal
[redacted]	[redacted]
VEGF / R	Vascular Endothelial Growth Factor / Receptor
wk	Week
WOBC	Women of childbearing potential
WONCBP	**Women of non-childbearing potential**

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Systemic Sclerosis (SSc) is a devastating disease of unknown etiology. The pathogenesis of SSc is characterized by systemic (multi-organ) immunological, vascular and fibrotic abnormalities. It is a rare disorder, an orphan disease, with prevalence rate of approximately 50 to 300 in US, 20 to 50 in Asia and 100 to 200 per million in Europe (R14-4918, R14-4927).

Patients suffer from multiple organ fibrosis, leading to chronic disability and premature death. Aside from skin, the lung is most often involved, but the disease may also manifest as proliferative and obliterative vascular abnormalities, kidney disease, oesophageal and gastrointestinal involvement (hypomotility), cardiac disorders and muscle disease. SSc-related mortality is mainly driven by interstitial lung disease and pulmonary arterial hypertension. Median survival is 5–8 years in SSc associated Interstitial Lung Disease (ILD) (P14-07919).

At time of writing the Protocol, no approved SSc treatment was available,-for chronic treatment of SSc-ILD. To date, nintedanib is the only drug approved in several countries for the treatment of patients with scleroderma-associated interstitial lung disease (SSc-ILD). Immunosuppressive therapy has been proposed as a treatment of SSc with limited controlled data.

According to the EULAR treatment guidelines (P15-00879) there are no therapies mandated for SSc-ILD. Cyclophosphamide, a lymphocyte-modulating agent, may have some effect on forced vital capacity (FVC) (R14-5407). EULAR recommends considering cyclophosphamide for the treatment of SSc-ILD, but its use is limited in regard of treatment duration due to its toxicity. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc (P15-00879). Small controlled, uncontrolled and retrospectively controlled studies suggest some immunosuppressive regimens (such as mycophenolate, azathioprine, tocilizumab, ciclosporine A) may have effect in selected manifestations of SSc. However, larger placebo-controlled studies are lacking (P15-00879). Endothelin receptor antagonists failed to show significant effects on pulmonary fibrosis outcomes in several large studies.

The rationale for development of nintedanib in SSc-ILD is based on the pre-clinical evidence of potential effects in SSc and clinical evidence of antifibrotic activity of nintedanib in Idiopathic Pulmonary Fibrosis (IPF) along with an acceptable safety profile. Investigation in a patient population with active SSc-ILD accompanied by varying degrees of skin and other organ fibrosis is medically rational. Nintedanib may offer a long term antifibrotic maintenance treatment option for SSc, a medical indication with high unmet medical need.

The herein described clinical trial is planned as an open label extension trial following SENSCIS® (1199.214) and 1199-0340 respectively.

The phase III trial SENSCIS® (1199.214) was investigating and has proven the safety and efficacy of nintedanib in Systemic Sclerosis interstitial lung disease (P19-04387).

The phase I trial 1199-0340 was investigating the drug-drug interaction of nintedanib and oral contraceptives in female patients with SSc-ILD (c26582112).

In the following, the acronym SENSCIS® will be used for trial 1199.214, standing for Safety and Efficacy of Nintedanib in Systemic Sclerosis (EudraCT no. 2015-000392-28).

1.2 DRUG PROFILE

Nintedanib is a small molecule that inhibits a distinct spectrum of receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs) including VEGFR (vascular endothelial growth factor receptor), PDGFR (platelet-derived growth factor receptor), FGFR (fibroblast growth factor receptor), and Src family kinases (Src, Lck and Lyn belonging to a family of proto-oncogene tyrosine-protein kinases).

All of these growth factor pathways and their down-stream signal cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling.

In experiments with dermal fibroblasts from patients with SSc, nintedanib inhibited migration and proliferation, reduced the expression of extracellular matrix markers, and attenuated transformation to myofibroblast. In four animal models of SSc with different features, nintedanib effectively attenuated skin and lung fibrosis, reduced extracellular matrix deposition in skin and lung, attenuated myofibroblast accumulation in skin and lung and reduced dermal thickening. Nintedanib also reduced dermal microvascular endothelial cell apoptosis and effectively attenuated pulmonary vascular remodelling by reducing the number of vascular smooth muscle cells and occluded pulmonary vessels.

A soft gelatin capsule formulation of nintedanib is used in humans. Maximum plasma concentrations occur between 2 - 4 hours after oral administration. Steady state is reached at latest within one week of dosing. After food intake, a trend towards an increased systemic exposure (around 20%) and a delayed absorption was observed compared to administration under fasted conditions. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87 and the terminal half-life is in the range of 7 to 19 h. The absolute bioavailability of nintedanib is slightly below 5%.

Nintedanib is mainly eliminated via faeces.

Coadministration of nintedanib with the P-glycoprotein (P-gp) inhibitor ketoconazole increased exposure to nintedanib by 60-70% based on area under the curve (AUC) and by 80% based on a maximum measured concentration of the analyte in plasma (Cmax) in a dedicated drug-drug interaction (DDI) trial.

In a DDI trial with the P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60. 3% based on Cmax upon coadministration with rifampicin compared to administration of nintedanib alone.

The clinical efficacy of nintedanib has been studied in over 1400 patients with IPF in one phase II dose finding trial (TOMORROW) including four different doses of nintedanib, and two replicate phase III (INPULSIS® 1 and 2) trials. These were randomised, double-blind, placebo-controlled trials comparing treatment with nintedanib twice daily to placebo for 52 weeks. A statistically significant reduction in the annual rate of decline of FVC (in mL) was demonstrated in patients receiving nintedanib 150 mg bid compared to patients receiving placebo. The treatment effect of nintedanib 150 mg bid compared to placebo on FVC was consistent in all 3 studies, i.e. a relative reduction of decline of approximately 50%. Supporting the effect of nintedanib on slowing disease progression (P14-07514, P11-11216), nintedanib 150 mg bid significantly reduced the risk of first acute exacerbation compared with placebo in INPULSIS® 2 and in the TOMORROW trial and reduced the risk of acute exacerbations (adjudicated) by 68% in a pre-specified sensitivity analysis of pooled data from the INPULSIS® trials.

In the Phase III trial 1199.214 (SENSCIS®) in patients with SSc-ILD, nintedanib, at a dose of 150 mg bid, significantly reduced the annual rate of decline in [redacted] after 52 weeks of treatment. The relative treatment effect, of a ~44% reduction in the annual rate of FVC decline compared with placebo, was in the same range as that previously observed in IPF. No effect of nintedanib on skin fibrosis or health-related quality of life was observed. No effect of nintedanib was seen on skin thickness and in patient-reported outcomes. There was no difference in mortality between the groups; however, the trial was not powered to detect such difference.

The safety profile of nintedanib has been investigated comprehensively in clinical Phase II to IV trials in patients with IPF, as well as postmarketing. The safety profile in phase III clinical trials in patients with SSc-ILD and patients with progressive fibrosing ILDs was generally consistent with that observed in the population of patients with IPF.

The risks of treatment with nintedanib in adult patients are primarily related to the gastrointestinal tract (nausea, vomiting, diarrhoea, abdominal pain, pancreatitis) and to drug induced liver injury/increases in liver enzymes (aspartate aminotransferase [AST], alanine transaminase [ALT], alkaline phosphatase [ALK], gamma-glutamyl transferase [GGT] and bilirubin).

Based on data from clinical trials and post-marketing with nintedanib in IPF patients 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.

The most frequently reported adverse event in the clinical trials was diarrhoea, which was mild to moderate in intensity for the majority of patients and led to treatment discontinuation

in less than five percent of patients treated with nintedanib. Nausea, vomiting and weight decrease and decreased appetite have also been associated with nintedanib treatment.

Risks of nintedanib treatment also include hypertension, bleeding, thrombocytopenia, gastrointestinal perforations, and thromboembolism. Thus, patients treated with full-dose anticoagulation or at known risk for bleeding were excluded from the INPULSIS® trials. Although cardiac disorder adverse events were balanced between the nintedanib and placebo groups, a higher proportion of patients (1.6%) in the nintedanib groups had myocardial infarctions compared to the placebo groups (0.5%). Conversely, a lower proportion of patients in the nintedanib groups had other ischemic heart disease, which includes terms such as coronary artery disease, angina pectoris, coronary angioplasty, coronary artery stenosis, myocardial ischemia, coronary artery stent insertion, electrocardiogram (ECG) ST segment depression. The clinical significance of this finding is unknown, and further observation is needed. No imbalances were found in SENSCIS®.

No evidence of QT prolongation was observed for nintedanib in the clinical trial program. As some tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administered nintedanib in patients who may develop QT prolongation.

For patients finalizing the 52 week trial treatment in the TOMORROW and INPULSIS® trials, participation, open label extension trials (1199.35 and 1199.33) were offered. Long term treatment in these open label extension trials have confirmed the safety profile observed in the phase II and III trials.

Nintedanib was developed in Idiopathic Pulmonary Fibrosis (IPF) and approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in October 2014 and January 2015 respectively.

Nintedanib was developed in Systemic Sclerosis associated ILD and approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in September 2019 and April 2020 respectively.

See also Investigator's Brochure (IB) nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis, Progressive Fibrosing Interstitial Lung Disease (c01783972) for more details.

1.3 RATIONALE FOR PERFORMING THE TRIAL

The aim of this extension trial is to provide nintedanib treatment for all patients who have completed (did not prematurely discontinue trial medication) the phase III parent trial SENSCIS® or the phase I trial 1199-0340 and who may have experienced benefit from the trial medication and wish to receive treatment.

This extension trial is designed to evaluate long term tolerability and safety of Nintedanib and the survival in SSc-ILD patients treated for a longer period of time. In addition, lung function

tests and assessment of the modified Rodnan Skin Score as well as patient and physician reported outcome measures will be performed.

1.4 BENEFIT - RISK ASSESSMENT

Initiating and amplifying events in SSc-ILD and IPF are described to be different, but culminate in fibroblast activation and myofibroblast accumulation that represent the final common pathways of lung fibrosis in both SSc-associated ILD and IPF (P14-07919). Nintedanib inhibits migration, proliferation and transformation of fibroblasts and thereby addresses this common pathway.

As shown for IPF patients, patients with SSc-ILD may also benefit from lesser decline in lung function and hence slower disease progression as a result of treatment with nintedanib.

The safety profile and the tolerability of nintedanib are expected to be similar in patients with IPF and SSc-ILD.

Based on the efficacy and safety shown in IPF patients, and considering the similarity of the pharmacological rationale between IPF and SSc, the same dose regimen of 150 mg nintedanib bid is considered appropriate.

The risks of treatment with nintedanib have been well delineated in patients with the fibrotic lung disease IPF. These risks are primarily related to the gastrointestinal tract (nausea, vomiting, diarrhoea, abdominal pain), and are usually managed with supportive therapy and with temporary or permanent dose reduction to 100 mg bid. In some cases, temporary interruption or permanent drug discontinuation is necessary. A reduction in appetite and weight decrease has also been reported in patients treated with nintedanib. Patients with SSc may already suffer from gastrointestinal symptoms and will be monitored for such events. Parenteral fed patients will be excluded from the trial.

Drug induced liver injury, increases in liver enzymes and bilirubin have been reported with the use of nintedanib and liver enzymes must be followed closely during treatment (see also Section 4.2.1.2). Nintedanib must be dose-reduced, or interrupted in the event of hepatic toxicity and further treatment withheld until recovery of the abnormal laboratory parameters.

Concomitant therapies with a known overlap in side effects with nintedanib (e.g. gastrointestinal [GI] adverse events, increase of AST, ALT, bilirubin) or concomitant use of therapies that interact with metabolism of nintedanib (through UGT1A1 and P-gp) should be used with caution and patients should be closely monitored (see Section 4.2.2.2).

Potential risks of nintedanib treatment also include gastrointestinal perforations, thromboembolism and bleeding. Therefore, patients who have planned major elective surgery, suffer from severe peripheral vascular disease, requiring full dose therapeutic anticoagulation, fibrinolysis or high-dose antiplatelet therapy will be excluded from this trial. Patients with severe pulmonary hypertension, Child Pugh A/B/C and Scleroderma renal crisis will not be included in this trial. Those patients will either not have been included in the

parent trial as per Inclusion/Exclusion criteria or discontinued in the parent trial due to these conditions occurring as adverse events.

The mode of action of nintedanib indicates a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality. In women of childbearing potential receiving nintedanib, contraceptive measures must be employed 28 days before treatment initiation, during the treatment and for a period of 3 months after last drug intake.

To address the organ-specific manifestations, immunosuppressive agents (e.g. mycophenolate, cyclophosphamide, methotrexate, azathioprine, prednisone) are commonly used and need to be considered although appropriate randomised-controlled data for these therapies are lacking.

The concomitant use of immunosuppressive agents as well as of non-immunosuppressive therapies for other SSc manifestations as for digital ulcers (e.g. bosentan), GI symptoms (e.g. proton pump inhibitors, prokinetic drugs), renal crisis (e.g. angiotensin-converting-enzyme inhibitor [ACE inhibitors]), pulmonary hypertension / pulmonary arterial hypertension (PH / PAH) (e.g. bosentan, sildenafil, epoprostenol) are not restricted. Cautionary notes are included in the protocol (Section 4.2.2.2) with regard to such therapies whose safety profile could interfere with that of nintedanib.

Safety of the patients will be monitored at site visits, including physical examinations, safety laboratory and specific monitoring procedure to follow-up potential hepatic enzyme elevation, to exclude pregnancy, to follow-up electrocardiographic assessments, and to monitor blood pressure, renal function, hypertension, and digital ulcers. Treatment with nintedanib must be discontinued and appropriate therapeutic measures taken in patients who develop severe symptoms of gastrointestinal toxicity not amenable to symptomatic treatment with standard measures or severe liver enzyme elevations or other severe adverse events as specified in Section 3.3.4.

Even if the balance of safety and efficacy from SENSCIS® is still unknown at the time point the patients are rolled over into the open label extension trial, long-term treatment is considered justifiable as there is currently no pharmacotherapy for long-term use approved to modify or prevent systemic progression of SSc/SSc-ILD.

To address current practice (although randomised-controlled data for these therapies are scarce), patients on a stable background therapy of mycophenolate, methotrexate or low dose prednisone were eligible in SENSCIS®.

In trial 1199-0340 patients on certain background therapy including mycophenolate and other treatments were excluded due to their potential effect on the PK assessment.

Continuation or initiation of immunosuppressives or other treatments or changes in their dose is allowed in the open label extension taking into consideration cautionary notes.

All patients will receive active treatment in this trial. Patients who were randomized to placebo in SENSCIS® will be receiving the active drug for the first time. Therefore the same close monitoring will be conducted as in SENSCIS® for the first 3 months of the trial.

Based on the pharmacological mechanism, existing non-clinical, clinical and post-marketing data there is no indication that treatment with nintedanib may increase the risk for infection with SARS-CoV-2 or for worsening the disease course of COVID-19.

It is currently unknown if SSc or SSc-LD conveys a higher risk for adverse outcomes in case of COVID-19.

The trial related risk to the COVID-19 pandemic situation is the general risk of travelling to site and being at site for assessments with increased infection risk for lung function testing. Risk mitigation and possible modifications are described in Section 6.1 and in Appendix 10.3

The extrapolated benefit risk ratio of chronic treatment with nintedanib 150 mg bid, with the possibility to be interrupted or reduced to nintedanib 100 mg bid during periods of intolerability, is judged positive for patients with SSc-ILD.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main Objectives

The main objective is to assess long term safety of treatment with oral nintedanib in patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD).

2.1.2 Primary Endpoint(s)

The primary endpoint is the incidence (number and % of patients) of overall adverse events over the course of this extension trial.

2.1.3 Secondary Endpoint(s)

Not applicable.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, prospective, open label extension clinical trial. It is anticipated that approximately 400 patients with SSc-ILD will complete the parent trial SENSCIS® and approximately 14 patients will complete 1199-0340 as planned. These patients will be eligible for enrolment in this extension trial. Patients who withdrew treatment prematurely in SENSCIS® / 1199-0340 will not be eligible for this open label extension trial.

After signing Informed Consent and if all eligibility criteria are met, patients will initiate treatment with nintedanib (Visit 2). Patients will be assigned to a dose of 150 mg bid if the patients last dose in SENSCIS® / 1199-0340 was 150 mg bid and to a dose of either 100 mg bid or 150 mg bid at the discretion of the investigator, if patients were on 100 mg bid of blinded trial medication in SENSCIS® / 1199-0340 (please refer to Section 4.1.2).

Once assessment of the pivotal trial SENSCIS® and resulting risk-benefit of Nintedanib has been concluded upon, patients that are on a reduced dose of trial medication may increase dose to 150 mg bid Nintedanib at the discretion of the investigator.

The trial will continue for long term data collection, as long as a reasonable number of patients enabling analyses remain in the trial. Treatment duration for each patient will be variable. Patients will continue to receive treatment until they meet a reason for discontinuation (refer to section 3.3.4.4) or until access to nintedanib is obtained outside the clinical trial. The trial is estimated to last a total of approximately 5 ½ years.

Treatment will be stopped if a reason for withdrawal is met (refer to Section 3.3.4).

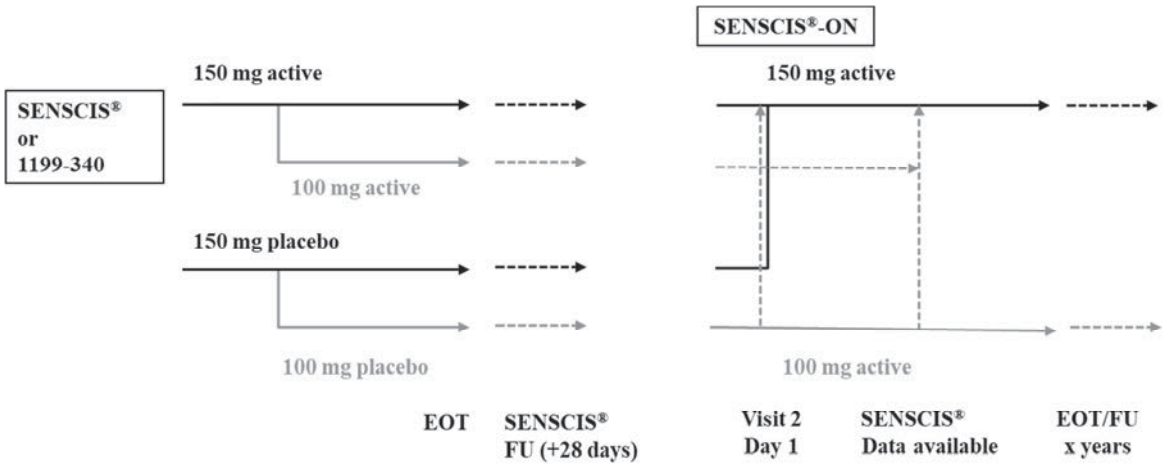


Figure 3.1: 1 Transition from parent trial SENSCIS® / 1199-0340

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The trial will be conducted as a prospective, open-label design. This design is appropriate for this rollover trial assessing the long-term safety on nintedanib in patients with SSc-ILD.

The purpose of this trial is to offer to all patients who completed SENSCIS® / 1199-0340 as planned, the option to receive nintedanib treatment if they perceive an individual benefit. The decision to continue treatment will be made by the patient following a discussion with the investigator. The aim of the trial is to allow treatment continuation to individual patients; therefore, randomization, blinding and use of placebo would not be appropriate.

The planned assessments are a subset of the assessments done in SENSCIS® / 1199-0340 and an additional patient related outcome score to assess gastrointestinal symptoms and their impact on the patient.

3.3 SELECTION OF TRIAL POPULATION

It is anticipated that approximately 400 patients will complete the SENSCIS® trial on treatment with nintedanib or placebo and that approximately 14 patients will complete the 1199-0340 trial. These patients will be allowed to participate in this open label extension trial. At the time point of the start of the open label extension trial it is not known what treatment the patients had received in SENSCIS®. Patients previously on active treatment will continue, patients who received placebo will initiate treatment with nintedanib for the first time at Visit 2 of the extension trial. Patients who completed 1199-0340 had open-label treatment with nintedanib and will continue with nintedanib treatment in 1199.225.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

Patients with SSc-ILD will be included in this trial if they fulfil all the inclusion and do not present any of the exclusion criteria.

Only patients who have completed the SENSCIS® / 1199-0340 on treatment (i.e. did not early permanently discontinue blinded treatment) are eligible. Patients should enrol into the extension trial as soon as possible after conclusion of SENSCIS® / 1199-0340.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Patients who completed the SENSCIS® / 1199-0340 trial per protocol and did not permanently discontinue study treatment

2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
3. Women of childbearing potential[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly as well as one barrier method for 28 days prior to nintedanib treatment initiation, during the trial and for 3 months after last intake of nintedanib. A list of contraception methods meeting these criteria is provided in the patient information.

3.3.3 Exclusion criteria

1. AST, ALT > 3 x ULN
2. Bilirubin > 2 x ULN
3. Creatinine clearance <30 mL/min calculated by Cockcroft–Gault formula (Appendix 10.2).
4. Clinically relevant anaemia at investigators discretion.
5. Bleeding risk, any of the following
    a. Known genetic predisposition to bleeding according to the judgement of the investigator
    b. Patients who require
        i. Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
        ii. High dose antiplatelet therapy.

    [Note: Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s. c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited].
    c. Hemorrhagic central nervous system (CNS) event after completion of the parent trial SENSCIS® / 1199-0340.
    d. Any of the following after last treatment of SENSCIS® / 1199-0340:
        i. Haemoptysis or haematuria

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

ii. Active gastro-intestinal bleeding or GI – ulcers

iii. Gastric antral vascular ectasia (GAVE)

iv. Major injury or surgery (investigators judgement).

e. Coagulation parameters: International normalised ratio (INR) >2, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by >1.5 x ULN at Visit 1.

6. New major thrombo-embolic events developed after completion of the parent trial SENSCIS® / 1199-0340:
    a. Stroke;
    b. Deep vein thrombosis;
    c. Pulmonary embolism;
    d. Myocardial infarction.
7. Major surgery (major according to the investigator's assessment) performed within the next 3 months
8. Time period > 12 weeks between last drug intake in SENSCIS® or > 1 week between last nintedanib intake in trial 1199-0340 and Visit 2 of this trial
9. Usage of any investigational drug after completion of SENSCIS® / 1199-0340, or planned usage of an investigational drug during the course of this trial.
10. A disease or condition which in the opinion of investigator may put the patient at risk because of participation in this trial (e.g. clinically relevant intestinal pseudoobstruction) or limit the patient's ability to participate in this trial
11. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial
12. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin).
13. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
14. Previous enrolment in this trial

3.3.4 Withdrawal of patients from therapy or assessments

3.3.4.1 Withdrawal from trial treatment

Nintedanib has to be permanently discontinued in the following circumstances

- The patient experiences signs of hepatic injury, defined in Section 4.2.1.2
- In the opinion of the investigator, the patient experiences unacceptable adverse events despite dose adjustments and supportive care.

- Use of concomitant treatment as defined in Section 4.2.2.
- Parenteral feeding requirement.
- The patient can no longer be treated with trial medication for other medical reasons
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future
- Pregnancy (refer to Section 5.2.11)
- If a patient becomes pregnant during the trial, nintedanib needs to be stopped and the patient should be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report (CTR) until patient´s last visit and any events thereafter will be reported in the BI drug safety database. Refer to Section 5.2.11 for detailed information on event reporting in case of pregnancy.

3.3.4.2 Recommendation to discontinue nintedanib

In the following cases discontinuation of nintedanib is highly recommended. Only in special circumstances, the investigator, upon thorough assessment of all available clinical data and taking into consideration the potential risks associated with administration of nintedanib, may decide not to withdraw the trial medication, even though one or more of the below mentioned criteria are fulfilled. In such a case, continuation of treatment with trial medication should be discussed with the patient, and the decision and reasoning documented in the source data.

- Major surgery, including any abdominal or intestinal surgery.
- Anti-coagulation. Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, hirudin, direct thrombin inhibitors, etc.), or high-dose antiplatelet therapy. (Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s. c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy is allowed.).
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.
- Confirmed severe hypertension, uncontrolled under treatment (≥160/100 mmHg),
- Unstable cardiac angina
- Increased risk of bleeding e.g. hemorrhagic CNS event, gross / frank haemoptysis or haematuria, active gastro-intestinal bleeding or GI-ulcers.

- Scleroderma renal crisis
- Significant pulmonary hypertension defined by any of the following:
  - Previous clinical or echocardiographic evidence of significant right heart failure
  - History of right heart catheterisation showing a cardiac index ≤ 2 l/min/m²
  - PH requiring therapy (parenteral or oral with epoprostenol, treprostinil, selexipag)

For conditions that allow treatment interruption please refer to Section 4.2.1.

3.3.4.3 Withdrawal of consent for trial participation

An individual patient is to be withdrawn from trial participation

- if the patient withdraws consent for trial participation, without the need to justify the decision
- if the patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)

Given the patient's agreement, the patient will undergo the procedures for trial discontinuation and follow up as outlined in the Flowchart and Section 6.2.3.

For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the Electronic Case Report Form (eCRF). These data will be included in the trial database and will be reported.

3.3.4.4 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
2. Marketing authorization, availability for compassionate use or early access program offered by the sponsor (depending on local laws),
3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

All patients will be treated with nintedanib in this trial; there is no active comparator or placebo.

Substance:	**Nintedanib**
Pharmaceutical formulation:	Soft gelatine capsule
Source:	BI Pharma GmbH & Co. KG
Unit strength:	150 mg, 100 mg
Posology:	bid
Route of administration:	Oral (swallowed)

4.1.2 Method of assigning patients to treatment groups and selection of dose

The objective of the SENSCIS® was to assess the efficacy and safety of a dose of 150 mg bid compared to placebo. Patients have been randomized either to blinded Nintedanib or to blinded placebo 150 mg bid. Dose reductions from 150 mg bid Nintedanib/placebo to 100mg bid Nintedanib/placebo were allowed to manage adverse events.

The objective of the trial 1199-0340 was to assess the potential influence of continuous intake of nintedanib on the systemic exposure of ethinylestradiol and levonorgestrel when administered in combination. The patients have all been treated with open label nintedanib. Also in trial 1199-0340 dose reductions from 150 mg bid nintedanib to 100mg bid nintedanib were allowed to manage adverse events.

Patients having taken 150 mg bid trial medication (active drug or placebo, blinded in SENSCIS®) at the end of SENSCIS® / 1199-0340 will start treatment with nintedanib 150 mg bid in the current extension trial.

Patients who receive 100 mg bid active drug or placebo within SENSCIS® / 1199-0340 will be allowed to start treatment with 100 mg or increase their nintedanib dose to 150 mg bid at the discretion of the investigator.

Interactive Response Technology (IRT) will be used to assign medication numbers to eligible patients. Distribution of nintedanib to sites will be triggered by IRT. Details on the IRT system are provided in the ISF.

After subsequent conclusions on benefit/risk upon unblinded data from SENSCIS®, patients who permanently reduced to 100 mg bid will be allowed to increase their nintedanib dose to 150 mg bid at the discretion of the investigator. Dose increase will need to be assigned through IRT during an additional visit (refer to Section 6.2.4).

4.1.3 Drug assignment and administration of doses for each patient

The treatment for an individual patient will be assigned by means of an IRT contact during Visits 2, 3, 4, 5, 6, 7 and following Visits. Patient will receive active drug at a dosage of 150 mg bid or 100 mg bid.

Trial medication will consist of 1 capsule twice daily throughout the trial. Wallets covering 4 weeks + 5 days reserve treatment (1 wallet = 6 blisters with 10 capsules each, plus 1 blister reserve) will be dispensed to the patient:

- 1 wallet at day 1 (Visit 2) (30 days plus 5 days reserve).
- 2 wallets at Visit 3 (60 days plus 10 days reserve).
- 3 wallets at Visits 4 and 5 (90 days plus 15 days reserve).
- 4 wallets at Visit 6, 7 and following (120 days plus 20 days reserve).

Nintedanib will be administered orally on a twice daily basis (bid). The patients should swallow the trial medication unchewed together with a glass of water (~250 mL), and should observe a dose interval of 12 hours. Nintedanib needs to be taken at the same time every day (between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening). Because nintedanib may cause stomach discomfort, it is recommended to take the trial medication with food.

A forgotten dose should be skipped if the time window to the next dose is less than 8 hours. The next dose should be taken as scheduled.

Nintedanib should only be dispensed to participating patients according to the protocol by authorised personnel as documented in the form “Investigator’s Trial Staff”.

The dose can be interrupted or reduced without prior interruption, i.e., immediately stepping down from 150 mg bid to 100 mg bid at the discretion of the investigator if necessary due to adverse events. Dose adjustions require a special trial visit according to procedures described in Section 4.2.1. Restart and re-escalation is possible as described in Section 4.2.1.

4.1.4 Blinding and procedures for unblinding

4.1.4.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. The eCRF will contain information on actual treatment.

The previous treatment received in SENSCIS® (active drug or placebo) will remain unknown until the database lock of SENSCIS® and until subsequent conclusions on benefit/risk. No individual unblinding regarding treatment received in SENSCIS® should occur prior to this point in time.
This is not applicable for patients who participated in trial 1199-0340, since they received open-label nintedanib treatment.

4.1.4.2 Unblinding and breaking the code

Not applicable.

4.1.5 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated clinical research organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Initial supply and re-supply to the sites will be managed via an IRT system. The IRT will assign an appropriate kit to each patient and will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

Primary trial material will be capsules containing 150 mg of nintedanib (or 100 mg of nintedanib if dose is reduced). All trial medication will be packaged in blister cards. Each blister card will contain 10 capsules. Seven blisters cards will be packaged into one child-resistant tamper-evident wallet (i.e. 70 capsules/wallet). Each wallet will be labelled with a multi-language booklet according to the requirements of the participating countries.

One wallet covers for one month of treatment.

Details of packaging and the description of the label will be provided in the ISF.

Re-supplies of trial medication are planned due to the short expiry date and the long duration of the trial. The medication for re-supply will be packaged in an identical manner as the medication for initial supply.

4.1.6 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

All unused trial medication must be returned to the sponsor or appointed CRO. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.7 Drug accountability

The investigator will receive the investigational drugs delivered by a clinical research organisation (CRO) appointed by the sponsor, when the following requirements are fulfilled:

- Approval of the trial protocol by the institutional review board (IRB) / ethics committee (EC).
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site.
- Approval/notification of the regulatory authority, e.g. competent authority.
- Availability of the curriculum vitae of the Principal Investigator.
- Availability of a signed and dated clinical trial protocol.
- In countries where it is required, availability of the proof of a medical license for the Principal Investigator.
- In the US, availability of Form 1572.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or appointed CRO.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator will maintain records that document adequately that the patients were provided the doses specified in the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Rescue medications to reverse the action of nintedanib are not available.

Dose reduction (from 150 mg bid to 100 mg bid) or treatment interruption should be considered to manage adverse events. No further dose reduction is possible for patients on the 100 mg bid dose. In case of persistent adverse events observed at this dose, or severe effects at 150 mg bid, permanent treatment discontinuation should be considered.

Treatment interruption and reduction and reescalation are repeatedly possible.

Table 4.2.1: 1 Allowed treatment reduction / interruption periods:

	AEs considered drug related	**AEs or other events not considered drug related**
Maximum interruption	4 weeks	12 weeks
Recommended restart	with reduced dose (100 mg bid)	with the same dose (100 mg bid or 150 mg bid)
Re-escalation	Any time to 150 mg bid	----

4.2.1.1 Management of diarrhoea

Other causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment).

Diarrhoea should be managed as early as possible after onset of first symptoms with standard antidiarrheal symptomatic treatment, e.g. loperamide.

If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and dose reduction of nintedanib should be considered based on the recommendations described in table 4.2.1.1:1.

Table 4.2.1.1: 1 Management of diarrhoea (considered related to trial medication)

Description	**Symptomatic Treatment***	**Action with trial medication**
Diarrhoea with increase of <4 stools per day over baseline[1].	Initiate anti-diarrhoeal medicines at first signs of symptoms (e.g. 4 mg loperamide followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 16 mg/day) until bowel movements cease for 12 hours.	Continue same trial medication dose.
Diarrhoea with increase of 4 to 6 stools per day over baseline[1].	Initiate/continue anti-diarrhoeal medicines; If diarrhoea of this severity persists for ≥48 to 72 hours assess for dehydration and electrolyte imbalance; In addition, consider IV fluids and electrolyte replacement as clinically indicated.	If diarrhoea persists for ≥48 to 72 hours despite optimal symptomatic care: 1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Re-escalate to 150 mg bid within 4 weeks if deemed clinically appropriate.

Table 4.2.1.1:1 Management of diarrhea (considered related to trial medication) (cont.)

Description	**Symptomatic Treatment***	**Action with trial medication**
Diarrhoea with increase of ≥7 stools per day over baseline[1]; stool incontinence, or life threatening consequences.	Follow recommendations above. In addition, consider stool work-up to exclude infectious colitis; adequate IV fluid replacement ≥24 hours, hospitalisation as clinically indicated; consider referral to a GI specialist to rule out potential differential diagnoses.	1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Consider re-escalation within 4 weeks to 150 mg bid if deemed clinically appropriate. In case of reoccurrence of diarrhoea of this severity despite optimal symptomatic treatment and dose reduction, treatment with trial medication should be permanently discontinued.

Footnotes:

* Other causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment)

[1] Baseline defined as usual stools/day prior to visit 2.

4.2.1.2 Management of liver enzyme elevation

Evaluate the concomitant use of other drugs known to cause liver enzyme elevations. For a detailed guidance on how to manage liver enzyme elevations, please refer to Table 4.2.1.2: 1.

Table 4.2.1.2: 1: Management of liver enzyme elevations

	AST or ALT increase to			Signs of hepatic injury* (Section 5.2.11)
	>1.5x to <3x ULN	≥3x to <5x ULN and no signs of hepatic injury (Section 5.2.11)	≥5x to <8x ULN and no signs of hepatic injury (Section 5.2.11)	
Visit 2 (treatment start)	Continue as planned[2]	Permanently discontinue trial medication	Permanently discontinue trial medication	Permanently discontinue trial medication
Any other Visit	Continue as planned[2]	Reduce dose or interrupt trial medication [3]	Interrupt trial medication	Permanently discontinue / Interrupt trial medication
		Close observation[4] After 2 weeks or any time later	Close observation[4] After 2 weeks or any time later	**CLINICAL EVALUATION OF HEPATIC INJURY**[5] (Section 5.2.11)
	<3x ULN	≥3x ULN	< 3x ULN	≥3x ULN
	Reduced: return to initial dose. Interrupted: restart at reduced dose. Monitor every 2 weeks for at least 8 weeks	Permanently discontinue trial medication Close observation[4]	Restart at reduced dose Monitor weekly for 4 weeks, then every 2 weeks for at least 8 weeks	Permanently discontinue trial medication. Close observation[4]

Footnotes:

* Signs of hepatic injury are defined as
- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥2 fold ULN
- ALT and/or AST ≥3 fold ULN and unexplained INR >1,5
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

[1] Investigator to confirm in writing that continuation is justified (e.g. intermittent fluctuation of transaminases).
[2] According to visit schedule. Consider additional control visits as adequate.
[3] To be decided by investigator, based on individual risk assessment.
[4] Close observation: Re-test ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then approximately 7 days, then approximately 2 weeks by using intermediate visit lab kit.
[5] If clear evidence for alternative cause for hepatic injury was identified and resolved (i.e. relation to trial medication excluded, hepatic injury confirmed to have alternative explanation [other than use of IMP]): return to trial medication would be possible, after consultation with the sponsor. Prior to restart, liver laboratory values must be normal. Monitor weekly for first 4 weeks of re-introduction and every 2 weeks for the following 8 weeks.

Initial assessment and blood sampling for liver enzyme elevation follow up should be performed at the investigational site. Blood samples for additional monitoring may be collected at the investigational site, primary care physician or external laboratory with specific trial lab kits and sent to the central laboratory for analysis.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Other investigational therapy is not allowed during the entire trial period and must not have been introduced in the interval between the parent trial SENSCIS® / 1199-0340 and enrolment into this open label extension trial.

4.2.2.2 Cautionary Notes

As nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4, concomitant use of P-gp and CYP3A4 inhibitors (e.g. erythromycin) with nintedanib may increase exposure to nintedanib. Patients taking potent P-gp inhibitors (e.g. ketoconazole, erythromycin or ciclosporine) should be monitored closely for tolerability of nintedanib.

Concomitant use of P-gp and CYP3A4 inducers (e.g. carbamazepine, phenytoin, and St. John's wort) with nintedanib may decrease exposure to nintedanib. For patients taking potent P-gp inducers, selection of alternative treatment with no or minimal P-gp induction should be considered.

As the most common side effects known for nintedanib are GI effects, the concomitant use of medication with an overlapping safety profile (e.g. mycophenolate mofetil/ sodium) should be carefully considered.

Nintedanib is also associated with increases in liver enzymes and bilirubin. If in addition to the trial medication, a treatment is introduced that is known to induce AST/ALT elevations (e.g. methotrexate, bosentan), adequate measures should be taken to ensure patients safety: perform additional measurement of liver enzymes (ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils) every 2 weeks for approximately 6 weeks, by using intermediated (a-visit) trial lab kit.

4.2.2.3 Restrictions on diet and life style

No restrictions on diet or life style.

4.2.2.4 Restrictions regarding women of childbearing potential

The anti-angiogenic properties of nintedanib indicate a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality. In women of childbearing potential receiving nintedanib, contraceptive measures described in the patient information must be

employed 28 days before treatment initiation, during the trial and for a period of 3 months after last drug intake.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on capsule counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of capsules actually taken} \times 100}{\text{Number of capsules which should have been taken}}$$

If the number of doses taken is not between 80-120%, site personnel will explain the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENTS OF EFFICACY

Not applicable.

5.2 ASSESSMENTS OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at timepoints specified in the Flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height and body weight will be performed at the time points specified in the Flowchart.

All abnormal findings at baseline in the extension trial will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions in the extension trial detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.2.2 Vital signs

Systolic and diastolic blood pressure and pulse rate will be measured prior to blood sampling with the patient seated after having rested. In case of abnormal vital signs medical work-up for exclusion or confirmation of a pathological condition should occur as per standard of care. All abnormal findings at baseline in the extension trial will be recorded on the baseline condition eCRF page. New abnormal findings or worsening of baseline conditions in the extension trial detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the Flowchart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.11 and the DILI Checklist provided in the ISF eDC system. The total amount of blood taken from the patient concerned over the course of the trial will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor.
The laboratory tests at regular site visits will include:

Table 5.2.3: 1 Laboratory tests

Category	**Laboratory test**
Haematology	Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (Hct) Mean corpuscular volume White blood cell count including differential Platelet count
Biochemistry	Aspartate aminotransferase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALK) Creatine kinase (CK) Lactate dehydrogenase (LDH) Total protein Total bilirubin Brain natriuretic peptide (BNP, at V2, V5, V7 and at all regular visits every 16 weeks until EOT) Creatinine Glucose (non fasting) Uric acid Thyroid stimulating hormone (at V2, V5 (after 6 month), V 7 (12 Month) and then every other year and at EOT ß-HCG (at Visit 2 only)
Electrolytes	Sodium Potassium Calcium Chloride Inorganic phosphorus
Coagulation	International normalized ratio (INR) Partial thromboplastin time (PTT) Prothrombin time (PT)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semiquantitative measurements; -, +, ++, +++)
Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.	

The laboratory tests at intermediate 'a' visits will include:

Table 5.2.3: 2 Laboratory tests at intermediate 'a' visits

Category	Laboratory test
Biochemistry	Total protein, creatinine, electrolytes and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semiquantitative measurements; -, +, ++, +++)
Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.	

Overall about 110 mL blood will be taken for standard safety laboratory during the first year and about 45 mL blood will be taken any other year.

If laboratory values indicate abnormality, adequate and more frequent blood sampling may be performed at the discretion of the investigator.

In case of liver function value elevations, close monitoring must be ensured by the investigator. Refer to Section 4.2.1.2 for monitoring elevations and Section 3.3.4 for withdrawal criteria.

Laboratory analysis will be done using central laboratory services.

Creatinine clearance will be calculated based on serum creatinine according to Cockcroft and Gault (R96-0690, Appendix 10.2).

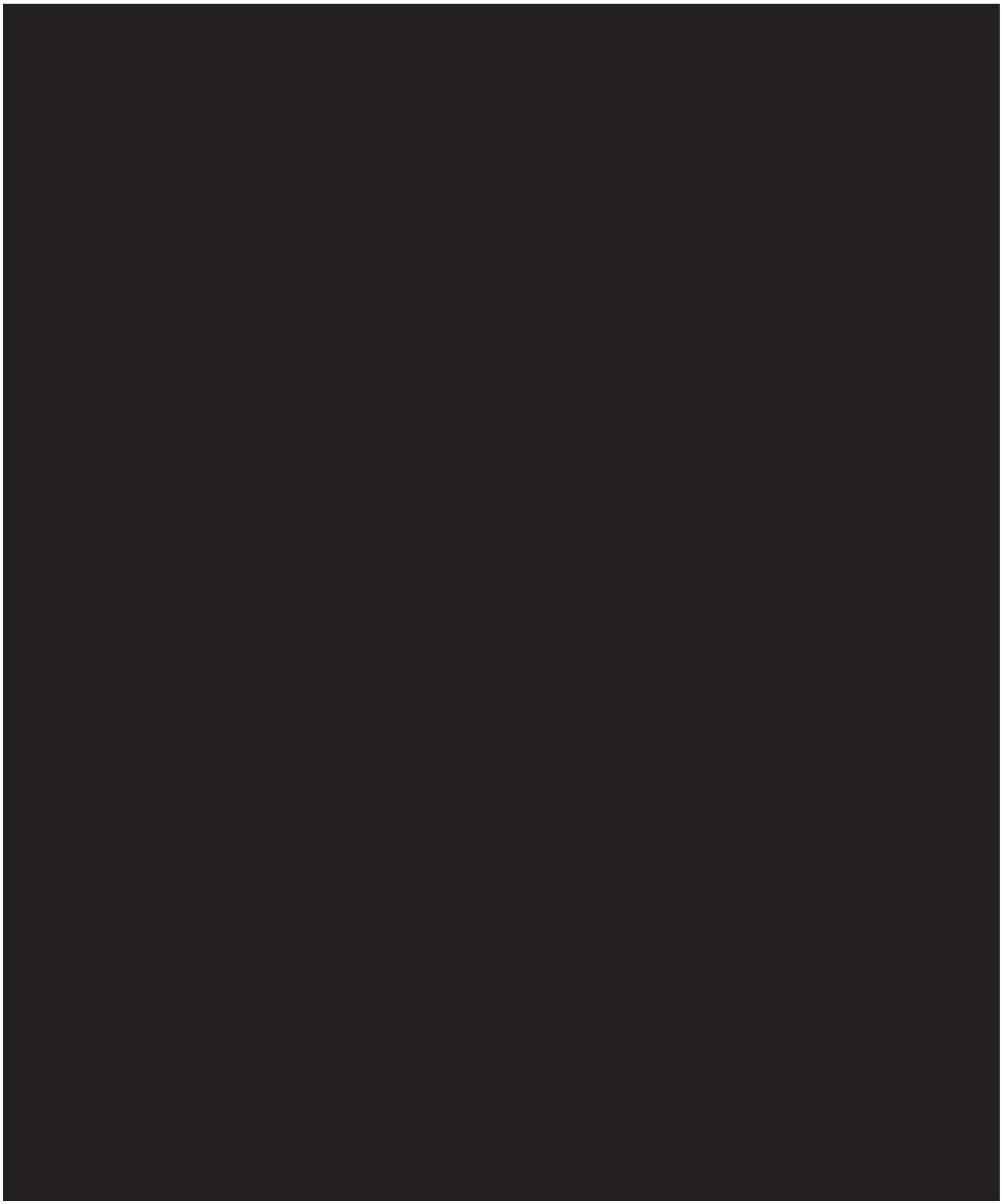
Venous whole blood will be collected in appropriate syringes provided by the sponsor through the assigned central laboratory. Details regarding centrifuge, processing, storage and shipment of samples will be determined by the central laboratory in accordance with the sponsor. The investigators will be informed and instructed by the central lab and detailed documentation will be included in the ISF.

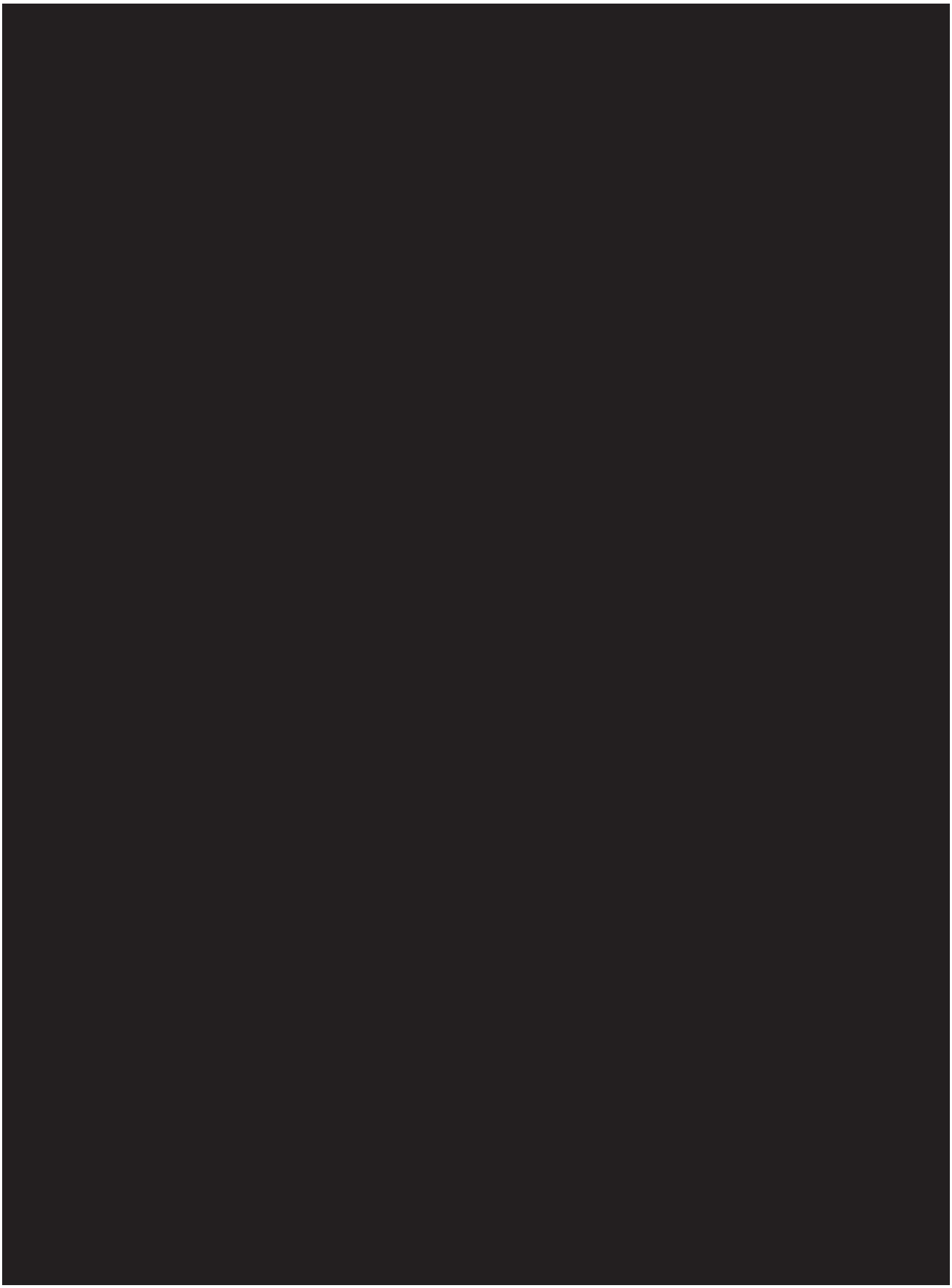
5.2.4 Electrocardiogram

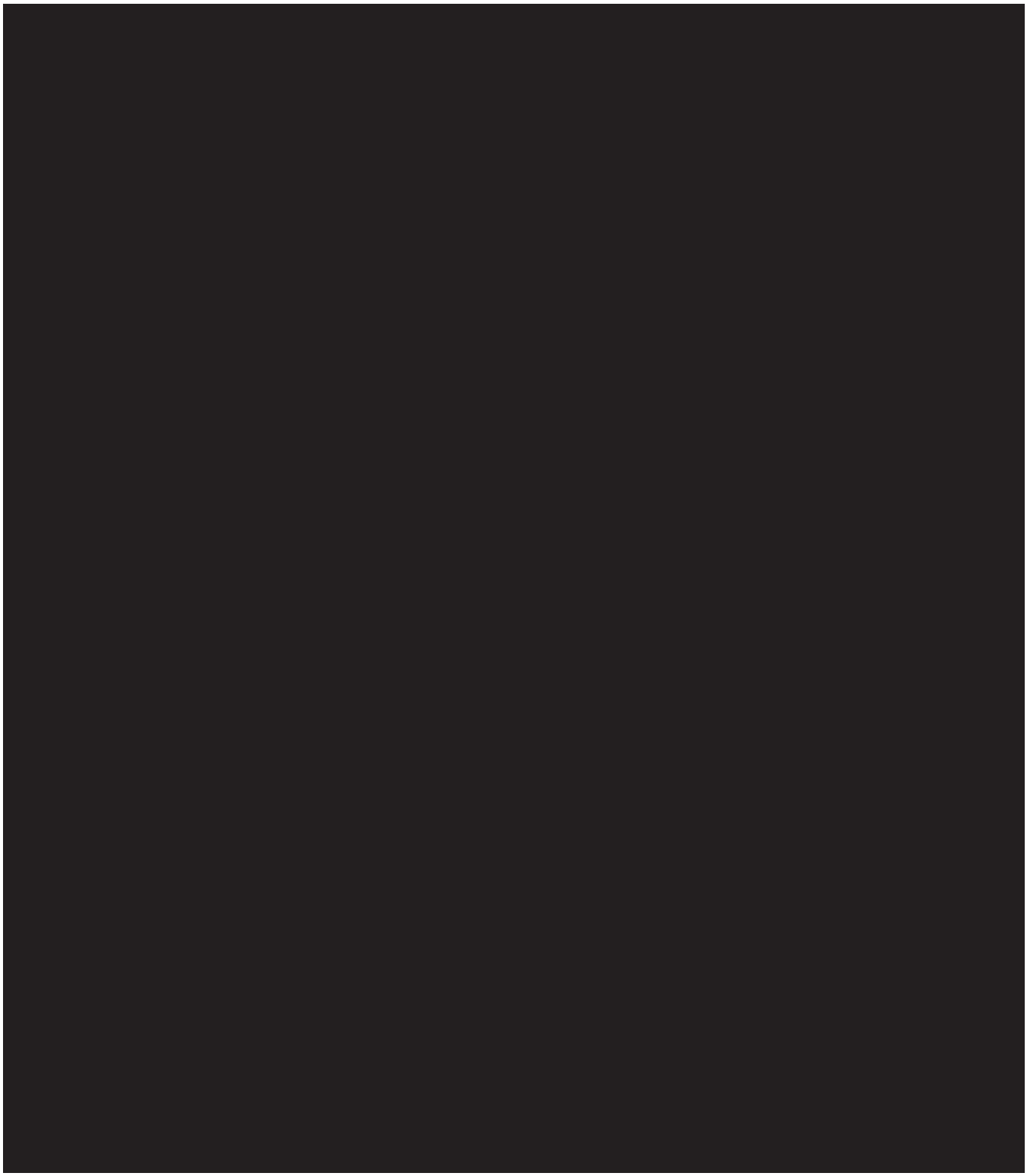
The 12-lead ECGs will be recorded as scheduled in the Flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.







5.2.10 Other safety parameters

Worsening or new onset of SSc organ involvement (e.g. renal, cardiac, GI, vasculopathy) will be assessed via evaluation of adverse events / serious adverse events.

5.2.11 Assessment of adverse events

5.2.11.1 Definitions of AEs

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 to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including 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 authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,

  or

- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as "deemed serious for any other reason". AEs which possibly lead to disability will be reported as SAEs.

AEs considered "Always Serious"

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the duration between discontinuation of the trial medication and must be reported as described in section 5.2.11, subsections "AE Collection" and AE reporting to sponsor and timelines".

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in section 5.2.11, subsections "AE Collection" and AE reporting to sponsor and timelines"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

Adverse events relating to gastrointestinal perforation and hepatic injury will be considered AESIs.

Hepatic injury

In this trial protocol, signs of hepatic injury are defined as:

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*

- ALT and/or AST ≥3 fold ULN and unexplained INR > 1,5*
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication and need to be followed up according to the "drug-induced liver injury (DILI) checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST and total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity (severity) of AEs

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

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Sufficient discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

In addition the intensity of diarrhoea adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for adverse events (CTCAE) version 4 (R10-4848, Table 5.2.11.1:1).

Table 5.2.11.1:1 CTCAE Categorisation for diarrhoea

CTCAE Grade	Diarrhoea
1	Increase of <4 stools per day over baseline
2	Increase of 4 to 6 stools per day over baseline
3	Increase of ≥7 stools per day over baseline; incontinence
4	Life threatening consequences
5	Death

Causal relationship of AEs

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 that there is a reasonable possibility of a 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 aetiologies that could explain the event (e.g. pre-existing 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 trial drug treatment continues or remains unchanged.

For Japan only: the reason for the decision on causal relationship for unlisted AEs needs to be provided in the CRF.

5.2.11.2 Adverse event collection and reporting

AE Collection

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

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), of at least 28 days until individual patient's end of trial:
  -all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

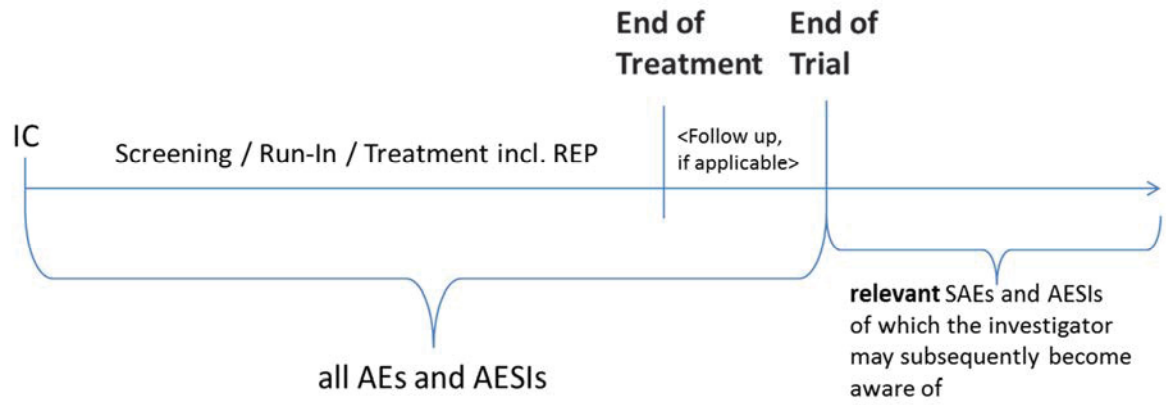


Figure 5.2.11.2: 1 AE collection

The REP is defined as 28 days after the last trial medication application and will apply only to patients that discontinue the trial early. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment, please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

For Japan only: all SAEs and AESIs must be reported immediately to the head of the trial site.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP)

The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of Pharmacokinetics

Not applicable.

5.3.2 Methods of sample collection

Not applicable.

[redacted]

5.3.4 Pharmacokinetic – Pharmacodynamic Relationship

Not applicable.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.4.1 Biobanking (optional)

Patients will be asked for two additional blood samples for biobanking to allow for future scientific analyses. Only if a separate specific informed consent is given in accordance with local ethical and regulatory requirements, one additional dedicated sample of approximately 10 mL serum will be taken at Visit 2 and one at Visit 7.

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual.

5.5 OTHER ASSESSMENTS

Not applicable.

5.6 APPROPRIATENESS OF MEASUREMENTS

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values and ECG. These endpoints are standard and accepted for evaluation of safety and tolerability of an oral drug, and they are widely used in this kind of trial. The timing of all measurements is presented in the Flowchart.

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flowchart. Some flexibility is allowed in scheduling the visits according to visit time windows as specified in the Flowchart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule (calculated from Visit 2). The trial medication kits contain sufficient medication to allow for these time windows. All deviations from the planned visit schedule will be documented.

The trial will run until all patients have discontinued treatment or a stopping criterion is met according to Section 3.3.4.

In exceptional circumstances (as e.g. in pandemic situations), when it is impossible to conduct study visits at the study site, study visits may be performed at patient's home or remotely (via telephone and/or internet based means of communication), and local lab liver enzyme testing. The visit may also be performed as a hybrid of home and remote visit. All home/remote visits need to be discussed with and authorised by the sponsor's trial team. The trial team's decision will be based on a thorough benefit-risk evaluation.

The procedures performed during a home/remote visit may be adjusted as compared to a regular visit, as detailed in Appendix 10.3.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

The trial will be explained to all patients who completed SENSCIS® / 1199-0340 and are willing to continue or start treatment with nintedanib. No trial related procedure or data collection should be performed until the patient has signed the Informed Consent for the extension trial.

The earliest timepoint for Visit 2 of the rollover trial is one day after the last visit, namely:

- the Follow-Up (FU) visit in SENSCIS® or
- the End of Treatment (EOT) Visit in trial 1199-0340

The last timepoint for Visit 2 is:

- 12 weeks after the last trial drug intake occurred within SENSCIS®
- 7 days after the last trial drug intake occurred within 1199-0340

Enrolment of patient into SENSCIS®-ON should be done as soon as possible to ensure gapless monitoring of a patient.

In order to assess eligibility for the extension trial, patients are required to perform a screening visit (Visit 1) which includes collection of samples for laboratory tests.

Visit 1 and Visit 2 may occur on the same day if the period between the last available laboratory test within SENSCIS® and Visit 2 of the extension trial (1199.225) is ≤ 6 weeks. If the medical condition is not stable and new Adverse Events occurred, a new laboratory test has to be performed. For patients performing Visit 1 and Visit 2 on the same day, eligibility assessment will be based on laboratory data from last laboratory test available within SENSCIS®. In case Visit 1 and Visit 2 takes place on the same day, laboratory tests, physical examination and vital signs are performed only once on that day and are recorded under Visit 2 in the eCRF. In case a new AE has occurred after the last visit of SENSCIS® new safety laboratory testing is required.

Patients who have a laboratory test value that is outside the range specified by the exclusion criteria may have the test repeated once to determine eligibility; however, the result must be available prior to Visit 2.

Details of any patient who has given informed consent for the trial but is found to be in-eligible must be entered in the enrolment log and documented in the eCRF.

Ongoing AEs from SENSCIS® / 1199-0340 are to be documented as Baseline Condition.

6.2.2 Treatment period(s)

If the patient has been determined eligible by the investigator to enter the trial (refer to Section 3.3), the investigator will assign a medication number to the patient through IRT at Visit 2 (refer to Section 4.1.2). First dose of nintedanib within 1199.225 will be administered at Visit 2 in the clinic (day 1).

Additional clinic visits will be scheduled after 4, 12, 24, 36 and 52 weeks of treatment (Visits 3-7). Liver function monitoring visits (a-visits) will be performed at 2, 8, 18, 30 and 44 weeks of treatment (Visits 2a, 3a, 4a, 5a and 6a). After the first year of treatment (Visit 7), complete clinic visits will be scheduled every 16 weeks with intermediate liver function monitoring visits (a-visits) every 16 weeks.

The self-reported outcome questionnaires must always be done by patients in a quiet place prior to any other visit procedure.

For detailed description of the trial procedures at each visit and dispensing schedule, please refer to the Flowchart.

End of Treatment (EOT)

If a reason for drug discontinuation is met or the trials terminated due to one of the reasons mentioned in Section 3.3.4 an End of treatment Visit (EOT) should be scheduled as soon as possible after last drug intake. Reason for discontinuation must be documented in the eCRF.

For detailed description of the trial procedures at the EOT visit, please refer to the Flowchart.

6.2.3 Trial Completion and Follow Up Period

The End of Treatment Visit will be the trial completion visit. A Follow-up (FU) Visit is only to be planned for 7 days after last trial drug intake in case trial medication had to be discontinued permanently due to adverse events.

For detailed description of the trial procedures at the FU Visit, please refer to the Flowchart.

If the reason for removal of a patient from the treatment is an adverse event or an abnormal laboratory test result, the patient must be followed until complete resolution or stabilization of the event for at least 7 days after onset of the event or until follow-up is considered adequate by the investigator and the clinical monitor.

A patient will be considered lost to follow-up if the investigator is not able to contact him/her despite multiple attempts. Every effort must be made; at least 2 telephone contacts plus 1 mailing should be documented. The site must notify the clinical monitor prior to designating a patient as lost to follow-up.

6.2.4 Dose modification visit

Every time a dose should be reduced or increased (refer to Section 4.1.3 and Section 4.2.1) patients will need to come to the site for a dose modification visit where the following will be performed:

- Physical examination including measuring weight;
- Vital signs;
- Safety laboratory;
- Assessment of adverse events and concomitant therapy since last visit;
- Assignment of new dose in IRT;
- Dispensing of trial drug;
- Drug accountability.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a multicentre, multi-national, open-label clinical trial to investigate the long term safety of nintedanib in patients with SSc-ILD previously treated in (SENSCIS®) or 1199-0340.

As the main objective of this extension trial is to study long-term safety, only descriptive statistics will be used. Some limitations due to the nature of extension trial should be considered when interpreting the data (bias in the selection of the population, no comparative arm). Further endpoints are considered as exploratory only.

This statistical paragraph deals with the analyses to be performed on the extension trial only. Although data of parent trial will not be described in the scope of these analyses, they will be taken into account for adverse events analyses, as described in Section 7.3.4.

7.2 NULL AND ALTERNATIVE HYPOTHESES

All analyses are descriptive and exploratory in nature. No formal statistical inference is planned.

7.3 PLANNED ANALYSES

The treated set (TS) will consist of all patients who received at least one dose of open-label trial medication.

The definition of important protocol violations (IPV) will be specified in the trial statistical analysis plan (TSAP). These IPV definitions will include consideration of important violations of entry criteria, treatment non-compliance, restricted medications and inadequate follow-up of hepatic events.

Patients will be analysed according to their randomized treatment group in the previous trial SENSCIS® / 1199-0340.

The last available value between Visit 1 and Visit 2 (before first trial drug intake) will be considered as the baseline, for this extension trial.

7.3.1 Primary endpoint analyses

The primary objective of the trial is to assess the safety of nintedanib, so please refer to Section 7.3.4. The list of main safety endpoints is included in Section 5.2.

7.3.2 Secondary endpoint analyses

Not applicable.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment in this extension trial and end of the residual effect period (REP), a period of 7 days after the last dose of trial medication in this extension trial, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events in this extension trial, i. e. all adverse events occurring between start of treatment in this extension trial until 7 days after last trial drug intake will be considered ‘treatment-emergent’. The residual effect period is defined as 7 days.

Adverse events that start before first drug intake in this extension trial and deteriorate under treatment will also be considered as ‘treatment-emergent’. Other adverse events will be assigned to the previous trial, between-trials, screening, post-treatment, or post-trial period, as appropriate.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations (including weight measurement), or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

[redacted]

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Not applicable

7.4 INTERIM ANALYSES

The first interim analysis may occur earliest in an adequate timeframe prior to or after SENSCIS® analysis. Additional interim analyses could be performed upon request from Health Authorities or for publication purpose. All the above mentioned analyses may be presented at each interim analysis.

7.5 HANDLING OF MISSING DATA

Missing or incomplete AE dates will be imputed according to BI rules. No imputation is planned for other safety criteria.

Missing or incomplete data for survival are managed by censored data analyses. No specific procedures need to be specified to handle them.

[redacted]

7.6 RANDOMISATION

Not applicable as this is an extension trial.

7.7 DETERMINATION OF SAMPLE SIZE

Not applicable as this is an extension trial. The number of patients included in this trial will correspond to the number of patients having completed SENSCIS® / 1199-0340 and are willing to participate in 1199.225.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP*.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report or interim reports.

For Japan only: the rights of the investigator / trial site and of the sponsor with regard to publication of the results of this trial are described in the investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report or interim reports.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File).

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

Additional information for Japan:

The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRF) for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.7.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see Section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly

been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.

- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

For Japan only: when the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The Coordinating Investigator is responsible to coordinate Investigators at the different centres participating in this multicentre trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF. The investigators will have

access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to manage the trial in accordance with applicable regulations and internal SOPs, direct the clinical trial team in the preparation, conduct, and reporting of the trial, ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs."

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

A list of responsible persons and relevant local information can be found in the ISF.

Central laboratory facilities will handle all laboratory analyses of the trial. Samples for intermediate measurements (liver enzymes, creatinine) and pregnancy tests may be collected at a local doctor by using trial specific lab kits that will be sent to central laboratory for analyses.

[redacted]

Interactive Response technology (IRT) vendor will be used in this trial.

Details will be provided in IRT Manual, the Spirometry Manual and Central Laboratory Manual, available in the ISF.

8.8 PROTOCOL VIOLATIONS

For Japan only: the Investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial patients or for other medically compelling reason, the principal Investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.9 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan only: in the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

[redacted] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J 2005. 26(2):319-338.

P11-11216 Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klueglich M, Bois RM du. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011. 365(12):1079-1087.

P14-07514 Richeldi L, et al, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine, published on May 18, 2014, doi: 10.1056/NEJMoa1402584 N Engl J Med 2014. 370(22):2071-2082.

P14-07919 Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis and Rheumatology, Accepted Article, Accepted: May 08, 2014, doi: 10.1002/art.38702 Arthritis Rheumatol 2014. 66(8):1967-1978.

[redacted] Pope J. Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). Arthritis Care Res (Hoboken) 2011. 63(Suppl 11):S98-S111.

[redacted] Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997. 40(11):1984-1991.

P15-00879 Kowal-Bielecka O, et al, EUSTAR Co-Authors. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis 2009. 68(5):620-628.

P19-04387 Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al, SENSCIS Trial Investigators. Nintedanib for systemic sclerosis-associated interstitial lung disease. New England Journal of

Medicine, published on May 20, 2019, doi: 10.1056/NEJMoa1903076; 2019. p. 2518-2528.

R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pd f 2010.

R14-4918 Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol 2012. 24(2):165-170.

R14-4927 Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med 2009. 360(19):1989-2003.

[redacted] Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005. 23(Suppl 39):S14-S18.

R14-5407 Tashkin DP, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006. 354(25):2655-2666.

R15-1205 Clements PJ, et al. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. J Rheumatol 1993. 20(11):1892-1896.

R15-2010 Ferraz MB, Quaresma MR, Aquino LRL, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990. 17(8):1022-1024.

R96-0690 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 16 (1), 31 - 41 (1976).

[redacted] Jones PW, Quirk FH, Baveystock CM. The St.George's respiratory questionnaire. Respir Med 1991. 85(Suppl B):25-31.

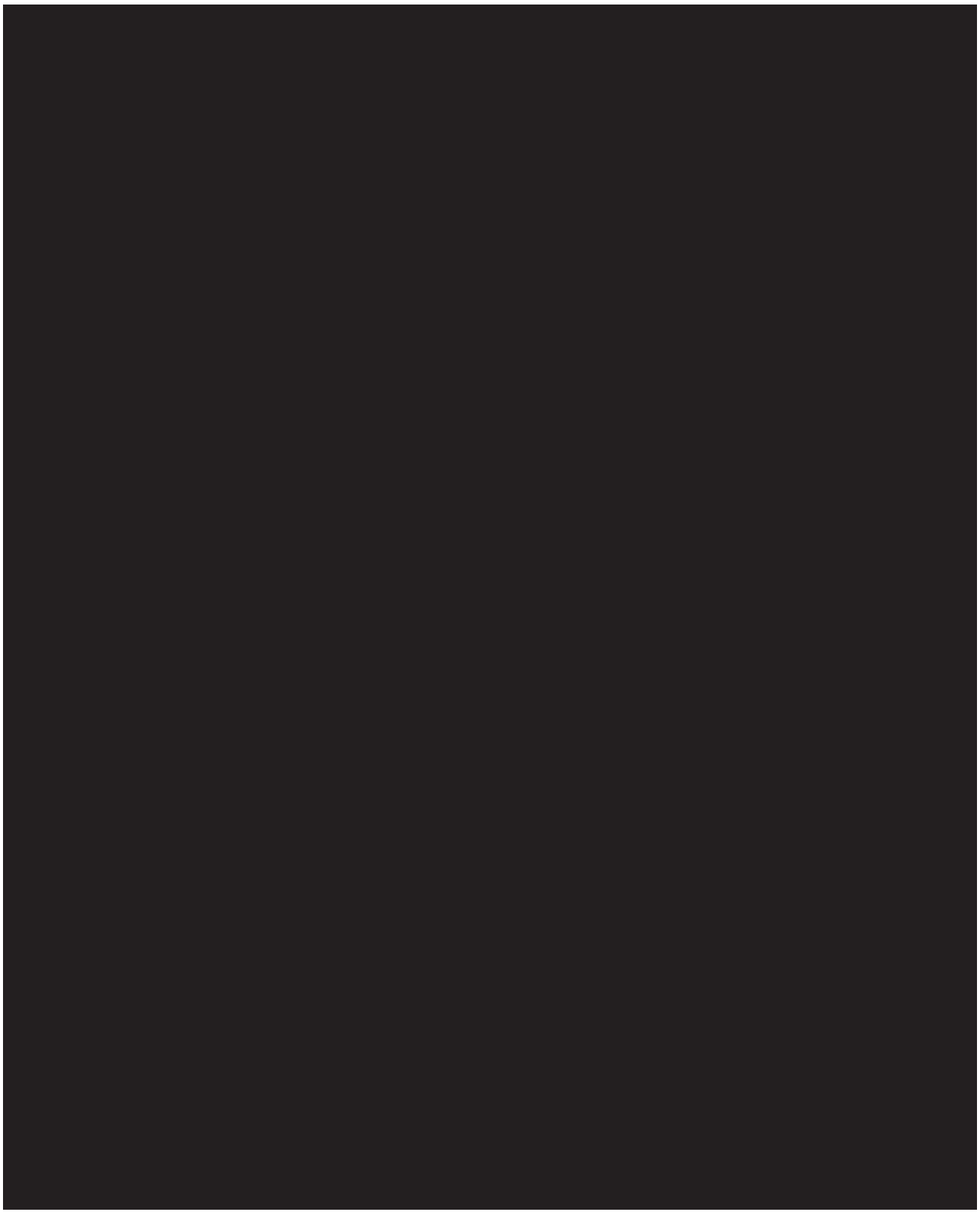
9.2 UNPUBLISHED REFERENCES

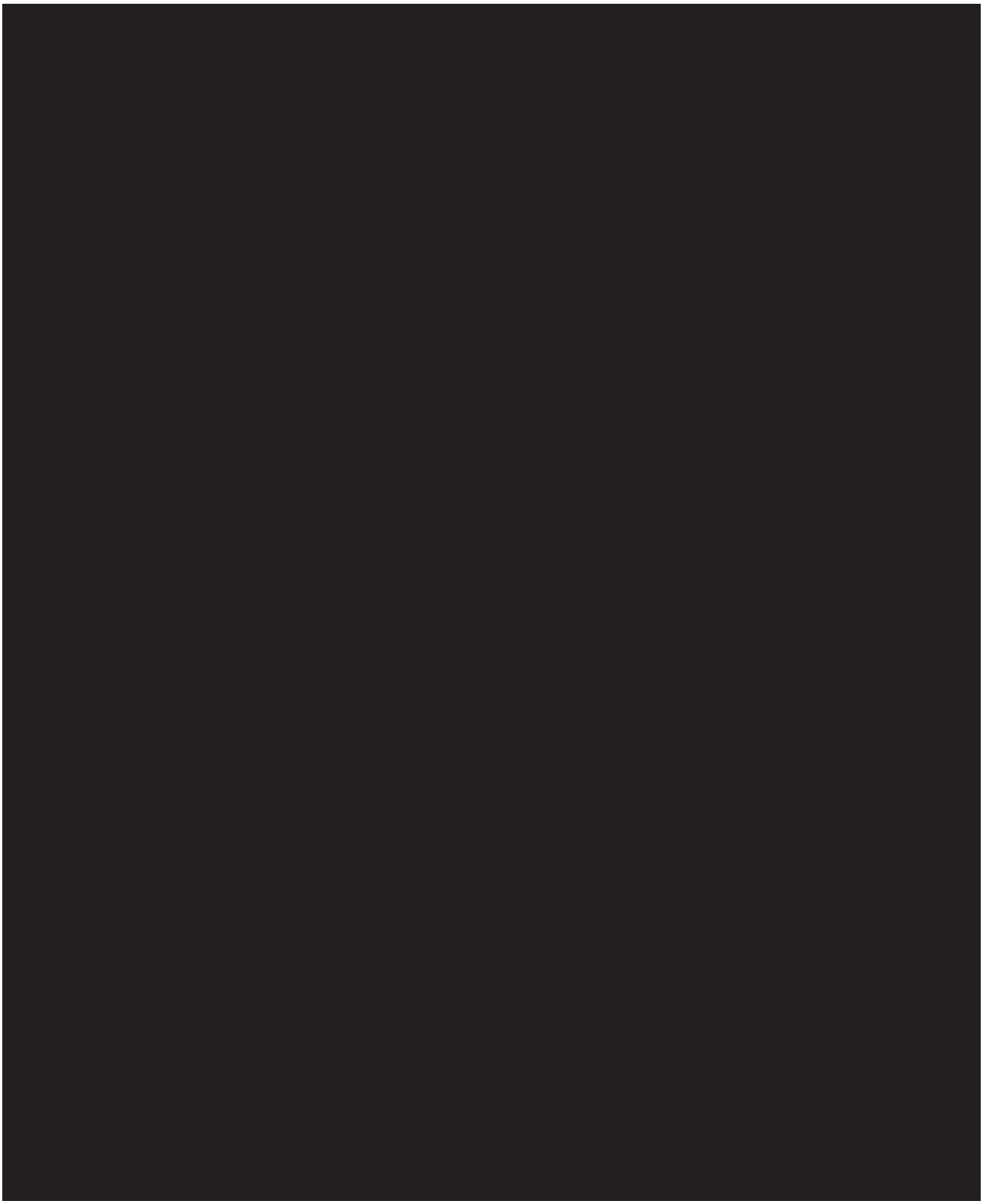
c01783972 Investigator’s Brochure Nintedanib (BIBF 1120)

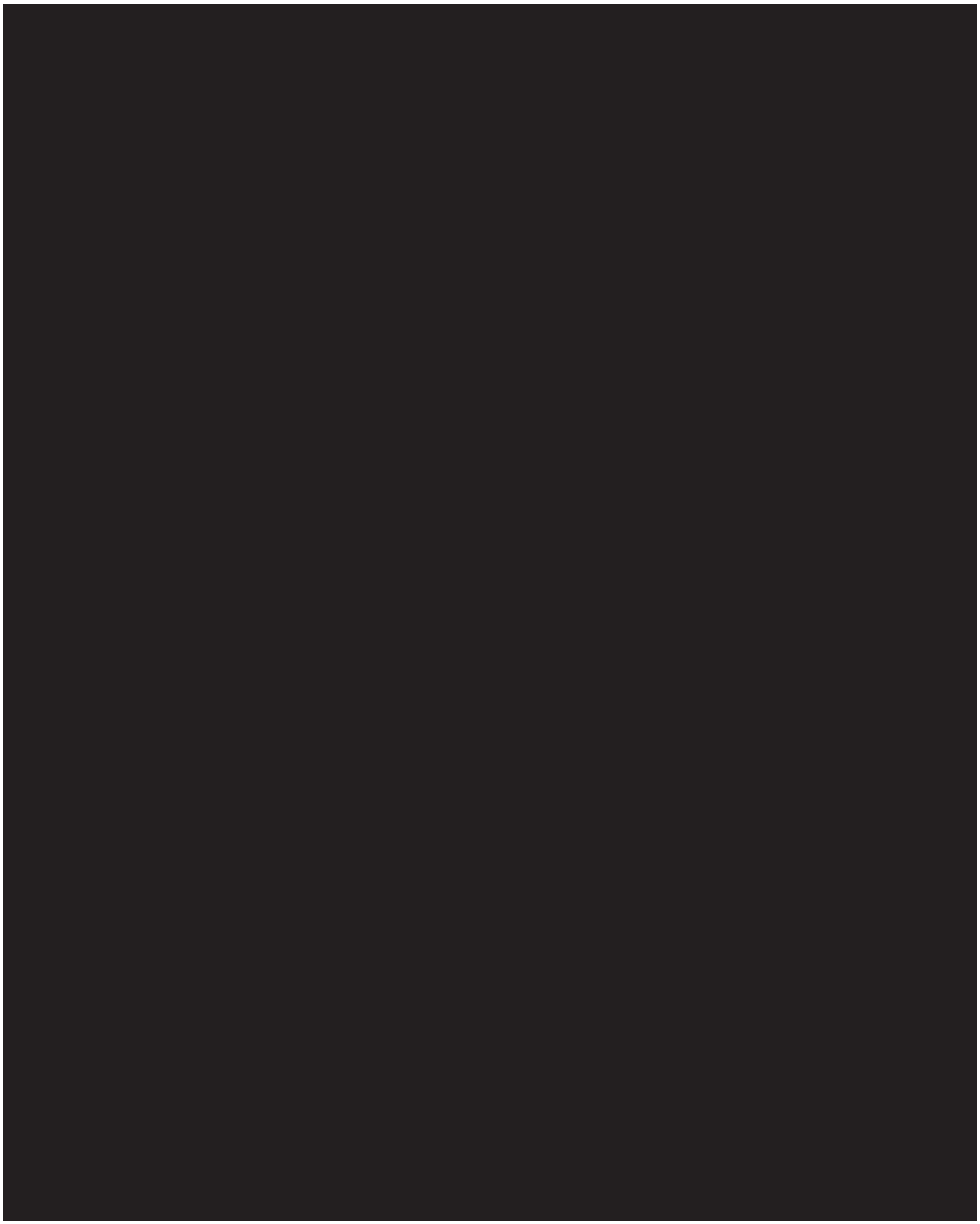
c26582112 Clinical Trial Report 1199-0340

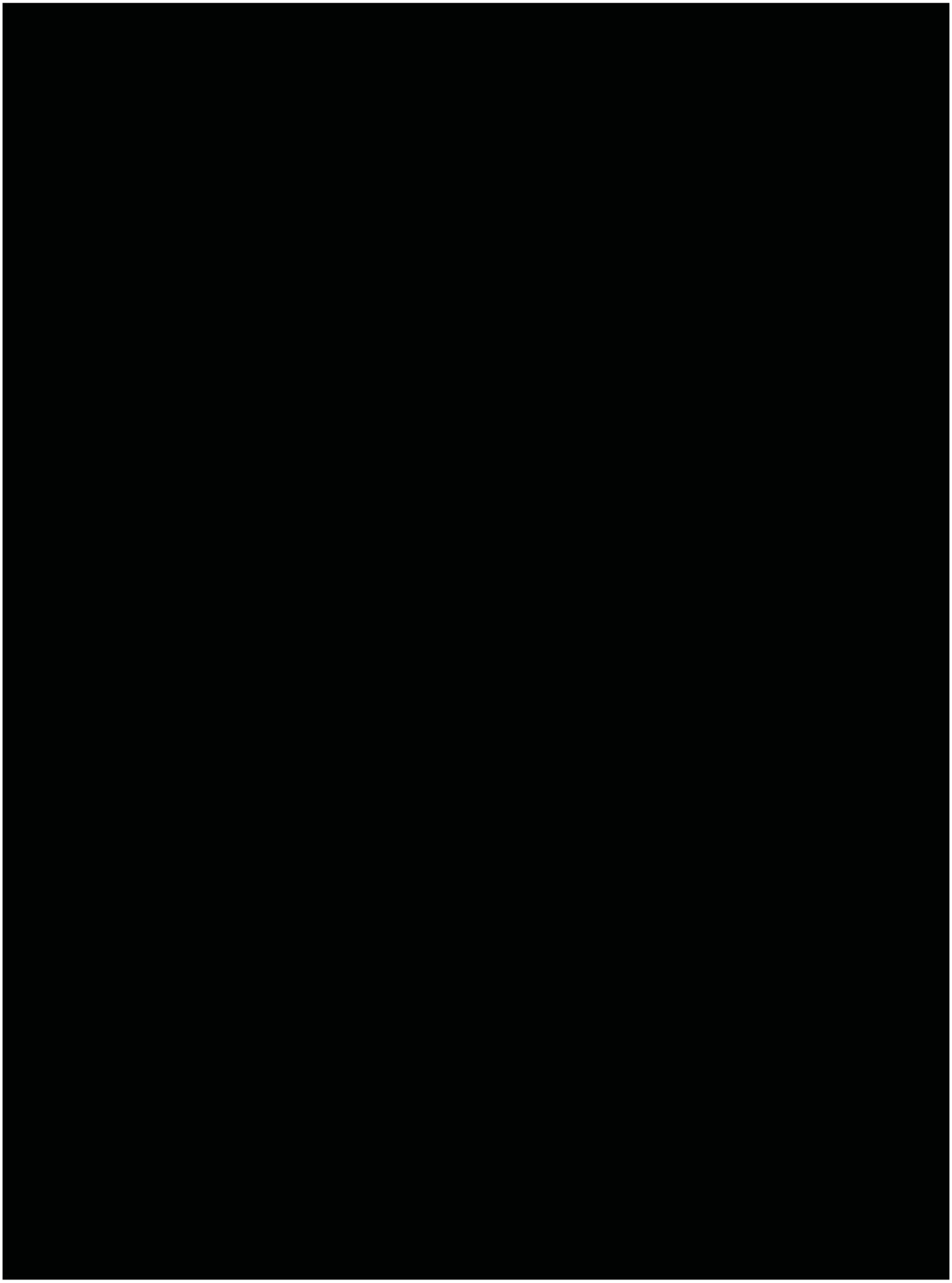
10. APPENDICES

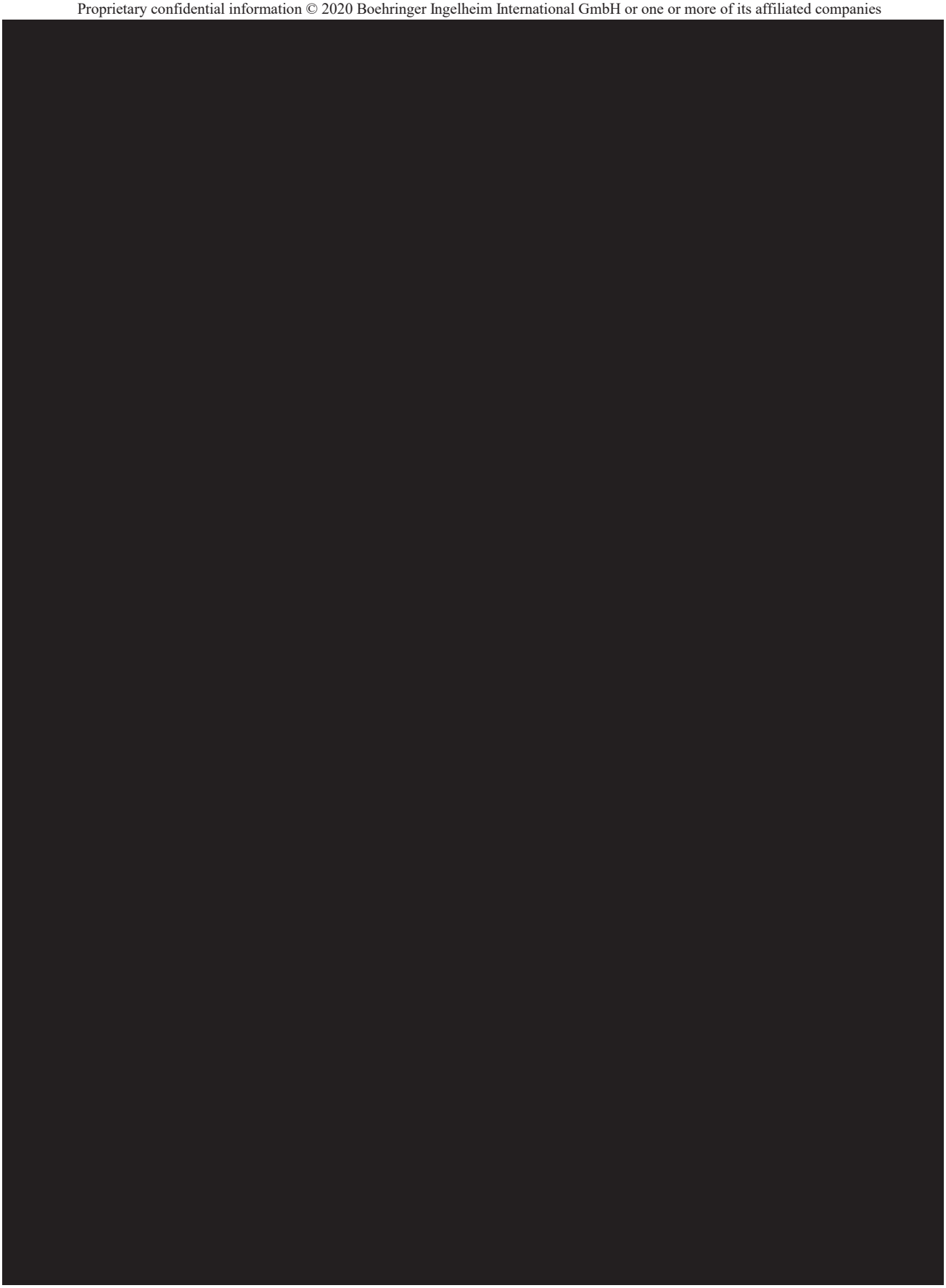
10.1 PATIENT REPORTED OUTCOME QUESTIONNAIRES

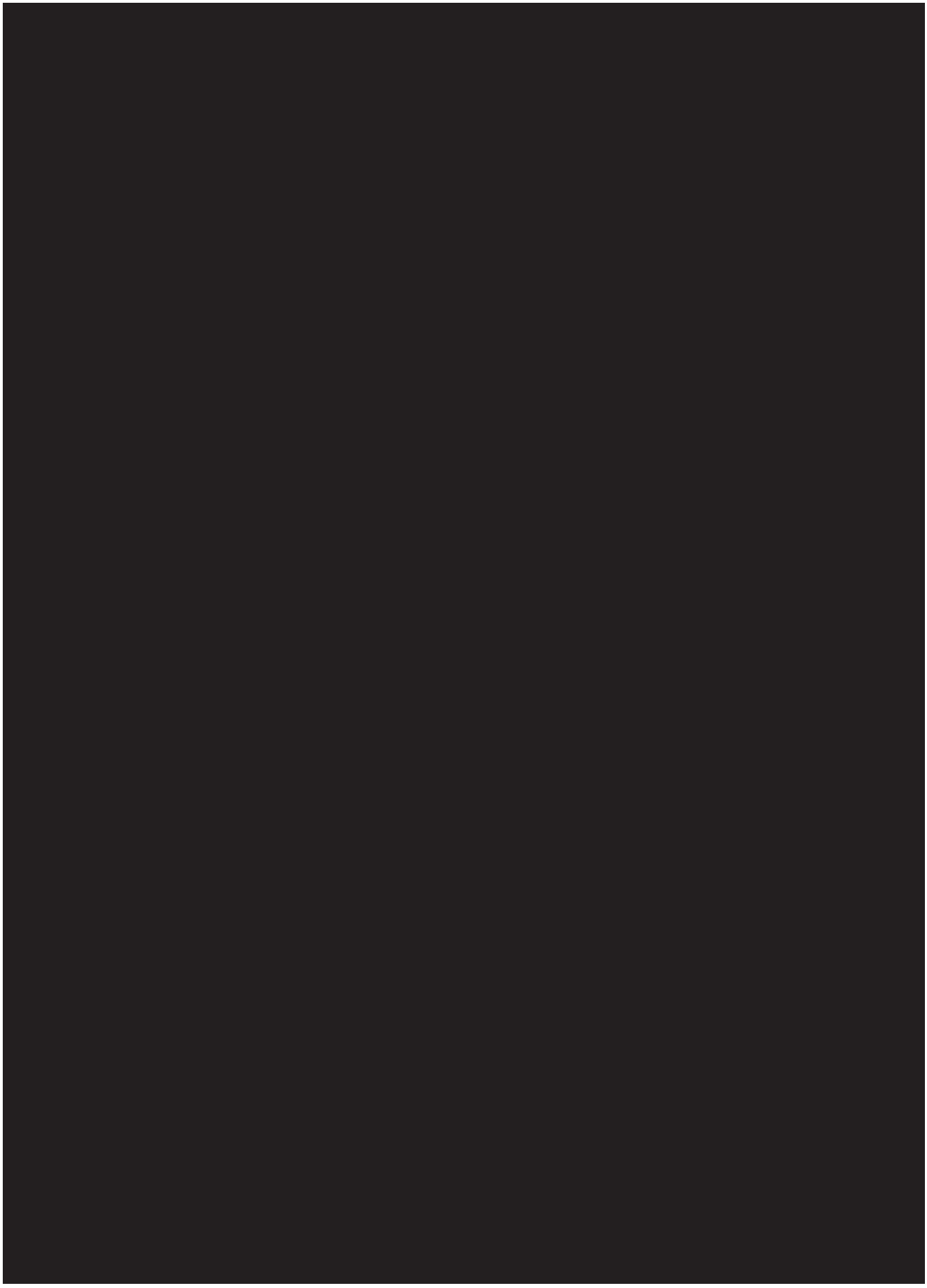


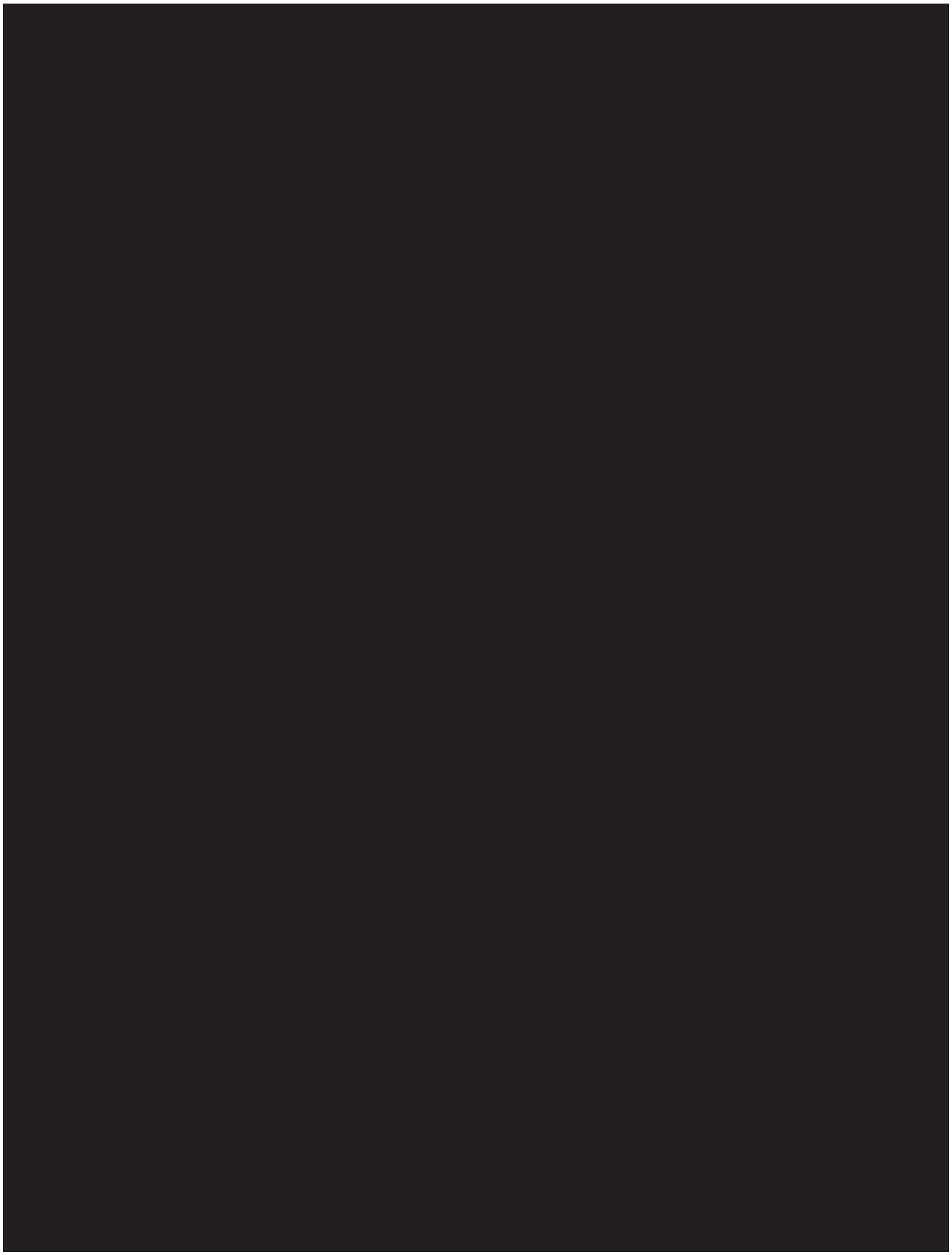


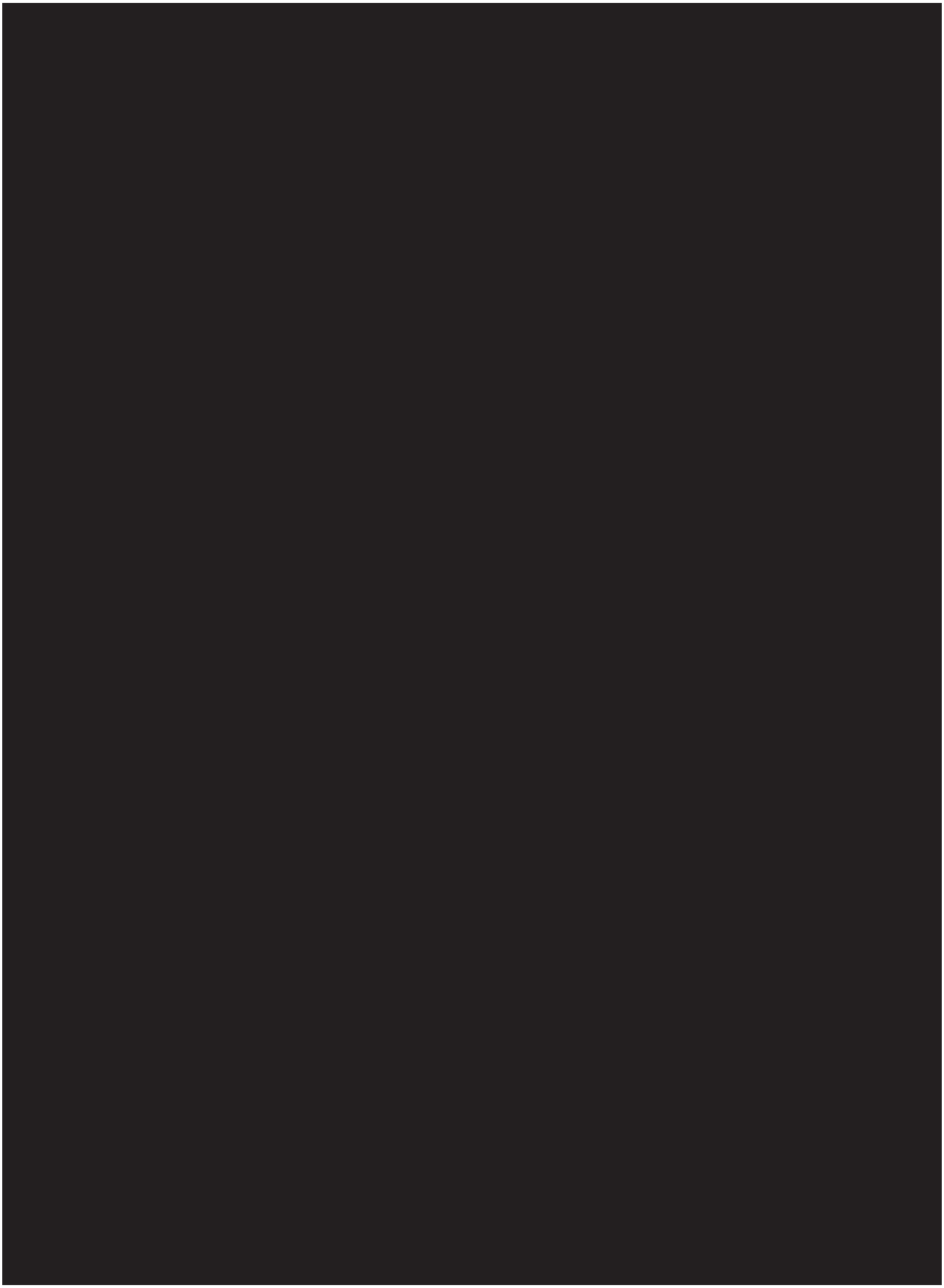


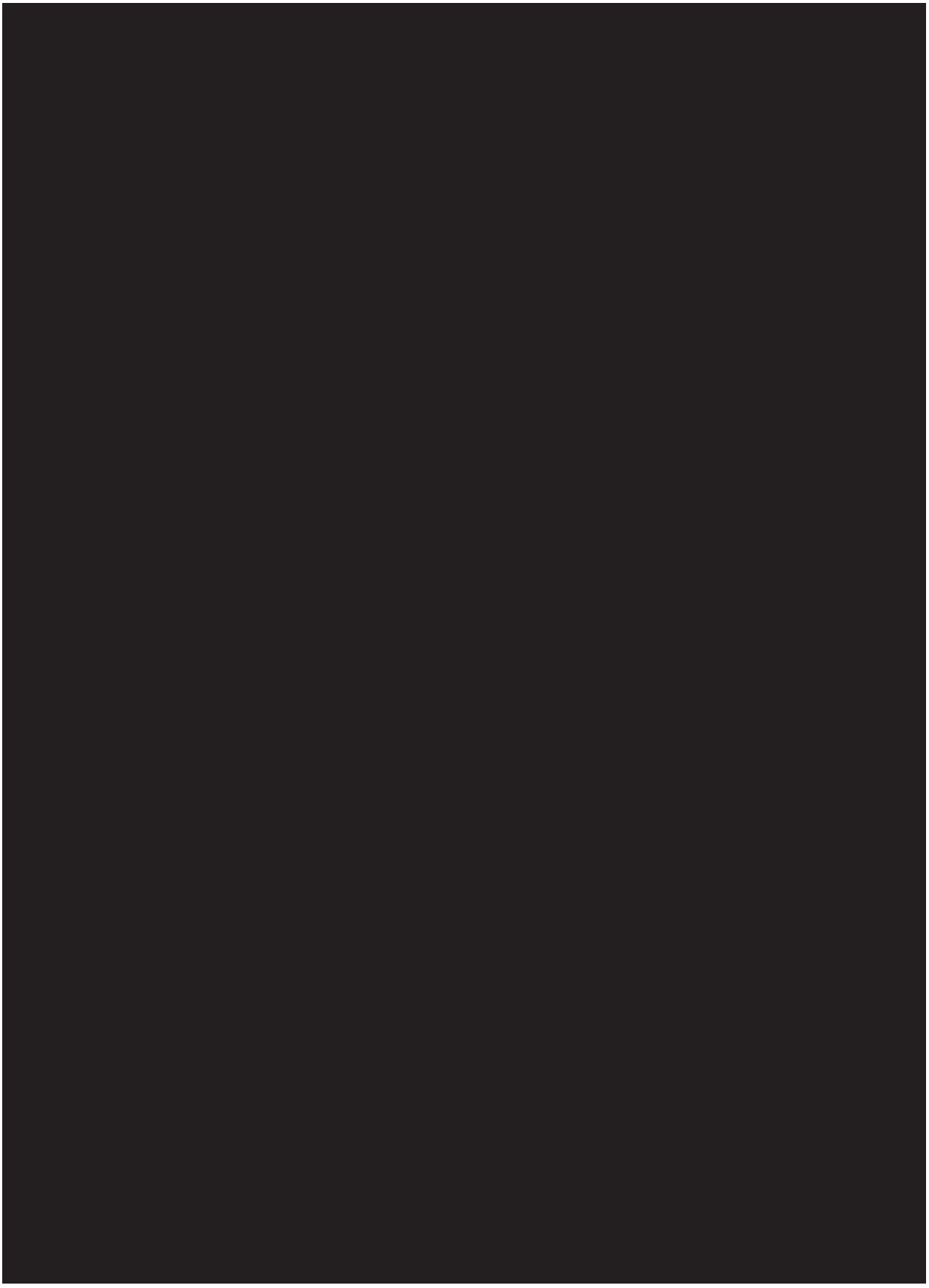


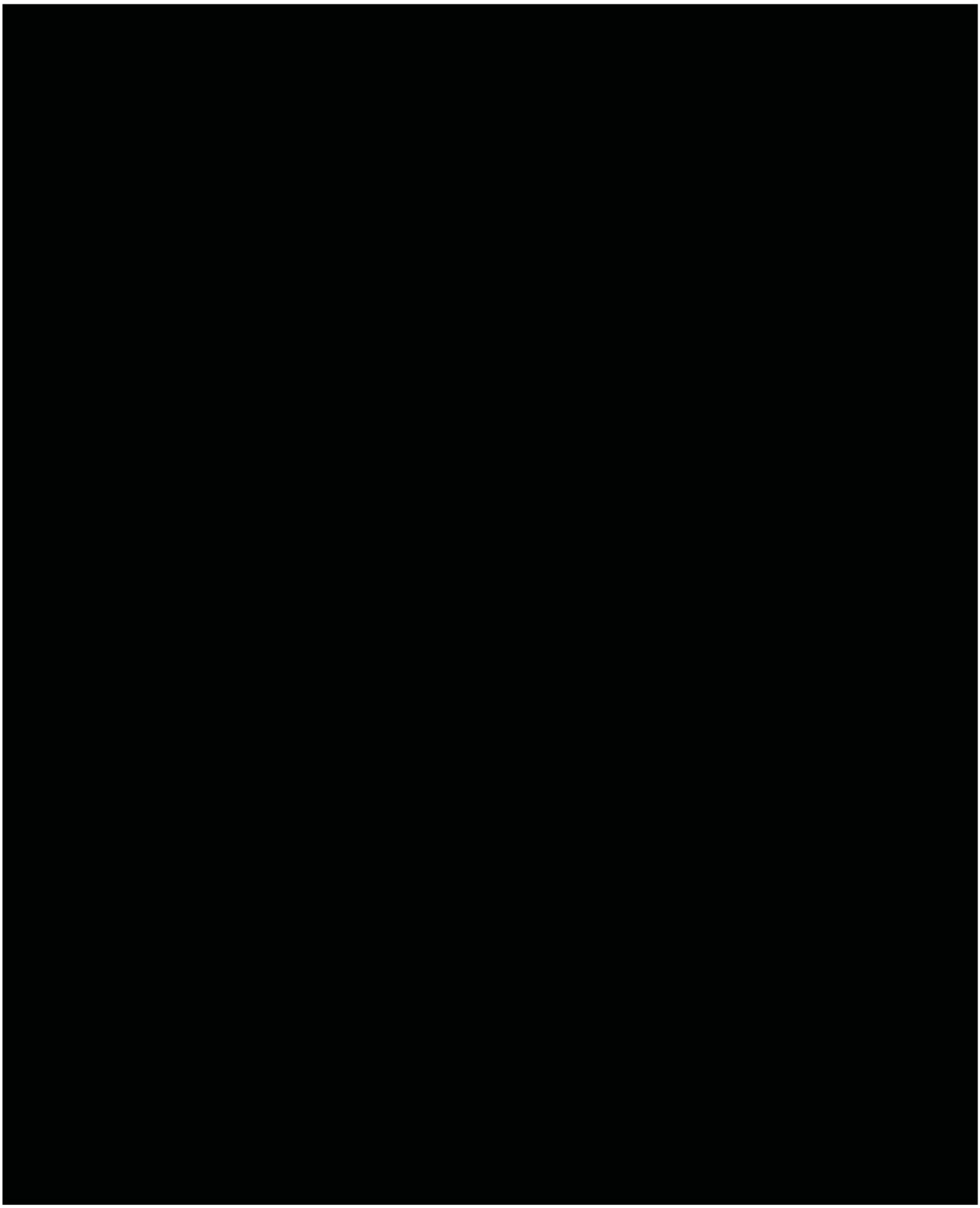


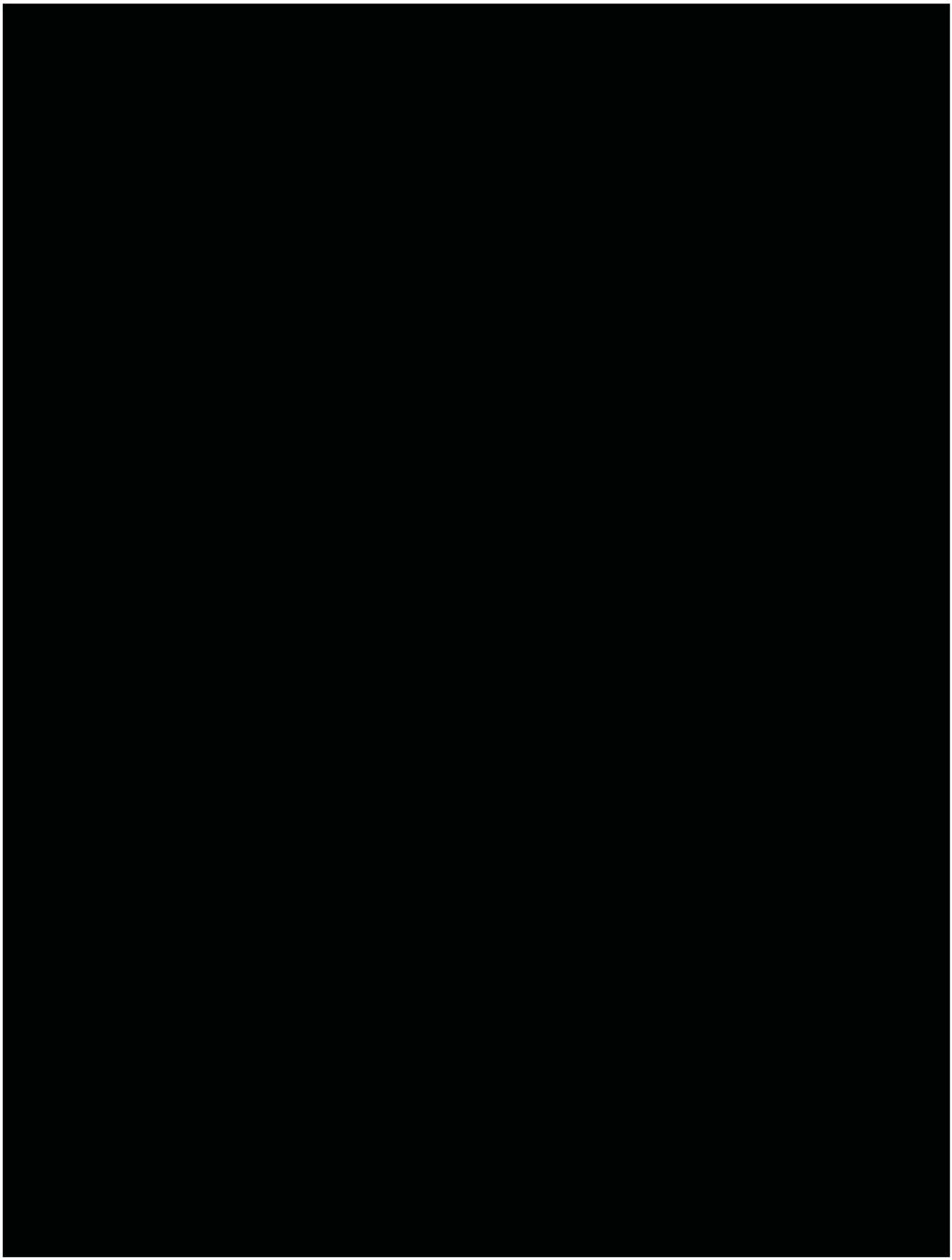


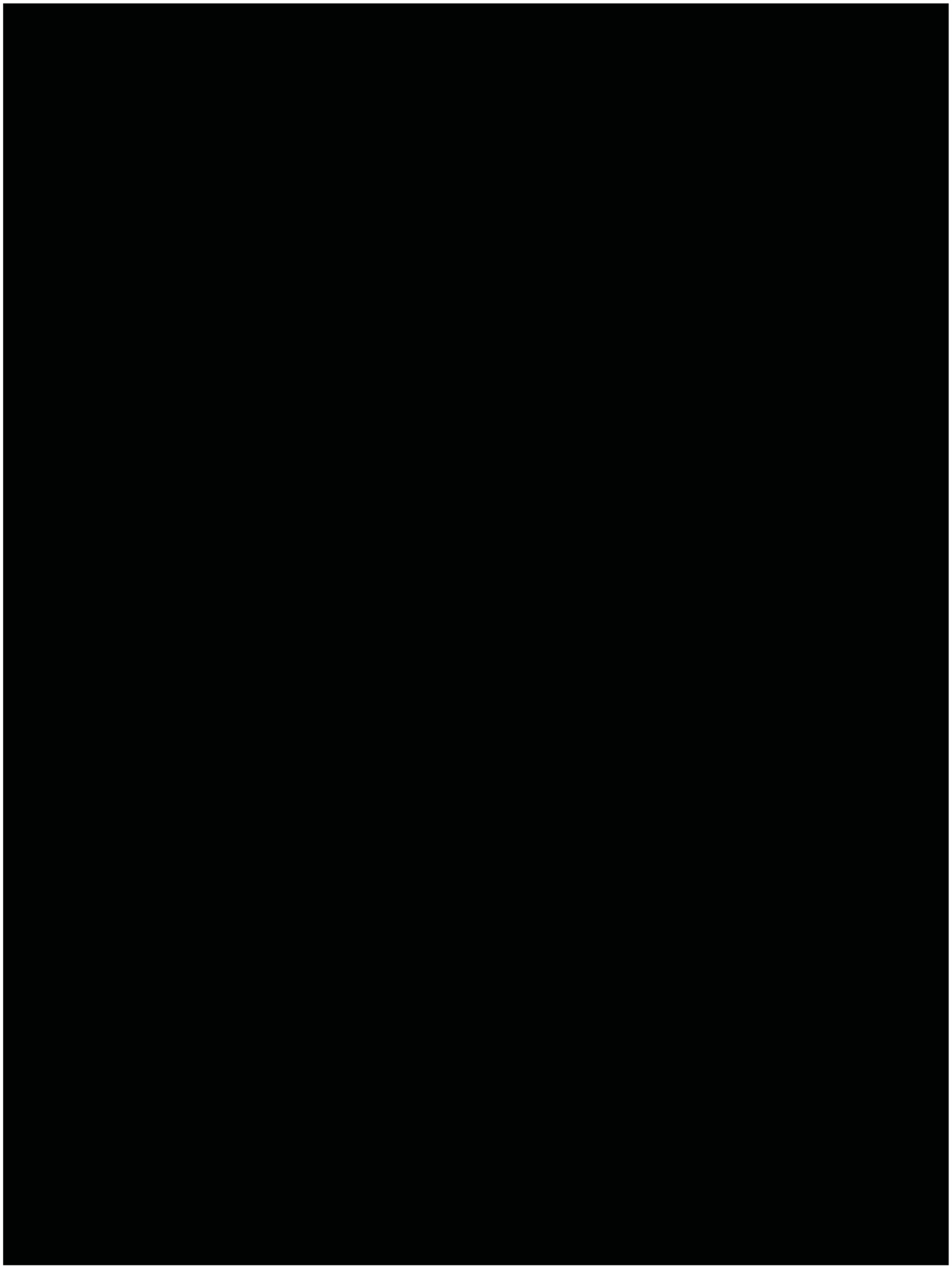


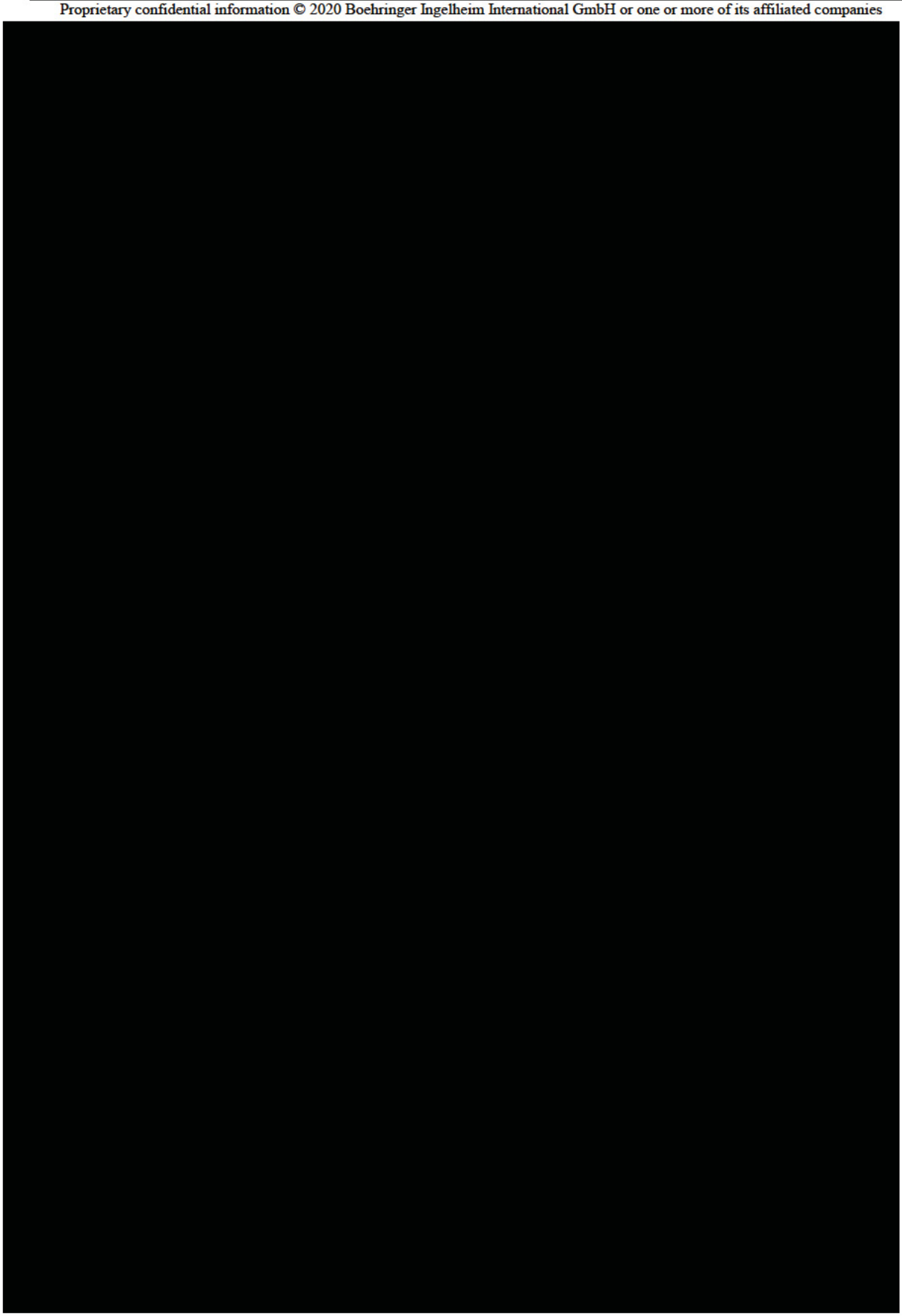


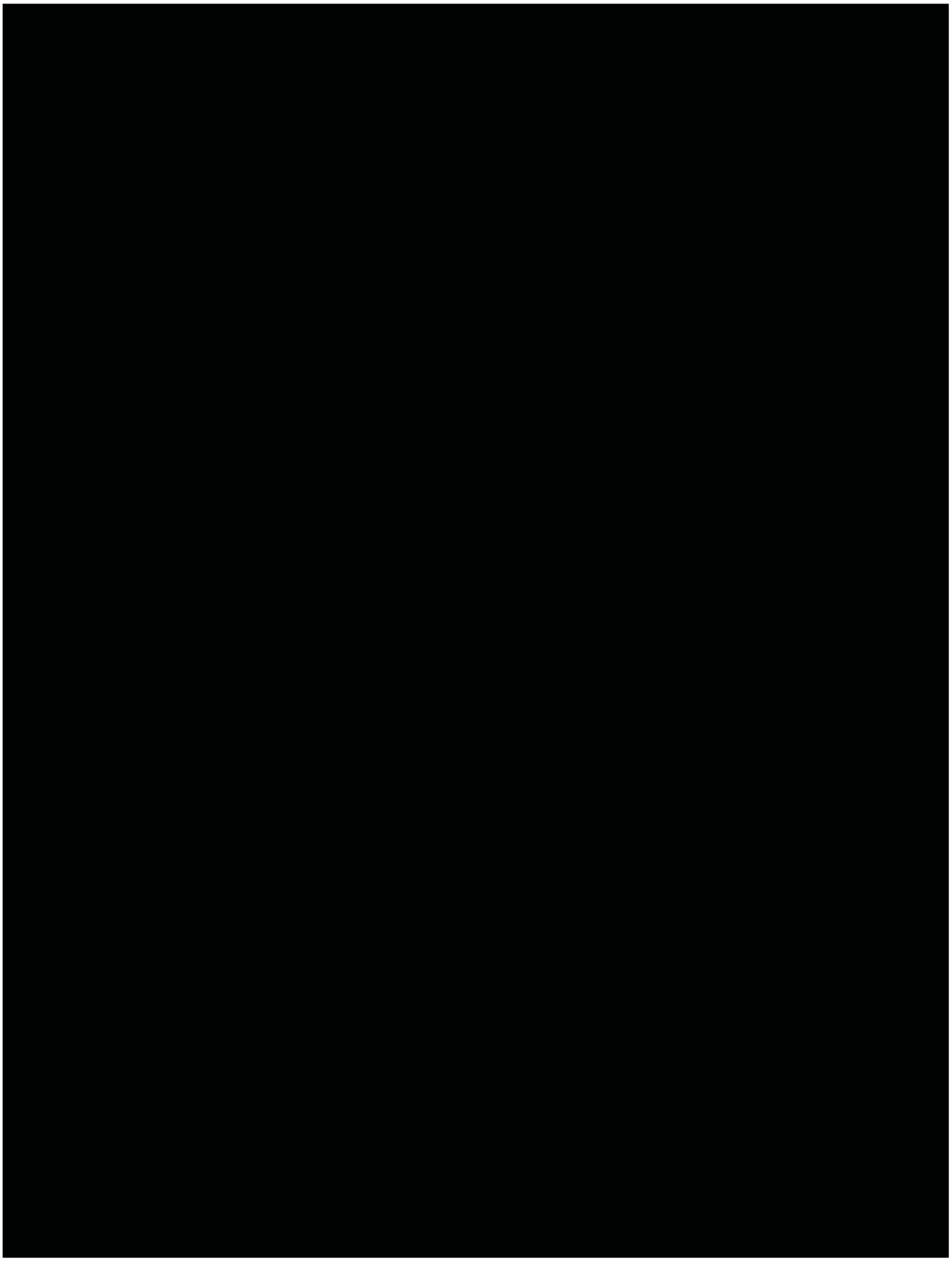


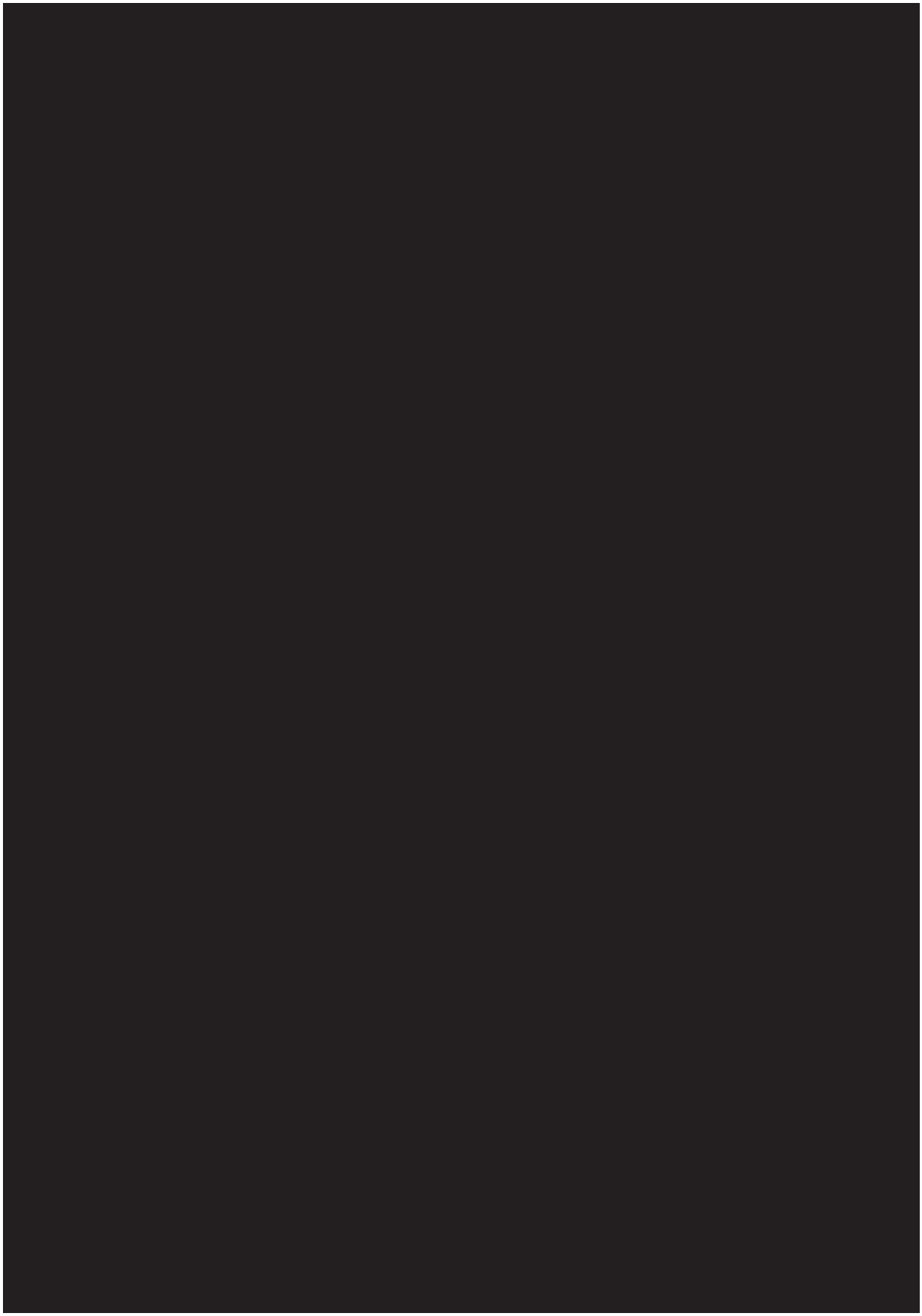


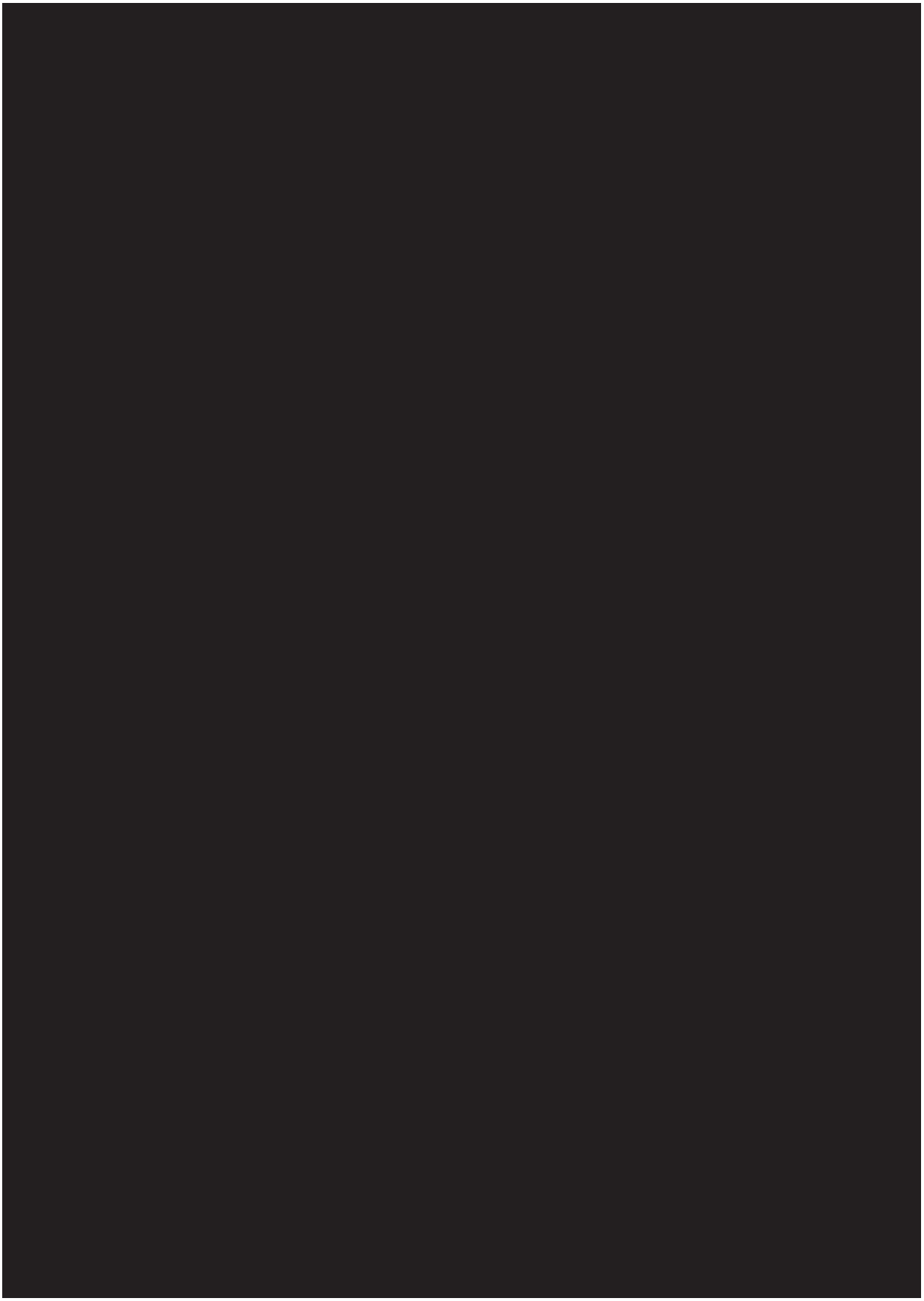












10.2 CREATININE CLEARANCE

Creatinine clearance calculation is done according to Cockroft and Gault (R96-0690).

- Creatinine clearance = (140 - age) x (Weight in kg) x (0.85 if female) / (72 x serum creatinine in mg/dL)

10.3 VISIT MODIFICATION IN EXCEPTIONAL CIRCUMSTANCES

INITIAL	MODIFIED or ADDED
Face-to-face patient visit performed by a physician/under the responsibility of a physician on site.	Remote or home visit performed by the investigational site physician/under the responsibility of the investigational site physician to ensure the wellbeing of a patient and to collect at least: **Adverse Events** / **Concomitant Treatments and Drug Interruption**
Regular on site safety lab test using central lab kits: • Haematology, Biochemistry, Electrolytes, Coagulation, Urinalysis every 16 weeks using central lab; Liver enzyme monitoring every 8 weeks, using central lab • Pregnancy test every 4-6 weeks (possible at home)	• Under treatment with nintedanib, regular liver enzyme monitoring is required and needs to be ensured by the investigational site, but can be done at a local lab / local doctor. The investigator has to ensure medical review and proper documentation in the eCRF. Minimum required safety lab paramenters are AST, ALT, GGT, ALK and total bilirubin. • Urine pregnancy tests (for women of childbearing potential only) are regularly required and may be done at local lab / local doctor, or at home. • Decision whether to continue nintedanib treatment should be made based on an individual risk assessment for that individual patient and weigh up the benefits of an extended lab interval to maximum 16 weeks versus an interruption of treatment. • Medical decision has to be documented in patient's source notes. If remote patient visits and/or local liver enzyme monitoring cannot be performed, nintedanib treatment needs to be interrupted.
If liver function tests are out of the range, the per protocol rules apply => dose reduction	If the patient cannot come to site for receiving new dose treatment and/ or patient safety and follow up safety lab testing cannot be guaranteed, treatment needs to be interrupted.
Dispensation of study treatment on site	• Site / Depot to patient IMP shipments • Patients must consent to providing contact details for shipping purposes • Patients should retain all unused IMP and packaging, and return it when they are able to return to the site.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 August 2017
EudraCT number		2016-003403-66
BI Trial number		1199.225
BI Investigational Product(s)		Nintedanib
Title of protocol		An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		Flowchart
Description of change		Visit 3a correction : day 57 Questionnaires: x at visit EOT
Rationale for change		Corrections of inconsistencies
Section to be changed		Table 5.2.3: 1 Laboratory tests
Description of change		Thyroid stimulating hormone (at V2, V5 (after 6 month), V 7 (12 Month) and then every other year and at EOT
Rationale for change		Clarification
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Clarification that creatinine clearance will be calculated by using the Cockroft-Gault formula
Rationale for change		Corrections of inconsistencies
Section to be changed		5.2.11.2 Adverse event collection and reporting
Description of change		Removed: Similarly, potential drug exposure

		during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.
Rationale for change		Correction: The sentence was part of an underlying Clinical Trial Protocol template and should have been deleted as not applicable in this trial: There is no evidence from reproductive toxicology studies for adverse effects of nintedanib on male fertility and health status of offspring. The use of male contraception, especially condoms by male patients receiving nintedanib is not mandatory and female partners of male patients receiving nintedanib are not required to follow contraceptive guidelines.
Section to be changed		11.2 Creatinine clearance
Description of change		Clarification that creatinine clearance will be calculated by using the Cockroft-Gault formula
Rationale for change		Corrections of inconsistencies

11.2 GLOBAL AMENDMENT 2

Date of amendment	17 August 2018
EudraCT number	2016-003403-66
BI Trial number	1199.225
BI Investigational Product(s)	Nintedanib
Title of protocol	An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		All sections
Description of change		SENSCIS™ has been changed to SENSCIS®
Rationale for change		Registration received
Section to be changed		Synopsis, Flowchart, 1. Introduction, 3. Description of Design and Trial Population, 4. Treatments, 6.2.1. Screening, 7. Statistical methods and Determination of Sample Size, 11. Description of Global Amendments
Description of change		The listed sections of the protocol have been updated in order to reflect that also the approximately 14 patients of the trial 1199-0340 will enter in this extension trial.
Rationale for change		To additionally assess the safety of ongoing nintedanib treatment in patients with Systemic Sclerosis associated Interstitial Lung Disease who have completed the phase I drug-drug interaction (DDI) trial 1199-0340.
Section to be changed		3.3.4.2 Recommendation to discontinue nintedanib
Description of change		Pulmonary Hypertension (PH) requiring parenteral therapy (parenteral or oral with epoprostenol/, treprostinil, selexipag). Selexipag added.
Rationale for change		New substance in the treatment of PH
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Overall about 110 mL blood will be taken for standard safety laboratory during the first year and about 45 mL blood will be taken any other year.
Rationale for change		Clarification of collected blood volume.
Section to be changed		6.2.4 Dose modification visit
Description of change		Safety laboratory added
Rationale for change		Corrections of inconsistencies
Section to be changed		6.2.3 Trial Completion and Follow Up Period 7.3.4 Safety analysis
Description of change		Change the residual effect period from 28 days to 7 days
Rationale for change		Corrections of inconsistencies

11.3 GLOBAL AMENDMENT 3

Date of amendment		13 Aug 2020
EudraCT number		2016-003403-66
BI Trial number		1199.225
BI Investigational Product(s)		Nintedanib
Title of protocol		An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		1.1 Medical Background; 1.2 Drug profile
Description of change		Section 1 was updated to ensure that current knowledge and recent data are reflected in the indroduction section.
Rationale for change		New data of pivotal trial (1199-0214) available.
Section to be changed		1.4 Benefit Risk Assessment
Description of change		Risk assessment due to COVID-19 pandemic situation added
Rationale for change		New information on benefit/risk due to COVID-19 pandemic situation.
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		The end of the trial description was revised and more precisely specified. Trial may last beyond availability of marketed drug.
Rationale for change		Clarification overall trial duration
Section to be changed		4.1.3 Drug assignment and administration of doses for each patient
Description of change		Amount of wallets provided to the patients at visits 5 and 6 were described incorrect and was corrected.
Rationale for change		Correction of wallets given to patient per visit
Section to be changed		4.2.1 Other treatments and emergency procedures
Description of change		The wording regarding withdrawal and interruption of trial medication was revised to for clarification. Furthermore it was added that trial medication may be resumed in case of clear evidence for alternative cause for hepatic injury was identified and resolved. It was specified that this is only possible after consultation with the sponsor and if prior to restart, liver laboratory values are normal.. Liver laboratory values should be monitored weekly for first 4 weeks of re-introduction and every 2 weeks for the following 8 weeks.
Rationale for change		Revision of the recommendations for hepatic injury.

Section to be changed		6.1 Visit schedule and 10.3 Visit modification in exceptional circumstances
Description of change		Specification that and how in exceptional circumstances (as e.g. in pandemic situations), when it is impossible to conduct study visits at the study site, study visits may be performed at patient's home or remotely combined by using local laboratories.
Rationale for change		Experiences from the COVID-19 first wave situation; to allow flexibility in visit conduct in case required due to pandemic or other exceptions situations to ensure patients safety by ensuring continuous treatment.

APPROVAL / SIGNATURE PAGE

Document Number: c11787364 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-04

Title: An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	18 Aug 2020 14:45 CEST
Author-Statistician		19 Aug 2020 11:48 CEST
Approval-Team Member Medicine		24 Aug 2020 08:35 CEST
Author-Clinical Trial Leader		27 Aug 2020 10:26 CEST
Verification-Paper Signature Completion		27 Aug 2020 11:24 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed