Clinical Trial Protocol

	Document Number:	**c29492723-04**
EudraCT No. **EU Trial No.**	2019-004167-45	
BI Trial No.	1305-0013	
BI Investigational Medicinal Product	BI 1015550	
Title	A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally.	
Lay Title	A study to test how taking BI 1015550 for 12 weeks affects lung function in people with idiopathic pulmonary fibrosis (IPF).	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Tel: [redacted] Fax: [redacted] Email: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax : [redacted]	
Version and Date	**Version: 4.0**	**Date: 09 Sep 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	17 Feb 2020
Revision date	09 Sep 2020
BI trial number	1305-0013
Title of trial	A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally.
Coordinating Investigator	[redacted] Phone: Fax :
Trial site(s)	Multi-centre trial conducted in approximately 20 countries
Clinical phase	II
Trial rationale	The purpose of this trial is to demonstrate proof of concept of clinical activity of BI 1015550 on the change of Forced Vital Capacity (FVC) between baseline and 12 weeks. New treatments are needed that further reduce the decline in FVC, positively affect symptoms and improve quality of life in patients with Idiopathic Pulmonary Fibrosis. This trial will investigate BI 1015550 to be used in this patient population either as stand-alone treatment or in addition to local standard of care (SoC), which may or may not include currently approved antifibrotic treatments (nintedanib or pirfenidone). FVC change from baseline will be used to generate sufficient evidence of efficacy in the subpopulation on no background antifibrotic treatment, to inform the phase III program.
Trial objective(s)	To investigate the efficacy of BI 1015550 18 mg b.i.d compared to placebo based on the change from baseline in FVC. To investigate the safety and tolerability of BI 1015550 in overall trial population.
Trial endpoints	The primary endpoint is the change from baseline in FVC at 12 weeks (in mL). The secondary endpoint is the Percentage of patients (%) N with Treatment Emergent Adverse Events (TEAE).
Trial design	Double-blind, placebo controlled, parallel design of 2 groups over 12 weeks.
Total number of patients randomised	Approx. 150 (min 120)
Number of patients on	Approx. 100 in BI 1015550 18 mg b.i.d. group

each treatment	Approx. 50 in placebo group
Diagnosis	IPF patients either treated with antifibrotic treatment or not.
Main in- and exclusion criteria	Inclusion criteria : ∀ Patients aged ≥40 years. ∀ IPF diagnosis confirmed by central review. ∀ FVC≥ 45%. ∀ DLCO≥25% and<80%. ∀ Either stable treatment with antifibrotics for at least 8 weeks prior to Visit 1 or not treated with antifibrotics for at least 8 weeks prior to Visit 1. Exclusion criteria : ∀ Relevant airways obstruction (pre-bronchodilator FEV1/FVC < 0.7) at Visit 1. ∀ Acute IPF exacerbation within 4 months prior to screening and/or during the screening period. ∀ Lower respiratory tract infection requiring antibiotics within 4 weeks prior to Visit 1 and/or during the screening period. ∀ Any suicidal behaviour in the past 2 years. ∀ Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1. ∀ Baseline condition or medical history of vasculitis. ∀ Confirmed infection with SARS-CoV-2 within 4 weeks prior to visit 1 or during screening period.
Test product(s)	BI 1015550
dose	18 mg b.i.d (36 mg daily)
mode of administration	Oral
Comparator product(s)	Placebo
dose	Matching
mode of administration	Oral
Duration of treatment	12 weeks
Statistical methods	The purpose of this trial is to demonstrate proof of concept of clinical activity of BI 1015550 on the primary endpoint. For the proof of concept an evaluation of a minimum relevant additional benefit of BI 1015550 compared to placebo is conducted. Hereby, the posterior probability of the difference in change from baseline in FVC between BI 1015550 and placebo will be evaluated for different boundary values. The primary endpoint change from baseline in FVC at week 12 will be evaluated separately in the patient group with antifibrotic treatment and in the patient group with no antifibrotic treatment. To account for the repeated nature of the data and the covariates in

	the model, MMRM analysis will be carried out for change from baseline of FVC after 12 weeks of treatment in each patient group. The adjusted mean change from baseline (and the related standard error) will be calculated for each group and will be used for the Bayesian borrowing approach. The analysis will include the fixed, categorical effect of treatment at each visit, and the fixed continuous effects of baseline FVC at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

FLOW CHART

Trial Periods	Screening	Randomised Treatment					Follow Up**
Visits	**1**	**2**	**3**	**4**	**5**	**6 – End of Treatment**	**7 - End of Trial**
Weeks		D 1*	2	4	8	12	EoT + 1 week
Days	-30[1]	1	15	29	57	85	EoT + 7d
Time window for visits	-14/+23 days		±3 days	±7 days	±7 days	-7/+4 days	+3 days
Informed consent[2]	X						
Demographics	X						
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Vital signs***	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Height	X						
Safety laboratory tests[3]	X	X	X	X	X	X	X
12 lead-ECG[4]	X	X		X		X	
Review of in-/exclusion criteria	X	X					
Randomisation		X					
Dispense trial drugs		X		X	X		
Administer trial drugs		X	X	X	X	X	
Return trial drugs			X	X	X	X	
[redacted]			[redacted]		[redacted]		
[redacted]		[redacted]		[redacted]		[redacted]	
Spirometry (FEV1, FVC)[6]	X	X	X	X	X	X	
C-SSRS[7]	X	X	X	X	X	X	X
[redacted]		[redacted]		[redacted]		[redacted]	
HRCT[9]	X						
DLCO[6]	X	X			X	X	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Optional 24hr Cough assessment substudy[12]		X				X	
IRT call/notification	X	X		X	X	X	
All AEs/SAEs/AESIs****	X	X	X	X	X	X	X
Compliance check			X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X
Completion of patient participation							X

1. Visit 1 (screening) is expected to be conducted in the 30 days prior to Visit 2 (randomisation), considering the time for HRCT central review. This period may be extended up to 44 days in case of administrative issue (eg result from HRCT central reading not available). If Visit 2 cannot be performed in this extended timeframe, the patient will have to be screen failed.

2. Before or at the latest at Visit 1. Informed consent (IC) needs to be signed before any procedure related to the trial is performed, including HRCT review. All adverse events (AEs) and concomitant therapies (CTs) from the day of signing informed consent have to be recorded.
3. Safety laboratory parameters will be evaluated at each visit, pre dose. This will include blood and urine collection.
4. All ECGs will be performed pre dose.
5. [redacted]
6. Order of lung function measurements: 1. Spirometry followed by patients rest; 2. DLCO. Measurements have to be performed at the same time each visit ± 90 min (reference time at Visit 2).
7. At Visit 1, the C-SSRS version to be used is the screening one. At all other Visits, starting at Visit 2, the version of C-SSRS to be used is the version "since last Visit".
8. [redacted]
9. Review of high resolution computer tomography (HRCT). Central review: a historical HRCT not older than 12 months should be sent; only if the patient does not have a HRCT within 12 months at Visit 1, or the available HRCT does not meet the required image acquisition specifications and patient meets all other inclusion and no exclusion criteria, screening HRCT can be performed as part of the study. To perform an HRCT within the trial, all local regulatory requirements to perform an HRCT has to be met. In Germany, no HRCT will be performed as a trial procedure, only historical HRCT will be submitted.
10. [redacted]

12. For the 24hr cough assesmentsubstudy, the patients will have to sign a separate informed consent at Visit 2.

(*) Day of Randomisation / Day of first intake of randomised medication.

(**) Patients who discontinue trial treatment prematurely should still follow the trial schedule, if possible, please see section 3.3.4.

(***) Measurements of vital signs should precede blood sampling

(****) After the EoTrial visit (=individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI SAE form, please see section.5.2.6.2.1.

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[redacted]

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
C_{max}	Maximum Concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRO	Contract Research Organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
DLCO	Diffusion capacity of the lung for carbon monoxide
DMC	Data Monitoring Committee
DNA	DesoxyriboNucleic Acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoT	End of Treatment
EoTrial	End of Trial
ESR	Erythrocyte Sedimentation Rate

ES	Entered Set
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in one second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GI	Gastro Intestinal
GMP	Good Manufacturing Practice
HA	Health Authority
HR	Heart Rate
HRCT	High Resolution Computed Tomography Scan
HV	Healthy Volunteers
IB	Investigator's Brochure
IC50	half maximal Inhibitory Concentration
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
iPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
[redacted]	[redacted]
[redacted]	[redacted]
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed effect Model Repeat Measurement
MRD	Multiple Rising Dose
mRNA	Messenger RiboNucleic Acid

[redacted]	[redacted]
OPU	Operative Unit
PDE	Phosphodiesterase
PI/IC	Patient Information/Informed Consent
[redacted]	[redacted]
[redacted]	[redacted]
PoC	Proof of Concept
PPS	Per Protocol Set
[redacted]	[redacted]
[redacted]	[redacted]
RA	Regulatory Authority
REP	Residual Effect Period
RMP	Risk Management Program
RNA	RiboNucleic Acid
RS	Randomised Set
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
t_{max}	Timepoint of Maximum Plasma Concentration
TEAE	Treatment Emergent Adverse Events
TK	Toxicokinetic
TNF	Tumor Necrosis Factor
TS	Treated Set
TSAP	Trial Statististical Analysis Plan
ULN	Upper Level of Normal
UIP	usual interstitial pneumonia
[redacted]	[redacted]
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

BI 1015550 is a selective inhibitor of the Phosphodiesterase 4 B (PDE4 B) with broad anti-inflammatory and anti-fibrotic activities. It is under development for the treatment of idiopathic pulmonary fibrosis (IPF).

1.1 MEDICAL BACKGROUND

IPF is a progressive, fibrosing interstitial lung disease (ILD) characterized by decline in lung function and worsening dyspnea [R18-2794]. IPF carries a poor prognosis, with a median post-diagnosis survival in untreated patients of approximately 3 years [R18-1413].
IPF occurs worldwide. The prevalence of the disease appears to be increasing, although it is unclear whether this reflects increased recognition or a true increase in incidence. The incidence of IPF appears to be higher in North America and Europe (3 to 9 cases per 100,000 person-years) than in South America and East Asia (fewer than 4 cases per 100,000 person-years) [R17-4284]. In the United States, the prevalence of IPF has been reported to range from 10 to 60 cases per 100,000 [R16-1737], [R18-0408], [R14-2284]. Increasing rates of hospital admissions and deaths due to IPF also suggest an increasing burden of disease [R17-4284], [R14-4266], [P13-05880].

Nintedanib and pirfenidone are the only drugs registered for the treatment of IPF and recommended in the recent ATS/ERS/JRS/ALAT Clinical Practice Guideline for the Treatment of Idiopathic Pulmonary Fibrosis [R18-2794]. Despite the availability of these drugs, the medical need remains high in this devastating disease.

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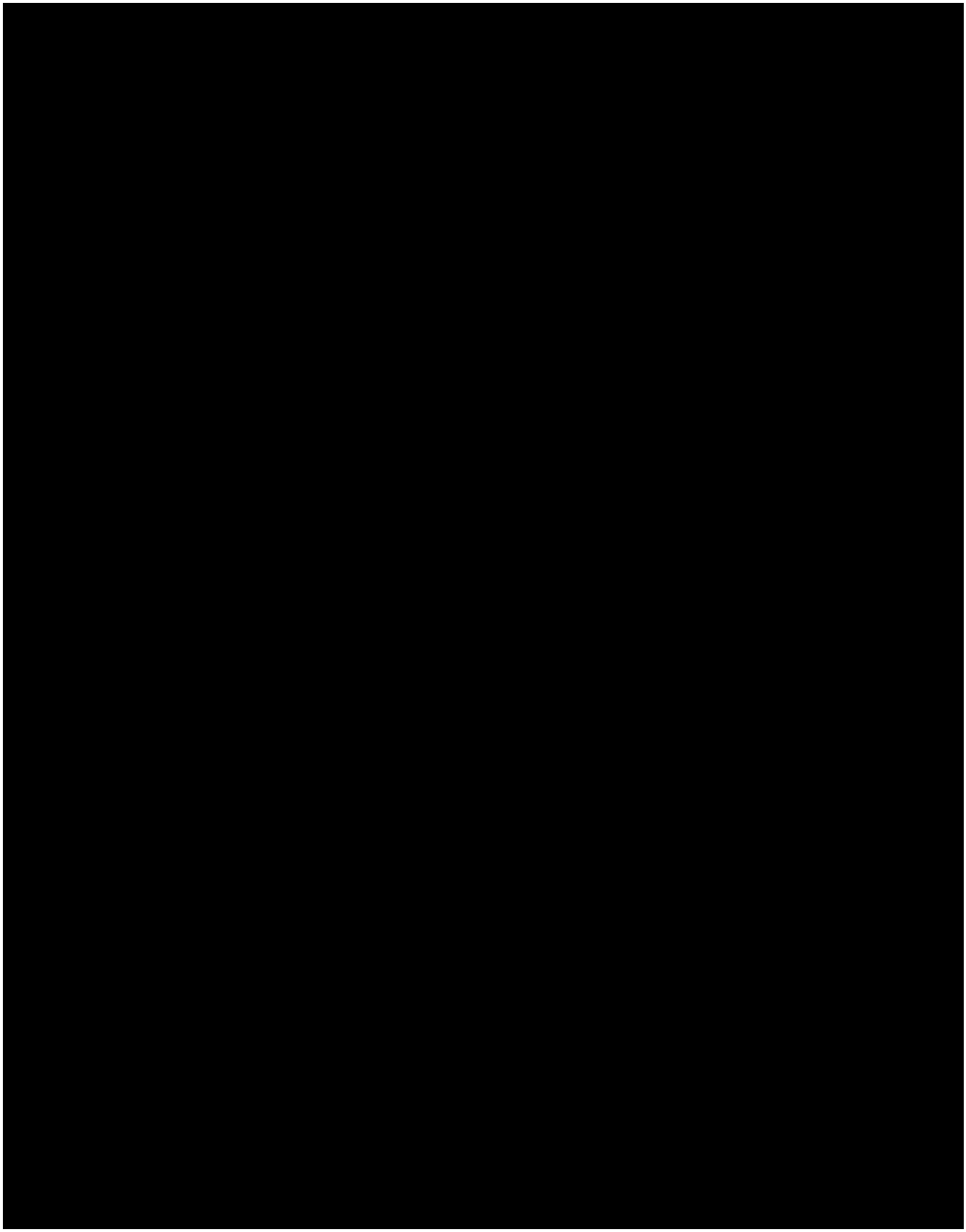
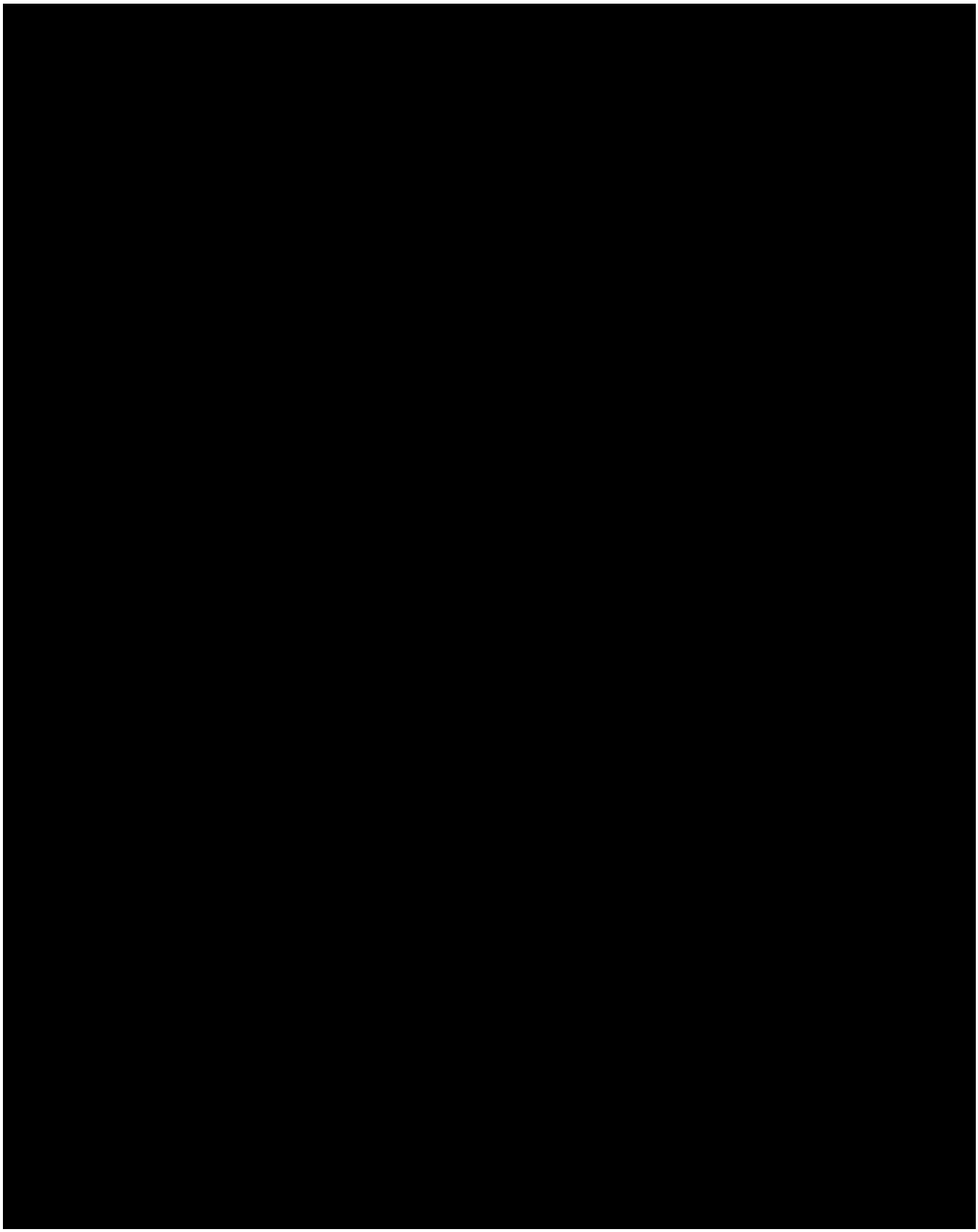
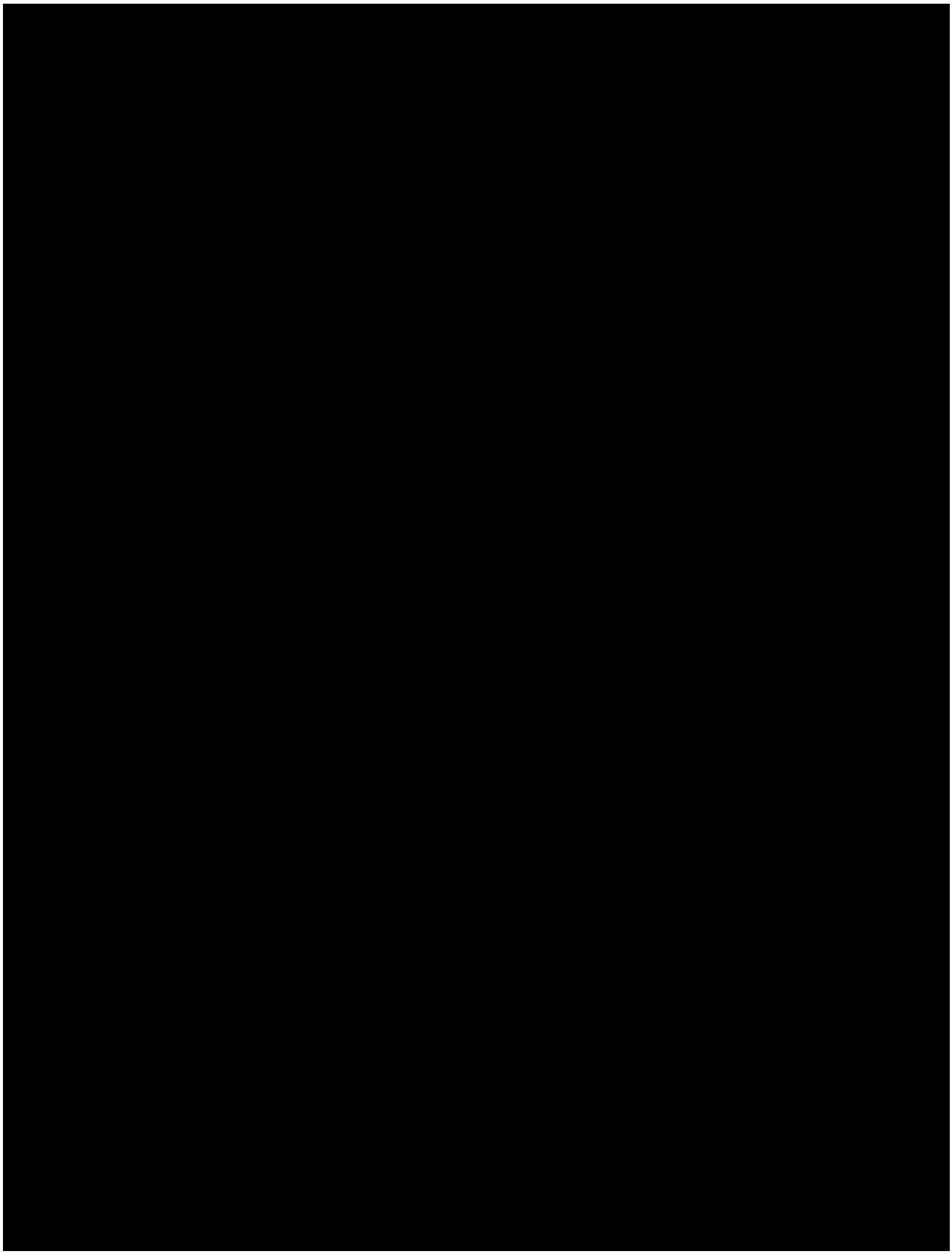






1.3 RATIONALE FOR PERFORMING THE TRIAL

This phase II trial will investigate the efficacy of BI 1015550 18 mg b.i.d. by comparing the change from baseline in FVC after 12 week of treatment compared to placebo. This trial will also evaluate the safety of BI 1015550 over 12 weeks compared to placebo where antifibrotic background treatment is introduced for the first time in the BI 1015550 clinical programme.

BI 1015550 will be evaluated as a stand-alone in patients on no background antifibrotic treatment and in addition to antifibrotic treatments, i.e. this trial will include patients with or without approved and available antifibrotic treatment (nintedanib or pirfenidone) at baseline and during the study.

As per the 1305-0012 Phase Ic study, the 12 weeks treatment duration is being adequately supported by the 13 weeks toxicology data.

Overall, the Proof of Concept (PoC) of this trial is primarily based on the efficacy results of the treatment group not on antifibrotics. PoC and safety of the overall study population of this trial will be used to inform the phase III program.

New treatments are needed that further reduce the decline in FVC, positively affect symptoms and improve quality of life in patients with IPF.

Overall, due to the in vitro/in vivo activity of BI 1015550 both in anti inflammatory and anti-fibrotic assays/models, BI1015550 is hypothesized to have complementary activity (on myofibroblast transformation) to current antifibrotic therapies in IPF and a synergistic effect

in combination with nintedanib on fibroblast proliferation if BI 1015550 is shown to be safe and well tolerated when combined with approved antifibrotics.
Please refer to section 1.4.1 for further details.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Preclinical experiments have shown that BI 1015550 affects the fibrotic pathway and the effects may be complementary and/or synergistic to those of nintedanib. Based on this, it is postulated that BI 1015550 may provide therapeutic benefit to patients with IPF or other progressive fibrosing ILDs but this has not yet been determined clinically [c02094779].

Due to the limited short treatment duration in this study, only patients on no background antifibrotic treatment may have an improvement of FVC versus baseline. Nevertheless, patients' participation in this 12 weeks trial in IPF patients with or without background antifibrotic therapy treated with BI 1015550, 18 mg b.i.d. is of utmost importance to investigate the safety, tolerability, efficacy [redacted] of BI 1015550 when administered alone or on background antifibrotic treatment prior to progressing to longer term treatment Phase III to show an effect on FVC decline in the overall IPF population.

Two PDE4 inhibitors are marketed with indications of psoriasis and chronic obstructive pulmonary disease (COPD). Studies conducted in non-human primates with both marketed compounds suggest that primates are less sensitive than rats to PDE4i-associated toxicity. No adverse vascular changes in humans have been reported.

Overall, BI 1015550 is expected to be safe and well tolerated with an improved tolerability compared to other marketed PDE4 inhibitors due to lower affinity for PDE4 D.

1.4.2 **Risks**

Table 1.4.2: 1 Overview over trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 1015550		
Pharmacokinetic interaction with strong CYP3A4 inhibitors	CYP450 3A4 is regarded as the major enzyme responsible for BI 1015550 metabolism in human hepatocytes. CYP3A is predicted to contribute to ~70% of the hepatic metabolism of BI 1015550. In a drug drug interaction trial, the strong CYP 3A4 inhibitor (itraconazole) increased the exposure to BI 1015550 by 1.3-fold (Cmax) and 2.2-fold AUC.	Potent CYP3A inhibitors are restricted medication.
Safety in addition of marketed antifibrotic treatments	At the start of this 12 weeks treatment trial, no safety data will be available on BI 1015550 given in addition to marketed antifibrotics.	DMC will be in place to assess the entire safety data on an ongoing basis.
Vasculitis	Vasculopathy is an established toxicity of PDE4 inhibitors in rats. Vasculitis has been shown in both the rats and minipigs following oral administration of BI 1015550 and it has been the basis of the NOAEL (No Observable Adverse Effect Level) definition. Vasculitis is listed as an important potential risk in the RMP for the marketed PDE4- inhibitors apremilast and roflumilast. In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans.	Baseline condition or medical history of vasculitis is an exclusion criterion. Patient's withdrawal in case of any vasculitis adverse event considered drug related or not. Increased awareness and expedite reporting (AESI).
Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, abdominal pain)	Vomiting and diarrhea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. Gastrointestinal disorders are very common or common side effect of the approved antifibrotics.	Increased awareness of symptoms. Careful monitoring of hydration in patients with diarrhoea is recommended. Management strategies as described in approved labels have to be followed.

Table 1.4.2: 1 Overview over trial related risks (cont'd)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		Treatment interruption/discontinuation is left at the investigator's discretion.
Reproductive toxicity	Specific studies to evaluate the potential for BI 1015550 to affect male and female fertility and developmental toxicity have not yet been conducted.	Women of childbearing potential are excluded from the trial. Contraception requirements for men able to father a child.
Weight decrease in underweight patients (BMI < 18.5 kg/m2)	For the marketed PDE4-inhibitors apremilast and roflumilast weight loss in underweighted patients is identified as an important risk.	Body weight evaluated at each visit. Patients who have a BMI <18.5 kg/m2 at visit 2, and subsequently experience unexplained and clinically significant weight loss (>10%) will be discontinued from trial treatment.
Suicidality	Two of the currently marketed PDE4 inhibitors are associated with increased risk of depression with some patients reporting suicidal ideation and attempts and also reported cases of completed suicide.	Any suicidal behaviour in the past 2 years and any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Ranking Score (C-SSRS) in the past 3 months or at Visit 1 are exclusion criteria. Prospective suicidality monitoring, will be performed throughout this trial using the C-SSRS. Patient's withdrawal criteria in case of suicidal behaviouror any suicidal ideation of type 4 or 5 in the C-SSRS.

Table 1.4.2: 1 Overview over trial related risks (cont'd)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Drug-induced liver injury (DILI)	Rare but severe event, standard topic of interest for products in development thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. Increased awareness and expedite reporting (AESI).
Trial procedures		
Blood Sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as - close clinical monitoring for AEs; - selection of experienced sites and site staff.
HRCT	The more radiation is received over the course of a life, the greater risk of having cancerous tumors or of inducing changes in genes. The changes in genes possibly could cause abnormalities or disease in future offspring. The radiation in this trial is not expected to greatly increase these risks, but the exact increase in such risks is not known.	HRCT only required in case no historical one (less than 12 months) is available or in case of insufficient quality. These risks will be addressed by careful safety monitoring and risk mitigation measures such as - close clinical monitoring for AEs; - selection of experienced sites and site staff.

Table 1.4.2: 1 Overview over trial related risks (cont'd)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Lung function measurements (Spirometry and DLCO)	Risks and discomforts associated with lung function testing may include shortness of breath, dizziness, or headache during the breathing tests.	These risks will be addressed by careful monitoring and risk mitigation measures such as - close clinical monitoring for AEs; - selection of experienced sites and site staff; - training from vendor to conduct correct manoeuvre.
Other risks		
Administration of Placebo	If the patient is randomised to receive a placebo, the patient´s condition could get worse during the course of the trial.	The placebo treatment until Week 12 is deemed acceptable from an ethical perspective.
SARS CoV-2 infection	Based on the pharmacological mechanism and existing non-clinical and clinical data there is no indication that treatment with BI 1015550 may increase the risk of severe clinical courses of SARS-COV-2 infection. However, patients with IPF may be at risk of severe clinical courses due to the underlying chronic progressing lung fibrosis, associated co-morbidities and potential use of immunosuppressive co-medications.	Even though an increased risk of SARS-CoV-2 infection – or of a more severe COVID-19 disease in case of such an infection appears unlikely, patients with active or recent SARS CoV-2 infection will not be included in the trial (see section 3.3.3). In addition, during the course of the trial, treatment with BI 1015550 will be discontinued in case of a confirmed SARS-CoV-2 infection (refer to section 3.3.4.1)

1.4.3 **Discussion**

Treatment with BI 1015550 has the potential to provide significant benefit to patients with IPF by ultimately slowing lung function decline, improving burdensome symptoms and quality of life over a long term period.

The purpose of this 12 week Phase II trial is to investigate the efficacy and safety of BI 1015550 and provide proof of concept of clinical activity for further progression to Phase III.

The available results of completed Phase I and Phase I C trials in HVs and IPF patients respectively,show a favorable safety profile at single doses tested up to 48 mg in HVs and at up to 18 mg b.i.d in multiple doses tested for up to 12 weeks in IPF patients.

In this trial, the dose of 18 mg b.i.d. administered orally for 12 weeks is considered appropriate from both a preclinical (i.e supported by the 13 weeks toxicology data) and clinical point of view, consequent to the benign safety profile to date.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

- To investigate the efficacy of BI 1015550 compared to placebo based on the change from baseline in Forced Vital Capacity (FVC).
- To investigate safety and tolerability of BI 1015550 in the overall trial population.

2.1.2 Primary endpoints

The primary endpoint is the change from baseline in FVC at 12 weeks (in mL).

2.1.3 Secondary endpoint

The percentage N (%) of patients with Treatment Emergent Adverse Events (TEAE).

[redacted]

[redacted]

2.2.2.2 Safety endpoints

Safety and tolerability

Further criteria of interest to evaluate the safety and tolerability of BI 1015550:

- ∀ Change in C-SSRS (Columbia Suicidal Severity Rating Scale) over time.
- ∀ Change from baseline in weight over time.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This phase II trial is a double-blind, placebo-controlled comparison of BI 1015550 18 mg b.i.d over 12 weeks in patients treated with antifibrotic treatment or not treated with antifibrotic treatment at baseline.

Patients randomised into the trial will be treated for 12 weeks. The patients will be included in the trial and during the screening period (up to 44 days), the eligibility criteria will be assessed. After this period, the eligible patients will be randomised in the trial in a 2:1 ratio (BI 1015550 18 mg b.i.d/ placebo b.i.d).
Patients will be proposed an optional substudy (restricted to some sites/countries). To participate, patient will be proposed to sign a dedicated informed consent. More details about this substudy can be found in section 5.6.

After the patients have terminated their treatment period, they will enter a 1-week follow-up period. Follow up visit will be the End of Trial.
In case of early treatment discontinuation, the patient is expected to follow the trial schedule as per protocol.

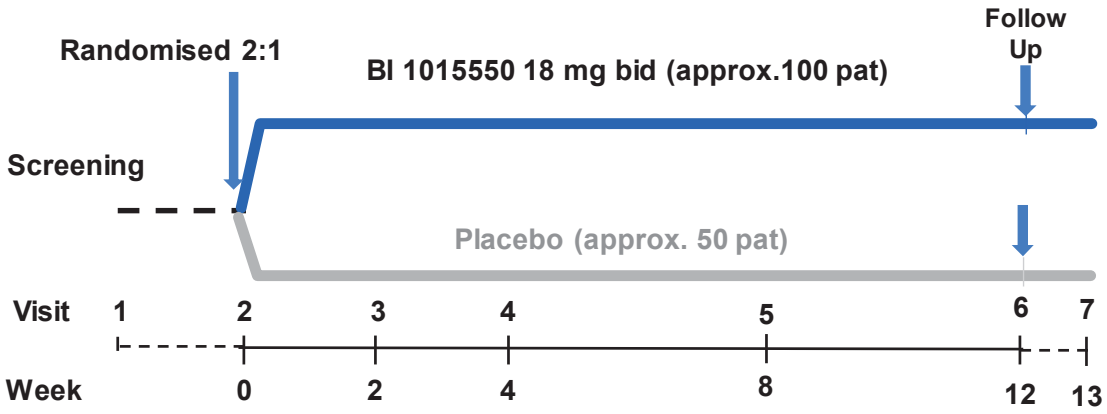


Figure 3.1:1 1305-0013 Study Design Overview

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

At the time of writing the protocol of this trial, the 1305-0012 trial has assessed the safety of BI 1015550 18 mg b.i.d over 4 to 12 weeks in 15 IPF patients not on antifibrotic treatment.

This trial is a placebo-controlled randomised trial to provide the most robust results and is thus considered the most appropriate design. However, whilst in situations where effective therapies are available and a placebo-controlled trial could be considered not to be ethical, there is currently no approved pharmacotherapy that can finally stop the FVC decline and the

impact on Quality of Life and premature death in these patients. In addition, none of the currently available treatments has shown a consistent effect on cough and dyspnea, the most debilitating symptoms in these patients.

A total minimum of 60 patients per group (with or without antifibrotic treatment) are included in this study with up to 150 patients in total with an unequal allocation ratio (1:2) selected for the placebo and the BI 1015550 treatment group. The usage of an unequal allocation ratio is explained by the incorporation of historical data from the nintedanib development program in IPF (via Bayesian borrowing). This approach leads to a better precision, while reducing the number of required patients on placebo at the same time and increasing the number of patients treated on BI 1015550 for the safety assessment.

A 12 weeks treatment duration is sufficient to observe differences in FVC change from baseline versus placebo in the patient group not on background antifibrotics. The duration is considered too short to assess changes from baseline in FVC versus placebo in the patient group on antifibrotic treatment. 12 weeks of treatment will be informative on safety and tolerability in both treatment groups.

This is a PoC trial and the 18mg bid dose is tested in order to show PoC as this was the highest tested dose in 1305.12.

Details of the statistical approach including a sample size justification are given in Section 7.

FVC has been choosen as primary endpoint as this is the only clinical endpoint approved by authories to assess disease status and progression.

A DMC will assess safety and tolerability during the course of the trial by performing a check of the entire safety data on an ongoing basis.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of male and female patients with a confirmed diagnosis of IPF will be screened in order to ensure the randomisation of approximately 150 patients.

This trial will include IPF patients treated with SoC which includes antifibrotic treatment with nintedanib or pirfenidone or no background antifibrotic treatment. At least 60 patients on antifibrotic background treatment and 60 patients not on antifibrotic treatment will be included in the trial. If necessary, recruitment of one group will be stopped in order to achieve this. The randomisation of patients will be stratified according their antifibrotic treatment background status at baseline.

Only male patients and postmenopausal or surgically sterilised female patients will be included into the study because hitherto no data on reproductive toxicology are available.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional

patients for this trial. Patients in screening at this time will be allowed to continue to randomisation if eligible.

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

Patients who do not meet all inclusion criteria or meet one or more exclusion criteria should not be randomized into the trial.
If a patient was randomized in error (did not meet all inclusion criteria or met one or more exclusion criteria on the day of randomization), the sponsor should be contacted immediately to reach a decision on treatment discontinuation or continuous trial participation based on individual benefit-risk assessment.

3.3.1 Main diagnosis for trial entry

Patients diagnosed with IPF and who comply with eligibility requirements may qualify for participation in the trial.

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 aged ≥40 years when signing the informed consent.
2. Diagnosis : for detailed specifications see also Appendix 10.5)
    a. IPF based on 2018 ATS/ERS/JRS/ALAT Guideline [R18-2794] as confirmed by the investigator based on chest HRCT scan taken within 12 months of Visit 1 and if available surgical lung biopsy.

       and

    b. UIP or probable UIP HRCT pattern consistent with the clinical diagnosis of IPF, as confirmed by central review prior to Visit 2*

       *if indeterminate HRCT finding IPF may be confirmed locally by (historical) biopsy
3. Stable for at least 8 weeks prior to Visit 1. Patients have to be either :

    ∀ not on therapy with nintedanib or pirfenidone for at least 8 weeks prior to Visit 1 (combination of nintedanib plus pirfenidone not allowed), or

    ∀ on stable* therapy with nintedanib or pirfenidone for at least 8 weeks prior to Visit 1 and planning to stay stable on this background therapy after randomisation.

    [*stable therapy is defined as the individually and general tolerated regimen of either pirfenidone or nintedanib]
4. Forced Vital Capacity (FVC) ≥45% of predicted normal at Visit 1
5. DLCO (corrected for haemoglobin [Hb] [Visit 1]) ≥ 25% to < 80% of predicted normal at Visit 1.

6. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

3.3.3 Exclusion criteria

1. Relevant airways obstruction (pre-bronchodilator FEV1/FVC < 0.7) at Visit 1.
2. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
3. Acute IPF exacerbation within 4 months prior to screening and/or during the screening period (investigator-determined).
4. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to Visit 1 and/or during the screening period.
5. Major surgery (major according to the investigator's assessment) performed within 3 months prior to Visit 1 or planned during the course of the trial. (Being on a transplant list is allowed).
6. Any documented active or suspected malignancy or history of malignancy within 5 years prior to Visit 1, except appropriately treated basal cell carcinoma of the skin, "under surveillance" prostate cancer or in situ carcinoma of uterine cervix.
7. Evidence of active infection (chronic or acute) based on clinical exam or laboratory findings (see table 5.2.3 :1) at Visit 1 or at Visit 2.
8. Any suicidal behaviour in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior).
9. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1 (i.e. active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan).
10. Baseline condition or medical history of vasculitis.
11. AST or ALT > 1.5 x ULN or total Bilirubin > 1.5 x ULN at Visit 1.
12. eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula or Japanese version of CKD-EPI for Japanese patients) ≤45 ml/min/1.73 m2 at Visit 1.

[Note: Laboratory parameters from Visit 1 have to satisfy the laboratory threshold values as shown above. Visit 2 laboratory results will be available only after randomisation. In case at Visit 2 the results do no longer satisfy the entry criteria, the Investigator has to decide whether it is justified that the patient remains on study drug. The justification for decision needs to be documented. Laboratory parameters that are found to be abnormal at Visit 1 are allowed to be re-tested (once) if it is thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there is no related clinical sign) or the result of a temporary and reversible medical condition, once that condition is resolved].

13. Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment).
14. Cardiovascular diseases, any of the following:
    a. Severe hypertension (uncontrolled under treatment ≥160/100 mmHg at multiple occasions) within 3 months of Visit 1
    b. Myocardial infarction within 6 months of Visit 1
    c. Unstable cardiac angina within 6 months of Visit 1
15. History of thrombotic event (including stroke and transient ischemic attack) within 6 months of Visit 1.
16. Surgery of the GI tract [redacted] (except appendectomy or simple hernia repair).
17. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1 and appendix 10.8) eg. strong CYP3A4 inhibitor, prednisone >15mg/day or any drug considered likely to interfere with the safe conduct of the trial

18. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled.
19. Previous randomisation in this trial.
20. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s).
21. In the opinion of the Investigator, active alcohol or drug abuse.
22. Inability to refrain from smoking on trial days.
23. Male patients who do not agree to minimize the risk of female partners becoming pregnant from first dosing day until 3 months after the study completion. Acceptable methods of contraception comprises barrier contraception and a medically accepted contraceptive method for the female partner (intra-uterine device with spermicide, hormonal contraceptive used for at least two months prior), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), or surgically sterilized, including vasectomy.
24. Women who are not surgically sterilised or who are not postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of Follicle-stimulating hormone (FSH) above 40 U/L and estradiol below 30 ng/L is confirmatory).
25. History of allergy or hypersensitivity or contraindications to the class of drugs under study including known hypersensitivity to the drug or its excipients.
26. Patients with a significant disease or condition other than IPF which in the opinion of theinvestigator, may put the patient at risk because of participation, interfere with study procedures, or cause concern regarding the patient's ability to participate in the study or any medical condition which could lead to a life expectancy <12months
27. The patient has a confirmed infection with SARS-CoV-2 within the 4 weeks prior to Visit 1 and/or during the screening period.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.2.1 and 5.2.6.2.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

∀ The patient wants to discontinue trial treatment, without the need to justify the decision.
∀ 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 adhere to the trial requirements in the future.
∀ The patient experiences unacceptable adverse events in the opinion of the investigator.
∀ The patient fulfills the AESI definition of hepatic injury (see section 5.2.6.1.6).
∀ The patient experiences an infection with SARS-CoV-2.
∀ The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment (see section 4.2.2).
∀ The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy). The patient exhibits serious suicidality, in the clinical judgment of the investigator or according to the following criteria:
  - any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
  - any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)
∀ The patient shows any vasculitis adverse event considered drug related or not.
∀ **For patients with a BMI<18,5 kg/m^2 at Visit 2 only :** unexplained and clinically significant (>10%) weight loss.
∀ The patient shows clinically relevant changes in ECG requiring intervention.
∀ The patient shows a QTc>500 ms in ECG.

In case of a temporary reason, trial treatment should be restarted if medically justified, please see section 4.1.4.
If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.
If the trial treatment is discontinued, the patients remain in the trial if possible and should still follow the trial schedule as outlined in the Flow Chart and section 6.2.3. Follow up Visit can be skipped in case the following Visit after the end of treatment is planned at least 7 days after the last drug intake.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 3.3.4.1 above.

3.3.4.3 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. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in section 3.3.4.1.
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

The investigational product has been manufactured by BI Pharma GmbH & Co. KG or a qualified vendor (placebo).

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Table 4.1.1:1 BI 1015550 6 mg

Substance:	BI 1015550
Pharmaceutical formulation:	film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	6 mg
Posology:	b.i.d
Mode of administration:	Oral

Table 4.1.1:2 Placebo matching BI 1015550 6 mg

Substance:	Placebo matching in size, weight, colour and shape to 6 mg tablet of BI 1015550
Pharmaceutical formulation:	film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a
Posology:	b.i.d
Method and route of administration:	Oral

Table 4.1.1: 3 BI 1015550 12 mg

Substance:	BI 1015550
Pharmaceutical formulation:	film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	12 mg
Posology:	b.i.d
Method and route of administration:	Oral

Table 4.1.1: 4 Placebo matching BI 1015550 12 mg

Substance:	Placebo matching in size, weight, colour and shape to 12mg tablet of BI 1015550
Pharmaceutical formulation:	film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a
Posology:	b.i.d
Method and route of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

Doses equal and above 12 mg b.i.d of BI 1015550 are assumed to be effective doses based on pre-clinical in vitro data from human IPF fibroblast proliferation and fibroblast-to-myofibroblast transition experiments.
These experiments showed IC50‘s of 210 – 250 nM for mono and 23–110 nM for synergistic action with nintedanib. Also, the clinical total coverage (at steady state) is equal or above the fibroblast IC50‘s, using doses equal or above 12 mg b.i.d (actual and modelled data, assuming that total concentrations of BI 1015550 are driving the desired effect).

This assumption is supported by clinical indirect target engagement ex vivo (LPS (Lipopolyssacharide)-stimulated TNF(tumor Necrosis factor)-α and IFN (interferon)-γ release), which may not be directly linked to an anti-fibrotic action, but can be linked to an anti-inflammatory action on macrophages and T cells in IPF. A substantial and significant

indirect target engagement was shown in 1305-0011 phase I trial using 12 mg b.i.d dose and 36 mg and 48 mg single doses.
Nintedanib, pirfenidone and BI 1015550 are effective in animal models of bleomycin induced lung fibrosis. Comparison of efficacious exposure levels in animals for the two marketed anti-fibrotics with the reached clinical exposure indicates an approx. 5-fold higher necessary exposure in the animal bleomycin studies.

Assuming that this 5-fold pre-clinical over-prediction is also relevant for BI 1015550 this leads to a predicted human efficacious dose of BI 1015550 in IPF of 12–15 mg b.i.d.

Taking together, therefore the maximum dose of 18 mg b.i.d is expected to be a therapeutic dose. This dose was tested in trial 1305-0012 in 15 IPF patients not on background antifibrotic treatment, administered for 4 to 12 weeks which was supported by the 13 weeks rat and minipig toxicology data.

In 1305-0012 trial, the preliminary results show geometric mean $C_{max,ss}$ and $AUC_{\tau,ss}$ values of 460 nM and 3720 nM·h reached respectively for BI 1015550 within the 18 mg dose group with good safety and tolerability of BI 1015550 18 mg b.i.d. in 15 IPF patients not on background antifibrotic treatment.

In this Phase II trial (1305-0013), the exposure in IPF patients at the planned dose of 18 mg b.i.d is expected:

a) to fall within range of the estimated therapeutic range and
b) to be below the pre-defined maximal acceptable human systemic exposure limit as defined in trial 1305-0012 on the basis of the 13 weeks rat toxicology data.

In addition, based on the current knowledge on BI 1015550 preclinical evaluation no significant DDI interactions neither between BI 1015550 and nintedanib, nor between BI 1015550 and pirfenidone are expected.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria by the investigator and/or his/her staff, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 2:1 ratio at Visit 2 via Interactive Response Technology (IRT). Note that the medication number is different from the patient number.

The randomisation will be stratified according the background status of the patient (either treated or not treated with antifibrotic treatment).

Each patient fulfilling all in- and exclusion criteria will be randomised via IRT at Visit 2 to one of the 2 following arms in a 2:1 ratio:

- ∀ BI 1015550 18 mg b.i.d
- ∀ Placebo b.i.d

4.1.4 Drug assignment and administration of doses for each patient

The patient will be treated starting at Visit 2 for 12 weeks (until Visit 6).

Table 4.1.4: 1 Dosage and treatment schedule

Treatment arm	BI 1015550 6 mg tablet	Placebo matching 6 mg tablet	BI 1015550 12 mg tablet	Placebo matching 12 mg tablet
	To be taken twice daily, in the morning and in the evening			
18 mg	1		1	
Placebo		1		1

Based on the treatment allocated at randomisation, the IRT system will be used to dispense the appropriate medication kits at each visit.

Medication is packaged in wallet containing 4 times 4 blisters stripes of 7 tablets each, each containing 28 film-coated tablets so 112 films-coated tablets per wallet to cover 4 weeks treatment. To ensure patients receive adequate supply of study medication, kits will be dispensed at clinic visits in quantities as outlined in table 4.1.4: 2

Table 4.1.4: 2 Number of IMP kits dispensed at each visit

Study Visits	2	3	4	5
Number of IMP kits dispensed	1+1*		1	1

*: the second kit dispensed at Visit 2 is a reserve kit to cover the time windows at each visit. It will be brought back at each visit by the patient to calculate the compliance and then returned to the patient unless it is empty. When less than 7 tablets left in the kit or when expiry date approaches, the site should perform an additional IRT call to allocate a new kit as reserve.

The patients should swallow the trial medication (“sun” column for the morning, “moon” column for the evening intake) together with a glass of water (~250 mL), and should observe a dose interval of 12 hours. Effort should be made to ensure that drug administration occurs at the same time every day +/- 30 min (between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening).

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.

The investigational product should only be dispensed to participating patients according to the protocol by authorised personnel as documented in the ISF.

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication may be

shipped to the patient's home if acceptable according to local law and regulations (for more details see section 6.2.2).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis (except bioanalytics and possibly DMC members) or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The access to the randomisation code will be kept restricted until its release for analysis. The randomisation codes will be provided to bioanalytics to allow samples from placebo patients to be excluded from the analyses of pharmacokinetic (PK) samples. Bioanalytics will not disclose the randomisation code, which patients have been tested or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).
Re-supply to the sites will be managed via an IRT system, which 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.

4.1.7 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 Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- ∀ Approval of the clinical trial protocol by the IRB / ethics committee, HA / RA approval.
- ∀ Availability of a signed and dated clinical trial contract between the sponsor and 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,
- ∀ Availability of the proof of a medical license for the Principal Investigator,
- ∀ Availability of FDA Form 1572 (if applicable).

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 or designee 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 warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the appointed CRO, the investigator or designee 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

There are no special emergency procedures to be followed.

Temporary treatment interruption for up to one week is allowed to manage adverse events (such as GI events, need to take restricted medication etc…) will be documented on the respective eCRF page.

A maximum total duration of interruptions of 2 weeks is allowed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate eCRF page.

Marketed antifibrotic treatment (nintedanib or pirfenidone) is allowed at baseline when stabilised according to eligibility criteria and is expected to be stable throughout the trial.

Temporary antifibrotics interruption/dose reduction are left at the discretion of the investi gator eg to manage gastrointestinal effects.

Table 4.2.2.1:1 Restricted medication

Medication	**Prior to Study**	**Screening Period**	**Treatment period**	**Follow up period**
Potent CYP3A inhibitors	Permitted	Not permitted	Not permitted	Permitted
Nintedanib/Pirfenidone if stable at Visit 1 (refer to inclusion 3)	Permitted	Permitted	Permitted	Permitted
Nintedanib/Pirfenidone for patients not on antifibrotic treatment at Visit 1	Not permitted[1]	Not permitted	Not permitted	Permitted
PDE inhibitors[2]	Not permitted[2]	Not permitted	Not permitted	Not permitted
Prednisone>15mg/day or equivalent	Permitted	Not permitted[3]	Not permitted[4]	Permitted

Footnotes to restricted medication Table 4.2.2.1:1

1. Not permitted during the 8 weeks prior to screening visit (Visit 1)
2. This covers non selective PDE inhibitors as well as PDE1, PDE3, PDE4 and PDE10 inhibitors. Not permitted 30 days prior to randomisation (Visit 2).
3. Not permitted during the 2 weeks prior to randomisation (Visit 2).
4. Prednisone >15mg/day or equivalent can be prescribed during the treatment period in case of acute exacerbation as described in section 5.2.6.1.5. Table of equivalent doses of corticosteroids can be found in Table 10.7: 1

Lists of potent CYP3A inhibitors and PDE inhibitors can be found in Appendix 10.8.

4.2.2.2 Restrictions on diet and life style

Patients should refrain from consuming Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) in the 24 h preceding each on site visit. Patients should also refrain drinking grapefruit juice during the course of the trial.

4.2.2.3 Contraception requirements

Men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 3 months after last trial drug intake : one barrier method, and one highly effective non-barrier method.

Men (trial participant or partner of a trial participant) must be vasectomised with documented absence of sperm or use a condom if their sexual partner is a WOCBP.
WOCBP (partner of a trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child.

- ∀ Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral [approved in Japan], intravaginal [unapproved in Japan], transdermal[unapproved in Japan]).
- ∀ Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable) [unapproved in Japan].
- ∀ Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- ∀ Bilateral tubal occlusion.

Or:
Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

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

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \exists 100}{\text{Number of tablets which should have been taken as directed by the investigator}}$$

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 FVC

FVC and FEV1 will be assessed using standardised spirometry equipment which will be provided centrally with supplies of pre-calibrated disposable flow sensors. These sensors demonstrate variability within the required standards of +/-3% determined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [P05-12782]. As such there is no need to conduct daily calibration prior to use.
Efforts should be made, to schedule the spirometric measurements at approximately the same time of the day at each visit ± 90 min , with reference to baseline measurement (Visit 2). On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odours (e.g. perfumes). If treated with bronchodilators, wash-out of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry.

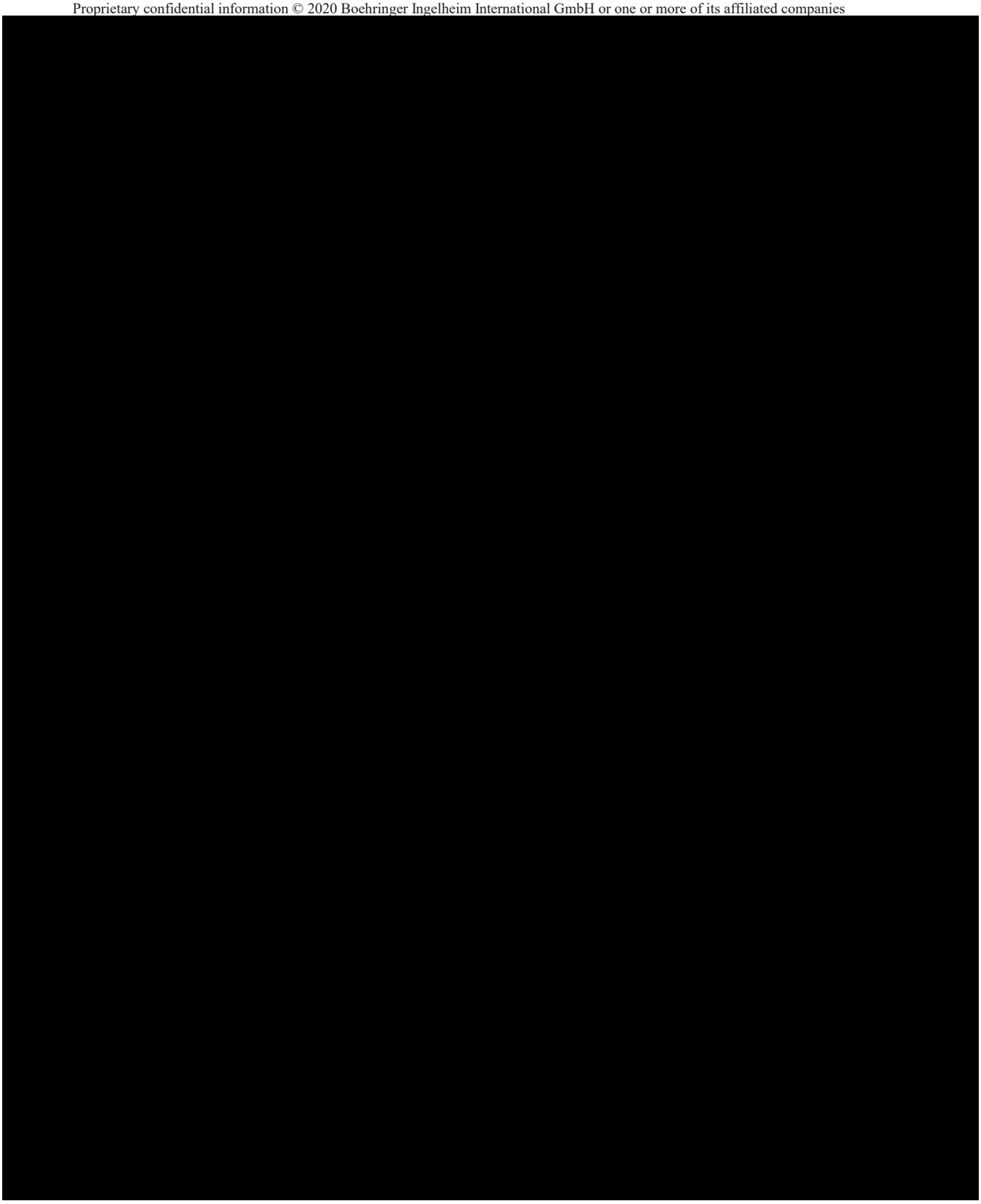
Spirometry will be conducted while the patient is in a seated position. . It is preferable that the same trained individual performs the PFTs for a given patient. The best of three efforts will be defined as the highest FEV1 and the highest FVC each obtained on any of three blows meeting the ATS/ERS criteria **(with a maximum of eight attempts).** Spirometry results captured by spirometers provided by the sponsor will be electronically transmitted and confirmed by central reading.

5.1.2 DLCO

The site will use its own equipment to assess carbon monoxide diffusion capacity during the single breath diffusion test and conduct all measurements with the same equipment. Single breath diffusion test will be carried out according to the ATS/ERS guidelines [R06-2002]. Before the test the maneuvers should be demonstrated and the patient carefully instructed. The mean value between at least two acceptable tests should be reported. Please refer to appendix 10.3 for additional information.

For each patient, spirometry testing and DLCO should always start at approximately the same time of day. DLCO should always been performed after spirometry.

[redacted]



5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. All abnormal findings at baseline will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.
Measurement of height will be performed at the time point specified in the Flow Chart.

Body weight will also be evaluated at each visit. It should be measured with the patient wearing indoor clothing and no shoes. For each individual patient, weight should be measured consistently in the morning at all visits after emptying the bladder.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.
This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

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 Flow Chart.

Analyses of most parameters will be performed by a central laboratory, the respective reference ranges will be provided in the ISF. ESR will be performed on-site using supplies provided by the central laboratory. The value for ESR will be reported directly by the site in the eCRF.
Patients do not have to be fasted for the blood sampling.

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 5.2.6.1 and the DILI Checklist provided in the eDC system.
The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3:1 Safety laboratory tests

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count Erythrocyte sedimentation rate (ESR)
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and INR) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Lipase Amylase
Hormones	Thyroid stimulating hormone (TSH) fT3, fT4
Substrates	Plasma glucose Creatinine Total bilirubin Direct and indirect bilirubin Total protein High sensitivity C-Reactive Protein (hs CRP) Brain Natriuretic Peptide (BNP) Uric acid Total cholesterol Triglycerides Albumin
Electrolytes	Sodium Potassium Chloride Calcium Inorganic phosphate
Urine analysis (semi-quantitative measurements; -, +, ++, +++)	pH Glucose Erythrocytes Leukocytes Protein Nitrite

eGFR will be analysed and calculated by the central laboratory at the same timepoints as other safety laboratory parameters (see in the Flow Chart).
eGFR will be calculated by using the CKD-EPI formula (see Section 10.6) and using the Jaffe assay for serum creatinine measurement, IDMS standardized.

5.2.4 Electrocardiogram Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph which will be provided to the sites, at the time points given in the Flow Chart.

In order to achieve a stable heart rate (HR) at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for 10-sec duration after the patients have rested for at least 10 min in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all patients are at complete rest during the recordings. ECG assessment will always precede all other study procedures (except PRO completion) of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid compromising the ECG quality.

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven or limb leads modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

ECGs will be recorded as single ECGs as indicated in the Flow Chart.
ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be recorded for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor's database.

Data transfer

All ECGs will be transferred electronically to the central ECG lab for storage and evaluation.

In case of repeat ECGs due to quality reasons, all ECGs will be transferred to the central ECG lab who will select the correct one for analysis.
Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Evaluation

a) Central ECG lab

Central ECG lab evaluation will be performed for the pre dose ECGs.

This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details).

All semi-automatic interval measurements in one petient will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the Clinical Trial Report.

For automatic interval measurements no lead will be provided.

For blinding arrangements see section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular patient should be evaluated by a single reader. For quality assurance and control of the measurements, all ECGs of a patient will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/or false patient assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study. Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

All ECGs will be evaluated by the investigator or a designee.

For the inclusion or exclusion (see section 3.3) of a patient and for the assessment of cardiac safety during the study, the QT and QTc values generated by the ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for centralised evaluation. In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the patient will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Suicidal risk assessed by the C-SSRS

For the marketed PDE4-inhibitors apremilast [R17-1539];[R17-1540] and roflumilast [R17-1542] an increased risk of suicidality has been described. Therefore prospective suicidality monitoring, will be performed throughout this trial using the Columbia Suicidal Severity Rating scale (C-SSRS).

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behavior and ideation.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the ‘screening’ version) with the aim to exclude patients suicidal ideation type 4 to5 within the preceding 3 months or at Visit 1 or any

suicidal behaviour in the past 2 years. The life time history of suicidal ideation and behavior will also be recorded.

After the screening/baseline visit the assessment 'since last visit' will be performed at each clinic visit ('since last visit' version).

For details on how C-SSRS will be assessed, refer to appendix 10.2.

C-SSRS results will be reported in terms of AEs as described in Section 5.2.6.1.4.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An 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.

The following should also be recorded as an AE in the CRF and BI 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 exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 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, which 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,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement 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.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 in section 5.2.6.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Suicidal Risk assessed by the C-SSRS

All C-SSRS reports of suicidal ideation type 4 and 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.

For 'self-injurious behavior, no suicidal intent'(type 11) standard AE/SAE reporting rules are to be applied.

For each negative report (Suicidal ideation type 1, 2 or 3) after the start of the trial, the investigator is to decide based on clinical judgement whether it represents an adverse event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.6.1.5 Acute IPF exacerbations

The most recent definition of acute IPF exacerbation will be used [P16-06899]. The AEs will not be adjudicated.

Acute exacerbation will be defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following:

- ∀ Acute worsening or development of dyspnea typically less than one month duration.
- ∀ Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with IPF.
- ∀ Deterioration not fully explained by cardiac failure or fluid overload.

This event must be reported "acute exacerbation of disease under investigation".

Events that are clinically considered to meet the definition of acute IPF exacerbation but fail to meet diagnostic criteria due to missing CT data must be reported as "suspected acute exacerbations of disease under investigation" (as long as this assessment persists).

5.2.6.1.6 Adverse events of special interest

The term adverse events of special interest (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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.
The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- ∀ an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- ∀ aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided via eDC. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, 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.

Vasculitis events
In this trial protocol vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels.

5.2.6.1.7 Intensity (severity) of AEs

The intensity (severity) 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.

5.2.6.1.8 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, 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 reduced).

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.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.
The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (the End of Trial (EoTrial) visit):
  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 new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of

communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the 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 contact details 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 the BI SAE form.

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

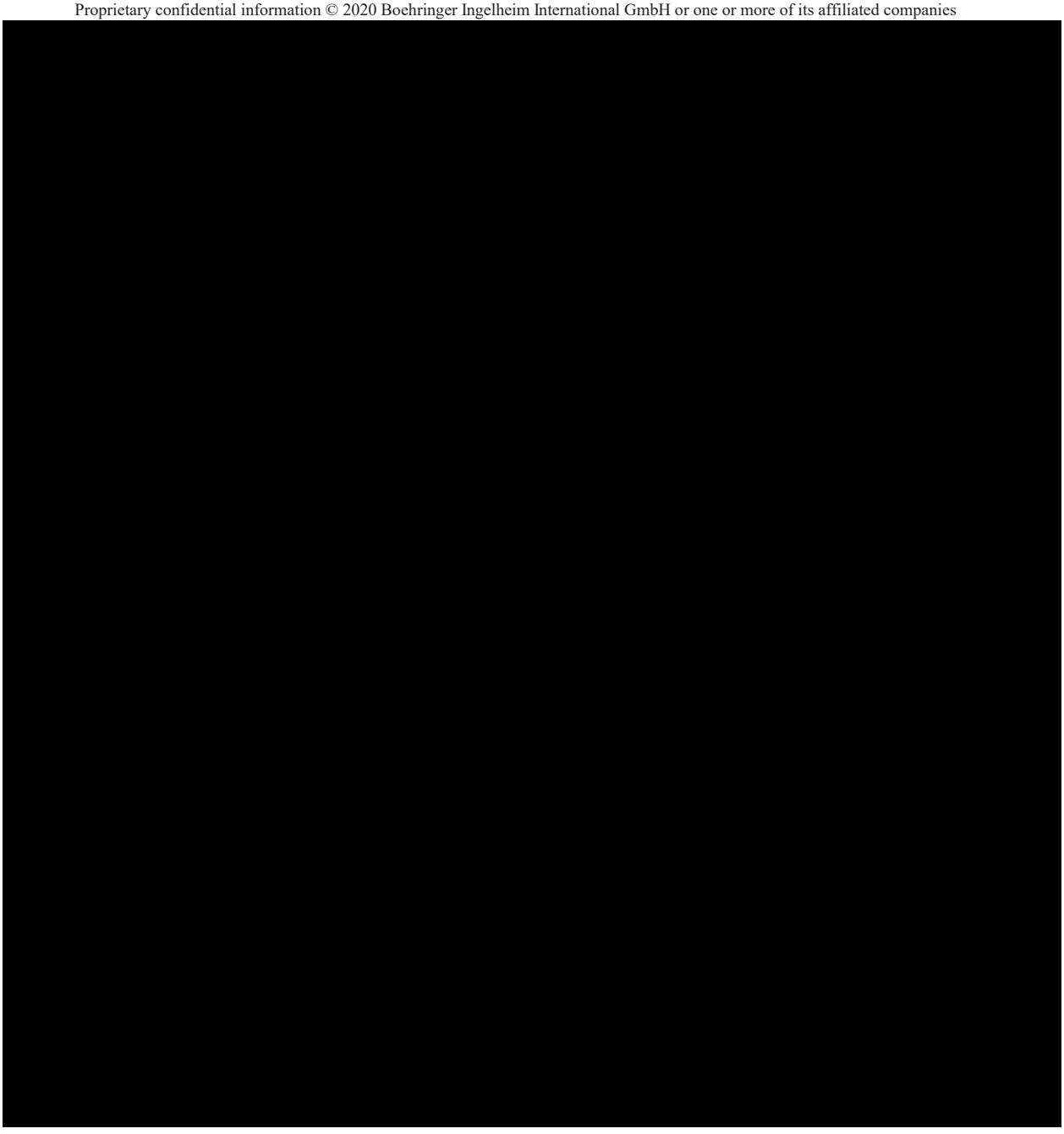
5.2.6.2.3 Pregnancy

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.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

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 Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (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 Studies 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.



[redacted]

[redacted]

5.6 OTHER ASSESSMENTS

One optional substudy can be proposed to the patients in case the site where he/she participates takes part of it.
Participating in this substudy is totally voluntary. Not participating in will not affect the participation to the main study.

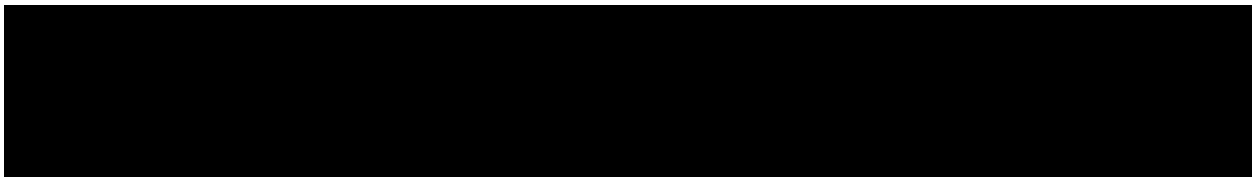
5.6.1 24 hr Cough measurement (substudy at dedicated sites only)

Subjects with a VAS severity ≥25 mm (on a scale of 100 mm) will be eligible for this sub-study
Objective cough count measurements will be collected over a 24-hour period via a device worn by the patient at Visit 2 and Visit 6 respectively as indicated in the Flow Chart.
The device will be removed by the patient and brought back by the patient to the site at the next Visit.

The records will be analysed quantitatively by isolating the cough records and change from baseline in cough frequency over 24 hours, during night-time and awake will be described.
Detailed instructions for the 24hr Cough measurement will be provided in the ISF.
Results may be included into the clinical trial report or reported separately.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted for primary and secondary endpoints are using standard methods. Refer to Section 3.2 for the discussion of the choice of FVC as primary endpoint.



6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The acceptable time windows for visits are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration [redacted]).

If several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the patient and possible influence on physiological parameters.

[redacted]

If a patient misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

In exceptional cases, if standard visits at the trial sites are impossible because of COVID-19 related safety risks, visits 3, 4, 5 and 7 may be performed at the patients's home or remotely via telephone and/or internet means of communication.

The visits may also be performed as a combination of home and remote visits.

All home/remote visits need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements of the participating country still apply.

For the details of the modifications refer to Section 6.2.

All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The following sequence of procedures at each visit (where applicable) is recommended:

Timing at Visit Days	Procedures
Pre-dose	∀ [redacted] ∀ Blood sampling including predose [redacted] Serum/Plasma and DNA sampling. ∀ ECG ∀ FVC ∀ DLCO ∀ Time record of pre-dose blood collection.

	∀ IRT call
∀ **Pre-dose or Post-dose**	∀ [redacted] ∀ Physical examination including vital signs and body weight *[at baseline only: demographics, medical history including pre-existing conditions]* ∀ AE and concomitant therapy collection, smoking status *[at baseline only: treatment history]* ∀ C-SSRS questionnaire. ∀ [redacted]
∀ **Treatment dispense and administration of trial drug** [redacted]	
∀ [redacted]	[redacted]

6.2.1 Screening period

Screening Period
After having been informed about the trial, all patients will be required to give written informed consent in accordance with ICH-GCP and local legislation prior to enrolment in the study.

After informed consent is obtained, inclusion and exclusion criteria should be checked according to Flow Chart.

At selected sites performing Digital lung Auscultation substudy, patients should be invited during the informed consent process to participate in the respective substudy.

At selected sites performing 24hr Cough Measurement substudy, patients should be invited during the informed consent process to participate in the respective substudy.

Patients will be asked to give informed consent to the DNA, Plasma and Serum banking samples (please note: the banking samples must not be taken prior to Visit 2). Participation is voluntary and is not a prerequisite for participation in the trial.

[redacted]

For information regarding laboratory tests, ECG, vital signs, body weight and physical examination, refer to sections 5.2.1 to section 5.2.4.

For information on spirometry (FEV_1 and FVC) and DLCO refer to section 5.1.1, 5.1.2 and appendix 10.3.

An historical HRCT can be used to determine eligibility, providing the scan was performed within the past 12 months prior to screening. If historical scan is not available, or an available scan fails to meet the required image acquisition specification, an HRCT may be performed after consent to determine eligibility. All HRCT scans will be sent to a central vendor for review and confirmation of IPF diagnosis, prior to randomisation. Confirmation of diagnosis must be available prior to visit 2. HRCT should not be repeated for eligibility if previous scan was taken within the past 3 months. To perform an HRCT within the trial, all local regulatory requirements to perform an HRCT have to be met.

If required, the HRCT scan should be performed as close to screening date as possible, preferably once eligibility is confirmed based on other parameters, to avoid unnecessary scans for patients who are found ineligible based on other criteria.

Screening period may be extended for administrative reasons. Approval should be obtained from the sponsor who will also determine if any tests specified in the protocol must be repeated before the randomisation visit (Visit 2).

6.2.2 Treatment period

All patients who fullfill all inclusion criteria and none of the exclusion criteria, including positive HRCT review, will be randomised at Visit 2 via IRT in one of the two treatment arms.

At the beginning of each visit during treatment phase, investigator and site personnel should check the well-being of the patient as well as prepare all requirements for conduct of the visits that are necessary.

[redacted]

For information regarding laboratory tests, ECG, vital signs, body weight and physical examination, refer to sections 5.2.3 to section 5.2.4

Each patient will receive the first dose of BI 1015550 or placebo the morning of Visit 2 (Day 1). Patients will take BI 1015550 18 mg (or placebo) twice daily (b.i.d) from Day 1 onwards. Trial medication will be taken orally. At clinic visits, trial medication will be taken under direct supervision of the investigator or [redacted] designee.
The patient will have to bring back all IMP kits, used and unused at each on site visit, including Visit 3.
The patient will have to come back home with the IMP kit dispense at the corresponding visit in addition to the reserve kit dispense at Visit 2.
The investigator has to check the expiry date of the reserve kit and replace it in case it expires before the next on site visit.

FVC has to be measured at the same time each visit ± 90 min (reference time at Visit 2).
DLCO should be done after FVC measurements. If it is done timely close to FVC measurement, patients should have the possibility to rest in between.

Patients not treated with antifibrotics at Visit 1 are not allowed to start an antifibrotic treatment during the treatment period.

[redacted]

Visit 6 will be the End of Treatment visit. The last drug intake will occur on site during the visit. All IMPs kits will have to be brought back to the site at Visit 6.

Due to COVID-19 pandemic restrictions, the trial conduct may need to be adjusted and remote visits may be performed for **Visits 3, 4, 5 and/or 7** if necessary.
If a patient is not able to come to the site for a trial visit, a remote visit (by phone or visio conference application) should be performed instead. At minimum, the following assessment should be done: **adverse events** (AE, SAE, AESIs), **C-SSRS, concomitant therapy**, **safety laboratory testing**, **trial medication compliance check**. Patients can report and/or send photos of trial medication kit used to their site staff, if needed and possible.

If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and documents a clinically relevant safety issue as an adverse event. Minimum required safety lab parameters are listed in Table 6.2.2.1.
If home visits are possible (preferable option), some assessments can be done at the patient's home (e.g. collection of blood and urine samples to be sent to the central lab, vital signs).

Applicable to Visits 4, 5: If a patient is not able to come as planned but the investigator considers it favorable and safe for the patient to continue on trial medication, the trial medication can be shipped from site directly to the patient (if acceptable according to local laws and regulations (see section 4.1.4). In this case, patients must consent to providing contact details for shipping purposes and should retain all unused IMP and packaging and return it when they are able to return to the site. Investigators should conduct phone visits first to discuss adverse events, concomitant therapies, C-SSRS, assess trial medication compliance and have reviewed (local) safety laboratory results.

Table 6.2.2:1 Minimum Required Safety Lab Parameters

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count Erythrocyte sedimentation rate (ESR)
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and INR) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Lipase
Substrates	Amylase Creatinine Total bilirubin Total protein High sensitivity C-Reactive Protein (hs CRP) Albumin
Electrolytes	Sodium Potassium Chloride Calcium Inorganic phosphate
Urine analysis (semi-quantitative measurements; -, +, ++, +++)	pH Glucose Erythrocytes Leukocytes Protein Nitrite

6.2.3 Follow-up period and trial completion

A follow up period of a minimum of 7 days (+3 days) will be required. All patients will complete an end of trial visit. For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see sections 5.2.2 to 5.2.4.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. All (S)AEs persisting after individual patient's end of trial must

be followed up until they have resolved, have been assessed as “chronic” or “stable” , or no further information can be obtained.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial (“Last Patient Completed”).

6.2.4 Optional substudy

Patients at dedicated substudy sites will be invited to optionally participate in the exploratory 24hr cough assessment test and will give their consent by a separate patient information / informed consent (PI / IC).

Participation in the substudy is voluntary and not a prerequisite for participation in the main trial. Participation in the main trial must not be affected if a patient withdraws from substudy participation.

Scheduling of optional substudy procedures is specified in the Flow Chart.

Substudy information for respective sites will be provided in the ISF.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary endpoint is the change from baseline in FVC at week 12. This endpoint will be evaluated separately per strata, in the patient group with antifibrotic treatment and in the patient group with no antifibrotic treatment. The purpose of this trial is to demonstrate proof of concept of clinical activity of BI 1015550 on the primary endpoint. For the proof of concept an evaluation of a minimum relevant additional benefit of BI 1015550 compared to placebo is conducted. Hereby, the posterior probability of the difference in change from baseline in FVC between BI 1015550 and placebo will be evaluated for different boundary values Δ.

Historical information for the placebo group (separately for patients treated with antifibrotic treatment and patients not treated with antifibrotic treatment) will be taken into account via the usage of a Bayesian approach with informative priors. The results in both patient groups will then be combined to assess if proof of concept could be shown.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No hypothesis testing will be performed in the confirmatory sense. All the analyses will be performed in an exploratory fashion to better understand the efficacy and safety profile of BI 1015550.
The primary analysis on the primary endpoint will be based on a Bayesian borrowing approach.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following analysis sets will be defined for statistical analyses:

Entered Set (ES): This patient set includes all patients who signed informed consent. The ES will be used for the analysis of protocol deviations.

Randomised Set (RS): This patient set includes all entered and randomised patients. The RS will be used for the analyses of patient disposition.

Treated Set (TS): This patient set includes all patients who received at least one dose of study drug. The TS is used for safety analyses as well as demographics and baseline characteristics.

Full Analysis Set (FAS): This patient set includes all patients in the TS who had a baseline and at least one post-baseline measurement available for FVC, FEV1 or DLCO. Patients in FAS are analyzed based on the trial medication they have actually received. The FAS is the main analysis set for the analysis of efficacy.

Per protocol set (PPS): includes all patients from the FAS without important protocol deviations (IPD) leading to exclusion from PPS. The PPS is used for efficacy analyses.

[redacted]

Data from patients who are screened but not randomised will be listed but not included in any summary statistics or inferential statistics. Specifications of important protocol deviations leading to exclusion will be provided in the trial Integrated Quality and Risk Management Plan (IQRMP) and all decisions concerning IPDs will be made before un-blinding.

Further Analysis Sets will be defined in the TSAP, if needed.

7.2.2 Primary endpoint analyses

Planned analyses for primary endpoint

The main analysis for the primary endpoint will be conducted separately for patients not on antifibrotic treatment and for patients on antifibrotic treatment at baseline, where baseline is defined as data collected at visit 2 prior to administration of first dose of study medication, or screening data if visit 2 data are missing.

To account for the repeated nature of the data and the covariates in the model, MMRM analysis will be carried out for change from baseline of FVC after 12 weeks of treatment The adjusted mean change from baseline (and the related standard error) will be calculated for each group and will be used for the Bayesian borrowing approach [R16-0278], [R16-0281].

In order to evaluate the treatment effects, historical data from the nintedanib development program in IPF will be included for the placebo groups in each stratum and posterior probabilities for the treatment difference of BI 1015550 vs. placebo with respect to the primary endpoint will be estimated. The median of the posterior probability (and 95% credible intervals) will be calculated.

The analysis will include the fixed, categorical effect of treatment at each visit, and the fixed continuous effects of baseline FVC at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

Procedures to follow if the analysis fails to converge will be described in the TSAP.

[redacted]

[redacted]

The primary analysis will be performed on the FAS. The primary estimand of interest is the treatment effect assuming all patients took randomized treatment for the duration of the trial using a hypothetical approach, i.e. trial drug is taken as directed. The primary analysis of the primary endpoint will include all data collected while on treatment. Any data collected at the follow up will not be included in the primary analysis. The resulting missing data will be assumed to be missing at random (MAR). Patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance.

[redacted]

7.2.2.1 Prior derivation

For both placebo groups (on antifibrotics and not on antifibrotics), an informative prior will be used based on historical data from the nintedanib development program in IPF.

The derivation of the informative prior is based on a meta-analytic predictive (MAP) prior approach, where a vaguely informative mixture component is added to the prior to obtain a prior which is robust against prior-data conflicts.

For the comparison of the BI 1015550 treatment with placebo, the posterior probability of the difference in change from baseline in FVC between BI 1015550 and placebo will be evaluated. This evaluation will be done based on the posterior probability P(BI – PBO > Δ ml | Data) > x using predefined thresholds Δ and x.

For the primary endpoints defined in Section 2.1.2 the used estimated placebo corrected adjusted means and standard deviations for the prior calculation are given in Table 7.2.2.1: 1 below.

Table 7.2.2.1: 1 Estimated placebo corrected adjusted means and standard deviations

Study*	Placebo group of patients not on antifibrotic treatment		Placebo group of patients on antifibrotic treatment	
	N	adj. mean change from baseline at week 12 (SE)	N	adj. mean change from baseline at week 12 (SE)
1199_0032	204	-71.45 (12.53)	307	-20.13 (10.22)
1199_0034	216	-87.89 (12.23)	327	-33.10 (9.97)
1199_187P1	53	-31.79 (24.33)	53	12.97 (24.33)
1199_227	230	-72.93 (12.53)	116	-1.98 (17.48)
1199_30	85	-81.54 (24.00)	84	0.09 (24.10)
1199_222	NA	NA	51	-29.77 (25.95)
1199_0036	NA	NA	135	-25.65 (15.82)

*Based on unpublished data. Trials were reanalysed using the analysis model planned for the primary analysis

The estimates from Table 7.2.2.1: 1 were used to generate informative priors for the two placebo groups (patients on antifibrotic treatment at baseline and patients not on antifibrotic treatment at baseline) based on a meta-analytic predictive (MAP) prior approach, where a vaguely informative mixture component is added to the prior to obtain a prior which is robust against prior-data conflicts [R16-0281]. Thus, the prior is a mixture of informative and non-informative beta priors and the weight of the non-informative beta prior is 50%. This prior is further downweighted by increasing the SD of all components by the same factor (to allow for the new data to have a sufficient weight). Therefore, the actual prior considered for the placebo group of patients not on antifibrotic treatment at baseline is (mixture normal distributed prior with 3 informative and 1 vaguely informative components):

$$\mu_{P,nAF} \sim 0.28\mathrm{N}(-74.0, 16.1) + 0.19N(-71.1, 42.2) + 0.03N(-70.2, 97.8) + 0.5N(-73.0, 315.7)$$

Likewise for the placebo group of patients on antifibrotic treatment at baseline the prior is given as

$$\mu_{P,AF} \sim 0.27\mathrm{N}(-20.0, 16.2) + 0.20N(-17.0, 39.8) + 0.03N(-15.4, 87.7) + 0.5N(-19.0, 385.7)$$

For the BI 1015550 treatment groups with and without antifibrotic treatment at baseline vaguely-informative priors are generated. These two priors do not consist of a mixture of priors:

$$\mu_{BI,nBTX} \sim \mathrm{N}(-73.0, 315.7)$$

$$\mu_{BI,BTX} \sim \mathrm{N}(-19.0, 385.7)$$

Details for the prior calculation can be found in Appendix 10.9.

The actual prior may be updated based on additional historical information being available before the trial starts. The final prior will be documented in the TSAP. All analyses based on informative priors will be repeated with vaguely informative priors as well to ensure comparability with a frequentist setting.

[redacted].

7.2.3 Secondary endpoint analyses

The analysis of the secondary endpoint percentage N (%) of patients with Treatment Emergent Adverse Events (TEAE) will be described in Section 7.2.5.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 7 days after the last dose of trial medication, will be assigned to the on-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 be conducted separately for the patients on antifibrotic treatment and the patients not on antifibrotic treatment and combined for the two strata.

The analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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) at database lock.

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 summarised. 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, 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.

Further details will be provided in the TSAP.

7.2.6 Other Analyses

7.2.6.1 Pharmacokinetic methods

In the Clinical Trial Report, plasma concentrations of BI 1015550 will be tabulated with descriptive statistics. In case of a positive outcome of the trial, i.e. when further studies are initiated and the project proceeds to a next phase, a population pharmacokinetic analysis will be performed on BI 1015550 plasma concentrations.

A separate Population PK Analysis Plan will be written, and results will be reported separately.

7.2.7 Interim Analyses

No interim analysis is planned but a Data Monitoring Committee (DMC) will be in place with tasks as described in section 8.7.

7.3 HANDLING OF MISSING DATA

In the primary analysis of all continuous endpoints, missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption". This means e.g. patients with missing data would have behaved similarly to patients with observed data.

Missing or incomplete AE dates will be imputed according to BI standards.

Handling of missing data for secondary endpoints as well as for sensitivity analysis will be described in the TSAP.

The handling of missing data for the Population PK Analysis is described in a separate PopPK Analysis Plan.

7.4 RANDOMISATION

Patients will be randomised to one of the treatment arms in a 2:1 ratio (BI 1015550 18 mg / placebo, all b.i.d), with approximately 100 patients in the BI dose group and approximately 50 patients in the placebo group (total maximum 150 patients). Randomisation will be stratified by antifibrotic treatment (patients treated with antifibrotic treatment vs patients not treated with antifibrotic treatment at baseline).

The Randomisation of patients to the treatment groups will be performed via an interactive response technology (IRT). This system will also include caps for use of antifibrotic treatment to ensure a certain balance required for the evaluation of the study objectives. In particular a minimum number of 60 patients treated with antifibrotic treatment and a minimum number of 60 patients not treated with antifibrotic treatment will be recruited.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

This is an exploratory trial and is planned to include at least 60 patients in the group with antifibrotic treatment and at least 60 in the patient group with no antifibrotic treatment, from a total of approximately 150 patients with a 1:2 ratio between placebo and BI 1015550. Calculations below are based on the minimum of 120 patients.

The sample size for the patient group not treated with antifibrotic treatment is based on the following evaluations of the posterior probabilities (see also Table 7.5:2). Hereby also the posterior probabilities of the patient group on antifibrotic treatment are taken into account.

However, the expected treatment effect of BI 1015550 vs. Placebo in addition to antifibrotic treatment is expected to be low after 12 weeks of treatment as the expected decline in FVC is only 20mL at 12 weeks. Therefore, the main driver for the decision probabilities presented below is the group without antifibrotic treatment at baseline.

The sample size of this trial is based on evaluation of the observed treatment effects in patients with and without antifibrotic treatment at baseline. In order to evaluate the treatment effects, historical data from the nintedanib development program in IPF will be included for the placebo groups in each stratum and posterior probabilities P(BI – PBO > 50mL | Data) for the treatment difference of BI 1015550 vs. placebo with respect to the primary endpoint will be estimated. The median of the posterior probability will be used for the assessment and described as observed treatment effect in the following. A stepwise approach will be used to assess the observed treatment effects within the strata:

1. **Treatment effect within the stratum without antifibrotic treatment only:**
   The observed treatment effect will be compared to a certain minimum treatment effect Δ_{nAF} (e.g. 50mL) in the group without antifibrotic treatment (independent of the observed treatment effect in the group with antifibrotic treatment)
2. **Treatment effect within the stratum without antifibrotic treatment and with antifibrotic treatment:**
   In a second step, if the treatment effect observed in the group without antifibrotic treatment is lower than Δ_{nAF}, but higher than another threshold $\Delta_{CnAF} <= \Delta_{nAF}$ (e.g. 35mL), then the group with antifibrotic treatment will be taken into account and the observed treatment effect in the patient group with antifibrotic treatment will be compared to a certain minimum treatment effect Δ_{CAF} (e.g. 30mL) ,see Table 7.5: 1 below for a clear definition of what a minimum effect based on the two patient groups means.

Table 7.5: 1 Minimum effect of BI 1015550 based on the two patients groups with and without antifibrotic treatment

	Change from baseline in FVC [ml] at week 12 in patients not on antifibrotic treatment	Change from baseline in FVC [ml] at week 12 in patients on antifibrotic treatment
Not on antifibrotics criterion	≥50 mL	-
Combined criterion	≥ 35 mL	≥30 mL

The assumed sample sizes for BI 1015550 18 mg b.i.d and placebo group (in both strata on antifibrotic treatment and without antifibrotic treatment) are 40 and 20, respectively, and historical information for the placebo groups (with an effective sample size of approximately 20 for each stratum) is included via Bayesian borrowing.

For example, if there is a true treatment difference of 70 mL in change from baseline in the not on antifibrotics group (assuming a disease progression of approx. -73mL over 12 weeks in the placebo group and a standard deviation of 200 mL in both groups) , and a true treatment difference of 20 mL in change from baseline in the antifibrotics group (assuming a disease progression of approx. -19mL over 12 weeks in the antifibrotics control group and a standard deviation of 200 mL in both groups), the probability is 75% to observe a treatment effect of $\geq$ 50 mL in the not on antifibrotics group or $\geq$35 mL in the not on antifibrotics group combined with a treatment effect of $\geq$ 30 mL in the antifibrotics group (based on the two criteria specified in Table 5.2.3: 1). If there is actually no true treatment difference in both groups, such sample size provides a chance of 89% to observe either a treatment effect of <35 mL in the not on antifibrotics group or <50 mL in the not on antifibrotics group combined with a treatment effect of <30 mL in the antifibrotics group.

The sample size calculation is conducted for several data scenarios using different effect sizes. The results are given in Table 7.5: 2 for a randomisation ratio of 1:2.

Table 7.5: 2 Outcome probabilities for each scenario under different settings (including historical information via information prior for the Pbo group) assuming a SD of 200 ml and 20+H/40 patients on PBO/BI 1015550

Assumed effect Sizes	N in each stratum	P(Outcome +[#])	P(Outcome -[#])	P(Outcome +/-)
Without antifibrotics/ With antifibrotics	With/Without antifibrotics (Pbo/BI)			
70mL/20mL	20+H/40	75%	11%	14%
60mL/15mL	20+H/40	65%	17%	18%
10mL/ 0mL	20+H/40	16%	60%	24%
0mL/ 0mL	20+H/40	11%	66%	23%

Numbers are each based on 10000 simulated trials for each scenario.

[#] Outcome +=not on antifibrotics or combined criterion are fulfilled, i.e,

- ∀ Observed treatment effect for the not on antifibrotics group $\delta_{nAF} \geq 50$mL OR
- ∀ Observed treatment effect for the not on antifibrotics group $\delta_{nAF} \geq 35$mL and observed treatment effect for the antifibrotics group $\delta_{AF} \geq 30$mL

Outcome -= Neither of the following two conditions is fulfilled,

- ∀ Observed treatment effect for the not on antifibrotics group $\delta_{nAF} \geq 35$mL
- ∀ Observed treatment effect for the antifibrotics group $\delta_{AF} \geq 30$mL

Outcome +/-:

- ∀ Observed treatment effect for the not on antifibrotics group $35\text{mL} \leq \delta_{nAF} < 50\text{mL}$ and observed treatment effect for the antifibrotics group $\delta_{AF} < 30$mL OR

- ∀ Observed treatment effect for the not on antifibrotics group $\delta_{nAF} < 35$mL and observed treatment effect for the antifibrotics group $\delta_{AF} \geq 30$mL.

+H=including historical information via informative prior (with an effective sample size of approximately 20).
Calculations were based on R version 3.6.1 using the RBest package.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

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 Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains 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, as well as 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 finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

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."

The investigator or delegate 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 or delegate 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 or [redacted] delegate 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.

If study conduct may need to be adjusted during the COVID-19 pandemic (see Section 4.1.4 and Section 6.2), the patient must be made aware of any modifications and provide their agreement to the modifications prior to them being implemented.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

CRFs for individual patients will be provided by the sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

For adverse events, an end date may not always be available (e.g. due to hospital discharge and later recovery, or change in treating physician), but should be recorded in the source if known.
For eCRF all data need to be derived from source documents, which need to be available on-site (this could be for example physician's notes in patient files, printouts, patient diaries).

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 patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. 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.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source files (HRCT) necessary for central eligibility reads will be provided to an imaging vendor. Before sending or uploading those copies, 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.

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
- ∀ Medical history (including trial indication and concomitant diseases, if applicable)
- ∀ 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)
- ∀ Patient related outcome worksheet completed by the patient and reviewed by the site.
- ∀ Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- ∀ Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow 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). They 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 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 local requirements valid at the time of the end of the trial (whatever is longer).
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 and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised 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 at the site 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, biobanking and future use of biological samples and clinical data, in particular

- ∀ Sample and data usage has to be in accordance with the separate biobanking informed consent
- ∀ The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- ∀ An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- ∀ A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- ∀ A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

- ∀ Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

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 Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT 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).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.
The DMC will evaluate the entire safety data and will meet on an ongoing basis during the course of the trial. The DMC can receive urgent significant safety concerns for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), 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 Clinical Trial Managers (CT Managers), 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 BI 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.

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

Bioanalysis of BI 1015550 is done by sponsor or a delegated laboratory.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a central images service, a central ECG review service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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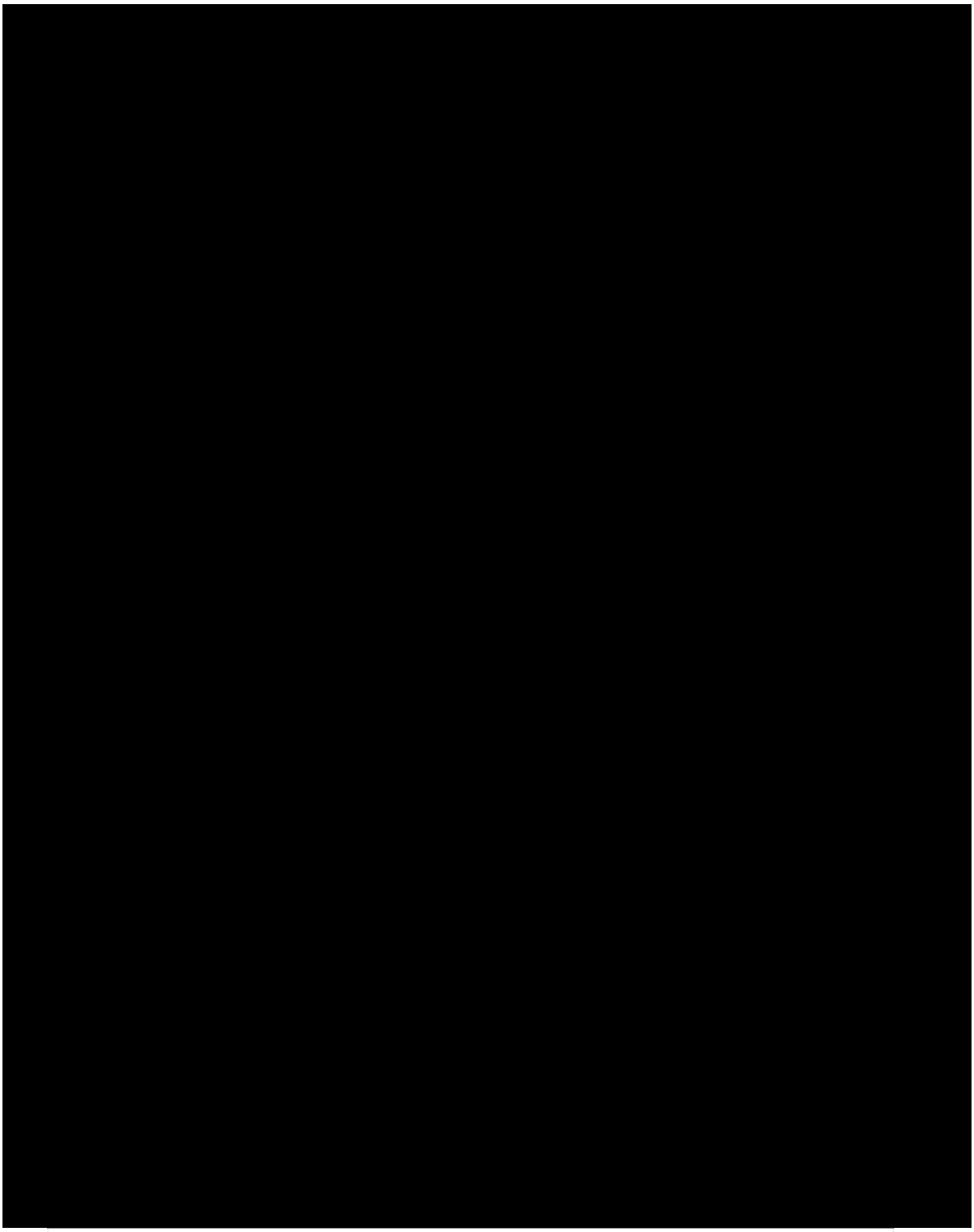
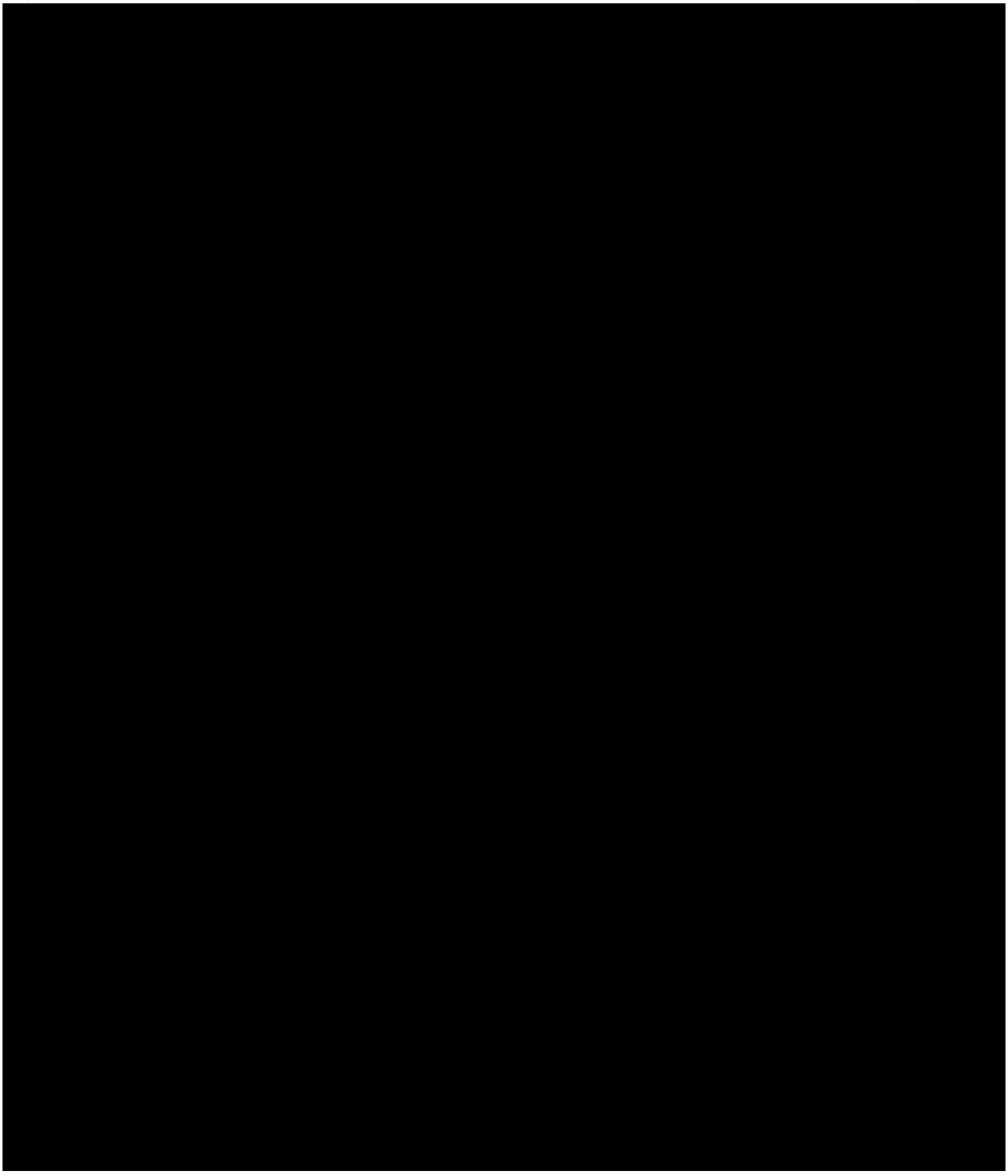
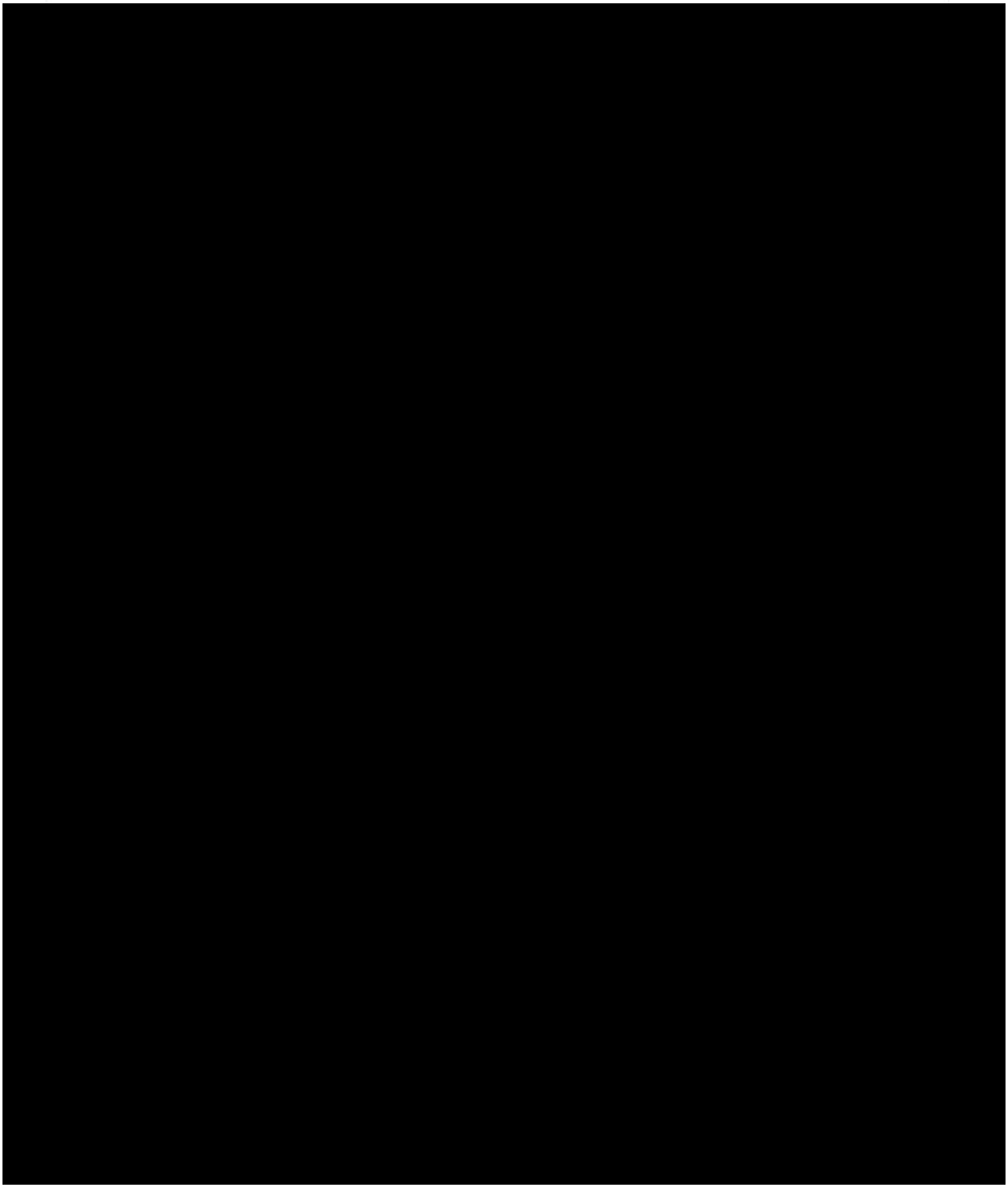
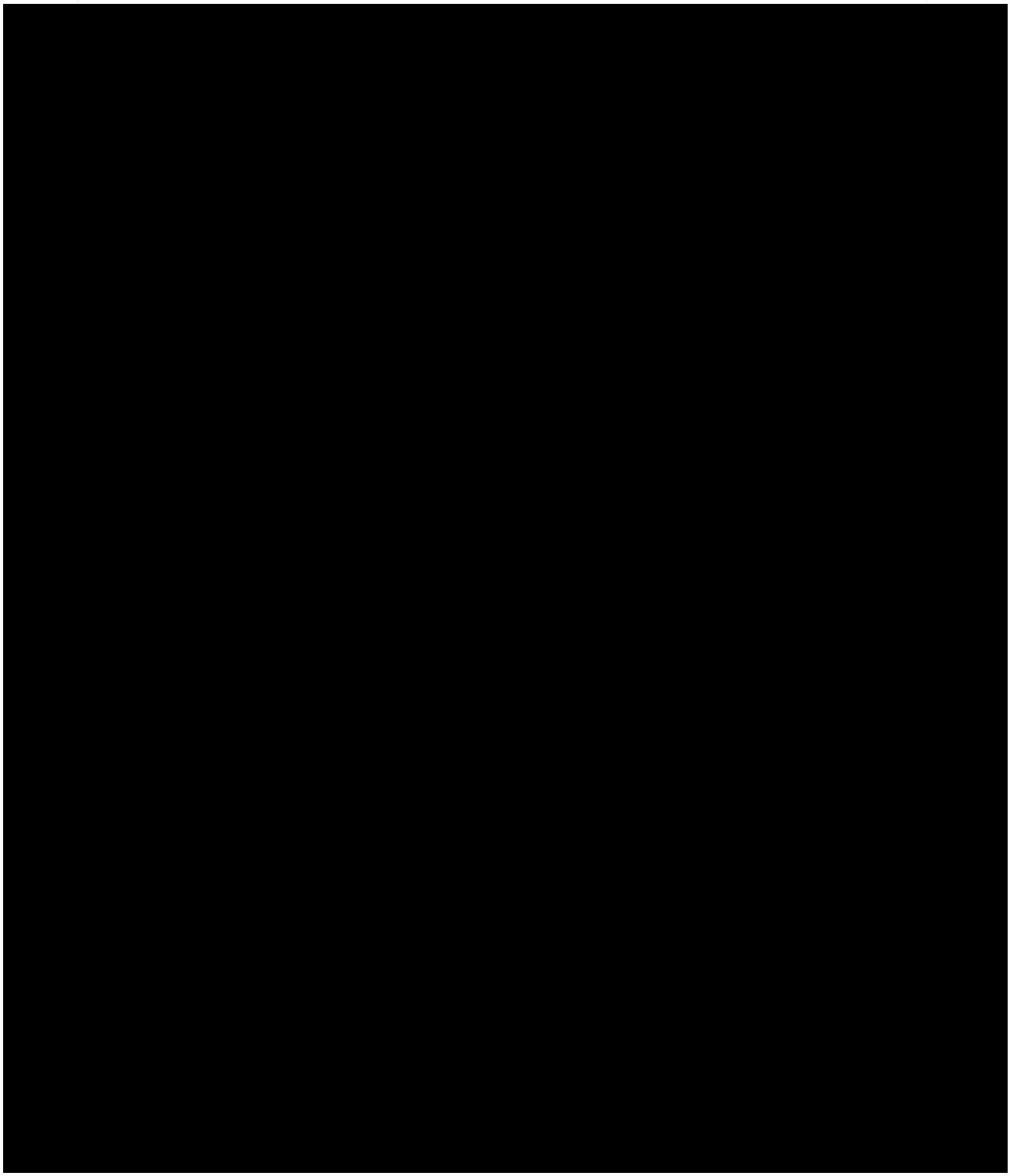
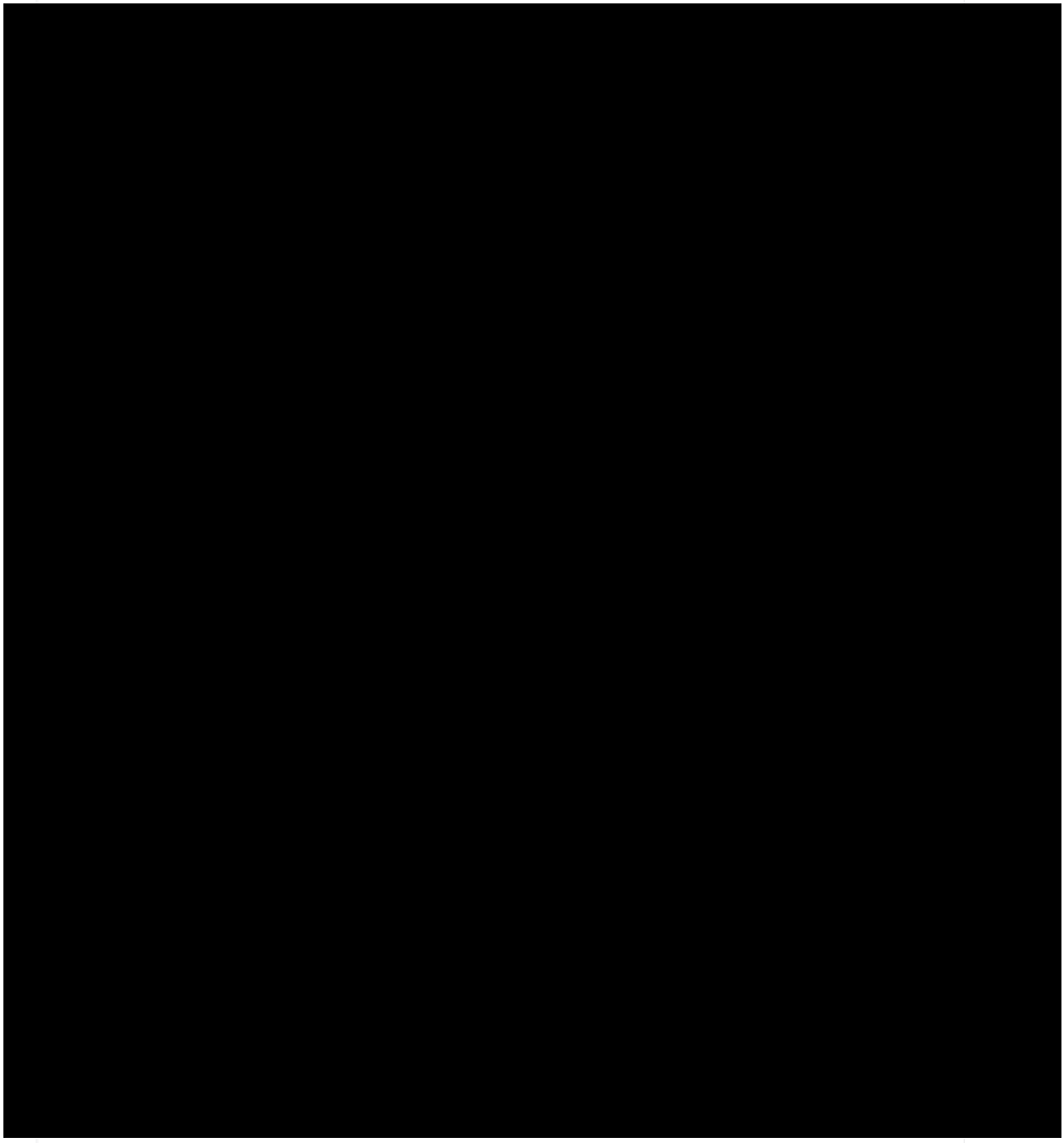
10. APPENDICES

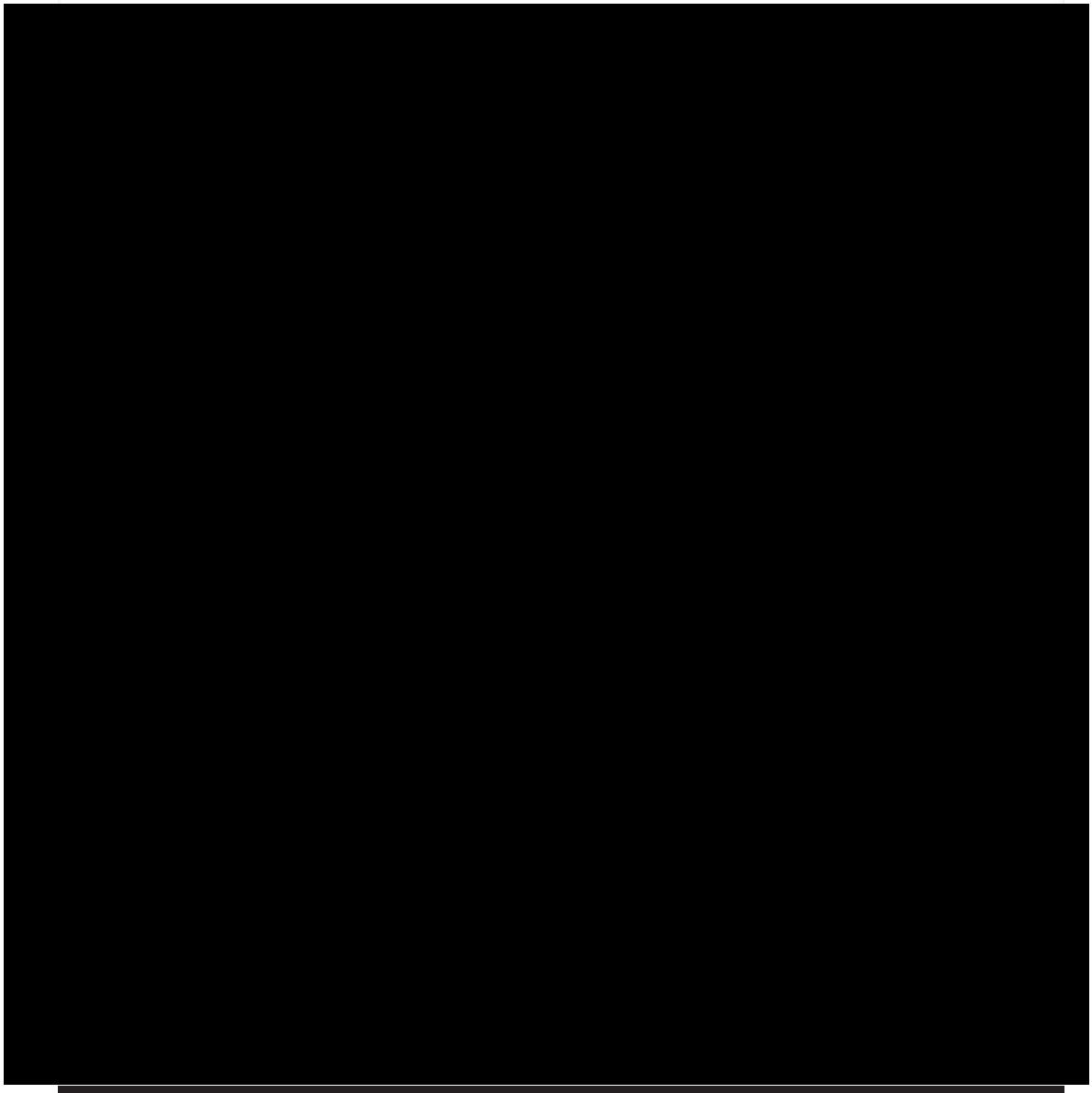


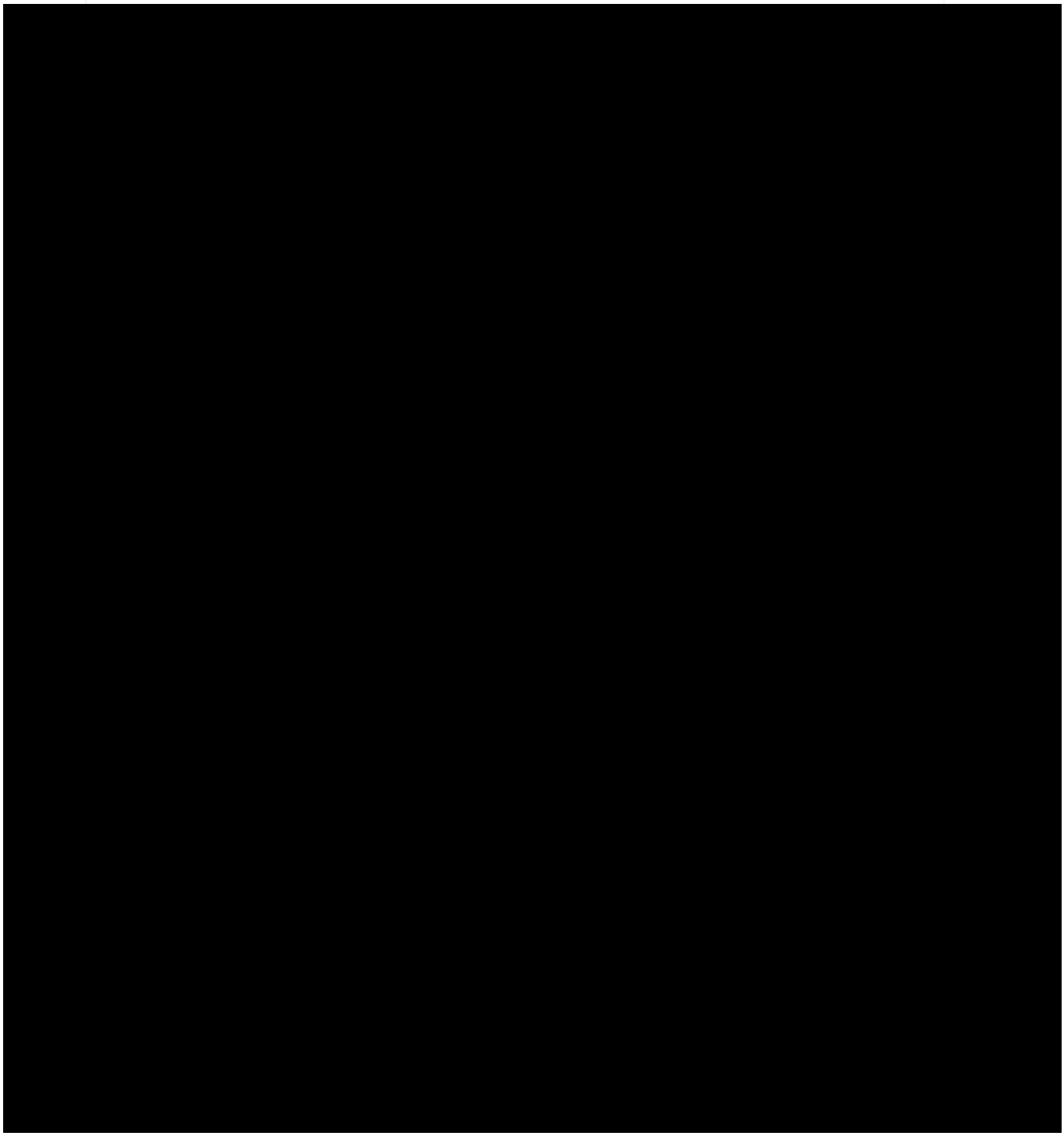


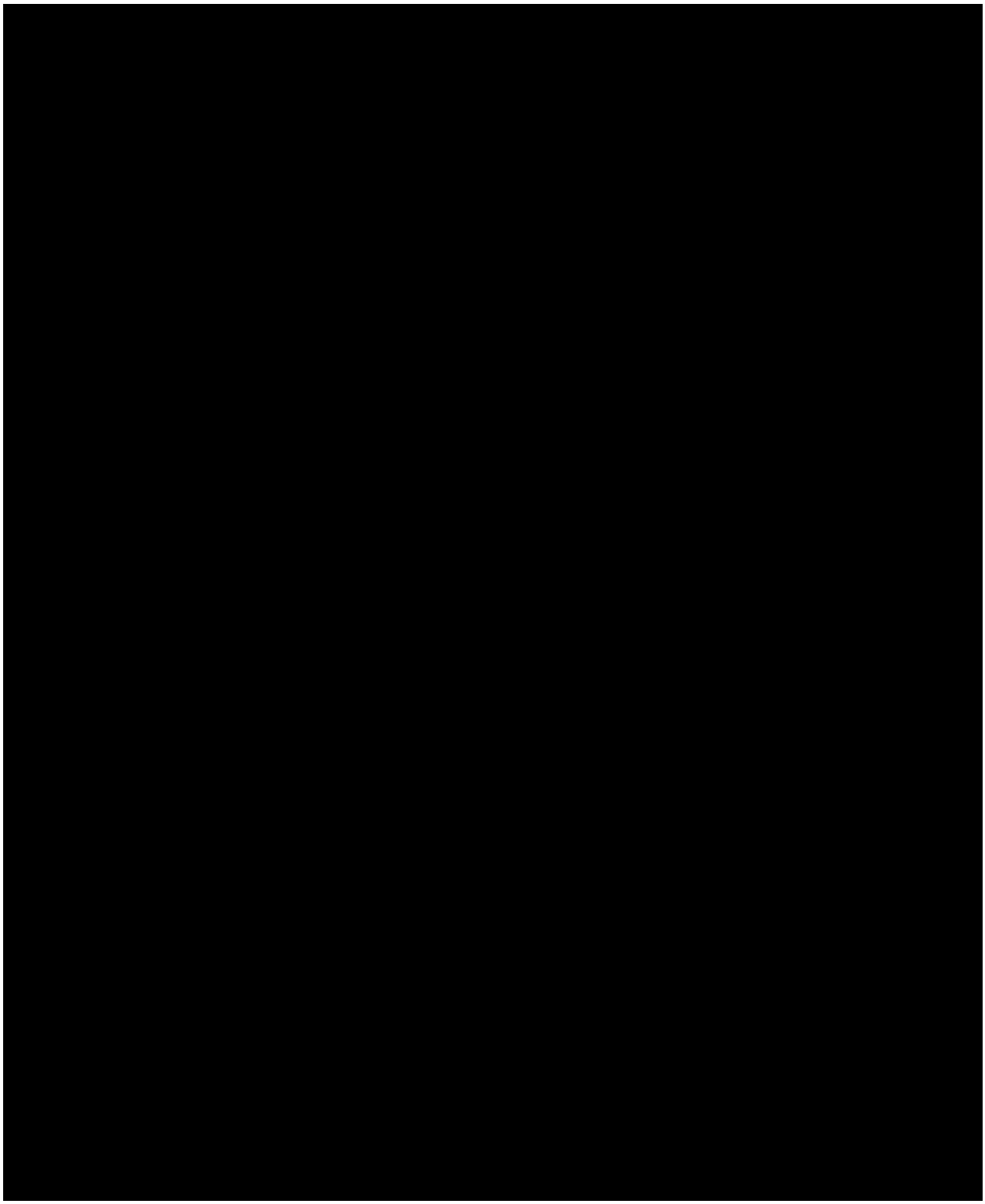


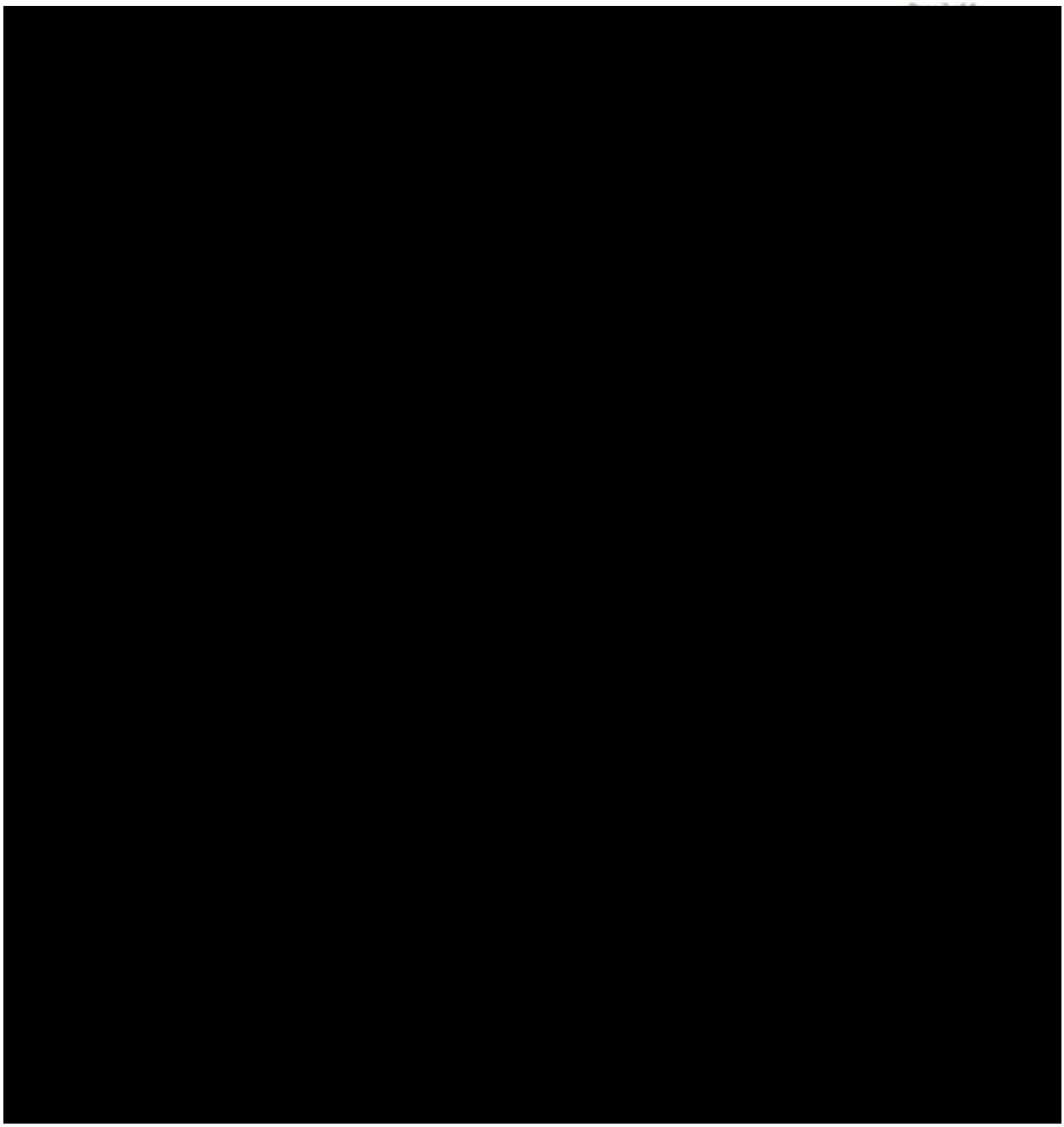


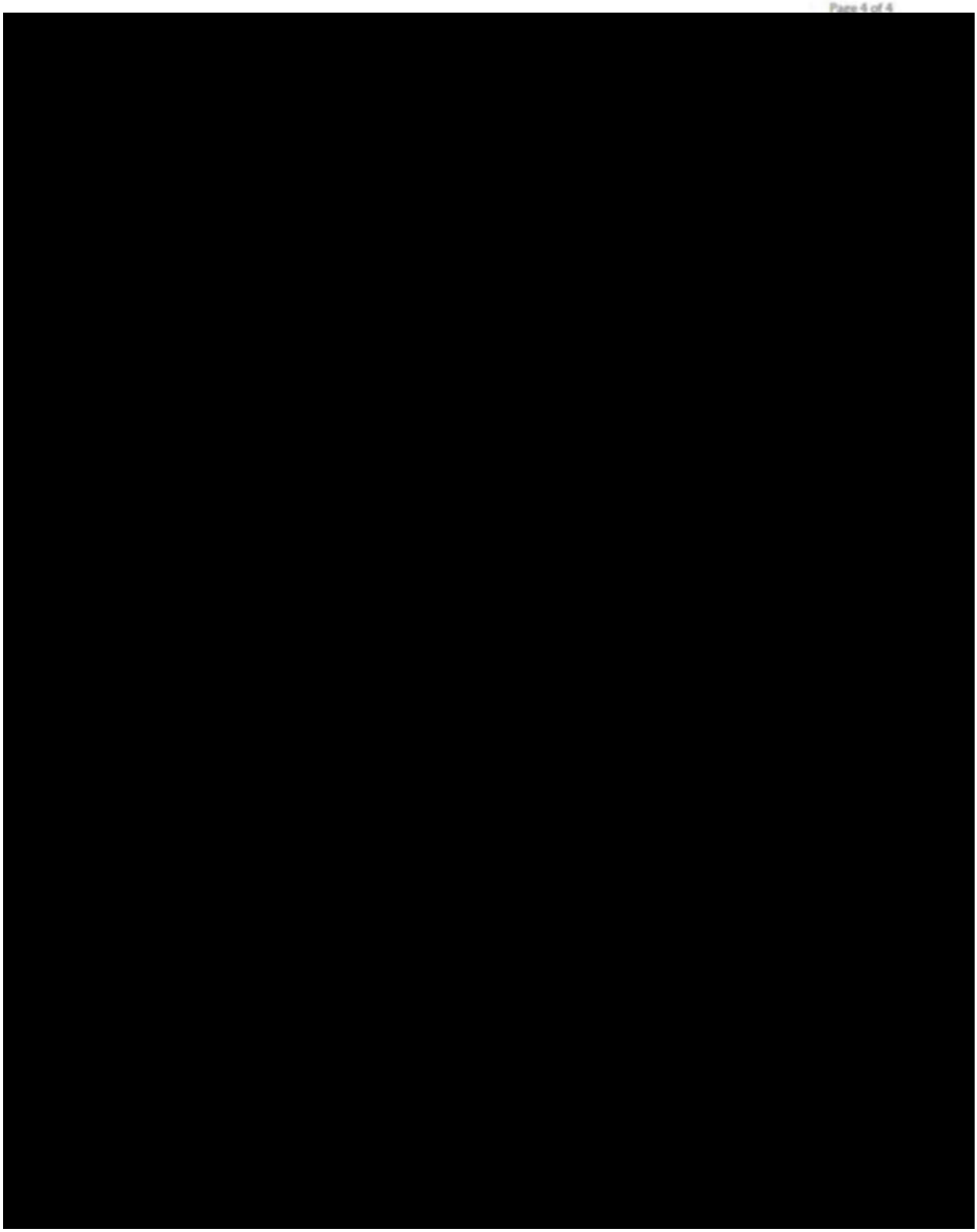


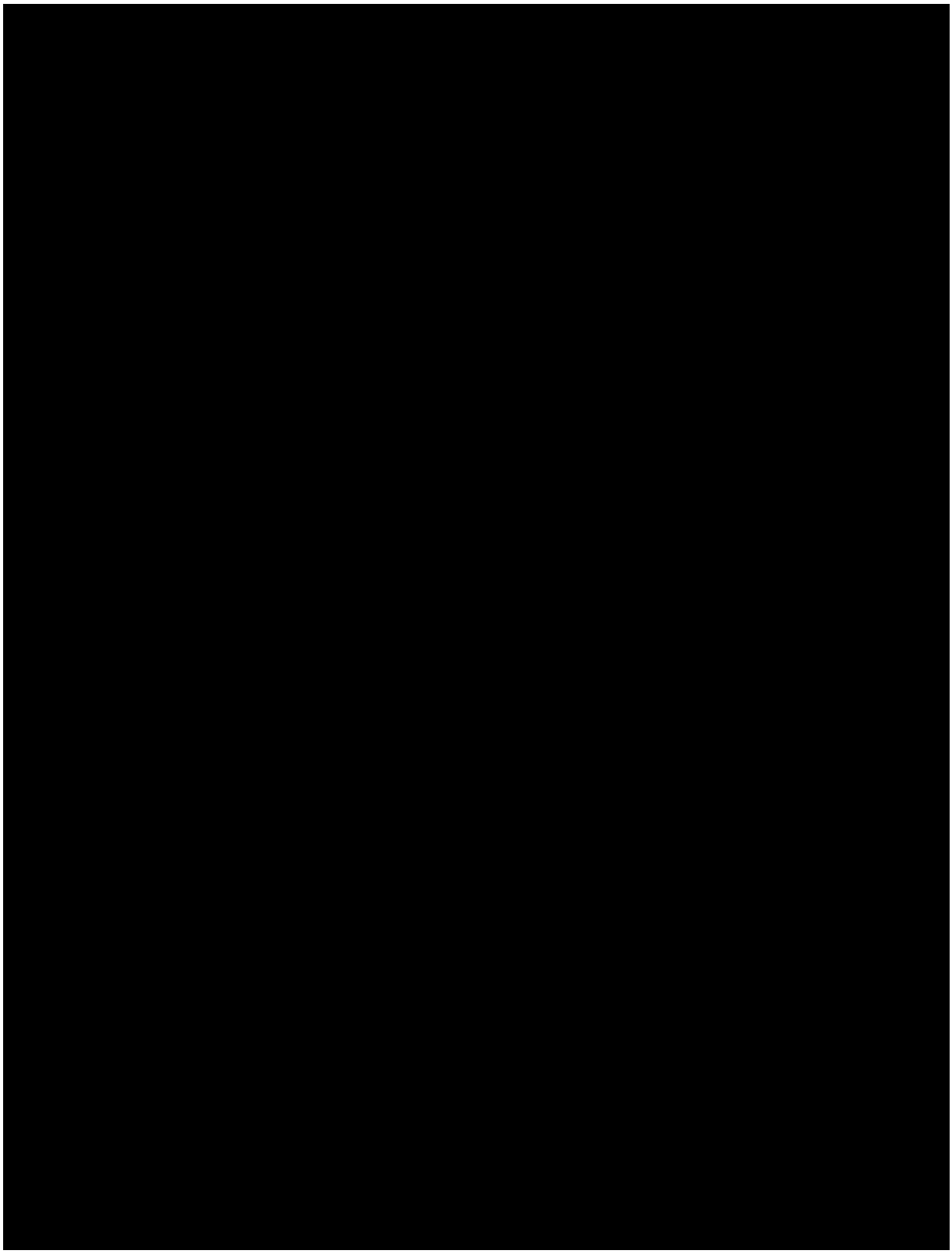


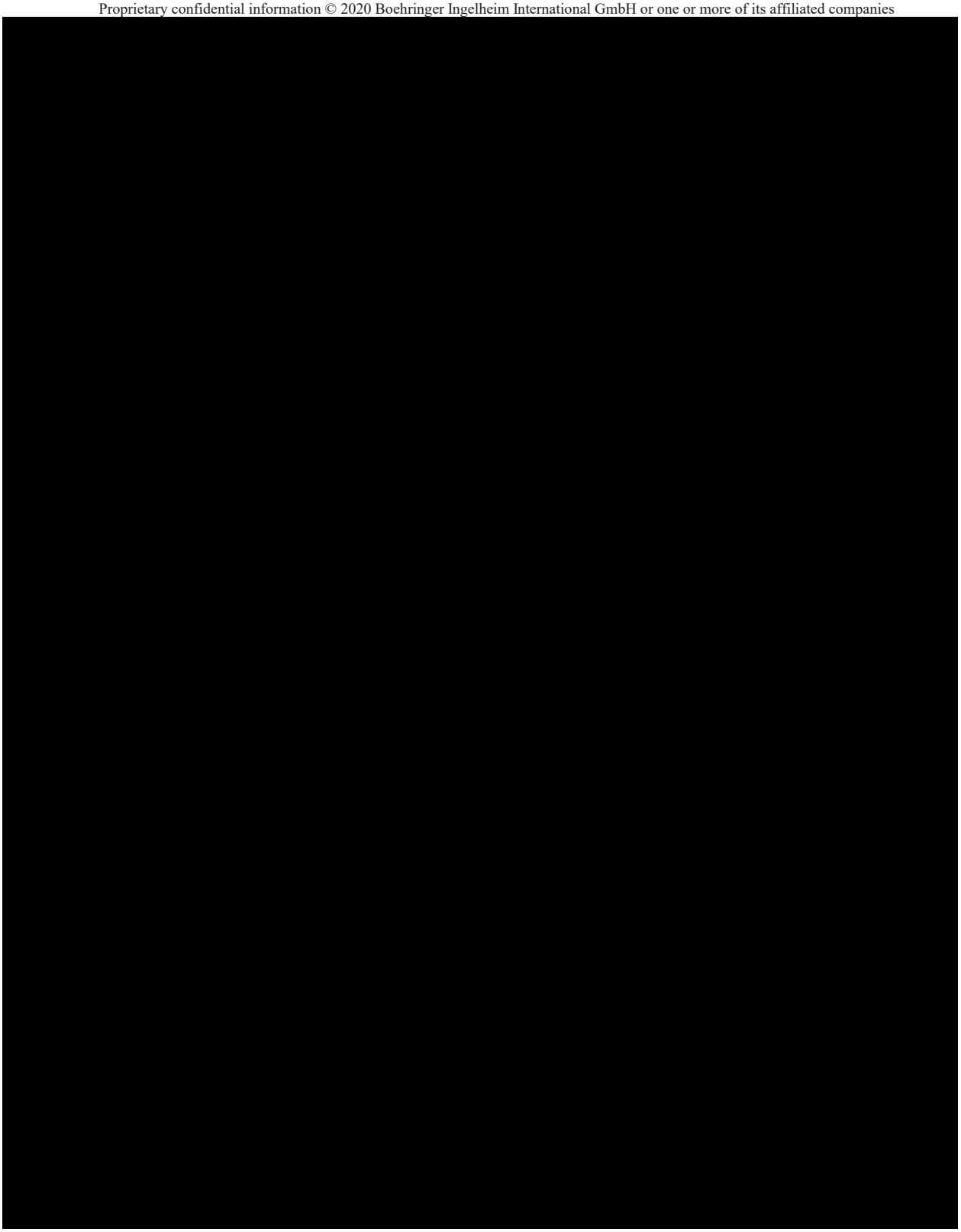


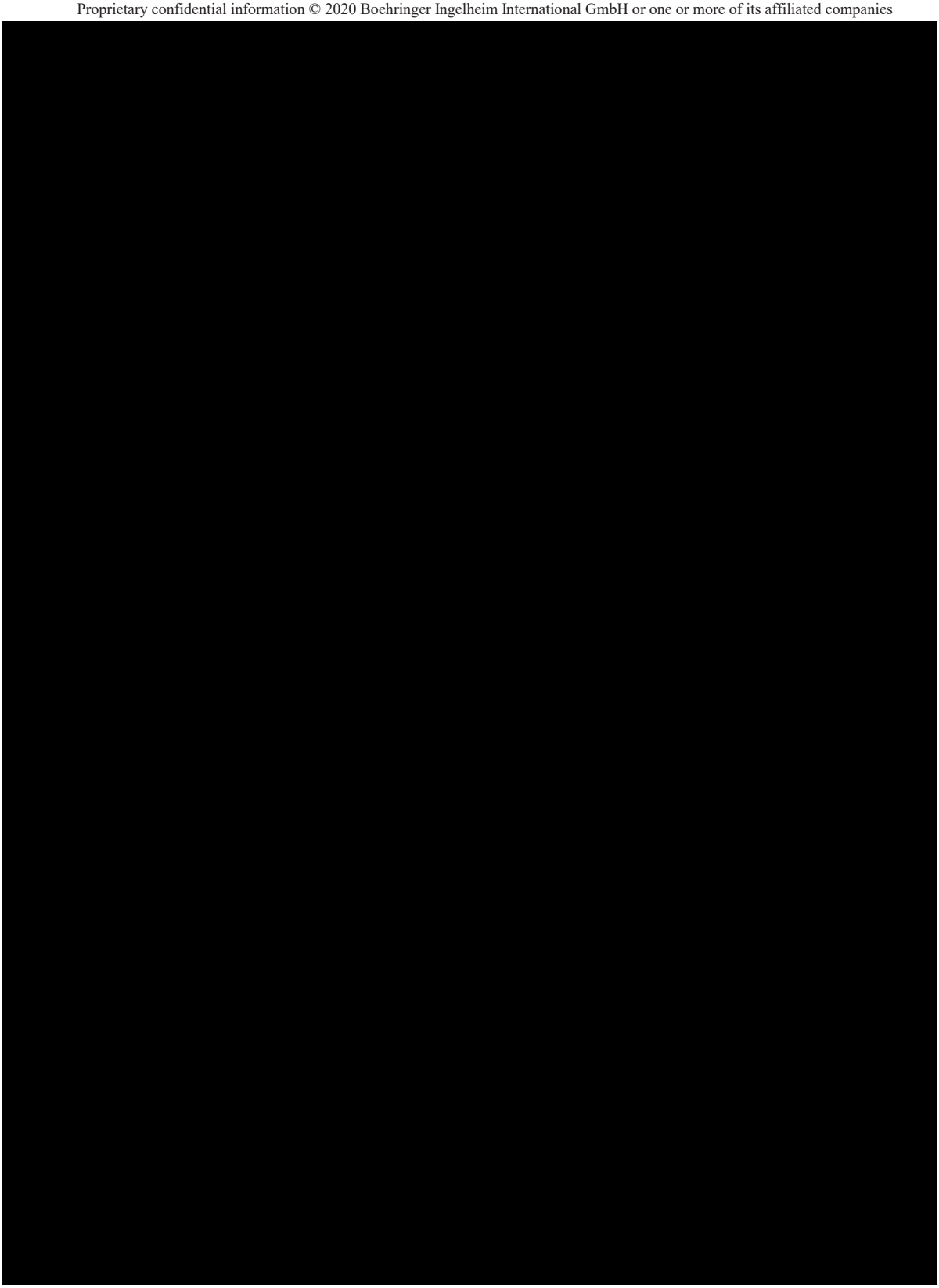


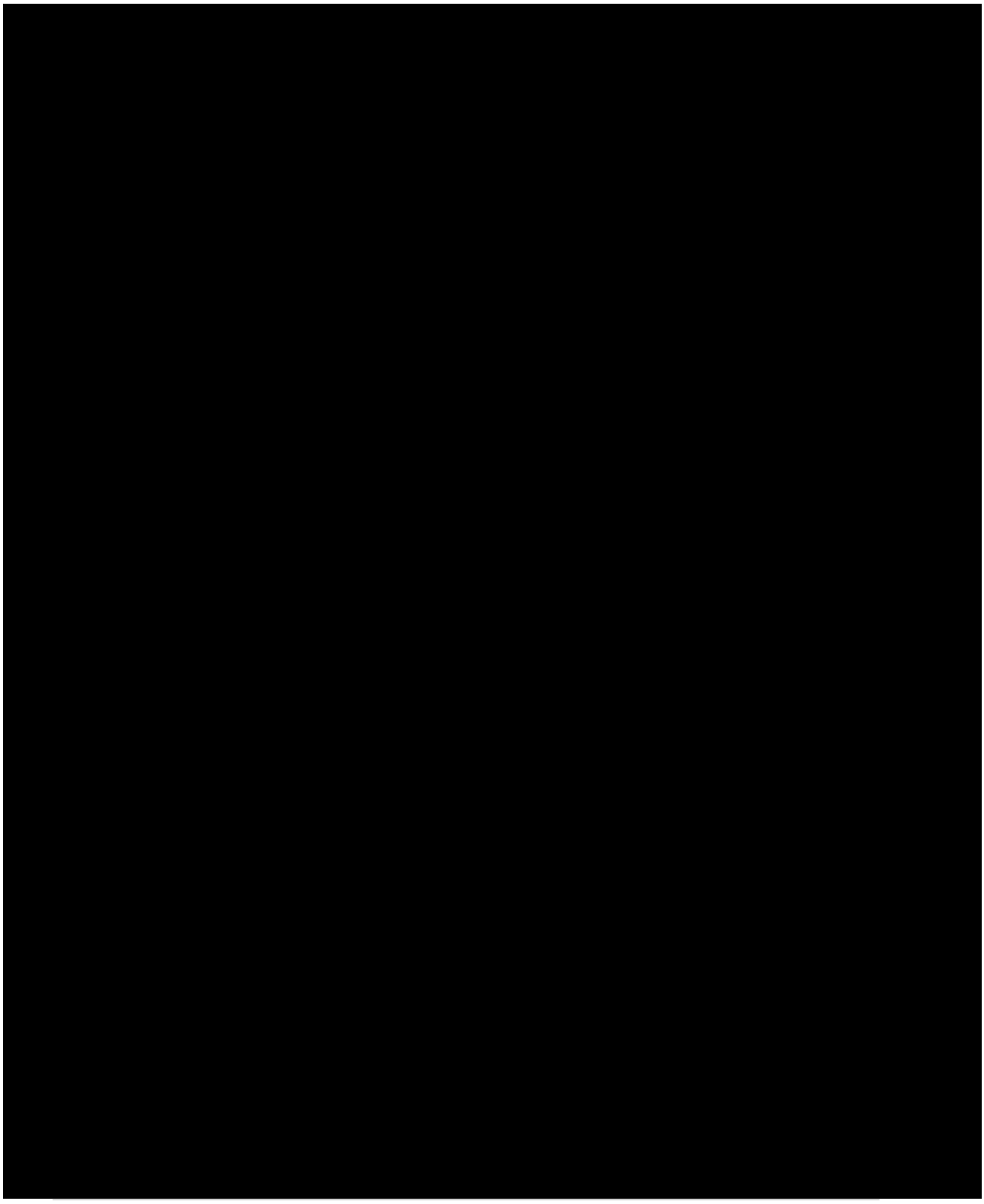












10.2 COLUMBIA SUICIDAL SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both, behavior and ideation. The C-SSRS was designed to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsel or, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on patients. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.
The investigator is to review all positive and negative reports for plausibility and clinical relevance. Doubtful reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the patient during the clinic visit and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the patient's safety have to be initiated.

At screening, C-SSRS (screening version) will be used with the aim to exclude patients with suicidal ideation type 4 to5 within the preceding 3 months or at Visit 1 or any suicidal behaviour in the past 2 years.
Subsequently, the C-SSRS "since last visit will be performed at the time points given in the Flow Chart. For assessment, paper forms will be used and results will be transcribed into the CRF.

All positive reports during trial treatment are treatment-emergent adverse events (AEs).
The results of further medical, including psychiatric examinations,Y should be documented as adverse events where appropriate.

The original Columbia Suicidal Severity Rating scales used in this trial are shown as follows:

- Visit 1 –Screening version
- Subsequent visits- Since last visit version.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Past X Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts: General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrent: ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events; must ask about all types)*	**Past X Years or Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 17Feb09

SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent*)* If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprain). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.3 DLCO

At Visit 1, DLCO must fulfil the following criteria:

∀ Within range 25% - 80% predicted of normal; corrected for Hb

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the method used must be in compliance with the ATS/ERS guideline on DLCO measurements [R06-2002], and the prediction formula

appropriate for that method. Raw data (gas mixture, equation for the prediction of normal, further adjustments made if so), must be traced.

Predicted DLCO corrected for haemoglobin (Hb) expressed in g x dL^{-1} [R06-2002] can be calculated as:
Predicted DLCO corrected for Hb = Predicted DLCO x (1.7Hb/(10.22+Hb)) for males
Predicted DLCO corrected for Hb= Predicted DLCO x (1.7Hb/(9.38+Hb)) for females

For decision on inclusion/exclusion, DLCO results from visit 1 will be corrected for haemoglobin (value obtained at visit 1) by the site.

For analysis of the trial data, DLCO results will be corrected for haemoglobin by central data management. This means that the site has to enter the DLCO results without haemoglobin correction, in the eCRF, at applicable visits.

There should be at least two acceptable tests that meet the repeatability requirement of either being within 3 mL CO (Standard Temperature and Pressure, Dry - STPD)•min-1 •mmHg-1 (or 1 mmol•min-1•kPa-1) of each other or within 10% of the highest value.

10.5 ELIGIBILITY CONFIRMATION OF IPF DIAGNOSIS

Eligible are Patients with a clinical diagnosis of IPF based on the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline on the diagnosis of IPF as confirmed by the investigator based on chest HRCT scan taken within 12 month of Visit 1 and if available surgical lung biopsy.

All chest HRCTs will be sent for central review by an experienced expert based on the recent ATS/ERS/JRS/ALAT guideline on the diagnosis of IPF and Fleischner Society white paper [R17-4075].

Patients with a centrally reviewed HRCT pattern qualifying as UIP or probable UIP are eligible for participation and are not required to have a surgical lung biopsy in the appropriate clinical context for the diagnosis of IPF.

Patients clinically suspected to have IPF with an HRCT pattern indeterminate for UIP, or suggesting an alternative diagnosis require historical (ie not taken for the purpose of this trial) surgical lung biopsy which will be reviewed locally (by the investigator/local histo-pathologist). In these patients, specific combinations of HRCT patterns and histopathology patterns may still allow a diagnosis of IPF based on the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline on the diagnosis of IPF. E.g. An HRCT pattern of "indeterminate for UIP" in combination with a surgical lung biopsy with an histopathology pattern of “UIP or probable UIP” could qualify for inclusion.

Appropriate documentation at site for these cases is required. Copies of the original, histopathological assessments and resulting diagnosis are required in patient files.

IPF suspected[1]		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)[2]	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)[2]	Indeterminate[3]	Non-IPF dx
	Alternative diagnosis	IPF(Likely)[2]/non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

dx = diagnosis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

(adapted from Figure 8 in R18-2794)
Idiopathic pulmonary fibrosis diagnosis based upon HRCT and biopsy patterns.
[1] “Clinically suspected of having IPF” = unexplained symptomatic or asymptomatic patterns of bilateral pulmonary fibrosis on a chest radiograph or chest computed tomography, bibasilar inspiratory crackles, and age greater than 60 years. (Middle-aged adults [.40 yr and ,60 yr], especially patients with risks for familial pulmonary fibrosis, can rarely present with the otherwise same clinical scenario as the typical patient older than 60 years.)
[2] IPF is the likely diagnosis when any of the following features are present:

- ∀ Moderate-to-severe traction bronchiectasis/bronchiolectasis (defined as mild traction bronchiectasis/bronchiolectasis in four or more lobes including the lingual as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man over age 50 years or in a woman over age 60 years
- ∀ Extensive (.30%) reticulation on HRCT and an age .70 years
- ∀ Increased neutrophils and/or absence of lymphocytosis in BAL fluid
- ∀ Multidisciplinary discussion reaches a confident diagnosis of IPF.

[3] Indeterminate for IPF

- ∀ Without an adequate biopsy is unlikely to be IPF
- ∀ With an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation.

10.6 CREATININE CLEARANCE

Calculation Name	**GFR CKD-EPI**	
Formula	**Units**	**Decimal Places**
Conventional: **Black or African American formulas:** Female with a serum creatinine value of ≤0.7 mg/dL $166 \times (\text{Serum Creatinine (mg/dL)} / 0.7)^{-0.329} \times (0.993)^{\text{age}}$ Female with a serum creatinine value of >0.7 mg/dL $166 \times (\text{Serum Creatinine (mg/dL)} / 0.7)^{-1.209} \times (0.993)^{\text{age}}$ Male with a serum creatinine value of ≤0.9 mg/dL $163 \times (\text{Serum Creatinine (mg/dL)} / 0.9)^{-0.411} \times (0.993)^{\text{age}}$ Male with a serum creatinine value of >0.9 mg/dL $163 \times (\text{Serum Creatinine (mg/dL)} / 0.9)^{-1.209} \times (0.993)^{\text{age}}$ **White, American Indian, Alaska Native, Asian, Native Hawaiian, Other Pacific Islander, Other formulas:** Female with a serum creatinine value of ≤0.7 mg/dL $144 \times (\text{Serum Creatinine (mg/dL)} / 0.7)^{-0.329} \times (0.993)^{\text{age}}$ Female with a serum creatinine value of >0.7 mg/dL $144 \times (\text{Serum Creatinine (mg/dL)} / 0.7)^{-1.209} \times (0.993)^{\text{age}}$ Male with a serum creatinine value of ≤0.9 mg/dL $141 \times (\text{Serum Creatinine (mg/dL)} / 0.9)^{-0.411} \times (0.993)^{\text{age}}$ Male with a serum creatinine value of >0.9 mg/dL $141 \times (\text{Serum Creatinine (mg/dL)} / 0.9)^{-1.209} \times (0.993)^{\text{age}}$ Creatinine in mg/dL is rounded to 2 decimal places prior to applying the formula.	mL/min/ 1.73m²	0
SI: Serum creatinine in µmol/L will be rounded to zero decimal	mL/min/ 1.73m²	0

place and converted to mg/dL by multiplying by 0.01131. This creatinine value in mg/dL will be rounded to 1 decimal place. This creatinine result will be used in the GFR Conventional formulas listed above.		
Limitations/Special Notes:	Age is truncated to a whole number prior to performing the calculation.	

Japanese formula will be used for Japanese patients.

10.7 EQUIVALENT DOSES OF CORTICOSTEROIDS

Table 10.7: 1 Equivalent Doses of Corticosteroids

Drug	Equivalent dose (mg)	Conversion factor
Prednisone	5	x 1
Prednisolone	5	x 1
Triamcinolone	4	x 1.25
6-Methylprednisolone	4	x 1.25
Dexamethasone	1	x 5
Betamethasone	0.75	x 6.7
16-Methylprednisolone	6	x 0.8
Fluocortalon	5	x 1
Cloprednol	3,75-5	x 1.0-1.5
Deflazacort	6	x 0.8
Cortisol (hydrocortisone)	20	x 0.25
Cortisone	25	x 0.20

10.8 RESTRICTED MEDICATIONS TABLES

Lists of medication can be found in the sections below. The lists are not exhaustive and will not be updated during the course of the trial.
Investigators are advised to verify product labelling /information.

10.8.1 Strong CYP3A4 inhibitors

Strong CYP 3A4 inhibitors:

- ∀ boceprevir
- ∀ clarithromycin
- ∀ cobicistat
- ∀ conivaptan

- ∀ diltiazem
- ∀ idelalisib
- ∀ itraconazole
- ∀ ketoconazole oral administration
- ∀ nefazodone
- ∀ nelfinafir
- ∀ posaconazole
- ∀ ritonavir
- ∀ telaprevir
- ∀ troleandomycin
- ∀ voriconazole

Combinations of CYP 3A4 inhibitors:

- ∀ danoprevir/ritonavir
- ∀ elvitegravir/ritonavir
- ∀ indinavir/ritonavir
- ∀ lopinavir/ritonavir
- ∀ paritaprevir/ritonavir/ombitasvir/dasbuvir
- ∀ saquinavir/ritonavir
- ∀ tipranavir/ritonavir

10.8.2 Restricted PDE inhibitors

Compound	Indication
Non-selective	
Theophylline (Theolair, Slo-Bid, Theo 24)	Asthma and bronchoconstriction
Aminophylline (Phyllocontin)	Asthma and bronchoconstriction
Oxtriphylline (Choledyl)	Asthma and bronchoconstriction
Dyphylline (inhibits PDE3, 4, 7, adenosine 2 receptors) (Dilor, Lufyllin)	Asthma and bronchoconstriction
Pentoxifylline (inhibits PDE4, 5, adenosine 2 receptors) (Trental, Pentoxil)	Intermittent claudication
Ibudilast (highest affinity for PDE10A, 4, 11, 3) (Ketas, Pinatos, Eyevinal)	Asthma and dizziness related to cerebral infarction
	Allergic conjunctivitis

Compound	Indication
Tofisopam (highest affinity for PDE4, 10, 3, 2) (Emandaxin, Grandaxin)	Anxiety
Dipyridamole (highest affinity for PDE8, 1, 3, 2, adenosine deaminase and ENT1) (Persantine)	Post-operative thromboembolism
PDE1	
Vinpocetine (Cavinton)	Cerebral vascular disorders and memory impairment
PDE3	
Cilostazol (Pletal, Ekistol)	Intermittent claudication
Milrinone (Primacor, Corotrope)	Congestive heart failure
Amrinone (Inamrinone, Inocor)	Congestive heart failure
Enoximone (Perfan)	Congestive heart failure
Olprinone (Coretec)	Heart failure
Pimobendan (Acardi)	Heart failure
Anagrelide (also inhibits phospholipase A2) (Agrylin, Xagrid)	Thrombocythaemia
PDE4	
Roflumilast (Daliresp, Daxas)	Chronic obstructive pulmonary disease
Apremilast (Otezla)	Psoriasis and psoriatic disorders
Crisaborole (Eucrisa)	Moderate atopic dermatitis (patients >2 years old)
Drotaverine (also inhibits L-type voltage-operated calcium channel) (No-Spa, Doverin)	Functional bowel disorders; pain caused by smooth muscle spasm
PDE10A	
Papaverine (Pavabid, Pavagen)	Visceral spasm, vasospasm and erectile dysfunction

10.9 PRIOR CALCULATION

Below are some further details on the informative priors for the placebo group of patients not on antifibrotic treatment and those on antifibrotic treatment

Prior for the placebo group of patients not on antifibrotic treatment
The estimated adjusted means and standard errors from Table 7.2.2.1:1 were used in the meta-analytic predictive (MAP) prior approach using the 'gMap' function from the RBest package. The used beta prior within the gMap function was defined as mean=0 and an SD=189. For the between-trial heterogeneity the tau prior was defined as mean=0 and SD=189/4. The graphical summary of this MAP analysis can be seen in Figure 10.9:1 below.

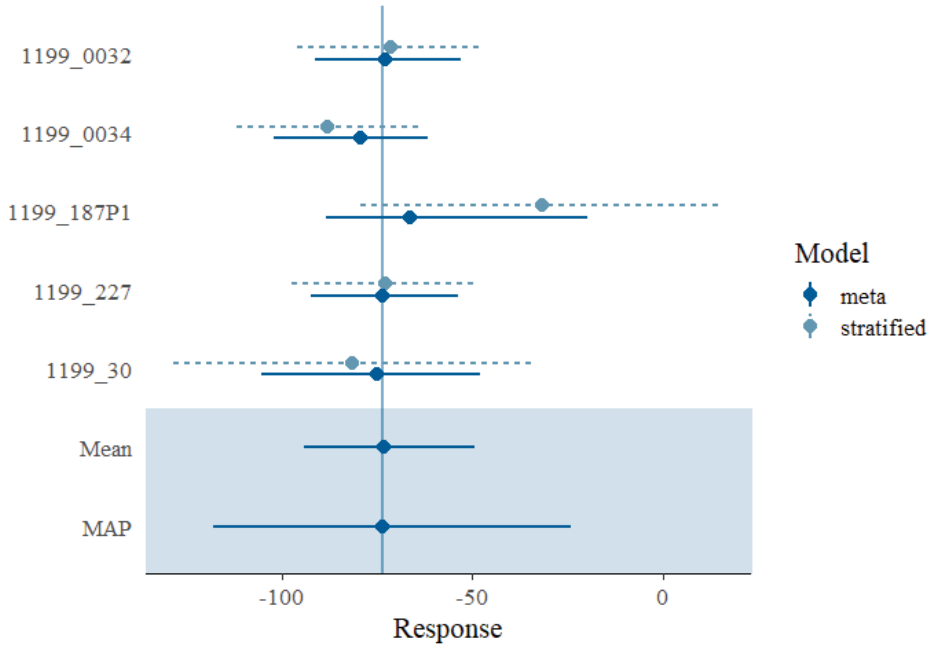

Figure 10.9:1 MAP forest plot using the 5 historical studies.

In a next step the 'automaxfit' function is used to approximate the MAP prior with parametric density. The informative prior now consists of the following 3 components:

	Component 1	Component 2	Component 3
Weight	0.5623	0.3714	0.0663
Mean	-74.0307	-71.1166	-70.2132
SD	9.4634	24.8125	57.5269

To achieve robustness in case of prior-data conflict, a vaguely informative mixture component is added (Components 4 with weight=0.5, mean=-73 and SE=185.7). Finally, the prior is further down weighted by increasing the SD of all components by a factor of 1.7 to come to an effective sample size of around 20. This allows approximate 50% weight for new data collected in this study. The density plot of the final prior for the placebo group of patients not on SoC antifibrotic treatment can be found in Figure 10.9:2.

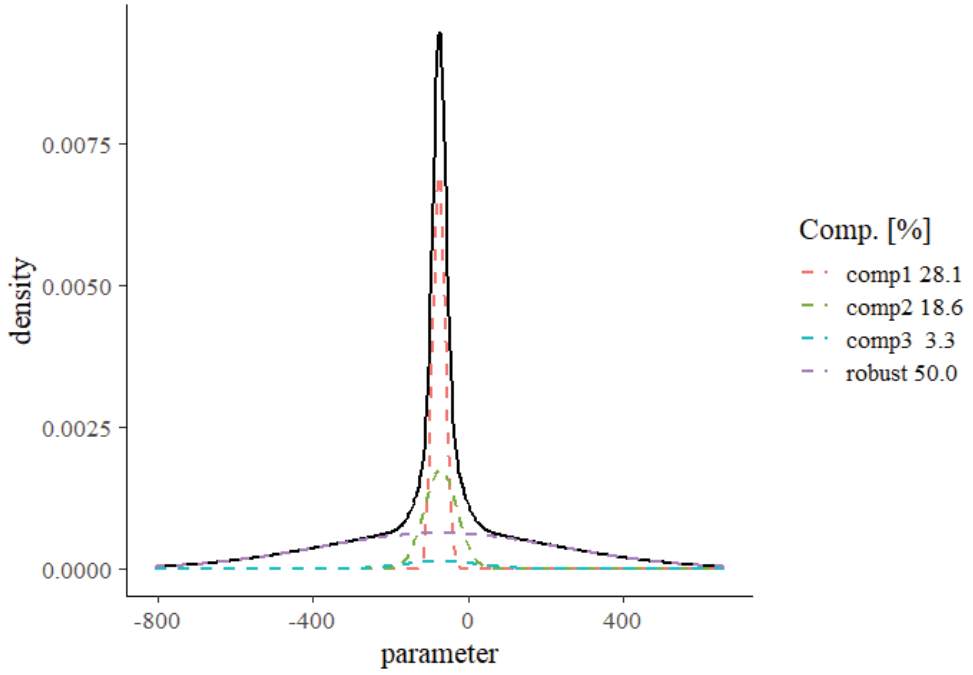

Figure 10.9:2 Density plot of the informative prior (black line) and its 4 components (coloured dashed lines).

The final informative prior consists of the following 4 components:

	Component 1	Component 2	Component 3	Component 4
Weight	0.2811	0.1857	0.0331	0.5
Mean	-74.0307	-71.1166	-70.2132	-73
SD	16.0807	42.1812	97.7958	315.7164

Prior for the placebo group of patients on SoC antifibrotic treatment
The estimated adjusted means and standard errors from Table 7.2.2.1: 1 were used in the meta-analytic predictive (MAP) prior approach using the 'gMap' function from the RBest package. The used beta prior within the gMap function was defined as mean=0 and an

SD=186. For the between-trial heterogeneity the tau prior was defined as mean=0 and SD=186/4. The graphical summary of this MAP analysis can be seen in Figure 10.9:3 below.

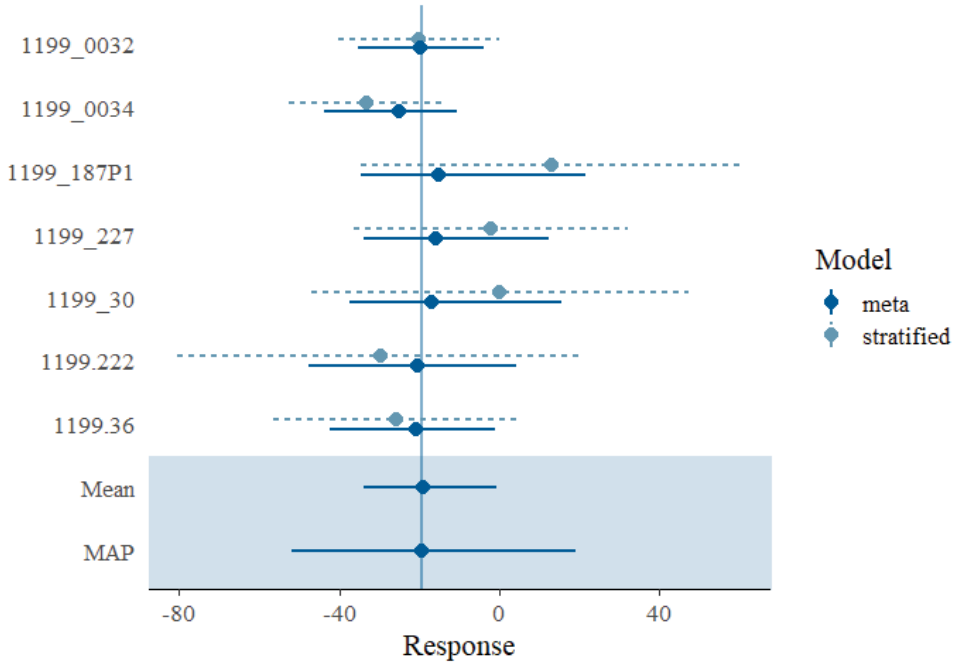

Figure 10.9:3 MAP forest plot using the 8 historical studies.

In a next step the‘automaxfit’ function is used to approximate the MAP prior with parametric density using the. The informative prior now consists of the following 3 components:

	Component 1	Component 2	Component 3
Weight	0.5436	0.3933	0.0631
Mean	-20.0640	-17.0402	-15.4163
SD	7.7454	18.9645	41.7590

To achieve robustness in case of prior-data conflict, a vaguely informative mixture component is added (Components 4 with weight=0.5, mean=-19 and SE=183.6661). Finally, the prior is further down weighted by increasing the SD of all components by a factor of 2.1 to come to an effective sample size of around 20. This allows approximately 50% weight for new data collected in this study. The density plot of the final prior for the placebo group of patients on SoC antifibrotic treatment can be found in Figure 10.9:4.

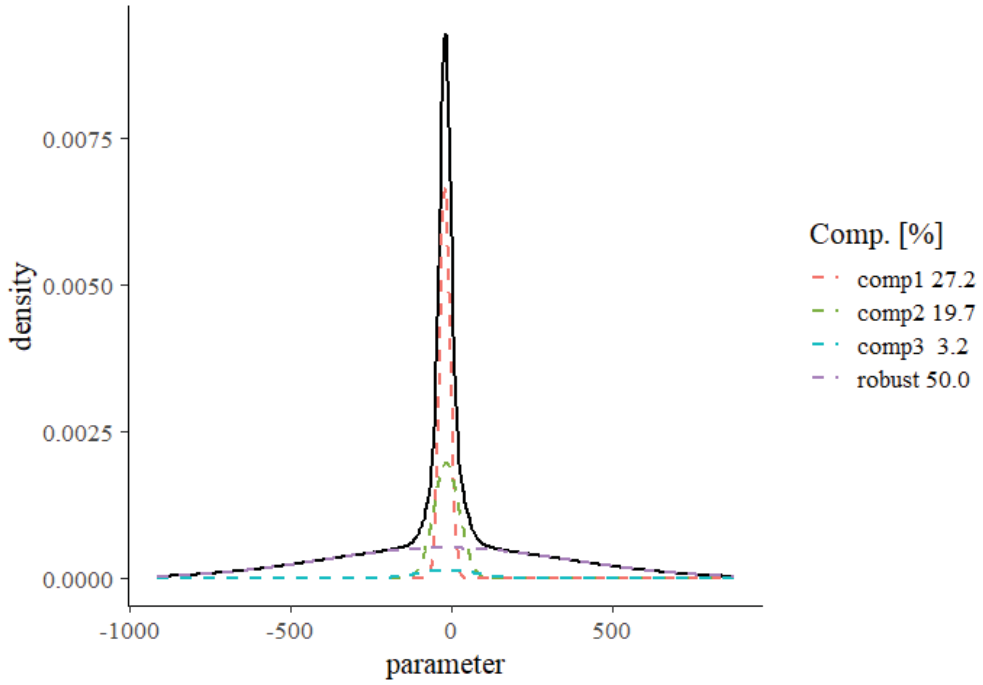

Figure 10.9:4 Density plot of the informative prior (black line) and its 4 components (coloured dashed lines).

The final informative prior consists of the following 4 components:

	Component 1	Component 2	Component 3	Component 4
Weight	0.2718	0.1966	0.0316	0.5
Mean	-20.0640	-17.0402	-15.4163	-19
SD	16.2653	39.8255	87.6940	385.6988

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		27 May 2020
EudraCT number **EU number**		2019-004167-45
BI Trial number		1305-0013
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally.
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title
Description of change		Dose and regimen deleted
Rationale for change		To fullfill internal rules of disclosure. No change of the trial design.
Section to be changed		Flowchart – footnote#11
Description of change		Clarification about DNA and serum/plasma biobanking samples.
Rationale for change		To correct a mistake which is already operationally corrected. The central laboratory builds laboratory kits for the trial according to this specification. To include the correction already described in a note to file prepared on 01 Apr 20. No changes to the procedures performed in the trial.
Section to be changed		Table 5.2.3.1
Description of change		Addition of a missing letter and deletion of a coma.
Rationale for change		Typo correction.

11.2 GLOBAL AMENDMENT 2

Date of amendment		02 Jun 2020
EudraCT number **EU number**		2019-004167-45
BI Trial number		1305-0013
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI

		1015550 taken orally.
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Flowchart – footnote#9
Description of change		Clarification for Germany that only historical HRCT can be used for the trial.
Rationale for change		To clarify this point. No change on the trial design.
Section to be changed		Section 1.4.2 – table risks
Description of change		Format change for some part which were in hidden text in version 1.0 : Risks associated with blood sampling, HRCT and lung measurements (PFT and DLCO) were missing as well as risk and mitigation plan for placebo use.
Rationale for change		To make the whole text legible. Risks are described in the informed consent of the trial from the beginning.
Section to be changed		Section 5.2.4 – Electrocardiogram recording
Description of change		Correction of a mistake : no post dose ECG at V2 and not triplicate ECG expected.
Rationale for change		To correct a mistake as this assessment was not expected to be performed.
Section to be changed		Section 5.2.6.1.5 Acute IPF exacerbations.
Description of change		Precision of the term to be reported. Deletion of the fact that a dedicated page has to be completed into the eCRF.
Rationale for change		To correspond to the final design of the eCRF.
Section to be changed		Section 5.6.1 Digital lung Auscultation Test
Description of change		Less points of auscultations used and clarification that the results will not be reported into the clinical trial report.
Rationale for change		To correct a mistake.
Section to be changed		Section 5.6.2 24 hours cough measurement.
Description of change		Addition of an inclusion criteria to enter the sub study. Clarification on the evaluations performed.

Rationale for change		To ensure that participants to the sub study cough enough to be evaluated and to clarify the comparisons which will be performed.
Section to be changed		Section 6.2
Description of change		Deletion of the mention of a post dose ECG at Visit 2.
Rationale for change		To correct a mistake as this assessment was not planned to be performed.

11.3 GLOBAL AMENDMENT 3

Date of amendment		09 Sep 2020
EudraCT number **EU number**		2019-004167-45
BI Trial number		1305-0013
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally.
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Flowchart + footnote #12, Section 3.1, Section 5.6, Section 5.6.1, 6.2.4
Description of change		Deletion of optional lung sound substudy
Rationale for change		This substudy will not be held because of timelines needed to validate the application to be used to record the lung sound and perform the quality check of the acquisition.
Section to be changed		1.2.5 Data from non-clinical studies
Description of change		Addition of information pertanining to histopathological changes observed during non-clinical studies.
Rationale for change		To have a better understanding of the toxicology profile of the molecule.
Section to be changed		Table 1.4.2:1 Overview of trial related risks
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		3.3 Selection of trial population
Description of change		Clarification of wording about eligibility requirements and randomization.
Rationale for change		To address a request by German Federal Institute for Drugs and Medical Devices (BfArM) and leading Ethics Committee.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Addition of exclision criteria #27 (exclusion of patients with infection with SARS-CoV-2)
Rationale for change		To exclude patients with potential additional risk due to SARS-CoV-2 infection.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Addition of criteria to discontinue patients who meet AESI definition of hepatic injury
Rationale for change		Provision of additional guidance in case AESI definitions are fulfilled.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Addition of criteria to discontinue patients who experience infection with SARS-CoV-2
Rationale for change		To ensure safety of patients who may become infected with SARS-CoV-2.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Information added outlining shipments direct to patient if required due to COVID-19 pandemic
Rationale for change		Direct shipments may be required in order to not interrupt treatment if a patient is not able to attend a visit due to COVID-19 related constraints.
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Correction to clarfy that ESR testing will be performed on-site not by central lab.
Rationale for change		Correction and clarification.
Section to be changed		6.1 Visit schedule, 6.2.2 Treatment period, 8.1Trial approval, patient information, informed consent
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 exceptional situations to ensure patients safety by ensuring continuous treatment.

Section to be changed		7.5 Determination of sample size
Description of change		Correction of rounding error of probabilities, and addition of footnote to table 7.5.2
Rationale for change		To address a request by German Federal Institute for Drugs and Medical Devices (BfArM) and leading Ethics Committee.