Clinical Trial Protocol

	Document Number:	**c40742178-04**
EU Clinical Trial No.	2022-502835-21-00	
Universal Trial Number	U1111-1291-2567	
BI Trial No.	1397-0013 (Clairafly™)	
BI Investigational Medicinal Product(s)	BI 1291583	
Title	A randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 one tablet once daily over 12 weeks versus placebo in adult patients with cystic fibrosis bronchiectasis (Clairafly™)	
Lay Title	A study to test how well BI 1291583 is tolerated by people with cystic fibrosis bronchiectasis (Clairafly™)	
Clinical Phase	IIa	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted] Email: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted] Email: [redacted]	
Current Version and Date	Version 4.0, 21-Nov-2023	
Original Protocol Date	Version 1.0, 09-May-2023	Page 1 of 125

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	Version 1.0, 09-May-2023
Revision date	21 Nov 2023
BI trial number **EU CT number** **Universal Trial Number**	1397-0013 (Clairafly™) 2022-502835-21-00 U1111-1291-2567
Title of trial	A randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 one tablet once daily over 12 weeks versus placebo in adult patients with cystic fibrosis bronchiectasis (Clairafly™)
Coordinating Investigator	[redacted]
Trial sites	Multi-centre trial conducted in approximately 7 countries
Clinical phase	IIa
Trial rationale	The intent of this profiling study is to assess safety, pharmacokinetics and pharmacodynamics of BI 1291583 in patients with cystic fibrosis bronchiectasis (CFB). [redacted]
Benefit-risk assessment and ethical considerations	The nature of the target and the mechanism of action of BI 1291583 is well understood. In the context of the unmet medical need and anticipated benefit of BI 1291583 for the study population, the benefit-risk evaluation of the compound, based upon the available preclinical and clinical information, is considered favorable.
Trial objectives	Primary objective: To investigate safety and tolerability of 5 mg BI 1291583 in patients with CFB following oral daily administration over 12 weeks. Secondary objectives: To investigate pharmacodynamics (PD) and to assess the PK after the first dose and at steady state after multiple dosing of BI 1291583 5 mg qd
Trial endpoints	Primary endpoint: Occurrence of TEAEs up to 16 weeks from first drug administration

Trial endpoints, cont.	Secondary endpoints: • Relative change from baseline in Neutrophil elastase (NE) activity in sputum at Week 8 after first drug administration • AUC over a dosing interval (AUC_{τ}) for the first dose • Maximum concentration (C_{max}) for the first dose • AUC_{τ} at steady state ($AUC_{\tau,ss}$) • C_{max} at steady state ($C_{max,ss}$)
Trial design	Multi-center, randomised, placebo-controlled, double-blind, parallel group trial to evaluate safety, tolerability, PD and PK of BI 1291583 5 mg p.o. qd over 12 weeks versus placebo in adult patients with CFB.
Total number of trial participants randomised	24 eligible patients
Number of trial participants per treatment group	• 16 patients on BI 1291583 5 mg qd • 8 patients on Placebo qd
Diagnosis, main inclusion and exclusion criteria	Main Diagnosis Cystic fibrosis bronchiectasis (CFB) Main inclusion criterion Adult patients of either sex with a diagnosis of CFB (confirmed by CT) treated or not treated with cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy (individual standard of care) Main exclusion criterion Any acute infection requiring systemic or inhaled anti-infective therapy or clinically relevant respiratory infection within 4 weeks prior first trial drug intake
Test product	BI 1291583
Dose and mode of administration	5 mg qd, p.o. (oral)
Comparator product	Matching placebo
Dose and mode of administration	Not applicable, p.o. (oral)
Duration of treatment	12 weeks
Statistical methods	The primary endpoint and secondary endpoints will be evaluated using descriptive statistics. No confirmatory testing is performed and hence no null and alternative hypotheses are defined. All evaluations are to be considered exploratory.

FLOW CHART

Trial Periods	**Screening**	**Treatment**					**End of study**
Visit	**1**	**2**	**3**	**4**	**5**	**6 / EoT [1]**	**7 / EoS[1] / FU**
Week	**-6**	**0**	**1**	**4**	**8**	**12**	**16**
Day	**-42**	**1**	**8**	**29**	**57**	**85**	**113**
Time window for visits [days]	**≥7 d prior V2**	**-**	**±3**	**±3**	**±3**	**±3**	**+7**
Informed consent[2]	X						
Demographics	X						
Medical history / proof of CFB diagnosis	X	X					
CT scan (proof of BE diagnosis)[3]	X						
Review of in-/ exclusion criteria	X	X					
Physical examination including skin	X	X	X	X	X	X	X
[redacted]							
Vital signs, pulse rate, blood pressure, aural body temperature[5]	X	X	X	X	X	X	X
Height (only at Visit 1) / body weight	X	X				X	
Sputum collection at site (spontaneous or induced)[6]	X	X		X	X	X	X
Sputum collected at home (backup sample, if needed)[7]		(X)		X	X	X	X
P. aeruginosa sputum sample for culture[8]	X					X	
Murray sputum colour chart	X	X					
[redacted]							
12-lead ECG	X	X		X		X	
[redacted]							
Panoramic radiography[11]	X						
Safety laboratory tests (blood / urine samples)[12]	X	X	X	X	X	X	(X)
Pregnancy tests[13]	X	X		X	X	X	X
Cotinine (urine)	X	X		X	X	X	X
[redacted]							
PK blood sample (profile)[15]		X				X	
PK blood sample (trough)[15]		X	X	X	X	X	

Trial Periods	**Screening**	**Treatment**					**End of study**
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[redacted]							
All AEs/SAEs/AESIs; concomitant therapy	X	X	X	X	X	X	X
Pulmonary exacerbation review, eCRF documentation		X	X	X	X	X	X
IRT call/notification	X[18]	X		X	X	X	
Randomisation		X[19]					
Dispense trial medication[20]		X		X	X		
Collect trial medication				X	X	X	
Compliance / drug accountability				X	X	X	
Completion of trial participant participation							X

1 Patients who completed treatment as planned will have an End of Treatment Visit (EOT) and a subsequent Follow up Visit after 28 (+7) days. The Follow-up Visit will be End of Study (EOS). Trial participants who discontinue trial treatment prematurely should undergo the EOT Visit as soon as possible and the EOS Visit 28 (+7) days thereafter.

2 Informed consent needs to be signed before any trial-related procedure is performed (before or at Visit 1).

3 CT scan not older than 5 years at randomisation. A new CT may be performed for the purpose of the study, if the patient is otherwise eligible. It has to be ensured that local regulatory requirements regarding radiation exposure are fulfilled.

4 [redacted]

5 Measurements of vital signs should precede blood sampling and intake of trial medication.

6 Sputum samples will be used for NE activity and other biomarker assessment, details are provided in the ISF / lab manual.

7 All patients will be provided sputum containers for sputum collection at home in the morning of visit days, if possible. At V2 only applicable in case patient's eligibility providing sputum sample at site already confirmed (see Section 5.4.1.3.2 for details).

8 *P. aeruginosa* culture from sputum samples will be performed at central lab.

9 [redacted]

10 [redacted]

11 A standard panoramic radiograph is required for baseline assessment of the periodontal status at the dentist, historical radiographs taken within 1 year prior to randomisation are acceptable. If a new radiograph needs to be performed within the scope of the trial, this should happen if the patient is otherwise eligible and, if applicable, in accordance with local regulations regarding radiation exposure.

12 Laboratory tests for safety monitoring: HBV and HCV tests to be performed only at Visit 1,

SARS-CoV-2 testing may be performed according to official local/national recommendations. At EOS, laboratory sample collection will be performed at the discretion of the investigator.

13 For WOCBP. At screening, a serum pregnancy test on β-HCG is performed. Urine dipstick pregnancy tests will be provided by central laboratory and should be performed at every visit (except at Visit 3).

14 [redacted]

(Note for Visit 1: fasting can only be asked for if informed consent was signed at least the day before V1)

15 PK trough samples will be taken at all visits just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded in the eCRF. Further PK samples for PK profile will be taken at Baseline and at EOT according to PK sampling time schedule (Appendix 10.2, PK time schedule). Patients will receive a PK-card at Visit 2 to support the recording of the exact clock time of medication intake for the previous two doses preceding PK sampling at subsequent visits.

16 [redacted]

17

18 Screening has to be registered in the Interactive Response Technology (IRT) system at time of informed consent to trigger initial medication supply to the site. The use of CFTR modulator therapy (CFTR-MT) has to be entered via the IRT module (CFTR-MT yes / no).

19 Randomisation V2: At randomisation the use of CFTR-MT has to be confirmed as stratification factor via the IRT module (CFTR-MT yes / no).

20 Patients should be instructed not to take their trial medication at home on scheduled visit days but bring it to the site and take it after respective pre-dose procedures have been performed.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse event of special interest
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine aminotransferase
AMP	Auxiliary medicinal product
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
BE	Bronchiectasis
BI	Boehringer Ingelheim
bid	Bis in die, twice daily
BM	Biomarker
BP	Blood pressure
CA	Competent Authority
CAT	COPD Assessment Test
CatC	Cathepsin C
CatG	Cathepsin G
CF	Cystic fibrosis
cfu	Colony forming units
CFB	Cystic fibrosis bronchiectasis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTR-MT	CFTR modulator therapy
[redacted]	
CI	Confidence interval
C_{max}	Maximum plasma concentration
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical research associate
CRF	Case report form, paper or electronic (sometimes referred to as "eCRF")
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organisation
CT	Computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical trial leader
CT Manager	Clinical trial manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DBL	Database lock
DILI	Drug induced liver injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DV	Deviation Domain
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EoS	End of study (corresponds with end of trial)
EoT	End of treatment
ERS	European Respiratory Society
[redacted]	
FU	Follow-up
[redacted]	
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health authority
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Reports
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator site file

IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LPLT	Last participant last treatment
LPLV	Last participant last visit
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed module with repeated measurements
MoA	Mode of Action
MRD	Multiple rising dose
NCFB	Non-cystic fibrosis bronchiectasis
NE	Neutrophil elastase
NOAEL	No observed adverse effect level
NSPs	Serine proteases released by neutrophils
OPU	Operative unit
p.o.	Per os (oral)
PD	Pharmacodynamics
PCD	Primary ciliary dyskinesia
PID	Primary immunodeficiency disorders
[redacted]	
PK	Pharmacokinetics
PKS	Pharmacokinetic set
PR	Pulse rate
PTM	Planned time
PV	Pharmacovigilance
qd	Quaque die (once a day)
[redacted]	
RA	Regulatory authority
RBC	Red blood cell
REML	Restricted maximum likelihood
REP	Residual effect period
RS	Randomised set
SAE	Serious adverse event

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCS	Screening set
[redacted]	
SoC	Standard of care
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent AE
TIR	Treatment Information Release
$t_{1/2}$	Half-life time
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	
WBC	White blood cell
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Bronchiectasis, a hallmark of cystic fibrosis (CF) lung disease, is a heterogenous lung disease characterised by abnormal and irreversible dilation of the airways caused by chronic infection, inflammation and airway obstruction. Patients suffer from high symptom burden (cough, production of large volumes of sputum, dyspnea, chronic fatigue, hemoptysis) and low quality of life. Recurrent exacerbations of bronchiectasis lead to worsened symptoms, hospitalisation, and increased mortality.

As CFB (cystic fibrosis bronchiectasis) was historically considered a pediatric disease, and NCFB (non-cystic fibrosis bronchiectasis) was considered a disease of adults, bronchiectasis research tended to consider CFB and NCFB as separate entities. Nowadays, the majority of CF patients are adults and NCFB is increasingly recognised and diagnosed in pediatric patient populations. Bronchiectasis is a neutrophilic airway disease in which serine proteases released by neutrophils (NSPs) are elevated and a major driver in the pathogenesis of bronchiectasis. [redacted]

Bronchiectasis, including bronchiectasis related to CF, is characterised by neutrophilic bronchial inflammation. NSPs, such as NE, cause structural damage to the airways, goblet cell metaplasia and mucus hypersecretion, impaired mucus clearance, and result in a vicious cycle of chronic airway infections, inflammation and progressive airway damage [P13-15562]. Free airway NE is particularly high in patients with bronchiectasis and CF [R18-3357]. Damaged and dilated airways filled with mucus are an ideal growth medium, leading to chronic infection with pathogens such as Pseudomonas (P.) aeruginosa. Irreversibly dilated airways, goblet cell metaplasia, mucus hypersecretion and impaired mucus clearance leads to recurrent acute worsening of respiratory symptoms commonly associated with a drop in lung function, referred to as acute pulmonary exacerbations. Exacerbations are a hallmark of bronchiectasis, leading to further airway damage and increased mortality. Even though airway dilation is irreversible, its detrimental consequences might be mitigated and its progression may be slowed. There is currently no registered therapy that ameliorates neutrophilic inflammation and tissue destruction mediated by uncontrolled NSP activity in the airways of patients with bronchiectasis, including patients with underlying CF.

The relevance of NE for the pathophysiology of bronchiectasis has been confirmed in a number of studies. NE represents the most abundant elastase in the sputum of chronically inflamed airways in CFB and NCFB patients and is a key driver of tissue destruction independent of the underlying disease [R18-3357, R18-3321, R22-1286, R22-1285]. Sputum NE activity is a biomarker of disease severity and a predictor of risk for exacerbations in patients with bronchiectasis [P19-09060].

The central role of neutrophilic inflammation driven by serine proteases is well described in both, CFB and NCFB [R19-3084]. Compared to NE, less evidence exists for proteinase 3 (PR3) and Cathepsin G (CatG), but these two proteases are also assumed to make a relevant contribution to extracellular matrix protein degradation. Hence, suppressing all three NSPs by inhibition of CatC is expected to have a stronger beneficial impact on bronchiectasis, compared to direct reduction of, e.g., NE activity alone.

As an effective airway host defence is absent in CFB and NCFB, *P. aeruginosa* can establish persistent bronchial infection in these patients, representing one of the most important pathogens across etiologies of bronchiectasis, and is associated with high mortality rates [R22-1343, R20-1169]. CFB and NCFB share a number of common characteristics, with NCFB already being the outcome of numerous etiologies of various origins. Underlying etiologies of NCFB range from other diseases such as primary ciliary dyskinesia (PCD), asthma, COPD, post infectious sequelae, primary immunodeficiency disorders (PID) and various autoimmune diseases such as inflammatory bowel disease or rheumatoid arthritis. Many patients have idiopathic bronchiectasis.

CF is an inherited life-threatening disease affecting the respiratory and gastrointestinal systems and characterised by respiratory manifestations, pancreatic exocrine insufficiency, and abnormally high sweat electrolytes. It affects more than 100,000 children and adults worldwide [R23-0768].

The gene responsible for the disease encodes a transmembrane protein called cystic fibrosis transmembrane conductance regulator (CFTR) that functions as an ion channel and is critical in the transport of anions (chloride and bicarbonate) and fluid across epithelial surfaces [R15-5856]. In CF patients, CFTR malfunction results in abnormally thick, sticky mucus that clogs the bronchi and leads to chronic airway infection and inflammation resulting in progressive bronchiectasis. Almost all patients with CF have bronchiectasis by the time they reach adulthood, and respiratory failure is the main cause of death.

CF patients represent a subset of the global population afflicted with bronchiectasis. The incidence of bronchiectasis is increasing worldwide. Previously classified as a rare disease, NCFB is estimated at 53 to 566 cases per 100,000 inhabitants, increasing with age and occurring more frequently in females than males [R21-3309, R21-3311]. CF makes up 10% of the total bronchiectasis population. Bronchiectasis is established in over 75% of CF patients and in most adults with this disease [R21-4488].

Standard therapy for adult and pediatric patients with CF includes pancreatic enzyme replacement, nutritional supplements, physiotherapy supported by airway clearance techniques and devices, antibiotics, anti-inflammatory therapies such as ibuprofen, inhaled drugs such as dornase alfa (Pulmozyme®), bronchodilators, inhaled hypertonic saline.

In patients with specific CFTR mutation types, CFTR modulators alone or in combination are SoC and offer substantial benefit to patients by restoring effectively the function of CFTR channels.

However, even with the majority of patients with CF responding to CFTR-MT, established bronchiectasis with significant structural damage is not reversible and inflammatory markers and NE remain elevated even in this patient population as seen with Ivacaftor monotherapy which is also CFTR-MT for patients with gating mutations [R22-3244]. A subset of patients treated with CFTR-MT (estimated 15 to 20%) still suffer from bronchiectasis symptoms and pulmonary exacerbations [R20-0582, R22-0627]. Some patients (approx. 10%) have CFTR genotypes that do not respond to CFTR-MT and a number of patients do not have access to CFTR-MT. All these subsets of patients continue to experience airway complications of bronchiectasis similar to patients with NCFB. Therefore, therapies that can reduce active serine proteases, could improve the clinical status of patients with bronchiectasis, including CFB and in conjunction with existing medications reduce the risk of bronchiectasis exacerbations, improve quality of life and potentially improve patient survival.

1.2 DRUG PROFILE

For a comprehensive description of the BI 1291583 profile, please refer to the current Investigator's Brochure (IB) [c18711868].

Mechanism of action

Cathepsin C (CatC) is a cysteine protease which is exclusively responsible for the activation of all NSPs (NE, CatG, PR3) during myelopoiesis of neutrophils in the bone marrow [R17-2915]. All three NSPs contribute to inflammation and tissue destruction. NE impairs ciliary function and promotes mucus secretion, it cleaves CXCR1, CD14, and CD16 on neutrophils and thus disables bacterial killing and impairs innate immunity. By crippling normal host opsonophagocytosis, bacterial persistence is promoted. Epithelial cells, induced by NE, release IL-8, which in turn recruits even more neutrophils that are unable to kill bacteria, i.e., excessive amounts of NE induce ineffective antibacterial defence [R18-3384]. Goblet cell metaplasia, mucus hypersecretion and impaired mucus clearance also contribute to an ineffective antibacterial defence.

BI 1291583 is a potent and highly selective inhibitor of CatC and is expected to improve the protease-antiprotease balance in the lungs of patients with chronic neutrophilic airway inflammation.
The anti-serine protease effects of CatC inhibition are not expected to be apparent in peripheral blood and non-myelogenic organs until several weeks after treatment is started, given the central nature of inhibition in the bone marrow and maturation time of inflammatory cell precursors in the bone marrow and subsequent release into the systemic circulation [R17-3119]. Inhibition of CatC is expected to decrease loading of active NE, CatG, and PR3 into neutrophils.

Reduction of NE, PR3 and CatG is expected to result in anti-inflammatory and tissue-preserving effects.

Improving the protease-antiprotease balance is expected to reduce goblet cell metaplasia, mucus hypersecretion, symptoms of cough and sputum, frequency and severity of pulmonary exacerbations, and hospitalisation thereby improving health-related quality of life. Supporting this hypothesis, another CatC inhibitor, brensocatib, has demonstrated proof of concept in a Phase II trial in NCFB. In that trial, sputum NE activity was reduced from baseline over the 24-week treatment period, and time to the first exacerbation was prolonged as compared with placebo. Patients exhibiting chronic airway infection with *P. aeruginosa* (30% of the overall trial population) benefitted equally from treatment [R21-0168] as patients that were not *P. aeruginosa* colonised. A PK study investigating brensocatib in patients with CF is completed. Similar levels of NE inhibition in blood might be reached by CatC inhibition in both NCFB and CF patients (clinicaltrials.gov identifier: NCT05090904; [R23-4200]).

Key pharmacokinetic and pharmacodynamic characteristics from clinical studies

In healthy subjects, following single dose administration of BI 1291583 ([redacted] in SRD trial 1397-0001 and multiple-dose administration ([redacted]) in multiple rising dose (MRD) trials 1397-0002 and 1397-0011 and 1397-0003 Japanese healthy volunteers, BI 1291583 was readily absorbed with peak plasma concentration observed 6 h to 7 h post-dose. Pharmacokinetic steady state is reached within 14 days of dosing. Renal clearance is low. In a relative bioavailability food effect study (1397-0008), no food effect was observed. Exposure to BI 1291583 was slightly higher (less than 2-fold) in Japanese than in non-Japanese and within the exposure thresholds established in non-clinical studies.

The following [redacted] human metabolites of BI 1291583 were identified and characterized:

[redacted]

The pharmacodynamic effects noted with CatC in MRD trials 1397-0002 and 1397-0011 were dose dependent. Peripheral inhibition of CatC activity was noted at 6 h post-dose on the first day of dosing. With repeat dosing, maximum effects were observed by Day 7 to Day 10. Inhibition of peripheral CatC activity declined over 2 to 4 weeks after stopping treatment. The duration of decline increased with dose.

The down-stream pharmacodynamic effects, for example inhibition of NE activity, were observed to commence after 20 days of dosing. Decreased PR3 was first demonstrated by Day 28.

This delay in onset of down-stream effects in peripheral blood is expected and is caused by the lag due to maturation time of neutrophils in the bone marrow, prior to their release into the systemic circulation.

Drug-drug interactions

BI 1291583 is mainly metabolised by CYP3A4 and is a P-gp transporter substrate. In trial 1397-0010, drug-drug interaction between BI 1291583 and itraconazole (a strong CYP3A4 and Pg-P inhibitor) was investigated. BI 1291583 systemic exposures increased approximately 2-fold when co-administered with itraconazole. Chronic treatment with concomitant strong CYP3A4 and P-gp inhibitors and inducers should be avoided.

BI 1291583 may inhibit the P-gp transporter at dosages of [redacted] or greater at the site of first contact (relevant for P-gp mediated transport at the luminal surface of enterocytes). It may inhibit BCRP at doses [redacted]. As the top dose to be administered in the current trial is 5 mg, there are no restrictions for concomitant therapies that are P-gp or BCRP substrates.

For the metabolites described above, no interactions with P-gp or CYP450 isoenzymes could be observed.

Residual Effect Period

As described previously, with the downstream pharmacodynamic effects of BI 1291583, there is a lag period for onset and offset of pharmacodynamic effects (recovery of NE activity in the periphery for example). Based on clinical data from studies 1397-0002 and 1397-0011, the pharmacodynamic Residual Effect Period (REP) of BI 1291583 is 28 days. This is the period after which pharmacodynamic effects are expected to have reversed.

Data from non-clinical studies

The toxicology program of BI 1291583 to date includes repeat-dose studies up to 26 weeks in Wistar rats, 39 weeks in Göttingen minipigs, and up to 13 weeks in CD1-mice, embryo-fetal development studies in Wistar rats and rabbits, a standard battery of genotoxicity studies both in vivo and in vitro, an immunotoxicology study, and a phototoxicity study.

Reproductive toxicology studies to evaluate fertility and early embryonic development, and pre- and postnatal development, as well as carcinogenicity studies are planned.

The multiples of exposure in minipigs were calculated compared to the total steady-state area under the curve (AUC) from time 0 to 24 hours (AUC_{0-24}) (187 nM·h in Caucasian and 273 nM h in Japanese) in humans at the top dose of 5 mg qd to be administered in this study. In rats, the multiples of exposure were calculated to the unbound AUC_{0-24} (26.6 and 38.8 nM·h in Caucasians and Japanese, respectively) due to differences in protein binding between rats and humans.

BI 1291583 induced findings considered to be related to phospholipidosis and/or lysosomal storage in all tested species, starting at 1.7-fold (1.1-fold in Japanese) and at 33-fold (23-fold

in Japanese) the expected AUC_{0-24} total/unbound, in the chronic toxicity studies in the minipig and rat, respectively.

These findings were considered relevant to humans, however, sufficiently high multiples of exposure to degenerative changes [starting at 169-fold (Japanese: 117-fold) in the rat and 170-fold (Japanese: 116-fold) in the minipig] and mortality [1,556-fold (Japanese: 1066-fold) in the minipig] were achieved. In the chronic toxicity studies, minimal findings of phospholipidosis and lysosomal storage were observed at the no observed adverse effect level (NOAEL) in the rat [AUC_{0-24}: 33-fold (Japanese: 23-fold)] and minipig [AUC_{0-24}: 1.7-fold (Japanese: 1.1-fold)] with a low incidence, severity and lack of additional degenerative changes and, therefore not considered adverse.

Findings considered to be related to altered bone remodelling were present in the minipig and in the rat and were considered potentially relevant to humans. In the minipig, immature woven bone formation and marrow cavity fibrosis were present after 4 and 13 weeks of administration at exposures equal or higher than 38-fold (Japanese: 26-fold) and absent at 8-fold (Japanese 5-fold) the AUC_{0-24} total at the therapeutic dose. These findings were considered adverse. After 39-weeks of treatment in minipigs, minimally increased amount of bone (hyperostosis), composed of well-formed and mature lamellar bone, was present at exposures equal or higher than 10-fold (Japanese: 7-fold) the AUC_{0-24} total, but was not accompanied by any change in the bone biomechanical parameters at any dose levels. This finding was conservatively considered adverse.

In the 26-week study in the rat, minimally increased amount of bone (hyperostosis) was present at exposures equal to or higher than 169-fold (Japanese: 116-fold) and absent at 33-fold (Japanese: 23-fold) the AUC_{0-24} unbound at the therapeutic dose and was accompanied by minimally decreased stiffness of the tibial diaphysis in males, at very high doses of BI 1291583 [resulting in exposures of 552-fold (Japanese: 379-fold) the AUC_{0-24} unbound at the expected human therapeutic dose], which was fully reversible after a 4-week recovery period. The minimally increased amount was conservatively considered adverse at all dose levels [c18711868].

For toxicological qualification, [redacted] human metabolites of BI 1291583 were tested for pharmacological activity on the target (cathepsin C), for off-target effects (CEREP-87 screen), for abuse potential (CEREP screen) and for genotoxicity. [redacted]. However later study results showed that all human metabolites were also formed from BI 1291583 in preclinical species including the rat:

- [redacted] do not show any pharmacological on- or off-target effects or relevant effects in binding assays for targets related to abuse potential.
  All four metabolites are non-genotoxic and were covered in rats and minipigs with comfortable safety margins

- [redacted] does not show any pharmacological on- or off-target effects or relevant effects in binding assays for targets related to abuse potential. In vivo repeat-dose toxicity studies in Wistar rats up to 13 weeks showed no adverse findings up to the highest tested dose of [redacted], resulting in exposure multiples of 552-fold (Japanese: 415-fold) the AUC0-24h at the expected human therapeutic dose of BI 1291583
- [redacted] was non-mutagenic and non-clastogenic in systemically exposed tissues (bone marrow and liver), but exerts a clastogenic, local effect at the direct site of contact (stomach). High exposure multiples comparing the concentration free of effects in the Comet assay in the rat stomach to the human concentration in the liver of patients in repeat dose trials administered [redacted] BI 1291583 qd (639- and 285-fold) were achieved. The dose multiples were still 389-fold for repeated administration of [redacted] qd of BI 1291583 to Japanese volunteers. Therefore, since clastogenicity is a threshold-related effect, the exposure to the metabolite is considered safe for patients with chronic administration in the current study

For [redacted] in silico assessments for the prediction of mutagenicity were negative. Testings for pharmacological activity on the target (CatC), for off-target effects (CEREP-87 screen), for abuse potential (CEREP screen) and for genotoxicity are planned. Based on available data, [redacted] is covered within the general toxicity studies in rats and the embryofetal development toxicity studies. It is not expected to be pharmacologically active based on structure-activity relationship considerations.

Human teratogenicity/fetotoxicity for BI 1291583 and its metabolites was not demonstrated in the embryofetal development (EFD) toxicity study in Wistar rats and New Zealand White Rabbits:

- In rats, a slight but dose dependent increase in the incidence of skeletal variations, affecting the sternebra (misshapen ossification site), ribs (misaligned costal cartilage) and pelvis (caudal shift in the position of the pelvic girdle) was observed. These variations occur naturally in control animals and at [redacted] the incidence of variations was within background data. At all dose levels, these minor variations were not considered adverse, since a variation is a change that occurs within the normal population under investigation and is unlikely to adversely affect survival or health. This might include a delay in growth or morphogenesis that has otherwise followed a normal pattern of development [R12-0355]. The NOAEL for maternal and embryo-fetal toxicity was therefore considered to be 100 mg/kg/day resulting in exposures of 788- fold and 538-fold to the expected human therapeutic dose of 5 mg in Caucasians and Japanese, respectively
- In rabbits, markedly lower food intake was observed in the pregnant females at highest dose administered (100 mg/kg). This resulted in corresponding body weight losses or reduced body weight gains, an increase in mortality and lower fetal weights in animals surviving to scheduled necropsy.

Nonetheless, in the animals that survived there was no indication that BI 1291583 induced malformations or structural variations in the fetuses. At 3 and 15 mg/kg/day, BI 1291583 was well tolerated. There was no maternal toxicity or effects on embryo fetal development.
The NOAEL for maternal and embryo-fetal toxicity was considered to be 15 mg/kg/day resulting in exposures of 184- fold and 126-fold to the expected human therapeutic dose of 5 mg in Caucasians and Japanese, respectively.

In summary, the currently available toxicology data support the administration of BI 1291583 up to 5 mg for an indefinite time period in humans with once daily oral administration.

For key safety data from clinical studies, please refer to Section 1.4.3.

For a more detailed description of the BI 1291583 profile, please refer to the current IB [c18711868].

1.3 RATIONALE FOR PERFORMING THE TRIAL

No approved treatments are available to diminish inflammation and tissue destruction in patients with bronchiectasis (BE), a chronic lung disease with neutrophilic bronchial inflammation. There is a high unmet medical need to break the vicious cycle of recurrent severe infections and further airway damage.

[redacted] will provide information on the efficacy, safety and optimal dosing regimen of BI 1291583 in preventing pulmonary exacerbations in patients with BE not related to CF. Approx. 240 BE patients, with a diagnosis confirmed by a CT scan, who are regular sputum producers and have had at least 2 pulmonary exacerbations in the previous year, (alternatively 1 pulmonary exacerbation plus high symptom burden as measured by the SGRQ questionnaire, Appendix 10.4.1), will be enrolled in a 2:1:1:2 ratio to receive once-daily oral doses of 5 mg, 2.5 mg, 1 mg of BI 1291583 or placebo. Commonly used stable maintenance treatment will be allowed as background treatment.

Trial 1397-0013 (Clairafly™) is mirroring the first 12 weeks of [redacted] and is by that adding important information on safety and PK similarity across bronchiectasis patients with and without CF treated with BI 1291583 5 mg qd or placebo.

Downstream suppression of NE activity will be used to link clinical outcomes assessed in [redacted] as established surrogate biomarker for exacerbations.

In order to be able to address future scientific questions, trial participants will be asked to voluntarily donate biospecimens for banking (please see Section 5.5).
If the trial participant 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.

Agreement on this banking is not a requirement for study enrolment.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

BI 1291583 is a potent CatC inhibitor with an expected inhibition of 99% in the bone marrow for the dose included in this study and is expected to improve the protease-antiprotease balance in the lungs of patients with chronic neutrophilic airway inflammation. The central role of neutrophilic inflammation driven by serine proteases is well described in both, CFB and NCFB. A complex interplay between infection and inflammation feeds the pro-inflammatory vicious cycle that drives the destruction of pulmonary architecture.
Inflammatory immune cells (mainly activated macrophages and neutrophils) represent the major infiltrating population in disease conditions associated with BE and contribute significantly to tissue damage and BE generation.
Cell-derived proteases and reactive oxygen species represent key mediators and particularly the protease-antiprotease imbalance is considered as key pathogenic component in degrading extracellular matrix [R21-3308].

Treatment with BI 1291583, and hence suppression of NSPs, has the potential to provide significant benefit to patients by disrupting this vicious cycle. Associated benefits would be sustained tissue protection and reduced symptoms (e.g. cough, volumes of sputum), prolonged time to exacerbation and reduction in exacerbation frequency, as well as better maintained quality of life and potentially even a reduction in mortality.

This premise has already been partially validated by the outcome of the Phase II study of the CatCi brensocatib in the NCFB WILLOW study [R21-0168].

Patients with CFB receiving the CatC inhibitor BI 1291583 in this ‘first-in-CF-patient’ trial may have a transient direct medical benefit from participation, as a treatment duration of 12 weeks is not expected to have a permanent impact on the long-term course of their disease. However, the NE pathway is anticipated to play an important role in bronchiectasis as sputum NE activity was found to be a biomarker of disease severity and future risk of exacerbations in patients with bronchiectasis [R18-3321]. For this trial, patients will be selected that have a history of pulmonary exacerbations, indicating that the targeted pathway is active. Considering the study treatment duration of 12 weeks, inhibition of NE activity may result in modulation of clinical efficacy endpoints. Some benefit in symptoms (e.g., sputum

volume, cough, mucus plugging), [redacted] might be expected with administration over 12 weeks.
In patients treated with placebo, no benefit is expected beyond the general benefits of regular medical assessment during participation in a clinical trial. All participants will have a close safety monitoring of their health status throughout the trial.

1.4.2 Risks

Factors of risks may derive from knowledge regarding the mode of action (MoA), the nature of the target, findings in animal models / non-clinical safety studies, and findings from clinical studies.

The clinical data of BI 1291583 showed an acceptable safety profile in healthy volunteers. A Phase II trial in patients with [redacted] A Phase II trial with another CatC inhibitor, brensocatib, in NCFB showed that 24 weeks treatment resulted in a slightly increased occurrence of periodontal disease and skin exfoliation in patients receiving brensocatib compared to those with placebo [R21-0168]. Despite the increase of periodontal diseases in patients treated with brensocatib, there was no difference among each treatment group in the progression of periodontal disease observed. In addition, the incidence rates of hyperkeratosis (trial-defined skin event of interest) were comparable across different treatment groups. No elevated risk of infection was reported in clinical studies with brensocatib. The PK – safety evaluation of brensocatib showed no clinically relevant relationships between brensocatib exposure and the incidence of adverse events of special interest (AESIs) [R22-2961].

Potential effects of life-long and complete CatC inhibition can be learned from Papillon-Lefèvre Syndrome (PLS), a rare genetic disease with loss of function mutations in both alleles of the CatC gene (see Table 1.4.2: 1).

Table 1.4.2: 1 Overview of trial related risks based on the mode of action (MoA), the nature of the target, findings in non-clinical safety studies and mitigation strategies

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Possible effects of CatC inhibition are - Hyperkeratosis - Periodontitis, which might lead to alveolar bone resorption,	Based on observations in patients with the rare genetic disease Papillon-Lefèvre Syndrome (PLS), clinical signs and symptoms of life-long complete absence of CatC, are palmoplantar hyperkeratosis, severe	- Exclusion of subjects with relevant immunodeficiency or receiving immunosuppressive medication or having an acute infection. - Regular clinical and laboratory monitoring for infection. - Exclusion of subjects having a history of hyperkeratosis on palms or soles.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
loss of deciduous and permanent teeth - Susceptibility to infections	periodontitis, alveolar bone resorption, loss of deciduous and permanent teeth, and an increased susceptibility to infections [R17-3100]. The immune-deficiency in PLS patients is generally mild [R17-3101]	- Close skin monitoring throughout the study (Flow Chart and Section 5.2.5.2). - Exclusion of subjects with moderate or severe periodontal disease. Requirement of dental examination for all subjects during screening. Subjects with signs of mild periodontal disease will receive standard periodontal care. - Periodontal assessment at EOT and during the study at the discretion of the investigator - Discontinuation from trial treatment in case of severe periodontal AEs or deterioration (Flow Chart and Section 5.2.5.1). A complete / near complete loss of CatC function is not expected An independent Data Monitoring Committee (DMC) will periodically evaluate clinical trial safety data.
Effects on lung, liver, kidney and bone	In non-clinical studies, daily treatment with BI 1291583 was associated with changes indicative of phospholipidosis / lysosomal storage in several tissues and organ systems. Most prominently affected organs were lung, liver, kidneys, and bone. Bone findings are possibly indicative of altered bone remodeling. Degenerative changes or changes in the clinical status of the animals were not observed at exposures targeted in clinical studies.	- Exclusion of subjects with a relevant concomitant disease assessed as clinically relevant by the investigator, particularly gastrointestinal, hepatic, renal, pulmonary, cardiovascular, metabolic, immunological, or hormonal disorders. - Laboratory testing, including blood cell count, liver function, renal function, bone turnover biomarkers and urinalysis, as well as physical examination, will be used to monitor lungs, livers, bones, and kidneys. The safety margins are sufficiently high in man from preclinical species where there were findings (see Section 1.2). An independent DMC will periodically evaluate clinical trial safety data.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Reproductive system	Genotoxicity for BI 1291583 and the [redacted] previously identified metabolites was not demonstrated in preclinical studies. The genotoxicity assessment has not yet been completed for the newly identified metabolite [redacted]. Data in humans are not available.	- Women who are pregnant or breastfeeding will be excluded. - Women of child-bearing potential must be willing and able to use two medically approved methods of birth control, one barrier method plus one highly effective non-barrier method (Section 4.2.2.3). - Men able to father a child must be willing and able to use male contraception (Section 4.2.2.3).
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators. Although not specifically expected with this molecule or mechanism, monitoring for DILI is standard in drug development.	- Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters (Section 5.2.6.1.4).
Blood sampling	Blood sampling is a standard clinical procedure. 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.	- Close clinical monitoring for AEs - Selection of experienced sites and site staff
Lung function measurements	Assessment of lung function is a standard clinical procedure that many of the patients will already have experienced. Risks and discomforts associated with lung function testing may include shortness of breath,	- Close clinical monitoring for AEs - Selection of experienced sites and site staff

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	dizziness, or headache during the breathing tests.	
Administration of 4 doses of inhaled salbutamol / albuterol (total dose approx. 400 µg), used as Auxiliary Medicinal Product (AMP) in this trial	Post-bronchodilator pulmonary function test is a standard test. Most common side effects of salbutamol / albuterol 100 µg includes: palpitation, chest pain, fast heart rate, shakiness, nervousness, headache, dizziness, sore throat, and runny nose	- Patients with concomitant cardiovascular disease that in the opinion of the investigator may put the patient at risk by participating in the study are excluded. - On-site use only and under direction of a healthcare provider. - Close clinical monitoring for AEs
Sputum induction	Sputum induction is a simple and non-invasive procedure used for patients who are not able to provide a sputum sample spontaneously. The patient inhales nebulised iso- or hypertonic saline solution, which could cause bronchoconstriction.	- Close clinical monitoring for AEs - Selection of experienced sites and site staff - Use of inhaled Salbutamol (Albuterol) is recommended before sputum induction if no Salbutamol (Albuterol) was administered within 4 hours at the visit for post-bronchodilator spirometry
Pandemic situations	Travelling to site, being at site for assessments (standard risk in the current pandemic situation).	- On-site visits are reduced to a minimum. - Testing and infection control will be done according local / national recommendations - For possible additional modifications in pandemic situation see Section 6

1.4.2.1 Risk related to the COVID-19 pandemic

The available evidence does not suggest an increased risk of acquiring an infection with a viral pathogen targeting the airways, including SARS-CoV-2, nor of a particularly more severe clinical presentation in case of such an infection, with suppression of Cathepsin C. There is no evidence to suggest an increased risk of bacterial superinfection in case of COVID-19.

An increased risk of severe COVID-19 is possible in patients with CFB due to their underlying condition but is not supported for CF patients by registry data and is not expected based on the mechanism of action of BI 1291583.

CatC inhibition is not expected to reduce the efficacy of a COVID-19 vaccine to induce an immune response; and vice versa, vaccination is not expected to reduce the efficacy of the CatC inhibitor.

1.4.3 Key safety data from clinical studies

The results of 6 Phase I trials show an acceptable safety profile in healthy volunteers at all doses tested, with no serious adverse events (SAEs), AE of special interest or death.
One subject treated with BI 1291583 (1 mg) discontinued treatment due to other significant AEs according to ICH E3 (PT 'thrombophlebitis' and 'increased CRP') which were assessed as non-drug-related. In the safety lab, vital signs and ECG data there were no clinically relevant findings. The most frequently reported adverse events (AEs) investigators considered drug-related are displayed in Table 1.4.3: 1. All AEs considered drug-related were mild to moderate and resolved.

Table 1.4.3: 1 Summary of AEs considered drug related by investigators across healthy volunteer trials performed

Healthy volunteer trials performed	**Summary of AEs considered drug related by investigators**
1397-0001, single-rising-dose • [redacted] • 54 healthy male subjects versus placebo. 40 subjects received BI 1291583, 14 subjects received placebo	Ten subjects (25.0%) receiving BI 1291583 and 2 subjects (14.3%) receiving placebo had AEs that were assessed as drug-related by the investigator. Drug-related AEs reported for more than 1 subject overall in the BI 1291583 groups were headache (4 cases of mild or moderate intensity) and dry skin (3 cases of mild intensity).
1397-0008, food-effect cross-over trial • [redacted] of BI 1291583 once in the fasted state and once following a standard high-fat, high-calorie meal • 12 healthy male subjects	No investigator-defined drug-related AEs were reported.
1397-0010, drug-drug interaction trial (itraconazole) • Single dose of [redacted] alone, followed by [redacted] together with multiple doses itraconazole • 14 healthy male subjects	Investigator-defined drug-related AEs were reported in 4 subjects (28.6%). The drug-related AEs were diarrhea, dyspepsia, increased alanine aminotransferase, increased aspartate aminotransferase, decreased appetite, and thermohyperaesthesia. Each AE was reported in 1 subject (7.1%) only after BI 1291583 + itraconazole.
1397-0002 and 1397-0011, multiple-rising-dose. 4 weeks treatment • [redacted] • 48 healthy male and female subjects. 36 subjects received BI 1291583, 12 subjects received placebo	Six subjects (16.7%) receiving BI 1291583 and 3 subjects (25.0%) receiving placebo were reported with AEs that were assessed as drug-related by the investigators. The only drug-related event reported for more than 1 subject overall in the BI 1291583 groups was skin exfoliation (3 subjects, 8.3%), whereas in placebo it was reported in 1 subject (8.3%). Drug-related skin events were not reported more frequently for subjects treated with BI 1291583 than for subjects receiving placebo (13.9% vs. 16.7%, respectively).

Healthy volunteer trials performed	Summary of AEs considered drug related by investigators
1397-0003, Japanese single rising dose and multiple dose study • [redacted] single dose; 24 healthy male subjects. 18 subjects received BI 1291583, 6 subjects received placebo • [redacted] once daily for 4 weeks; 12 healthy male subjects. • 9 subjects received BI 1291583, 3 subjects received placebo	Single-dose and multiple-doses in healthy Japanese subjects were well tolerated. No AEs leading to treatment discontinuation, or AEs defined by the investigator to be related to the study drug were reported.

For clinical assessment of bone turnover biomarkers, following the International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry (IFCC) recommendations [R21-0018], CTX-I and P1NP were chosen as most sensitive reference markers for bone resorption and formation, respectively.

No effects on bone turnover biomarkers were seen in the 4-week MRD studies in humans at exposures up to twofold higher than will be tested in the Phase II trials, suggesting that repeat-dose administration of BI 1291583 is not associated with any clinically relevant changes in bone turnover.

For a more detailed description of the BI 1291583 profile, please refer to the current IB for BI 1291583 [c18711868].

1.4.4 Discussion

The clinical data of BI 1291583 showed an acceptable safety profile in healthy volunteers at all doses tested, with no serious adverse events (SAEs) or adverse events of special interest (AESIs). No clinical data of BI 1291583 in patients are available to date.

In a study investigating 24 weeks of treatment in patients with bronchiectasis with the CatC inhibitor brensocatib a significant prolongation in the time to first pulmonary exacerbation was reported, even in the 1/3 colonised with *P. aeruginosa*, suggesting that pharmacological inhibition of CatC may decrease the rate of bacterial airway infections in this population

[R21-0168]. The safety evaluation of brensocatib showed no clinically relevant relationships between brensocatib and AESIs or infections [R22-2961].
Twenty-four weeks treatment resulted in a slightly increased occurrence of periodontal disease but not progression, and skin exfoliation in patients receiving brensocatib compared to those with placebo, with no relationship to dose [R21-0168]. The mechanism of action of brensocatib is the same as for BI 1291583.

Based on the properties and the mode of action of BI 1291583, no specific safety concerns for patient with CF are expected:

- No specific liability to the GI tract was identified in preclinical and clinical studies. Based on the observation of no dependency of exposures on food (fasted versus high-calory/high-fat meal), it is not expected that absorption will be affected by gastric pH or pancreatic exocrine insufficiency and the management thereof by using enzyme-replacement therapy.
- For CF patients an increased risk for periodontitis is not described.
- The pathophysiology of CF specific aquagenic palmoplantar keratoderma is different to the skin lesion related to CatC inhibition and can be clinically distinguished from hyperkeratosis.
- A treatment duration of 4 weeks (Phase I MRD trials, 9 healthy volunteers in each dose group), 12 weeks (Clairafly™, 18 patients with CF treated with BI 1291583, 5 mg) and at least 24 weeks ([redacted], 80, 40 and 40 patients in respective dose groups) will provide relevant insights on the effect of BI 1291583 on bone biomarkers.
- No specific risk for extrapulmonary infections is expected in CF patients. The migration of neutrophils to the site of infection is not affected by BI 1291583. Neutrophils that lack NSPs are still equipped with other microbicidal tools, such as myeloperoxidase and the α-defensin group of antimicrobial peptides.
- No saftey concerns are attributed specifically to concomitant use of modulators and BI 1291583. BI 1291583 and its metabolites are not expected to affect pharmacokinetics of CFTR modulators. BI 1291583 and its metabolites are not inhibitors of Cyp3A4 and inhibition of P-gp may only occur at higher doses (≥ 9 mg) than are used in Clairafly™. BI 1291583 and its metabolites are not critically affected by concomitant use of CFTR modulators (except lumacaftor, see Section 4.2.2). Conservatively assessed, co-administration of a CFTR modulator containing Ivacaftor may lead to an increase in exposure to BI 1291583 of max. 30%. Based on pre-clinical and clinical data to date, it is not expected that BI 1291583 will increase the risk of liver diseases as references the risk from modulator therapies.

A comprehensive safety analyses will also be performed based on all available data prior to Phase III, including [redacted], a Phase II study currently underway in patients with nCFB [redacted] 240 patients planned to be randomized (2:1:1:2) to BI 1291583 5 mg, 2.5 mg, 1 mg or placebo respectively).

To mitigate the potential risk associated with a placebo-controlled trial in this patient population, usual SoC will be allowed as stable background treatment.

To ensure safety of trial participants, an independent DMC which includes experts also in the field of CF will conduct regular reviews of all unblinded safety data.

The nature of the target and the mechanism of action of BI 1291583 are well understood. In the context of the unmet medical need and anticipated benefit of BI 1291583, the benefit risk evaluation of the compound, based upon the available preclinical and clinical information, is considered favourable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The aim of the trial is to investigate whether 5 mg qd of BI 1291583 (the expected human therapeutic dose) in patients with CF is safe and to assess PD and PK. Based on these data, an across-trial comparison will be performed. [redacted]

The primary objective, is to estimate the number and percentage of patients who have at least one treatment-emergent AE (TEAE) during the trial.

The secondary objective is to estimate the PD effect, at Week 8, after the first drug administration. The other secondary objective is to estimate the PK effect, after the first dose and at steady state, after multiple dosing of BI 1291583 5 mg qd.

All treatment effect estimations will be as randomised, including the effects of any changes of treatment.

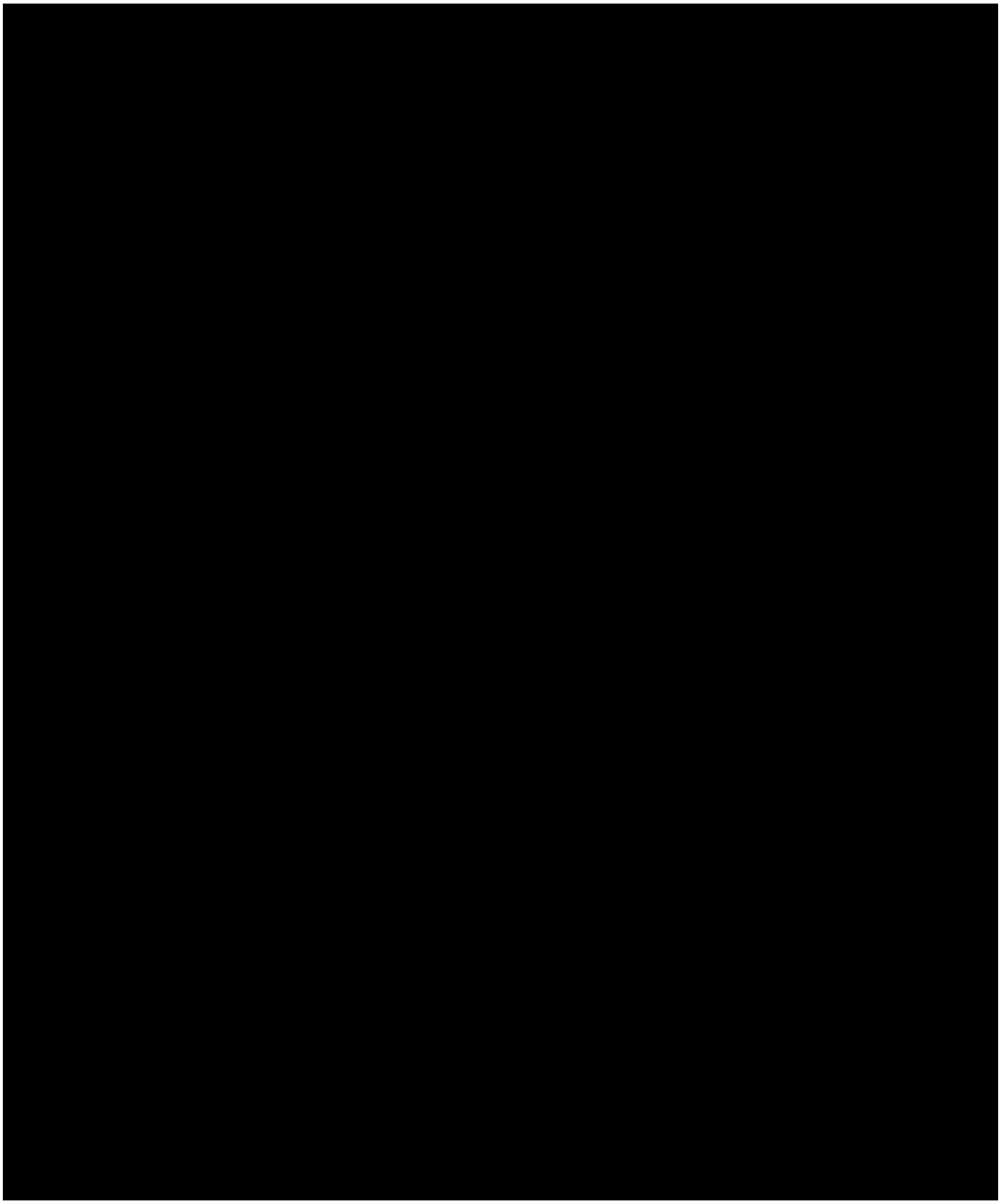
2.1.2 Primary endpoint

The primary endpoint is to evaluate the occurrence of TEAEs, up to 16 weeks, from first drug administration.

2.1.3 Secondary endpoint(s)

The following secondary endpoints will be determined:

- Relative change from baseline in NE activity, in sputum, at Week 8 after first drug administration (8 weeks was chosen as timepoint for this secondary endpoint to synchronise with potential cycling antibiotic use)
- AUC, over a dosing interval (AUC_{τ}), for the first dose
- Maximum concentration (C_{max}) for the first dose
- AUC_{τ} at steady state ($AUC_{\tau,ss}$)
- C_{max} at steady state ($C_{max,ss}$)



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

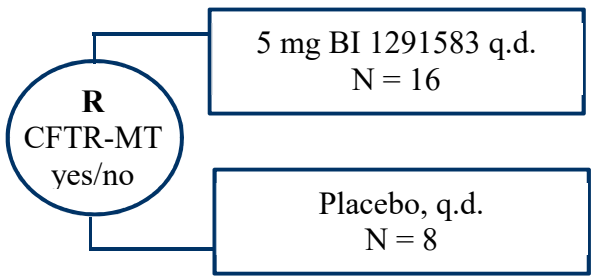
This is a multi-centre, randomised, placebo-controlled, double-blind, parallel group, Phase IIa clinical trial to investigate the safety, tolerability, PD and PK of 5 mg BI 1291583 (oral, qd) in patients with CFB.

Approximately 24 eligible patients will be randomised in a 2:1 ratio to either BI 1291583 or placebo. Approximately 50% of patients will be treated with CFTR-MTs, for restricted CFTR-MT also refer to Section 4.2.2. The randomisation will be stratified based on whether the patient is on stable maintenance use of CFTR-MT or not (yes / no). The stratification should assure that sufficient patients are recruited within each treatment population. Screening of patients into any single stratum will be closed in order to ensure that not more than 18 patients are randomised into that stratum. The rationale is to assess whether both treatment populations will fit into the NCFB population regardless of their background medication.

The design outline is depicted in Table 3.1: 1.

Table 3.1: 1 Design outline

Design outline



R = Randomisation

The screening period may last up to maximal 6 weeks, the planned treatment period is 12 weeks, afterwards patients are followed up for additional 28 days (REP). SoC is allowed; however for an antibiotic cycling regimen, start days of a new cycle needs to be aligned with visit schedules. The visit schedule is shown in Figure 3.1: 1.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

Due to the fact that participating sites are experienced CF sites and considering a treatment duration of 12 weeks, patient loss to follow-up is assessed as minor risk. Patients who discontinue the trial early for whatever reason should perform EOT and EOS visit (refer to Section 6.2.3 and Flow Chart) and will not be replaced.

An independent Data Monitoring Committee will evaluate safety and efficacy data on a continuous basis. For details please refer to Section 8.7.

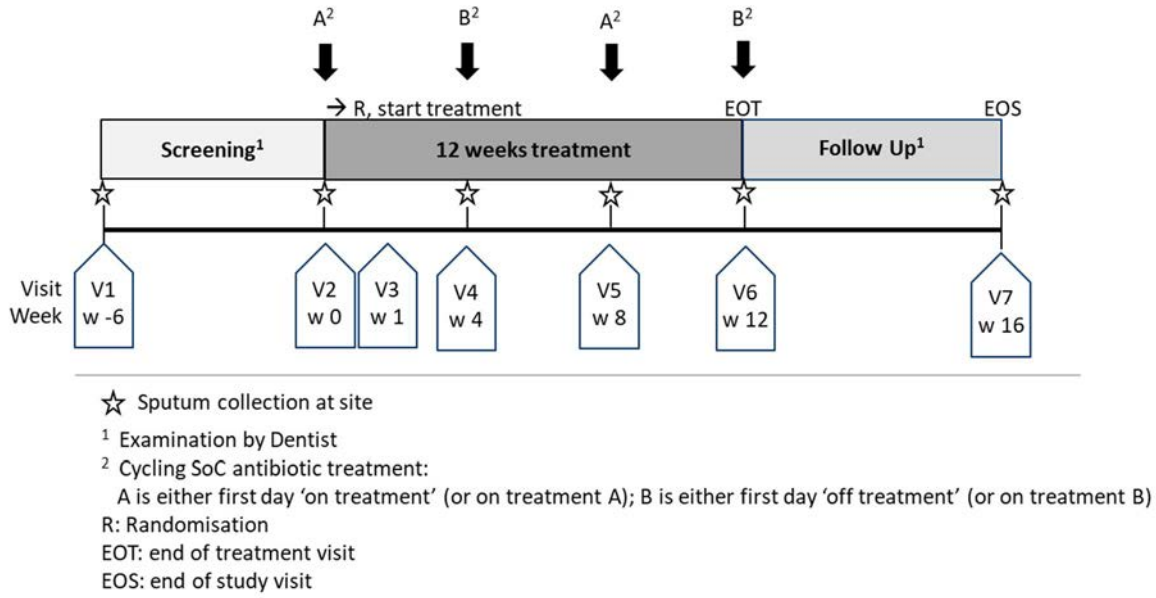


Figure 3.1: 1 Visit schedule

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

Since this trial evaluates BI 1291583 for 12 weeks and for the first time in a CF patient population, safety and tolerability is the primary objective. A randomised, double-blind, placebo-controlled, parallel group trial is considered the most robust design to assess safety, tolerability, pharmacodynamic and pharmacokinetics of BI 1291583. A double-blind concept was chosen to reduce the bias with regards to treatment-dependent effects as much as possible. Due to a close safety monitoring and the fact that no SoC treatments are restricted, this approach is considered acceptable for patients. A placebo group is included in order to reduce bias and to provide a comparator arm to reliably assess safety, tolerability, and pharmacodynamic effects of the trial medication.

Availability of clinical safety, efficacy and surrogate biomarker (i.e. free NE activity) data in a patient population with BE not related to CF [c35703911-05] are considered sufficient to evaluate their similarity in CF patients with BE. Detection of early signs of clinical efficacy and safety of BI 1291583 are expected over a 12-week treatment period.

Evaluation of NE inhibition at Week 8 (secondary endpoint) takes into account potential effects of maintenance cycling antibiotic treatment.

Before initiating future trials including CF and NCF patients with BE within one study, the data from [redacted] and 1397-0013 (CFB) will be reviewed (Figure 3.2: 1).

[redacted]

Although there is no evidence that genetic defects causing CF directly lead to altered pharmacokinetics, differences in the PK of CFB patients compared to healthy volunteers could result from pathophysiological differences in the gastrointestinal tract which may impact absorption. In addition, higher volume of distribution and clearance were observed in CF patients potentially related to an altered body composition [R22-1342]. Deficiency of functional CFTR in CF leads to decreased ductal cell secretions of Cl−, water and HCO3−, which also lowers pH [R22-2965, R22-2966].

However, BI 1291583 exhibits moderate to high solubility over GI tract pH range. In combination with the high permeability found in CaCo-2 cells, BI 1291583 is classified as a BCS class I compound. These physico-chemical characteristics support an expectation of similar PK profiles across non-GI diseases. BI 1291583 at a dose level of 5 mg qd is fully soluble in the gastric volume irrespective of pH. No difference in relative bioavailability was observed in healthy volunteers under fed and fasted conditions (study 1397-0008, [redacted] BI 1291583, high-fat and high caloric meal). Due to the absence of a pH dependent absorption, a difference in exposure for patients with CF is considered unlikely. The sampling regimen with two full profiles on Day 1 and at steady state on Day 85, allows to characterise the absorption as well as the initial elimination and distribution phase. Additional trough samples especially before steady state (before 2 weeks) will provide information on the accumulation profile of BI 1291583. Overall, trough samples serve a better characterisation of clearance in CF patients. Together with PK information from Phase I and Phase II studies, the PK sampling regimen may enable identification of covariate effects in case there are differences between the different study populations.

A 28-days follow-up period without treatment covers the residual effect period during which BI 1291583 exposures are expected to return to levels below quantification and after which pharmacodynamic effects are expected to have reversed.

There is currently no approved pharmacotherapy available to treat the inflammatory component of BE in CF patients. Thus, no active control group is included in the trial. To mitigate the potential risk associated with a placebo-controlled trial in this patient population, usual SoC will be allowed as stable background treatment or in case of complications of CF.

To ensure safety of trial participants, an independent DMC will conduct regular reviews of the trial safety data.

Given that not all patients with CF will benefit from modulator therapies and as inflammation with elevated free NE activity [R22-3244] will proceed particularly in established BE, patients with established CFB are likely to benefit from anti-inflammatory therapies irrespective of CFTR-MT. Therefore, there is a remaining unmet need for anti-inflammatory therapies in the management of CF lung disease [R22-1347]. Observational studies have shown that NE activity and other inflammation markers remain highly elevated in CFTR-MT treated CF patients compared to healthy people [R20-0748].

The overall feasibility of the trial is considered possible, as experienced investigators will be selected who can ensure the required safety monitoring, have access to patients with CFB and are proficient in required trial procedures.

3.3 SELECTION OF TRIAL POPULATION

It is planned to enrol approximately 24 eligible adult patients of either sex with a diagnosis of CF and BE (confirmed by CT), treated or not treated with CFTR-MT (individual SoC) in the trial.
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 in both strata (CFTR-MT yes / no) has been screened. Screening of patients into any single stratum will be closed in order to ensure that not more than 18 patients are randomised into that stratum. Investigators will be notified about termination of screening and will then not be allowed to screen additional patients for this trial or in a specific stratum, respectively. Patients already in screening at this time will be allowed to continue to randomization, if eligible.

- **Re-tests** during screening are allowed, for example, if a laboratory test has been cancelled by the central laboratory (e.g. for specimen not received or received beyond stability) or in case of a laboratory result that is considered to be a spurious result if compared to previously available laboratory results (at investigator's discretion).
  The re-test should be carried out as soon as possible so the laboratory test results will be received within the planned visit windows. Re-tests may similarly be performed for other visits upon investigator's discretion
- **Re-screening** of patients will be permitted in circumstances where safety is not compromised and where the patient is expected to become eligible, as the screening failure was due to a transient, potentially reversible, condition. This could be, for example, a pulmonary exacerbation requiring use of i.v./oral/inhaled antibiotics.
  A maximum of 2 re-screenings will be permitted. Upon re-screening, a new patient number will be assigned by the IRT. The previous patient number, with which the patient failed screening, will be recorded in the eCRF. The current approved version of the patient information and consent form should be signed again

A log of all participants 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.

Even for screen failure participants a minimum of information will be collected: participant number, visit date, demographics, eligibility criteria, information on adverse events (if applicable), concomitant treatment relevant for the adverse event.

If retrospectively it is found that a trial participant has been entered in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in adult male or female patients with a diagnosis of CF and BE, treated or not treated with CFTR-MT (individual SOC).

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

3.3.2 Inclusion criteria

1. Age of patients when signing the informed consent ≥18 years
2. Historical clinical diagnosis of CF (symptoms of CF and sweat chloride ≥ 60 mmol/L and/or 2 CF-causing CFTR mutations [R22-1344])
3. Investigator-confirmed diagnosis of BE by CT scan and clinical history consistent with BE (e.g., cough, chronic sputum production, recurrent respiratory infections). Subjects whose past chest CT records are not available will undergo a chest CT scan during Screening. Historical scans must not be older than 5 years
4. History of pulmonary exacerbations requiring antibiotic treatment. In the 12 months before Visit 1, patients must have had either:
    a. at least 2 exacerbations, or
    b. at least 1 exacerbation and an [redacted] at screening Visit 1

    For patients on stable oral or inhaled antibiotics as chronic treatment for BE, at least one exacerbation must have occurred while on stable antibiotics (see Table 4.2.2.1: 1).
5. Patients must be able to provide spontaneous or induced sputum samples.
6. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

7. Male or female patients (also refer to Section 4.2.2.3).
   Women of childbearing potential (WOCBP)[1] must be ready and able to 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, as well as one barrier method.
   A list of contraception methods meeting these criteria is provided in the patient information.
   Men participating in this clinical trial must use male contraception (condom or sexual abstinence) if their sexual partner is a WOCBP.

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

3.3.3 Exclusion criteria

Laboratory and medical examination:

1. Moderate or severe liver disease (defined by Child-Pugh score B or C hepatic impairment) or AST and/or ALT > 3.0x ULN at Visit 1
2. Estimated glomerular filtration rate (eGFR) according to CKD-EPI formula < 30 mL/min at Visit 1
3. Absolute blood neutrophil count < 1,000/mm^3 (equivalent to < 1000 cells/µL or < 10^9 cells/L) at Visit 1
4. Any findings in the medical examination (including BP, PR, or ECG) and/or laboratory value assessed at Visit 1 or during screening period that in the opinion of the investigator may put the patient at risk by participating in the trial
   [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 in the trial. The justification for decision needs to be documented.]
5. Positive serological tests for hepatitis B, hepatitis C (also confirmed with HCV RNA), or human immunodeficiency virus (HIV) infection, or known infection status

Concomitant diagnosis and therapy:

6. A current diagnosis of:
   a. Hypogammaglobulinemia
   b. Common variable immunodeficiency
   c. α1-antitrypsin deficiency being treated with augmentation therapy
   d. Allergic bronchopulmonary aspergillosis being treated or requiring treatment
   e. Tuberculosis or non-tuberculous mycobacterial infection being treated or requiring treatment according to local guidelines
      [Laboratory tests (e.g. Quantiferon Gold test) may be performed at the discretion of the investigator]

f. Palmoplantar keratosis; or keratoderma climactericum
g. Hypothyroidism, myxedema, chronic lymphedema with associated hyperkeratosis of the skin, acrocyanosis. If a subject has hypothyroidism but is treated and compensated, the subject is allowed into the trial
h. Psoriasis affecting palms and soles; or body surface area for psoriasis ≥10%
i. Reactive arthritis (Reiter's syndrome); keratoderma blennorrhagicum
j. Pityriasis rubra pilaris
k. Atopic dermatitis affecting palms and soles; or body surface area for atopic dermatitis ≥10%
l. Active extensive verruca vulgaris, as per investigator's discretion
m. Active fungal infection of hand and/or feet not adequately treated and responsive to antifungal therapy, as per investigator's discretion

7. Any clinically relevant respiratory infection within 4 weeks prior Visit 2
8. Any acute infection requiring systemic or inhaled anti-infective therapy within 4 weeks prior Visit 2
9. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus)
10. Any evidence of a concomitant disease, such as Papillon-Lefevre Syndrome, relevant pulmonary, gastrointestinal, hepatic, renal, cardiovascular, metabolic, immunological, hormonal disorders, or patients who are immunocompromised with a higher risk of invasive pneumococcal disease or other invasive opportunistic infections (such as histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis), that in the opinion of the investigator, may put the patient at risk by participating in the study
11. Received any live attenuated vaccine within 4 weeks prior Visit 2
12. Medical conditions associated with periodontal disease (to be evaluated by a periodontist or dentist):
    a. Any tooth that can potentially cause pain or infection as noted in the oral exam unless they are corrected before Visit 2 (e.g., pulp necrosis)
    b. 2 or more teeth with pocket depth measurements ≥ 4 mm and bleeding or ≥ 5 mm due to periodontitis
    c. Class-3 mobility or Class-3 furcation involvement
    d. Scheduled tooth extraction during the trial period
13. Patients who must or wish to continue the intake of restricted medications (see Table 4.2.2.1: 1) or any drug considered likely to interfere with the safe conduct of the trial; patients who take / had taken Lumacaftor / Ivacaftor dual combination (see Table 4.2.2.1: 1)

Others / general conditions:

14. Lung transplanted patients and patients with a planned transplantation while participating in the trial

15. Major surgery (major according to the investigator's assessment) performed within 6 weeks prior to randomisation or scheduled during trial period
16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated in situ non-melanoma skin cancers or in situ carcinoma of uterine cervix
17. Current smokers, or stopped smoking only within 3 months of screening, or not willing to maintain non-smoking status for the duration of the trial
18. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled, i.e., chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant
19. Recent significant hemoptysis (≥ 300 mL or requiring blood transfusion) in the preceding 4 weeks before Screening Visit 1 (and during screening phase)
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. Previous randomisation in this trial
22. Any vulnerable person (defined as: pregnant or breastfeeding women; women who plan to become pregnant while in the trial; persons deprived of their liberty; minors; persons that may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests; or unable to explicitly give consent), as per local regulation
23. Contraindications to the class of drugs under study including known hypersensitivity to the drug or its excipients
24. History of any illness or clinical condition that in the opinion of the investigator might confound the study results

For study restrictions, refer to Section 4.2.2.

3.3.4 Discontinuation of trial participants 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, 3.3.4.2, and 3.3.4.3 below.

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.

Discontinued patients will not be replaced.

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, the requirements for Adverse Event collection and reporting (see Section 5.2.6.2) should be considered.

3.3.4.1 Discontinuation of trial treatment

An individual trial participant will discontinue trial treatment if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he/she is not willing or able to adhere to the trial requirements in the future
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product as evaluated by the investigator, if needed in consultation with the sponsor
- The patient can no longer receive trial treatment for medical reasons as per judgement of the investigator
- Serious or severe Drug Induced Liver Injury attributable to the trial drug (see Section 5.2.6.1.4)
- Pregnancy
- The patient experiences an AE where the PI considers that it is drug related (see Section 5.2.6) and evaluates that it is not in the best interest of the subject to continue in the study
- The investigator considers that treatment continuation is negatively impacting well-being and treatment discontinuation is in the best interest of the patient
- Serious infections, e.g., life-threatening infections or infections requiring hospitalisation (except hospitalisations for exacerbations, where the investigator will evaluate whether it is in the best interest of the subject to continue in the trial)
- The trial participant meets the following criteria of periodontal progression:
  - Severe periodontal findings, particularly if at least 3 teeth with pocket depth ≥ 6 mm (upon the average of 2 measures).
  - If at least 3 teeth have progressed (pocket depth increase ≥ 2 mm upon the average of 2 measures). The Investigator and the dentist, in conjunction with the patient, upon thorough assessment of all available clinical data and taking into consideration the potential risks and benefits associated with administration of BI 1291583, may decide not to discontinue the trial medication. In such a case, continuation of treatment with trial medication should be discussed with the patient, and the decision and reasoning should be documented in the source data (see also Section 5.2.5.1).

Even if the trial treatment is discontinued the trial participants remain in the trial and, given their agreement, will undergo the procedures for end of treatment visit and follow-up as outlined in the Flow Chart and Section 6.2.3.

If a patient becomes pregnant during the trial, the investigational product must be discontinued, and the patient should be followed up until birth or otherwise termination of the pregnancy.
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 trial participants or take any other appropriate action to guarantee the safety of the trial participants.

3.3.4.2 Withdrawal of consent to trial participation

Trial participants may withdraw their consent to trial participation at any time without the need to justify the decision. If a trial participant wants to withdraw consent, the investigator should be involved in the discussion with the trial participant 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.

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 treatment and follow up of trial participants 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

BI 1291583 and placebo will be manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG. The clinical trial supplies will be provided in bottles containing 20 tablets each. The tablets should be handled according to the labelled storage instructions and shelf life.
One tablet strength (5 mg) was prepared for clinical evaluation. In addition to the drug substance, the tablets contain the following standard pharmaceutical excipients in common amounts: mannitol, microcrystalline cellulose, hydroxypropylcellulose, crospovidone, and magnesium stearate. Placebo tablets, apart from being devoid of the drug substance, also lack the excipients hydroxypropylcellulose and crospovidone, but are otherwise identical to BI 1291583 tablets.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the two test products are given below:

Table 4.1.1: 1 BI 1291583 5 mg tablets

Substance:	BI 1291583
Pharmaceutical formulation:	Tablets
Unit strength:	5 mg
Posology:	qd
Method and route of administration:	Oral

Table 4.1.1: 2 Placebo tablets

Substance:	No substance (placebo to BI 1291583 5 mg)
Pharmaceutical formulation:	Tablets
Unit strength:	matching placebo
Posology:	qd
Method and route of administration:	Oral

4.1.2 Selection of doses in the trial

Based on MRD data, doses up [redacted] qd BI 1291583 were safe and well tolerated in healthy volunteers. With 5 mg qd dosing at a mean AUC_{0-24} of 187 nM·h, a plateau effect at 83.1% inhibition of CatC in blood was observed. BI 1291583 at its expected human therapeutic dose (5 mg qd) inhibited NE in a range from 67.2% up to 86.8% in blood of a healthy volunteer population which may translate to > 90% reduction of NE in sputum in NCFB patients and similar reduction levels in patients with CFB. Five mg qd represents the dose with the highest expected clinical benefit of reduced exacerbation risk in a BE patient population, and thus a favourable benefit/risk profile.

4.1.3 Method of assigning trial participants to treatment groups

After the assessment of all in- and exclusion criteria, each eligible trial participant will be randomised to a treatment group according to a randomisation plan in a 2:1 ratio (verum / placebo), please see Section 7.4. This randomisation will be stratified according to SoC CFTR-MT yes / no, assuming approx. 50% will be on CFTR-MT. Randomisation codes will be generated through a validated software and kept blinded to the trial team, sites and trial participants. Access to the codes will be controlled and documented. An Interactive Response Technology (IRT) system will be used to screen participants, create a participant number, perform drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency unblinding.

4.1.4 Drug assignment and administration of doses for each trial participant

A double-blind design is required to keep the blind (see Section 4.1.5) of trial participants and investigators. Patients will receive bottles containing 20 tablets each of either active or placebo. Once a day, they will take one tablet for 12 weeks.
The patients should swallow the trial medication unchewed together with a glass of water (~250 mL). Trial medication should be taken at the same time each morning (e.g., 8:00 am) during the treatment phase, within a time window of +/- 1 hour. Missed dose(s) will not be replaced. If a dose is missed by more than 12 hours, that dose should be skipped, and the next dose should be taken as scheduled.

No restrictions apply whether to take the medication with food or close to a meal as no food effect was observed in clinical Phase I.

On visit days, trial medication will be taken at the site from the new kits assigned at the respective visits, even if outside the normal schedule to accomplish assessments at the site. Patients will then return to their usual intake time.
The last dose will be administered at EOT.
The investigational product should only be dispensed to participating patients by authorised personnel as documented in the ISF.
The kits will be used for treating the patient at visits at the site and at the respective time points at home in between site visits.
In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see Section 6) physical visits to the sites may not be feasible or may need to be restricted to ensure participant safety. Based on a thorough assessment of benefits and risks, the investigator may still decide to continue the trial treatment. Where permitted by local law and regulations, trial medication may be shipped directly to the participants' home.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This trial is planned as double blinded. Table 4.1.5.1: 1 below summarises the masking/blinding level of individual functions, roles and responsibilities involved in the trial.

Table 4.1.5.1: 1 Blinding level of functions involved in the trial

Role/function	Timing of unblinding/receiving access to the treatment information (including rationale)
Patients	Blinded until data ready for final analysis
Investigator/site staff	Blinded until data ready for final analysis
Sponsor, clinical trial team	Blinded until data ready for final analysis
Independent Data Monitoring Committee (DMC)	Unblinded for periodic safety review. The release of the treatment information at individual time points will be documented.
Sponsor, independent evaluation team	Unblinded for optional interim PD/PK review. The release of the treatment information will be documented.
Bioanalytical staff	As requested for analysis of bioanalytical samples

During the time a role/function is blinded, the randomisation schemes and medication kit lists (i.e. the treatment information) are kept restricted by the global Randomisation Team per Sponsor Standard Operating Procedure (SOP), with the following exceptions:

The independent DMC (refer to Section 7.2.8) will periodically review unblinded data related to safety under conditions that ensure that patients, investigators and trial team will remain blinded. Respective documentation will be done according to sponsor SOPs.

A trial independent evaluation team will be appointed to support the optional interim PD/PK analysis. Details on the interim PD/PK analysis will be described in a separate logistics and access plan, see also Section 7.2.8.

The responsible bioanalyst of the external bioanalytical laboratory will receive the randomisation codes prior to last patient completed to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo / comparator patients.

The Trial Bioanalyst may receive unblinding data from the external bioanalytical laboratory after the last patient completed the last visit but prior to official unblinding (TIR approval) of the trial for preparation of data transfer, e.g. check file structure prior to data upload and SDTM transformation and bioanalytical report writing.

4.1.5.2 Emergency unblinding and breaking the code

Emergency unblinding will be available to the investigator via emergency service and via IRT. It must only be used in an emergency 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 treatment allocation should not be disclosed to the sponsor unless this is explicitly requested. 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 trial participants during trial conduct. The access to the code will only be given to authorised PSPV representatives for processing in the Pharmacovigilance database and not be shared further.

To ensure patient's safety during the trial, a fully external DMC, independent of the trial and project teams, will review periodically all available safety data. A DMC SAP which describes the analyses required for assessment by the DMC will be produced. Further details will be provided in a DMC charter.

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.

The label will be prepared according to regulation (EU) No 536/2014, Annex 6, Section D.8., omitting certain particulars with the following justifications:

- The investigator name was omitted from the label due to the IRT system.

Should local regulations outside the EU require these particulars they will be added to the country specific label text.

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. Further information will be also provided in the ISF. A temperature log must be maintained for documentation. If the storage conditions at site 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 or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol (CTP) by the IRB/ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate 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 CTP
- If applicable per local regulations, availability of the proof of a medical license for the Principal Investigator
- For USA: 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. Trial participants should be instructed to return unused investigational drug and empty medication kits (i.e. bottles).

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 trial participant, 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 participants. The investigator or designee will maintain records that document adequately that the trial participants were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the trial participant 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 specific special emergency procedures to be followed. Requirements regarding specific monitoring and potential action to be taken is described in Section 5.2.5.

4.2.1.1 Additional treatments

Salbutamol / albuterol is being used to assess a further endpoint in the clinical trial (measurement of post-bronchodilator pulmonary function during spirometry) and hence is considered an auxiliary medicinal product (AMP). Its use is described in detail in Section 5.1.2.
The total dose of salbutamol / albuterol administered during each of the spirometric assessments (at the timepoints indicated in the Flow Chart) is approximately 400 µg (delivered as four separate doses of approximately 100 µg by oral inhalation from a metered dose inhaler (MDI) at approximately 30 sec intervals).
This use of salbutamol / albuterol is in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Technical Statement [R20-2419] on the conduct of spirometry and is a well-established standard.
For the AMP salbutamol / albuterol, the safety reference document for global safety reporting purpose is the ProAir HFA US prescribing information [R23-3789]. A version of the prescribing information / summary of product characteristics of the salbutamol / albuterol metered dose inhaler (MDI) product used for pulmonary function testing should be filed in the ISF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

While enrolled in this trial, trial participants must not participate in another investigational drug or device trial or receive other investigational treatment(s). For details about restrictions regarding concomitant treatment, refer to Table 4.2.2.1: 1 below.

The medical management of acute exacerbations is not restricted.

To minimise variability not related to the investigational product, medications with potential effect on bone turnover biomarkers (e.g., medications to treat osteoporosis, heparin, selective estrogen receptor modulators, thiazolidinediones, Vitamin K antagonists, systemic ketoconazole, anti-convulsant, etc., a list of examples will be provided in the ISF) should be stable at baseline for > 4 weeks and continue to be stable throughout the trial, if possible.

Table 4.2.2.1: 1 Restrictions regarding concomitant treatment

Medication restrictions	**Prior to randomisation (Day 1, Visit 2)**	**During treatment period (12 weeks)**	**During REP (EOT + 28 days)**
Drugs with effect on immune response			
Immunosuppressants or other drugs with immunosuppressive effects that can increase the risk of infections (e.g., Methotrexate, Azathioprine, Cyclosporine, Tacrolimus, Mycophenolate, Rituximab, Tocilizumab, Mepolizumab, Lebrikizumab, Dupilumab, Benralizumab, Omalizumab, Leflunomide and similar)	NOT permitted within 3 months	NOT permitted	NOT permitted
Oral corticosteroids defined as Prednisone >10 mg/day or equivalent (see Appendix 10.3)	NOT permitted within 2 weeks	NOT permitted*	NOT permitted*
Medications that may cause palmoplantar keratoderma unless on stable treatment > 3 months prior randomisation without skin reactions			
Tegafur/fluorouracil, Bleomycin, Hydroxyurea, Lithium, Venlafaxine, Quinacrine, Imatinib mesylate	NOT permitted within 4 weeks	NOT permitted	NOT permitted
Antibiotic therapy, unless on stable treatment > 3 months prior randomization and to be continued throughout the trial, if possible			
Maintenance dose/regimen for oral or inhaled antibiotics as chronic treatment for BE, permanent or cycling[#] (Seasonal use of antibiotic doses is not considered stable treatment)	NOT permitted within 4 weeks	NOT permitted*	Permitted*
CFTR-MT, unless on stable treatment > 3 months prior randomization			
CFTR-MT maintenance dose/regimen for CFTR defect	NOT permitted within 3 months	NOT permitted	NOT permitted
Lumacaftor / Ivacaftor dual combination (as being a strong CYP3A4 inducer)	NOT permitted	NOT permitted	NOT permitted

Medication restrictions	**Prior to randomisation (Day 1, Visit 2)**	**During treatment period (12 weeks)**	**During REP (EOT + 28 days)**
Maintenance therapy with bronchodilators is permitted except prior to pulmonary function tests as specified below			
Short-acting bronchodilators (e.g., Salbutamol/Albuterol, Terbutaline, Ipratropium)	NOT permitted 6 hours before PFT	NOT permitted 6 hours before PFT	NOT permitted 6 hours before PFT
Long-acting bid bronchodilators (e.g., Salmeterol, Formoterol, Theophylline)	NOT permitted 12 hours before PFT	NOT permitted 12 hours before PFT	NOT permitted 12 hours before PFT
Long-acting qd bronchodilators. (e.g., Olodaterol, Indacaterol, Tiotropium, Tulobuterol, Theophylline)	NOT permitted 24 hours before PFT	NOT permitted 24 hours before PFT	NOT permitted 24 hours before PFT
Other			
Chronic use of strong CYP3A4 and P-gp inhibitors (e.g. clarithromycin, itraconazole, ketoconazole, ritonavir, and grapefruit) as well as strong CYP3A4 and/or P-gp inducers (e.g. rifampicin and phenytoin)	NOT permitted within 4 weeks	NOT permitted	NOT permitted

* Acute exacerbations should be treated according to best standard practice
# Defined as course of antibiotics leading to continuous exposure (e.g., every day, every other day or Week, 2 weeks on-followed by 2 weeks off-treatment) For patients who are on a stable regimen of cycling antibiotics, every other month, Visit 2 should occur on the Day 1 of an "On-cycle" (+3 days) whatever the antibiotic is. Further visits should then always occur on the same day of the monthly cycle (e.g., always on Day 1).

4.2.2.2 Restrictions on diet and lifestyle

Please refer to Sections 4.2.2.1 and 4.2.2.3, there are no further restrictions on diet and lifestyle.

4.2.2.3 Contraception requirements

The following measures are defined to prevent pregnancy during participation in the clinical trial:

Female patients

WOCBP, if their sexual partner is a man able to father a child, must use two medically approved methods of birth control throughout the trial and for a period of at least 9 months after the last trial drug intake: one barrier method, and one highly effective non-barrier method. Accepted highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Sexual partner is vasectomised

Male patients

Men participating in this clinical trial, if their sexual partner is a WOCBP, must use a condom from the first administration of trial medication until 6 months after the last administration of trial medication. They should also agree to refrain from donating sperm for the same time period.

Alternatively to the contraceptive methods described above, trial participants (male or WOCBP) 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

Trial participants 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 or delegate.

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Pulmonary exacerbation

The pulmonary exacerbation definition is following the definition that will be used to cross-reference between patient groups ([redacted] and 1397-0013 Clairafly™) and [redacted].

A pulmonary exacerbation in this study is defined as having 3 or more of the following symptoms for at least 48 hours resulting in a physician's decision to prescribe antibiotics (oral or intravenous):

- Increased cough
- Increased sputum volume or change in sputum consistency
- Increased sputum purulence
- Increased breathlessness and/or decreased exercise tolerance
- Fatigue and/or malaise
- Hemoptysis

Further CF specific symptoms to allow for exacerbation evaluation according to Fuchs criteria [R02-1107] will be collected in the eCRF of all Phase II and Phase III trials ongoing or planned.

Subjects on chronic macrolide therapy whose only change in therapy is minor dose or frequency adjustment will not meet the definition of exacerbation.

Dose or frequency change of background antibiotic treatment of ≥ 2 fold when administered for ≥ 3 symptoms will meet the definition of exacerbation.

Severe pulmonary exacerbations are defined as exacerbations leading to hospitalisation and/or intravenous antibiotic administration.

"Onset of exacerbation" will be defined by the onset of first recorded symptom.
The "end of exacerbation" will be the end date of the related antibiotic treatment.

5.1.2 Pulmonary function testing

Pulmonary function will be assessed using standardized spirometry. Spirometry will be conducted at clinic visits using the site's own equipment and procedures, which must meet 2019 ATS/ERS criteria [R20-2419]. Spirometry will be conducted with the subject 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 criteria (with a maximum of eight attempts). The highest FEV1 and FVC will be selected regardless of whether they come from different

spirometric manoeuvres or from the same manoeuvre. As reference values the global lung function 2012 equations will be used [R15-0845]. On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to PFTs. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odors (e.g., perfumes). If treated with bronchodilators, patients should not take their daily bronchodilator inhalation until after completion of the spirometry, refer to Table 4.2.2.1: 1.

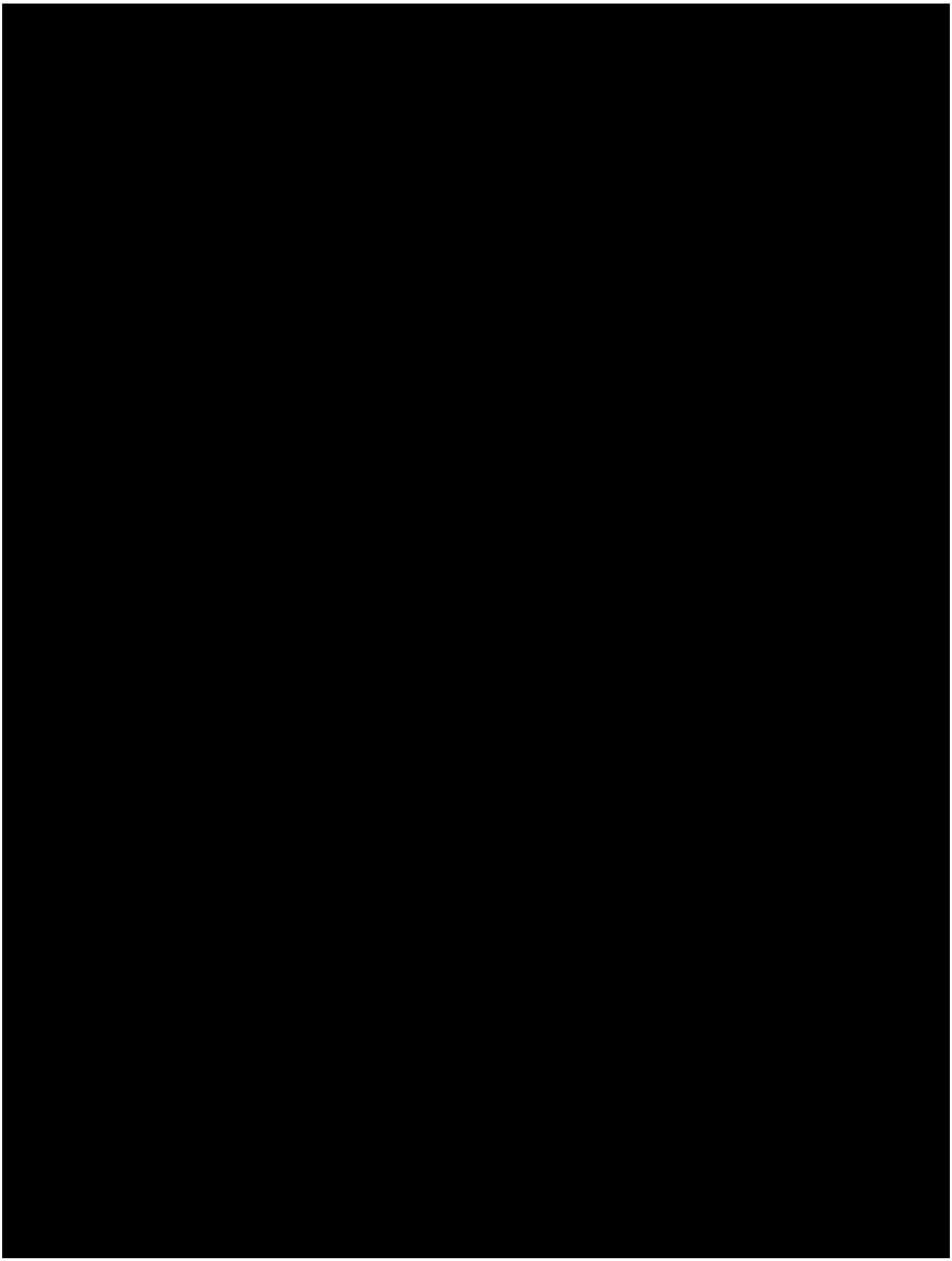
PFTs should preferably be started after spontaneous sputum collection and approximately at the same time at visit days (e.g. always at 11:00 am) with an allowed time window of 1 hour. In case sputum needs to be induced, this should happen after PFT.

Post-bronchodilator (salbutamol (albuterol)) testing:

Following the completion of three acceptable pre-bronchodilator forced expiratory maneuvers, salbutamol (albuterol) will be administered to each patient. After a gentle and incomplete expiration, a dose of approximately 100 µg of salbutamol (albuterol) is inhaled in one breath to total lung capacity. The breath is held for 5 – 10 sec before the patient exhales. Four separate doses (total dose approximately 400 µg) are delivered at approximately 30 sec intervals (this dose ensures that the response is high on the salbutamol (albuterol) dose-response curve). Three to five additional, acceptable post-bronchodilator forced expiratory manoeuvre tests are recorded 15 – 30 minutes after the last dose of salbutamol (albuterol) is inhaled.

The absolute values of FEV1 and FVC will be reported in the eCRF. Further instructions regarding PFT measurements will be provided in the ISF.

[redacted]



[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.

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

Specific periodontal and dermal assessments have to be performed in this trial which are not part of standard physical examination, see Sections 5.2.5.1 and 5.2.5.2.

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 and aural body temperature.

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 Tables 5.2.3: 1 and 5.2.3: 2 . For the sampling time points, please refer to the Flow Chart.

Trial participants should be fasted, if possible, for the blood sampling for bone metabolism biomarkers.

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

Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the Laboratory Manual / 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 5.2.6.1.4 and the DILI Checklist provided in the ISF). The amount of blood taken from the trial participant concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor or delegate.

Table 5.2.3: 1 Safety laboratory tests

Functional lab group	**Test name**
Haematology	Haematocrit Haemoglobin Red Blood Cell Count/Erythrocytes (RBC) Reticulocyte count Reticulocytes/Erythrocyte White Blood Cells/Leucocytes (WBC) Platelet Count/Thrombocytes (quant)
Automatic WBC differential, relative (per Leukocytes) and absolute	Neutrophils Eosinophils Basophils Monocytes Lymphocytes

Functional lab group	Test name
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time – INR (International Normalised Ratio) Fibrinogen
Enzymes	Aspartate aminotransferase (AST/GOT) Alanine aminotransferase (ALT/GPT) Alkaline Phosphatase [AP] Gamma-Glutamyl Transferase (GGT) Creatine Kinase (CK) Creatine Kinase Isoenzyme MB (CK-MB), if CK is elevated
Substrates	Creatinine Total bilirubin Direct bilirubin Total protein Albumin C-Reactive Protein (CRP) Blood urea nitrogen (BUN) Uric Acid Total cholesterol Triglycerides Glucose
Electrolytes	Sodium Potassium Chloride Calcium
Drug screening (urine)	Cotinine (except V3)
Serum Pregnancy test for WOCBP at screening	Human Serum Chorionic Gonadotropin
Urine Pregnancy test (Dipstick) for WOCBP[1]	Human Chorionic Gonadotropin in urine
Urine analysis (Stix)	Urine nitrite (qual) Urine protein (qual) Urine glucose (qual) Urine ketone (qual) Urobilinogen (qual) Urine bilirubin (qual) Urine RBC/erythrocytes (qual) Urine WBC/leucocytes (qual) Urine pH
Urine analysis	Urine albumin creatinine ratio

[1] Urine pregnancy testing will be performed at site as indicated in the Flow Chart

eGFR will be analysed and calculated by the central laboratory at the same timepoints as other safety laboratory parameters (see in the Flow Chart), by using the CKD-EPI formula (see Appendix 10.1) and using an enzymatic assay for serum creatinine measurement, IDMS standardized.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which are planned during screening only but may be repeated as required. The investigator will use the exclusionary lab test results for the assessment of the participants' eligibility for the trial. The lab results will not be reported to the sponsor.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Infectious serology (blood)	Hepatitis B surface antigen (qual)* Hepatitis B core antibody (qual)* Hepatitis C antibodies (qual) HIV-1 and HIV-2 antibody (qual)

* An HBV-DNA test should be conducted if Hepatitis B core antibody is positive and Hepatitis B surface antigen is negative.
**An HCV-RNA test should be performed if Hepatitis C antibodies result is positive to confirm if the infection is active.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart.

The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis. Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in participant's medical record. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Periodontal assessments

Before start of trial treatment

CFB patients will be, on average, significantly younger compared to NCFB patients and thus concomitant periodontal issues are expected to be rare. An increased susceptibility to periodontal disease is not described [R22-3121].
The entry criteria in the study have been specified to exclude subjects with underlying moderate or severe periodontal conditions.
All patients considered eligible are required to have a periodontal assessment by a trial-designated local dentist during screening period, including parameters such as pocket depth, attachment loss, bleeding on probing etc.
All patients should have a panoramic radiograph available at baseline (except if edentulous), as detailed in the Flow Chart.

- Patients without teeth (edentulous)

The dentist will confirm the edentulous status and check for implants supporting a denture. Implant sites will be examined. [redacted]

- Patients with no or mild periodontitis

Defined as with pocket depth up to 3 mm or up to 4 mm (4 mm only if no bleeding on probing), will receive a professional plaque removal.

[redacted]

Details on the parameters to be assessed will be provided in the ISF.

5.2.5.2 Dermatological assessment

The entry criteria of the trial have been defined to exclude subjects with underlying dermatologic conditions that could impair the ability to detect a potential safety signal or might put the subject at increased risk.

[redacted]

Treatment continuation or discontinuation decisions will be made by the investigator considering the dermatologist's evaluation if applicable.
Forms to document skin assessments will be provided in the ISF, and data will be transferred into the eCRF.

5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this protocol.

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 trial participant 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 considered related or not.
The following should also be recorded on the appropriate eCRF(s) 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 participant 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 participant 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

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 in Section 5.2.6.1.2. 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 Adverse events of special interest

The term "adverse event 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:

Potential Severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters:

For patients with normal transaminase levels (AST and ALT ≤1 x ULN) at baseline:

- 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 sample, or in samples drawn within 30 days of each other, or
- ALT and / or AST elevations ≥ 10-fold ULN.

For patients with abnormal aminotransaminase levels between > 1 and < 3 x ULN at baseline:

- An elevation of AST and / or ALT ≥ 3-fold the baseline value combined with an elevation of bilirubin ≥ 2-fold ULN or ≥2-fold the baseline value (if bilirubin is elevated at baseline), measured in the same blood sample, or in samples drawn within 30 days of each other; or;
- Aminotransferase elevations ≥ 5-fold the baseline value.

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 in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, 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.

Details on documentation and reporting are provided in the ISF.

5.2.6.1.5 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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, 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 trial 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 trial drug concerned)
- Continuation of the event despite the withdrawal of the medication, considering 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
- There is an 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 participant files.

Per default, SAEs/AESIs should be reported via the eCRF in the EDC system. If the EDC system is not or no longer available (e.g. after database lock), the paper BI SAE form should be used; please see Section 5.2.6.2.2.

The following must be collected and documented:

- From signing the informed consent onwards until the individual participant's end of trial (usually the End of Study (EoS) visit: all AEs (serious and non-serious) and all AESIs
- After the individual participant's end of trial:
  The investigator does not need to actively monitor the participant for new AEs but should only report any occurrence of cancer of new histology and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call

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 AE or SAE eCRF pages to the sponsor's unique entry point immediately (within 24 hours of becoming aware of the event), the country specific process will be described 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 in addition.

With receipt of any further information on these events, follow-up reports have 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 participant'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.

Should the EDC system not be available for more than 24 hours, reporting must occur via the BI paper SAE forms.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a trial participant 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 Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for 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 Studies is to be completed. However, if a SAE and/or AESI is associated with the pregnancy it must be reported as described in Section 5.2.6.2.2.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood samples for assessment of BI 1291583 plasma PK will be collected as indicated in the Flow Chart and Table 10.2: 1. The exact date and actual 24-hour clock time of PK samples will be recorded in the CRF. The exact date and actual 24-hour clock time of doses administered at Visit 2 and Visit 6/EOT will be recorded in the CRF. The exact date and actual 24-hour clock time of doses administered in the 2 calendar days prior to all visits in Table 10.2: 1 will be recorded in the CRF.

The actual sampling times will be used for determination of pharmacokinetic parameters if available; otherwise, nominal times may be used.

5.3.2 Methods of sample collection

For the quantification of BI 1291583 plasma concentrations, blood samples will be collected as indicated in the Flow Chart. The actual sampling times and time of dosing will need to be recorded. Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. Plasma samples will be stored frozen at about -20°C or below at the participating sites, logistics CRO/central laboratory and bioanalytical laboratory. The samples will be shipped on dry ice.

After completion of the trial the plasma samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. Left-over PK samples will be discarded at the latest within 6 months of signature of the clinical trial report.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

The PK and PD data from this study may be used for an exploratory investigation of PK/PD relationship of BI 1291583.

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in Sections 5.1 and 5.2.

5.4.1 Pharmacodynamics, safety, and patient selection biomarkers

Biomarker assessments will be conducted for baseline patient characterisation as well as for pharmacodynamic investigations.

5.4.1.1 Baseline patient characterisation:

- *P. aeruginosa* colonisation correlates with the frequency of pulmonary exacerbation. *P. aeruginosa* sputum cfu (colony forming units) assessment will be done at central lab

- Murray Colour Chart**:** Sputum purulence, reported to correlate to bacterial colonisation [R20-2792], will be assessed by use of the Murray sputum colour chart.
  The Murray colour chart is a tool for visual comparison of sputum colour, allowing to characterise sputum according to the three categories mucoid, mucopurulent, or purulent
- NEATstik®: Semi-quantitative sputum NE activity based on point of care test performed at analysis lab [R19-3083]

5.4.1.2 Pharmacodynamic investigations

Pharmacodynamic biomarkers will be assessed over time to characterise the mode of action of BI 1291583 in patients with CF for comparison with data from NCFB patients obtained in study 1397-0012 [c35703911-05].

NE activity

Sputum NE activity will be quantified to determine how target engagement in blood, demonstrated in healthy volunteer trials, translates into target engagement in patients' sputum as surrogate for the target organ lung.

[redacted]

5.4.1.3 Methods and timing of sample collection

5.4.1.3.1 Blood

Whole blood, serum and plasma samples will be collected. Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the ISF / laboratory manual. For sampling timepoints see the Flow Chart.

5.4.1.3.2 Sputum

Sputum collection at site

Sputum collection on visits indicated in the Flow Chart should occur with active breathing techniques, supported by the site staff, if needed. In case of difficulties producing sputum and no adequate sputum sample is produced spontaneously, induction of sputum is mandatory.

Recommendations for sputum induction will be provided in the ISF, however sites can also follow their own standards of saline inhalation or follow the standard operating procedure of the Cystic Fibrosis Therapeutics Development Network.

Sputum induction should only be performed after the pulmonary function test (details in Section 6.2.2).

If a sputum sample cannot be obtained on the day of the visit, it is generally possible that the patient returns the next day to provide the sputum sample.

To assess patient's eligibility for trial participation, at least one adequate sputum sample must be obtained at the site prior randomisation at V2 as indicated in the sputum decision tree for the screening period, Figure 5.4.1.3.2: 1.

Sputum collection at home

After having confirmed patient's eligibility, the patient will be asked to collect spontaneous sputum accrued during the morning routine on visit days, if possible. This sample should be taken to the site in the provided collection containers and will serve as backup sample in case all attempts failed to obtain a sputum sample at site.

Sites will assess the quality of the backup sample macroscopically, including using the Murray Colour Chart.

A sputum decision tree for the treatment period is depicted in Figure 5.4.1.3.2: 2. This approach is also applicable for a patient, who could provide a sputum sample at the site prior to Visit 2.

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

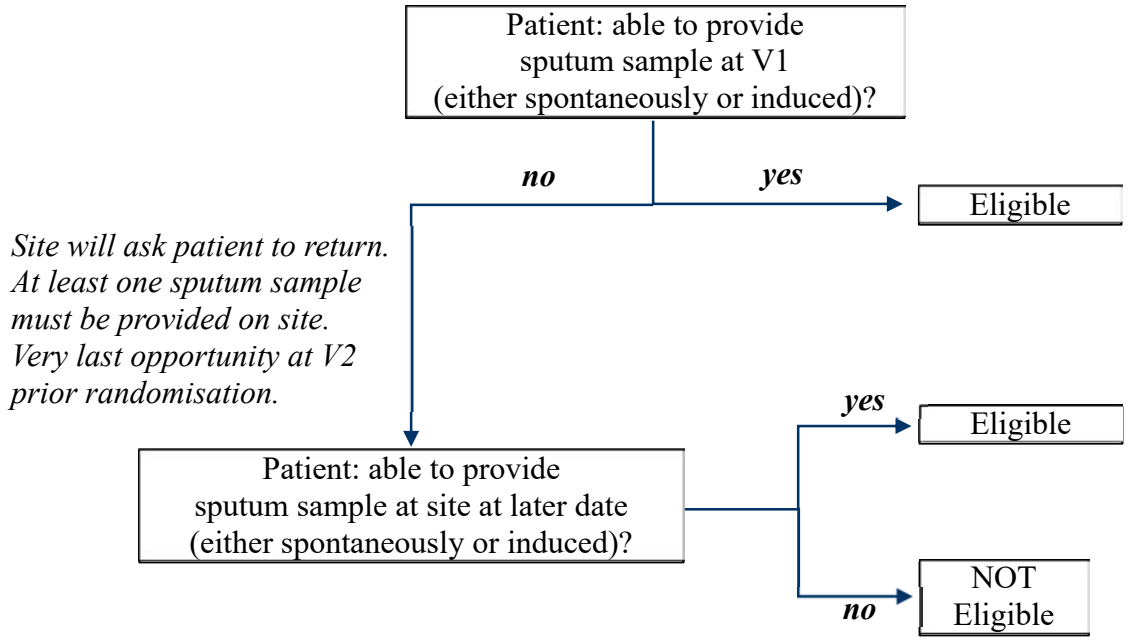


Figure 5.4.1.3.2: 1 Sputum decision tree – screening period V1 – V2 / eligibility

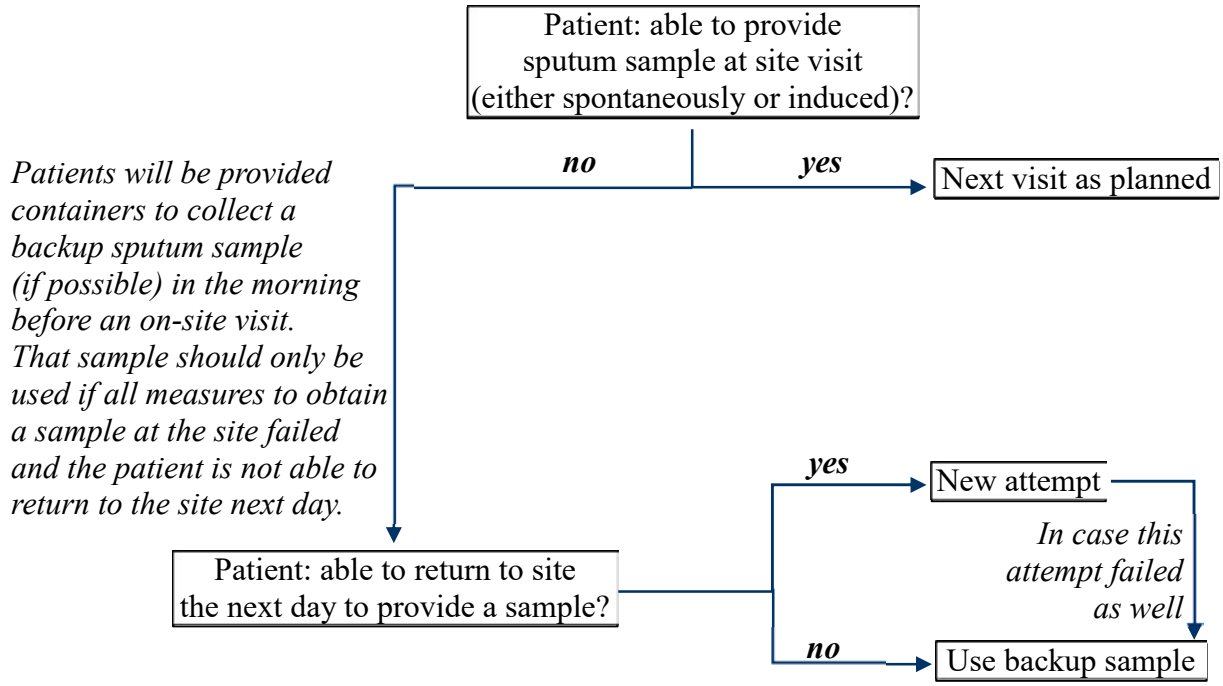


Figure 5.4.1.3.2: 2 Sputum decision tree – treatment period V4 – EOS; applicable for V2 only, if sputum sample already obtained at the site prior V2

[redacted]

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

Additional biomarker analysis may help to better characterise the patients and their disease course. This may support future drug developments by delivering in depth patient characterisation for patient selection as well as deliver detailed insights into the MoA of the CatC inhibition allowing for differentiation approaches.

To enable this, additional serum samples and a DNA sample will be taken. In case more sputum could be collected than required for biomarker analyses and *P. aeruginosa* culture, an aliquot will be taken and transferred into the biobank.

5.5.1 Methods and timing of sample collection

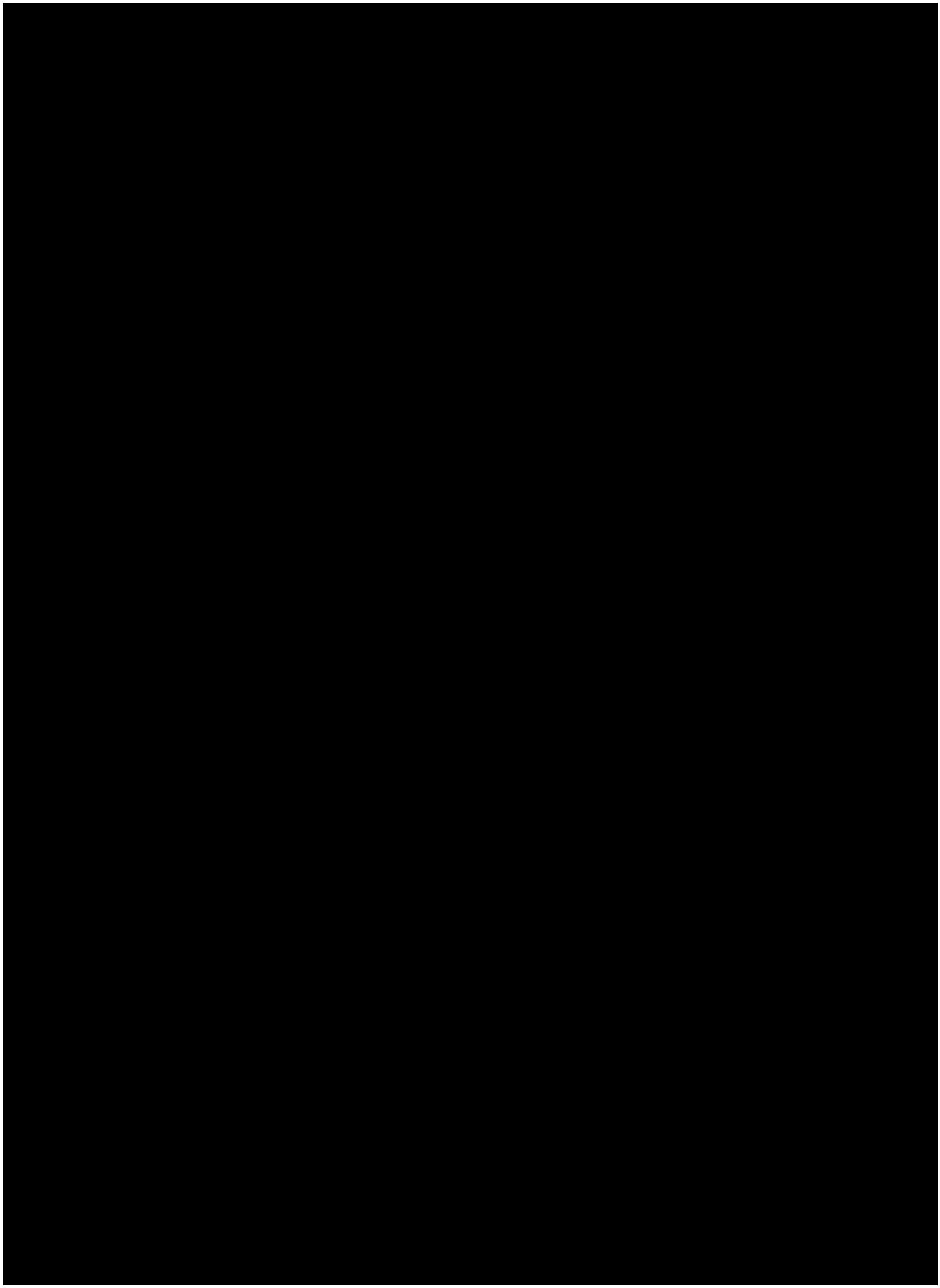
Blood will be drawn for optional serum and DNA banking at timepoints indicated in the Flow Chart. The analysis lab will take a sputum aliquot for biobanking purposes, if feasible.

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see the Flow Chart.

5.6 OTHER ASSESSMENTS

There are no other assessments planned.

[redacted]



6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the execution of the investigational plan as per this clinical trial protocol may not be feasible. With the consent of the participant, the sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual trial participant visits and assessments, home healthcare nurse visits, direct-to-participant/direct-from-participant shipments of trial treatment or bio-sample pick up from the participant's home. The implementation of these measures will depend on participant's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Each visit date (with its window) up to EOS is to be counted from Day 1 (Visit 2). If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator. All deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

[redacted] This applies also to the randomisation visit (V2).

Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits.

If possible, blood sampling should always be performed at the same time of the day [redacted]

Patients should be instructed not to take the trial medication at home on scheduled visit days but bring it to the site and take it after pre-dose procedures were performed.
Procedures that should be performed pre-dose are [redacted] and safety assessment as AE and concomitant therapy collection, physical examination incl. vital signs and skin monitoring, ECG, and urine pregnancy test, if applicable. Also blood and urine sampling, incl. the pre-dose PK sample, should precede intake of study medication.
Sputum collection and pulmonary function test may be performed after intake of study medication, considering operational aspects and that no immediate effect on the lung is expected.

The order of the different trial procedures should be planned, taking into account the structure of the individual investigational site and following the requirements outlined in the clinical trial protocol and ISF/Lab Manual.

Visit days with full PK profile, i.e. V2 (randomisation visit) and EOT Visit, may be split over 2 consecutive days, i.e. procedures as [redacted] AE collection, physical examination and ECG could be completed the day before the main visit.

Preferred order of procedures during trial visits, where applicable:

1. [redacted])
2. **AE and concomitant therapy collection,** [redacted]
3. **Physical examination including vital signs and skin monitoring**
4. **ECG**
5. **Urine pregnancy test** (if applicable)
6. **Blood and Urine sampling, including trough (predose) PK sampling, safety lab and biomarkers**
7. **Sputum sample collection (if spontaneous)**
8. **Pulmonary function test**
   spirometry should preferably happen after spontaneous sputum collection and at the same time of the day at each visit ± 60 min.
9. **Sputum sample collection (if induced)**
   In case a patient does not expectorate sputum spontaneously, expectoration may be triggered by pulmonary function testing. In case sputum needs to be induced, this should happen after PFT. If patient is exhausted, it may be considered to postpone sputum expectoration or lung function measurement to the next day.
10. **Study medication administration**
    (may be done prior to 7. considering operational aspects, see above)
11. **Post dose PK samples** should be taken according to the time schedule provided in Appendix 10.2 after IMP intake. The exact time of sample collection is to be recorded in the eCRF.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, patients will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

Patients will be asked to give informed consent to biobanking of specified sample types DNA, serum and a sputum sample, if feasible. Participation to biobanking is voluntary and is not a prerequisite for participation in the trial.

Note: banking samples must not be taken prior to Visit 2.

Patients will be asked to complete the [redacted] on his/her own in a quiet area/room before any other screening assessments. [redacted] will be completed at screening.

Inclusion and exclusion criteria have to be checked according to Section 3.3.

At the screening visit, patients have to donate a spontaneous or induced sputum sample at site (Section 5.4.1.3.2):

- An appropriate part of the sputum sample will be taken for *P. aeruginosa* culture, if possible
- Sputum colour will be characterised by use of the Murray Colour Chart
- Samples will be sent frozen to the central lab for further processing

During the screening visit, demographic information will be collected. This includes:

- Age on the day of informed consent (in years)
- Sex (male, female in order to describe the subject`s sex at birth)
- For women: if they are of childbearing potential, yes / no; in order to characterise the patient population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterise the patient population, to support possible subgroup analyses if needed, and to support the calculation of the kidney function via the CKD EPI formula unless not acceptable according to local regulations. [redacted]

Further assessments/measurements at Screening include (see Flow Chart and Sections 5.2.1, 5.2.2, 5.2.3, 5.2.4, 5.2.5, 5.2.6.2.3):

- Relevant Baseline Conditions and Medical History (stable maintenance use of CFTR-MT has to be entered as stratification criterion at screening and confirmed at randomisation)
- Physical examination including vital signs (BP, PR, aural body temperature), height and body weight
- 12-lead ECG
- Safety laboratory tests
- Blood and urine sampling for biomarkers
- Pregnancy testing in blood (if applicable)
- Pulmonary function test
- A CT must be available for confirmation of BE diagnosis at Visit 2. The scan may be historical (up to 5 years prior randomisation). If a new CT scan needs to be performed within the scope of the trial, this should happen (if a patient is otherwise eligible) during screening period before Visit 2. If applicable, accordance with local regulations regarding radiation exposure has to be ensured

The Screening Visit 1 can cover a period of up to 6 weeks, e.g., to wait for appointment at dentist, or if washout or stabilisation of certain medication is required (see Section 4.2.2.1). If the screening period of 6 weeks has to be exceeded for unforeseen reasons (e.g. scheduling dentist's appointment, infection) the sponsor has to be contacted immediately. In this case specific safety assessments have to be repeated prior V2 in an unscheduled visit (safety lab, physical examinations, vital signs, pregnancy testing, if applicable).

The Screening has to be registered in IRT to trigger the first medication shipment to the site.

In case eligibility of a patient is not confirmed, the patient will be registered as screen-failure. Re-screening would be allowed for screen-failed patients who are considered eligible at a later time point. Re-screening for a second time would be allowed if for independent reasons where one of these was an infection. These patients will receive a new patient number (Section 3.3).

6.2.2 Treatment period

When eligibility of the patient is confirmed, randomisation via IRT will be performed at Visit 2.

Prerequisite for randomisation is information on stable maintenance use of CFTR-MT (yes / no) which will be used as stratification factor.

The treatment period is from Day 1 to Week 12.

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 for all required procedures during the visit, e.g. sputum sampling, PK sampling.

A sputum sample should be collected at site, either spontaneously or induced, see Section 5.4.1.3.2. Additionally, patients should be instructed at each visit to collect sputum accrued during the morning routine on visit days, if possible, and bring the sputum collection containers to the site.

Information on dose assignment and drug administration by the patient is provided in Section 4.1.4.

Procedures at the visits should be performed as described in the Flow Chart, see also details described above (Section 6.2.1), in Section 5 and in Lab Manuals/ISF.

Patients using bronchodilators should adhere to the following wash-out times before pulmonary function tests (for further details, refer to Table 4.2.2.1: 1):

24 hours for qd long acting bronchodilators,

- 12 hours for bid long acting bronchodilators, and
- 6 hours for short acting bronchodilators

For PK samples, the provided planned time according to the time schedule (Appendix 10.2) is approximate, the actual time when the samples were collected has to be documented.

[redacted]

After completion of the treatment period, male subjects with WOCBP partners and WOCBP participants should be reminded to continue to use contraception after the last administration of trial medication as provided in Section 4.2.2.3.

6.2.3 Follow-up period and trial completion

Patients who completed treatment (as planned or premature) will have an End of Treatment (EOT) Visit and a subsequent Follow-up Visit after 28 (+ 7) days. The Follow-up Visit will be End of Study (EOS).

[redacted]

After the EOS (End of Trial) Visit any abnormal assessments or lab values, or ongoing AEs, will be followed up as medically required in the opinion of the investigator. For reporting of AEs after patient's completion of the trial, please see Section 5.2.6.2.2.

Early treatment discontinuation

In case a patient has to permanently discontinue trial medication prematurely for whatever reason, discontinuation of treatment should be registered in IRT and documented in the eCRF. The patient should attend an EOT Visit and 28 (+ 7) days later a Follow-up Visit to ensure patient safety and data integrity.

[redacted]

Treatment completion (EOT)

Treatment completion is defined as a patient having completed treatments until planned EOT Visit (Week 12).

Trial completion (EOS)

For patients who completed treatment (as planned or premature), the trial completion (individual patient's EOS) is achieved when the Follow-up Visit (EOS Visit) has taken place.

The EOS eCRF page has to be filled-in when the patient has ended the trial.

After the EOS Visit any abnormal assessments, abnormal lab values, or ongoing AEs, will be followed up as medically required in the opinion of the investigator.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The trial is designed to assess safety and tolerability of 5 mg qd of BI 1291583, in CF patients, and to investigate the pharmacokinetic properties and pharmacodynamic effects over a 12-week treatment period. All evaluations are to be considered exploratory.

[redacted]. Analysis details will be included in a separate statistical analysis plan.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The study is exploratory in nature and no confirmatory testing will be performed. Hence no null and alternative hypotheses are defined. Any confidence intervals or p-values provided are to be interpreted in the perspective of the exploratory character of the study. A justification of the sample size is provided in Section 7.5.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following analysis sets will be defined for statistical analyses:

- Screening set (SCS): This patient set includes all patients who signed informed consent. The SCS will be used for the analyses of patient disposition.
- Randomised set (RS): This patient set includes all randomised patients. The RS will be used for the analyses of patient disposition.
- Treated set (TS): This patient set includes all randomised patients who received at least one dose of trial medication. The TS is the main analysis set for the efficacy analyses, the safety analyses as well as for demographics and baseline characteristics and protocol deviations.
- Pharmacokinetic set (PKS): This patient set includes all patients from the TS who provided at least one post-dose plasma BI 1291583 concentration that was not excluded due to a protocol deviation relevant to the evaluation of PK, or due to PK non-evaluability.

For all analyses, patients will be analysed according to planned treatment group. In case of patients receiving the wrong medication unintentionally (i.e., different to their planned treatment), the impact to study outcomes will be assessed with details specified in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories (including violations of the key inclusion and exclusion criteria, incorrect medication taken and any other deviations of the protocol deemed important) will be specified in the Protocol Deviation Domain.

Protocol deviations will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed. All decisions concerning important protocol deviations will be made prior to database lock.

Further analysis sets will be defined in the TSAP, if needed.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events (ICEs) of interest in this trial are:

- Treatment discontinuation
- Initiation of macrolides during trial
- Start of cyclic doses of antibiotic treatment during the trial
- Initiation or Change of CFTR-MT during the trial

For the primary objective, intercurrent events will be handled by using the while-on-treatment strategy, as defined in ICH E9(R1) [R21-0743]. Measurements, taken prior to the intercurrent event, will be used to assess treatment effect.

For the secondary objective, intercurrent events will be handled by using the treatment policy strategy, as defined in ICH E9(R1). Use of the “treatment policy” approach disregards the intercurrent event and uses measurements regardless of the occurrence of an intercurrent event. Additional details regarding intercurrent event handling strategy will be described in the TSAP.

7.2.3 Primary objective analyses

The primary endpoint as described in Section 2.1.2, will be derived according to BI standards. The analysis will be based on the TS and will be descriptive in nature. The number and proportion of patients, with at least one TEAE per treatment group, will be derived. TEAE is defined as all adverse events occurring between the start of treatment and the end of the REP (see Section 1.2). Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

7.2.4 Secondary objective analyses

7.2.4.1 Neutrophil elastase activity in sputum

The biomarker endpoint as described in Section 2.1.3 will be analysed based on the TS. The analysis of this endpoint will be performed on log transformed data.

Baseline NE activity, in sputum, will be derived as the mean value of available valid samples of Screening and Week 0, prior to the first treatment intake. The change from baseline of NE activity, in sputum, at different visits (X) is calculated as:

$$Change\ from\ baseline\ in\ NE\ activity\ at\ Visit\ X = NE\ activity\ at\ Visit\ X - NE\ activity\ at\ Baseline$$

The change from baseline, in NE activity in sputum, at Week 8, will be analysed by descriptive statistics and graphical representations across all visits.

[redacted]

7.2.4.2 Pharmacokinetic endpoints

The PK parameters, described in Section 2.1.3, will be estimated using a population PK modelling approach. The PK endpoints (concentrations and parameters) will be reported descriptively, based on the PKS. For all patients, the following descriptive statistics will be calculated for plasma concentrations and PK parameters: number (N), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and the geometric coefficient of variation. The following statistics will additionally be provided for PK parameters: the 10^{th}, 25^{th}, 75^{th}, and 90^{th} percentiles.

[redacted]

7.2.6 Safety analyses

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

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 the start of treatment and the end of the REP, a period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

Statistical analysis and reporting of AEs will concentrate on TEAEs (see Section 7.2.3).

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 of the reference range, as well as values defined as clinically relevant, will be summarised.

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 with findings before start of treatment.

Clinically relevant abnormal findings of ECG will be reported and analysed as baseline conditions (at screening) or as AEs (during the trial).

7.2.7 Other Analyses

Other analyses are not planned.

7.2.8 Interim Analyses

Given the exploratory nature of this study, the sponsor may choose to conduct an interim PD/PK analysis [redacted]. The decision to conduct an optional interim analysis, and the timing of the analysis, will be documented in the sponsor's trial master file, in a logistics and access plan, prior to the conduct of the interim analysis. There is no plan to adjust sample size based on the interim analysis results. The interim analysis will be performed and interpreted, by an independent evaluation team of the sponsor, which is independent of the trial team. No interim report will be written.

To ensure patient's safety during the trial, a fully external DMC, independent of the trial and project teams, will review periodically all available safety data. A DMC SAP, which describes the analyses required for assessment by the DMC, will be produced. Further details will be provided in a DMC charter.

7.3 HANDLING OF MISSING DATA

In general, missing data will not be imputed.

Primary endpoint

Missing or incomplete AE dates will be handled according to BI standard.

[redacted]

Secondary PK endpoints

Handling of missing PK data will be performed according to the Sponsor's SOPs.
PK parameters, that cannot be reasonably calculated based on the available drug concentration-time data, will not be imputed.

7.4 RANDOMISATION

The randomisation will be stratified according to the use of SoC CFTR-MT (yes vs. no). Within each stratum, patients will be randomised, in a 2:1 ratio, to either receive BI 1291583 5 mg qd, or placebo.

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. Specific parameters, used for the creation of the randomisation schedule (e.g. block size or biasing coin probabilities), will be documented in the CTR. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

For this exploratory trial, it is planned to include a total of 24 treated patients. Sixteen (16) patients will receive BI 1291583, 5 mg qd, and 8 patients will receive placebo. The planned sample size is not based on a power calculation but is considered sufficient, for the exploratory evaluation of safety, tolerability of BI 1291583, as well as to investigate PD and PK properties.

Apart from the safety assessment, NE inhibition, in sputum, is one of the main interests of the study to support further drug development decisions for BI 1291583. A variety of different effect sizes for % NE reduction were investigated, and Table 7.5: 1 shows the simulated operating characteristics of the design for different scenarios and sample sizes for the active arm.

With 16 (24) patients in the active group, there is approximately 65% (70%) probability to observe a % reduction in NE activity, in sputum, of at least 80% when the true effect size is 90%. In contrast, if the true effect size is 40%, the probability to observe a % NE reduction of at least 80% would be 21%, for 16 patients in the active group, and 18% if there are 24 patients randomised, in the active group. If only 12 patients are evaluable for the assessment of % NE reduction at week 8 (e.g., due to dropouts) the increased uncertainty for a correct decision is considered acceptable.

Overall, a sample size of 16 patients, in the active group, is regarded as sufficient for the objectives of this trial.

Table 7.5: 1 Simulated probabilities for observing at least a given % reduction in NE activity, in sputum, at 8 weeks

Sample size	%Reduction	Probability to observe at least a 70% reduction (%)	Probability to observe at least an 80% reduction (%)	Probability to observe at least a 90% reduction (%)
12	95%	82.4%	75.5%	61.2%
	90%	70.0%	61.5%	45.4%
	80%	55.5%	45.7%	30.9%
	70%	45.7%	37.7%	22.6%
	50%	34.3%	25.9%	14.9%
	40%	30.1%	23.2%	12.4%
16	95%	86.9%	80.1%	64.2%
	90%	74.3%	64.7%	46.6%
	80%	57.7%	47.2%	29.5%
	70%	47.5%	36.7%	21.4%
	50%	34.4%	24.0%	12.8%
	40%	29.5%	21.1%	10.2%
24	95%	92.0%	86.0%	80.3%
	90%	80.3%	70.3%	48.4%
	80%	60.5%	47.9%	26.6%
	70%	47.8%	35.3%	17.3%
	50%	32.1%	21.2%	8.5%
	40%	26.8%	18.0%	6.9%

Assumptions: SD= 2.15 (on a log10 scale).
Simulations were performed using R Version 4.0.2, with 10000 simulation runs per scenario.

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 Harmonised Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU Regulation 536/2014 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 will be treated as "protocol deviation".

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

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial participants 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 CTR.

The certificate of insurance cover is made available to the investigator and the trial participants 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 participation in the trial, written informed consent must be obtained from each participant 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 form and any additional participant-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional participant information must be given to each participant or the participant's legally accepted representative.

The trial participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the trial participant's own free will with the informed consent form after confirming that the trial participant 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.

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 participant protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, 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 trial participants 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

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 participant. 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 participant 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 participant, documented in their medical records, would be acceptable.

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

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

- Participant identification: sex, year of birth (in accordance with local laws and regulations)
- Participant participation in the trial (substance, trial number, participant number, date participant was informed)
- Dates of participant's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of participant's participation in the trial" (end date; in case of premature discontinuation document the reason for it)
- Prior to allocation of a trial participant 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 participant or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the participant eligible for the clinical trial
- Data related to safety monitoring [redacted])

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 always be available 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 or delegate will also monitor compliance with the protocol and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war; please see Section 6), site access may be restricted, thus limiting the ability to perform standard site

monitoring activities on-site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

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.
SAE/AESI are processed in the global Safety Database and assessed for the company causal relationship as well as the expectedness of the event according to the reference safety information. Individual Case Safety Reports (ICSR) are subsequently reported according to local Regulations.
Reporting suspected unexpected serious adverse reactions (SUSARs) to the EMA will be done via E2B transmission of ICSRs to the Eudravigilance CT Module.

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of trial participant data in accordance with the principles 7 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited: personalised treatment data may be given to the trial participant's personal physician or to other appropriate medical personnel responsible for the trial participant'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.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

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 have 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 **first act of recruitment** represents the **start of the trial** and is defined as the date when the first trial participant in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last trial participant in the whole trial ("Last Participant Completed").

The "**Last Participant Last Treatment"** (LPLT) date is defined as the date on which the last trial participant 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 trial participants 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 trial participant (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 Data Monitoring Committee (DMC) is already in place [redacted] and will be extended for trial 1397-0013 (Clairafly™). Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation, in addition [redacted] and a statistician.

The DMC is responsible for routine evaluation of all safety data and efficacy data periodically as well as being alerted to blinded safety concerns noted by the sponsor 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 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

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operative Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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

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, and IRT service will be used in this trial. Details will be provided in the IRT Manual and Laboratory Manual, available in the ISF.

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9.2 UNPUBLISHED REFERENCES

c18711868 Investigator's Brochure BI 1291583. Current Version.

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10. APPENDICES

10.1 CREATININE CLEARANCE

Calculation Name	**GFR CKD-EPI**	
Formula	**Units**	**Decimal Places**
<u>Conventional</u>: **Black or African American formulas:** Female with a serum creatinine value of ≤0.7 mg/dL 166 x (Serum Creatinine (mg/dL) / 0.7) $^{-0.329}$ x (0.993)^{age} Female with a serum creatinine value of >0.7 mg/dL 166 x (Serum Creatinine (mg/dL) / 0.7) $^{-1.209}$ x (0.993)^{age} Male with a serum creatinine value of ≤0.9 mg/dL 163 x (Serum Creatinine (mg/dL) / 0.9) $^{-0.411}$ x (0.993)^{age} Male with a serum creatinine value of >0.9 mg/dL 163 x (Serum Creatinine (mg/dL) / 0.9) $^{-1.209}$ x (0.993)^{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 x (Serum Creatinine (mg/dL) / 0.7) $^{-0.329}$ x (0.993)^{age} Female with a serum creatinine value of >0.7 mg/dL 144 x (Serum Creatinine (mg/dL) / 0.7) $^{-1.209}$ x (0.993)^{age} Male with a serum creatinine value of ≤0.9 mg/dL 141 x (Serum Creatinine (mg/dL) / 0.9) $^{-0.411}$ x (0.993)^{age} Male with a serum creatinine value of >0.9 mg/dL 141 x (Serum Creatinine (mg/dL) / 0.9) $^{-1.209}$ x (0.993)^{age} Creatinine in mg/dL is rounded to 2 decimal places prior to applying the formula.	mL/min/ 1.73m²	0
<u>SI</u>: Serum creatinine in µmol/L will be rounded to zero decimal 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.	mL/min/ 1.73m²	0
Limitations/Special Notes:	Age is truncated to a whole number prior to performing the calculation.	

10.2 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

PK trough samples will be taken at all visits and additional blood samples for PK profiles will be taken at Visits 2 and EOT (see Table 10.2: 1 below). The PK analysis for this group will use a population PK approach. Therefore, samples do not have to be taken precisely at the planned time. Instead, they must be taken at any time during the sampling window that corresponds to the planned time in this table.

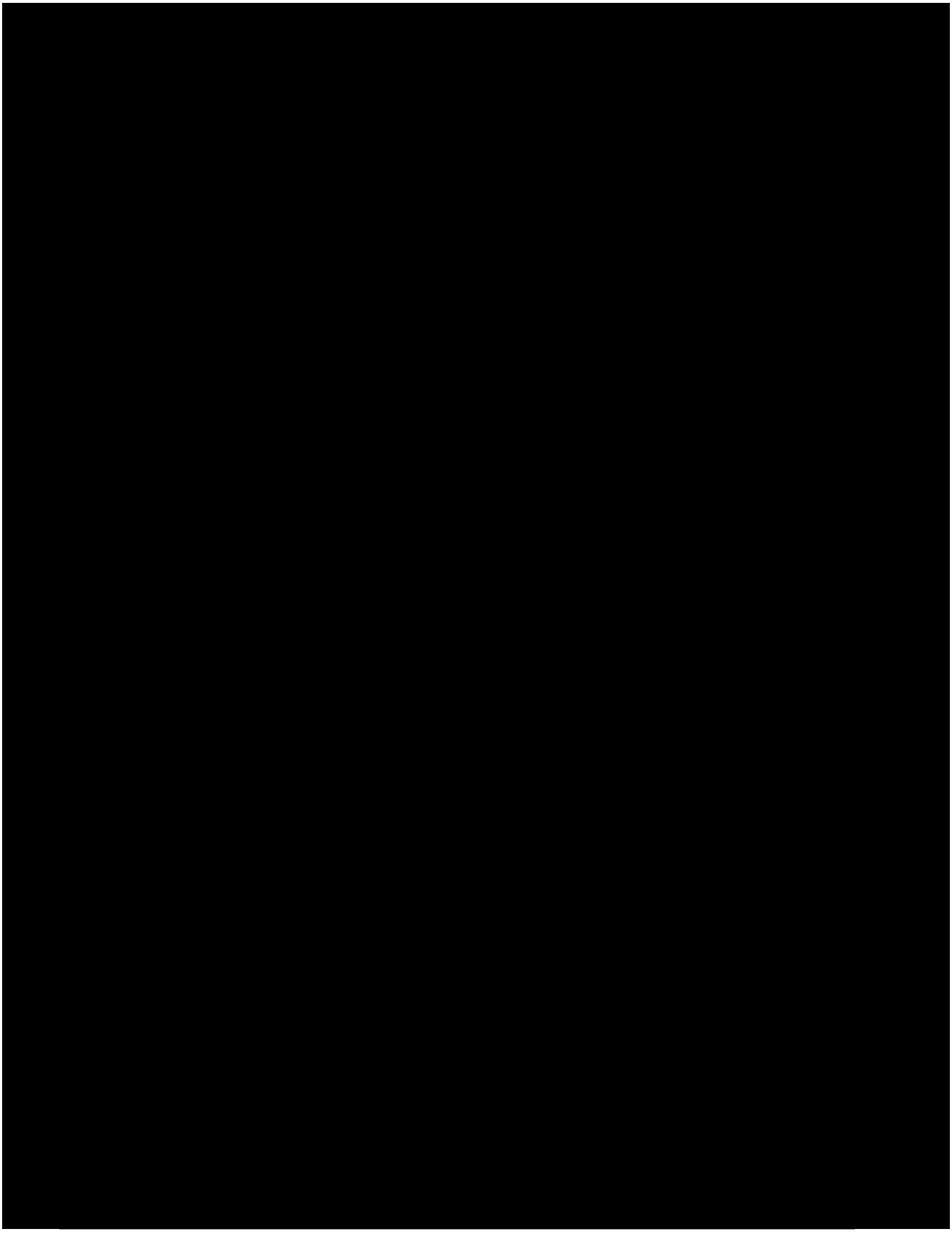
Table 10.2: 1 Time schedule for PK blood sampling

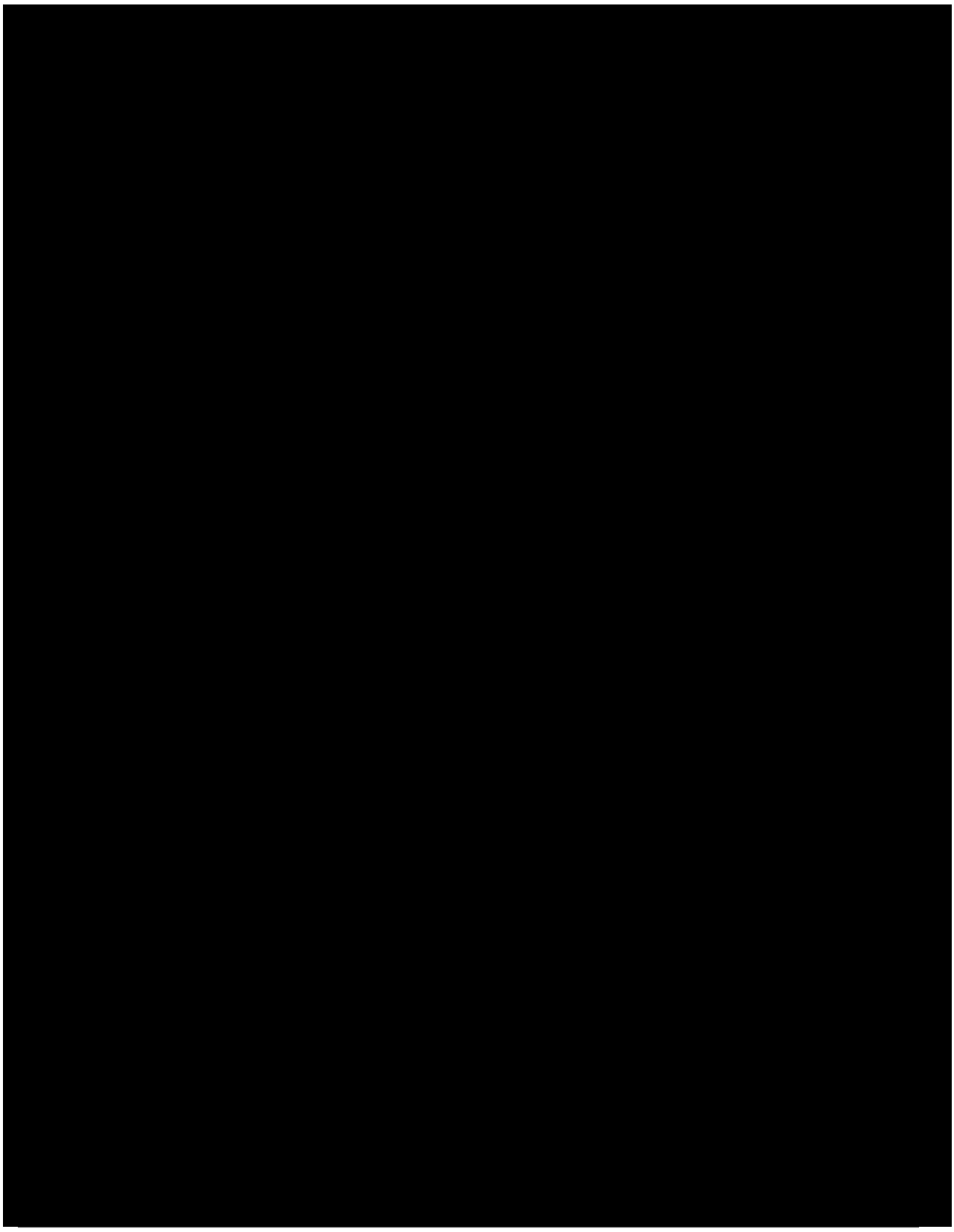
Visit	Week	Day	Time Point [hh:min]	Event	Trough (T)	e.g., clock time
2	0	1	Before drug administration	PK Blood	T	07:55
			0:00	Drug admin.		8:00
			1:00 (±45 min)	PK Blood		9:00
			3:30 (±1 h)	PK Blood		11:30
			6:00 (±1 h)	PK Blood		14:00
			8:00 (±1 h)	PK Blood		16:00
3	1	8	Before drug administration (-1 h)	PK Blood	T	
4	4	29	Before drug administration (-1 h)	PK Blood	T	
5	8	57	Before drug administration (-1 h)	PK Blood	T	
6 / EOT	12	85	Before drug administration (-1 h)	PK Blood	T	07:55
			0:00	Drug admin.		8:00
			1:00 (±45 min)	PK Blood		9:00
			3:30 (±1 h)	PK Blood		11:30
			6:00 (±1 h)	PK Blood		14:00
			8:00 (±1 h) (optional)	PK Blood		16:00

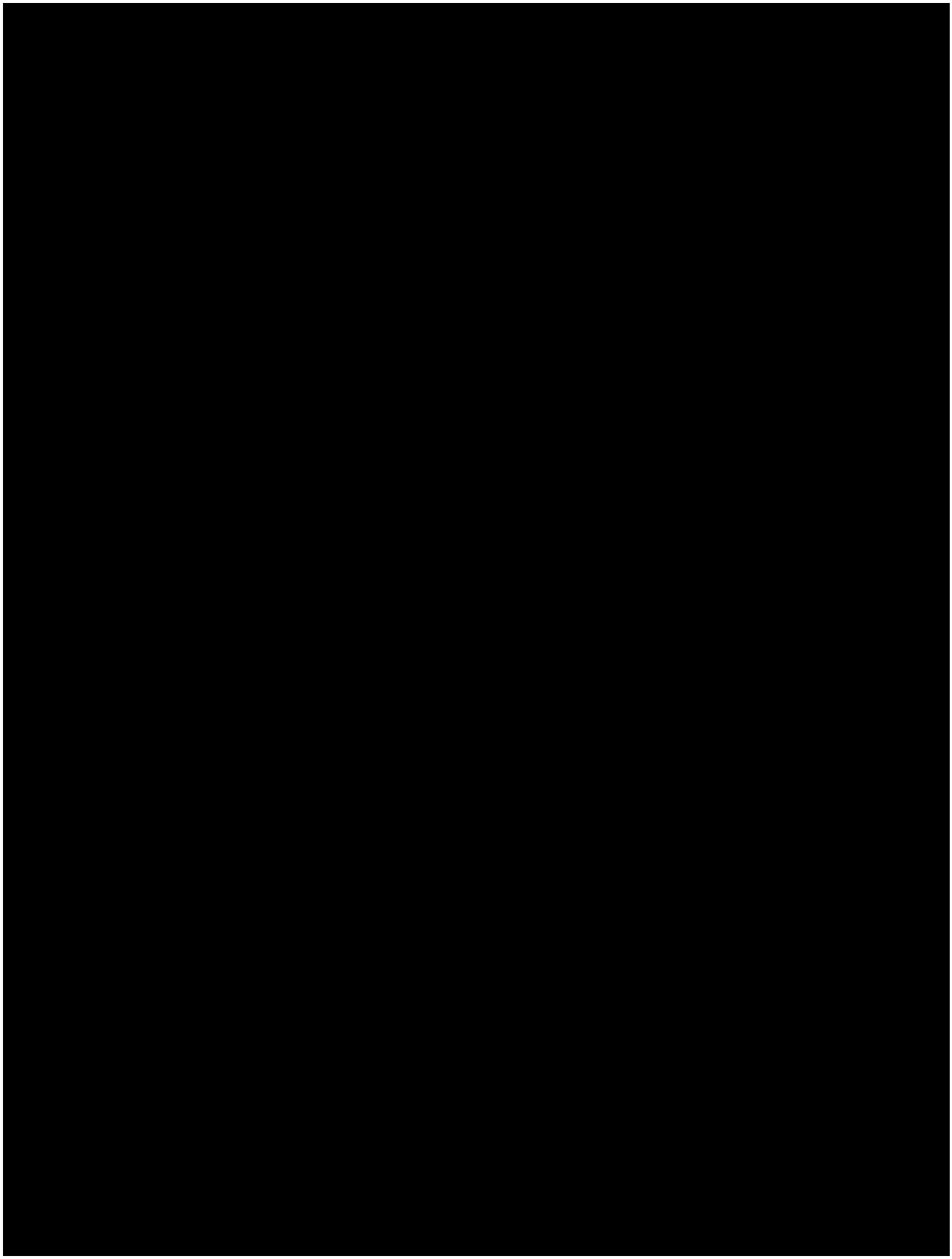
10.3 EQUIVALENT DOSES OF CORTICOSTEROIDS

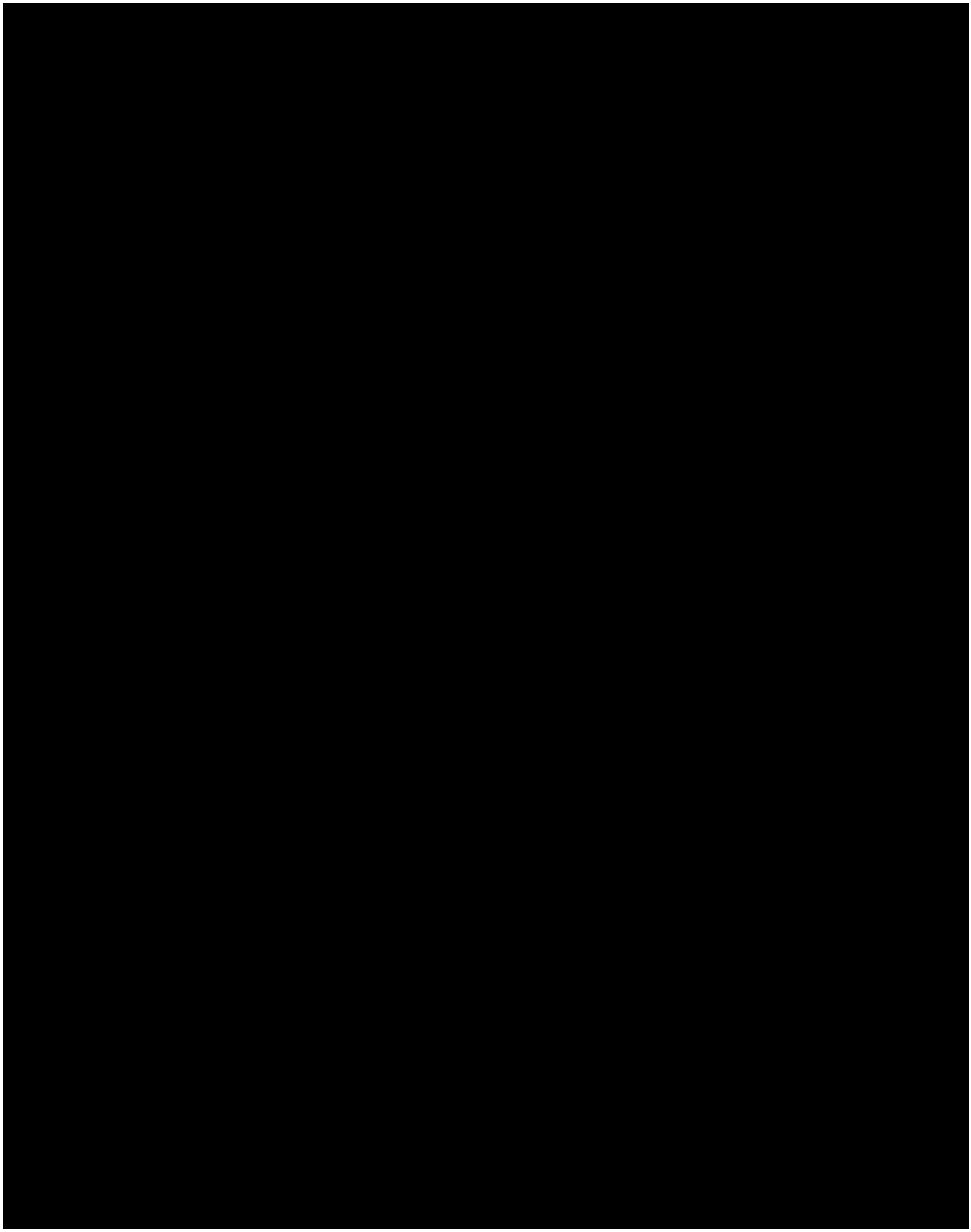
Table 10.3: 1 Equivalent Doses of Corticosteroids

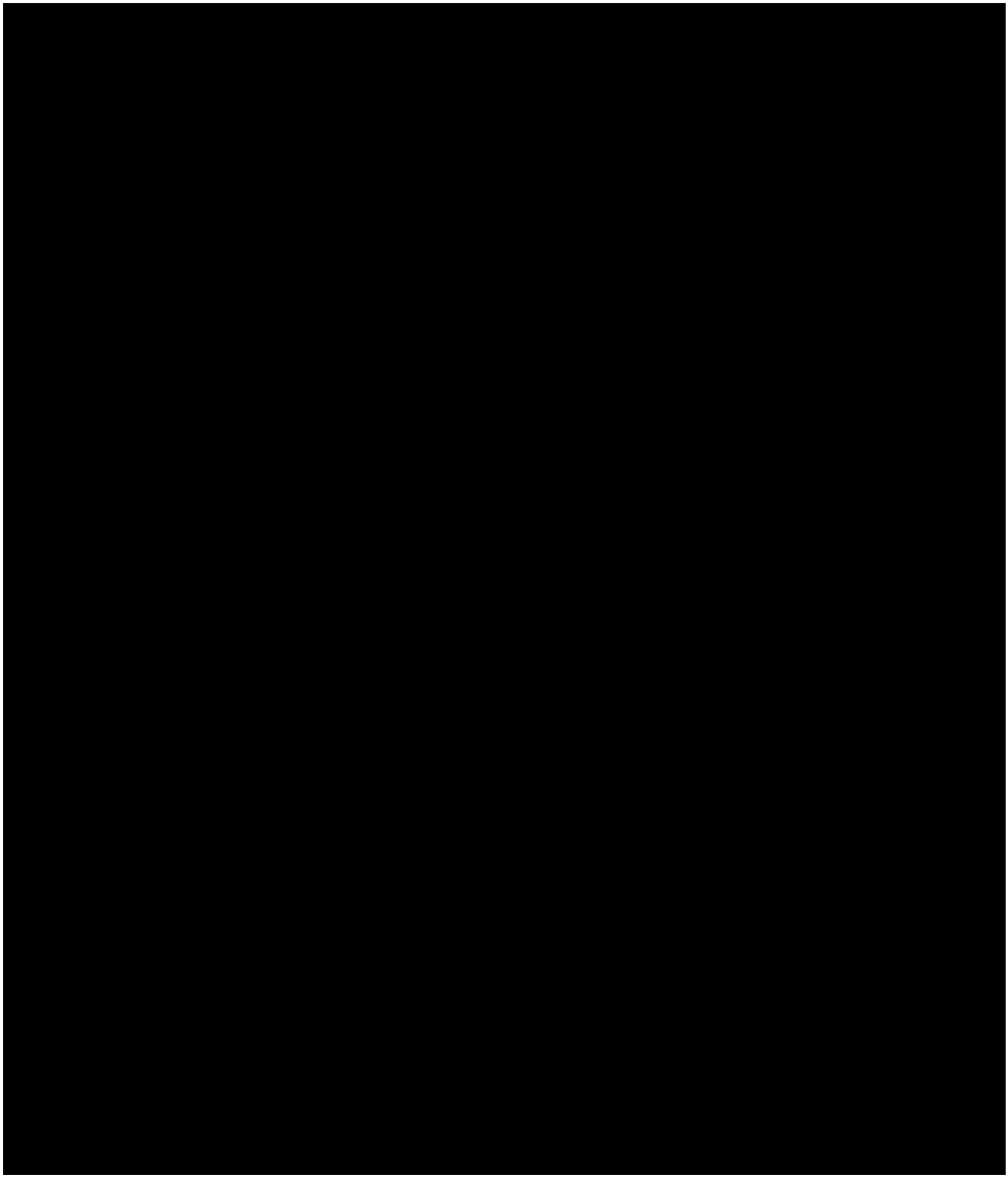
Drug	Equivalent dose (mg)	Conversion factor
Prednisone	10	x 1
Prednisolone	10	x 1
Triamcinolone	8	x 1.25
6-Methylprednisolone	8	x 1.25
Dexamethasone	2	x 5
Betamethasone	1.5	x 6.7
16-Methylprednisolone	12	x 0.8
Fluocortalon	10	x 1
Cloprednol	7.5-10	x 1.5-1.0
Deflazacort	12	x 0.8
Cortisol (hydrocortisone)	40	x 0.25
Cortisone	50	x 0.20

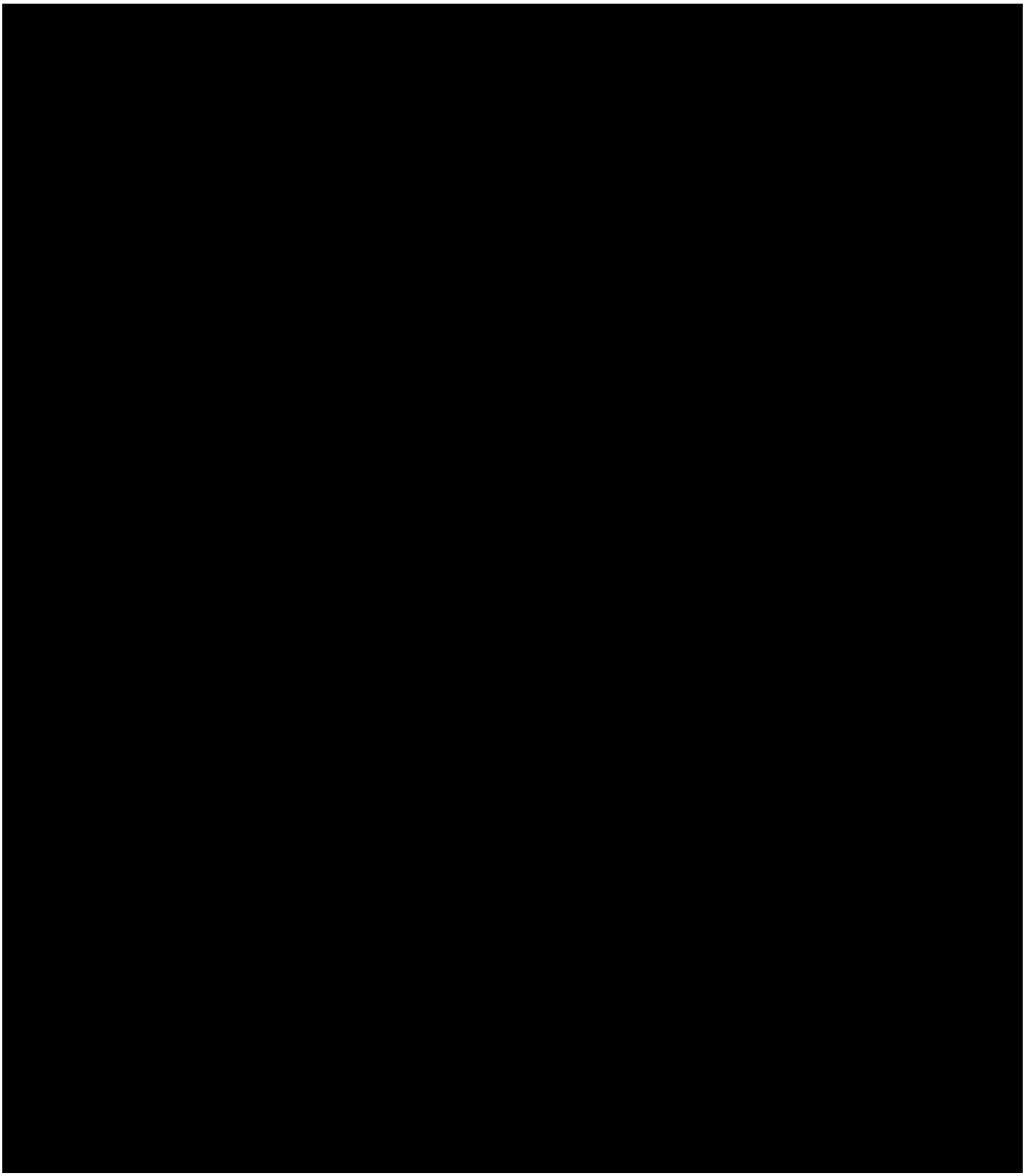


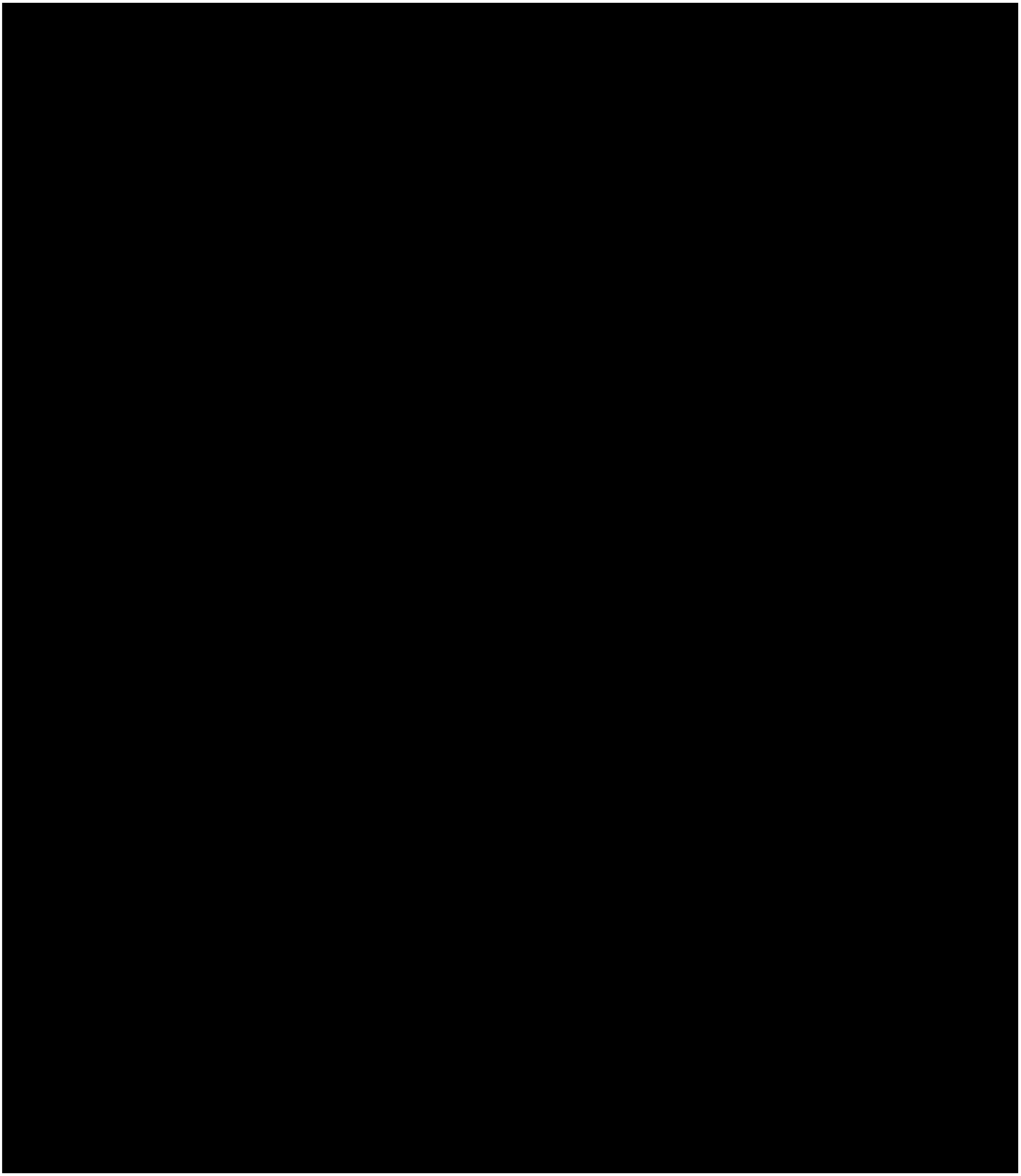


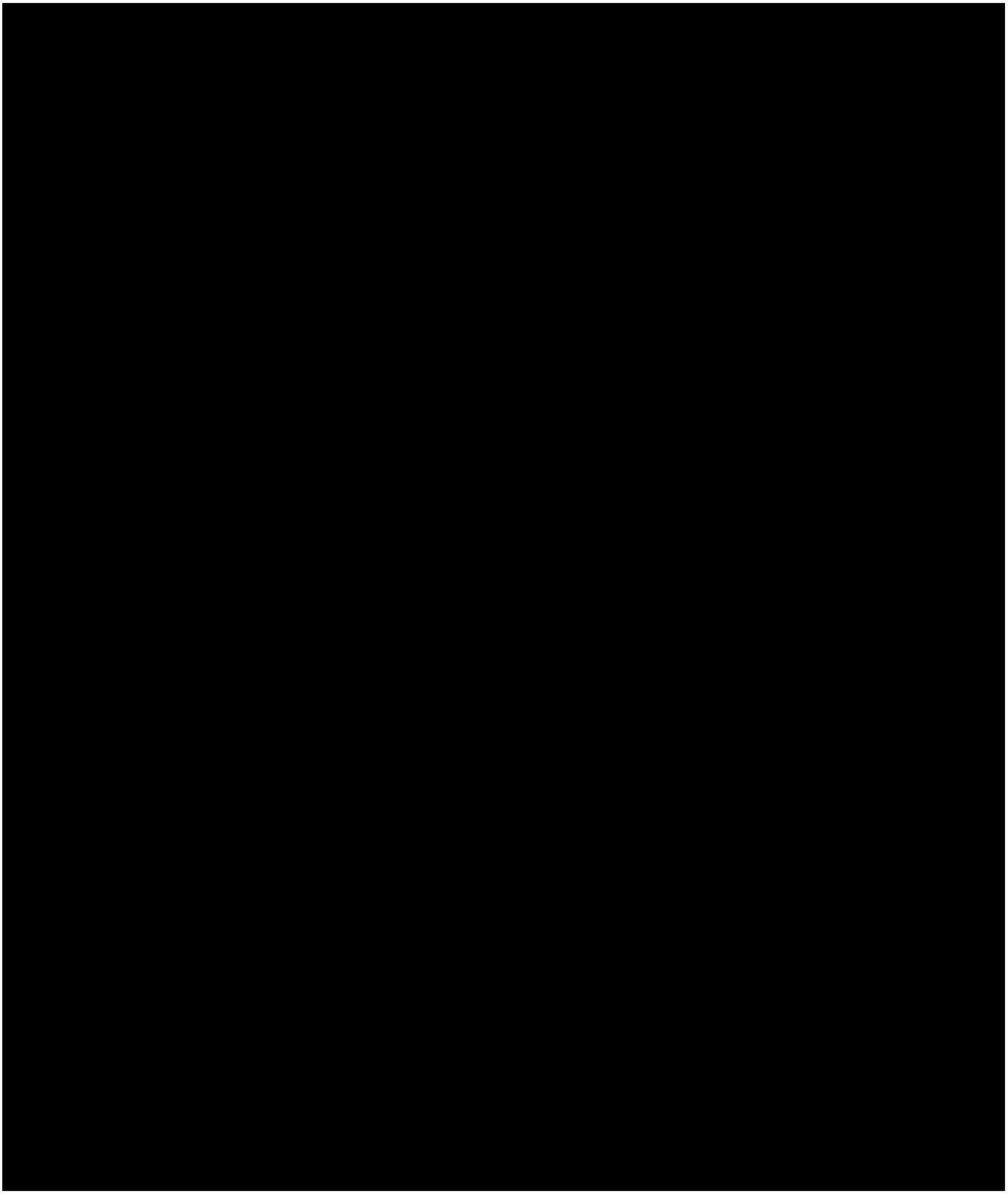


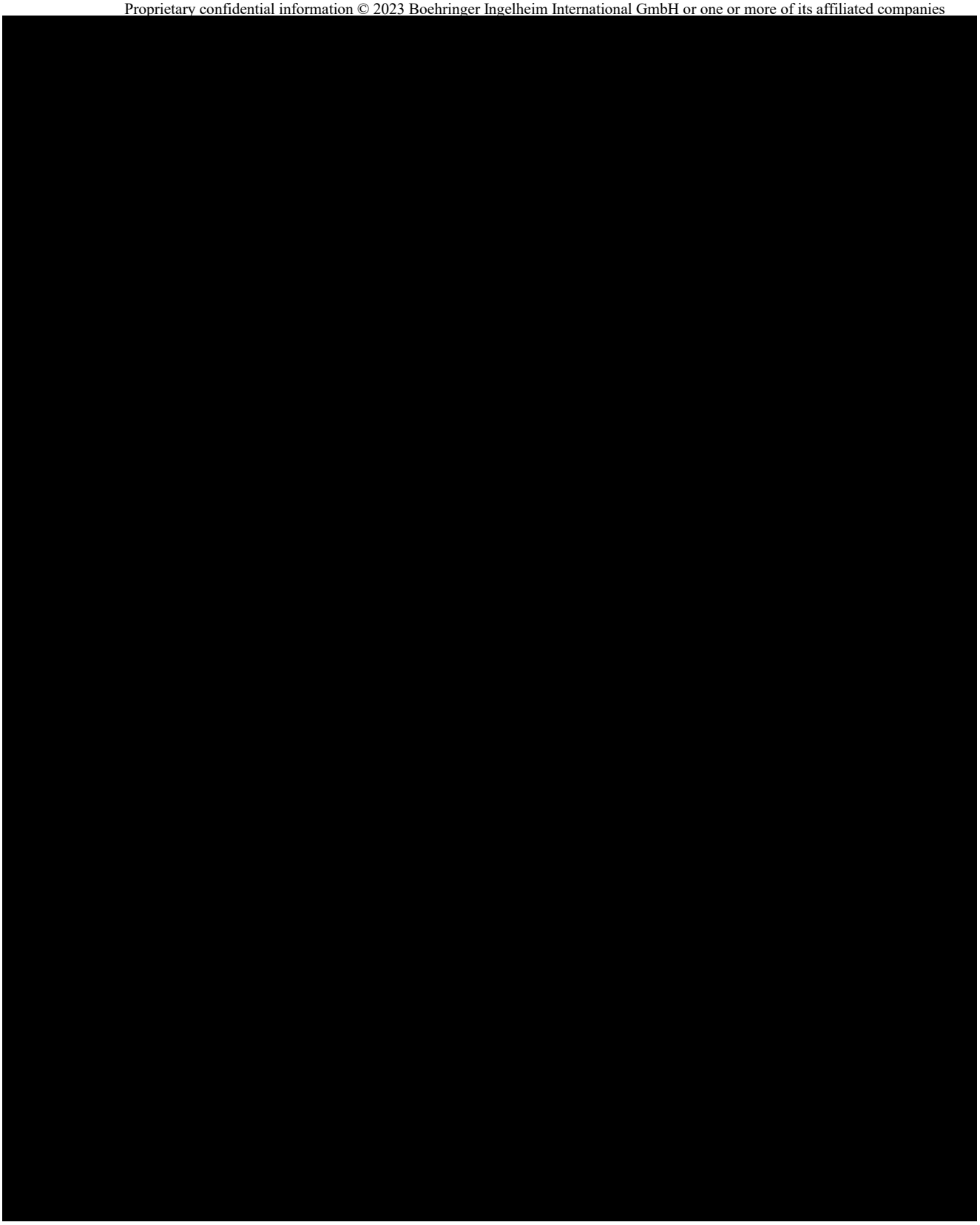


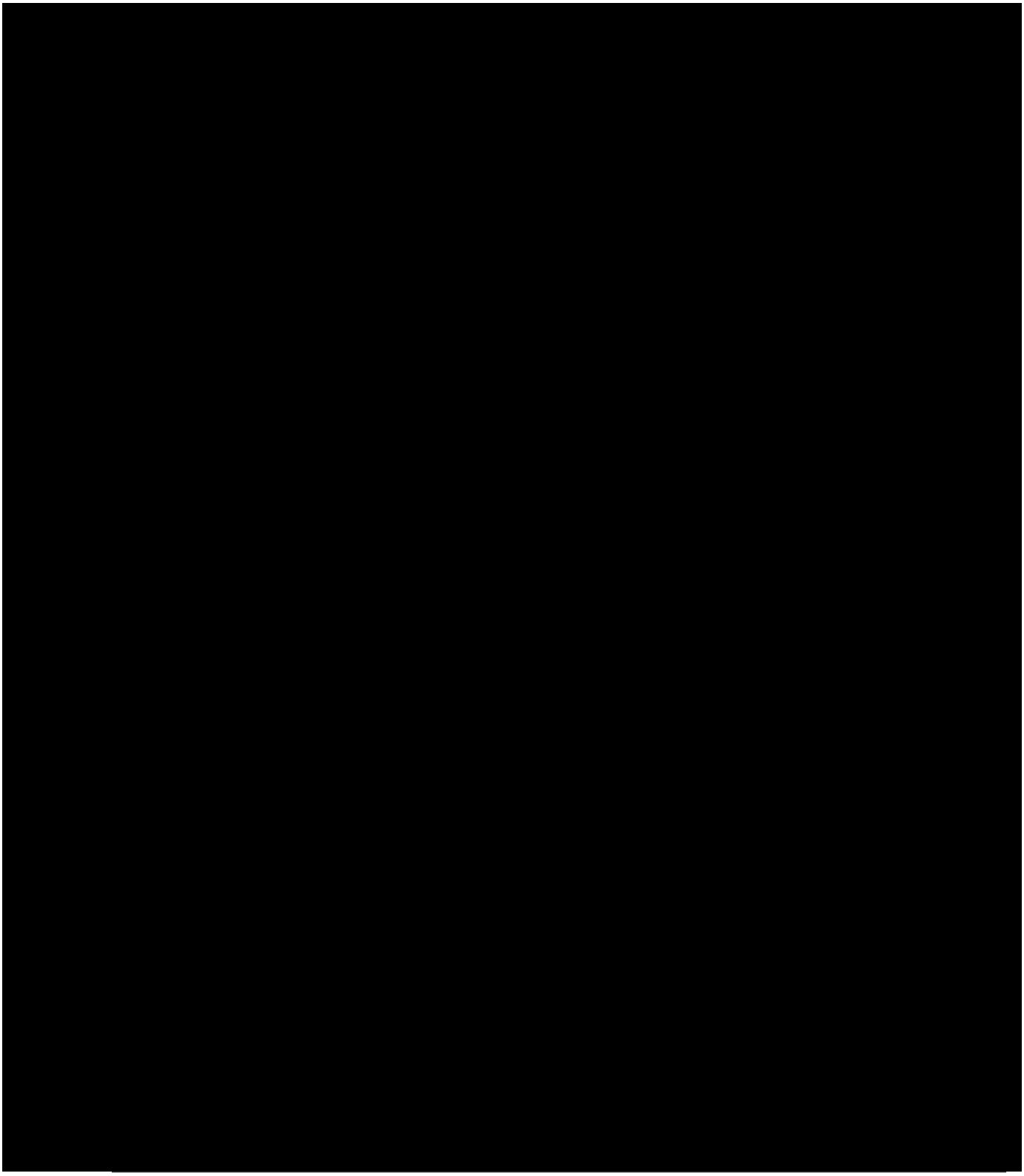


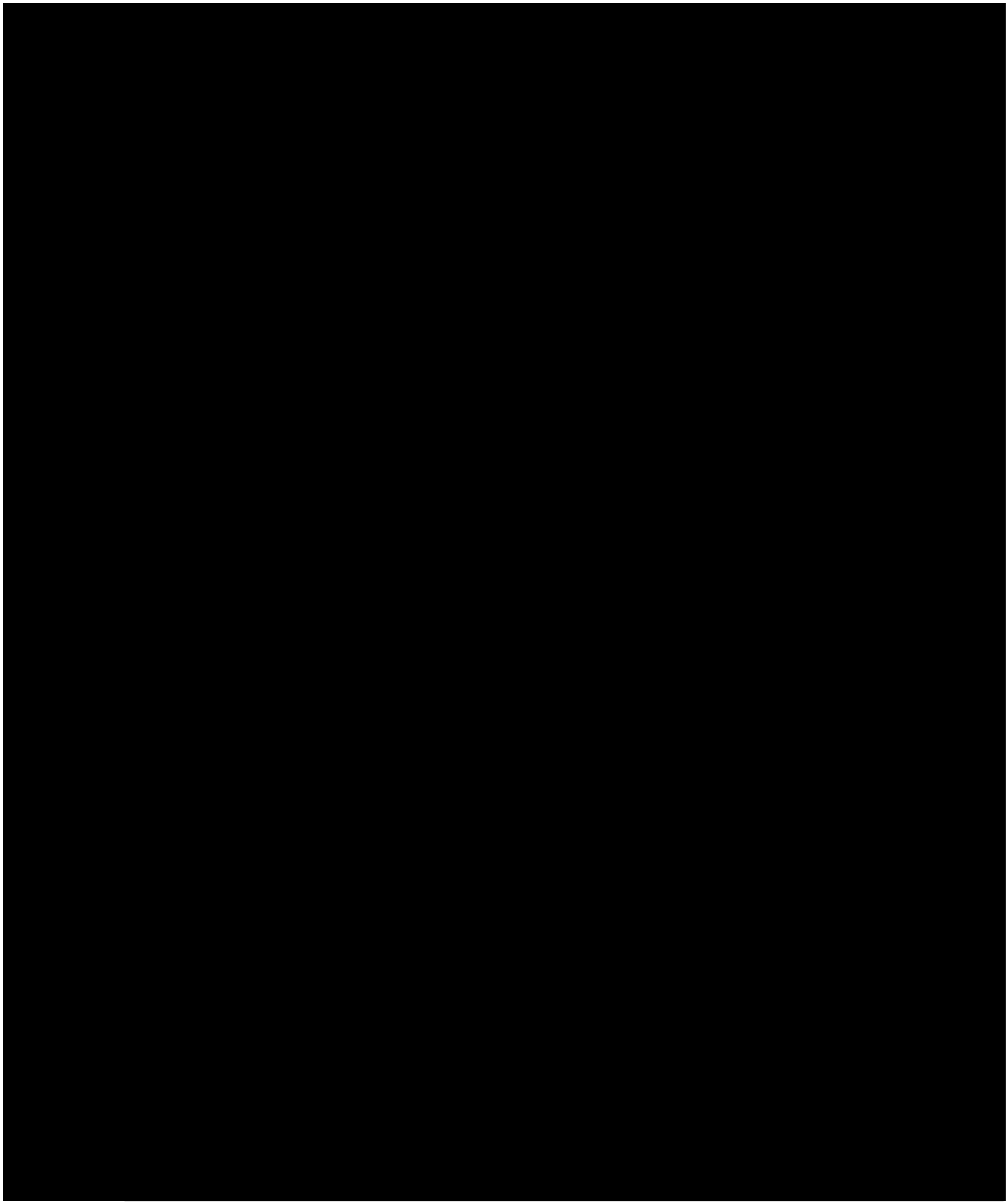


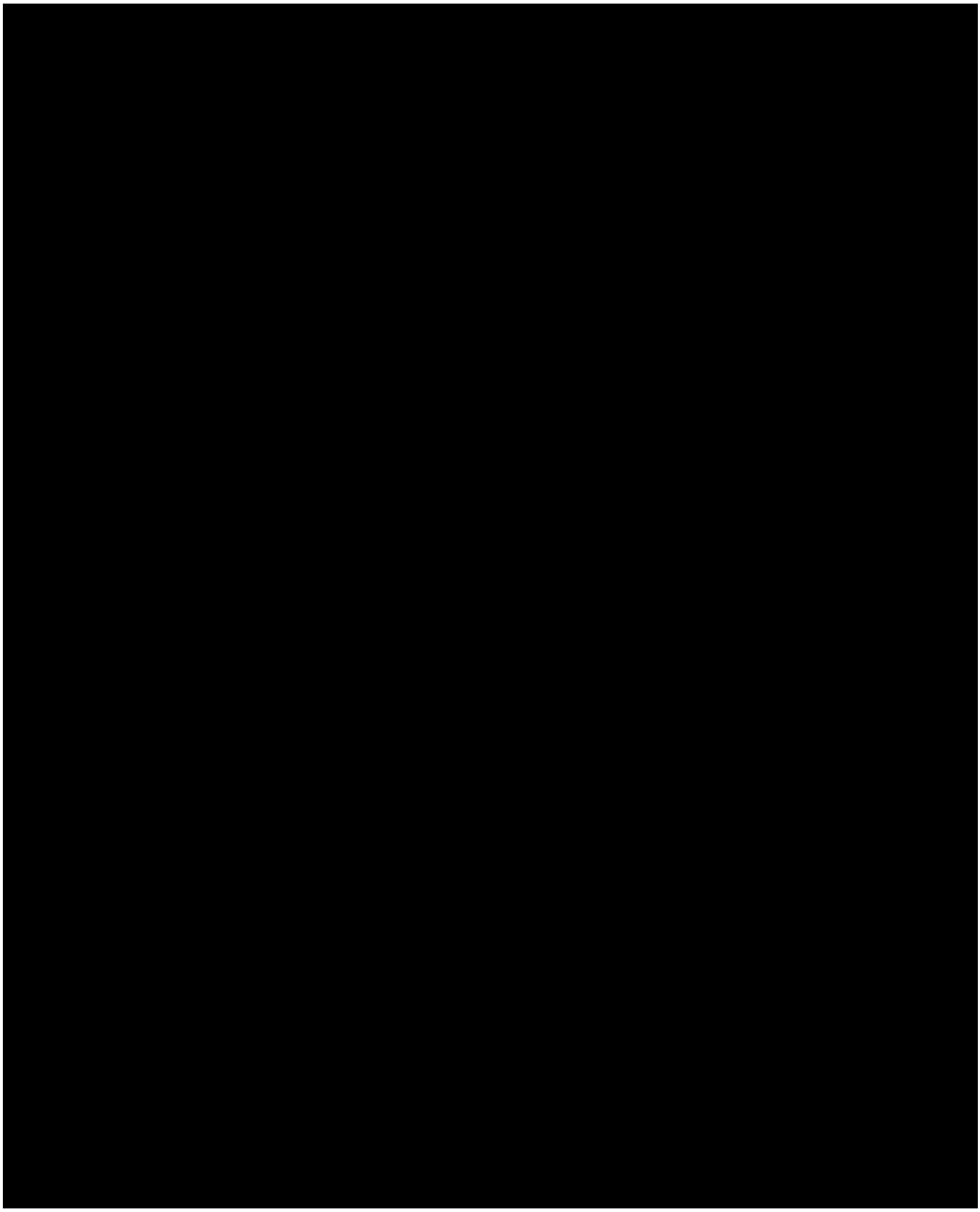


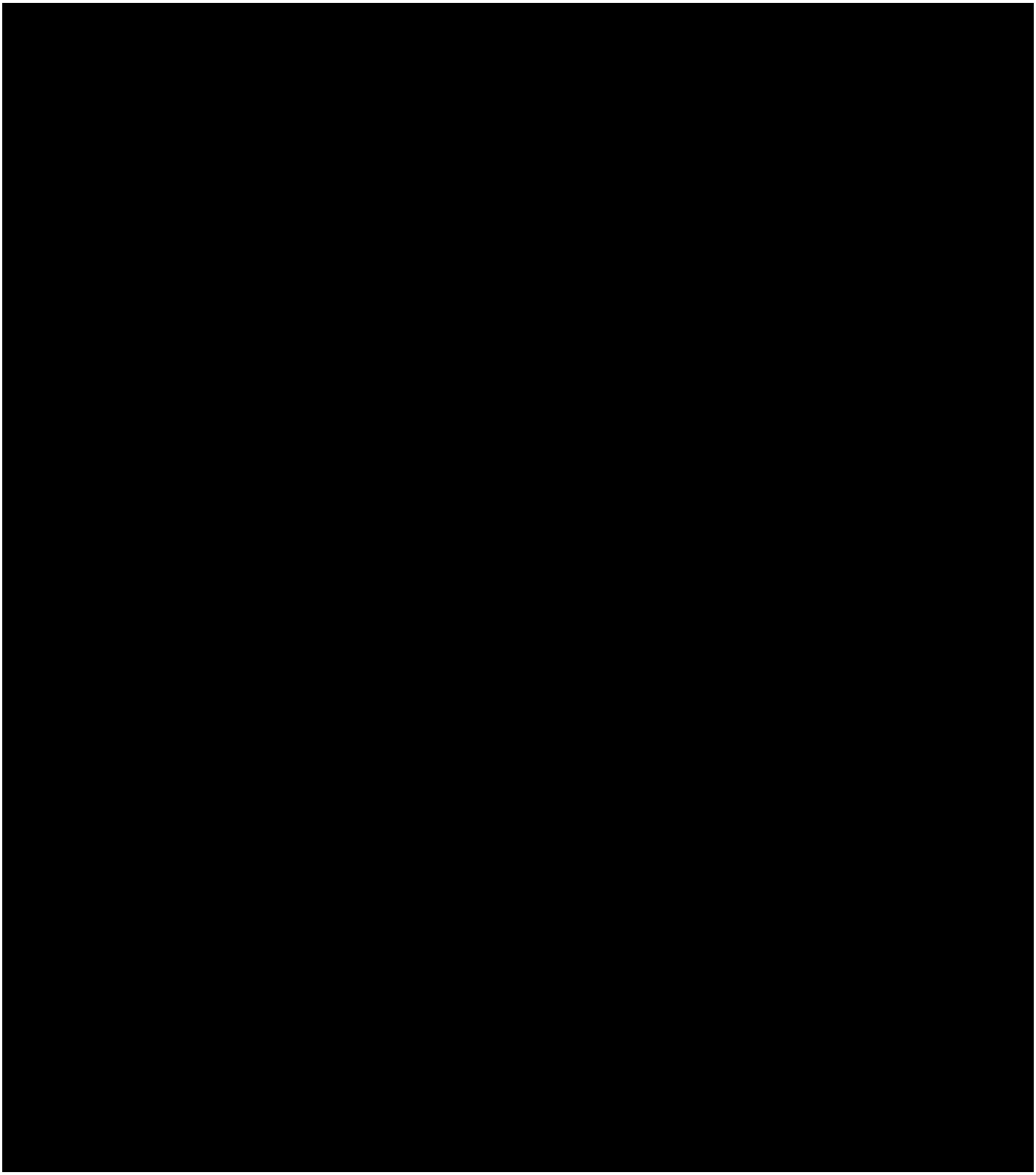


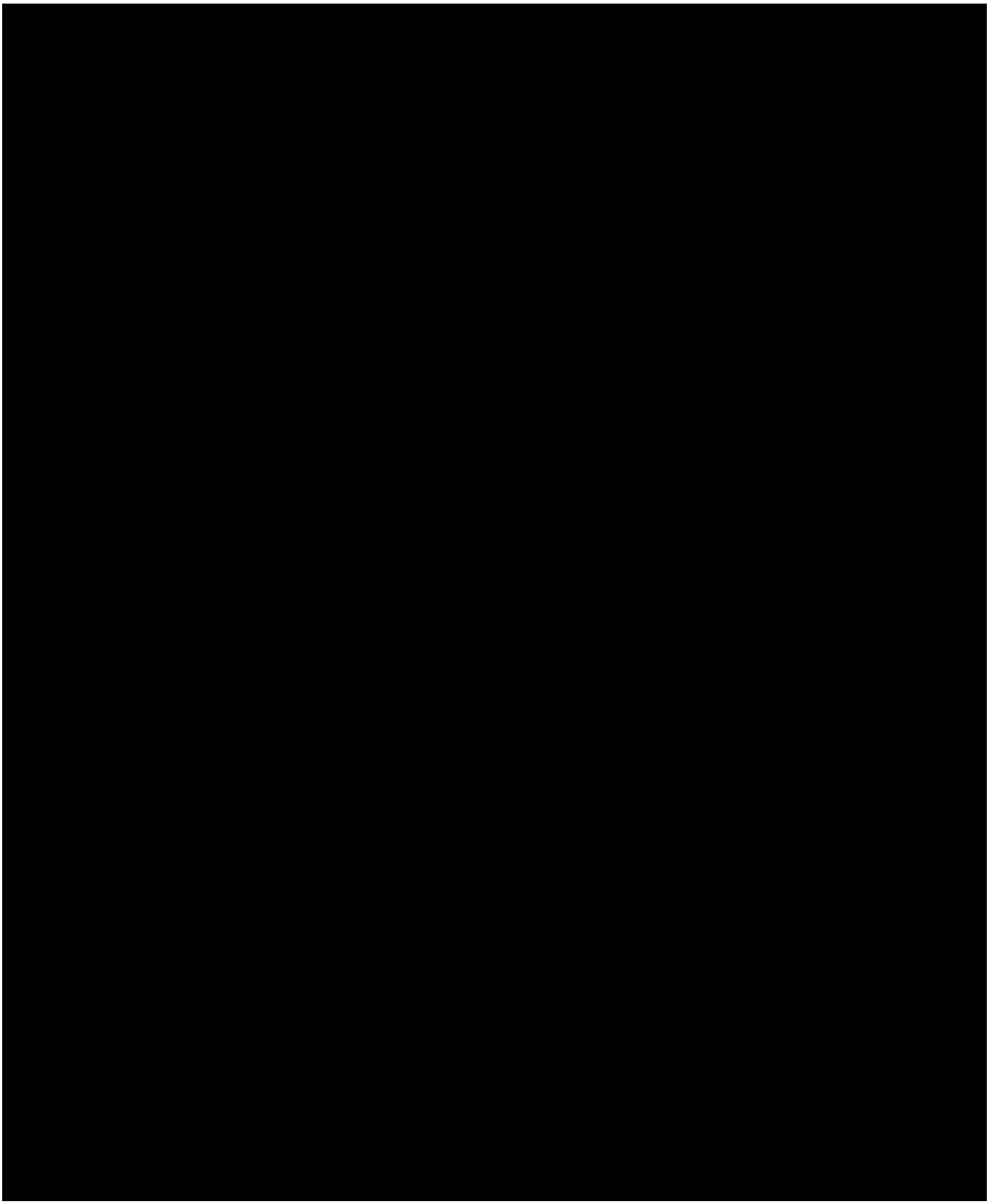


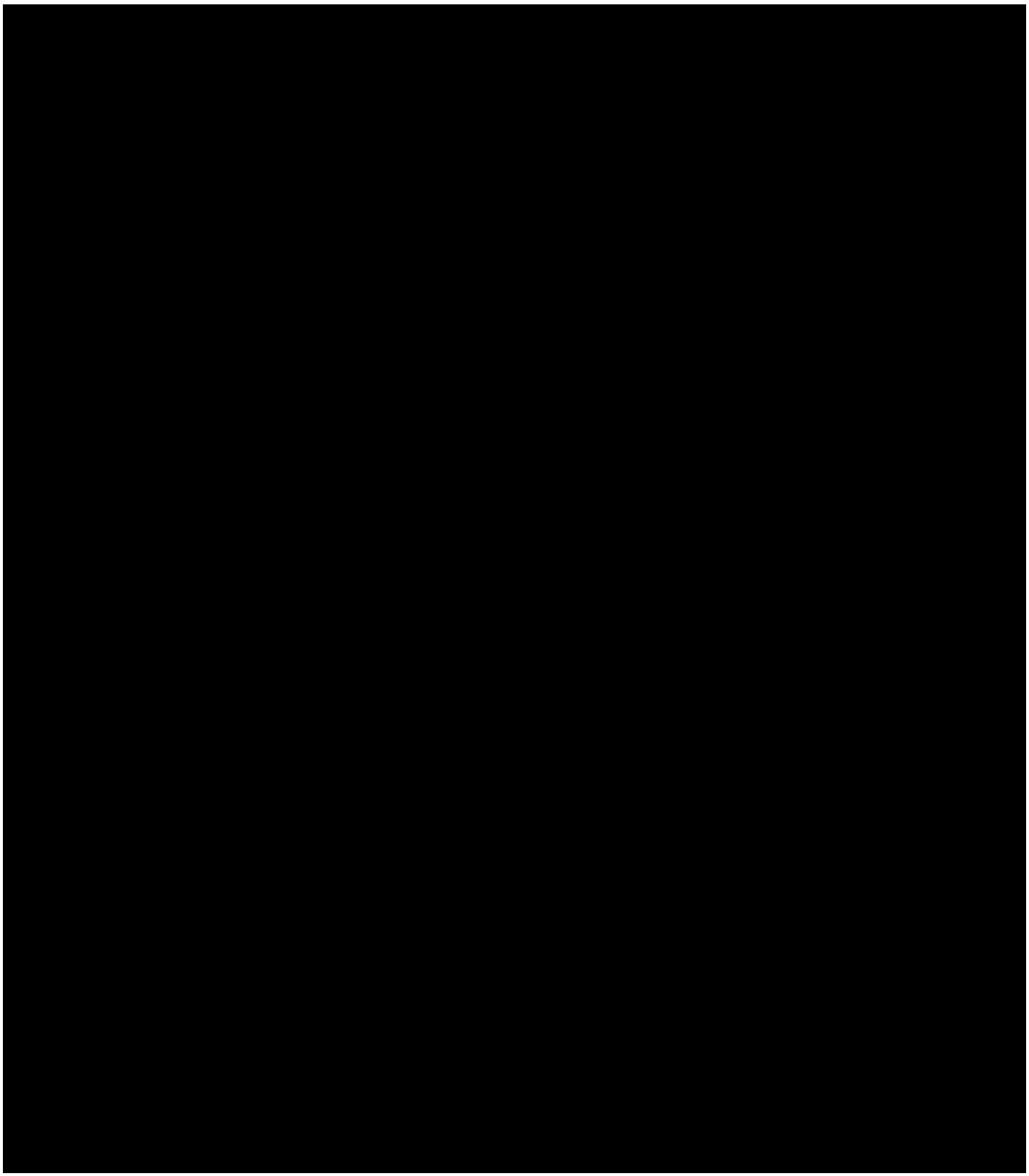


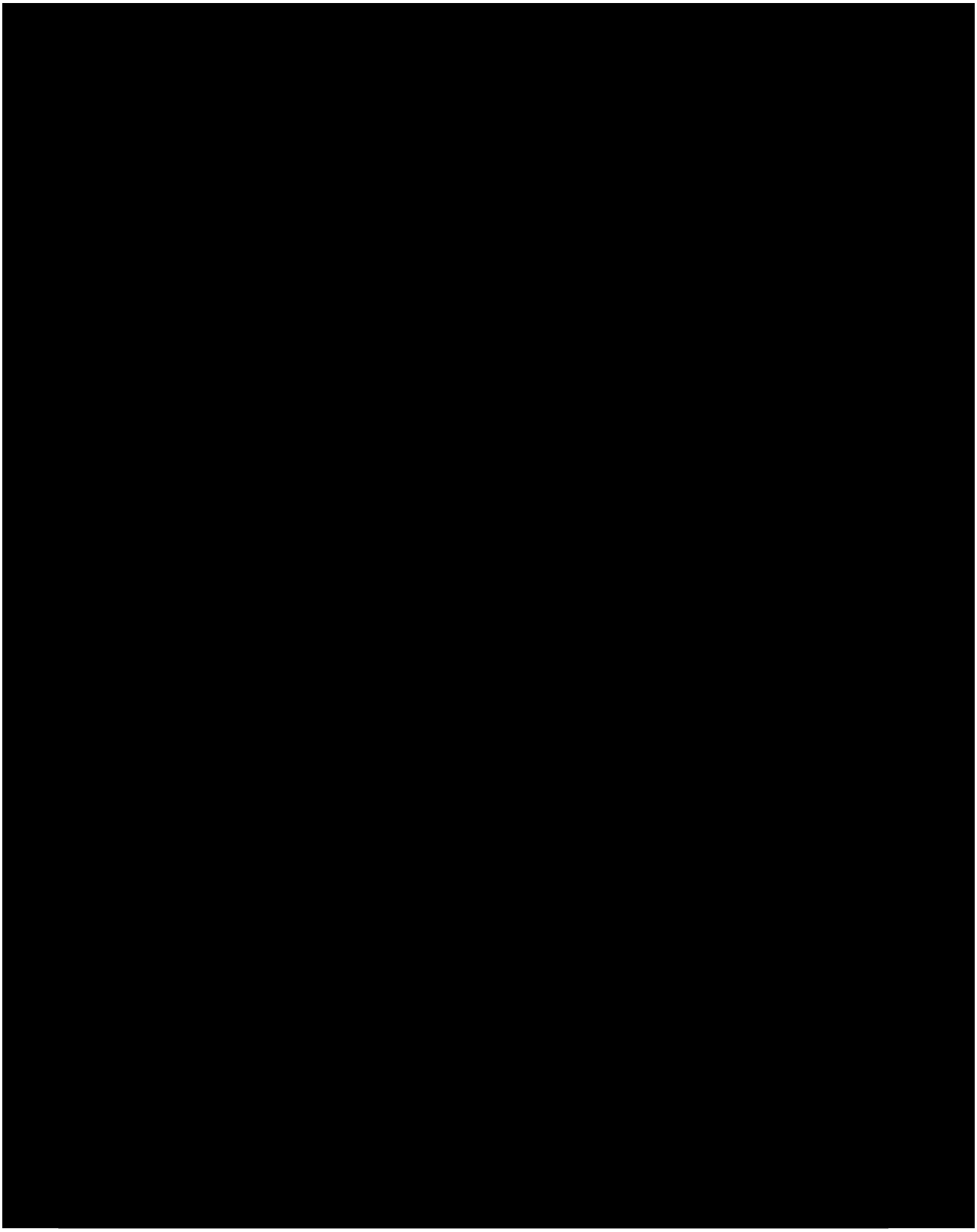


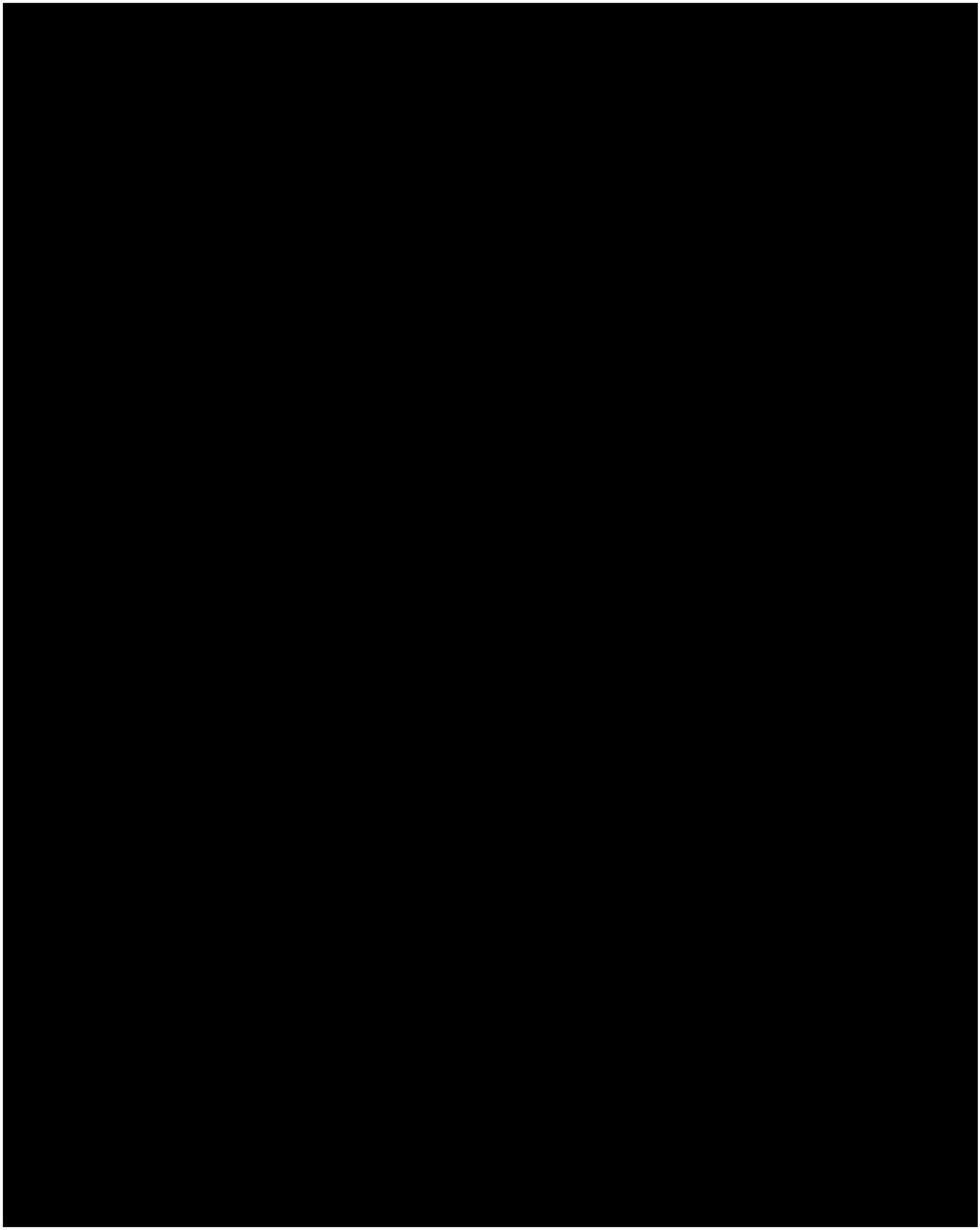


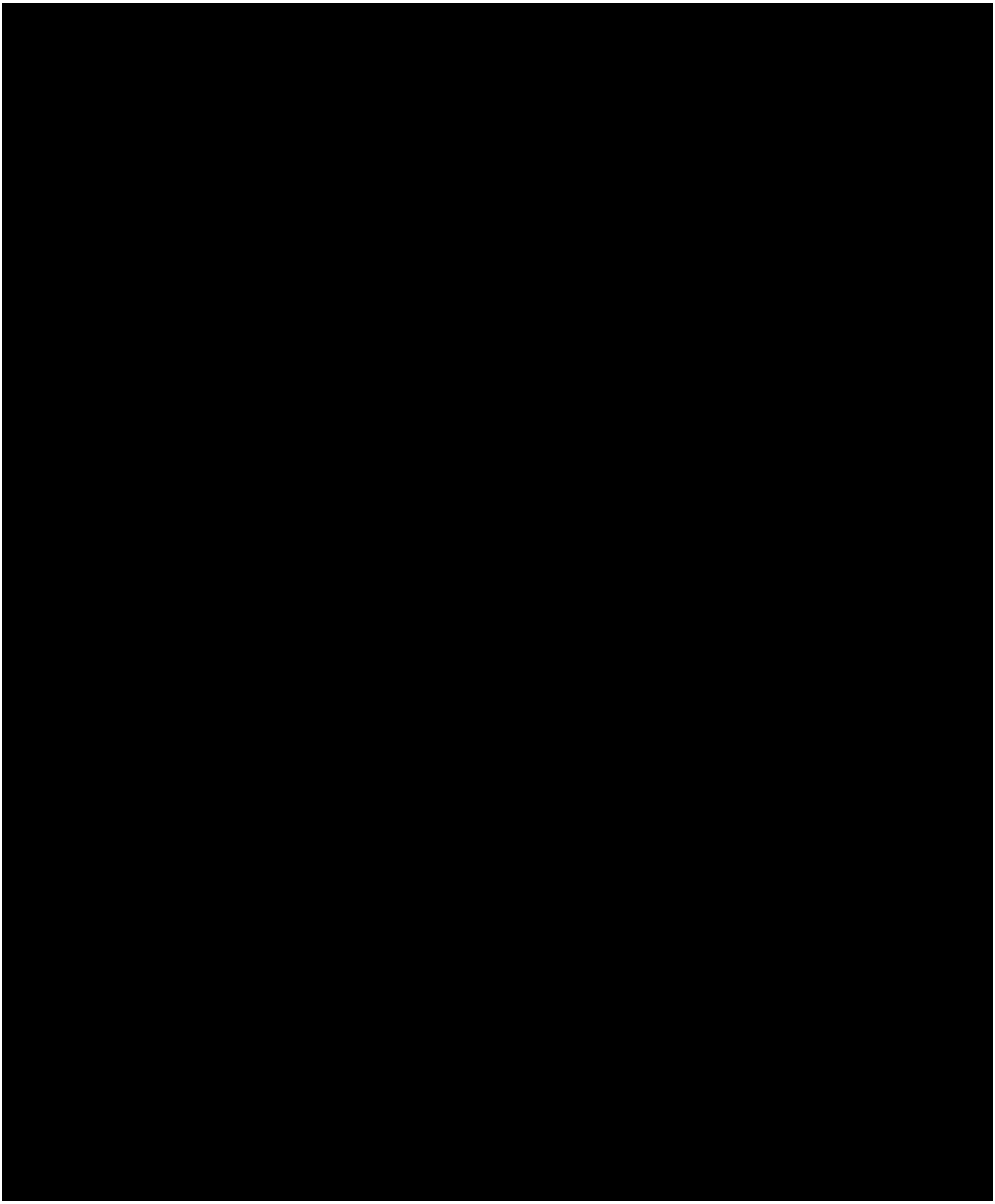












11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 Jun 2023
EU CT number		2022-502835-21-00
BI Trial number		1397-0013 (Clairafly™)
BI Investigational Medicinal Product(s)		BI 1291583
Title of protocol		A randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 one tablet once daily over 12 weeks versus placebo in adult patients with cystic fibrosis bronchiectasis (Clairafly™)
Global Amendment due to urgent safety reasons		
Global Amendment ***Note: global amendment was needed prior to first clinical trial application submission.***		X
Category	**Section No.**	**Description**
Section to be changed		Title page
Description of change		Typo (Berlin) corrected
Rationale for change		Typographical error
Section to be changed		Abbreviations and Definitions
Description of change		Missing abbreviation (MoA) added
Rationale for change		Consistency
Section to be changed	1.2	Drug profile: a) Key pharmacokinetic and pharmacodynamic characteristics from clinical studies b) Drug-drug interactions c) Data from non-clinical studies
Description of change		a) & b) Added information about new pre-clinical toxicological data [redacted] which was also identified as a major metabolite of BI 1291583. c) Added new information about [redacted] metabolite and deleted the following

		paragraph: [redacted] *covered within the general toxicity studies, including the embryofetal development toxicity studies. It is not expected to be pharmacologically active based on structure activity relationship considerations. In silico assessments for the prediction of mutagenicity were negative. The genotoxicity assessment has not yet been completed."*
Rationale for change		a), b), and c) New pre-clinical toxicological data available
Section to be changed	1.4.2	Risks, Table 1.4.2: 1: Overview of trial related risks based on the mode of action (MoA), the nature of the target, findings in non-clinical safety studies and mitigation strategies
Description of change		Reproductive system: Summary of data and rationale for the risk: Updated wording that genotoxicity for BI 1291583 and its major metabolites was not demonstrated. Deletion of sentence "T*he genotoxicity assessment is still underway for the newly identified metabolite* [redacted] Mitigation strategy: Updated that WOCBP must be willing and able to use a highly effective method of birth control. Deletion of the requirement to use one barrier method in addition. Deletion of sentence *"Men able to father a child must be willing and able to use male contraception."*
Rationale for change		Because of the negative outcome of the completed BI teratogenicity and genotoxicity studies, a double barrier method of contraception is not required. Contraception of male trial participants and female partners of male trial participants are not required.
Section to be changed	3.3.2	Inclusion criteria WOCBP (#7)
Description of change		Updated wording. Deletion of requirement to use one barrier method in addition for WOCBP.

		Deletion of sentence "*Men participating in this clinical trial must use male contraception (condom or sexual abstinence), if their sexual partner is a WOCBP."*
Rationale for change		Because of the negative outcome of the completed BI teratogenicity and genotoxicity studies, a double barrier method of contraception is not required. Contraception of male trial participants and female partners of male trial participants are not required.
Section to be changed	4.2.2.3	Contraception requirements
Description of change		Updated wording for WOCBP: Use of a highly effective method throughout the trial and for a period of at least 75 days after the last trial drug intake. Deletion of the requirements to use one barrier method in addition and to use contraception for at least 9 months. Deletion of the paragraph *"Men participating in this clinical trial, if their sexual partner is a WOCBP, must use condom from the first administration of trial medication until 6 months after the last administration of trial medication. They should also agree to refrain from donating sperm for the same time period."*
Rationale for change		Because of the negative outcome of the completed BI teratogenicity and genotoxicity studies, a double barrier method of contraception is not required. Contraception of male trial participants and female partners of male trial participants are not required.
Section to be changed	5.2.6.2.3	Pregnancy
Description of change		Deletion of the following paragraph: *"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."
Rationale for change		Contraception of male trial participants and female partners of male trial participants are not required. Systematic collection of pregnancy data in female partners of clinical trial participants is not required.
Section to be changed	6.2.2	Treatment period
Description of change		Updated wording regarding reminder to continue to use contraception for WOCBP, reminder deleted for male subjects.
Rationale for change		Contraception of male trial participants and female partners of male trial participants are not required.

11.2 GLOBAL AMENDMENT 2

Date of amendment		17 Oct 2023
EU CT number		2022-502835-21-00
BI Trial number		1397-0013 (Clairafly™)
BI Investigational Medicinal Product(s)		BI 1291583
Title of protocol		A randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 one tablet once daily over 12 weeks versus placebo in adult patients with cystic fibrosis bronchiectasis (Clairafly™)
Global Amendment due to urgent safety reasons		
Global Amendment.		X
Category	**Section No.**	**Description**
Section to be changed	1.4.4	Benefit/Risk assessment / Discussion
Description of change		Details added for the rationale of a comprehensive safety analyses in conjunction [redacted], as there are no specific safety concerns due to the MoA and properties of BI 1291583 for patients with CF.

Rationale for change		Request from regulators
Section to be changed	3.1	Overal trial design
Description of change		Justification added why patients who discontinue early won't be replaced
Rationale for change		Request from regulators
Section to be changed	3.3.2	Inclusion Criteria
Description of change		#7: added "male or" female patients
Rationale for change		Clarification
Section to be changed	3.3.3	Exclusion Criteria
Description of change		#13: added "intake of Lumacaftor / Ivacaftor dual combination"
Rationale for change		Clarification
Section to be changed	3.3.3	Exclusion Criteria
Description of change		#22: rephrased (any vulnerable person as per local regulation)
Rationale for change		Clarification
Section to be changed	5.4.1.2	Pharmacodynamic investigations
Description of change		What will happen to samples after completion of the trial / destruction of samples: "Urine" added
Rationale for change		Clarification
Section to be changed	7.2.1	Planned Analysis / General considerations
Description of change		Clarification of data handling for patients who unintentionally received treatment not according to their randomization
Rationale for change		Request from regulators
Section to be changed	7.5	Determination of sample size
Description of change		Added additional simulated probabilities for sample size of 12
Rationale for change		Request from regulators
Section to be changed	8.1	Trial Approval, Patient Information, Informed Consent
Description of change		Reference to "participant's legally accepted representative" deleted
Rationale for change		Request from regulators

Section to be changed	8.4	Expedited reporting of Adverse Events
Description of change		Additional information on expedited reporting of adverse events added
Rationale for change		Request from regulators
Section to be changed	9	References
Description of change		Update safety reference document to most current version (ProAir HFA US)
Rationale for change		Currentness of references

11.3 GLOBAL AMENDMENT 3

Date of amendment		21 Nov 2023
EU CT number		2022-502835-21-00
BI Trial number		1397-0013 (Clairafly™)
BI Investigational Medicinal Product(s)		BI 1291583
Title of protocol		A randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 one tablet once daily over 12 weeks versus placebo in adult patients with cystic fibrosis bronchiectasis (Clairafly™)
Global Amendment due to urgent safety reasons		
Global Amendment.		X
Category	**Section No.**	**Description**
Section to be changed	1.2	Drug Profile
Description of change		Information on recently detected metabolite [redacted] added and text rephrased accordingly
Rationale for change		Wording updated due to to recently detected, [redacted]
Section to be changed	1.2	Drug Profile
Description of change		Nomenclature of metabolites standardized, use of CD numbers instead of M numbers
Rationale for change		Alignment with nomenclature used in investigator's brochure

Section to be changed	1.2	Drug Profile
Description of change		Reference added (PK and safety of brensocatib in patients with CF)
Rationale for change		Results just recently published
Section to be changed	1.4.2	Risks - Table
Description of change		Reproductive system: information added and text rephrased *Genotoxicity for BI 1291583 and the* [redacted] *previously identified metabolites was not demonstrated in preclinical studies. The genotoxicity assessment has not yet been completed for the* [redacted]*. Data in humans are not available.* Mitigation strategy adapted: contraception requirements for WOCBP (2 methods) and men able to father a child
Rationale for change		Contraception requirements added due to recently detected, [redacted]
Section to be changed	3.3.2	Inclusion criteria
Description of change		Consecutive numbering of Inclusion Criteria
Rationale for change		Correction, formatting issue in previous version
Section to be changed	3.3.2	Inclusion Criteria
Description of change		#7: information on contraception requirements for male and WOCBP trial participants added
Rationale for change		Criterium updated due to to recently detected, [redacted]
Section to be changed	4.2.2.3	Contraception requirements
Description of change		Information updated: WOCBP, if their sexual partner is a man able to father a child, must use two medically approved methods of birth control throughout the trial and for a period of at least 9 months after last trial drug intake.

		Men participating in this clinical trial, if their sexual partner is a WOCBP, must use condom from the first administration of trial medication until 6 months after the last administration of trial medication.
Rationale for change		Requirements updated due to to recently detected, [redacted]
Section to be changed	5.2.6.2.3	Pregnancy
Description of change		Information added: 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.
Rationale for change		Detection of previously unidentified metabolite [redacted]
Section to be changed	6.2.2	Treatment period
Description of change		Reminder for male participants with WOCBP partners added, to continue use of contraception after last administration of trial medication
Rationale for change		Updated contraception requirements for male participants with WOCBP partners

APPROVAL / SIGNATURE PAGE

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

Title: A randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 one tablet once daily over 12 weeks versus placebo in adult patients with cystic fibrosis bronchiectasis (ClairaflyTM)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Statistician	[redacted]	21 Nov 2023 12:33 CET
Approval-Clinical Program [redacted]		21 Nov 2023 13:26 CET
Approval-Clinical Trial Leader		21 Nov 2023 13:35 CET
Verification-Paper Signature Completion		22 Nov 2023 08:17 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed