CLINICAL TRIAL PROTOCOL

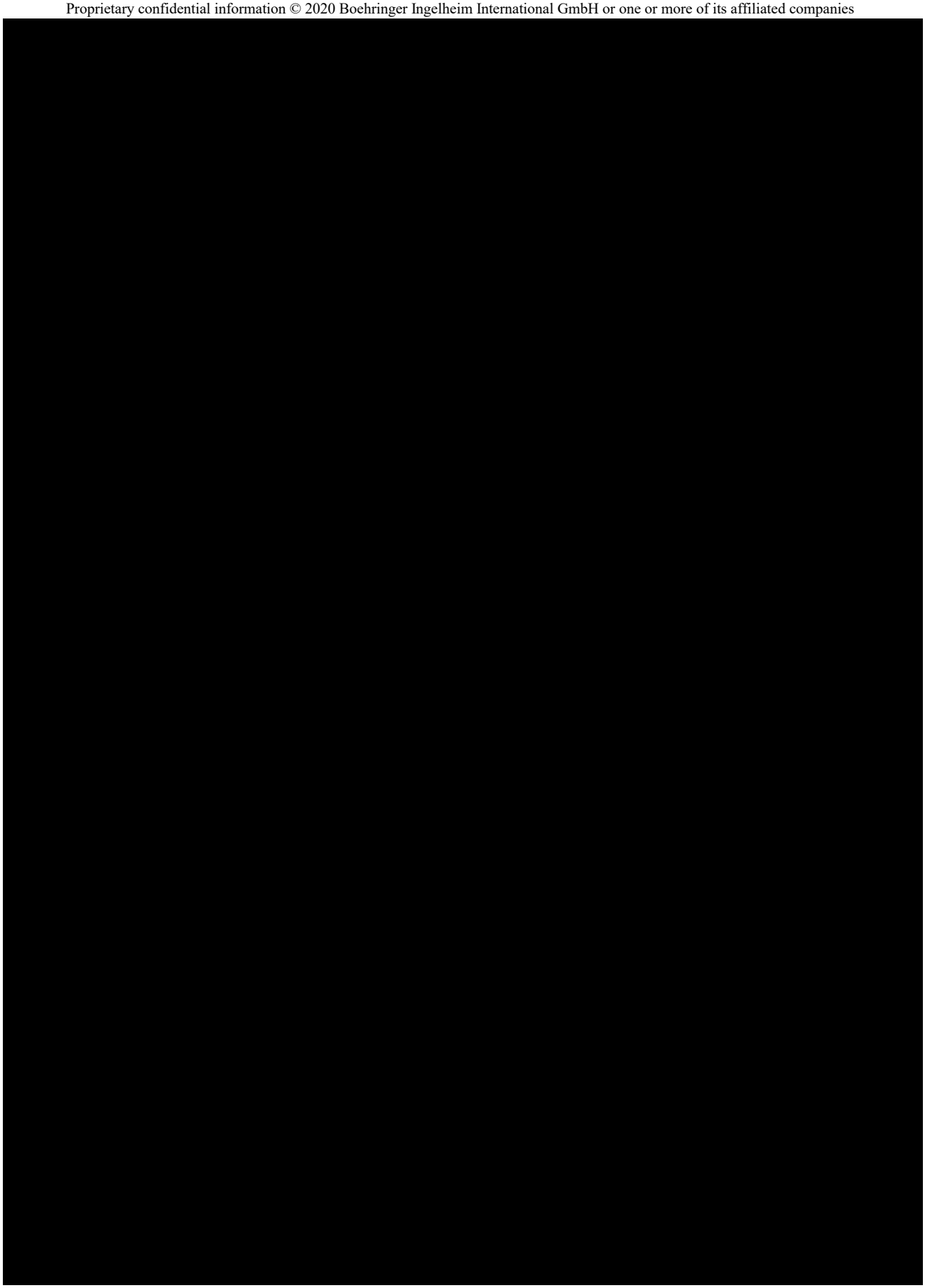
	Document Number:	**c21861538-08**
EudraCT No.	2018-004238-13	
BI Trial No.	1405-0002	
BI Investigational Medicinal Product	BI 1323495	
Title	Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)	
Lay Title	A study in healthy men and women to test how well different doses of BI 1323495 are tolerated	
Clinical Phase	Ib	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax:	
Principal Investigator	[redacted] Phone: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 7))	
Version and Date	Version: 8.0	Date: 10 Dec 2020

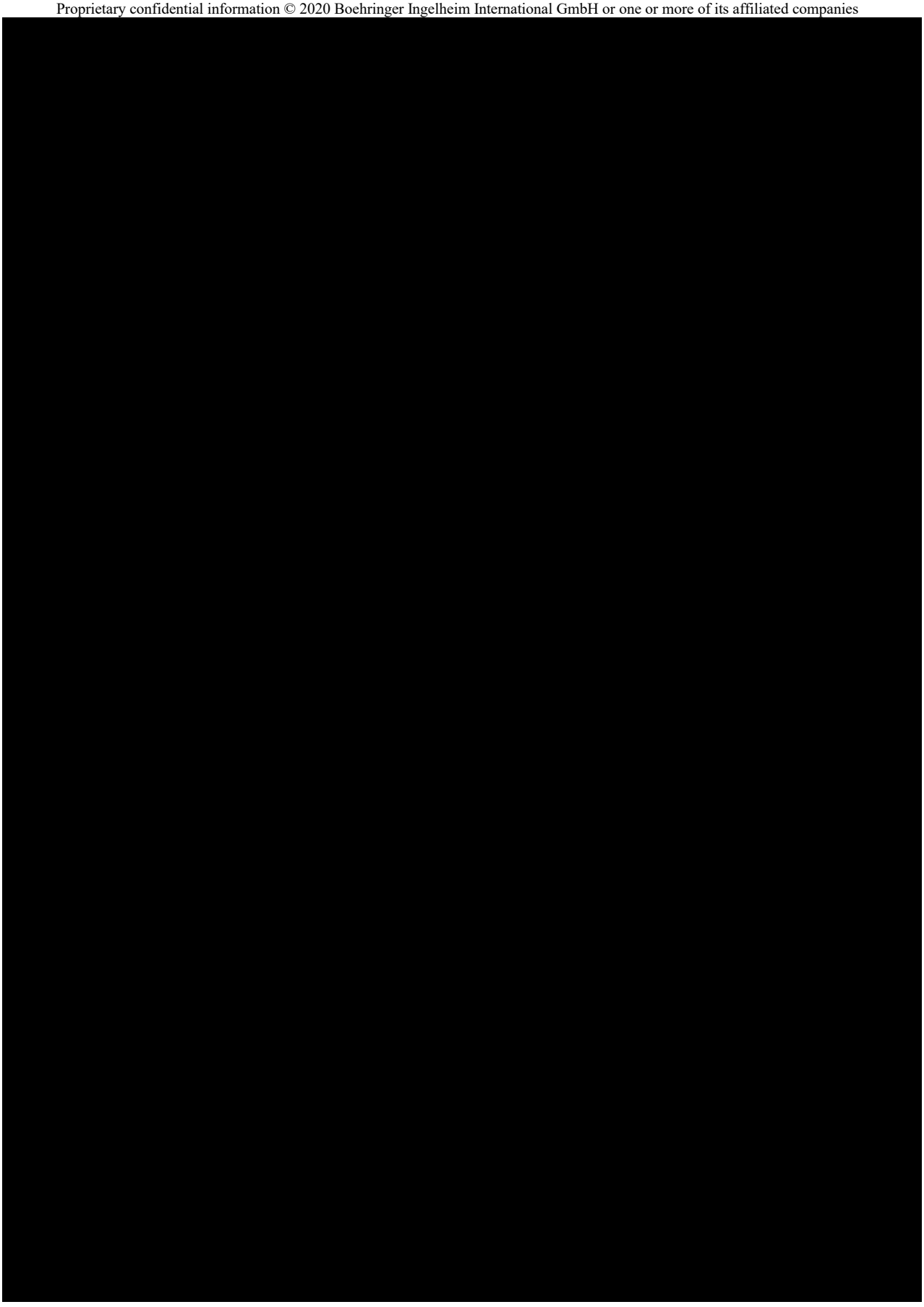
CLINICAL TRIAL PROTOCOL SYNOPSIS

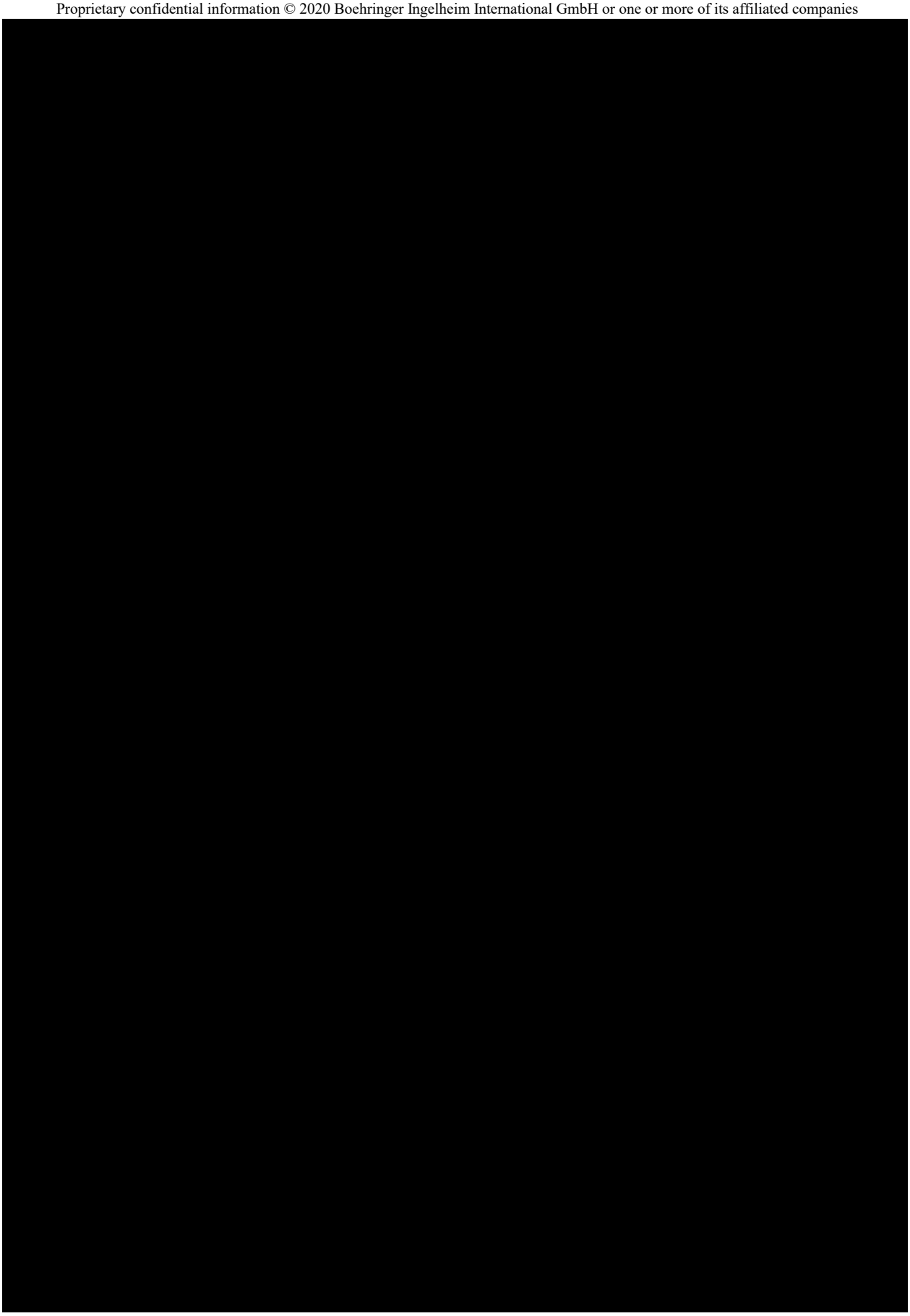
Company name	Boehringer Ingelheim
Protocol date	06 Aug 2019
Revision date	10 Dec 2020
BI trial number	1405-0002
Title of trial	Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)
Principal Investigator	[redacted] Phone: [redacted]
Trial site	[redacted]
Clinical phase	Ib
Trial rationale	Based on results from a single-rising dose trial in healthy volunteers, the trial is intended to show the safety and tolerability of multiple doses of BI 1323495 and [redacted] The results will provide the basis for a potential ongoing clinical development of BI 1323495 in the indications [redacted]
Trial objectives	To investigate safety, tolerability, pharmacokinetics, and pharmacodynamics of (increasing) multiple bid or qd oral doses of BI 1323495 versus placebo in healthy subjects.

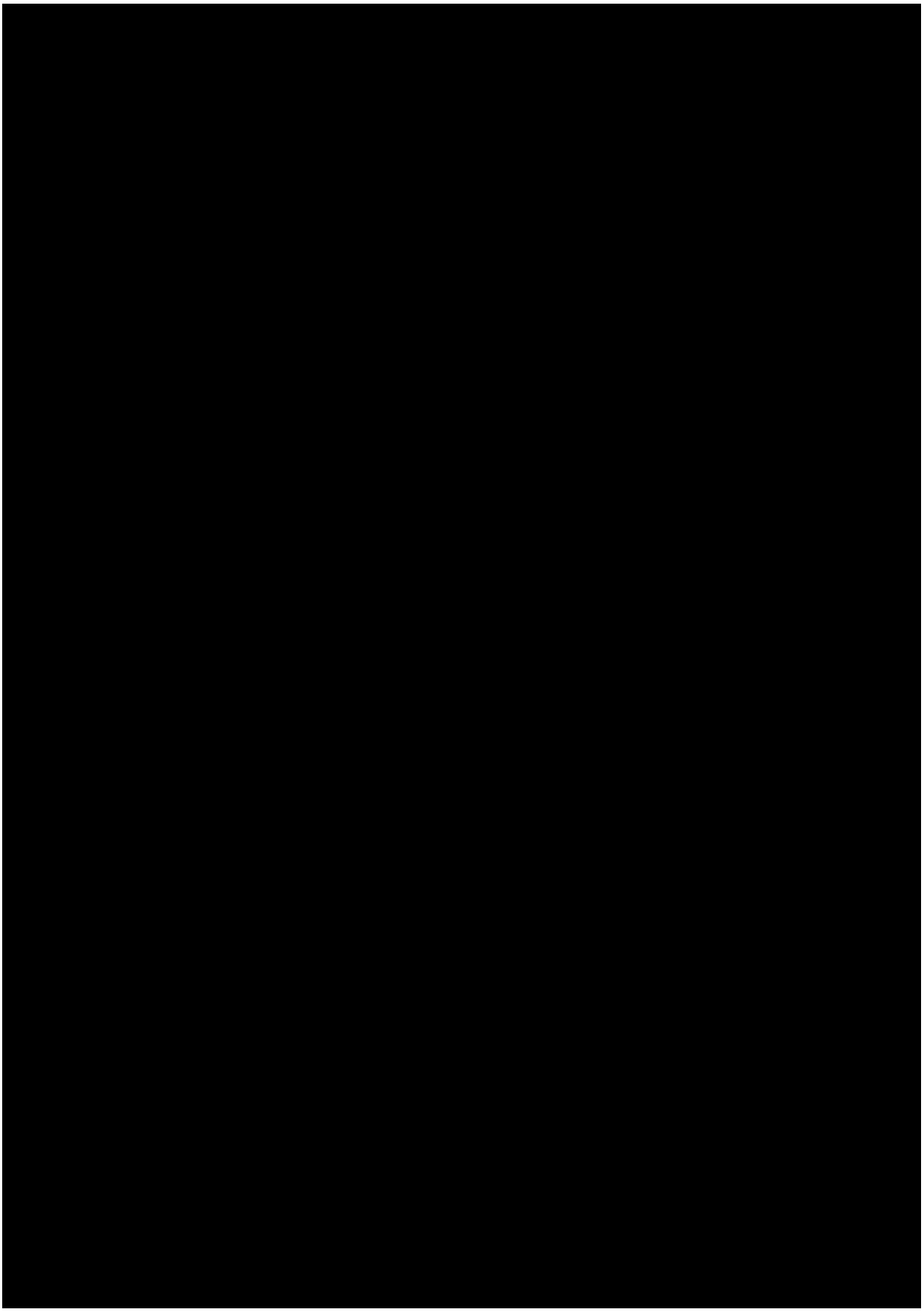
Trial endpoints	<u>Primary endpoint:</u>
	• To assess safety and tolerability of BI 1323495
	  o Number of subjects with treatment-emergent drug-related adverse events.
	<u>Secondary endpoints:</u>
	• Pharmacokinetics
	  o After the first dose: $AUC_{0-12,}$ AUC_{0-24} (only for qd dosing) and C_{max} of BI 1323495
	  o After the last dose: $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1323495

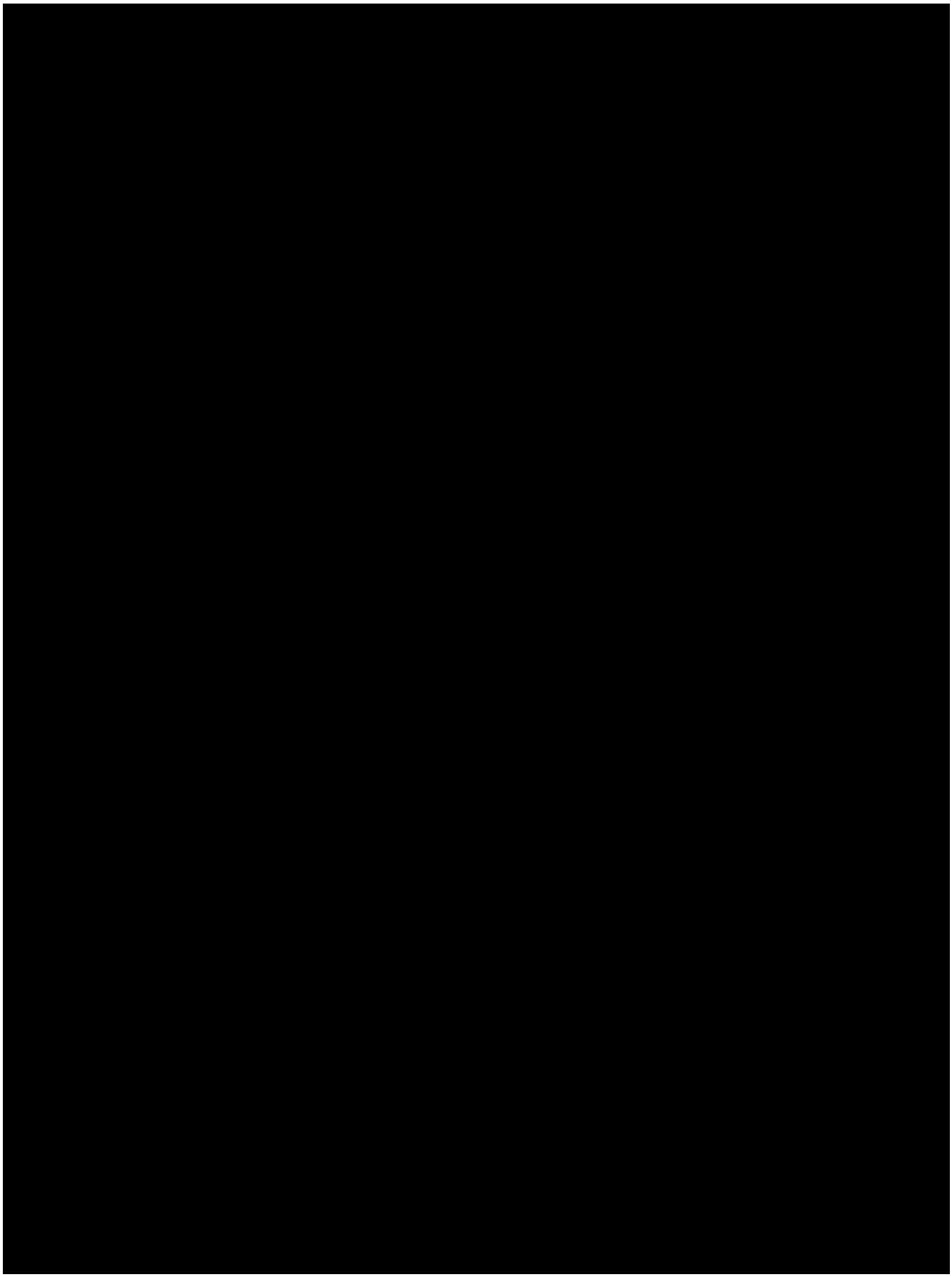
Trial design	Randomised, placebo-controlled, multiple rising dose, double blind within dose groups, 2-part trial with 8 dose groups
Total number of subjects randomised	88* healthy subjects
Number of subjects on each treatment	Part I (Extensive Metabolizer Part): 12 subjects per each of 6 dose groups (9 on active drug and 3 on placebo) Part II (Poor Metabolizer Part): 8 subjects per each of 2 dose groups(6 on active drug and 2 on placebo)
Diagnosis	Not applicable
Main in- and exclusion criteria	• Healthy male and female subjects, age of 18 to 70 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2 • Part I: UGT2B17 extensive-metabolizer genotype (*1/*1 or *1/*2) • Part II: UGT2B17 poor metabolizer genotype (*2/*2)
Test product 1	BI 1323495 film-coated tablets (dose strengths 10, 50, and 150 mg)
dose	Part I in extensive metabolizer subjects: 6 ascending doses • 10 mg, 30 mg, 70 mg, 150 mg and an intermediate dose of 120 mg, as multiple twice daily doses, • 120 mg as multiple once daily dose Part II in poor metabolizer subjects: 2 ascending doses • 10 mg and 30 mg as multiple twice daily doses
mode of administration	Oral with 240 mL of water and within 30 minutes of a meal
Comparator product	Matching placebo
dose	Not applicable
mode of administration	Oral with 240 mL of water and within 30 minutes of a meal
Test product 2	Midazolam solution for injection, diluted for use as oral solution (target concentration of dilution: 50 µg/mL midazolam)
dose	75 µg
mode of administration	Oral followed by 240 mL of water and within 30 minutes after a standard breakfast
Duration of treatment	<u>BI 1323495</u> 11 days, 10 days twice daily (bid) dosing, or once daily dosing for 120 mg qd dose group, and single dose on day 11 <u>Midazolam solution:</u> Single dose in the 3 highest bid dose groups of Part I on day -1 and day 11
Statistical methods	Descriptive statistics will be calculated for all endpoints.

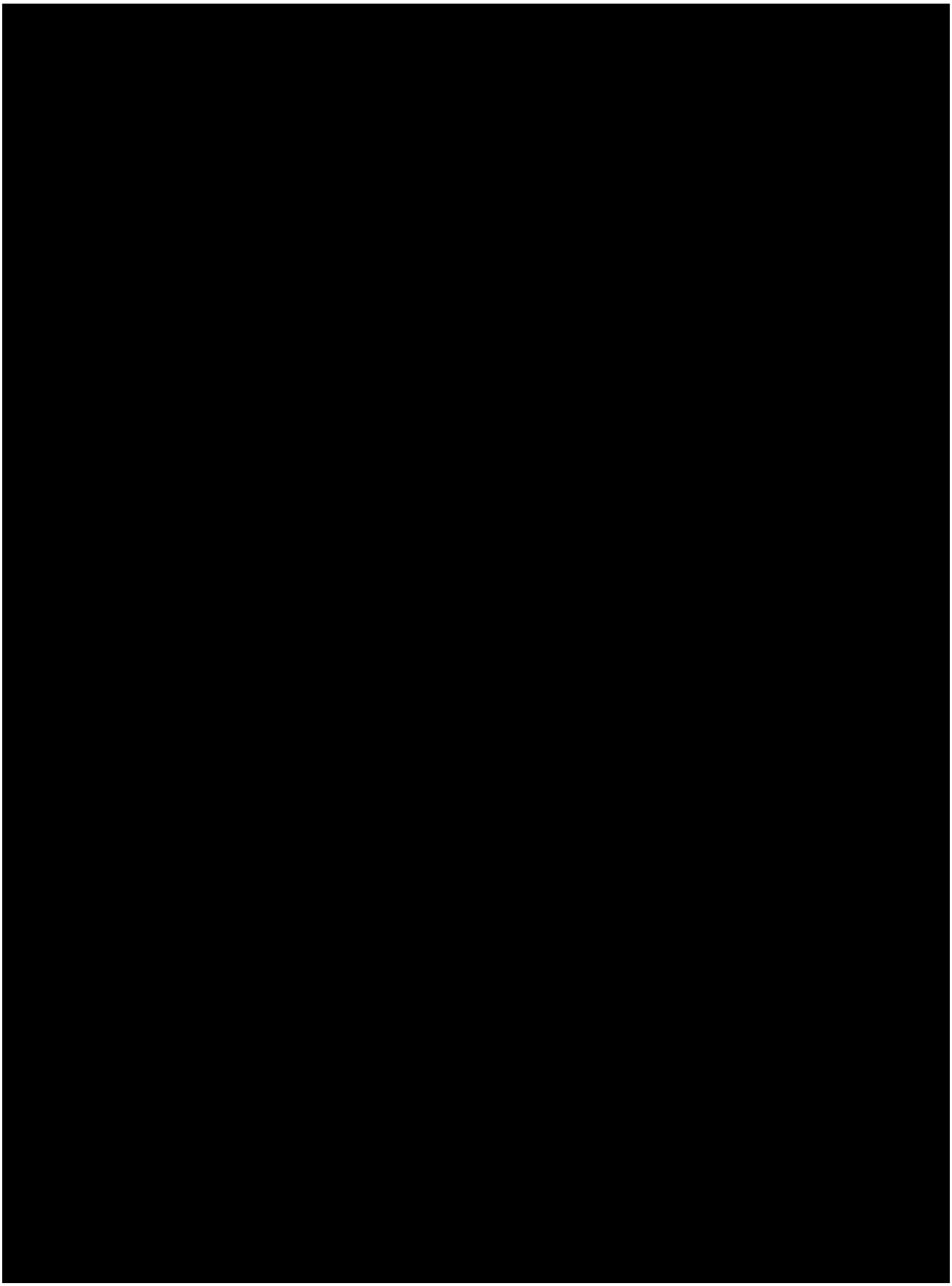


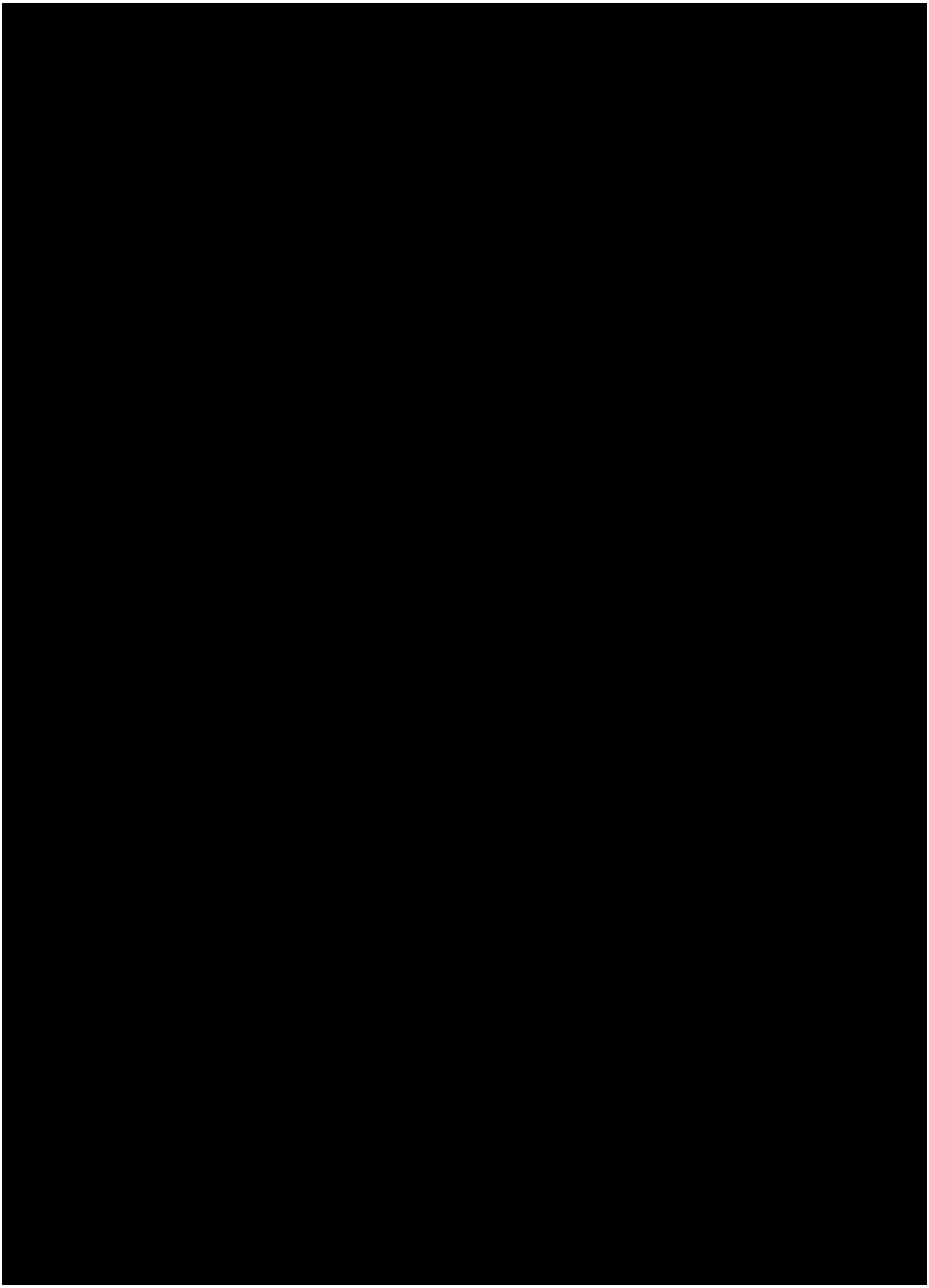


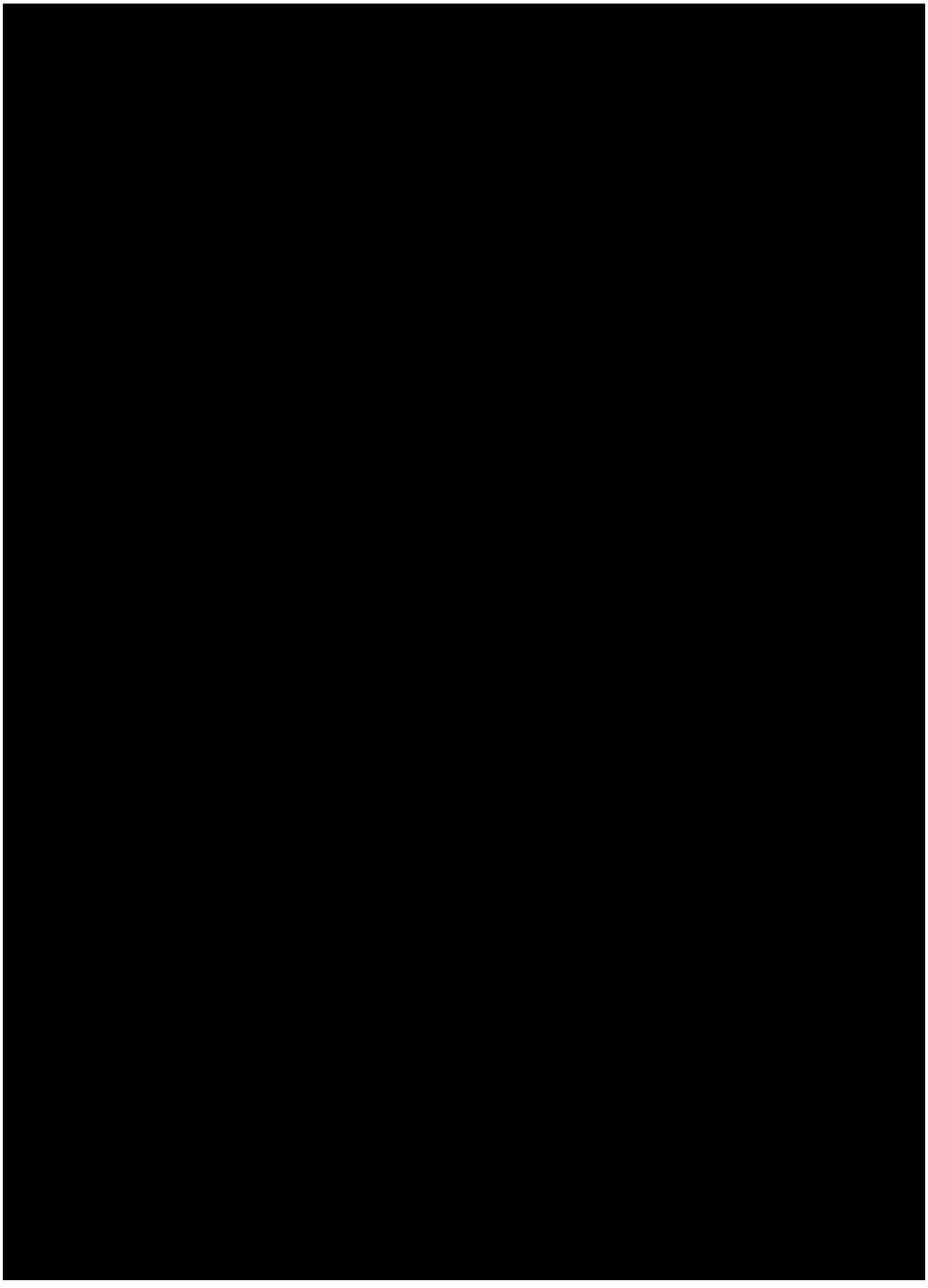


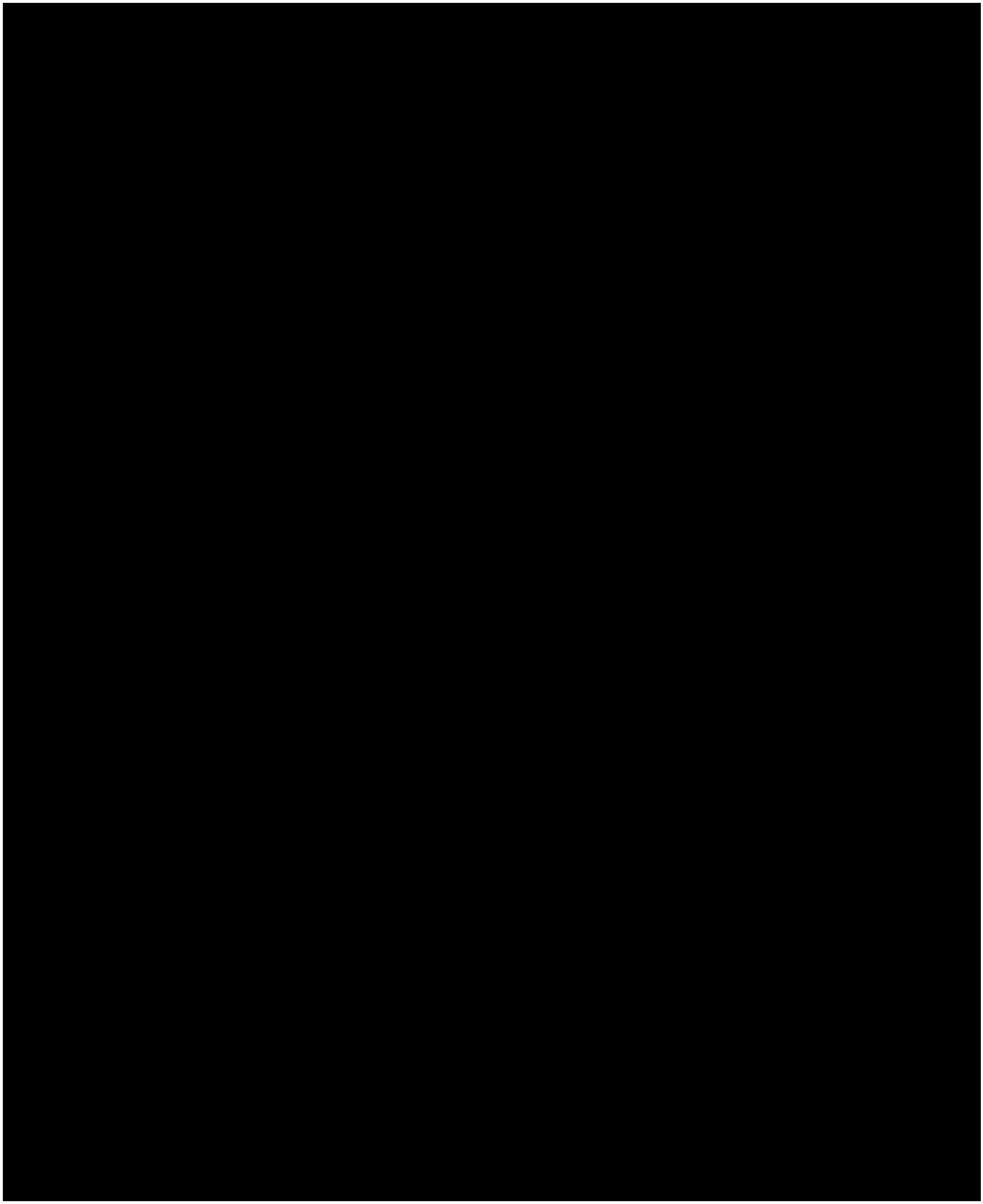


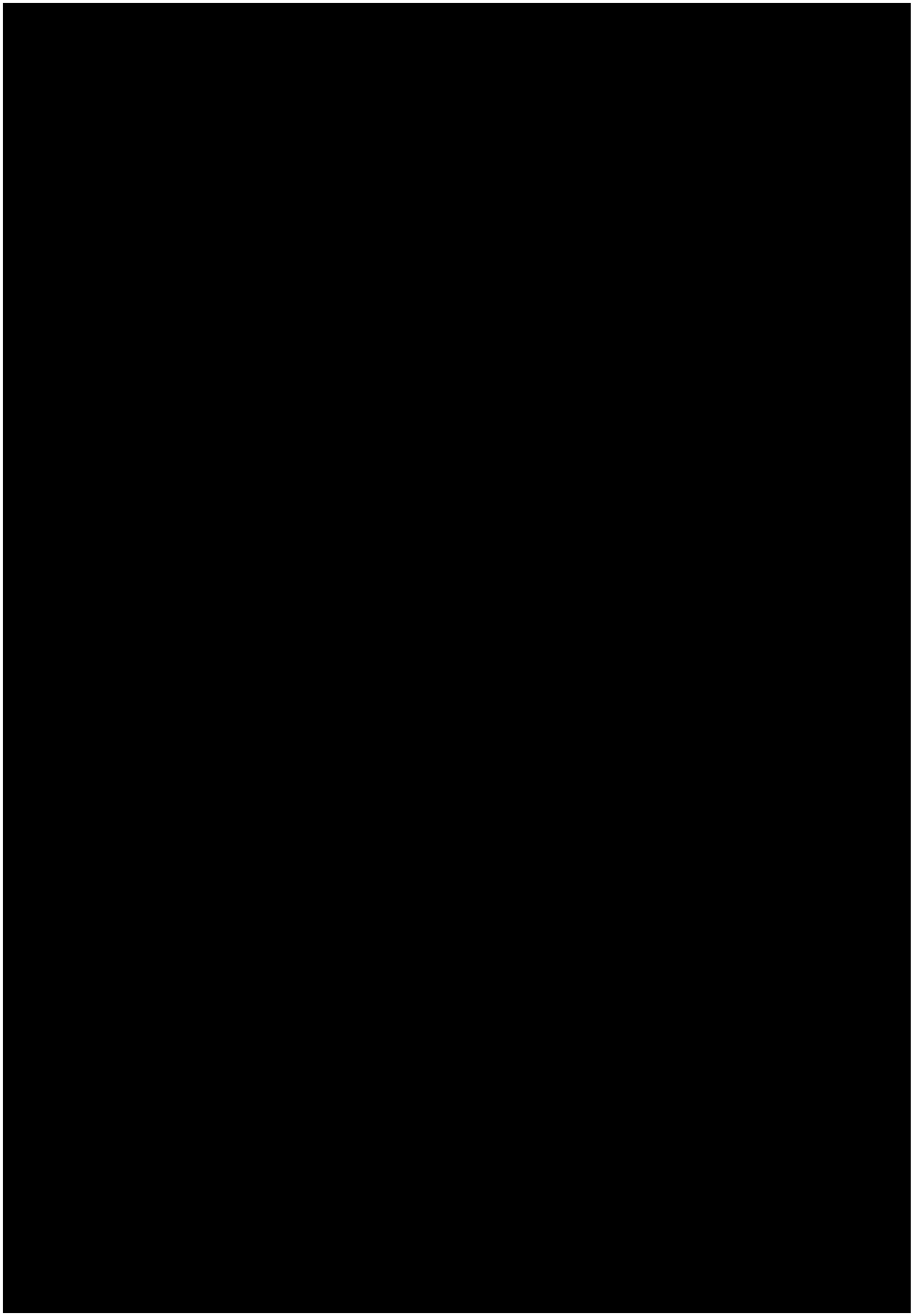


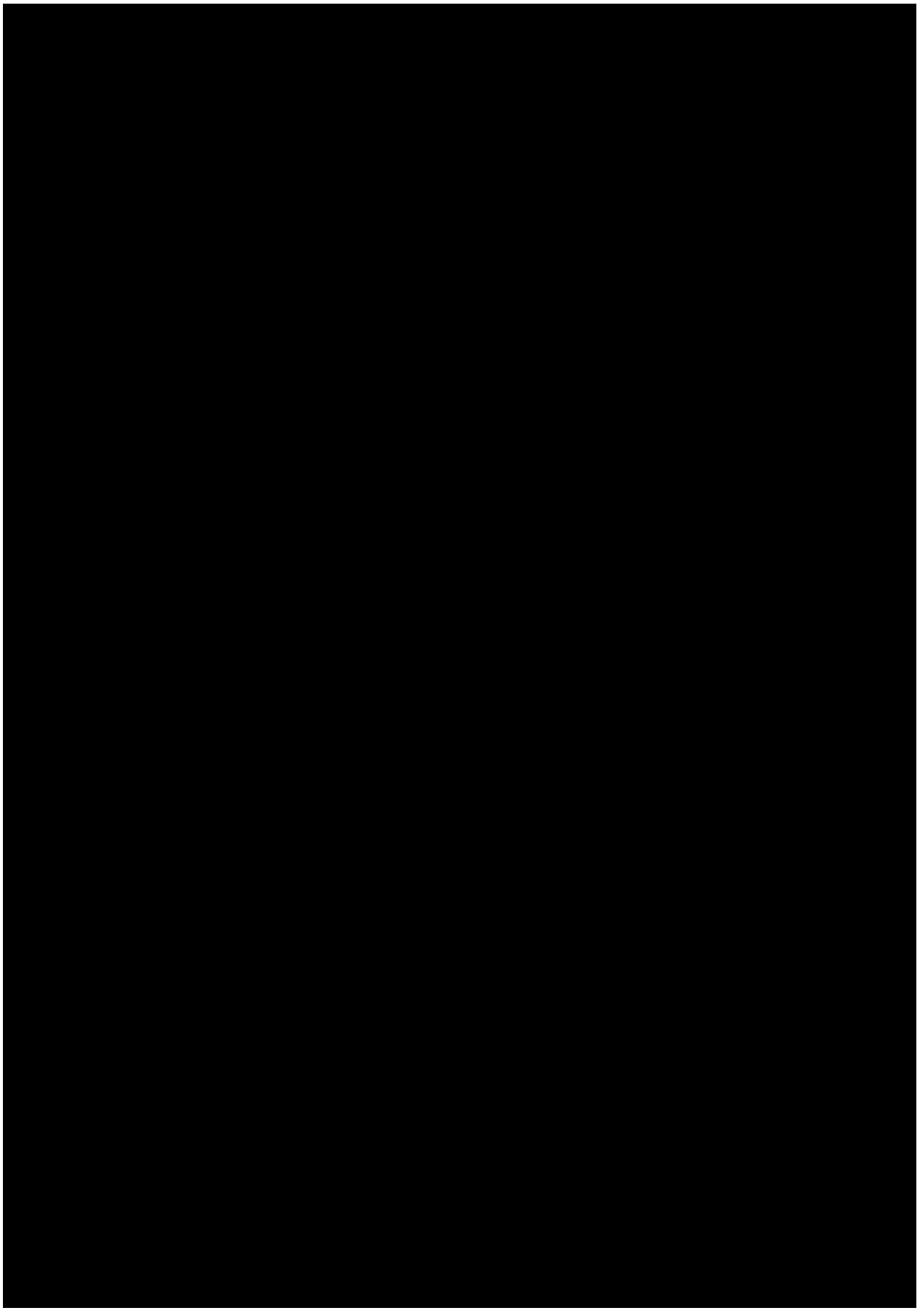


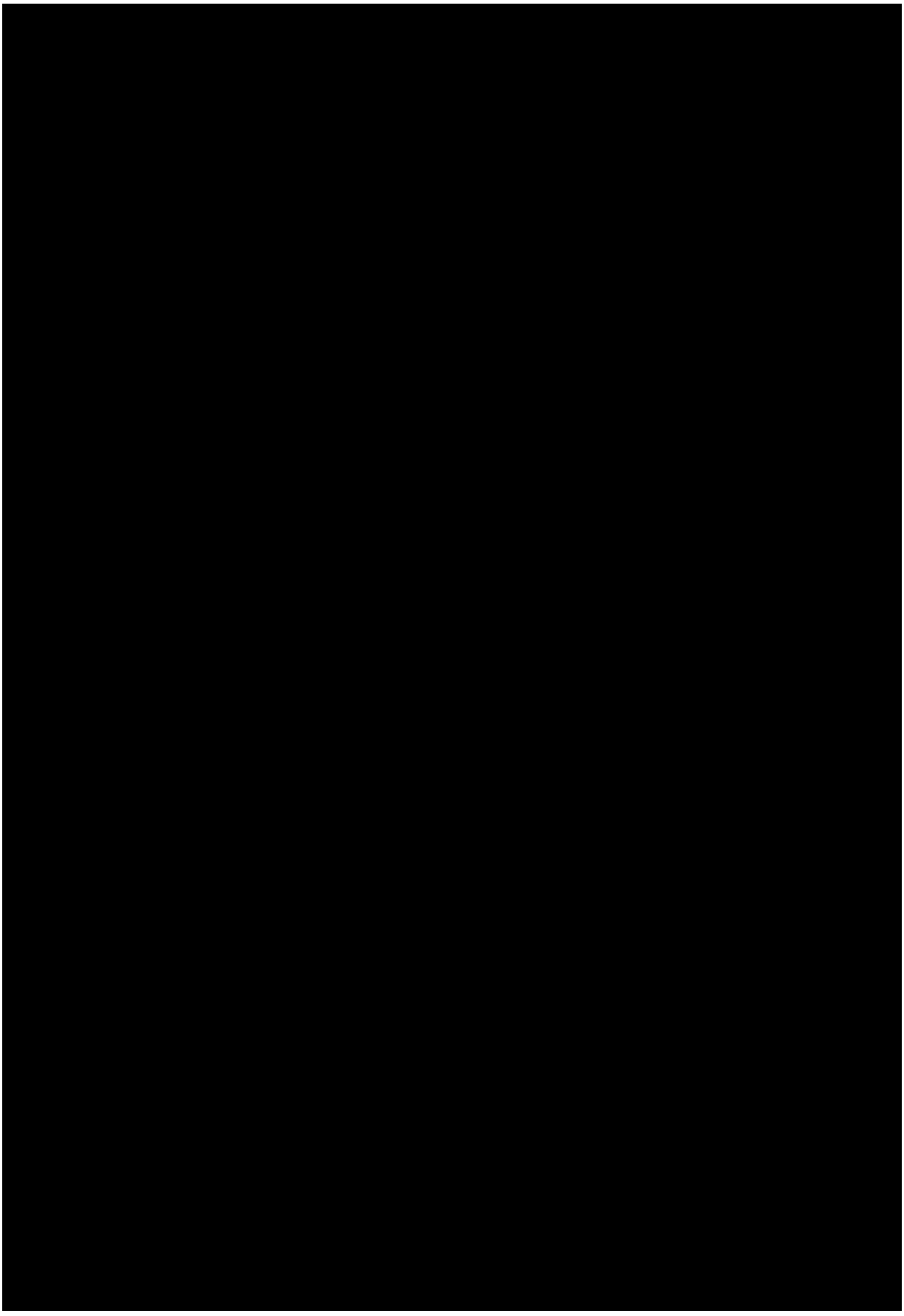


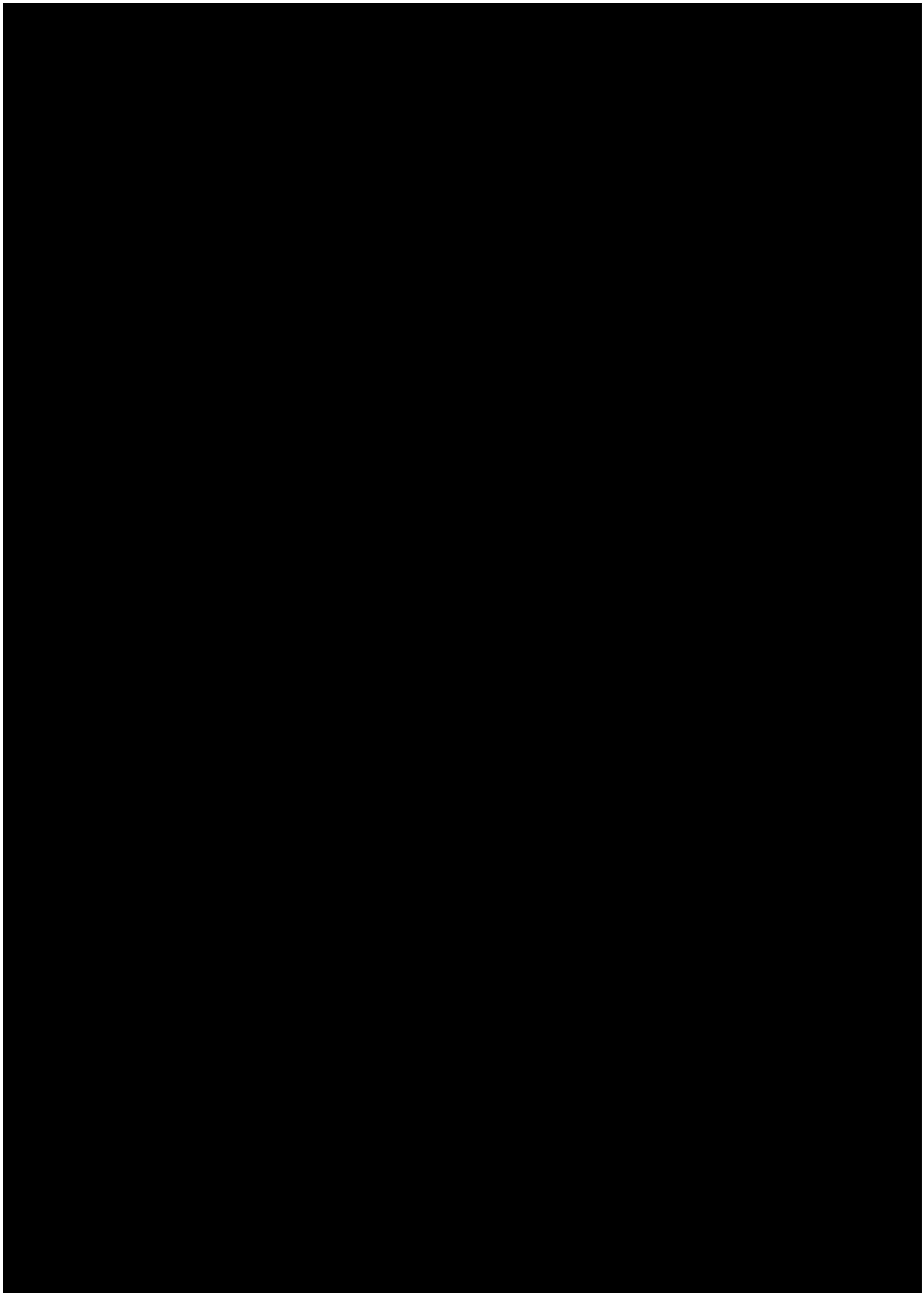












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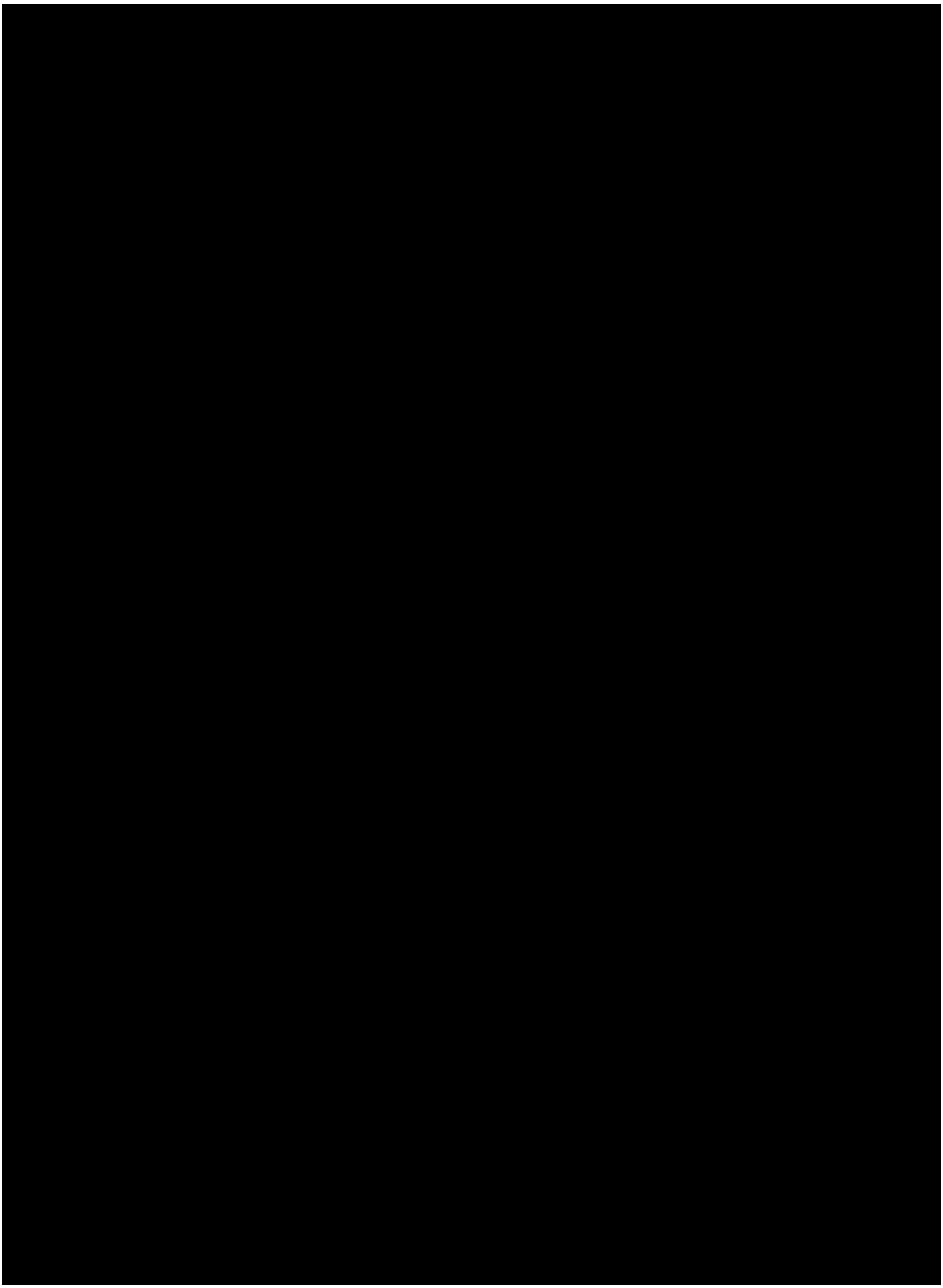

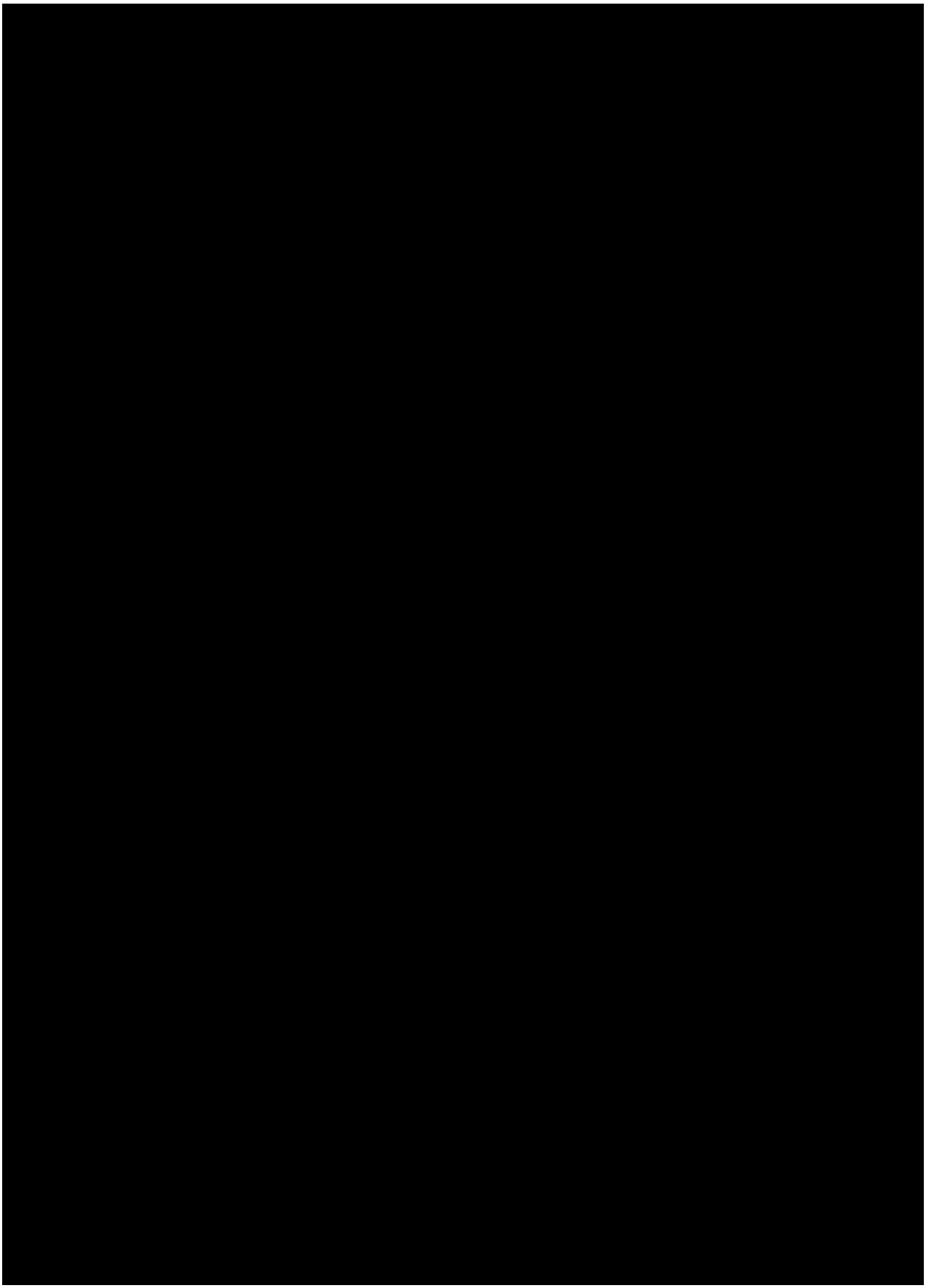

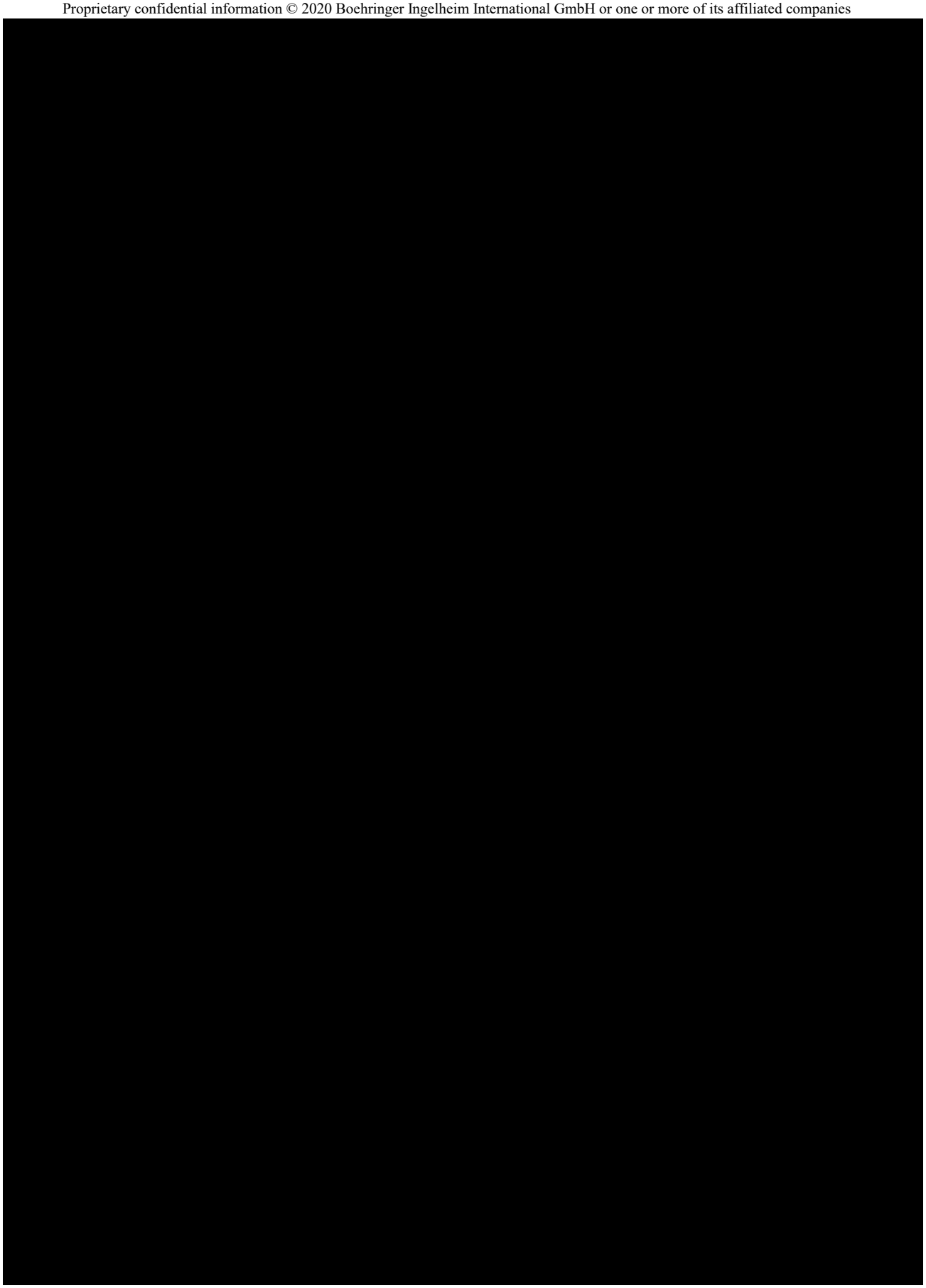

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
bid	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BM	Biomarker
BP	Blood Pressure
CA	Competent Authority
CatC	Cathepsin C
CatG	Cathepsin G
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus disease
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP450	Cytochrome P450
DEC	Dose Escalation Committee
DG	Dose Group
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Effective Dose
eDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid

eGRF	estimated Glomerular Filtration Rate
EM	Extensive metabolizer(s)
EoS	End of Study
EoT	End of Treatment
EudraCT	European Clinical Trials Database
FC	Flow Chart
FDA	Food and Drug Administration (United States of America)
GCP	Good Clinical Practice
gCV	geometric Coefficient of Variation
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPV	Global Pharmacovigilance
GSH	Glutathione
hERG	human Ether-à-go-go-Related Gene
HR	Heart Rate
IB	Investigator's Brochure
IC_{50}	Concentration at which 50% inhibition of target occurs
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
ISF	Investigator Site File
LSLT	Last Subject Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Multiple Rising Dose
MRT	Mean Residence Time
NA	Not applicable
NE	Neutrophil Elastase
NOAEL	No Observed Adverse Effect Level
NSP	Neutrophil Serine Protease
OPU	Operative Unit
p.o.	per os (oral)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PM	Poor metabolizer(s)

PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PTF	Peak-Trough Fluctuation
PTS	Peak-Trough Swing
qd	quaque die (once a day)
REP	Residual Effect Period
SAE	Serious Adverse Event
SCR	Screening
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIMP	Tissue Inhibitor of Metalloproteinase
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
TMM	Team Member Medicine
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
UDP	Uridine 5'-diphosphate
UGT	UDP Glucuronosyltransferase
UGT2B17	UDP Glucuronosyltransferase family 2 member B17
ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

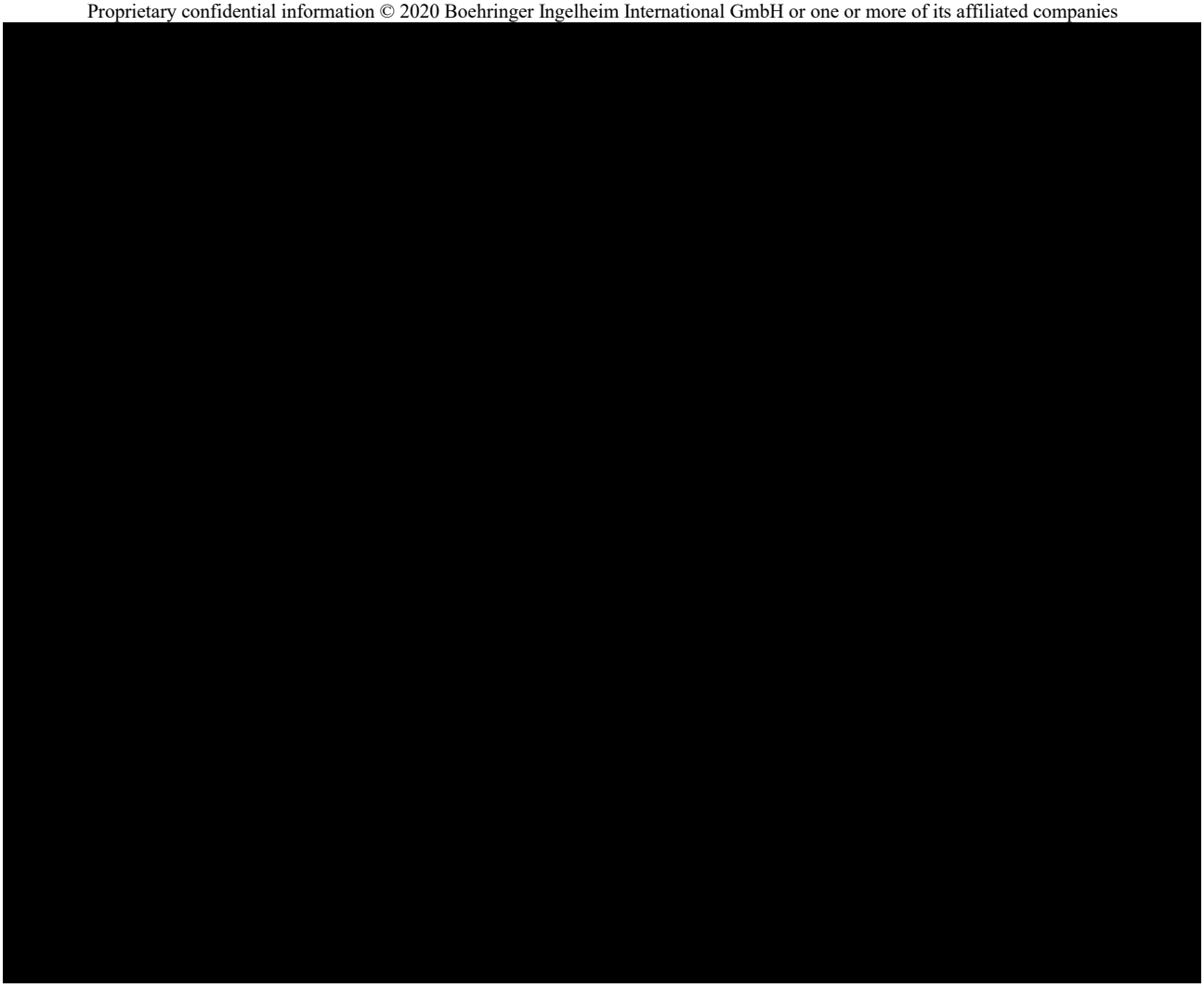
[redacted]

In this study, for the first time multiple doses of BI 1323495 will be administered. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of BI 1323495 will be investigated.

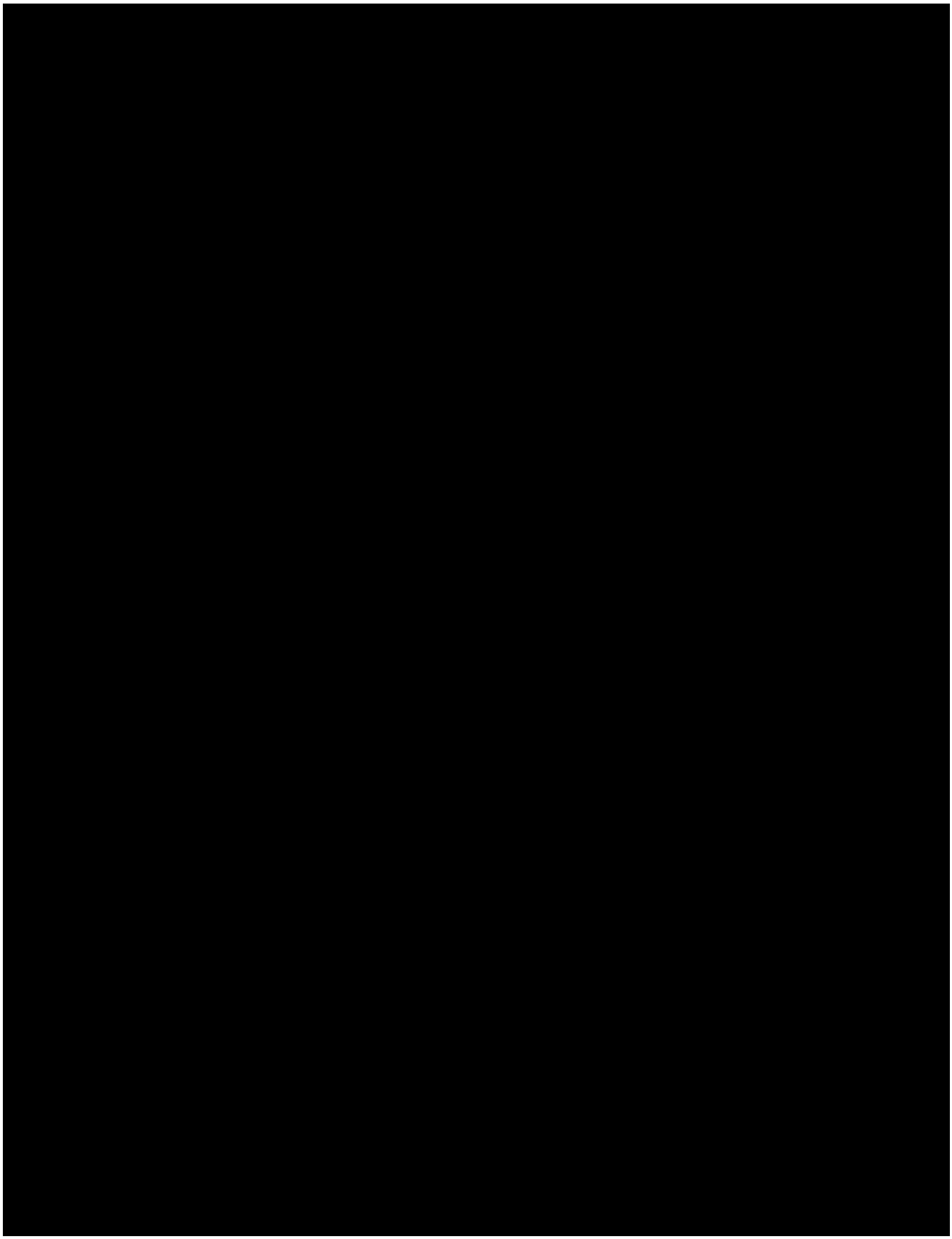
[redacted]

1.1 MEDICAL BACKGROUND

[redacted]



1.2 DRUG PROFILE



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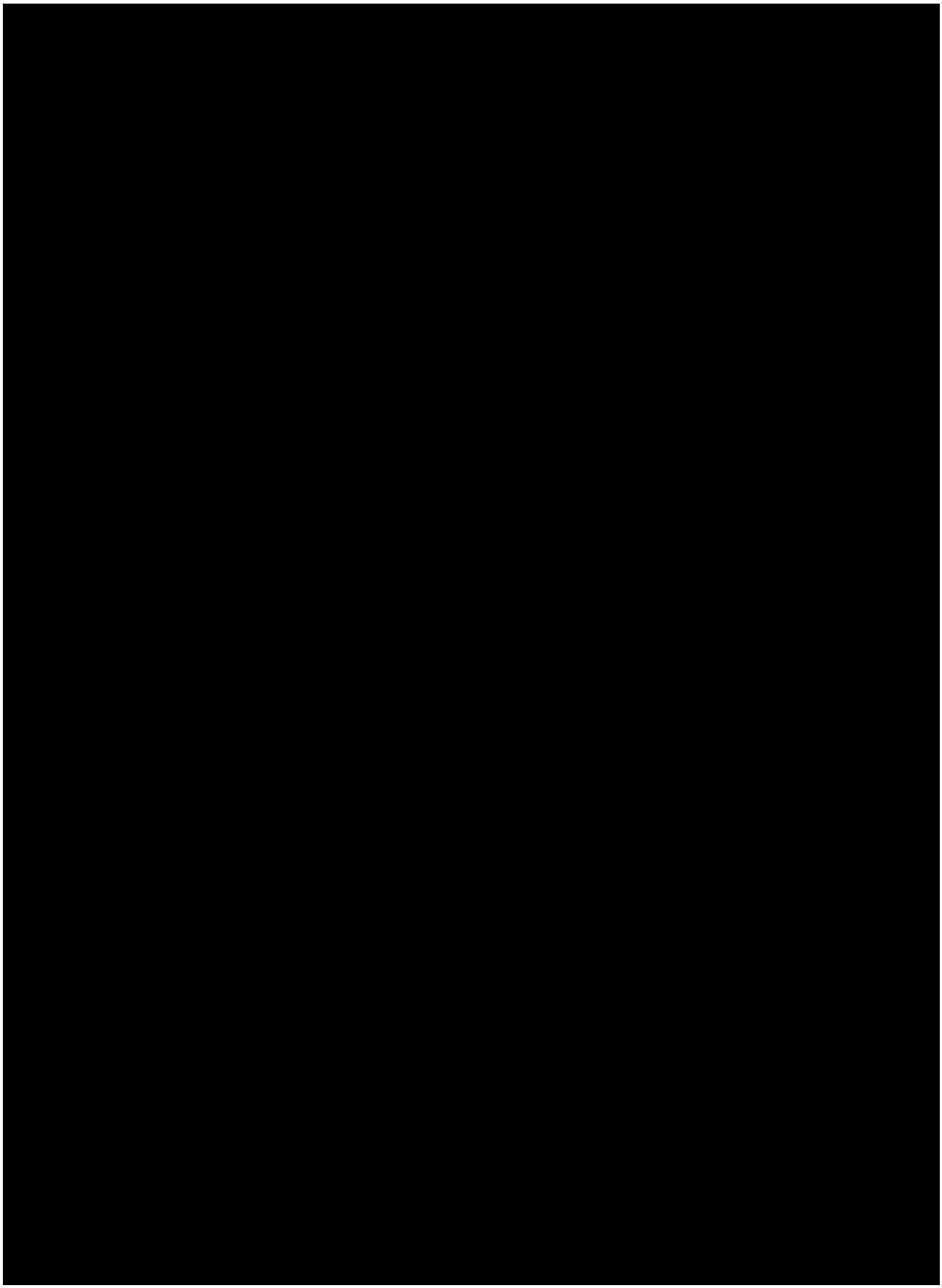

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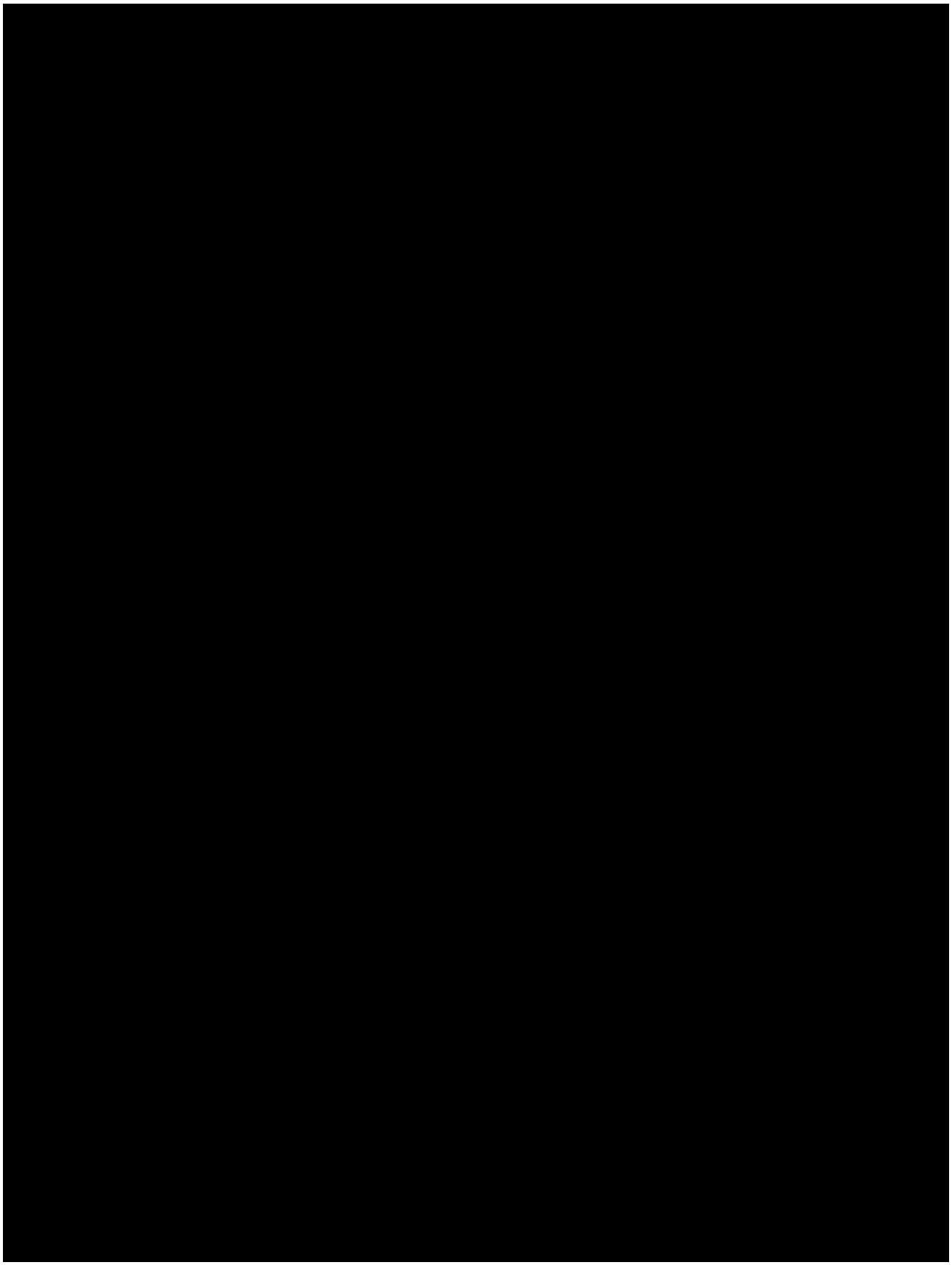

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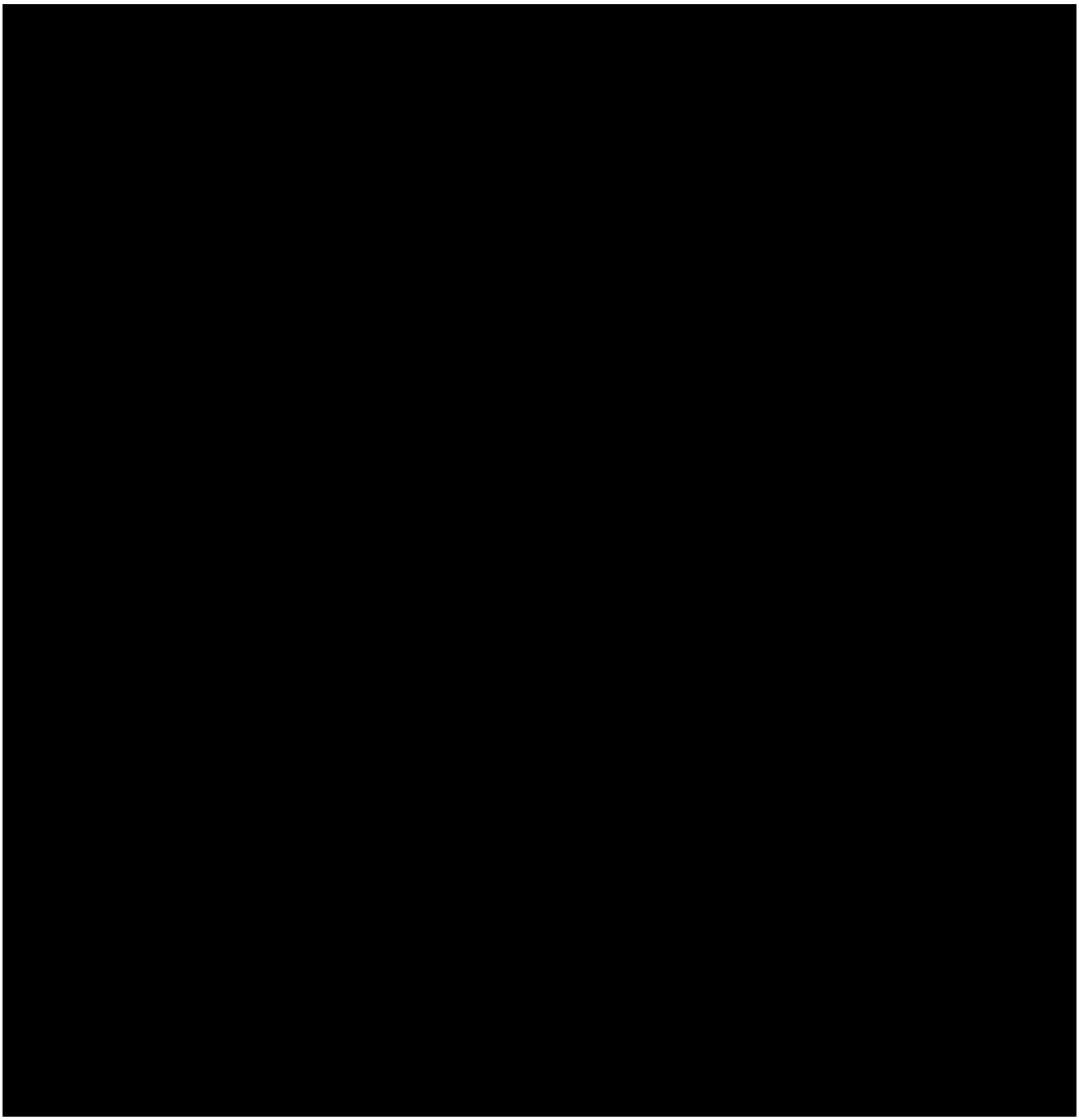

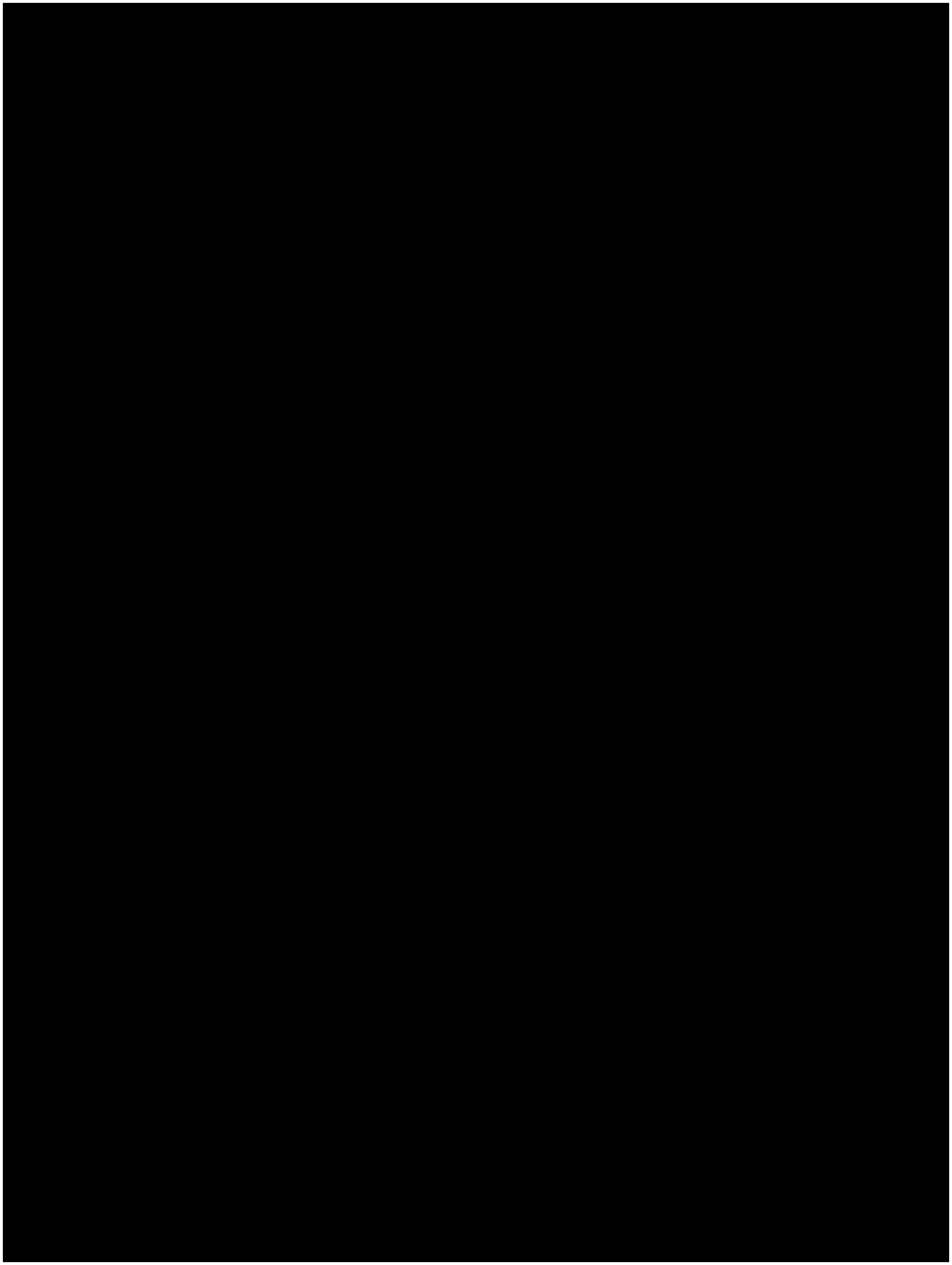

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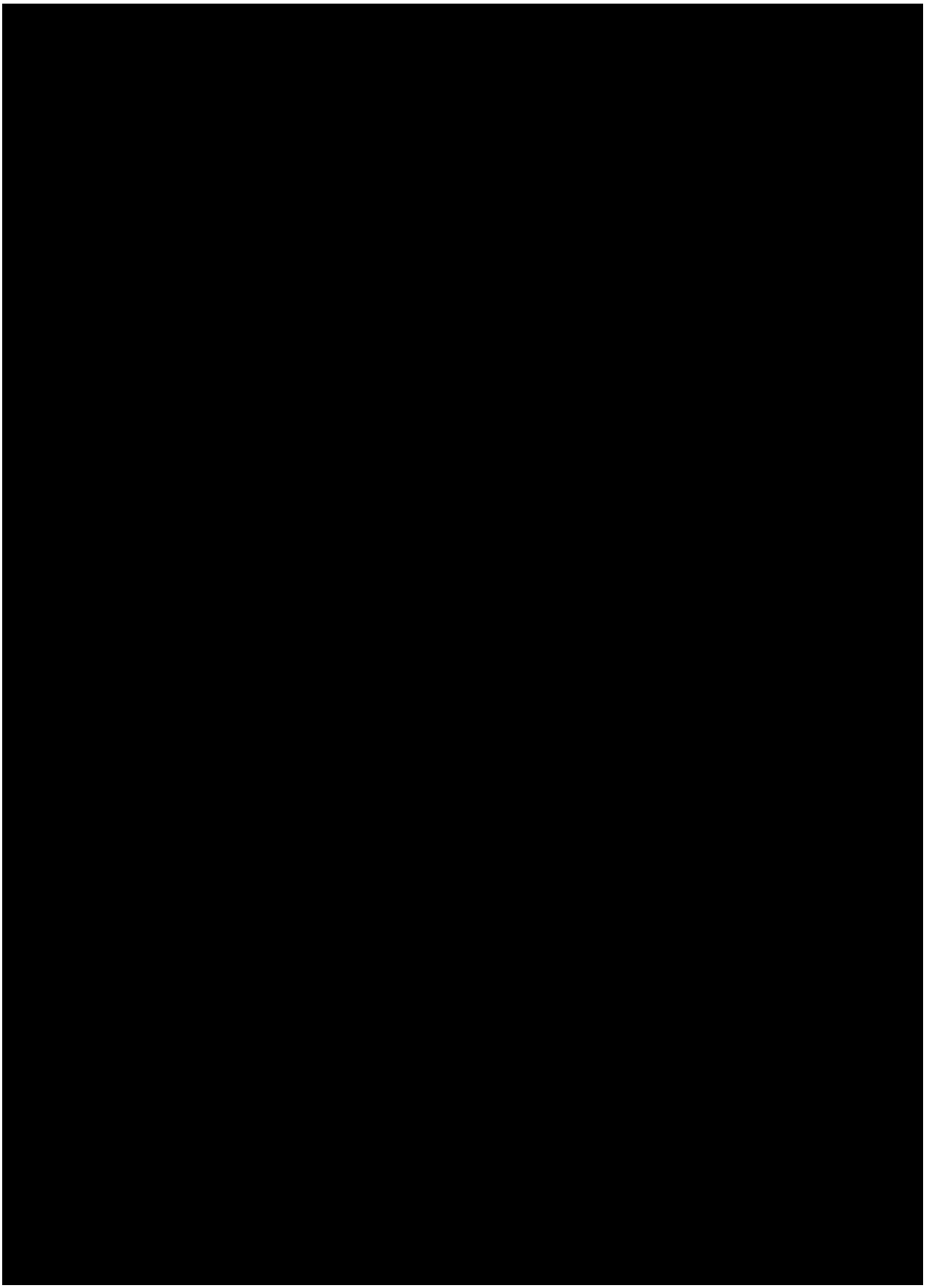

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[redacted]

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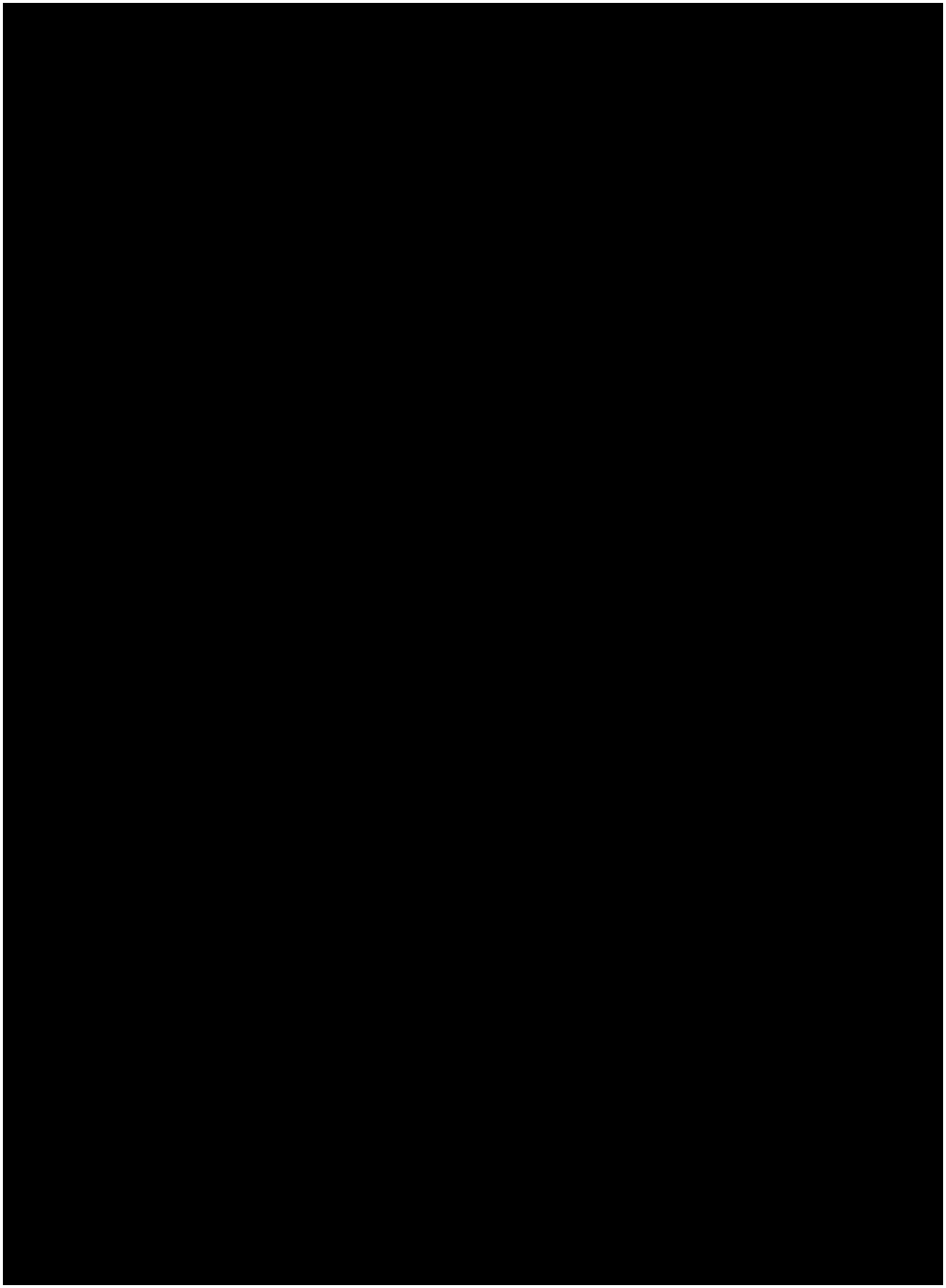
1.3 RATIONALE FOR PERFORMING THE TRIAL

In this trial, for the first time the effects of multiple doses of BI 1323495 will be assessed in humans. This will be done in healthy subjects. [redacted]



1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance for the development of a new orally available drug, [redacted]

1.4.2 Risks

Trial subjects are exposed to risks related to the exposure to the trial medication and to risks of the study procedures.

At the time of completion of EM DG 2 in this trial, the COVID-19 pandemic emerged with worldwide impact on daily life. To allow for thorough evaluation of potential additional risks to trial participants in the course of this pandemic, the trial was temporarily put on hold after completion of EM DG 2 and prior to the start of EM DG 3. Potential additional risks for study participants with regard to COVID-19 have been evaluated and risk management measures implemented in ctp version 4.0 (see Sections 1.4.2.1.1 and 1.4.2.3)

1.4.2.1 Risks related to study medication (Investigational Medicinal Product BI 1323495)

Risk factors may derive from particular knowledge or the lack thereof, regarding the mode of action, the nature of the target, and/or findings in non-clinical safety studies.

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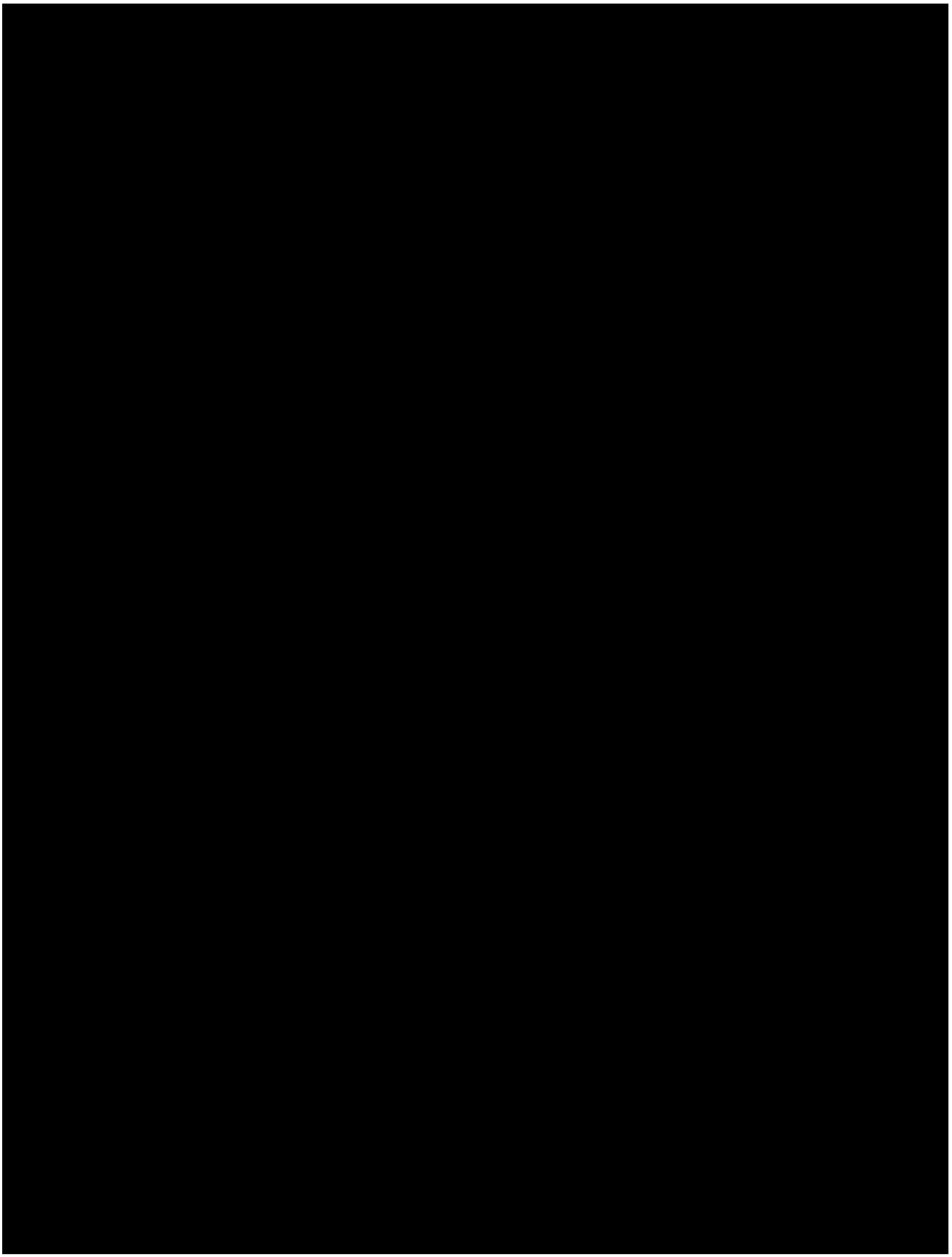

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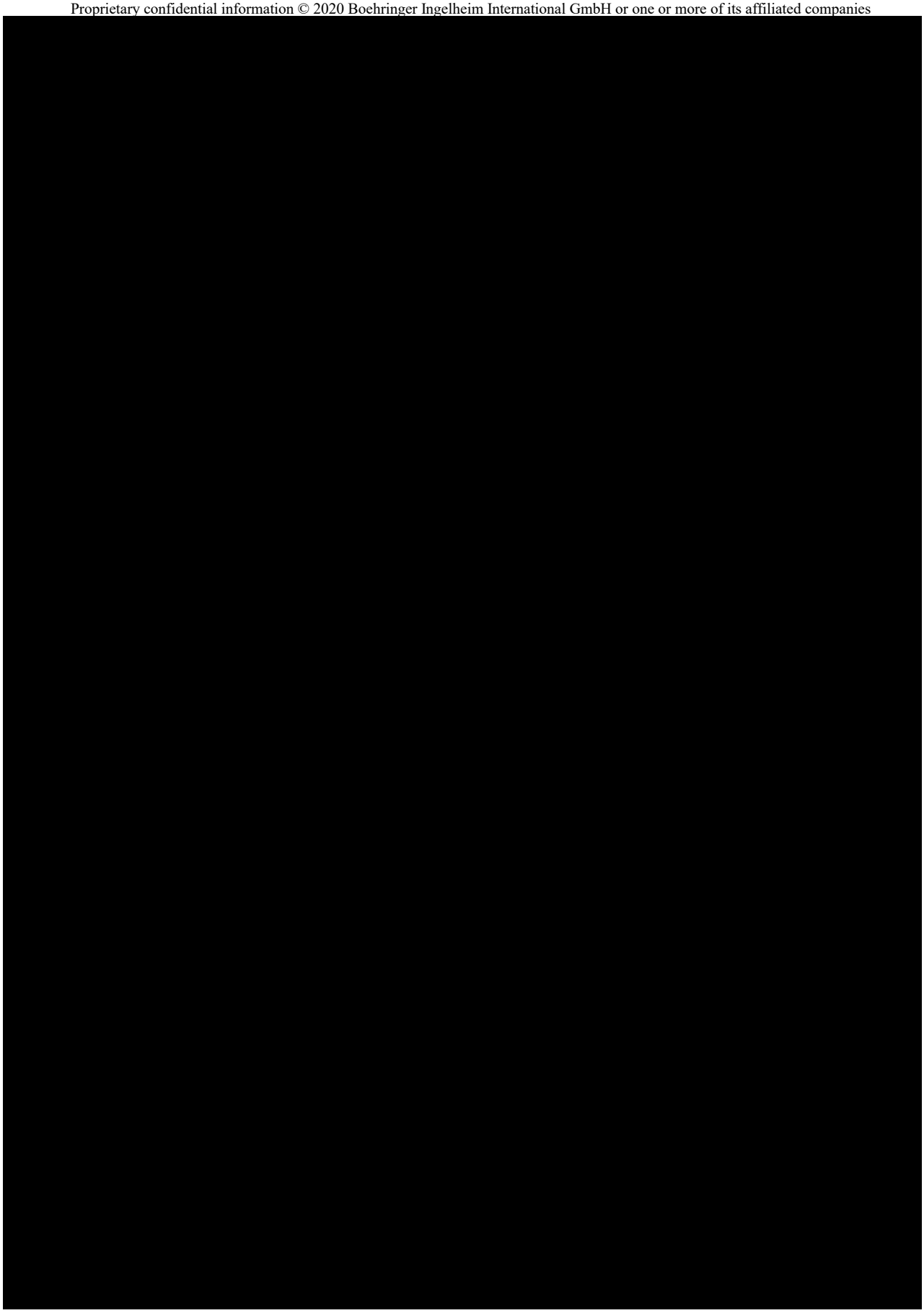

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1.4.2.1.4 Patient data

The substance has not been administered to patients so far.

1.4.2.1.5 Drug-induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety. Laboratory findings of an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) or findings of elevations of ALT and/or AST ≥10 fold ULN constitute a hepatic injury alert, and a trial subject showing these lab abnormalities needs to be followed up according to the 'DILI checklist' provided in the ISF. See also Section 5.2.6.1.4, adverse events of special interest.

1.4.2.2 Risks related to microdose midazolam

The evaluation of a potential CYP3A4 interaction with BI 1323495 using a microdose of midazolam is acceptable. The administered dose is 1/100th of a therapeutic dose and not expected to have any pharmacological effects. Microdoses of midazolam have been administered orally as a microdose in previous clinical studies without any reports of AEs [R17-3022, R17-3023]. Therefore, subjects are not exposed to undue risks. Also, the safety and tolerability evaluation of BI 1323495 should not be influenced.

1.4.2.3 Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein, and can cause syncopation. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

The total volume of blood withdrawn during the entire study per subject will be less than 500 ml and thus not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from blood withdrawals.

During Covid-19 pandemic, within the usual phase I settings, where subjects stay stationary at the site for several days in small groups, there is a potential risk for spreading the infection within the group/to the site staff, if an infected subject was enrolled into the trial. Also, there are trial procedures, e.g. collecting blood samples, recording of ECG, or assessing vital signs, that are impossible to perform from a distance of 1.5 to 2 meters, which is the generally

recommended distance to keep between humans, in order to prevent the transmission of SARS-CoV-2.

Risk mitigation:

- A risk management plan has been set up at the site detailing specific cautionary measures, e.g. hygiene rules, wearing of face masks and physical distance which is filed in the ISF.
- In addition, a screening on SARS-CoV-2 has been implemented, to be performed as part of the safety assessments on Day -4 to -2. Subjects positive in the SARS-CoV-2 test will be informed about the test result and that they are not eligible to the trial in accordance to exclusion criterion #24, prior to coming to the site for stationary admission.
- In case COVID-19 is suspected in a subject during trial participation, SARS-CoV-2 testing is to be initiated without delay to enable treatment discontinuation according to the extended withdrawal criteria, i.e., based on a confirmed COVID-19 infection (see Section 3.3.4.1).

1.4.3 Discussion

The following general safety measures are planned to mitigate potential risks associated with the IMP BI 1323495:

- Dose selection for this trial is based on PK predictions derived from clinical data of a single rising dose trial (1405-0001) and a food effect trial (1405-0007), as well as preclinical data (see IB and Section 4.1.2).

[redacted]

- exposures may exceed exposures that have as yet been observed in healthy volunteers in the single rising dose trial 1405-0001. In that trial, due to the less than linear increase of exposures with dose, the expected human therapeutic exposure range could just be reached for C_{max}, without establishing a safety margin, and could not be reached for AUC_{0-24}, in UGT2B17 EMs. Therefore, careful dose escalation (see Section 3.1) will be used to explore exposures above the limited SRD exposures. This will allow assessment of higher exposures that may be required for efficacy (also covering AUC and C_{min}). Dose

escalations will occur in the setting of a multiple rising dose trial under clinically tightly monitored conditions, in a fashion similar to that obtained in the first in man study 1405-0001.

- A Dose Escalation Committee (DEC) will be constituted which will ensure appropriate and documented safety review before deciding on each dose escalation step (see Sections 3.1 and 8.7). Only if the respective dose of BI 1323495 was safe and showed acceptable tolerability, also considering gender differences, and if no stopping criterion was met (see Section 3.3.4.2) within a dose group, the next dose group will be started at least 7 days after last subject completed End of Treatment of the previous dose group.
- Estimation of exposures for subsequent dose groups will be done based on preliminary PK values of preceding dose groups [redacted]
- To reduce PK variability, UGT2B17 EMs and PMs will be included in separate parts (Part I: EMs; Part II: PMs) of the study and will be administered different dose ranges. [redacted]
- Part of the subjects within each dose group will be treated with placebo, which is considered standard in phase I trials, to allow for a reliable assessment of safety and tolerability.
- For safety reasons, each dose group of 12 subjects in Part I (9 on active, 3 on placebo) and 8 subjects in Part II (6 on active and 2 on placebo) will be divided into two cohorts. The first ("sentinel") cohort will consist of 4 subjects for Part I and Part II (3 on active, 1 on placebo). The second cohort will consist of 8 subjects in Part I (6 on active, 2 on placebo) and 4 subjects in Part II (3 on active, 1 on placebo). These two cohorts will be separated by at least 7 days (between first dose of the last subject of 1st cohort and first dose of the first subject of 2nd cohort) which is expected to cover the period until pharmacokinetic steady state is reached. Both cohorts will be dosed in a randomised fashion.
- Extensive safety laboratory assessments will be performed (see Section 5.2.3), particularly including parameters to monitor liver and renal function as well as infection.
- A thorough ECG monitoring comprised of repetitive 12-lead ECGs will be performed.

- Potential effects of BI 1323495 on embryo-fetal development have not yet been assessed, and no data are available from its use in pregnant women. Therefore BI 1323495 should not be administered to pregnant women and should not be used in women of child-bearing potential without adequate contraception.
- Upon start of treatment until Day 12, subjects will stay at the site being kept under medical surveillance under stationary conditions, and monitored for both expected and unexpected adverse events (see Flow Chart 1/2/3/4).
- Healthy subjects up to ≤ 70 years of age will be enrolled in this trial. Accordingly, exclusion criteria have been defined in order not to expose subjects within this age range to a particular risk due to the presence of concomitant conditions. In particular, subjects with a history of cardiovascular disease or evidence of clinically relevant ECG alterations will be excluded from participating in this trial. Neither non-clinical toxicity testing nor clinical safety in the first-in-human trial 1405-0001 have revealed a potential of BI 1323495 to be associated with cardiovascular adverse effects. The general risk-mitigation measures in this trial, i.e., step-wise dose escalations, dosing in two subcohorts within each dose level, and close medical surveillance during stationary stay during the entire treatment period, also serve to ensure that healthy subjects up to ≤ 70 years of age will not be exposed to any undue risks.
- Potential risks for the subject in relation to the COVID-19 pandemic situation have been evaluated together with the principle investigator. With regard to study treatment, no relevant impact is expected on the subject's health condition (like e.g. increased susceptibility to infections, immune suppression, or impaired lung function). In the very unlikely case that despite all implemented measures a COVID-19 case occurs in a trial subject while in the study, the withdrawal criterion for subjects experiencing an infection has been extended to also cover discontinuation of treatment in case of laboratory-confirmed COVID-19 disease.
- To minimize the risk that infected subjects take part in the trial, who might spread the infection to others, subjects are only to be admitted to the site for Visit 2 if fulfilling the strict criteria laid out by the Robert Koch Institute (RKI) in the current national testing strategy regarding admission or re-admission of patients to hospital, see: https://www.rki.de, particularly https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Teststrategie/Nat-Teststrat.html. This includes a negative PCR test (see Section 5.2.3), and patients need to confirm a symptom-free interval of 48 hours. As RKI recommendations may be subject to change, current recommendations will be re-assessed on a periodic basis and trial procedures adapted accordingly, if applicable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 1323495 in healthy subjects following bid or qd oral administration of multiple rising doses, each over an 11 day treatment period.

Secondary objectives are the exploration of the pharmacokinetics (PK), [redacted] This includes exploration of a therapeutic exposure range, a range not adequately achieved in the single-rising dose trial 1405-0001.

2.1.2 Primary endpoint

The primary endpoint to assess safety and tolerability of BI 1323495 is the percentage of subjects with treatment-emergent drug related Adverse Events. The timeframe for primary endpoint is from the first drug administration, until 7 days after the last drug administration, up to 18 days.

2.1.3 Secondary endpoints

The following pharmacokinetic endpoints are considered as secondary endpoints and will be determined if feasible:

After the first dose of BI 1323495:

- AUC_{0-12} (area under the concentration-time curve of the analyte in plasma over a time interval of 12 h after administration of the first dose)
- C_{max} (maximum measured concentration of the analyte in plasma after the first dose)
- Only for qd dosing: AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 24 h after administration of the first dose)

The time frame for secondary endpoints after the first dose of BI 1323495: Before the first drug administration and 20 minutes (min), 40 min, 1 hour (h), 1.5h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, and 12h after drug administration on Day1. For the qd dose group (EM DG7), an additional time point at 24h after drug administration on Day1 is considered.

After the last dose of BI 1323495:

- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)
- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)

The time frame for secondary endpoints after the last dose of BI 1323495: Before the last drug administration and 20 min, 40 min, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, and 12h after

the last drug administration on Day11. For the qd dose group (EM DG7), an additional time point at 24h after the last drug administration on Day11 is considered.

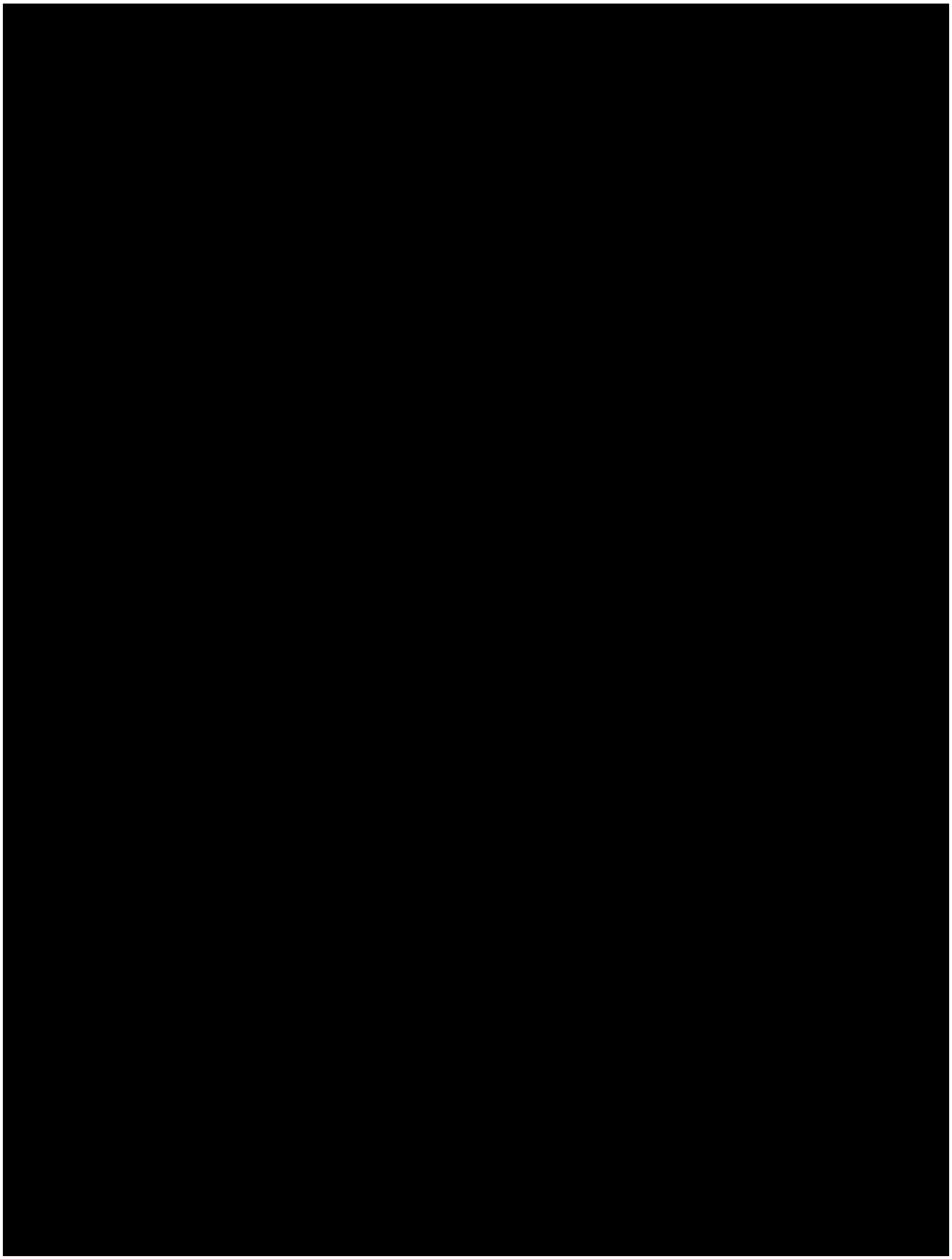
[redacted]

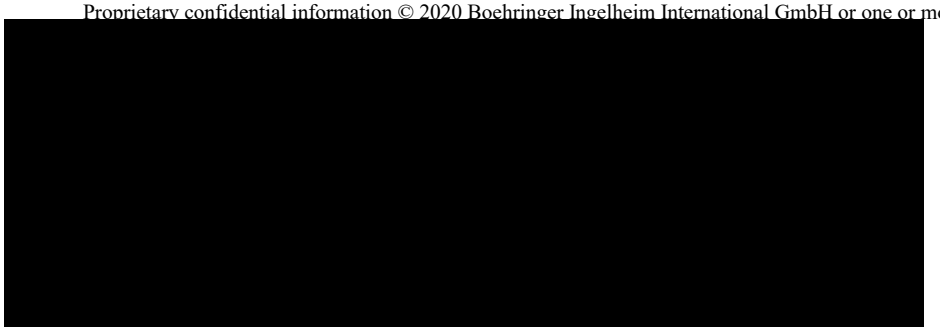
2.2.2.1 Safety and tolerability

Safety and tolerability of BI 1323495 will be assessed based on:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, aural body temperature)

[redacted]





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This multiple rising-dose trial will be randomised, double-blind within dose groups, and placebo controlled. Eligible population are healthy subjects of both genders and aged ≥ 18 and ≤ 70 years.

The trial consists of two parts. An overview on the main characteristics of the two parts is provided in the below table.

Table 3.1:1 Comparison of main characteristics of Part I and Part II of the trial

Topic	**Part I**	**Part II**
Eligibility	UGT2B17 genotypes *1/*1 and *1/*2 "Extensive Metabolizer (EM)" subjects	UGT2B17 genotype *2/*2 "Poor Metabolizer (PM)" subjects
Dose groups	6 EM dose groups: 5 bid dose groups: 10 mg, 30 mg, 70 mg, 120 mg*, 150 mg 1 qd dose group**: 120 mg	2 PM dose groups: 10 mg, 30 mg bid
Sample size per dose group	9 subjects will receive BI 1323495 3 subjects will receive placebo	6 subjects will receive BI 1323495 2 subjects will receive placebo
Gender proportion requirement	Minimum 4 female subjects required per dose group	No restrictions for either gender applicable
Midazolam microdosing	Within the three highest bid dose groups	Not applicable
Assessment of biomarkers (PD)	As specified in the flowchart and in Section 5.4.	Not applicable
BI 1323495 metabolite sampling	In EM Dose Group 4	In PM Dose Group 2

* with global amendment 6, an intermediate dose of 120 mg bid was added

** with global amendment 7, a 120 mg *qd* dose group was added; and decision to finally not use the initially planned 300 mg bid dose group was implemented (see Section 4.1.2)

Start of the Part II dose groups is possible only after EM DG 3 is completed and the subsequent DEC meeting has come to a positive decision (see Section 3.1.1). Separate DEC

meetings will be held after completion of dose groups for trial parts I and II, allowing to independently decide for each part on further dose escalations. However, the totality of clinical safety and pharmacokinetic data available at the respective time point from both trial parts will be considered for the dose escalation decision.

Subjects will be enrolled (screened) in the trial once they have signed the informed consent. Subjects who are suitable after screening and who still meet the inclusion/exclusion criteria will be randomised into the treatment period in which they will receive either BI 1323495 or placebo. No concomitant therapy is allowed (restrictions see Section 4.2.2).

A total of 88 healthy male and female subjects will participate in the trial (Part I: 6 sequential groups of 12 subjects each, Part II: 2 sequential groups of 8 subjects each).

Note: with global amendment 6, an intermediate dose of 120 mg bid (DG 6) in EMs was added.
Note: with global amendment 7, a 120 mg qd dose group (DG 7) in EMs was added, and decision to finally not use the initially planned 300 mg bid dose group (DG 5) in EMs was implemented (see Section 4.1.2).

The addition of a dose group for the evaluation of safety findings would require a substantial amendment and could only be implemented after approval.

Only one dose is tested within each dose group.

Additionally, the potential for DDI with a CYP3A4 substrate will be assessed in the three highest bid dose groups of Part I. This will be conducted in parallel to BI 1323495 administration, using a microdose of midazolam (a sensitive CYP3A4 substrate) administered at 2 different time points (on Day -1 and Day 11/EoT) to examine potential CYP3A4 induction effects of BI 1323495.

The following figures show an overview over the visit structure. Detailed schedules of all relevant trial activities are provided in the Flow Charts 1, 2 and 3.

Table 3.1:2 Overview over visit structure for EM DG 1, EM DG 2, EM DG 7, PM DG 1 and PM DG 2 (without Midazolam), for details see Flow Charts 1/3/4.

Visit No.	**1**	**2**																**3**
Day	-28 to -1	-3 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18 to 21
Drug admin. morning			X	X	X	X	X	X	X	X	X	X	X						
Drug admin. evening			X	X	X	X	X	X	X	X	X	X							
Type of Visit	Ambulatory	Ambulatory/ Admission on day -1	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Discharge	Ambulatory	Ambulatory	Ambulatory	Ambulatory	Ambulatory

Table 3.1:3 Overview over visit structure for EM DG 3, EM DG 4, and EM DG 6 (with Midazolam), for details see Flow Chart 2.

Visit No.	1	2																	3
Day	-28 to -2	-4 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18 to 21
Drug admin. morning				X	X	X	X	X	X	X	X	X	X	X						
Drug admin. evening				X	X	X	X	X	X	X	X	X	X							
Midazolam admin.			X											X						
Type of Visit	Ambulatory	Ambulatory/ Admission on day -2	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Discharge	Ambulatory	Ambulatory	Ambulatory	Ambulatory	Ambulatory

For safety reasons, each dose group will consist of 2 cohorts. The trial medication will be administered accordingly:

Part I:

- Cohort 1: 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)
- Cohort 2: 6 subjects on active treatment and 2 subjects on placebo (in total 8 subjects)

Part II:

- Cohort 1: 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)
- Cohort 2: 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)

Between start of the last subject of the first cohort and start of second cohort there will be a time interval of at least 7 days (see Section 6.2.2).

Two cohorts (within one dose group) are considered as appropriate based on the clinical data from the first-in-man single-rising dose trial that investigated and confirmed the safety of single doses up to 600 mg. No acute effects were observed at exposures expected in this trial.

Within each trial part, treatment in the next higher dose group will only be started if the treatment in the preceding dose groups was safe and showed acceptable tolerability.

The dose groups to be evaluated are outlined in Table 3.1: 4 below.

Table 3.1:4 Dose groups

Dose Group	**EM DG 1, PM DG 1**	**EM DG 2, PM DG 2**	**EM DG 3***	**EM DG 4***	**EM DG 6***	**EM DG 7#**
Total daily dose (mg)	20	60	140	300	240	120
Dose strength (mg)	10	10	50+10	150	50+10	50+10
Posology§	1-0-1	(3)-0-(3)	(1+2)-0-(1+2)	1-0-1	(2+2)-0-(2+2)	(2+2)-0-0
No. of subjects per DG	EM DGs:12, PM DGs: 8					
No. of subjects receiving active drug	EM DGs: 9, PM DGs: 6					
No. of subjects receiving placebo	EM DGs: 3, PM DGs: 2					

* Subjects in the three highest EM bid dose groups will receive a microdose of midazolam (75 µg) on Day -1 (prior to the first administration of study medication) and at Day 11.
# with global amendment 7, a 120 mg qd dose group (DG 7) was added; and decision to finally not use the initially planned 300 mg bid dose group (DG 5) was implemented (see Section 4.1.2)
§ At day 11 only qd administration in all dose groups

The end of the trial is defined as "last subject completed" (i.e. EoS completed by the last subject in the trial). For further details regarding the definition of the end of the trial, please see Section 8.6.

3.1.1 Dose Escalation Committee review

The different dose groups will be investigated, within each study part, consecutively in ascending order of daily doses, maintaining a time interval of at least 7 days between last drug administration in the preceding dose group and first drug administration of the subsequent dose group. The decision to proceed to the next dose level, no matter if in Part I or Part II of the trial, will be based upon the safety and tolerability data of all preceding dose levels, which will be assessed by a Dose Escalation Committee (DEC, see Section 8.7). The next dose will only be given if, in the documented opinion of the DEC, no safety concerns arise in the previous dose groups (i.e. no dose-limiting events occur) and if none of the pre-specified trial-specific stopping criteria are met (Section 3.3.4.1).

The minimum data set for DEC review consists of the following data:

- Adverse events of the current and preceding dose levels (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of safety reviews and AE information may change prior to Database Lock).
- Results from 12-lead EGG of the current and preceding dose levels.
- Vital signs of the current and preceding dose levels.
- Clinical laboratory tests of the current and preceding dose levels.
- Check of criteria for stopping subject treatment as per Section 3.3.4.
- Preliminary PK data [redacted] from at least 5 subjects on active treatment [redacted] from previous dose group and exposure predictions for subsequent dose group, to make sure the next applied dose regimen will not exceed the predefined exposure limits.

[redacted]

The DEC will review unblinded data. As the DEC is reviewing data only retrospectively, i.e., after the relevant subjects have completed the trial, this is not considered as having impact on the Principal Investigator's blinded assessment of subjects during their trial participation.

Furthermore, an unscheduled safety review by the DEC can be requested anytime for any reasonable cause by the Principal Investigator or the sponsor of the study, e.g. because of any unforeseen adverse events.

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

This trial will investigate the safety and tolerability as well as pharmacokinetics of multiple rising doses of BI 1323495, administered twice daily or once daily together with a meal. As the therapeutic exposure range has not been reached following administration of single doses in trial 1405-0001 in UGT2B17 extensive metabolizers, [redacted] dose levels in this multiple-rising dose trial have been selected to explore necessary exposures in a Phase I setting.

[redacted]

With the rising-dose design, double-blind conditions regarding the subjects' treatment allocation (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to potential dose-dependent effects, but this design, also involving review of the data from each dose group by a Dose Escalation Committee (see Section 3.1.1), is inevitable when sequentially studying ascending doses in order to minimize subject risk.

Due to the small number of subjects, the study will not allow for hypothesis testing but will allow for gathering safety, PK, and PD data for decision on the definition and possible limitation of the number of dose levels to be explored in later clinical development trials.

The control group will be treated with placebo, which is considered standard in phase I trials, to allow for a reliable assessment of safety and tolerability and PD.

The group size (9 subjects in Part I and 6 subjects in Part II per active treatment group) is in general considered sufficient for the assessment of safety and tolerability as well as for the exploratory evaluation of pharmacokinetics, but will only allow for a descriptive analysis of pharmacodynamic effects (in Part I) (see Section 7.5). The number of 4 females per dose group in Part I (3 on active, 1 on placebo) is considered adequate to allow for an assessment of the effect of gender on pharmacokinetic parameters and on safety.

The treatment period of 11 days is considered adequate for collection of safety, pharmacokinetic, and pharmacodynamic data after multiple dosing at steady state to inform subsequent studies along the clinical development path. The treatment period is adequately covered by non-clinical toxicology data from animal studies.

[redacted]

A strong PK/PD relationship has been observed in the SRD trial. [redacted]

3.3 SELECTION OF TRIAL POPULATION

It is planned that 88 healthy subjects will be randomised. Subjects will be recruited from the volunteers' pool of the trial site.

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

No data on reproductive toxicology are available at this time, therefore male subjects will be included and female subjects either not of childbearing potential (i.e. postmenopausal or surgically sterilised) or women of childbearing potential willing and able to use a highly effective method of contraception as described in Section 4.2.2.3. The age range has been selected to allow the identification of postmenopausal women for the purpose of stratification by gender in the EM dose groups. The defined age range also enables the inclusion of healthy subjects representative for the typical age ranges of patients of both targeted indications, i.e., COPD and CF, which differ substantially: COPD is a disease of advanced age, with populations of typical large clinical trials in COPD having a mean age of > 60 years. Among CF patients, on the other hand, only few reach an age of > 50 years. Therefore, in order to also cover females of a CF-adequate age range, it is allowed that women of child-bearing potential are enrolled if they are willing and able to use adequate, non-hormonal contraception methods, as defined in Section 4.2.2.3. This is also expected to facilitate the identification of a sufficient number of female subjects to be recruited. The selected age

range will make the safety/tolerability information to be collected during this trial more meaningful.

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

Subjects will only be included in the trial if they meet the following criteria:

1. Healthy subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests.
2. Age of 18 to 70 years (inclusive).
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive).
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation.
5. For Part I: Subjects genotyped as UGT2B17 extensive metabolizers, i.e., carrying at least one functional allele of the UGT2B17 gene (*1/*1 or *1/*2).
   For Part II: Subjects genotyped as UGT2B17 poor metabolizers, i.e., carrying no functional allele of the UGT2B17 gene (*2/*2).
6. Male or female subjects.
   - For 'female subjects not of childbearing potential' at least one of the following criteria must be fulfilled:
     - Permanently sterile (permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy)
     - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea without an alternative medical cause (in questionable cases a blood sample with FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)
   - Female subjects of childbearing potential must use a highly effective contraception method from at least 30 days before the first administration of trial medication until 14 days after trial completion as described in Section 4.2.2.3.

3.3.3 Exclusion criteria

Subjects will not be allowed to participate if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR, or ECG) deviating from normal and assessed as clinically relevant by the investigator. In particular a marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) at screening.
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm.
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance; safety laboratory screening evaluation can be repeated a maximum of two times.

4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator or at risk of requiring concomitant drug therapy, e.g., gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, or hormonal disorder, diseases of the central nervous system (including, but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders.
5. History of cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair).
6. History of relevant orthostatic hypotension, fainting spells, or blackouts.
7. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients); mild seasonal allergy adequately managed by topic administration of drugs to eyes or nose is not excluded.
8. Subjects with a documented active malignancy, or malignancy for which the subject has undergone resection, radiation therapy, or drug therapy (e.g., cytostatic, protein kinase inhibitor, or immune checkpoint inhibitor therapy), within the last 5 years.
9. Subjects who have been previously randomised in this study.
10. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation).
11. Intake of an investigational drug in another clinical trial within 60 days, or within 5 half-lives of the investigational drug (whichever is longer), of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered.
12. Major surgery (major according to the investigator's assessment) performed within 6 weeks prior to randomisation or planned within 3 months after screening, e.g. hip replacement.
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day), also inability to refrain from smoking during in-house confinement.
14. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males) or any other drug abuse or positive drug screening.
15. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial.
16. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial.
17. Inability to comply with the dietary regimen of the trial site.
18. A history of additional risk factors for Torsade de Pointes (such as heart failure, hypokalaemia, or family history of Long QT Syndrome).
19. Subjects with veins unsuited for venipuncture (for instance, veins which are difficult to locate, access or puncture, veins with a tendency to rupture during or after puncture) as assessed by the investigator.
20. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study.

In addition, the following trial-specific exclusion criteria apply:

21. Male subjects with 'women of childbearing potential' (WOCBP) partner who are unwilling to use male contraception (condom or sexual abstinence) from the first

administration of trial medication until 30 days after the last administration of trial medication
22. Known relevant immunodeficiency, as judged by the investigator
23. Chronic or relevant acute infections
24. History and/or presence of tuberculosis; positive result for interferon gamma release assay (IGRA) (i.e., QuantiFERON TB-Gold), or history of pneumococcal infection
25. Positive results for Hepatitis B antigen, Hepatitis C antibodies, and/or human immunodeficiency virus (HIV) 1 antigen or HIV1/2 antibodies, at screening
26. Aural body temperature of more than 37.7°C on Day -3 to -1, or Day -4 to -2 for subjects receiving Midazolam microdosing.
27. Subjects who have received live or live-attenuated vaccine in the 4 weeks prior to dosing
28. C-reactive protein above upper limit of laboratory reference range at screening and/or on Day -3 to -1, or Day -4 to -2 for subjects receiving Midazolam microdosing.
29. Subjects with signs of current gingivitis/periodontitis. Inspection of the oral cavity will be performed by the investigator.
30. Current or history of relevant kidney, urinary tract diseases or abnormalities (e.g. nephrolithiasis, hydronephrosis, acute or chronic nephritis, renal injury, renal failure), according to investigator.
31. Estimated glomerular filtration rate (eGFR) according to CKD-EPI formula < 80 mL/min at screening.
32. Known clinically relevant impairment of liver function or clinically relevant laboratory abnormality at the screening visit (V1) regarding liver aminotransferases, alkaline phosphatase, gamma glutamyl transferase, bilirubin, serum albumin, as judged by the investigator.
33. Subjects with a known coagulopathy or abnormal coagulation laboratory parameters at screening, or subjects who, within 10 days prior to administration of trial medication, used any drug that could reasonably inhibit coagulation.
34. Females with a positive pregnancy test or breastfeeding.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.
If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.

At the time of discontinuation, an End of Treatment examination followed by an End of Study Visit will be performed as indicated in the Flow Chart 1/2/3/4, if possible, and the information will be recorded in the CRF.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the subject files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.6.2.1 and 5.2.6.2).

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.4.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

- The subject wants to discontinue trial treatment, without the need to justify the decision.
- The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment (see Section 4.2.2).
- The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.
- The subject experiences an infection with SARS-CoV-2 (as confirmed by PCR Test, see Section 5.2.3) or an infection requiring systemic antibiotic treatment.

In addition to these criteria, the physician may discontinue a subject at any time based on his or her clinical judgment.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the FC and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
3. The sponsor decides to discontinue the further development of the investigational product.
4. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment.

5. Dosing will be stopped upon occurrence of a serious adverse reaction or of severe non-serious adverse events considered as drug related by the investigator in 2 subjects on active treatment of the same dose group. No further subjects will be treated without thorough re-evaluation of the benefit-risk ratio.
6. Dosing will be stopped if at least 2 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline or absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording.
7. Dose escalation will be stopped if, based on preliminary PK results of preceding dose groups, the estimated systemic exposure (group gMean values) of the next dose level is expected to exceed a C_{max} of 1900 nM or an AUC_{0-24} of 11500 nM*h. In this case, one or two dose levels lower than the planned next dose level may be given, as long as the expected systemic exposure (group gMean values) of each dose is not expected to exceed the aforementioned thresholds.
8. Dose escalation will be stopped (within the relevant study Part, I or II) if at least one subject of the preceding dose group exceeds individual exposures of a C_{max} of 1900 nM or an AUC_{0-24} of 11500 nM*h.

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

3.3.5 Replacement of trial participants

In case some subjects do not complete the trial or there is not a sufficient number of subjects on active treatment within one dose group (see Section 3.1), the Clinical Trial Leader together with the Trial Clinical Pharmacokineticist and the Trial Statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he or she replaces.

Subjects withdrawn due to drug-related adverse events will not be replaced. In addition, the subjects will not be replaced in the following cases:

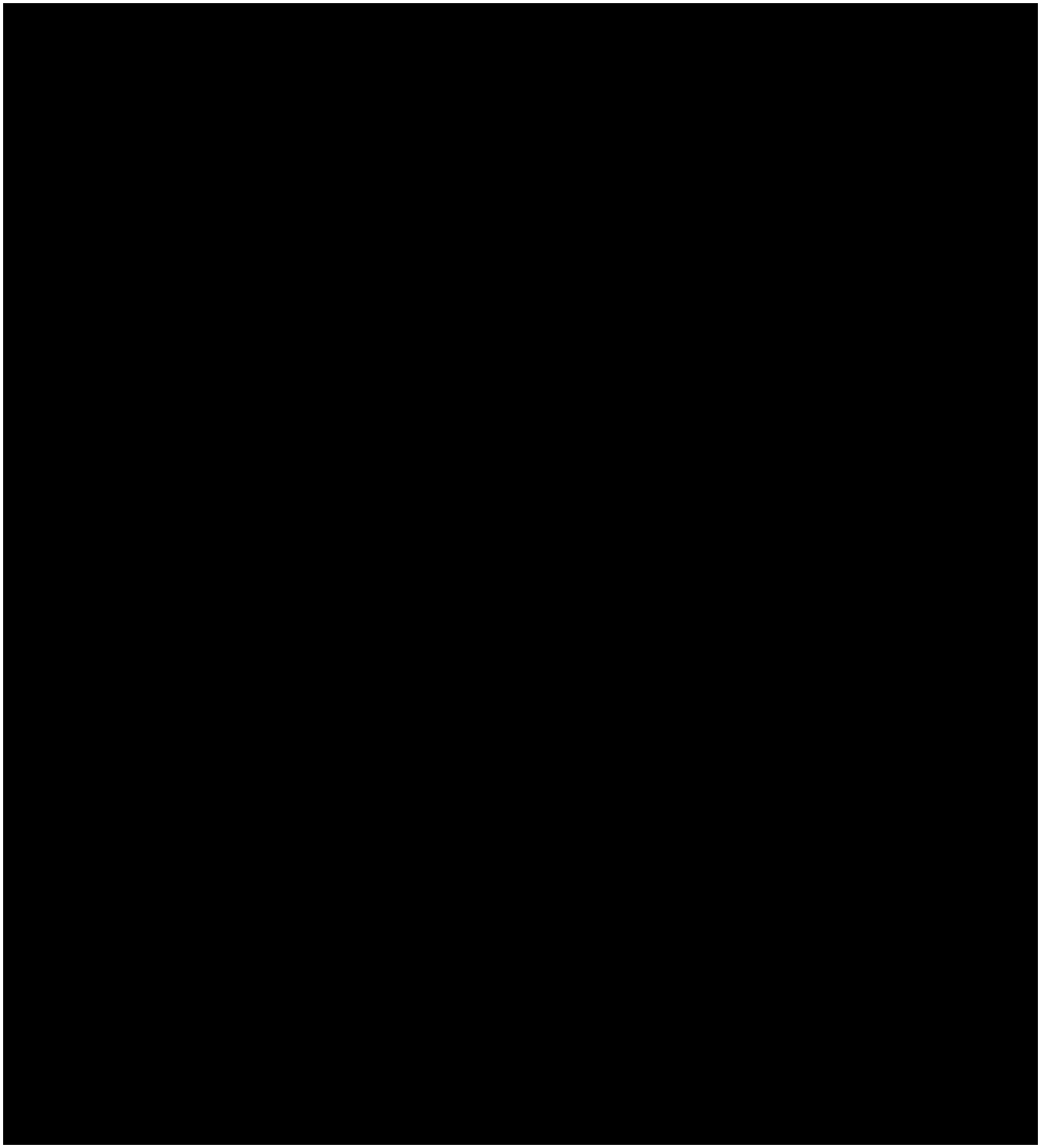
1. If a subject within the first cohort discontinues trial medication prior to reaching the decision point (at PK steady state) for the initiation of the second cohort of the current dose group, the safety decision would still be valid based on three subjects (of which at least 2 have to be on active treatment). No replacement is necessary to complete the first cohort.
2. Within a dose group, subjects will not be replaced, if at least 5 subjects on active treatment (for Part I: at least two per each gender) complete the trial.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products and Matching Placebo

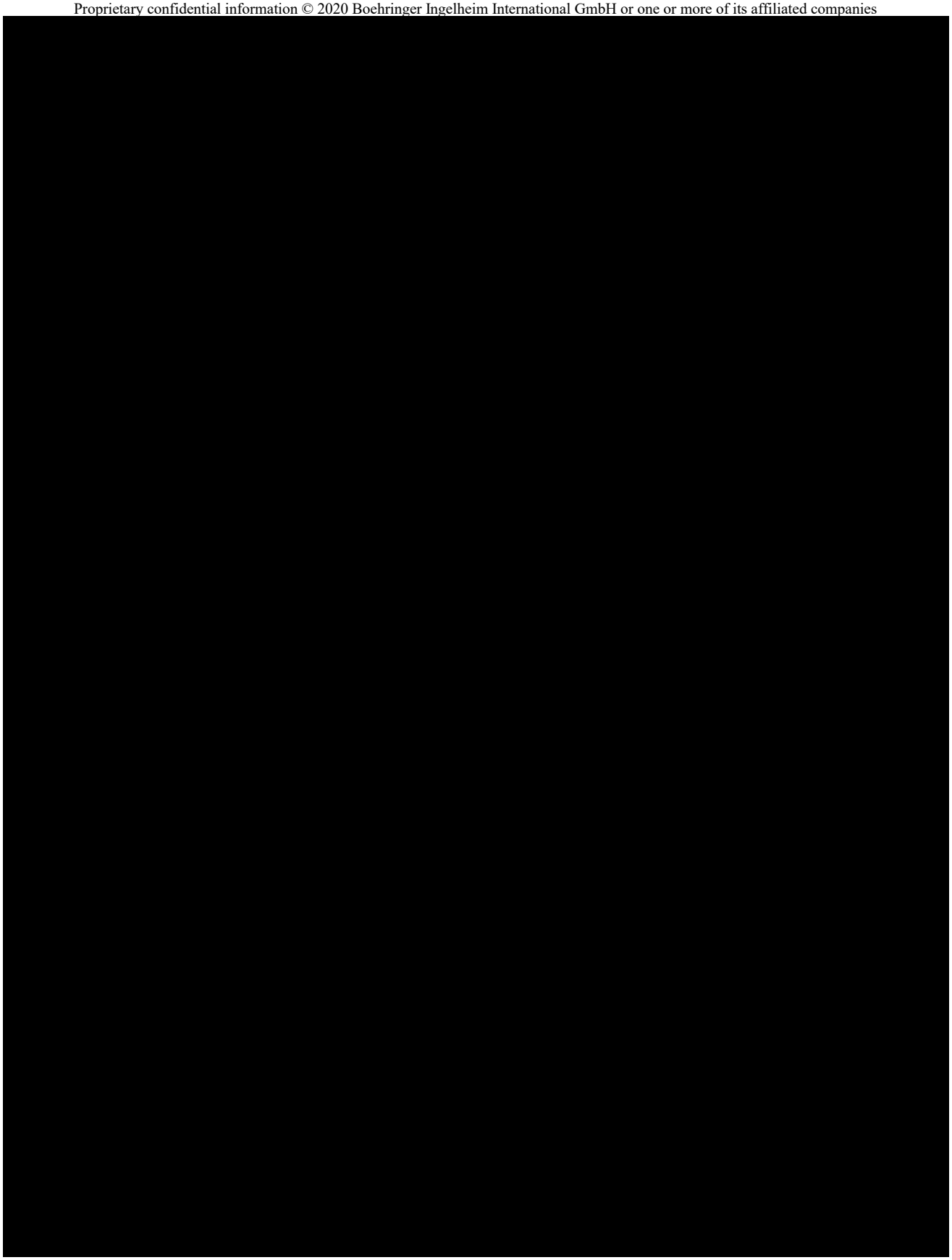
The investigational products used in this trial are manufactured by Boehringer Ingelheim



[redacted]

4.1.2 Selection of doses in the trial and dose modifications

[redacted]



Midazolam

For testing the potential of BI 1323495 to induce CYP3A, an oral dose of 75 µg midazolam has been chosen to be administered once in the absence of BI 1323495 and once at PK steady state following multiple doses of BI 1323495. This dose is within the definition of a microdose ($1/100^{th}$ of the therapeutic dose, or 100 µg, whichever is smaller). Since midazolam exposures have been shown to be dose proportional over the microdose-to-therapeutic-dose range, the microdose is considered adequate to accurately assess the CYP3A induction potential, while remaining below a pharmacologically active and toxicologically relevant concentration of midazolam.

For oral administration of midazolam, the preparation of the dose by dilution of the marketed solution for IV administration has been selected instead of preparation from the marketed oral solution. This decision was made as the preparation of a microdose of 75 µg with adequate precision and reproducibility requires dilution from the more highly concentrated original solution. Whereas data regarding the stability and compatibility of a dilution prepared from the solution for IV administration are available, this is not the case for a dilution prepared from the solution for oral administration. Furthermore, the IV solution contains midazolam in isotonic saline solution, while the oral solution has added excipients, which would result in additional elements of risk. Finally, there is the aspect of feasibility, whereby the oral

solution would need to be diluted 1:400, which may not be possible to be accurately achieved, while the IV solution requires a dilution of only 1:200. The IV solution of midazolam has been successfully diluted and administered orally as a microdose in previous clinical studies without any reports of AEs.

4.1.3 Method of assigning subjects to treatment groups

Prior to screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups (2 cohorts per dose group) according to their temporal availability.
In this trial a sentinel cohort design is used within each Dose Group. As soon as enough subjects have been allocated to the first cohort, the following subjects will be allocated to the second cohort of the respective dose group. Therefore, the allocation of subjects to cohorts is not influenced by trial personnel, but only by the subjects' temporal availability.
Prior to first administration of trial medication, eligible subjects will be randomised to receive active compound (BI 1323495) or matching placebo in a 3:1 ratio according to a randomisation plan.
The list of subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to trial subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a subject number by the method 'first come-first served'. Once a subject number has been assigned, it cannot be reassigned to any other subject.
The randomisation procedure is described in Section 7.5.
Subjects will first be randomised into Dose Group 1. Randomisation into a following dose group will only be possible after the DEC has cleared the next dose group for randomisation after assessment of all available data from the subjects of the preceding dose group (see Section 3.1).
In- and exclusion criteria are applicable for all dose groups.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4:1 below. The number of units for placebo corresponds to the number of units of the respective dose group of the active substance.

On Day 11, Subjects will receive a single dose in the morning only. On all other trial days, BI 1323495 will be administered bid (except for 120 mg qd dose group).

For safety reasons, each dose group will consist of 2 cohorts. The trial medication will be administered accordingly:

- Cohort 1 ("sentinel"): 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)
- Cohort 2: For Part I, 6 subjects on active treatment and 2 subjects on placebo (in total 8 subjects); for Part II, 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)

Between start of last subject of cohort 1 and start of cohort 2 there will be a time interval of at least 7 days. This ensures that the safety of subjects in cohort 1 who have reached pharmacokinetic steady state of BI 1323495 [redacted] will have been evaluated before subjects of cohort 2 start treatment.

In case safety data cannot be assessed for all 4 subjects of the first cohort of a dose group, safety data of at least two subjects on active study drug must be available for safety evaluation.

In the following paragraphs of this chapter, information regarding the evening dose (time, food intake etc.) is applicable for all bid dose groups. For the DG 7 with 120 mg qd, drug administration takes place only in the morning.

Subjects who qualify will be randomised to either BI 1323495 or placebo and will be instructed to self-administer the trial medication depending on the dose group that is open for randomisation at that timepoint. The morning dose will be administered to the subjects at the site under supervision of authorized site staff. Generally, subjects should take the study drug while in a standing or sitting position, as an oral dose together with about 240 mL of water. On first day of treatment (Day 1) and last day of treatment (Day 11), where PK profile sampling takes place, administration of BI 1323495 and administration of midazolam (Day -1, Day 11, Part I DG 3, 4, and 6) in the morning will be performed following a standardized breakfast, which is to start and be completed within 30 minutes before the scheduled dosing.

On all other treatment days and in the evening of Day 1, subjects should take the study medication with food, preferably within 30 min after a meal. On treatment days, breakfast will be provided 30 minutes prior to the morning dose administration and dinner will be provided 30 minutes prior to the evening dose administration.

Subjects should take their morning doses on all treatment days at the same time as on the first day, +/- 1 hour. The evening dose should be taken 12 hours +/-1 hour after the scheduled time of the morning dose.

Following the first administration of trial medication, subjects will stay in inhouse confinement until Day 12. During the first 2 h after drug administration, and in Part I DG 3, 4, and 6 in the first 2 h after midazolam administration on Day -1, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep. For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed double-blind with regard to the subjects and the investigator (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subject's treatment (active or placebo). According to the rising dose design, the current dose level will be known to subjects and investigators.
At the trial site, access to the randomisation schedule is restricted to unblinded pharmacist. The unblinded pharmacist together with a further staff member will assign the medication numbers to the random numbers. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF. Persons directly involved in the clinical conduct of the trial will not have access to the treatment allocation prior to database lock.

Regarding the sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical trial leader, clinical trial manager, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug

metabolism scientist as well as dedicated CRO personnel if not involved in the clinical conduct of the trial). The objective of the trial is not expected to be affected.
DEC Members will receive unblinded data, for details see Section 3.1.1.
Within the central ECG lab, the staff involved with interval measurements and morphological analyses will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via contact to the unblinded pharmacist or, in exceptional case of non-availability, by calling the emergency unblinding provider contracted for the trial (Global Emergency Unblinding & Medical Support in Clinical Trials). Instructions will be provided in the ISF, and subjects will receive the contact information on their Trial Identification Card. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The sponsor must be informed immediately. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who unblinded.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from [redacted] to access the randomisation code for individual subjects during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

4.1.6 Packaging, labelling, and re-supply

BI 1323495

Drug supplies will be provided by the [redacted]

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. The clinical trial supply containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use’ (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Subject or medication number

- Batch number

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

Examples of the labels will be available in the ISF.

Re-supply will be provided if applicable, e.g. in case of prolonged study timelines with regard to expiry dates. For details of packaging and the description of the label, refer to the ISF.

Midazolam solution for injection
Midazolam solution for injection will be obtained by the clinical trial site from a public pharmacy. The drug will be used out of the original, unmodified packages in order to prepare a dilution for oral administration. Instructions for dilution and application of Midazolam are provided in 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 storage conditions recommended on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Trial Manager (as provided in the list of contacts in the ISF) must be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,

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

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, 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 subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. All unused medication will

be disposed locally by the trial site upon written authorisation by the Clinical Trial Manager. The investigator or designee must verify that all unused or partially used drug supplies have been returned by the subjects and that no remaining supplies are in the investigator's possession.

Source data documentation and full drug accountability in regard to dispensed and returned medication to investigational site and to subjects is required.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

No special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. In particular, drugs must be avoided which are known to induce CYP3A4. Strong inhibitors of CYP3A4/P-gp have to be avoided in Part I, since a modest effect of the strong CYP3A4/P-gp inhibitor itraconazole on the PK of BI 1323495 has been observed (see Section 1.2.4). For PM subjects participating in Part II of the trial, inhibitors of CYP3A4/P-gp have to be avoided in general.

Live or live-attenuated vaccine should be avoided during the trial.

All concomitant therapy will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

On Day 1 and Day 11 where PK profile sampling is performed, while admitted to the trial site, the subjects are restricted from consuming any other foods or beverages than those provided by the site staff. Standardised meals will be served at the time points described in Flow Chart 1/2/3/4. A standardized normal caloric breakfast (e.g., a roll with cheese or sausage, including some dietary fat) should be served and finished within 30 minutes prior to dose administration. In addition, in Part I DG 3, 4, 6, and 7, breakfast will be served 30 minutes before midazolam intake on Day -1 and should be finished within 30 minutes prior to dose administration.

In the evening of Day 1 and on Days 2 to 10, drug intake should occur with food. Breakfast will be provided 30 minutes prior to the morning dose administration and dinner will be provided 30 minutes prior to the evening dose administration (for DG 7 with qd dosing, instructions regarding evening dose are not applicable).

On Days 1 and 11, from 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3.0 litres.

On Day -1 in Part I DG 3, 4, and 6, from 1 h before midazolam intake until 4 h after midazolam intake, fluid intake is restricted to the water administered with midazolam and an additional 240 mL of water served at 2 h and 4 h after midazolam (mandatory for all subjects).

During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the administration of trial medication until after the last PK sample is collected.

Methylxanthine-containing beverages or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 4 h before until 4 h after each administration of trial medication.

Smoking is not allowed during in-house confinement while admitted to the trial site.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the administration of trial medication until the EoS Visit.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.2.2.3 Contraception requirements

Women of child-bearing potential (WOCBP) must use one of the following 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, from at least 30 days before the first administration of trial medication until 14 days after trial completion:

- Use of intrauterine device (IUD) *plus* condom (Note: intrauterine hormone-releasing systems (IUS) will not be allowed).
- Sexual abstinence: This is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable.
- A vasectomised sexual partner who received medical assessment of the surgical success (documented absence of sperm) (see Section 3.3.2).

The investigator should take care to inform WOCBP that hormonal contraception methods are not considered highly effective in this trial. However, female subjects regularly taking hormonal contraception are not required to interrupt administration during the trial, as long as they are aware that the effectiveness of hormonal contraception may be reduced (see also Section 1.2.4), and another method (as described above) has to be used in addition.

Men able to father a child must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the subject information.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed

from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

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 1/2/3/4 including inspection of the oral cavity.
Measurement of height and body weight will be performed at the time points specified in the Flow Chart 1/2/3/4.
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 1/2/3/4, prior to blood sampling.
This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a supine position after at least 5 minutes of rest. The results must be included in the source documents available at the site.
Aural body temperature will be measured at the time points indicated in the Flow Chart 1/2/3/4.

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 see the Flow Chart 1/2/3/4. Reference ranges will be filed in the ISF.
Blood and urine samples will be analysed by the local laboratory of the site. Laboratory data will be collected and captured in the eCRF. Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automated blood cell count or if erythrocytes, leukocytes, nitrite, or protein are abnormal in the urinalysis, respectively.

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

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF). In this case, the amount of blood taken from the subject concerned will be increased due to the additional sampling.

Table 5.2.3:1 Safety laboratory tests

Functional lab group	Test name	A[1]	B[1]	C[1]	D[1]
Haematology	Haematocrit	X	X	X	X
	Haemoglobin	X	X	X	X
	Red Blood Cell Count/Erythrocytes (RBC)	X	X	X	X
	Reticulocyte count	X	-	-	-
	Reticulocytes/Erythrocyte	X	-	-	-
	White Blood Cells/Leucocytes (WBC)	X	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X	X
Automatic WBC differential, relative (per Leukocytes) and absolute	Neutrophils	X	X	X	X
	Eosinophils	X	X	X	X
	Basophils	X	X	X	X
	Monocytes	X	X	X	X
	Lymphocytes	X	X	X	X
Manual differential WBC relative (per Leukocytes) (if automated differential WBC is abnormal)	Polymorphonuclear neutrophils (segs)	X	X	X	X
	Band neutrophils	X	X	X	X
	Eosinophils	X	X	X	X
	Basophils	X	X	X	X
	Monocytes	X	X	X	X
	Lymphocytes	X	X	X	X
Coagulation	Activated Partial Thromboplastin Time (aPTT)	X	X	X	-
	Prothrombin time – INR (International Normalized Ratio)	X	X	X	-
	Fibrinogen	X	X	X	-
Enzymes	Aspartate transaminase (AST/GOT)	X	X	X	-
	Alanine transaminase (ALT/GPT)	X	X	X	-
	Alkaline Phosphatase [AP]	X	X	X	-
	Gamma-Glutamyl Transferase (GGT)	X	X	X	-
	Glutamate Dehydrogenase (GLDH)	X	X	X	-
	Creatine Kinase (CK)	X	X	X	-
	Creatine Kinase Isoenzyme MB (CK-MB), if CK is elevated	X	X	X	-
	Lactate Dehydrogenase (LDH)	X	X	X	-
Hormones	Thyroid Stimulating Hormone (TSH)	X	-	-	-
Substrates	Plasma glucose	X	X	-	-
	Creatinine	X	X	X	-
	GFR/ CKD-EPI	X	X	X	-
	Total bilirubin	X	X	X	-
	Direct bilirubin	X	X	X	-
	Total protein	X	X	X	-
	Albumin	X	-	-	-
	C-Reactive Protein (CRP)	X	X	X	-
	Uric Acid	X	-	X	-
	Urea	X	X	X	-
	Total cholesterol	X	-	X	-
	Triglycerides	X	-	X	-
Electrolytes	Sodium	X	X	X	-
	Potassium	X	X	X	-
	Chloride	X	X	X	-
	Calcium	X	X	X	-

Table 5.2.3:1 (continued) Safety laboratory tests

Functional lab group	Test name	A[1]	B[1]	C[1]	D[1]
Urinalysis[2] (Stix)	Urine nitrite (qual)	X	X	X	-
	Urine protein (qual)	X	X	X	-
	Urine glucose (qual)	X	X	X	-
	Urine ketone (qual)	X	X	X	-
	Urobilinogen (qual)	X	X	X	-
	Urine bilirubin (qual)	X	X	X	-
	Urine RBC/erythrocytes (qual)	X	X	X	-
	Urine WBC/leucocytes (qual)	X	X	X	-
	Urine pH	X	X	X	-
Urine sediment[2] (microscopic examination, if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	X	X	X	-

[1] A, B, C, and D are different sets of laboratory assessments. The Flow Chart 1/2/3/4 defines at what time point which set is to be investigated
[2] Urinalysis/urine sediment only at screening, Day 11 and Visit 3.

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 results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests at screening only. Pregnancy testing in women will be performed at screening, prior to each treatment start, and as part of the end of study examination. Drug screening will be performed at screening and prior to treatment start.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qual) Hepatitis B core antibody (qual) Hepatitis C antibodies (qual) HIV-1 and HIV-2 antibody (qual)
Immunology*	Interferon-ɣ release assay to tuberculosis (qualitative), e.g. QuantiFERON®-TB-Gold Test
Molecular Diagnostics**	PCR test for detection of SARS-CoV-2 according to recommendations of Robert-Koch-Institute in Germany (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Entlassmanagement.html) i.e. performed on two swabs obtained at the same time from oro- and nasopharynx (single PCR test sufficient after transfer of two swabs from oro- and nasopharynx to the same transport media, or use of the same swab in both oro- and nasopharynx)

*Test results already available for a subject do not have to be repeated, if assessment took place within 4 weeks before randomisation
**Applicable to Part I DG 3, DG 4, DG 5, and DG 6; and Part II DG 1 and DG 2, to be performed on Visit 2 Day -4 to -2, and at any time if COVID-19 infection is suspected

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 7410, [redacted]) will be performed prior to treatment, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

5.2.4 Electrocardiogram

5.2.4.1 12 –lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised system at the time points given in the Flow Chart 1/2/3/4. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart 1/2/3/4. Recording time points may be adapted based on information obtained during the trial. Such changes would be implemented as non-substantial amendment.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 sec applies as well. The repeat ECGs are assigned to the respective scheduled time point.

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

Storing

All ECGs will be stored electronically on the system provided by [redacted]. Screening and EoS ECGs will not be transferred to central ECG lab.

Data transfer

For time points specified in the Flow Chart 1/2/3/4, ECGs will be transferred electronically to the central ECG lab ([redacted]) for evaluation.

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab.

Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) Central ECG laboratory

Central ECG lab evaluation will be performed for the first of three replicate ECGs per time point as specified in the Flow Chart 1/2/3/4.

RR and QT intervals will be determined semi-automatically, whereas PR, QRS intervals, and QRS-axis are measured automatically by a validated GE 12-SL-algorithm or equivalent.

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

All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.
For automatic interval measurements no lead will be provided. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

For blinding arrangements see Section 4.1.5. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the computerised ECG system or their manual corrections by the investigators will be used.

In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator.

Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Other safety parameters

This section is not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.6.1.3 AEs considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported

as described in Section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

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

The latest list of "Always Serious AEs" can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the subjects 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.

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, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge,

confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end time, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart 1/2/3/4. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until the individual subject's end of trial:
  - All AEs (serious and non-serious) and all AESIs.
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
  The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however not be reported in the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject 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 a written consent of the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and exact clock time of drug administration and pharmacokinetic sampling for BI 1323495 and Midazolam will be recorded in the eCRF.
The actual sampling times will be used for determination of pharmacokinetic parameters.
PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g., preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 ml. Such changes would be implemented via non-substantial CTP amendments.
If a subject has to be withdrawn from treatment at one of the above mentioned time points and the PK sample was already obtained, this PK sample might be registered as EOS sample instead. It will be collected and analysed accordingly.

5.3.2 Methods of sample collection

5.3.2.1 Plasma sampling for pharmacokinetic analysis

BI 1323495

For quantification of BI 1323495 plasma concentrations, blood will be taken from an antecubital or forearm vein into an EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Charts 1/2/3. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.
For details, please see lab manual/ISF:

Midazolam

For quantification of midazolam and 1-OH midazolam plasma concentrations, blood will be taken from an antecubital or forearm vein into a K-EDTA (potassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart 2. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.
For details, please see lab manual/ISF:

BI 1323495, Midazolam and 1-OH midazolam

After completion of the trial, the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, assessment of metabolites. 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. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.3.2.2 Plasma sampling for metabolism analysis

Additional EDTA plasma samples for the identification of drug metabolites will be investigated in the 150 mg bid EM dose group (DG4 in Part I) and 30 mg bid PM dose group (DG2 in Part II) and will be pooled per dose group.
Based on the knowledge gained during the trial conduct, e.g. from preliminary PK results, the dose group may be changed to a different one. The change would be implemented via a non-substantial CTP Amendment.
The blood samples will be drawn in parallel to PK samples at Day 11 including the 24 h sample (see Flow Chart 2/3). At each of these time points, approx. 3 ml blood will be needed for metabolite analysis. The blood samples will be processed in the same way as the PK samples described in the lab manual.
Only data related to the parent compound and its metabolites will be acquired. Evaluation of the drug metabolism will be reported separately but not included in the CTR of this trial. The study samples will be discarded after completion of the experiments but not later than 5 years after the final study report has been signed.

5.3.2.3 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (within 3 h before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.
All urine voided during the sampling intervals indicated in the Flow Chart 1/2/3/4 will be collected in 2 L polyethylene (PE) containers and stored at room temperature. Subjects are told to empty their bladders at the end of each sampling interval.
The urine weight/volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done, i.e. 1 L is defined to be equal to 1 kg).
For details please see lab manual/ISF.

5.4 ASSESSMENT OF BIOMARKER(S)

5.4.1 Biochemical and cellular biomarkers

Biomarkers will be assessed to monitor pharmacodynamic drug effects over the course of the observation time. Assessment of biomarkers in blood will be done in all subjects.
Direct target engagement of BI 1323495 in blood will be evaluated in Part I of the trial [redacted]

5.4.1.1 Methods of sample collection

Blood samples will be taken at time points indicated in the Flow Chart 1/2/4.

A maximum of approximately 20 ml blood will be collected per biomarker sampling time-point per subject for the pre-specified biomarker analyses. This sums up to a total blood volume of approximately 60 mL collected for biomarker analyses over the 3 weeks observational period.

Detailed instructions for biomarker blood sampling, processing, storage and shipment of the different biofluids will be provided in the lab manual/site's ISF.

[redacted]

[redacted]

5.5 BIOBANKING

This section is not applicable.

5.6 OTHER ASSESSMENTS

This section is not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

[redacted]

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and pharmacodynamic parameters in an adequate way allowing for appropriate risk mitigation in a clinical trial during the early clinical development phase when only limited information is available yet on the IMP. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication.
The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are established assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Sections 5.4 are of exploratory nature.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period, an 11 days multiple dose treatment and a Follow-up period. The acceptable time windows for visits and trial procedures are given in the Flow Chart 1/2/3/4. Exact times of measurements outside the permitted time windows will be documented.

Screening Visit and Day -3 to -1 (or Day -2 to -4 for midazolam dose groups) may be combined if feasible.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 and Day 11 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

The acceptable deviation from the scheduled time for vital signs, ECG, PK and laboratory tests will be ± 15 min for the first 4 h after trial drug administration and ± 30 min thereafter. Starting from 48 h post administration a deviation from the scheduled time for vital signs, ECG and laboratory tests (including PK) of ±120 min is acceptable, except for V3 (EoS Visit), where a deviation of -120 min to + 72 h is acceptable.

If several activities are scheduled at the same time point in the Flow Chart 1/2/3/4, ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times and urine collection intervals refer to Flow Chart 1/2/3/4. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

6.2.1.1 Screening Period

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local regulations prior to enrolment in the study and before any study procedures are started.

Screening procedures include a complete medical examination (including documentation of demographics, smoking and alcohol history, medical history, inclusion/exclusion criteria, concomitant therapy), measurement of blood pressure, heart rate, body weight and height, 12-

lead ECG, as well as an assessment of laboratory values including drug and virological screening, and pregnancy testing in females will be performed.

If V1 takes place within the last three days before first drug administration, or first midazolam administration, respectively, and all required assessments are completed before V2/Day 1, the visit Day -3 to -1 (resp. Day -4 to -2 in the midazolam groups) and related assessments may be skipped.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

The subject should be recorded on the enrolment log as screened.

6.2.2 Treatment period

In any case, within the last three days before single dose administration, or midazolam administration, as applicable, subjects will visit the site and main eligibility criteria will be reviewed and safety lab performed.

Subjects will be admitted to the site in the evening before first drug administration on Day 1 (Part I: DG 1, DG 2 and DG 7, and Part II), and in the evening before first midazolam administration on Day -1 (Part I: DG 3, DG 4 and DG 6), respectively. A subject who is eligible for the study will be randomised into the current dose group and receive the first dose of BI 1323495 or placebo on Day 1. During treatment phase up to Day 10, each subject will receive multiple bid doses of BI 1323495 or placebo, or multiple qd doses of BI 1323495 or placebo in DG 7, and a last single dose on Day 11.

Trial medication will be taken orally by each subject under direct supervision of the investigator or [redacted] designee.

Study participants will stay at the site under medical surveillance during the treatment phase. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee, and return to further visits as indicated in the Flow Chart 1/2/3/4.

For details on time points and procedures for collection of blood and urine samples for PK analysis, refer to Flow Chart 1/2/3/4 and Section 5.3.2.

The safety assessments performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart 1/2/3/4.

For details on time points for all other trial procedures, refer to the Flow Chart 1/2/3/4. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

Safety evaluation between 1st and 2nd cohort of each Dose Group

Between start of the last patient of cohort 1 and start of cohort 2 there will be a time interval of at least 7 days. Subjects of cohort 2 will only enter treatment if the following safety-relevant data from the subjects in cohort 1, who are expected to have reached PK steady state [redacted] have been evaluated:

- Adverse events as recorded at that time

- Any findings from physical examination, vital signs, ECG assessment, or safety laboratory testing

Day 11 (End of Treatment)

On Day 11 in the morning, subjects will take their last dose of trial medication. For AE assessment, laboratory tests, ECG measurements, vital signs, and physical examination during the end of trial period, see Sections 5.2.1 to 5.2.6.

Male subjects with 'women of childbearing potential' (WOCBP) partner will be reminded to use male contraception (condom or sexual abstinence) until 30 days after the last administration of trial medication.

6.2.3 Follow up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.1 to 5.2.6.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the End of Study Visit.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained. All visit procedures of the Visits during Follow-up period Day 12 to Day 16 and at Visit 3 (Day 18 to 21) (EoS) Visit have to be completed as indicated in the Flow Chart 1/2/3/4.

Male subjects with 'women of childbearing potential' (WOCBP) partner will be reminded to use male contraception (condom or sexual abstinence) until 30 days after the last administration of trial medication.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 6 different dose groups of BI 1323495 in Part I and two different dose groups in Part II are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.
Confidence intervals will be computed and will be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Analysis sets
Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomised and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.
- Further PK and PD sets for different strata may be defined in TSAP, if needed.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the Integrated Quality and Risk Management Plan (IQRMP). IPDs will be identified no later than in the Blinded Report Planning Meeting, and the iPD categories will be updated as needed.

Pharmacokinetics
The pharmacokinetic parameters listed in Section 2.1 and 2.2 for drug BI 1323495 or midazolam and 1-OH midazolam will be calculated according to the relevant BI internal procedures.

Plasma and urine concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Blinded

Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol deviation may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma and urine concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- Missing samples/concentration data at important phases of PK disposition curve.

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. Inferential statistics is not planned here. The analysis will be based on the treated set (TS) and will be descriptive in nature. For Part I only, this analysis will be repeated for all categories of stratification factor (gender).

7.2.3 Secondary endpoint analyses

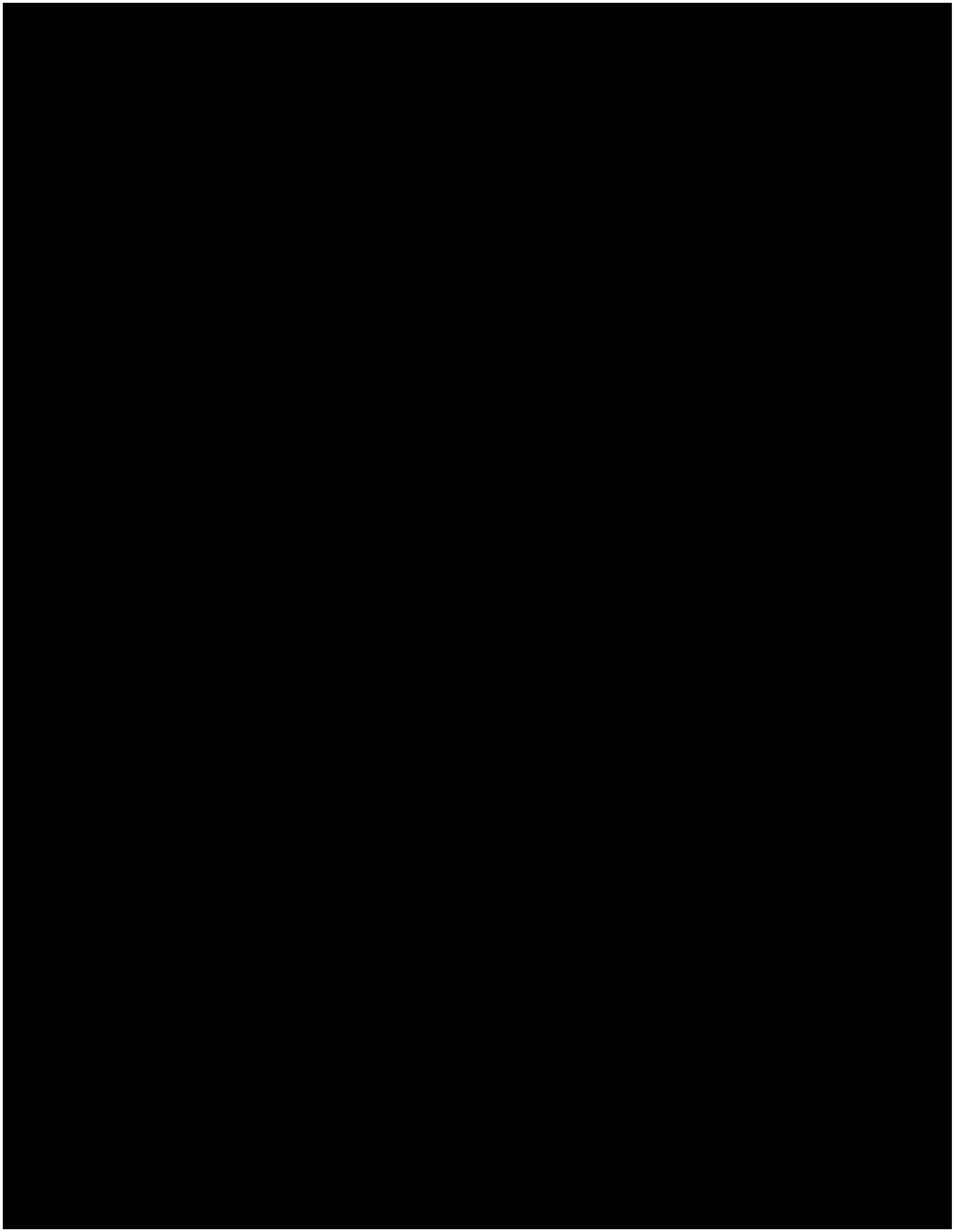
Primary analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively. Analyses will be performed for the parent drug.

Further exploratory analyses

[redacted]

[redacted]



[redacted]

7.2.5 Safety analyses

All treated subjects will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.
For all analyses the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Blinded Report Planning Meeting).
Treatments will be compared in a descriptive way. The placebo group in the safety evaluation will consist of all subjects treated with placebo, regardless of the dose group in which they were treated. The test treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between the first trial medication intake and end of REP (see Section 1.2.6) will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and post-study intervals).

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

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with

regard to frequency and percentage of subjects with abnormal values or clinically relevant abnormal values.

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

7.2.6 Other analyses

This section is not applicable.

7.2.7 Interim analyses

No interim analysis is planned for this trial.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

It is not planned to impute missing values for safety parameters.

7.3.2 Plasma/urine drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant BI internal procedure. Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule applies also to the lag phase, including the predose values).

7.3.3 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedure.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

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

The randomisation list will contain additional blocks to allow for subject replacement (refer to 3.3.5).

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 88 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8-12 subjects per dose group is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics. The sample size in the PM dose groups of 8 subjects (6 on active treatment and 2 on placebo) is lower than in the EM dose groups (12, of which 9 on active treatment and 3 on placebo), as an additional objective in the EM dose groups is the assessment of potential gender effects on exposures with BI 1323495. It is assumed that stratification by gender in each EM dose group leads to 8 trial subjects being males (6 on active treatment and 2 on placebo), whereas 4 will be females (3 on active treatment and 1 on placebo). Hence, the sample size of the PM dose groups, that do not look at potential gender effects, is equivalent to the sample size of the larger male subpopulation in the EM dose groups.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU 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 as will be treated as "protocol deviation".

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects 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 finalization of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, SUBJECT 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 subject participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative."
The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject 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 subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual subjects 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 subject. 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 subject 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.

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- ECG results (original or copies of printouts)
- 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 subject's participation in the trial (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a subject 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 subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site(s):

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site

as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

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

8.6 TRIAL MILESTONES

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

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

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 subjects 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 subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The Principal Investigator is responsible to coordinate tasks and responsibilities at the site as defined in a contract.

BI has appointed a Clinical Trial Leader (CTL), 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 (CTMs), Clinical Research Associates (CRAs), and investigators of participating countries.

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

The trial medication will be provided by the [redacted]

Midazolam-[redacted] solution for injection will be obtained by the clinical trial site from a public pharmacy.

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

The genotype assessment for eligibility determination will be performed by a central laboratory.

Logistics for PK, PD and biomarker samples will be coordinated by the site.

Safety laboratory tests will be performed in local laboratories selected by the investigational site.

All other laboratory analyses, i.e. PK and biomarker assessments, will be handled by central laboratory facilities.

The digitally recorded 12-lead ECGs will be submitted to a specialised contract research organisation for evaluation.

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

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.

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

Dose Escalation Committee

A Dose Escalation Committee (DEC) composed of Principal Investigator, the Team Member Medicine (TMM), the Trial Clinical Pharmacokineticist (TCPK), and the Clinical Trial Leader (CTL) will be established to review individual and aggregated safety data at regular intervals to determine the safety profile and risk/benefit ratio and decide on each dose escalation step.

Details of the DEC responsibilities and procedures are described in the DEC charter (see also Section 3.1.1).

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

This section is not applicable.

10.2 PHARMACOKINETIC METHODS AND ANALYSES

This section is not applicable in the trial.

10.3 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

This section is not applicable.

10.4 TRIAL BIOMARKER PLAN

This section is not applicable.

10.5 ADDITIONAL INFORMATION REGARDING IN/EXCLUSION CRITERIA

Calculation of number of pack years

$$\text{Pack years} = \frac{\text{Number of cigarettes/day}}{20} \times \text{years of smoking}$$

11. DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Date of amendment		4 Oct 2019
EudraCT number **EU number**		2018-004238-13
BI Trial number		1405-0002
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Flowchart 1 and Flowchart 2, sections 4.1.4 and 6.2.2, other minor locations within the document
Description of change		Previous visit schedule included ambulatory visits from Day 5 to Day 10. In the current visit schedule, all visits during treatment phase will be stationary. All relevant parts of the CTP have been updated accordingly.
Rationale for change		Due to competent authority request, to minimize safety or compliance related risks.
Section to be changed		3.1, other minor locations within the document
Description of change		Clarification that the implementation of an intermediate dose group via non-substantial amendment is possible if based on preliminary PK data if still within approved ranges, but not due to safety findings.
Rationale for change		Due to competent authority request.
Section to be changed		3.3.3
Description of change		Exclusion criteria, wording clarified for criterion #13 and

		adding a further condition to criterion #25.
Rationale for change		Due to competent authority request.
Section to be changed		3.3.4.3
Description of change		Clarification of criteria for trial discontinuation.
Rationale for change		Due to competent authority request.

11.2 GLOBAL AMENDMENT 2

Date of amendment		04 Mar 2020
EudraCT number **EU number**		2018-004238-13
BI Trial number		1405-0002
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis, 1.3, 1.4.2.1.2, 1.4.3, 3.3, 3.3.2 incl. crit. #6, 3.3.3 excl. crit. #35, 3.3.4, 5.2.6.2.4
Description of change		Inclusion of female subjects either not of child-bearing potential, or not pregnant/not breastfeeding and willing and able to use adequate highly effective contraception methods.
Rationale for change		Recruitment of female healthy volunteers not of child bearing potential only, as per the initial protocol, turned out to be a major challenge for the trial. BI 1323495 should not be administered to pregnant women and should not be used in women of child-bearing potential without adequate contraception. 1. Potential effects of BI 1323495 on embryo-fetal

		development have not yet been assessed, and no data are available from its use in pregnant women. There is no evidence indicating human teratogenicity or fetotoxity, 2. Short term exposure of only 10.5 days in this trial under adequate contraception appears justifiable. 3. This will allow including also females representing the age range of the relevant target population of patients with cystic fibrosis.
Section to be changed		Flowchart 1 and Flowchart 2, both footnote 12, 6.1
Description of change		Time to perform procedures prior to drug administration on Day 1 and Day 11 changed from 2 h to 3 h.
Rationale for change		Minor administrative change to facilitate conduct of trial procedures at the site.
Section to be changed		1.2.4, 1.2.7, 4.2.2.1
Description of change		Added new information from trial 1405-0009: modest effect on BI 1323495 exposure upon co-administration of a strong CYP3A4 inhibitor, with the consequence that concomitant treatment only with strong (not all) CYP3A4/P-gp inhibitors is to be avoided, no safety issues reported.
Rationale for change		New information available
Section to be changed		1.4.3, 4.2.2.3
Description of change		Added instruction on adequate, non-hormonal contraception methods
Rationale for change		Inclusion of WOCBP is only justifiable with adequate highly effective contraception. Due to potential CYP3A4 induction by BI 1323495, hormonal contraception might be less effective, thus instruction on acceptable highly effective contraception methods is provided.
Section to be changed		3.1.1
Description of change		Added details on how the population PK model is updated to predict exposure in the next dose group.
Rationale for change		Clarification of procedures for exposure predictions for subsequent dose groups
Section to be changed		Table 3.1:1, Table 3.1:2
Description of change		Correction of screening phase start from -84 days to -21 days
Rationale for change		Correction
Section to be changed		3.3.3 Excl. crit. #7

Description of change		Added that mild seasonal allergy adequately managed by topic administration of drugs to eyes or nose is not excluded.
Rationale for change		Clarification of exclusion criterion.
Section to be changed		Table 4.1.4:1
Description of change		Number of units per administration in Dose Group 1 changed from 2 tablets bid to 1 tablet bid
Rationale for change		Correction
Section to be changed		Table 5.2.3:2
Description of change		Added Immunology lab group/ tuberculosis assay
Rationale for change		Clarification (in alignment to 3.3.3, excl. crit. #25)
Section to be changed		5.2.6.2.2
Description of change		Removed “via fax” from SAE reporting instruction
Rationale for change		More flexible wording, to adapt to potential future reporting procedure

11.3 GLOBAL AMENDMENT 3

Date of amendment		06 May 2020
EudraCT number **EU number**		2018-004238-13
BI Trial number		1405-0002
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Flowchart 2, 1.4.2 Risks, 1.4.2.1.1 Mode of action, 1.4.2.3

		Procedure related risks, 1.4.3 Discussion, 3.3.4.1 Discontinuation of trial treatment, 5.2.3 Safety laboratory parameters
Description of change		Implementation of risk assessment and risk mitigation procedures with regard to Covid-19 pandemic.
Rationale for change		At the time of completion Part I DG 2 in this trial, the COVID-19 pandemic emerged with worldwide impact on daily life. To allow for thorough evaluation of potential additional risks to trial participants in the course of this pandemic, the trial was temporarily put on hold after completion of Part I DG 2 and prior to the start of Part I DG 3. Potential additional risks for study participants with regard to COVID-19 have been evaluated and risk management measures implemented within the sections cited above.

11.4 GLOBAL AMENDMENT 4

Date of amendment		04 Jun 2020
EudraCT number **EU number**		2018-004238-13
BI Trial number		1405-0002
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Throughout the whole document
Description of change		Extending the subject population with subjects characterised by the genotype UGT2B17 *2/*2, so called “Poor Metabolizers”, i.e. including the investigation of

		safety and PK in these subjects in two dose groups. Previous Dose Groups are named Part I or EM Dose Groups, new Dose Groups are named Part II or PM Dose Groups. In the whole document the allocation of dose groups to either Part I or Part II of the trial was specified. Procedures or analyses only applicable to certain dose groups were clearly indicated.
Rationale for change		Extending the subject population by additional two dose groups to include poor metabolizers will allow the drug exposure to be effectively explored. Most other procedures remain unchanged.
Section to be changed		Flowchart 1, 2; Table 3.1:2; Table 3.1:3
Description of change		Screening window changed from 21 to 28 days
Rationale for change		Improve feasibility regarding subject recruitment
Section to be changed		Flow Chart 2, 4.1.3, 6.2.2
Description of change		Wording updated to clarify that allocation to treatment is not restricted to Day 1 (i.e. for Midazolam dose groups on Day -1)
Rationale for change		Correction/clarification
Section to be changed		Flowchart 3
Description of change		Flowchart added for the 2 additional PM dose groups
Rationale for change		The new Flowchart lists slightly different procedures for trial Part II
Section to be changed		1.2.7
Description of change		Addition new information from current trials
Rationale for change		New information available
Section to be changed		1.2.7.1, 4.2.2.1
Description of change		Inclusion of a statement that the effects of CYP3A4/P-gp inhibition in PM subjects have not yet been assessed, therefore treatment with drugs known to inhibit CYP3A4 must be avoided
Rationale for change		Specific information related to new subject sub-population
Section to be changed		1.4.2.1.3, 1.4.3
Description of change		The start of the first PM DG depends on the decision of DEC upon completion of EM DG 3
Rationale for change		The risk assessment performed prior to the start of PM DG1 1 should be based on the most current data

Section to be changed		2.1.2, 2.2.2.1
Description of change		"number" of subjects was replaced with "percentage"; Listing of safety assessment was moved to Section 2.2.1
Rationale for change		As number of subjects in EM and PM dose groups are different, percentage will be a better unit to compare results of primary endpoint for all dosing groups
Section to be changed		3.1
Description of change		Overview table included to highlight difference between Part I and Part II of the trial
Rationale for change		Inclusion of overview to enhance clarity
Section to be changed		3.2
Description of change		Addition of an evaluation regarding the inclusion of PM dose groups
Rationale for change		Relevant for rationale of current amendment
Section to be changed		Table 4.1.1:1 Test product
Description of change		Posology descriptions: information for PM dose groups added, posology entry for Midazolam corrected
Rationale for change		Update regarding inclusion of PM dose groups, correction of mistake
Section to be changed		4.1.6
Description of change		Wording changed to state that re-supply of study medication will be provided if applicable
Rationale for change		Update necessary due to prolonged trial duration e.g. due to additional dose groups
Section to be changed		Table 5.2.3:1
Description of change		Removed absolute values for manual differential WBC
Rationale for change		Test not required

11.5 GLOBAL AMENDMENT 5

Date of amendment		29 Sep 2020
EudraCT number **EU number**		2018-004238-13
BI Trial number		1405-0002

BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Comment: This protocol amendment implements administrative changes and does not meet the criteria of a substantial amendment according to sec. 10 (1) of the German GCP ordinance, or Article 10 a EU Directive 2001/20/EC		
Section to be changed		Flowchart 1/2/3, Table 3.1:2, Table 3.1:3, Table 5.2.3:1 footnote 2, Section 6.2.3
Description of change		A time window of +3 days was implemented to the End of Study Visit (Visit 3), changing the definition of the EoS Visit from “Day 18” to “Day 18 to 21”.
Rationale for change		For site and subjects the time window allows for more flexibility in planning the last study visit.

11.6 GLOBAL AMENDMENT 6

Date of amendment		04 Nov 2020
EudraCT number EU number		2018-004238-13
BI Trial number		1405-0002
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)

Global Amendment due to urgent safety reasons	☐
Global Amendment	☒

Comment: This non-substantial amendment is implemented to add an intermediate dose group following provisions as given in earlier versions of the protocol:
"Additional subjects may be entered to allow testing of an additional (intermediate) dose based on preliminary PK data). The approved highest dose for each of the two trial parts will not be exceeded. Thus, the actual number of subjects entered may exceed 76, but will not exceed 96 subjects. Such a change would be implemented as a non-substantial CTP amendment."

Section to be changed		4.1.2 Selection of doses
Description of Changes		Addition of a rationale for introduction of an intermediate dose group (EM DG 6, 120 mg bid).
Rationale For Changes		Requirement to provide a rationale for introduction of the intermediate dose group.
Section to be changed		Synopsis Flowchart 2 2.2.1 Further objectives 2.2.2.2 Further pharmacokinetic endpoints 2.2.2.3 Pharmacodynamic endpoints in Part I 3.1 Overall trial design and plan 4.1.1 Identity of IMP 4.1.4 Drug assignment 4.2.2.2 Restrictions on diet and lifestyle Table 5.2.3:2 Exclusionary laboratory tests 6.2.2 Treatment period 7.2.4 Further endpoint analyses 7.1 Null and alternative hypotheses 7.2.7 Interim analyses
Description of Changes		Addition of dose group 6 at text locations where the different dose groups are mentioned or listed.
Rationale For Changes		Introduction of an intermediate dose group (EM DG 6, 120 mg bid).
Section to be changed		1.2.7 Clinical Studies 1.2.7.1 Clinical Pharmacokinetics 1.2.7.2 Clinical Pharmacodynamics 1.2.7.3 Preliminary clinical safety data Table 4.1.2:1
Description of Changes		Addition of data and findings from new clinical data (from the completed dose groups of this trial).
Rationale For Changes		Provision of data to support the rationale for introduction of the intermediate dose group.

Section to be changed		1.4.3 Discussion 7.2.7 Interim analyses 7.2.3 Secondary endpoint analyses 7.2.4 Further endpoint analyses
Description of Changes		Minor changes of wording, addition of a further endpoint.
Rationale For Changes		New wording implemented for clarification/definition purposes.

11.7 GLOBAL AMENDMENT 7

Date of amendment		10 Dec 2020
EudraCT number		2018-004238-13
BI Trial number		1405-0002
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis Flowchart 1.3 Rationale for performing the trial 2.2.1 Further objectives 2.2.2.2 Further pharmacokinetic endpoints 3.1 Overall trial design and plan 3.2 3.2 Discussion of trial design, including the choice of control group 4.1.1 Identity of IMP 4.1.2 Selection of doses in the trial and dose modifications 4.1.4 Drug assignment 4.2.2.2 Restrictions on diet and lifestyle 6.2.2 Treatment period

		7.2.4 Further endpoint analyses
Description of Changes		At text locations where the different dose groups are mentioned or listed, 1. a 120 mg qd dose group (DG 7) in EMs has been implemented, and 2. in parallel it was clarified that the initially planned 300 mg bid dose group (DG 5) in EMs will not be used. At several of these text locations, wording was adapted to clarify that qd dosing takes place only in the morning, compared to bid dosing in the morning and in the evening.
Rationale For Changes		[redacted]
Section to be changed		Synopsis 2.1.3 Secondary endpoints 2.2.2.2 Further pharmacokinetic endpoints 7.2.3 Secondary endpoint analysis
Description of Changes		Wording was updated with regard to the qd dose group, in particular a new secondary endpoint AUC_{0-24} was added only applicable for qd dosing.
Rationale For Changes		Adaptation was required due to different dosing scheme in the new qd dose group.
Section to be changed		Synopsis 3.1 Overall trial design 3.3 Selection of trial population 7.5 Determination of sample size
Description of Changes		The sample size was updated to planned 88 healthy subjects, and wording regarding the possibility to implement additional (intermediate) dose groups based on preliminary PK values via non-substantial amendment was removed.
Rationale For Changes		Based on the available data from completed dose groups, the flexibility to implement additional dose groups is no

		longer relevant.
Section to be changed		Synopsis 3.1 Overall trial design and plan 3.3 Selection of trial population 7.5 Determination of sample size
Description of Changes		Wording was removed which described the possibility to increase the sample size by adding an (intermediate) dose group, via non-substantial amendment.
Rationale For Changes		Based on the currently available data, no further dose group will be implemented based on the initial protocol.
Section to be changed		Flowchart
Description of Changes		Flowchart 4 was added indicating times of drug administration and sampling for qd dose group
Rationale For Changes		Specific information on qd dosing and sampling times was implemented in line with the addition of a qd dose group.
Section to be changed		1.2.7.1 Clinical pharmacokinetics
Description of Changes		Data from the current trial was added, including the rationale to use a once-daily dosing schedule.
Rationale For Changes		New information from already completed dose groups were added as they had become available at the time of the amendment. [redacted]
Section to be changed		1.2.7.3 Clinical safety
Description of Changes		Content in this section, particularly the overview on number of subjects per dose group reporting treatment-emergent AEs in the current multiple-rising dose trial 1405-0002 (Table 1.2.7.3: 1), was updated.
Rationale For Changes		New data from already completed dose groups were included as they had become available at the time of the amendment.
Section to be changed		1.4.3 Discussion
Description of Changes		Reference regarding COVID-19 testing of trial subjects was updated.
Rationale For Changes		Updated information/advice on COVID-19 test strategy is available from Robert-Koch-Institute.

Section to be changed		4.1.2 Selection of doses
Description of Changes		PK predictions for qd dosing were included.
Rationale For Changes		PK predictions for qd dosing were added to provide the basis for dose selection in EM DG 7.
Section to be changed		7.2.1 General considerations, 7.3.2 Plasma/urine drug concentration – time profiles 7.3.3 Pharmacokinetics
Description of Changes		The references to specific BI Standard Operation Procedures was changed.
Rationale For Changes		The initial references have been changed at BI.
Section to be changed		Throughout the document
Description of Changes		Administrative updates or clarifications were implemented, reference to flow chart 4 was included.
Rationale For Changes		The mentioned updates were implemented where applicable.

APPROVAL / SIGNATURE PAGE

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Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	11 Dec 2020 11:38 CET
Approval-Therapeutic Area [redacted]		11 Dec 2020 11:42 CET
Approval-Team Member Medicine		11 Dec 2020 12:24 CET
Author-Trial Clinical Pharmacokineticist		11 Dec 2020 15:44 CET
Author-Trial Statistician		11 Dec 2020 15:47 CET
Verification-Paper Signature Completion		14 Dec 2020 11:34 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed