# Clinical Trial Protocol

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| | **Document Number: c08854973-04** |
| **EudraCT No.:** | 2015-005049-29 |
| **BI Trial No.:** | 1386.8 |
| **BI Investigational Product:** | BI 1467335 |
| **Title:** | Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects (double-blind, randomised, placebo-controlled within dose groups) |
| **Clinical Phase:** | I |
| **Trial Clinical Monitor:** | [redacted]<br>Phone: [redacted]<br>Fax: |
| **Principal Investigator:** | [redacted]<br>Phone: [redacted]<br>Fax: |
| **Status:** | Final Protocol (Revised Protocol (based on global amendment 3)) |
| **Version and Date:** | Version: 4.0 Date: 05 OCT 2016 |

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# CLINICAL TRIAL PROTOCOL SYNOPSIS

| | | | |
|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>Not applicable | | | |
| **Name of active ingredient:**<br>BI 1467335 | | | |
| **Protocol date:**<br>09 March 2016 | **Trial number:**<br>1386.8 | | **Revision date:**<br>05 OCT 2016 |

| | |
|---|---|
| **Title of trial:** | Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects (double-blind, randomised, placebo-controlled within dose groups) |
| **Principal Investigator:** | [redacted] |
| **Trial site:** | [redacted] |
| **Clinical phase:** | I |
| **Objectives:** | To investigate safety, tolerability, pharmacokinetics and pharmacodynamics following multiple rising doses of BI 1467335 |
| **Methodology:** | Double-blind, randomised, placebo-controlled within dose groups, parallel-group design |
| **No. of subjects:** | |
| **total entered:** | 36* |
| **each treatment:** | 12 per dose group (9 on active drug and 3 on placebo)<br>* Additional subjects may be entered to allow testing of an additional dose within the approved dose range on the basis of experience gained during trial conduct (e.g. preliminary PK, ECG and safety data),. In this case up to 48 subjects may be included. |
| **Diagnosis:** | Not applicable |
| **Main criteria for inclusion:** | Healthy male/female of non-childbearing potential subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m² |
| **Test product:** | BI 1467335, Powder for oral solution (PfOS) |
| **dose:** | Dose group 1: 10 mg BI 1467335, q.d.<br>Dose group 2: 15 mg BI 1467335, q.d.<br>Dose group 3: 20 mg BI 1467335, q.d. |
| **mode of admin.:** | Oral with 240 mL of water after an overnight fast of at least 10 h |
| **Comparator product:** | Solvent for Oral Solution (Sucralose 4 mg/ml + Menthol 2 mg/ml) as placebo |
| **dose:** | Not applicable |
| **mode of admin.:** | Oral with 240 mL of water after an overnight fast of at least 10 h |
| **Duration of treatment:** | 28 days with multiple doses of BI 1467335 q.d. |

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|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>Not applicable | | | |
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| **Protocol date:**<br>09 March 2016 | **Trial number:**<br>1386.8 | | **Revision date:**<br>05 OCT 2016 |
| **Criteria for pharmacokinetics:** | Secondary endpoints:<br>After the first dose: $AUC_{0-24}$ and $C_{max}$<br>After the last dose: $AUC_{0-24,28}$ and $C_{max,28}$<br><br>Further PK parameters of interest will be calculated as appropriate | | |
| **Criteria for pharmacodynamics:** | [redacted] | | |
| **Criteria for safety:** | Primary endpoint to assess safety and tolerability of BI 1467335 is the number [N (%)] of subjects with drug-related adverse events (AEs).<br>[redacted] | | |
| **Statistical methods:** | Descriptive statistics will be calculated for all endpoints.<br>Dose proportionality of BI 1467335 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed.<br>Linearity index will be estimated using a linear model providing a two-sided 95% CI, if $AUC_{0-\infty}$ is possible to determine and steady state is achieved.<br>[redacted] | | |

# FLOW CHART

| Visit | Day | Planned time (relative to first drug administration [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | PK $_{blood}$ [9] | PK $_{urine}$ [10] | PD $_{blood}$ [17] | 12-lead ECG [8] | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -21 to -3 | | | Screening (SCR)[1, 12] | x | | | | x | x | |
| 2 | -2 | -48:00[7] | 08:00 | Ambulatory visit | x | | | | x | x | x |
| | -1 | -12:00 | 20:00 | Admission to trial site | x[5] | | | | | | x |
| | 1 | -2:00 | 06:00 | Allocation to treatment[2] | x[13] | | x[2] | x[2] | x[2] | x[2] | x[2] |
| | | 0:00 | 08:00 | First drug administration | | x[14] | ▲ | x[2] | | | |
| | | 0:15 | 08:15 | | | x | \| | x | x | | |
| | | 0:30 | 08:30 | | | x | \| | x | x | x | |
| | | 0:45 | 08:45 | | | x | \| | x | x | x | |
| | | 1:00 | 09:00 | | | x[15] | \| | x | x | x | x |
| | | 1:30 | 09:30 | | | x | \| | x | x | | |
| | | 2:00 | 10:00 | 240 mL fluid intake and light breakfast[3] | | x | \| | x | x | x | x |
| | | 3:00 | 11:00 | | | x | \| | x | | | |
| | | 4:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | | x | ┼ | x | x | x | x |
| | | 6:00 | 14:00 | | | x | \| | x | | | |
| | | 8:00 | 16:00 | Snack (voluntary)[3] | | x | ┼ | x | x | x | x |
| | | 10:00 | 18:00 | Dinner[3] | | x | \| | x | | | |
| | | 12:00 | 20:00 | | | x | ┼ | x | x | x | x |
| | 2 | 24:00 | 08:00 | Drug administration[11] | | x[14] | ▼ | x[14] | x[2] | x[2] | x[2] |
| | 3 | 48:00 | 08:00 | Drug administration[11] | x | | | | x[2] | x[2] | x[2] |
| | 4 | 72:00 | 08:00 | Drug administration[11] | | x[14] | | | x[2] | | x[2] |
| | | 73:00 | 09:00 | Discharge from trial site (confirmation of fitness)[4] | | x | | | x | x | x |
| | 5 | 96:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | x[2] | x[2] |
| | 6 | 120:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | | | x[2] |
| | 7 | 144:00 | 08:00 | Ambulatory visit, Drug administration[11] | x | x[14] | ▲ | x[14] | x[2] | x[2] | x[2] |
| | | 145:00 | 09:00 | Discharge | | x | \| | | x | x | |
| | 8 | 168:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | ▼ | | x[2] | | x[2] |
| | 9 | 192:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | | x[2] |
| | 10 | 216:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | | x[2] |
| | 11 | 240:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | x[2] | x[2] |
| | 12 | 264:00 | 08:00 | Ambulatory visit, Drug administration[11] | x | x[14] | | | x[2] | x[2] | x[2] |
| | | 265:00 | 09:00 | Discharge | | x | | | x | x | x |
| | 13 | 288:00 | 08:00 | Ambulatory visit, Drug administration[11] | | x[14] | | | x[2] | x[2] | x[2] |
| | | 289:00 | 09:00 | Discharge | | x | | | x | x | x |
| | | 300:00 | 20:00 | Admission to trial site | x[5] | | | | | | x |

| Visit | Day | Planned time (relative to first drug administration [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | PK $_{blood}$ [9] | PK $_{urine}$ [10] | PD $_{blood}$ [17] | 12-lead ECG [8] | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 14 | 310:00 | 06:00 | | x[2] | | | | x[2] | x[2] | x[2] |
| | | 312:00 | 08:00 | Drug administration | | x[14] | ▲ | x[14] | | | |
| | | 312:15 | 08:15 | | | x | \| | | x | | |
| | | 312:30 | 08:30 | | | x | \| | | x | x | |
| | | 312:45 | 8:45 | | | x | \| | | x | x | |
| | | 313:00 | 09:00 | | | x[15] | \| | | x | x | x |
| | | 313:30 | 09:30 | | | x | \| | | x | | |
| | | 314:00 | 10:00 | 240 mL fluid intake and light breakfast[3] | | x | \| | | x | x | x |
| | | 315:00 | 11:00 | | | x | \| | | | | |
| | | 316:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | | x | + | | x | x | x |
| | | 318:00 | 14:00 | | | x | \| | | | | |
| | | 320:00 | 16:00 | Snack (voluntary)[3] | | x | + | | x | x | x |
| | | 322:00 | 18:00 | Dinner[3] | | x | \| | | | | |
| | | 324:00 | 20:00 | | | x | + | | x | x | x |
| | 15 | 336:00 | 08:00 | Drug administration[11, 12] | | x[14] | ▼ | | x[2] | x[2] | x[2] |
| | 16 | 360:00 | 08:00 | Drug administration[11] | | x[14] | | | x[2] | x[2] | x[2] |
| | 17 | 384:00 | 08:00 | Drug administration[11] | | x[14] | | | x[2] | x[2] | x[2] |
| | | 385:00 | 09:00 | Discharge from trial site (confirmation of fitness)[4] | | x | | | x | x | x |
| | 18 | 408:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | | x[2] |
| | 19 | 432:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | | x[2] |
| | 20 | 456:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | | x[2] |
| | 21 | 480:00 | 08:00 | Ambulatory visit, Drug administration[11] | x[2] | x[14] | ▲ \| | x[14] | x[2] | x[2] | x[2] |
| | | 481:00 | 09:00 | Discharge | | x | \| | | x | x | x |
| | 22 | 504:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | ▼ | | x[2] | | x[2] |
| | 23 | 528:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | | x[2] |
| | 24 | 552:00 | 08:00 | Ambulatory visit, Drug administration[11] | | | | | x[2] | | x[2] |
| | 25 | 576:00 | 08:00 | Ambulatory visit, Drug administration[11] | | x[14] | | | x[2] | x[2] | x[2] |
| | | 577:00 | 09:00 | Discharge | | x | | | x | x | x |
| | 26 | 600:00 | 08:00 | Ambulatory visit, Drug administration[11] | | x[14] | ▲ \| | | x[2] | x[2] | x[2] |
| | | 601:00 | 09:00 | Discharge | | x | \| | | x | x | x |
| | 27 | 624:00 | 08:00 | Ambulatory visit, Drug administration[11] | | x[14] | ▼ ▲ | | x[2] | x[2] | x[2] |
| | | 625:00 | 09:00 | Discharge | | x | \| | | x | x | x |
| | | 636:00 | 20:00 | Admission to trial site | x[5] | | \| | | | | x |

| Visit | Day | Planned time (relative to first drug administration [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | PK blood [9] | PK urine [10] | PD blood [17] | 12-lead ECG [8] | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 28 | 646:00 | 6:00 | | x[2] | | ┼ | | x[2] | x[2] | x[2] |
| | | 648:00 | 08:00 | Last drug administration | | x[14, 16] | ▼▲ | x[14] | | | |
| | | 648:15 | 08:15 | | | x[16] | ┼ | x | x | | |
| | | 648:30 | 08:30 | | | x[16] | ┼ | x | x | x | |
| | | 648:45 | 08:45 | | | x[16] | ┼ | x | x | x | |
| | | 649:00 | 09:00 | | | x[15, 16] | ┼ | x | x | x | x |
| | | 649:30 | 09:30 | | | x[16] | ┼ | x | x | | |
| | | 650:00 | 10:00 | 240 mL fluid intake and light breakfast[3] | | x[16] | ┼ | x | x | x | x |
| | | 651:00 | 11:00 | | | x[16] | ┼ | x | | | |
| | | 652:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | | x[16] | ┼ | x | x | x | x |
| | | 654:00 | 14:00 | | | x[16] | ┼ | x | | | |
| | | 656:00 | 16:00 | Snack (voluntary)[3] | | x[16] | ┼ | x | x | x | x |
| | | 658:00 | 18:00 | Dinner[3] | | x[16] | ┼ | x | | | |
| | | 660:00 | 20:00 | | | x[16] | ┼ | x | x | x | x |
| | 29 | 672:00 | 08:00 | Ophthalmological investigation[12] | | x[16] | ▼ | x | x | x | x |
| | | 673:00 | 09:00 | Discharge from trial site (confirmation of fitness)[4] | | | | | | | |
| | 30 | 696:00 | 08:00 | Ambulatory visit | x | x | | x | x | x | x |
| | 31 | 720:00 | 08:00 | Ambulatory visit | | x | | | | | x |
| | 32 | 744:00 | 08:00 | Ambulatory visit | | x | | x | | | x |
| | 34 | 792:00 | 08:00 | Ambulatory visit | | x | | x | | | x |
| | 36 | 840:00 | 08:00 | Ambulatory visit | | x | | x | | | |
| | 38 | 888:00 | 08:00 | Ambulatory visit | | x | | x | | | |
| | 40 | 936:00 | 08:00 | Ambulatory visit | | x | | x | | | |
| 3 | 42 to 48 | | | End of trial (EOT) examination[4, 5, 12] | x | | | x | x | x | x |

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the respective procedure is to be performed and completed within 2 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. Confirmation of fitness includes physical examination.
5. Urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time point.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
7. Safety laboratory, ECG, blood pressure assessment and AE questioning to be done and medically evaluated within 3 days prior to first administration of study drug; this visit can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. The ECG recording has to be performed as triple on Day 1 and Day 2, Day 14 and Day 15, Day 21, Day 28 and Day 29. All other ECG recordings will be single ECGs.
9. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 510 mL per subject.

10. A blank urine sample (x) is to be obtained prior to the first administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) [on Day 1, Day 14 and Day 28 fractionated sampling 0-4, 4-8, 8-12, and 12-24 h, otherwise 0-24 hour collection].
11. Administration under fasting conditions, light breakfast (or snack) 2 h p.a.
12. Ophthalmological examinations (exclusion of cataract).
13. Includes a blood sample for pharmacogenetic analysis.
14. Samples to be drawn immediately (within 30 minutes) prior to drug administration.
15. Additional blood samples for stability testing in the 10 mg and 15 mg dose group.
16. Additional blood samples for metabolite analysis.
17. Analysis of selected PD samples may be omitted based on information obtained during the trial.

# TABLE OF CONTENTS

[redacted]

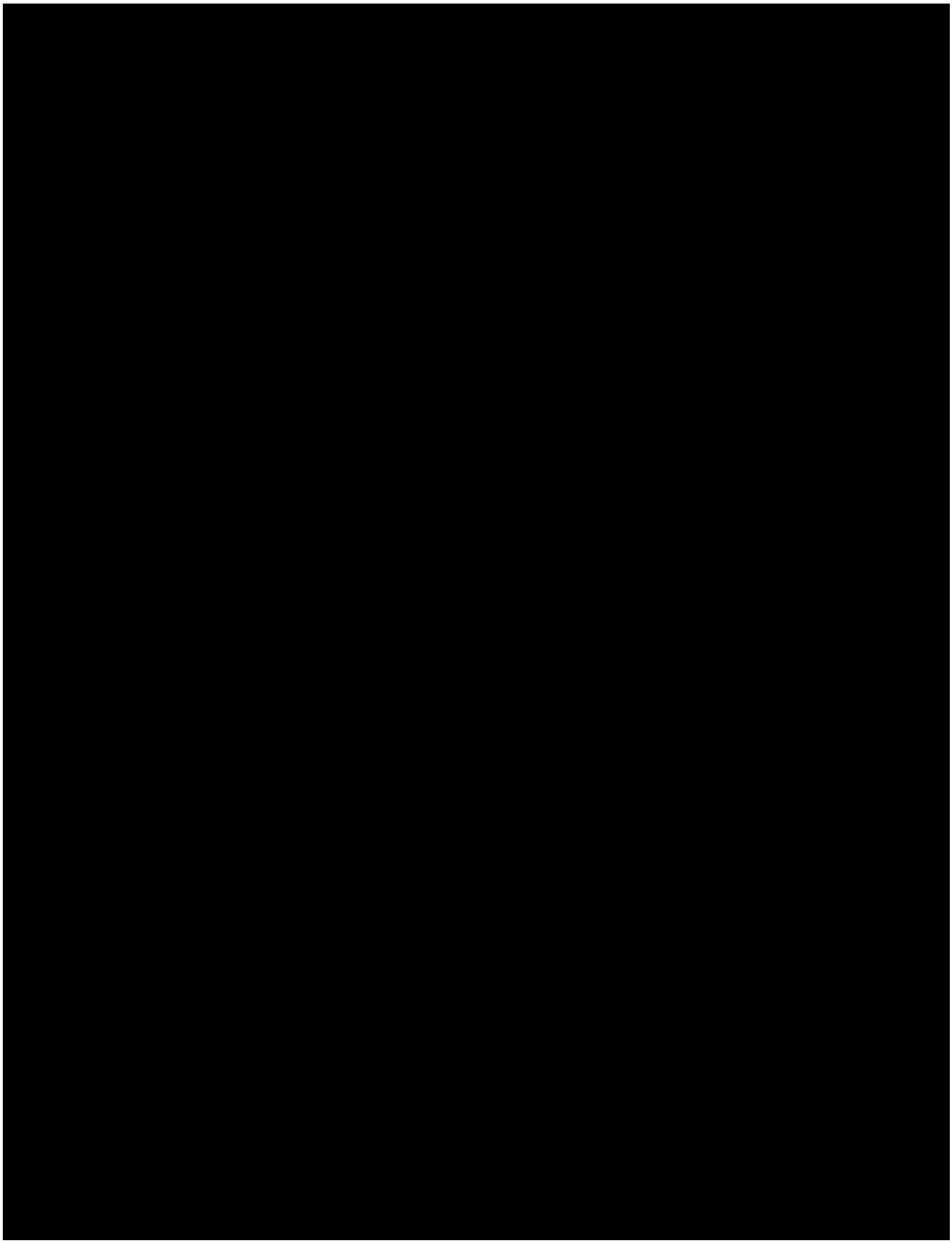
# ABBREVIATIONS

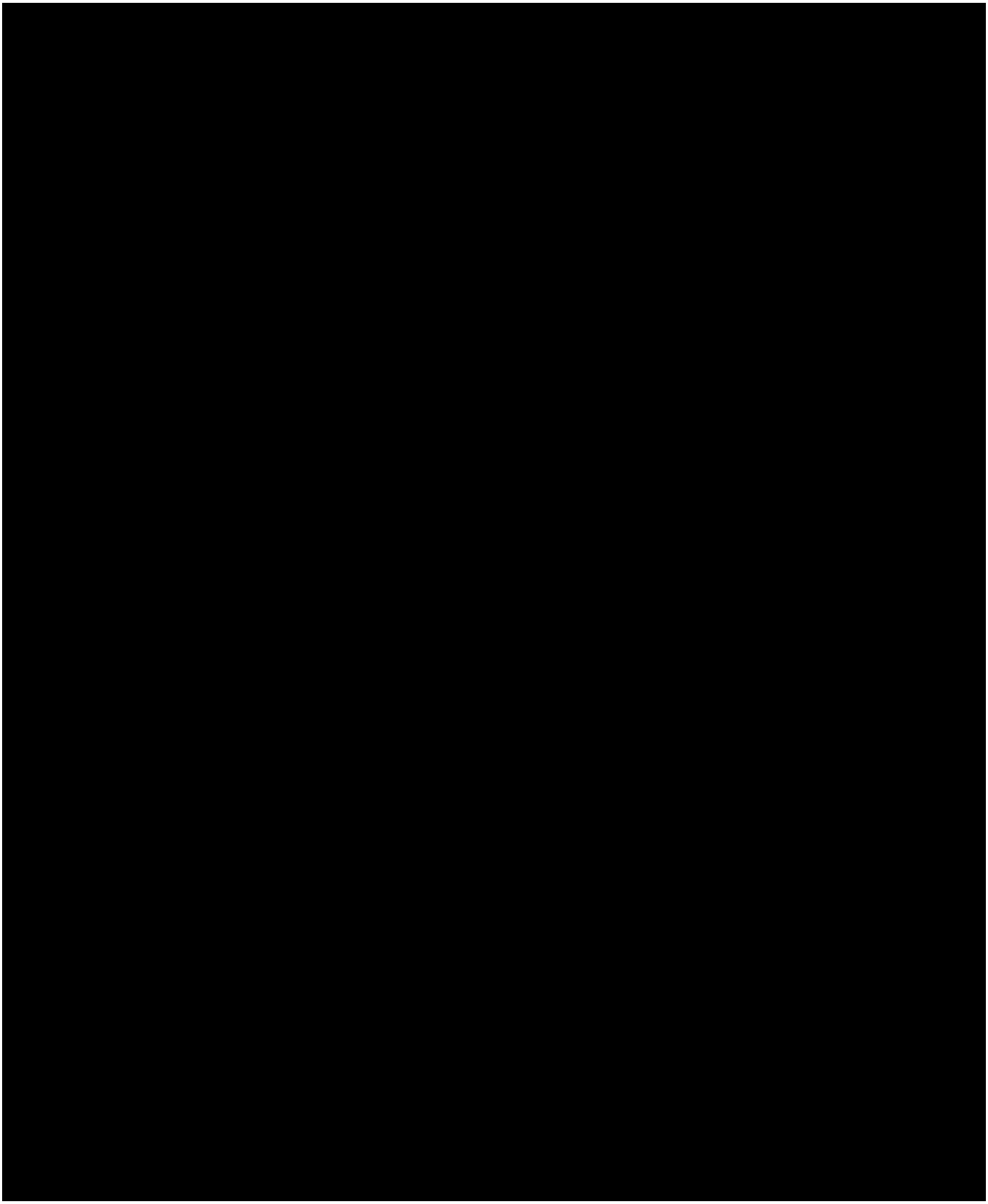
| | |
|---|---|
| ADME | Absorption, Distribution, Metabolism and Excretion |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| $Ae_{t1\text{-}t2(,N)}$ | Amount of analyte eliminated in urine over the time interval $t_1$ to $t_2$ (after the $N^{th}$ dose) |
| ANOVA | Analysis of variance |
| [redacted] | [redacted] |
| APC | Absolute platelet count |
| $AUC_{0\text{-}\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| $AUC_{0\text{-}24(,N)}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to 24h (after the $N^{th}$ dose) |
| $AUC_{t1\text{-}t2(,N)}$ | Area under the concentration-time curve of the analyte in plasma over the time interval $t_1$ to $t_2$ (after the $N^{th}$ dose) |
| $AUC_{0\text{-}tz(,N)}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point (after the $N^{th}$ dose) |
| $\beta$ | Slope parameter associated with the power model used to evaluate dose proportionality |
| BA | Bioavailability |
| BI | Boehringer Ingelheim |
| BLQ | Below limit of quantification |
| BMI | Body mass index (weight divided by height squared) |
| BP | Blood pressure |
| CA | Competent authority |
| $CCl_4$ | Carbon tetrachloride |
| CI | Confidence interval |
| CL | Total clearance of the analyte in plasma after intravascular administration |
| $CL/F_{(,N)}$ | Apparent clearance of the analyte in plasma after extravascular administration (after the $N^{th}$ dose) |
| $C_{max(,N)}$ | Maximum measured concentration of the analyte in plasma (after the $N^{th}$ dose) |
| CML | Clinical Monitor Local |
| CNS | Central nervous system |
| $C_{pre,N}$ | Predose concentration of the analyte in plasma immediately before administration of the $N^{th}$ dose after N-1 doses were administered |
| CRA | Clinical Research Associate |
| CRF | Case report form |
| CRO | Clinical Research Organisation |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| CTSU | Clinical Trial Supplies Unit |
| CV | Arithmetic coefficient of variation |
| DEDP | Drug exposure during pregnancy |
| DILI | Drug induced liver injury |

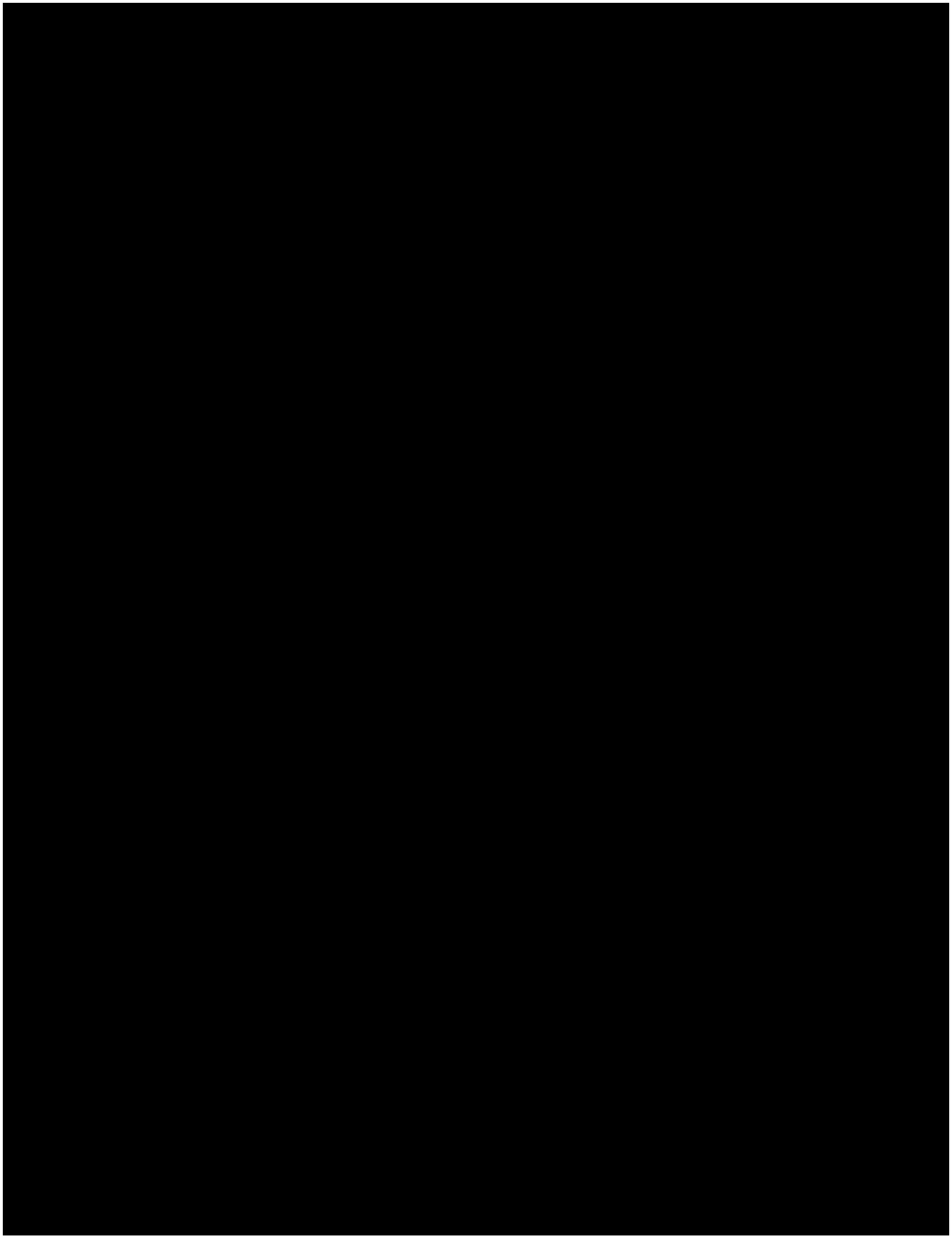
| | |
|---|---|
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| EDTA | Ethylenediaminetetraacetic acid |
| EOT | End of trial |
| F | Absolute bioavailability factor |
| FDA | Food and Drug Administration |
| $fe_{t1\text{-}t2(,N)}$ | Fraction of administered drug excreted unchanged in urine over the time interval from $t_1$ to $t_2$ (after the $N^{th}$ dose) |
| FIH | First in human |
| FOB | Functional observational battery |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| gCV | Geometric coefficient of variation |
| GFR | Glomerular filtration rate |
| GI | Gastro-intestinal |
| GLP | Good Laboratory Practice |
| gMean | Geometric mean |
| GMP | Good Manufacturing Practice |
| HCC | Hepatocellular carcinoma |
| HR | Heart rate |
| IB | Investigator's brochure |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| $\lambda_{z(,N)}$ | Terminal rate constant of the analyte in plasma (after the $N^{th}$ dose) |
| LC-MS/MS | Liquid chromatography tandem mass spectrometry |
| LLOQ | Lower limit of quantification |
| LOX | Lysyl Oxidase |
| LSD | Lysergic acid diethylamide |
| MAD | Multiple ascending dose |
| MAO | Mono Amine Oxidase |
| MCD | Methionine-Choline deficient Diet |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIST | Metabolites in safety testing |
| MRD | Multiple-rising dose |
| MRT | Mean residence time of the analyte in the body after intravenous bolus administration |
| $MRT_{po(,N)}$ | Mean residence time of the analyte in the body after oral administration (after the $N^{th}$ dose) |
| [redacted] | [redacted] |
| NBE | New biological entity |
| NC | Not calculated |
| NCE | New chemical entity |
| NOA | Not analysed |

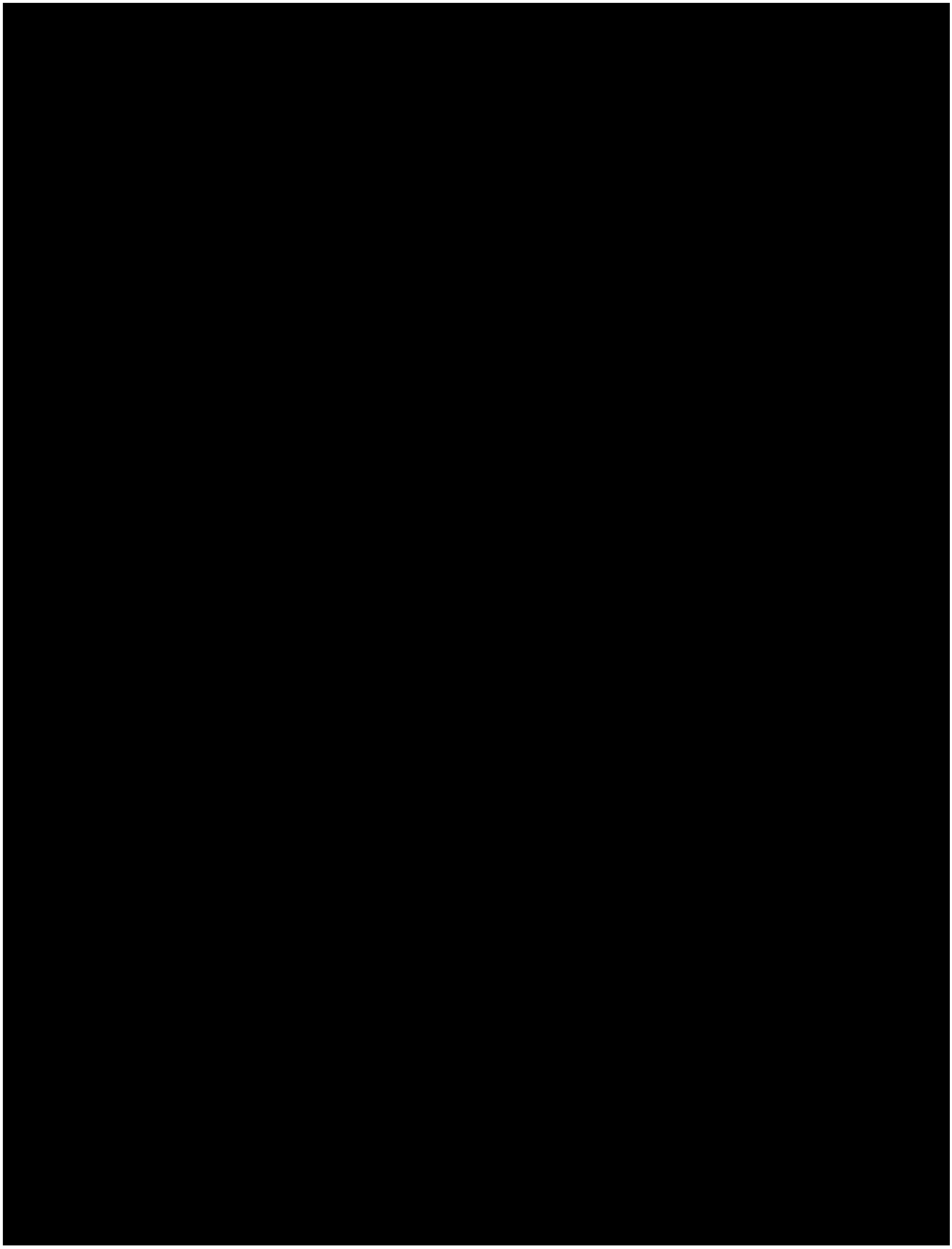
| | |
|---|---|
| NOAEL | No observed adverse effect level |
| NOR | No valid result |
| NOS | No sample available |
| PD | Pharmacodynamic(s) |
| PE | Polyethylene |
| PfOS | Powder for oral solution |
| PIB | Powder in the bottle |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic set |
| PR | Pulse rate |
| q.d. | *Quaque die*, once daily |
| QT | Time between start of the Q-wave and the end of the T-wave in an electrocardiogram |
| QTc | QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB) |
| R | Reference treatment |
| RA | Accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval $\tau$ |
| RDC | Remote Data Capture |
| REP | Residual effect period |
| SAE | Serious adverse event |
| SCR | Screening |
| SfOS | Solvent for Oral Solution |
| SmPC | Summary of Product Characteristics |
| SOP | Standard Operating Procedure |
| SRD | Single-rising dose |
| ss | (at) steady state |
| SSAO | Semi-carbazide-sensitive amine oxidase |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T | Test product or treatment |
| TDMAP | Trial Data Management and Analysis Plan |
| t.i.d. | *Ter in die*, three times daily |
| $t_{\lambda z,start(end)}$ | Lower (upper) limit on time for values to be included in the calculation of $\lambda_z$ |
| $t_{1/2(,N)}$ | Terminal half-life of the analyte in plasma (after the $N^{th}$ dose) |
| $t_{max(,N)}$ | Time from (last) dosing to the maximum measured concentration of the analyte in plasma (after the $N^{th}$ dose) |
| TMF | Trial master file |
| TS | Treated Set |
| TSAP | Trial statistical analysis plan |
| TSH | Thyroid stimulating hormone |
| $t_{z(,N)}$ | Time of last measurable concentration of the analyte in plasma (after the $N^{th}$ dose) |
| ULN | Upper limit of normal |
| VAP-1 | Vascular adhesion protein-1 |

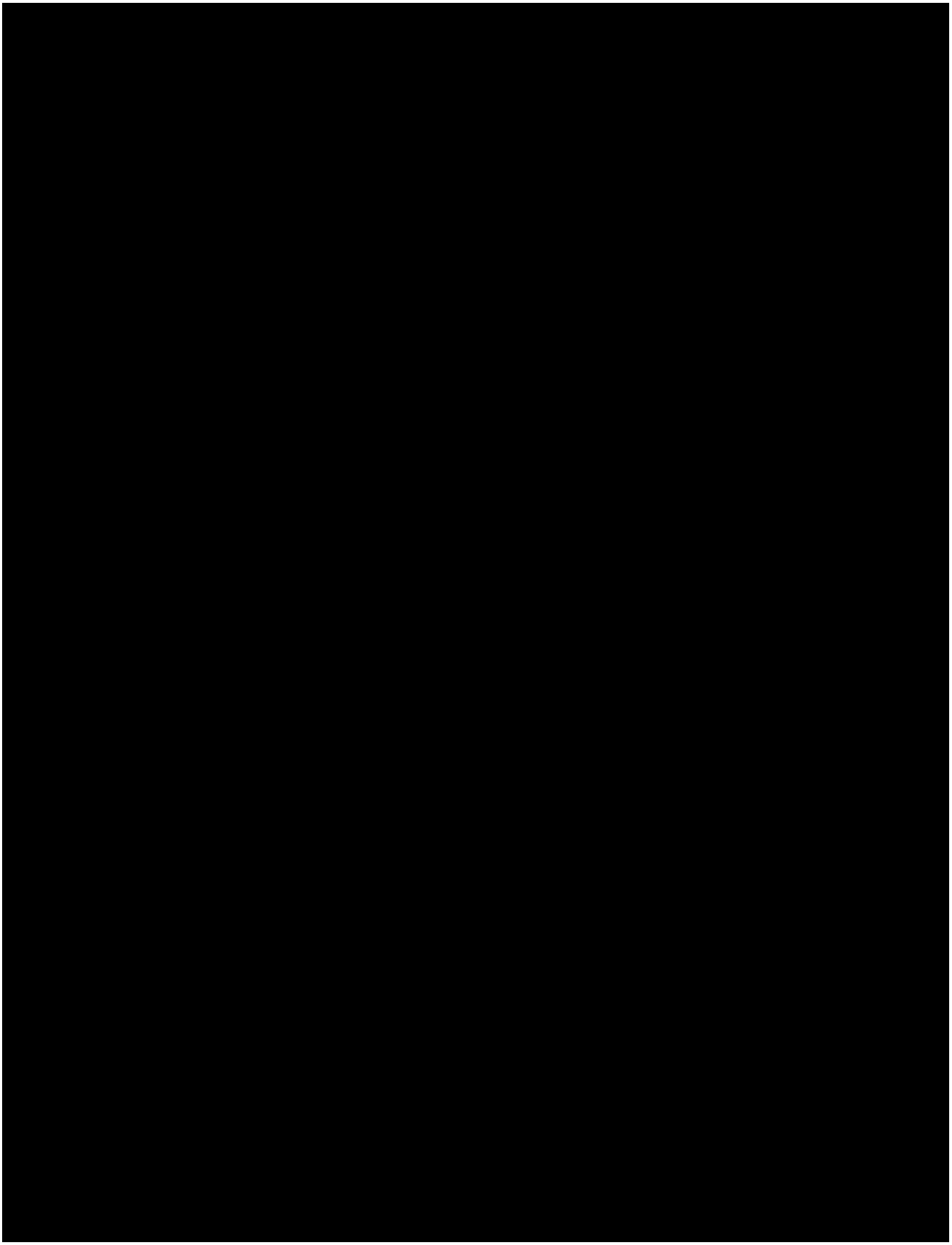
| | |
|---|---|
| $V_{ss}$ | Apparent volume of distribution at steady state after intravascular administration |
| $V_z/F_{(,N)}$ | Apparent volume of distribution during the terminal phase after extravascular administration (after the $N^{th}$ dose) |

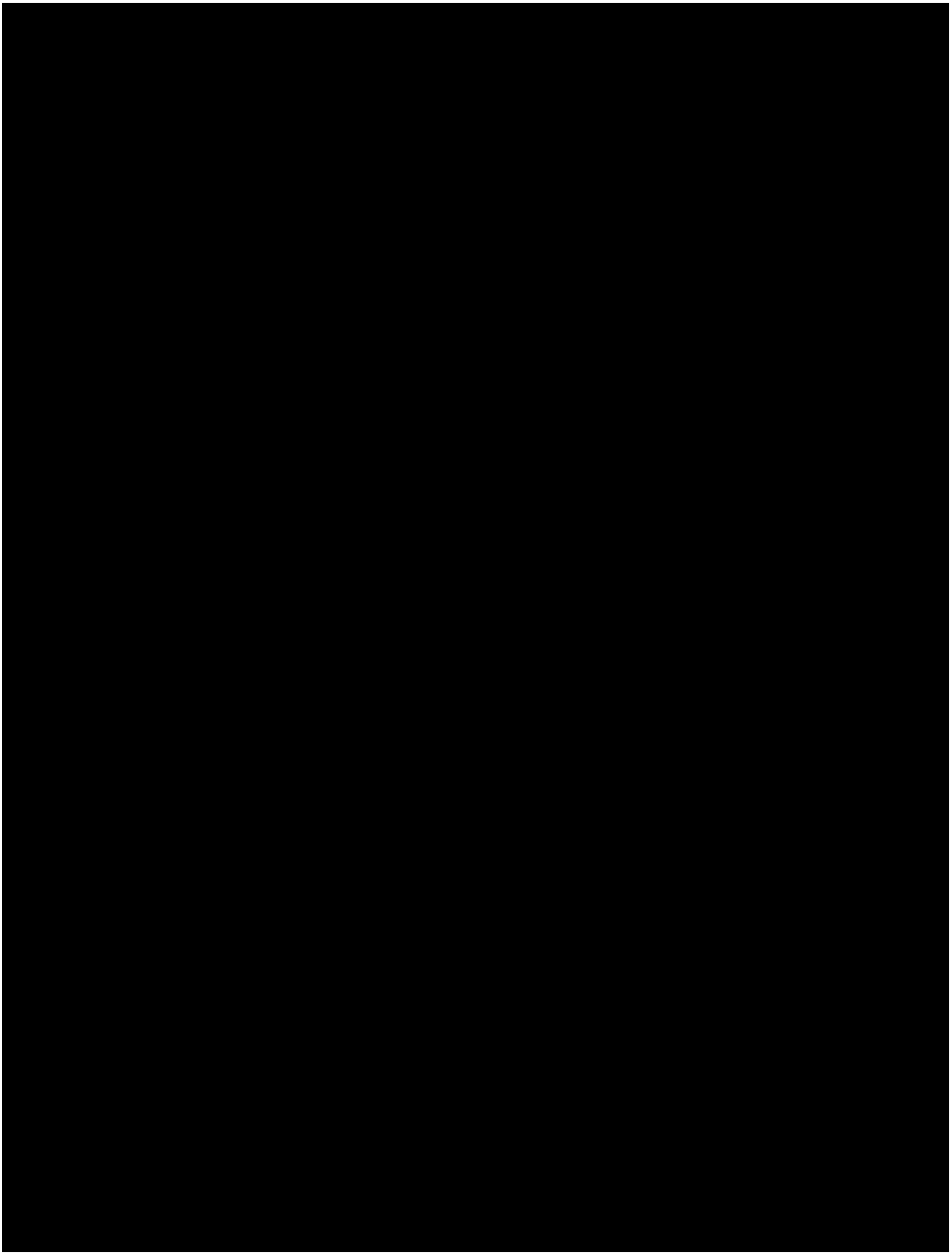


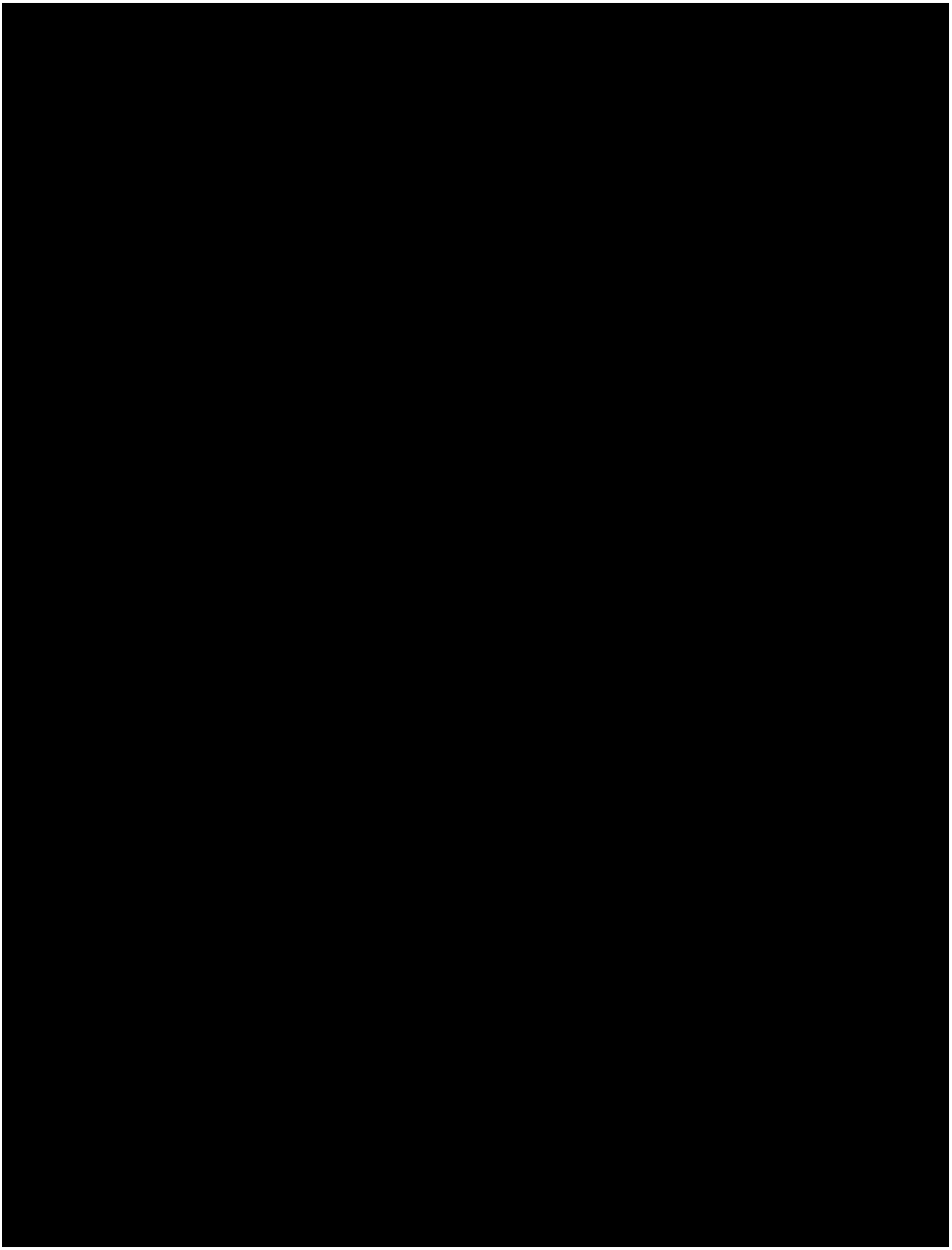


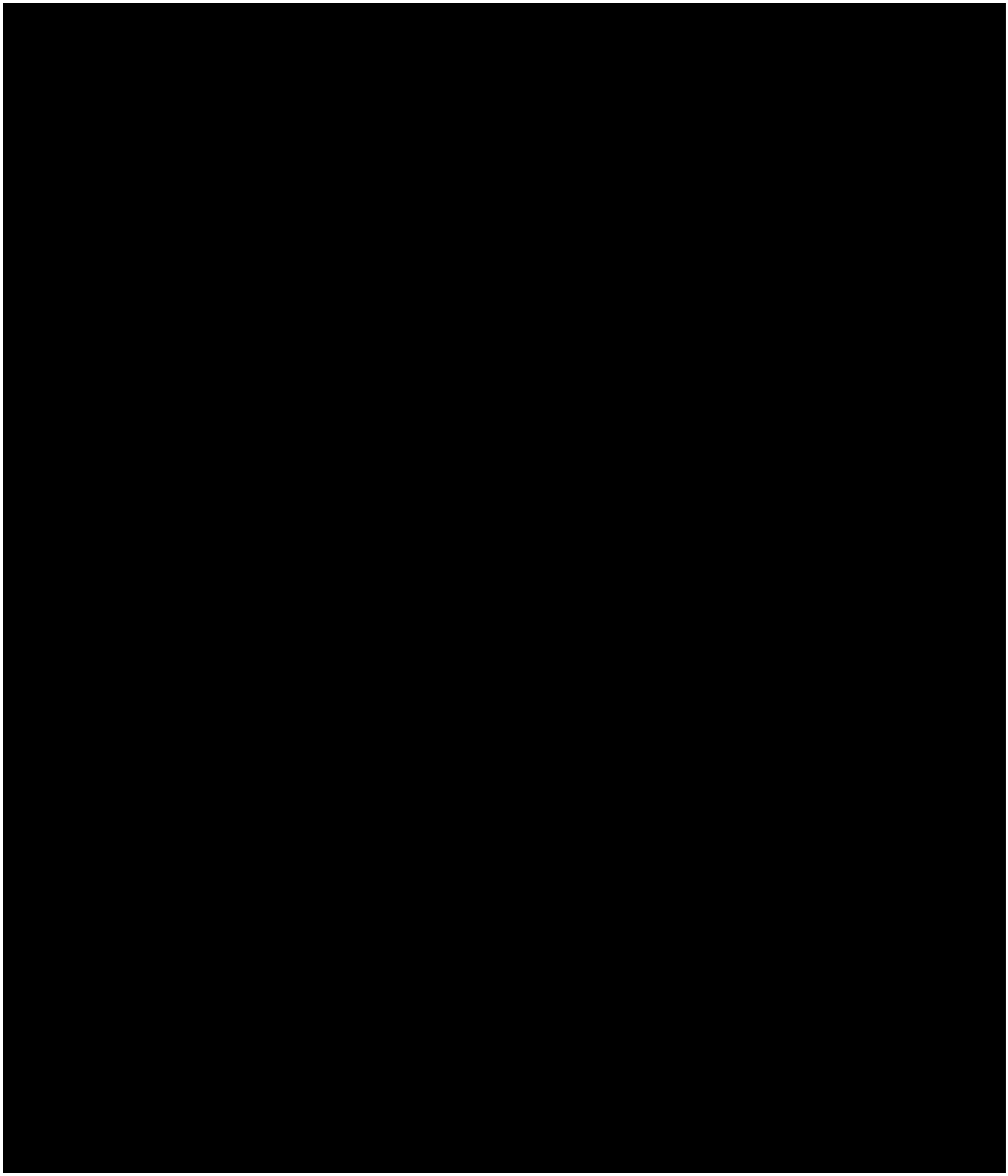


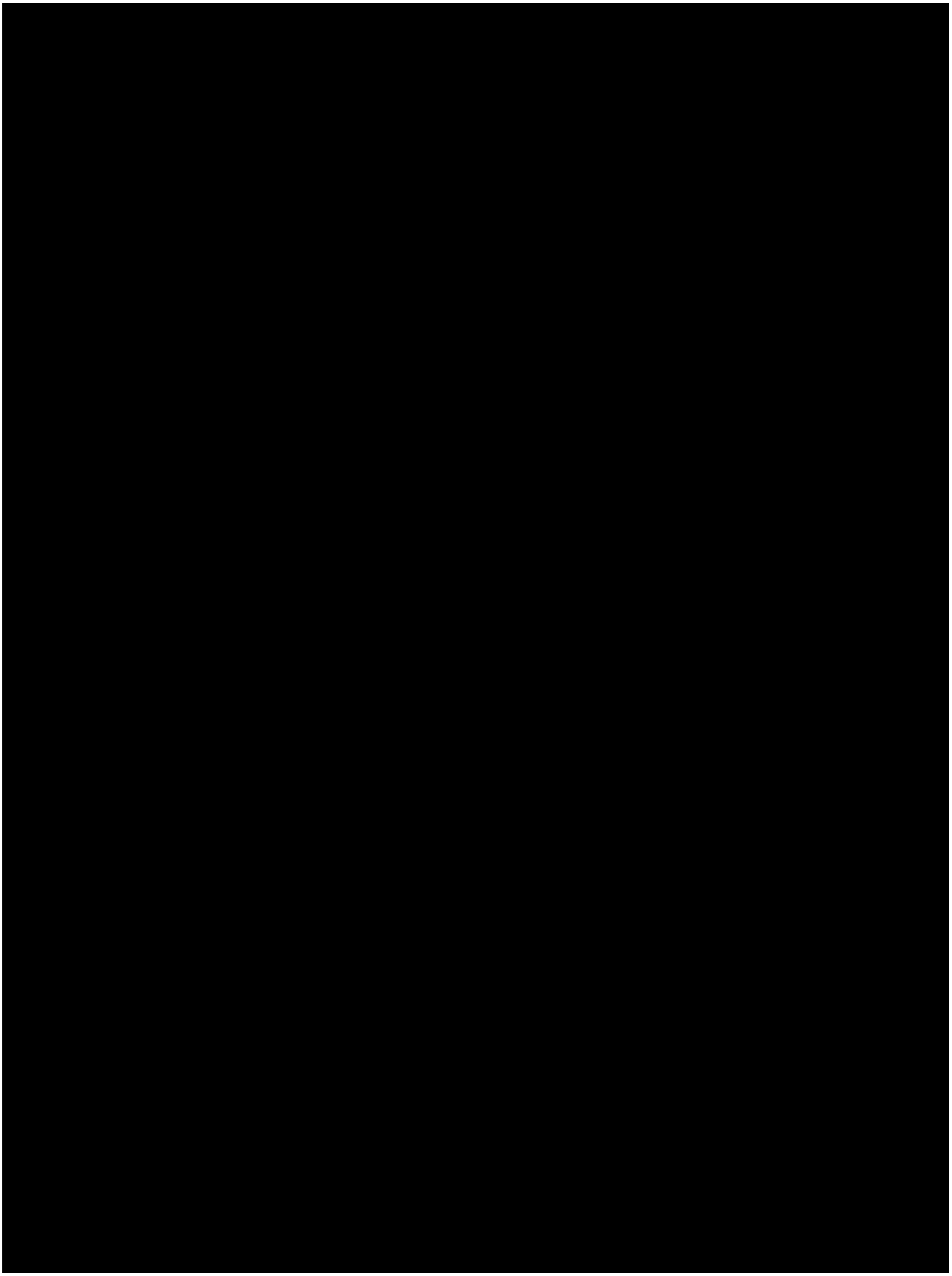


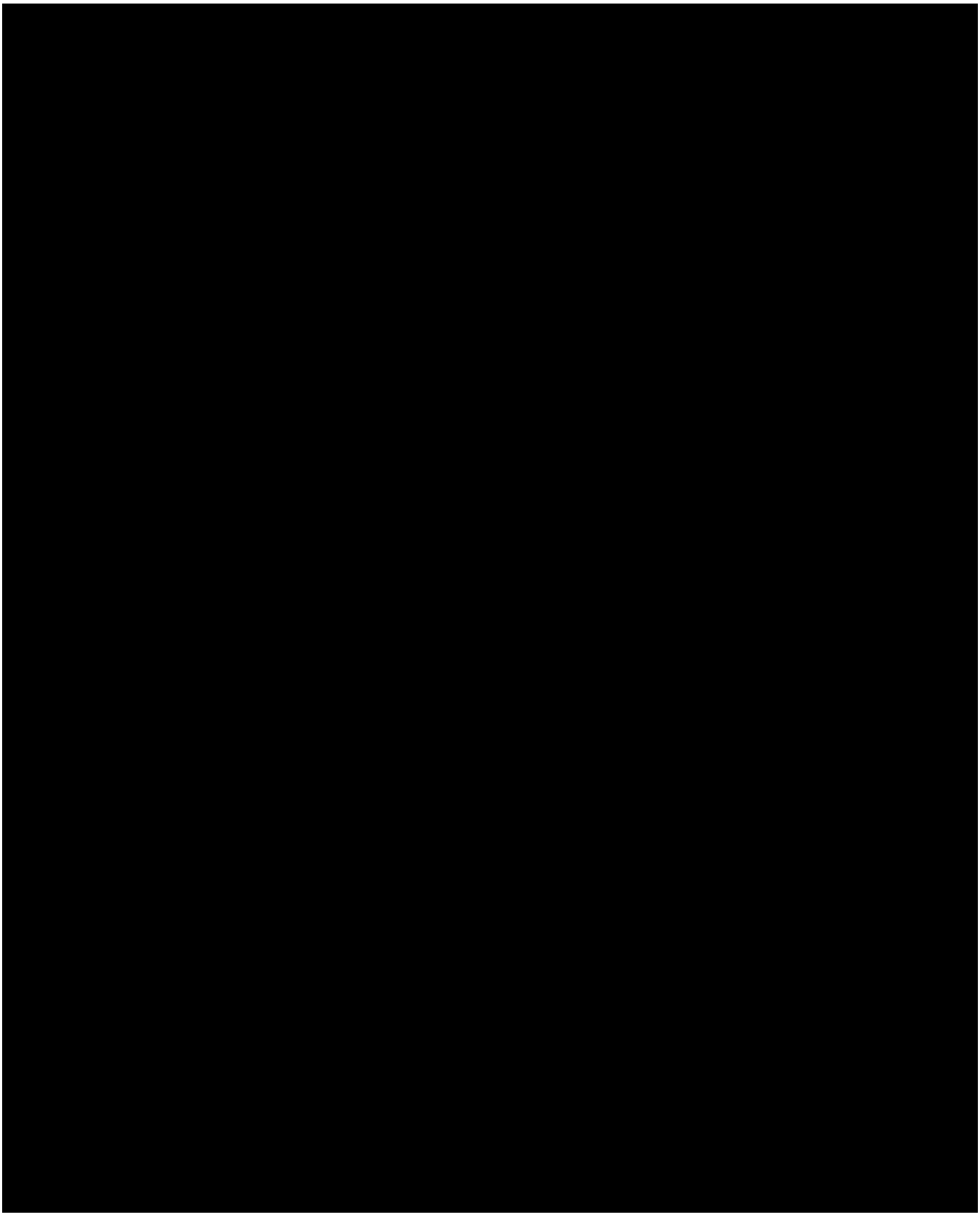


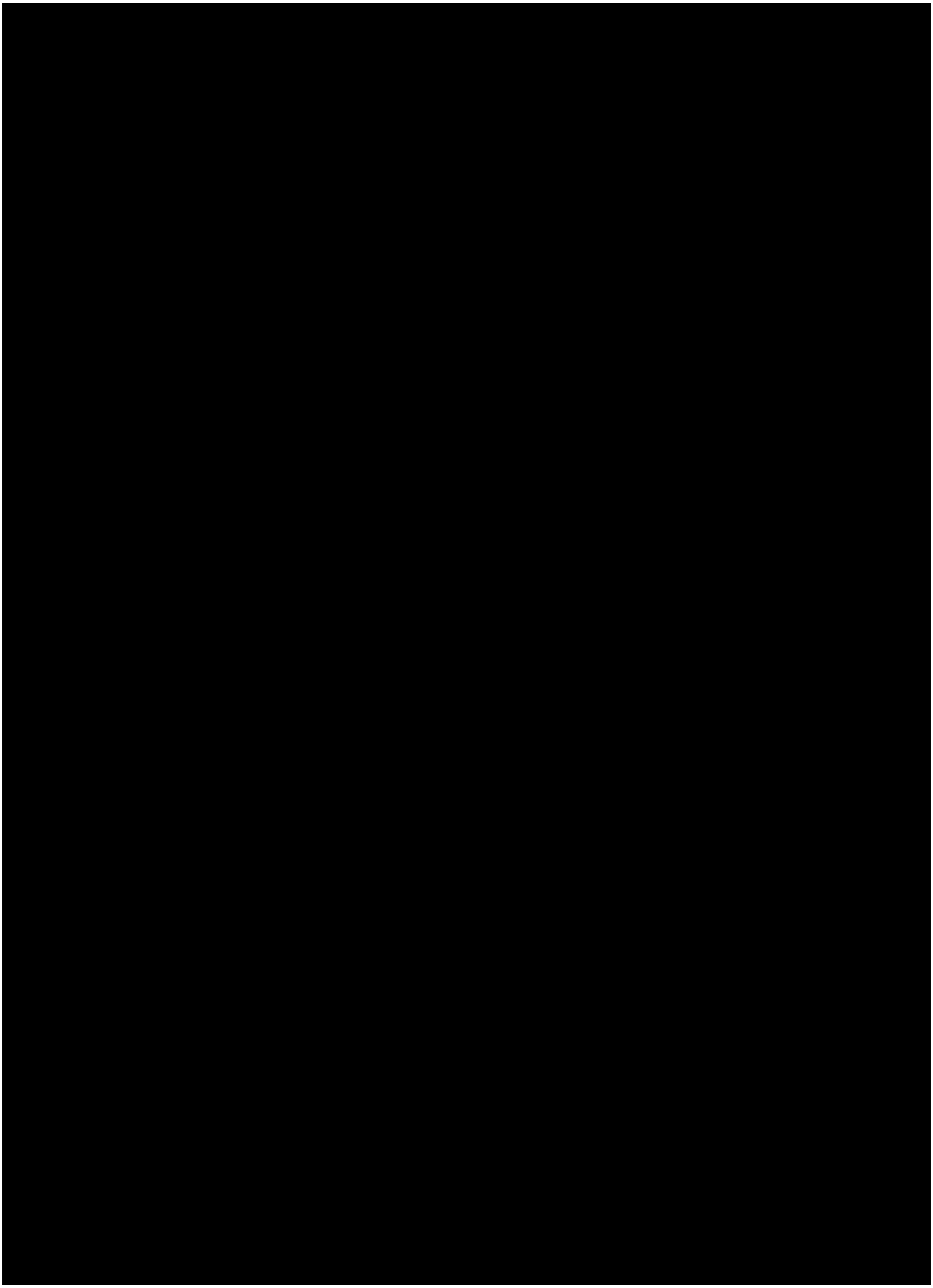


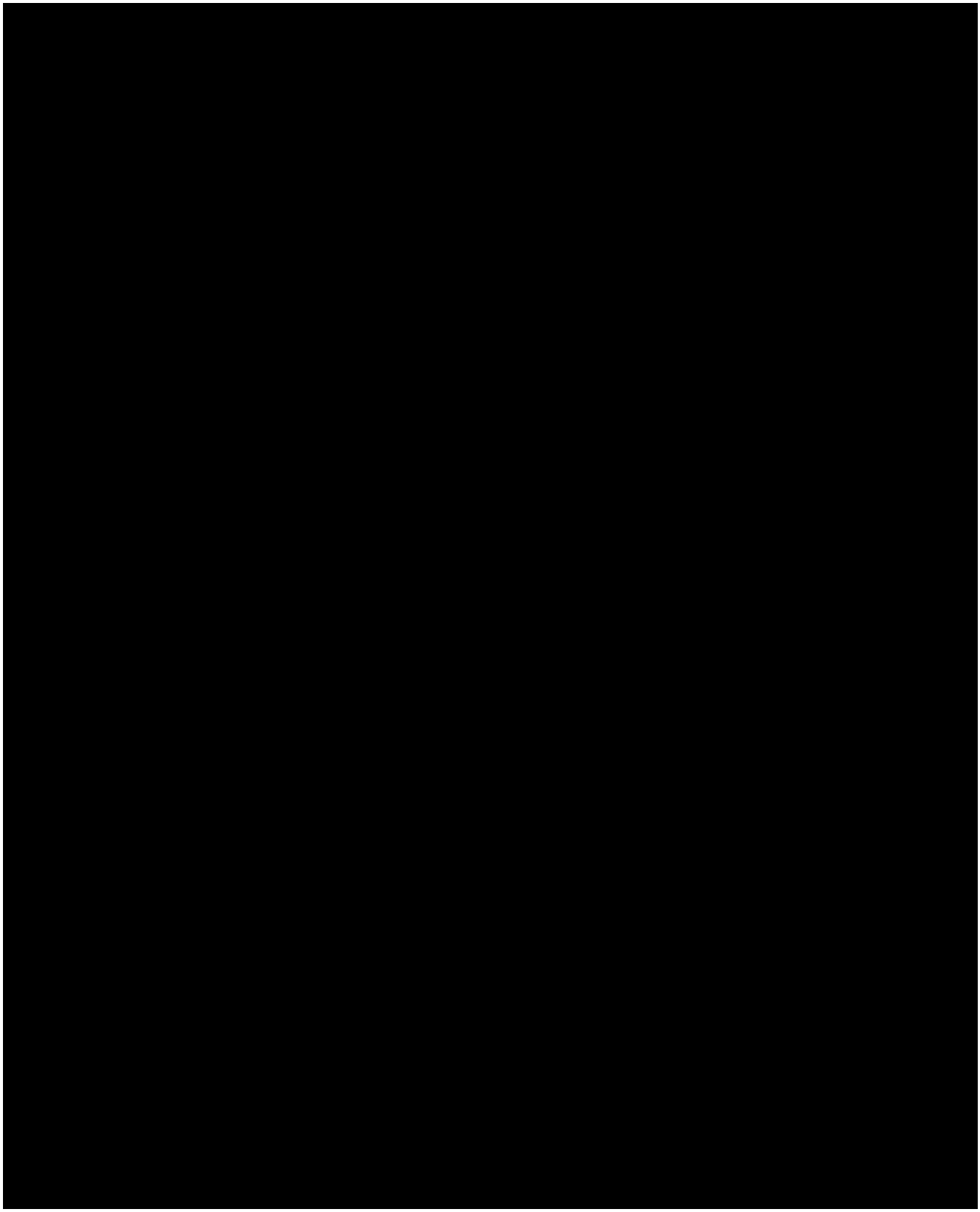




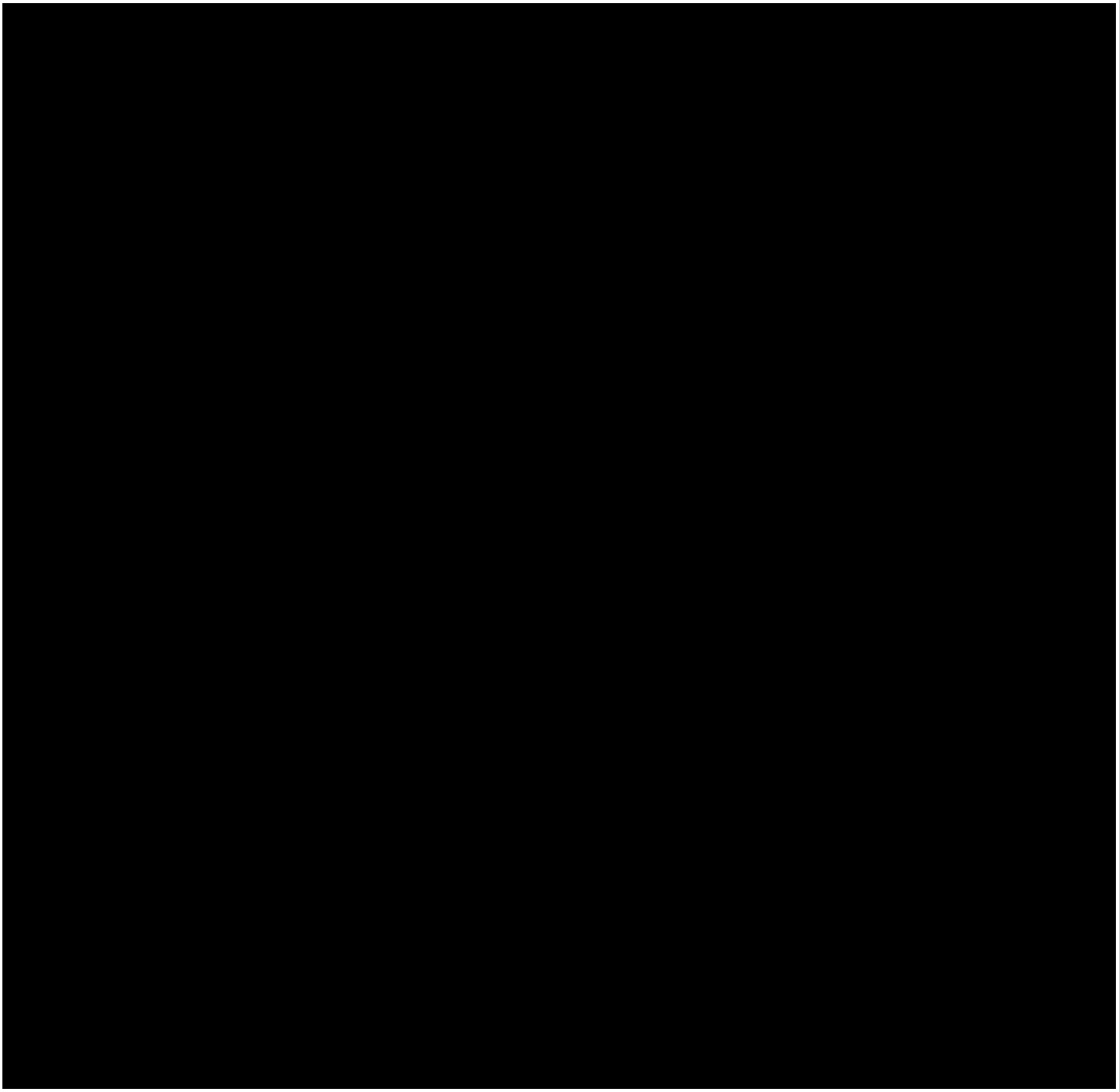








# 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

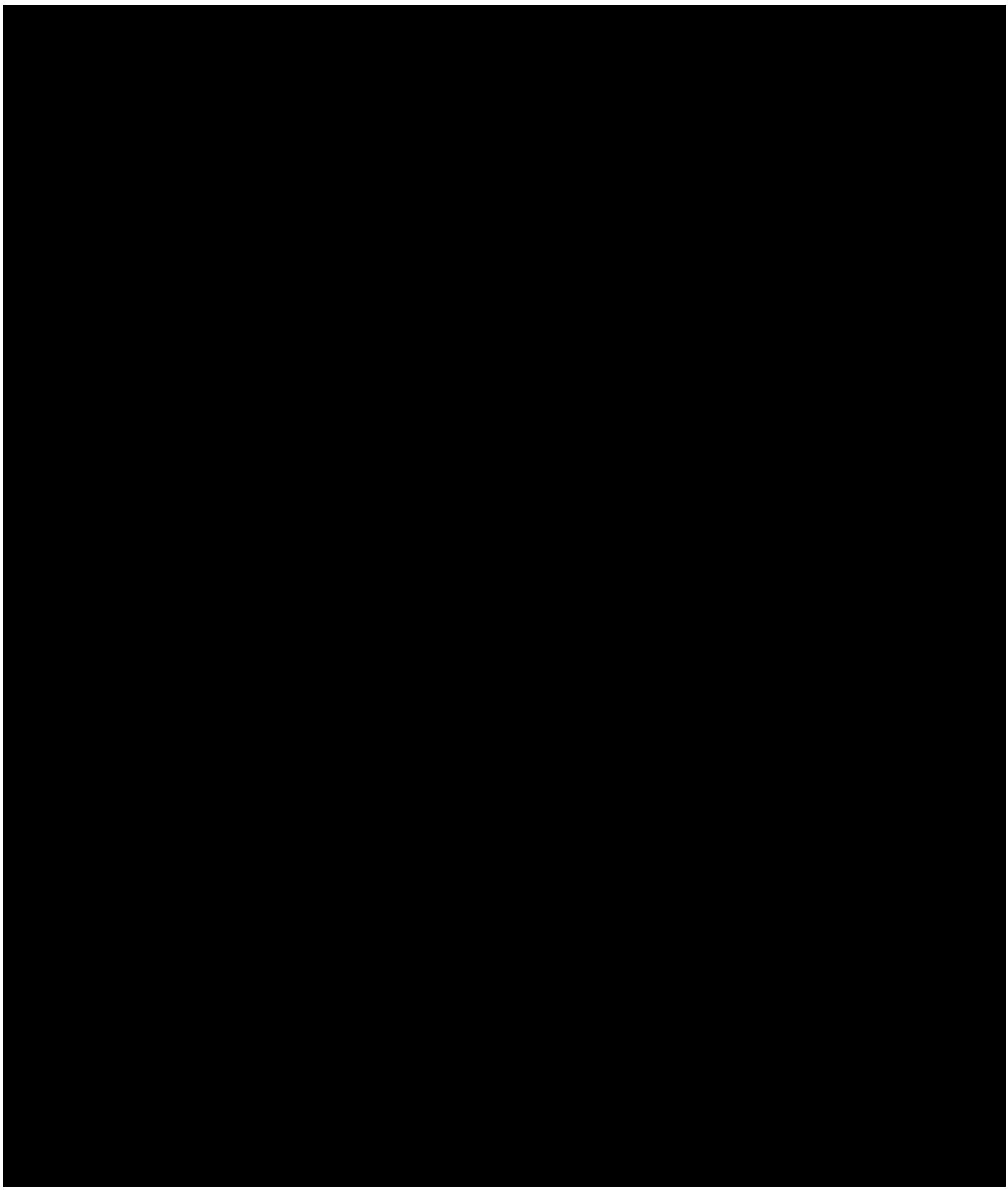


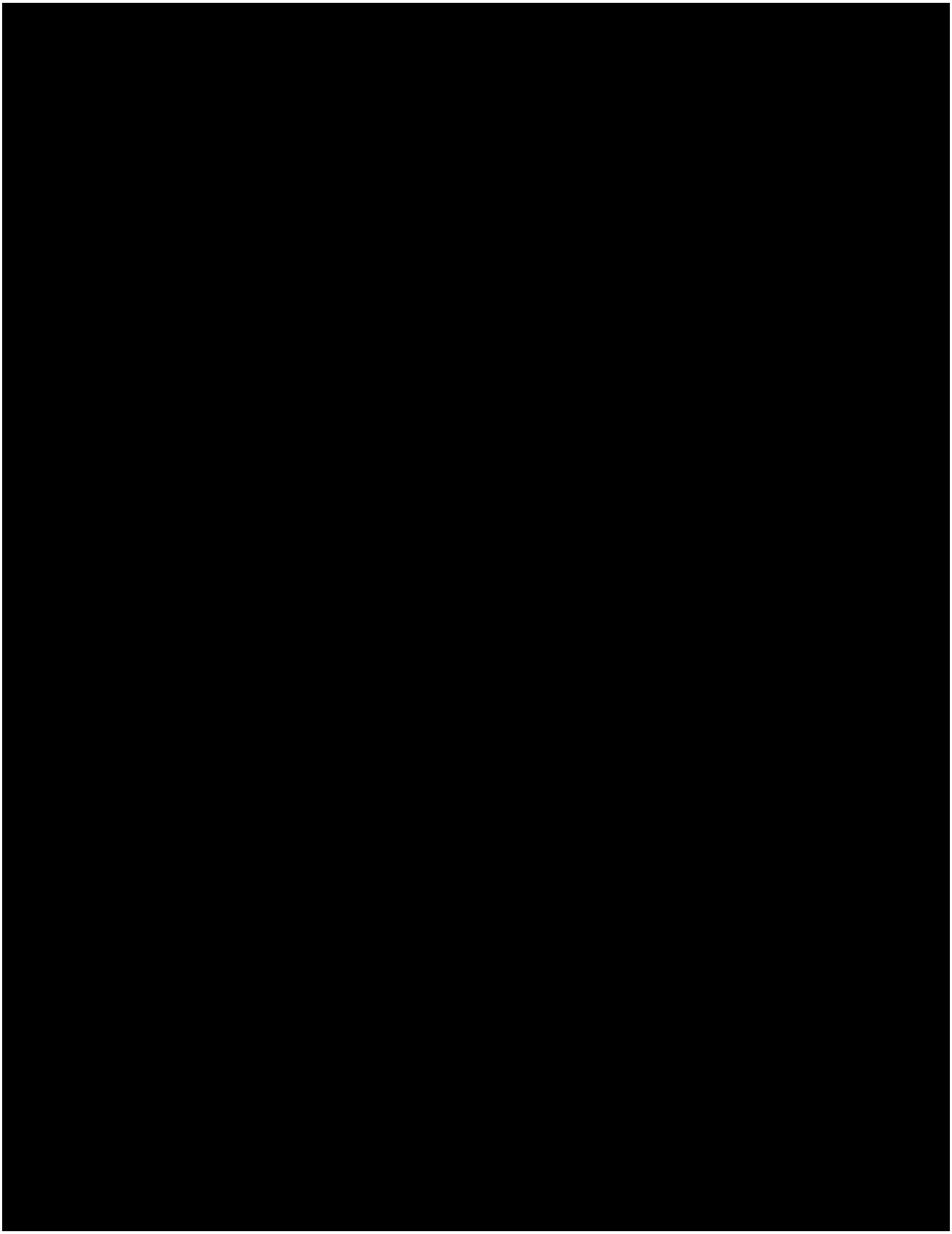
## 2.2 TRIAL OBJECTIVES

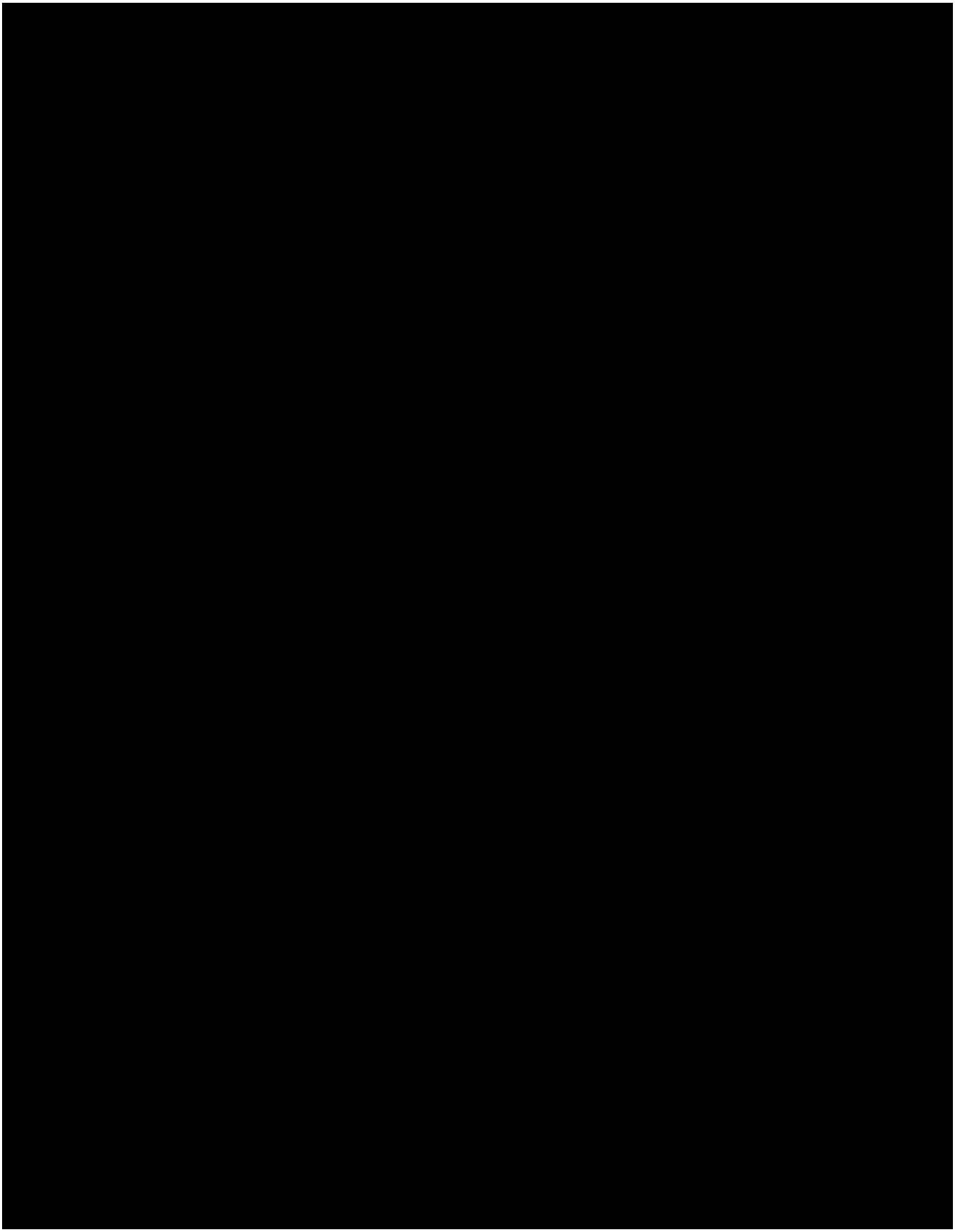
The primary objective of this trial is to investigate the safety and tolerability of BI 1467335 in healthy male and female subjects following oral administration of multiple rising doses of 10 mg, 15 mg, 20 mg, of BI 1467335 q.d. over 28 days. Based on the experience gained during the study, intermediatedoses within the approved dose range may be optionally tested.

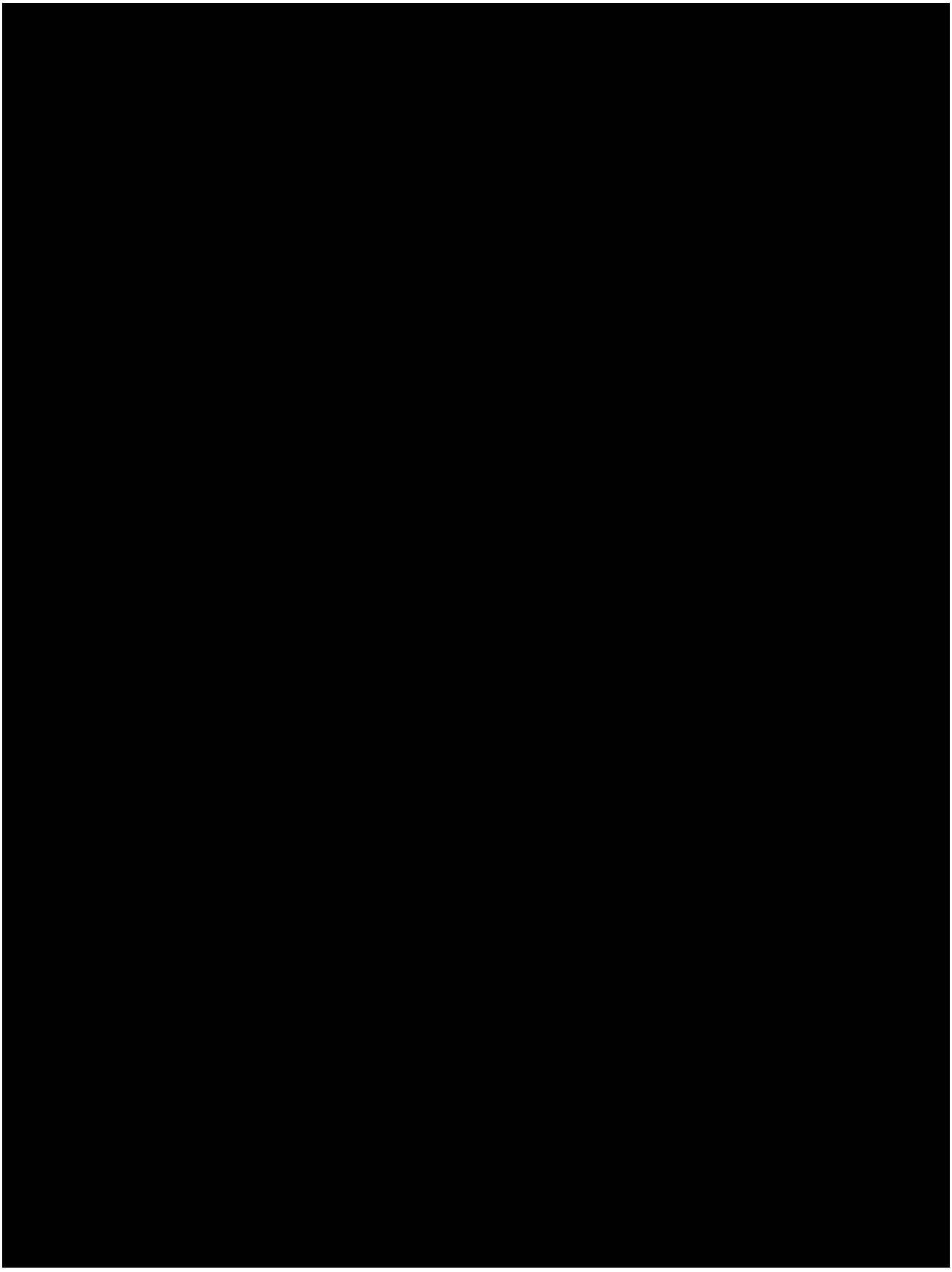
Secondary objectives are the exploration of the pharmacokinetics (PK) and target engagement biomarkers of BI 1467335 after multiple dosing.

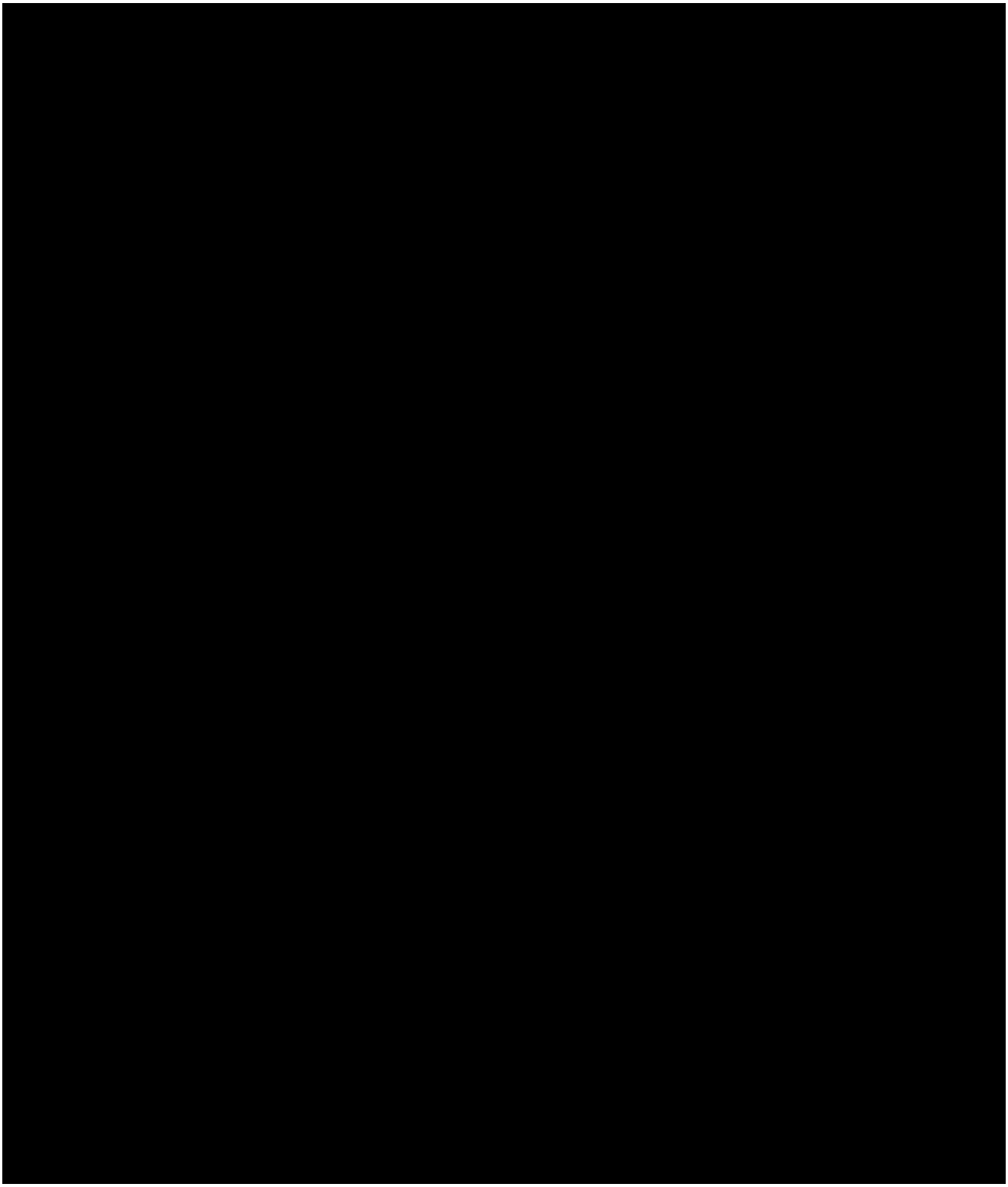
A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.











# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This multiple-rising dose trial is designed as double-blind, randomised, and placebo-controlled within parallel dose groups.

A total of 36 healthy male and female subjects is planned to participate in the trial, according to at least 3 sequential groups comprising 12 subjects per group. However, additional subjects may be entered to allow testing of intermediate doses within the approved dose range on the basis of experience gained during trial conduct (as described in Section 2.3), i.e. the actual number of subjects entered may exceed 36 but no more than 48. Such changes may be implemented via non-substantial CTP Amendments.

Within each dose group, 9 subjects will receive the active drug and 3 will receive placebo. Only one dose is tested within each dose group.

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups

| Dose Group | 1 | 2 | 3 |
|---|---|---|---|
| Daily dose (mg) | 10 | 15 | 20 |
| Number of subjects | 12 | 12 | 12 |
| Subjects receiving placebo | 3 | 3 | 3 |
| Subjects receiving active drug | 9 | 9 | 9 |
| Subject number<br><br>Subject replacement number | [redacted] | | |

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 14 days between last dosing of the previous dose group and the first drug administration of the subsequent dose group. The decision to proceed to the next cohort at the same dose level or the next higher dose group will be based upon the safety, tolerability and PK of the preceding cohort or dose groups as described in Section 2.3, Section 3.1 and in Section 3.3.4.1. The inclusion of the second cohort of the 10 mg dose group will be based exclusively on safety and tolerability including checking for individual stopping rules (see Section 3.3.4.1), but not on PK data.

A documented Safety Review must take place prior to inclusion of any new cohort and between dose groups. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator

(or an authorised deputy) and the trial clinical monitor (or an authorised deputy) as described in Section 2.3.

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

- AEs in the current and, if applicable, preceding dose groups (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 be subject to change prior to Database Lock)
- Results from 12-lead EGG in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Check of criteria for stopping subject treatment as per Section 3.3.4.1
- PK data including extrapolation to support conclusions about safety margins (not required for inclusion of second cohort of the 10 mg dose group since based on the results from the previous SRD/MRD study (see Section 1.2.5) exposure is not expected to exceed $C_{max}$ and 1/2 of the AUC of the 4-week rat toxicology study at NOAEL.

The decision to continue with the next cohort at the same dose level or the next higher dose level will be made jointly by the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy) based on the criteria described in Section 2.3. In-depth analysis includes preliminary PK data, if possible extrapolations of exposure for the current and any new cohorts, all available safety data, especially SAEs (if occurred), AEs fulfilling stopping criteria, other AEs and out-of-range laboratory results (if considered clinically significant) and ECG results. Safety Reviews can be conducted face-to-face or by video/telephone conference. The trial clinical monitor is responsible for organizing and minuting the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

To proceed to the next higher dose level at least data up to Day 28 from 10 evaluable subjects of the preceding dose level (with at least 7 subjects on active treatment) are required.

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels within the planned dose range on the basis of experience gained during the study.

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

### 3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,

- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

The trial will be conducted at [redacted] under the supervision of the Principal Investigator.

Safety laboratory tests will be performed by the local laboratory of the trial site [redacted].

The analyses of BI 1467335 (and its metabolites and stability) concentrations in plasma will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The analysis of the concentration [redacted] will be performed by the [redacted].

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation ([redacted]) for central evaluation.

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

Data management and statistical evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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

For multiple-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 1467335.

With the rising dose design, double -blind conditions regarding the subject's treatment (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 the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability and pharmacodynamic effects. Each dose group consists of 12 subjects with 9 on active treatment, and 3 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. At the 10 mg dose level there will be a staggered inclusion of 2 cohorts of 6 subjects. At any higher dose level there will be a staggered inclusion of 3 cohorts each consisting of 4 subjects with 3 subjects randomized to active treatment and 1 subject randomized to placebo. The criteria to proceed with any new cohort are provided in Section 2.3 and Section 3.1.

## 3.3 SELECTION OF TRIAL POPULATION

It is planned that 36 healthy male and female subjects will enter the study. The actual number of subjects entered may exceed the total of 36 if intermediate doses will be tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

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

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.

### 3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

### 3.3.2 Inclusion criteria

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

1. Healthy male or female subjects according to the investigator’s assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m$^2$ (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
5. Male subjects, or female subjects who meet any of the following criteria starting from at least 30 days before the first administration of trial medication and until 30 days after trial completion:
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

### 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) is deviating from normal and judged as clinically relevant by the investigator
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
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Intake of drugs with a long half-life (more than 24 h) within 30 days or less than 10 half-lives of the respective drug prior to administration of trial medication
12. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial or that might prolong the QT/QTc interval
13. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication
14. Used nicotine-containing products (e.g., cigarettes, cigars, chewing tobacco, snuff) within 6 weeks before screening and unable to abstain from using these products until study completion
15. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTcB interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening

21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. Detection of cataract in slit lamp examination
24. GFR according to CKD-EPI-Formula < 90 mL/min at screening [R12-1392]

**Female subjects will not be allowed to participate if any of the following applies:**

25. Females who are not surgically sterilised or who are not postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)
26. Positive pregnancy test
27. Lactation period

For study restrictions, refer to Section 4.2.2.

### 3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as pregnancy, surgery, adverse events, or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. 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.
6. Relevant individual QT prolongation, i.e. a QTcB increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.
7. eGFR calculated with the CKD-EPI formula is determined to be below 80 ml/min on 2 consecutive assessments 24 h apart
8. If a patient develops symptoms of muscle or tissue injury (e.g., muscle aches, dark urine or other signs of rhabdomyolysis), in line with clinically significant increased CK levels.

9. Neutropenia will lead to individual discontinuation from trial medication if any of the following applies:
   - Febrile Neutropenia at any time, i.e. absolute neutrophil count (ANC) below lower limit of normal with concomitant body temperature greater or equal 38 degrees C
   - ANC below 1000/microliter at any time
   - ANC below 1500/microliter (but greater 1000/microliter) if still present after 1 week
10. Leukopenia will lead to individual discontinuation from trial medication if any of the following applies:
    - Febrile leukopenia at any time, i.e. absolute lymphocyte count (ALC) below lower limit of normal with concomitant body temperature greater or equal 38 degrees C
    - ALC below 2500/microliter at any time
    - ALC below 3000/microliter (but greater 2500/microliter) if still present after 1 week
11. Thrombocytopenia will lead to individual discontinuation from trial medication if any of the following applies:
    - Thrombocytopenia, i.e. absolute platelet count (APC) below lower limit of normal at any time if associated with clinical signs or symptoms of bleeding
    - APC below 80,000/microliter at any time
    - APC below 100,000/microliter (but greater 80,000/microliter) if still present after 1 week

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

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication has to be stopped immediately, and the subject has to be removed from the trial. The subject is to be followed until she has given birth or until the end of pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the clinical trial report. For reporting of pregnancy and all related events refer to Section 5.2.2.2.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.
2. The expected enrolment goals overall or at a particular trial site are not met.
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product.
5. Inclusion of any new cohort, and the treatment of current cohorts will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.
6. Inclusion of any new cohort, and the treatment of current cohorts will be stopped as soon as at least 2 subjects at one dose level on active drug shows AEs fulfilling stopping criteria (Section 3.1).
7. This multiple dose study is planned not to exceed the $C_{max}$ or $1/10^{th}$ of the AUC observed at NOAEL in the 4-week rat toxicity study as stated in Section 1.2.3. For this reason preliminary PK assessments will be performed at each dose level before starting with the next cohort (not applicable at the 10 mg dose level).

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

[redacted]

# 4. TREATMENTS

## 4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

### 4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below:

| | |
|---|---|
| Substance: | BI 1467335 |
| Pharmaceutical formulation: | Powder for oral solution (PfOS) |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | 40 mg (target solution concentration BI 1467335: 0.5 mg/ml) |
| Posology: | 1-0-0 |
| Route of administration: | p.o. |
| Duration of use: | 28 days q.d. dosing |

BI 1467335 will be provided as a powder for oral solution in 100 mL amber glass bottles.

Solvent for reconstitution is Sucralose (4 mg/mL) and Menthol (2 mg/mL) solution provided in 100 mL clear glass vials.

Solvent for reconstitution will be used as placebo.

At the time of use, the oral solution for dosing will be prepared as detailed in the instruction given in Appendix 10.1 using the PfOS and co-supplied Solvent for Oral Solution (SfOS).

The solvent for reconstitution will be transferred to an empty 100 mL amber glass bottle, which will be appropriately labeled:

| | |
|---|---|
| Substance: | Matching placebo |
| Pharmaceutical formulation: | Solvent for oral solution (SfOS) |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | Not applicable |
| Posology: | 1-0-0 |
| Route of administration: | p.o. |
| Duration of use: | 28 days q.d. dosing |

Solvent is Sucralose (4 mg/mL) and Menthol (2 mg/mL) solution provided in 100 mL clear glass vials.

### 4.1.2 Method of assigning subjects to treatment groups

Prior to the 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 according to their temporal availability. As soon as enough subjects have been allocated to the first dose group, the following subjects will be allocated to the next dose level. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The list of subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study 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.

### 4.1.3 Selection of doses in the trial

The doses selected for this trial cover the subtherapeutic as well as the estimated therapeutic range and include a safety margin (see Section 1.2).

### 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 dose volume for placebo corresponds to the number of dose volume of the respective dose level.

Table 4.1.4: 1 BI 1467335 and placebo treatments, oral administration

| Dose | Substance | Pharmaceutical form | Unit strength** | Dose volume per administration | Total daily dose** |
|---|---|---|---|---|---|
| 1 | BI 1467335 | oral solution | 0.5 mg/mL | 20 mL (10 mg) q.d. for 28 days | 10 mg |
| 2 | BI 1467335 | oral solution | 0.5 mg/mL | 30 mL (15 mg) q.d. for 28 days | 15 mg |
| 3 | BI 1467335 | oral solution | 0.5 mg/mL | 40 mL (20 mg) q.d. for 28 days | 20 mg |
| 1-3 | Placebo* | oral solution | -- | identical to active treatment | -- |

* Subjects receiving placebo are equally distributed across dose groups

** Unit strength and dose refer to free base of BI 1467355

The oral solutions for dosing (active drug and placebo) will be prepared according to the instruction given in Appendix 10.1 by pharmacists or qualified pharmacy staff members or qualified medical study personnel at the trial site under the responsibility of the investigator.

The trial medication will be administered to the subjects, while in a sitting position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution),

if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing.

To ensure a dosing interval of 24 h, the administration of trial medication should take place at the same time every day.

Subjects will be kept under close medical surveillance from the evening of Day -1 to the morning of Day 4, from the evening of Day 13 to the morning of Day 17, and from the evening of Day 27 to the morning of Day 29. During the first 2 h after drug administration, subjects 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 investigators (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 pharmacists. 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.

At the ECG laboratory all staff will be blinded with respect to treatment. Within the ECG laboratory, the staff involved with interval measurements and assessments will also be blinded with regard to the recording date and time as well as time points of the ECGs. Semi-automatic interval measurements for a given subject will be performed in random and blinded sequence by a single technician.

In addition, the trial bioanalyst, will receive the randomisation codes prior to official unblinding to perform the interim / preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

In addition, the drug metabolism scientist will receive the randomisation codes prior to official unblinding to perform metabolites in safety testing analysis (MIST). He or she will confirm in writing that the codes will be treated confidentially.

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 monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist, clinical research associate as well as dedicated CRO personnel). The objective of the trial is not expected to be affected.

4.1.5.2 Procedures for emergency unblinding

For blinded trials, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or to assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope or appropriate CRF page along with the date and the initials of the person who broke the code. At the close-out visit all envelopes are collected.

### 4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

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. Smaller boxes and bottles within 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.

No re-supply is planned.

### 4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

### 4.1.8 Drug accountability

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- 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 or immediately imminent signing of the clinical trial protocol

Only authorised personnel as documented in the form 'Site Delegation Log' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorization by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator / pharmacist / investigational drug storage manager 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 alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator / pharmacist / investigational drug storage manager must verify that no remaining supplies are in the investigator's possession.

## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

### 4.2.1 Rescue medication, emergency procedures, and additional treatments

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies 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

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. From Day 1 to Day 28, no food is allowed for at least 10 h before and 2 h after administration of the study drug.

From Day 1 to Day 28, starting from 1 hour before drug administration until 2 h after drug intake fluid intake is not allowed except from the 240 mL water administered with the drug intake. From breakfast until 22 hours post-dose water intake will be within 1000 to 3000 mL.

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 first administration of trial medication until after the last PK sample is collected.

[redacted] nicotine-containing products (e.g., cigarettes, cigars, chewing tobacco, snuff) should be stopped at least 6 weeks before screening and abstained from using these products until study completion.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed at days of inhouse confinement. On the ambulatory days, it is restricted up to max 200 ml (coffee, tea, cola, red bull, energy drinks), or 50 g (chocolate and chocolate products).

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

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

## 4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study center under supervision of the investigating physician or a designee. The measured plasma concentrations and urinary excretion will provide additional confirmation of compliance.

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. VARIABLES AND THEIR ASSESSMENT

## 5.1 EFFICACY - CLINICAL PHARMACOLOGY

### 5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

### 5.1.2 Assessment of efficacy

Not applicable.

## 5.2 SAFETY

### 5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 1467335 is the number [N (%)] of subjects with drug-related AEs.

[redacted]

### 5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

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

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

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered ‘Always Serious’

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

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 given above.

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

Adverse events of special interest (AESIs)

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

Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:

- 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
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided 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.

AESIs are also those AEs fulfilling individual stopping rules as described in Section 3.3.4.1.

Intensity of AEs

The intensity of adverse events should be classified and recorded in the (e) CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated 14 June 2010 [R10-4848] in the (e)CRF.

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

#### 5.2.2.2 Adverse event collection and reporting

AEs 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.

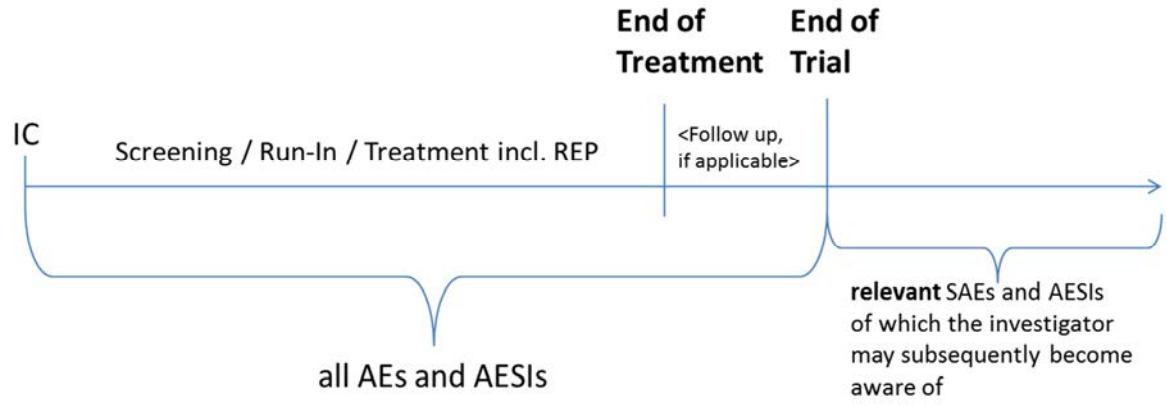
Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. 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 careful 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, and intensity of the event as well as 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 through the residual effect period (REP), until 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 AEs but should only report relevant SAEs and relevant AESIs of which he may become aware of.




The REP for BI 1467335, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known at this early stage of development. Therefore, all AEs reported until the trial termination date will be considered on treatment; please see Section 7.3.3.

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours of awareness) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. 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.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication. The following should also be recorded as an (S)AE in the CRF and on the SAE form (if applicable):

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

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

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

Pregnancy

In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

### 5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designee for retests.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is a clinically relevant abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

| Functional lab group | Test name |
|---|---|
| Haematology | Haematocrit<br>Haemoglobin<br>Red blood cell count (RBC)<br>White blood cell count (WBC)<br>Platelet count |
| Automatic WBC differential (relative and absolute) | Neutrophils, eosinophils, basophils, monocytes, lymphocytes |
| Manual differential WBC (if automatic differential WBC is clinically relevant abnormal) | Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes |
| Coagulation | Activated partial thromboplastin time (aPTT)<br>Prothrombin time (Quick's test and INR)<br>Fibrinogen |
| Enzymes | Aspartate transaminase (AST/GOT)<br>Alanine transaminase (ALT/GPT)<br>Alkaline phosphatase (AP)<br>Gamma-glutamyl transferase (GGT)<br>Glutamate dehydrogenase (GLDH)<br>Creatine kinase (CK)<br>CK-MB, only if CK is elevated<br>Lactate dehydrogenase (LDH)<br>Lipase<br>Amylase |
| Hormones[1] | Thyroid stimulating hormone (TSH)<br>fT3, fT4<br>FSH[2] |
| Substrates[1] | Plasma glucose<br>Creatinine<br>eGFR (derived from creatinine using CKD-EPI formula)<br>Cystatine<br>Total bilirubin<br>Direct bilirubin<br>Total protein<br>Protein electrophoresis (only at screening examination)<br>Albumin<br>Alpha-1-Globulin<br>Alpha-2-Globulin<br>Beta-Globulin<br>Gamma-Globulin<br>C-Reactive Protein (CRP)<br>Uric acid<br>Total cholesterol<br>Triglycerides |
| Electrolytes | Sodium<br>Potassium<br>Chloride<br>Calcium<br>Inorganic phosphate |

Table 5.2.3: 1 Routine laboratory tests (cont).

| Functional lab group | Test name |
|---|---|
| Urinalysis (Stix) | Urine nitrite<br>Urine protein<br>Urine glucose<br>Urine ketone<br>Urobilinogen<br>Urine bilirubin<br>Urine erythrocytes<br>Urine leukocytes<br>Urine pH |
| Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are clinically relevant abnormal in urine) | Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes) |

[1] Protein electrophoresis only at screening. Hormones only at screening and end of trial.
[2] Only if confirmation of postmenopausal stage is needed

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which 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 test and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, Day -1, Day 13, Day 27, and as part of the end of trial examination. Drug screening will be performed at screening, Day -1, Day 13, Day 27and end of treatment.

Table 5.2.3: 2 Exclusionary laboratory tests

| Functional lab group | Test name |
|---|---|
| Drug screening (urine) | Amphetamine/MDA<br>Barbiturates<br>Benzodiazepine<br>Cannabis<br>Cocaine<br>Methadone<br>Methamphetamines/MDMA/XTC<br>Opiates<br>Phencyclidine<br>Tricyclic antidepressants |
| Infectious serology (blood) | Hepatitis B surface antigen (qualitative)<br>Hepatitis B core antibody (qualitative)<br>Hepatitis C antibodies (qualitative)<br>HIV 1+2-antibody/p24-antigen Combitest |
| Pregnancy test (urine) | Beta human chorionic gonadotropin (beta-HCG) |

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed at screening and prior to each treatment period, 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.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of the urinalysis (stix), drug screening and pregnancy tests. These tests will be performed at the trial site using, Combur 9 Test, MAHSAN® –Kombi/DOA10 rapid test and TestPack+Plus hCG Urin respectively.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

### 5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, and modified Goldberger and Einthoven (Mason-Likar). The same electrode positions on a specific subject should be used for all ECG recordings throughout the study.

Triple ECGs (recorded within 180 sec) will be recorded on all time points on Day 1, Day 2, Day 14, Day 15, Day 21, Day 28 and Day 29. On all other visits/time points single ECGs will be obtained. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). For time points with triple ECGs, all three single ECGs will be repeated.

In order to achieve a stable heart rate at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for 10-sec duration after the subjects have rested for at least 5 min in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all subjects are at complete rest during the recordings. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

All locally printed ECGs will be evaluated by the investigator or a designee. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

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 ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for centralized evaluation (see below). In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings 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.

All recorded ECGs will be sent electronically to an independent ECG core lab. The centralised evaluation of all 12-lead ECGs recorded on Day 1 to Day 4, Day 7, Day 14 to

Day 17, Day 21, and Day 28 to Day 29 will be performed by an independent ECG laboratory. In case it is needed ECGs recorded at other visits/time points may also undergo centralized evaluation.

For this analysis, all cardiac intervals (PR, QRS, RR and and QT intervals) will be determined semi-automatically, whereas PR and QRS intervals are determined by a validated GE 12-SL-algorithm or equivalent. Other parameters (e.g. cardiac axis) are determined by a validated GE 12-SL-algorithm or equivalent but do not undergo semiautomatic evaluation. All interval measurements for each 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 blinding status see Section 4.1.5.1. No more than two different blinded readers will evaluate all ECGs of the study. 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 with respect to the overall variance of the measured intervals, in order to detect accidentally switching of leads and/or false subject assignments of the ECGs. After the quality control the fiducial point markings will be reviewed by the cardiologist assigned to the study. Abnormalities detected during centralized ECG evaluation will not necessarily qualify as AE.

The results of the centralized evaluation will be sent from the ECG core lab to the data management of BI according to a pre-specified data transmission agreement.

Assessed ECGs will comply with the ICH E14 guidance document and supplements [R05-2311, R13-0801, R13-4095] as well as the FDA requirements for annotated digital ECGs [R09-4830].

### 5.2.5 Assessment of other safety parameters

#### 5.2.5.1 Vital signs

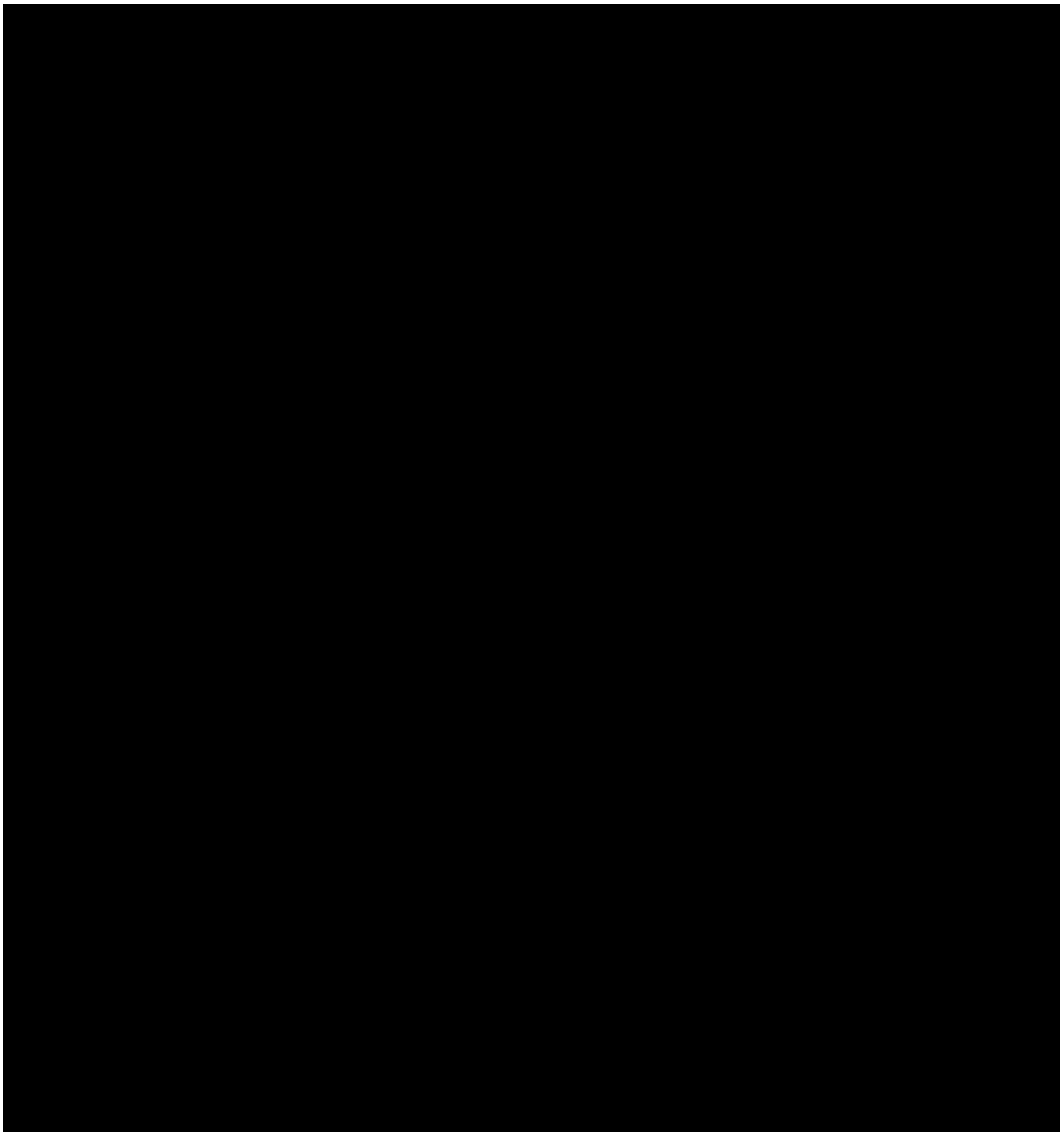
Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (Dinamap, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position and after ECG recording was taken. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

#### 5.2.5.2 Medical examinations

At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination with determination of weight.

5.2.5.3 Ophtalmological examination

A slit lamp examination (Carl Zeiss Jena RSL 110) will be conducted by an ophthalmologist at screening, Day 15, Day 29 and EOT to exclude findings suspicious for signs of cataract.



## 5.4 APPROPRIATENESS OF MEASUREMENTS

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 appropriate way. 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 5.5 are generally used assessments of drug exposure. The biomarker measurements outlined in Section 5.6 are of exploratory nature only.

## 5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and exact time points of blood sampling will be documented in the CRFs by the medical personnel. 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 510 mL. Such changes would be implemented via non-substantial CTP Amendments.

### 5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

#### 5.5.1.1 Secondary endpoints

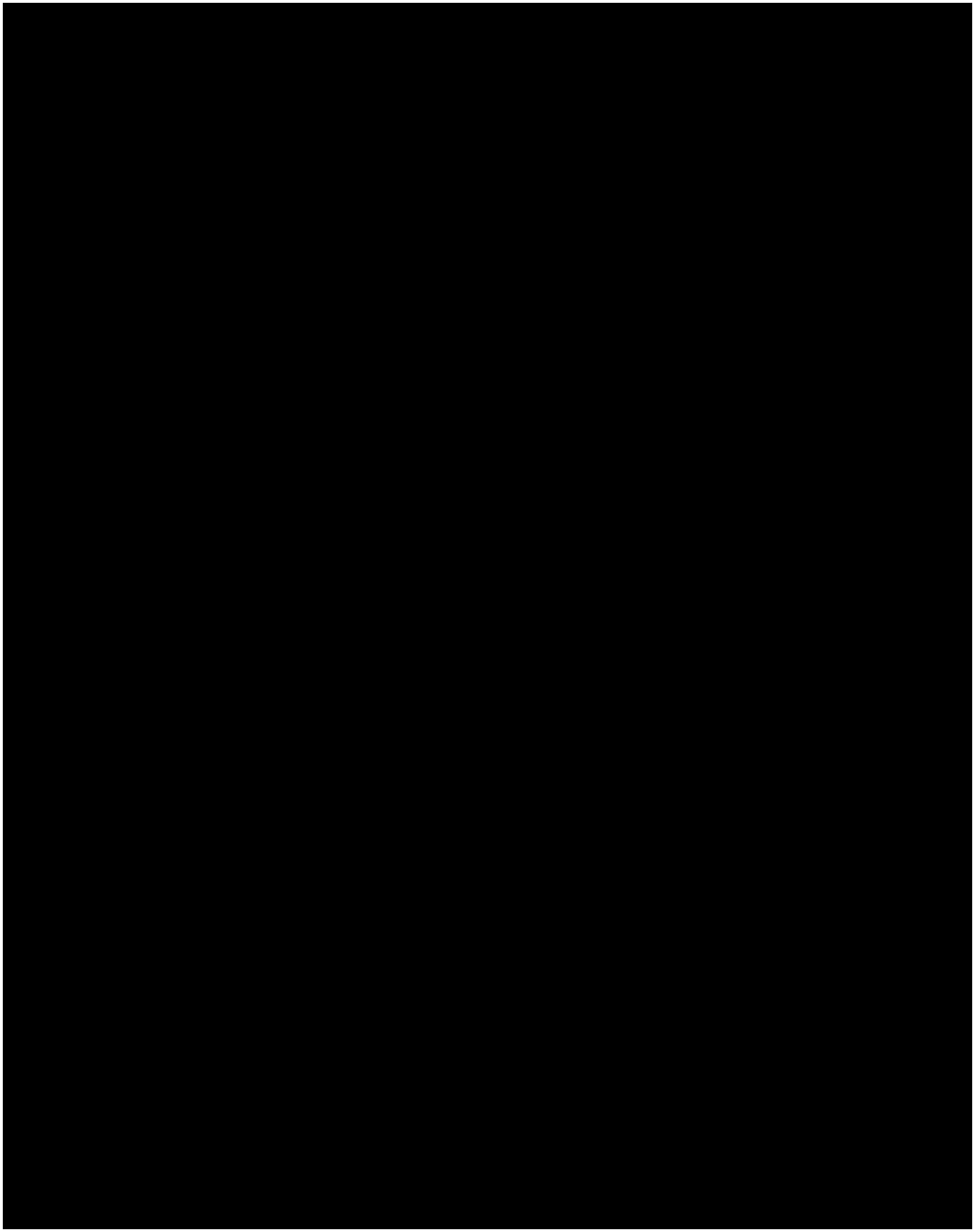
After the first dose (Day 1):

- $AUC_{0-24}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration of the first dose)
- $C_{max}$ (maximum measured concentration of the analyte in plasma after administration of the first dose)

After the last dose (Day 28):

- $AUC_{0-24,28}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration of the $28^{th}$ dose)
- $C_{max,28}$ (maximum measured concentration of the analyte in plasma following administration of the $28^{th}$ dose)

[redacted]



### 5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1467335 plasma concentrations, approx. 2.7 mL of blood will be taken from an antecubital or forearm vein into a $K_3$-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

30 µL phenelzine solution (approx. 50 mM/L) will be added to all blood samples before withdrawal. All blood samples will be centrifuged using a cooled centrifuge at about 2000 x g to 4000 x g and at a temperature of 4 - 8°C for at least 10 minutes (intermittent storage on ice). The obtained $K_3$-EDTA plasma will be split into two cryotubes (e.g. Nunc tubes) which will be frozen immediately and not later than 60 min after blood sampling with interim storage on ice. One of the aliquots should contain at least 0.7 mL plasma. The second aliquot containing the remaining plasma will be used as analytical back-up sample. Until transfer on dry ice to the analytical laboratory, the plasma samples will be stored frozen and in upright position at about –20°C or below at the clinical site and at the analytical laboratory until analysis.

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) 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.

5.5.2.2 Plasma sampling for drug metabolism analysis

Additional $K_3$-EDTA plasma samples for the identification of drug metabolites will be investigated in all dose groups. The blood samples will be drawn in parallel to the PK

samples on Day 28 to 29 (see Flow Chart). At each of these time points, 2.7 ml blood will be needed for metabolite analysis. The blood samples will be centrifuged using a cooled centrifuge at about 2000 x g to 4000 x g and at a temperature of 4 - 8°C for at least 10 minutes (intermittent storage on ice). The obtained K3-EDTA plasma (approximately 1 mL) will be transferred into a single polypropylene tube. Samples will be stored at about -70°C or below until transfer to the metabolism laboratory.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, planned sampling time and 'MetID'. Further information such as matrix and analyte may also be provided.

Metabolite analysis will be performed under non-GxP conditions in the laboratory of

Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics
Birkendorfer Straße 65
88397 Biberach/Riß, Germany

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 3 years after the final study report has been signed.

#### 5.5.2.3 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (within 2 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 will be collected in 2 L polyethylene (PE) containers and stored at room temperature. Subjects will be told to empty their bladders at the end of each sampling interval.

The urine weight/volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented and two 2 mL aliquots (e.g. Nunc tubes) will be stored for bioanalytical measurement. The weight of the empty container will be determined and the weight of the container at the end of each sampling interval will be determined.

Until transfer to the analytical laboratory, the urine samples will be stored at about -20°C or below at the clinical site and stored at the analytical laboratory at –20°C or below until analysis. The back-up aliquots will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot.
After completion of the trial the urine 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) 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.

5.5.2.4 Additional blood sample for stability-testing

In order to assess the stability of the analyte in whole blood, one additional blood sample each on days 1, 14 and 28 will be taken from all subjects of dose group 10 mg and 15 mg.

Approximately 3.6 mL blood will be taken from an antecubital or forearm vein using three 1.2 mL $K_3$ EDTA-blood drawing tubes at the time indicated in the Flow Chart (immediately after the drawing of a regular blood PK sample, which is to say that no additional venous puncture will be necessary).

To the first two 1.2 mL $K_3$ EDTA-blood drawing tubes 10µL phenelzine solution (approx. 50 mM/L) will be added before taken from all subjects of dose group 1 and 2 at the time indicated in the Flow Chart.

Approx. 0.5 mL of plasma will be generated out of each blood sample:

- Sample handling for stability samples of dose group 2, procedures will be provided in a separate lab manual.Blood sample one (‘stability reference’) will be centrifuged within 10 min after collection. Centrifugation will last for about 10 min (at about 2000 g to 4000 g and 4 to 8 °C), plasma will be separated and transferred into a freezer.
- Blood sample two and three (‘stability test’) will be stored for about 4 h at room temperature and ambient light conditions (documentation of storage time necessary) and will then be centrifuged and stored according to the first sample. To the plasma sample from blood sample three 5µL phenelzine solution (approx. 50 mM/L) will be added before freezing.

At a minimum, the aliquots should be labelled with the following information: BI trial number, administered drug, subject number, planned sampling time, ‘stability reference’ or ‘stability test’.

Until transfer to the analytical laboratory, all aliquots will be stored at about -20 °C or below at the clinical site. All aliquots will be provided to the responsible bioanalyst together with the information about sample handling (i.e. storage time of ‘test sample’ at room temperature). After receipt, the aliquots will be stored at the bioanalytical laboratory at about -20°C or below until analysis.

The results of the analysis of these samples will not be reported within this clinical trial but will be used for bioanalytical assay validation and therefore included in the corresponding method validation report. The remaining sample volume will be discarded upon completion of the method validation report at the latest.

### 5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 1467335 plasma concentration

BI 1467335 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay.

The analysis will be performed at:

Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics
Birkendorfer Straße 65
88397 Biberach/Riß, Germany

As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis.

5.5.3.2 Analytical determination of analyte urine concentration

BI 1467335 concentrations in urine will be determined by a validated LC-MS/MS assay

The analysis will be performed at:

Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics
Birkendorfer Straße 65
88397 Biberach/Riß, Germany

# 6. INVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1, Day 14, and Day 28 are to be performed and completed within a 2 h-period prior to the trial drug administration (including blank values for PK and biomarkers collected predose on Day 1).

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min for the first 4 h after trial drug administration and ± 30 min thereafter when not already stated otherwise in the flowchart.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. 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 the Flow Chart. 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 Blinded Report Planning Meeting.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

Before first dosing on day 1 pharmacogenomic genotyping will be performed in all subjects (for details see Section 5.3).

### 6.2.2 Treatment period

Each subject will receive a single dose of BI 1467335 or placebo from Day 1 to Day 28.

Study participants will be admitted to the trial site in the evening of day -1 and kept under close medical surveillance for at least 24 h following the first /last drug administration. The

subjects will be kept hospitalized from the evening of Day -1 to the morning of Day 4, the evening of Day 13 to the morning Day 17 and from the evening of Day 27 to the morning of Day 29.On all other time periods the study will be performed in an ambulatory fashion provided there are no medical reasons preventing the discharge from the unit.

For details on time points and procedures for collection of plasma and urine samples for PK analysis, refer to Flow Chart and Section 5.5.2.

The safety measurements performed during the treatment period are specified in Section 5.2. of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

### 6.2.3 End of trial and follow-up period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial 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. Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised.

The end of the trial as a whole is defined by the ‘last regular visit completed by last subject’ or ‘end date of the last open AE’ or ‘date of the last follow-up test’ or ‘date of an AE has been decided as sufficiently followed-up’, whichever is latest.

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN – MODEL

### 7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 1467335 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) [redacted] ) of BI 1467335. Endpoints as specified in 5.5.1 and 5.7.1 will be analysed by descriptive statistics. Secondary endpoints as defined in Section 5.5.1.1 will be subjected to analysis of dose proportionality by use of the power model. [redacted]

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 3 different dose groups of BI 1467335 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 have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

## 7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified no later than in the Report Planning Meeting and provided in the TSAP.

### 7.3.1 Primary analyses

All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the treated set.

The primary endpoint will be analysed only descriptively on the treated set. For more details see Section 7.3.3.

The secondary endpoints (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472].

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 violation relevant to the evaluation of PK (to be decided no later than in the 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 violations 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.

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description above. All statistical evaluations of PK parameters will be based on the PKS.

Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

Assessment of dose proportionality

Dose proportionality will be assessed using the pharmacokinetic endpoints $AUC_{0-24}$, $C_{max}$, $AUC_{0-24,28}$ and $C_{max,28}$ as specified in 5.5.1.1.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

| | |
|---|---|
| $Y_{ij}$ | logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, 3, j = 1, 2, …, N; |
| $\alpha$ | intercept parameter; |
| $\beta$ | slope parameter; |
| $X_i$ | logarithm of dose i; |
| $\varepsilon_{ij}$ | random error associated with subject j at dose level i (assumed to be independent and identically normally distributed). |

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

When steady state is already reached after 14 days of treatment, dose proportionality will be also investigated for $AUC_{0\text{-}24,14}$ and $AUC_{0\text{-}24,28}$ together ($C_{max,14}$ and $C_{max,28}$ respectively) using the following model accounting for the repeated measurement per subject:

$$Y_{ijk} = \alpha + \beta * X_i + \gamma T_k + \varepsilon_{ijk}$$

where

| | |
|---|---|
| $Y_{ijk}$ | logarithm of the pharmacokinetic endpoint for subject j at dose level I on day k; where i = 1, 2, 3, j = 1, 2, …, N; |
| $\alpha$ | intercept parameter; |
| $\beta$ | slope parameter; |
| $X_i$ | logarithm of dose i; |
| $T_k$ | Categorical day variable where $T_k = 0$ when PK parameter is from day 14 and $T_k = 1$ when PK parameter is from day 28 |
| $\varepsilon_{ijk}$ | random error associated with subject j at dose level i (assumed to be independent and identically normally distributed). |

Linearity index

Linearity will be explored if data allow using the linearity index (LI) that will be computed as follows:

$$LI = \frac{AUC_{\tau,ss}}{AUC_{0-\infty}}$$

The $AUC_{\tau,ss}$ can be $AUC_{0-24,14}$ and/or $AUC_{0-24,28}$ depending on when the steady state is reached. If steady state is not reached within the 28 days, no linearity index will be evaluated.

In order to construct a confidence interval for LI, a statistical model using $AUC_{\tau,ss}$ and $AUC_{0-\infty}$ will be set up: A linear model on the logarithmic scale including effects for 'subject' and 'AUC type' can be applied, where 'subject' is a random and 'AUC type' a fixed effect.

[1] $Y_{ij} = \mu + \tau_i + s_j + e_{ij}$, where

$Y_{ij}$ logarithm of the response (AUC after first dose and at steady state) for subject j and AUC type i; where i = 1 (after first dose) or 2 (at steady state) and j=1, 2,…, n

$\mu$ the overall mean

$\tau_i$ the AUC type i

$s_j$ the effect associated with subject j (random effect)

$e_{ij}$ random error associated with subject j at AUC type i (assumed to be independent and identically normally distributed).

A pairwise comparison of both areas via the log transformed difference

$\log(\frac{AUC_{\tau,ss}}{AUC_{0-\infty}}) = \log(AUC_{\tau,ss}) - \log(AUC_{0-\infty})$

will then be performed including calculation of a 2-sided 95% CI. The back transformed point estimate then represents the estimate of LI. Perfect linearity holds true if this index equals unity.

Generally, this model will be applied to each dose level separately. If there is evidence that the areas are comparable across dose levels, they can be analysed simultaneously. The corresponding model will then include the log transformed dose as (additional) covariate

[redacted]

[redacted]

*Graphical displays*

To support the analyses of dose proportionality, linearity and [redacted] graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough and 1 h post-dose plasma concentrations and the (geometric) mean plasma concentration time profiles.

[redacted]

### 7.3.3 Safety analyses

Safety will be assessed for the primary endpoint and parameter of interest listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. The active 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.

The analyses will be done by ‘treatment at onset’.

Measurements (such as ECG, 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 'screening', those between first trial medication intake until the trial termination date will be assigned to the treatment period, and those after the trial termination date will be assigned to ‘post-study’. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity according to CTCAE grading and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline will be evaluated.

For vital signs, the differences from baseline will be evaluated.

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the derivation of further ECG parameters based on the ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR. The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to drug administration. It is planned to evaluate the difference to placebo of change from baseline for QTcF, QT and HR over time via a repeated measurements model as well as the exposure response relationship of change from baseline for QTcF, QT and HR. More details on this and further analysis as well as the derivation of the quantitative and qualitative ECG endpoints are given in the TSAP.

### 7.3.4 Preliminary PK analyses

At least 7 preliminary analyses of plasma PK parameters ($C_{pre}$, $C_1$, $AUC_{0-24}$ and $C_{max}$) are planned to be performed to ensure that assessed or extrapolated systemic exposure to BI 1467335 will not exceed predefined margins (see Section 2.3). Additional preliminary PK analyses may be performed based on the request of the Trial Clinical Monitor, the Investigator, or Trial Clinical Pharmacokineticist if deemed necessary based on the results of available preliminary PK analyses, tolerability and safety of the compound, or changes of dosing schedule (e.g. additional intermediate doses).

1st analysis: after both cohorts of the first dose group (10 mg) have been treated for 28 days. All plasma samples collected up to this time point will be analysed, and the data (if possible, together with data from a previous multiple rising dose study [c09036683-01]) will be used for extrapolation of $C_{max}$ and $AUC_{0-24}$ on days 14 and 28 with higher doses of BI 1467335, to support the decision to start with the first cohort of the second dose group (planned: 15 mg).

2nd analysis: after the first cohort of the second dose group (15 mg) has been treated for 7 days. All plasma samples collected up to this time point will be analysed and the data will support the decisions to continue with the treatment of the first cohort and to start with treatment of second cohort.

3rd analysis: after the second cohort of the second dose group (15 mg) has been treated for 14 days. All plasma samples collected up to this time point will be analysed and the data will support the decisions to continue with the treatment of the first and second cohort and to start with treatment of the third cohort.

4th analysis: after all three cohorts of the second dose group (15 mg) have been treated for 28 days. All plasma samples collected up to this time point will be analysed, and the data (together with those from the previous preliminary analyses) will be used for extrapolation of $C_{max}$ and $AUC_{0-24}$ on days 1, 14 and 28 with higher doses of BI 1467335, to support the decision to start with the first cohort of the third dose group (20 mg).

5th analysis: after the first cohort of the third dose group (20 mg) has been treated for 7 days. All plasma samples collected up to this time point will be analysed and the data will support the decisions to continue with the treatment of the first cohort and to start with treatment of second cohort.

6th analysis: after the second cohort of the third dose group (20 mg) has been treated for 14 days. All plasma samples collected up to this time point will be analysed and the data will support the decisions to continue with the treatment of the first and second cohort and to start with treatment of the third cohort.

7th analysis: after all three cohorts of the third dose group (20 mg) have been treated for 28 days. All plasma samples collected up to this time point will be analysed, and data (together with those from the previous preliminary analyses) will be used for extrapolation of $C_{max}$ and $AUC_{0-24}$ on days 1, 14 and 28 with higher doses of BI 1467335, to support the decision whether to include further dose groups into the study.

In contrast to the final PK calculations, the preliminary analyses will be based on planned sampling times rather than on actual times. Therefore, minor deviations of preliminary and final results may occur. The preliminary analyses will provide individual concentration-time data and PK parameters (without subject identification) and descriptive statistics thereof.

The preliminary results will be distributed to the Investigator and the trial team. The PK data together with safety and tolerability results will be used for decisions to continue with treatments as described above. No formal preliminary PK report will be written.

No inferential statistical interim analysis is planned.

### 7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1467335 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472].

Subjects who are not included in the PKS (refer to Section 7.3.1) will be reported with their individual plasma / urine concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for, pharmacokinetic parameters or other statistical assessment.

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 provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

Descriptive evaluations of PK parameters listed in 5.5.1.2 are based on PKS.

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic coefficient of variation, standard deviation, minimum, median, and maximum. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

In addition, the PK data from this study may be included in a population PK analysis at the project level. This analysis will not be part of the CTR, but will be reported separately.

[redacted]

## 7.4 HANDLING OF MISSING DATA

### 7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

### 7.4.2 Plasma/urine drug concentration - time profile

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor [001-MCS-36-472].

For tabulation and graphical displays, drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), or BLQ (below the lower limit of quantification) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

For the calculation of PK parameters by non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

### 7.4.3 Pharmacokinetic parameters

No imputation of missing PK parameters will be performed.

[redacted]

## 7.5 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

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

## 7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 36 subjects in this trial. The planned sample size is not based on a power calculation. The size of 12 subjects per dose group (9 on active treatment, and 3 on placebo) 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 [R95-0013].

Additional subjects may be entered to allow testing of additional doses within the planned dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 36.

# 8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

## 8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND 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 a subject's 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 are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## 8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

## 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

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

### 8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

## 8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP. Furthermore the U.S. Food and Drug Administration (FDA) will also receive all SAEs and AESIs expedited.

## 8.5 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

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

## 8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last subject/subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

P13-02280 Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2012; 10:837-58.

R95-0013 Broom C. Design of first-administration studies in healthy man. Early Phase Drug Evaluation in Man. O'Grady J, Linet OI (Eds.), Macmillan Press: London, 1990, 206 213.

R05-2311 ICH E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH harmonised tripartite guideline, recommended for adoption at step 4 of the ICH process on 12 May 2005 by the ICH Steering Committee). www.emea.eu.int 2005:1-14.

R05-0788 Hoffman D, Kringle R, Lockwood G, Turpault S, Yow E, Mathieu G. Nonlinear mixed effects modelling for estimation of steady state attainment. Pharm Stat. 2005.

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

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

R12-1392 Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Lente F van, Greene T, Coresh J, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-612.

R13-0801 E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs - Questions and Answers (R1). October 2012. website.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm323656.htm

R13-4095 European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP): ICH guideline E14 - questions and answers: step 5 (May 2012, EMA/CHMP/ICH/310133/2008). website.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002878.pdf

R15-1863 Inoue T, Morita M, Tojo T, Nagashima A, Moritomo A, Miyake H. Novel 1H-imidazol-2-amine derivatives as potent and orally active vascular adhesion protein-1 (VAP-1) inhibitors for diabetic macular edema treatment. Bioorg. Med. Chem. 2013; 21:3873-3881.

R15-1868 Foot JS, Deodhar M, Turner CI, et al. The discovery and development of selective 3-fluoro-4-aryloxyallylamine inhibitors of the amine oxidase activity of semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1). Bioorg. Med. Chem. Lett. 2012; 22:3935.

R15-2803 Stolen CM, Marttila-Ichihara F, Koskinen K, et al. Absence of the endothelial oxidase AOC3 leads to abnormal leukocyte traffic in vivo. Immunity. 2005; 22:105-115.

R15-5365 Weston CJ, Shepherd EL, Claridge LC et al. Vascular adhesion protein-1 promotes liver inflammation and drives hepatic fibrosis. Journal of Clinical Investigation. 2015; 125:501-520.

R15-5652 Bonder CS, Norman MU, Swain MG, et al. Rules of recruitment for Th1 and Th2 lymphocytes in inflamed liver: a role for alpha-4 integrin and vascular adhesion protein-1. Immunity 2005; 23:153-163.

R15-5654 Koskinen K, Vainio PJ, Smith DJ, et al. Granulocyte transmigration through the endothelium is regulated by the oxidase activity of vascular adhesion protein-1 (VAP-1). Blood. 2004; 103: 3388-3395.

R15-5697 Karim S, Liaskou E, Fear J, Garg A, Reynolds G, Claridge L, Adams DH, Newsome PN, Lalor PF. Dysregulated hepatic expression of glucose transporters in chronic disease: contribution of semicarbazide-sensitive amine oxidase to hepatic glucose uptake. Am J Physiol 2014; 307 (12): G1180 - G1190.

R15-5770 Vainio PJ, Kortekangas-Savolainen O, Mikkola JH, Jaakkola K, et al. Safety of blocking vascular adhesion protein-1 in patients with contact dermatitis. Basic Clin. Pharmacol. Toxicol. 2005; 96: 429-435.

R15-5803 Jaakkola K, Nikula T, Holopainen R, et al. In vivo detection of vascular adhesion protein-1 in experimental inflammation. Am. J. Pathol. 2000; 157: 463471.

R15-5804 Jalkanen S, Salmi M. VAP-1 and CD73, endothelial cell surface enzymes in leukocyte extravasation. Arterioscler. Thromb. Vasc. Biol. 2008; 28:18-26.

R15-6044 Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association Hepatology. 2012; 55:2005-2023.

R15-6045 Marttila-Ichihara F, Smith DJ, Stolen C, et al. Vascular amine oxidases are needed for leukocyte extravasation into inflamed joints in vivo. Arthritis Rheum. 2006; 54:2852.

R15-6046 Lalor PF, Edwards S, McNab G, et al. Vascular adhesion protein-1 mediates adhesion and transmigration of lymphocytes on human hepatic endothelial cells. J. Immunol. 2002; 169: 983.

R15-6047 Salter-Cid LM, Wang E, O'Rourke AM, et al. Anti-inflammatory effects of inhibiting the amine oxidase activity of semicarbazide-sensitive amine oxidase. J. Pharmacol. Exp. Ther. 2005; 315: 553.

R15-6048 Xu HL, Salter-Cid L, Linnik MD, Wang EY, Paisansathan C and Pelligrino DA. Vascular adhesion protein-1 plays an important role in post ischemic inflammation and neuropathology in diabetic, estrogen-treated ovariectomized female rats subjected to transient forebrain ischemia. J. Pharmacol. Exp. Ther. 2006; 317:19.

R15-6056 O'Rourke AM, Wang EY, Miller A, Podar EM, et al. Anti-inflammatory effects of LJP 1586 [Z-3-fluoro-2-(4-methoxybenzyl)allylamine hydrochloride], an amine-based inhibitor of semicarbazide-sensitive amine oxidase activity. J. Pharmacol. Exp. Ther. 2008; 324: 867.

R15-6057 Murphy SL, Xu J and Kochanek KD. Deaths: final data for 2010. Centers for Disease Control and Prevention website: www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf (Updated May 8, 2013. Accessed February 6, 2014).

R15-6058 Merinen M, Irjala H, Salmi M, Jaakkola I, Hanninen A, Jalkanen S. Vascular adhesion protein-1 is involved in both acute and chronic inflammation in the mouse. Am J Pathol. 2005;166:793-800.

R15-6059 Lee WY, Salmi M, Kelly MM, Jalkanen S and Kubes P (2013) Therapeutic advantage of anti-VAP-1over anti-α4 integrin antibody in concanavalin Ainduced hepatitis. Hepatology 2013; 58:1413.

R15-6070 Dharel N, Fuchs M. Nonalcoholic Fatty Liver Disease – A Major Public Health Challenge for the 21st Century. JSM Gastroenterology and Hepatology. 2014; 1018.

## 9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

c04751792 [redacted] Investigator's Brochure: BI 1467335 in NASH 09 Feb 2016.

c09036683 Single ascending dose and multiple ascending dose Phase 1 study of PXS-4728A administered orally in healthy adult males. PXS-4728A-101. 13 Nov 2015.

n00244592 BI 1467335: 4-week oral (gavage) supplementary toxicity study in Sprague Dawley rats. 15B108.

n00244640 [redacted] PART: FORMULATION ANALYSIS REPORT 15B108.

n00246522 [redacted] Study to investigate the protein binding of the test compound, 4728A, in human and rat plasma CYP0526 R1, R3, R3A 12 Oct 2015.

n00247448 PXS-4728A: 7-day Oral Dose Range Toxicity Study in Beagle Dog. VPT1073. 25 Sep 2013.

n00247807 Functional Observational Battery (FOB) Study of PXS-4728A in Sprague Dawley Rats. 53702-14-001. 30 Oct 2014.

n00247816 A Cardiovascular Safety Pharmacology Study of PXS-4728A in Beagle Dogs. 53702-14-005. 07 Nov 2014.

n00247850 [redacted] A Four-Week Oral Repeat Dose Toxicity and Toxicokinetic Study of PXS-4728A in Beagle Dogs 53703-13-825 04 Nov 2014.

n00247851 A 4-Week Oral Dose Toxicity and Toxicokinetic Study of PXS-4728A in Sprague-Dawley Rats. 53703-13-828. 27 Feb 2014.

n00248307 In Vitro Investigation of Effects on hERG Tail Currents recorded from Stably transfected HEK293 Cells. VPT2417. 29 Aug 2014.

n00248308 A Respiratory Safety Pharmacology Study of PXS-4728A in Sprague Dawley Rats. Study No. 53702-14-999. 30 Oct 2014.

# 10. APPENDICES

## 10.1 RECONSTITUTION INSTRUCTION

### 10.1.1 Drug supplies overview

a) BI 1467335 Powder for Oral Solution 40 mg (target solution concentration BI 1467335: 0.5 mg/mL), provided in 100 mL amber glass bottles with plastic screw cap

b) Solvent for Oral Solution 80 mL (Sucralose 4 mg/ml +Menthol 2 mg/ml) provided in 100 ml glass vials with tear-off caps

c) Empty appropriately labeled amber glass bottle, 100ml with plastic screw-cap

### 10.1.2 Required equipment and dosing aids - overview

a) Mechanical (reciprocal) shaker for bottles (e.g. Bühler Type KL2)

b) Dosing dispensers/syringes and bottle adapters

For the withdrawal of respective volume aliquots from the final oral solution to be administered amber BAXA ExactaMed oral dispensers/ syringes should be used in a size as close as possible to the required dose volume. For this purpose a range of syringe sizes from 1 mL up to 60 mL should be stocked in the trial sites.
In order to ease the withdrawal of the oral solution from the glass bottles with the amber BAXA ExactaMed syringes BAXA bottle adapters and dispenser tip caps (e.g. Order No 50300) should be used and stocked in the trial sites, preferably BAXA Press-In Bottle Adapters (PIBA$^{TM}$) – e.g. Order No. H9382001or BAXA AdaptaCap Bottle Adapters (E-28 mm) –e.g. Order No. 5105.

Possible amber BAXA ExactaMed dispensers/ syringes

- BAXA ExactaMed amber oral dispenser 1 mL – e.g. Order No – 1601
- BAXA ExactaMed amber oral dispenser 3 mL – e.g. Order No – 1602
- BAXA ExactaMed amber oral dispenser 5 mL – e.g. Order No – 1605
- BAXA ExactaMed amber oral dispenser 10 mL – e.g. Order No – 1610
- BAXA ExactaMed amber oral dispenser 20 mL – e.g. Order No – 1620
- BAXA ExactaMed amber oral dispenser 35 mL – e.g. Order No – 1635
- BAXA ExactaMed amber oral dispenser 60 mL – e.g. Order No – 1650

Only CE certified syringes are to be used!

### 10.1.3 Reconstitution procedure

2 bottle concept, see also Chapter 10.1.4.

10.1.3.1 Reconstitution procedure for the preparation of the active BI 1467335 oral solution 0.5 mg/mL

**Necessary materials**

a) BI 1467335 Powder for Oral Solution 40 mg (target solution concentration BI 1467335: 0.5 mg/mL), provided in 100 mL amber glass bottles with plastic screw cap.

b) Solvent for Oral Solution 80 mL (Sucralose 4 mg/ml + Menthol 2 mg/ml) provided in 100 mL glass vials with tear-off caps.

**Reconstitution procedure**

**Step 1:** Open the vial containing the Solvent for Oral Solution 80 mL (Sucralose 4 mg/mL + Menthol 2 mg/ml)

**Step 2:** Transfer the content of the Solvent for Oral Solution 80 mL (Sucralose 4 mg/mL + Menthol 2 mg/ml) completely and carefully into the bottle containing the BI 1467335 Powder for Oral Solution 40 mg

**Step 3:** Close the bottle with the plastic screw cap and shake the bottle manually until the BI 1467335 powder is wetted. Mount the bottle in a horizontal recumbent position on a mechanical shaker (e.g. Bühler Type KL2)

**Step 4:** Let the bottle shake for 30 min at 350 rpm in its horizontal recumbent position. Visually control that the powder is dissolved (clear to almost clear solution). After dissolution the solution is ready to use

**The final BI 1467335 Oral Solution concentration is 0.5 mg/mL.**

The allowable dose range is from 0.1 mg - 40 mg.

lowest possible dose in mg = C1 * V1
highest possible dose in mg = C1 * V2

C1 = oral solution concentration = 0.5 mg/mL
V1 = 0.2 mL corr. to the minimum volume to be withdrawn from the oral solution (assumption: use of 1 mL syringe)
V2 = 80 mL, corr. to the maximum allowable administration volume per dose

10.1.3.2 Preparation of the solvent for oral solution for use as placebo solution

**Necessary materials**

a) Solvent for Oral Solution 80 mL (Sucralose 4 mg/ml + Menthol 2 mg/ml)) provided in 100 mL glass vials with tear-off caps.

b) Empty appropriately labeled amber glass bottle, 100ml with plastic screw cap

**Solution transfer procedure**

**Step 1:** Open the vial containing the Solvent for Oral Solution 80 mL (Sucralose 4 mg/ml + Menthol 2 mg/ml)

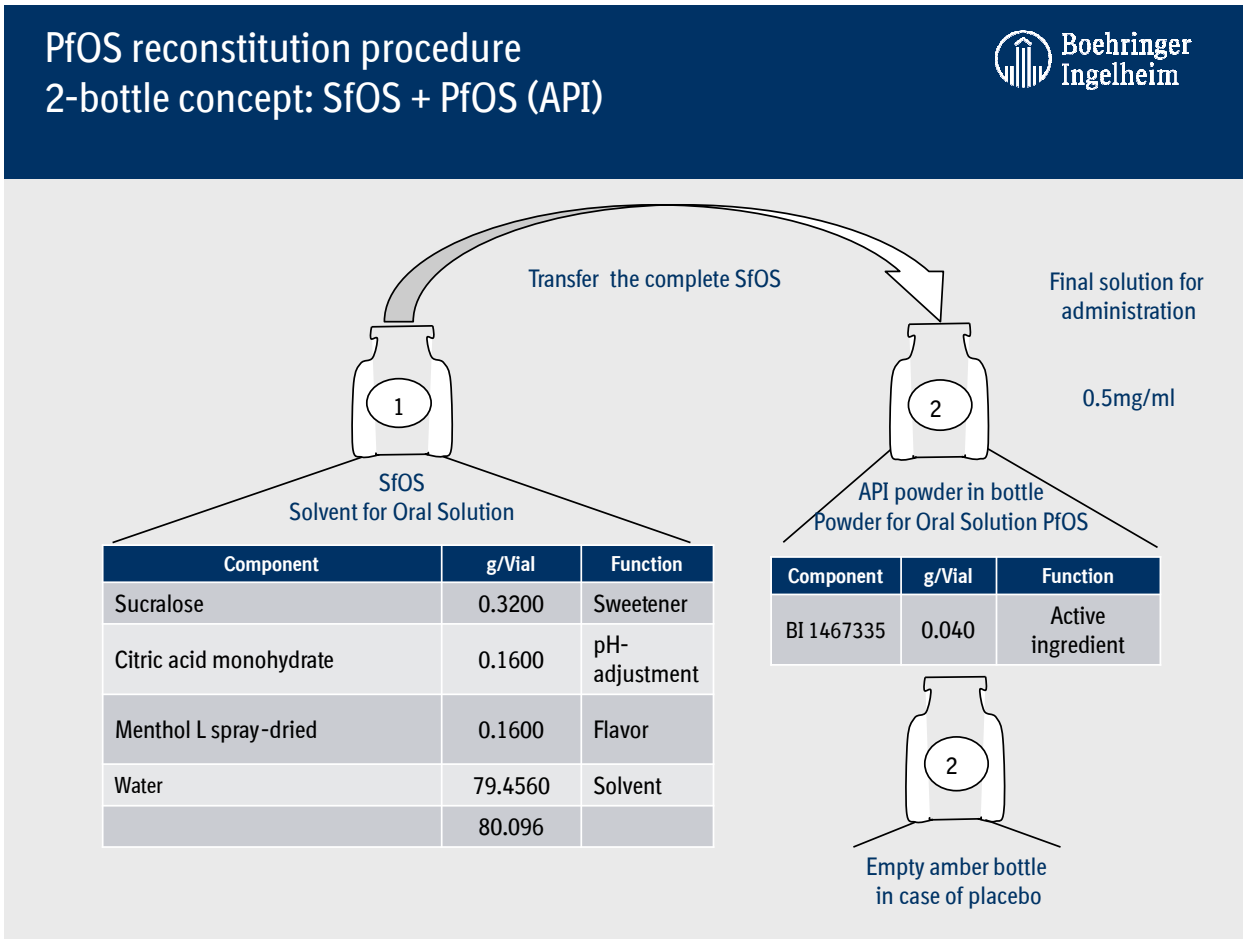
**Step 2:** After removing the screw cap, transfer the content of the Solvent for Oral Solution 80 mL (Sucralose 4 mg/ml + Menthol 2 mg/ml) completely and carefully into the empty labeled amber bottle, and reclose as appropriate with the plastic screw cap.

**Step 3:** From the transferred solution volume aliquots can be withdrawn with the Baxa Adaptacap bottle adapter and the Baxa dispenser (as outlined in section 10.1.2) according to the clinical trial protocol dose escalation step.

**The Placebo Solution is the Solvent for Oral Solution 80 ml (Sucralose 4 mg/ml + Menthol 2 mg/ml).**

### 10.1.4 Illustration of reconstitution procedure

The following scheme on the principle followed for the present PfOS formulation incl. placebo, 2-bottle concept, should serve as an additional illustration to clarify, how the reconstitution has to be performed.



The following picture shows the original powder and solvent bottles needed for the preparation of the final oral solution for administration.


### 10.1.5 In-use stability

The in-use stability of the reconstituted solution is 6 hours after its preparation, incl. storage in BAXA dispensers/syringes until administration. Further details are given on the CTS labels.

### 10.1.6 Mode of application

Withdraw the required volume aliquot with amber BAXA ExactaMed dispensers/syringes to obtain the required doses. In case the complete content of a bottle is to be used, it can be administered directly out of the bottle.
Use BAXA ExactaMed syringes at a volume size as close as possible to the volume to be withdrawn.
Please note that it is the responsibility of the investigator to assure that appropriate supplies are used for administration of a dose, based on guidance in the clinical trial protocol, and dosing is limited to the allowed dosing range for a specific dose formulation as stated in this Reconstitution Instruction.

### 10.1.7 General remarks - important!

Because of lacking analytical coverage beyond the instructed preparation procedure of the different dose formulations no further (external) dilutions of the reconstituted solutions are allowed!

The present reconstitution instruction does not contain any advice how to withdraw a specific dose from the reconstituted solutions. The specific dose volumes to be withdrawn from the described dose formulations in order to obtain a required dose will be calculated and documented by TransMed in the Clinical Trial Protocol (CTP) and subsequent documents (e.g. work sheets)!

# 11. DESCRIPTION OF GLOBAL AMENDMENTS

| | | |
|---|---|---|
| **Number of global amendment** | | 1 |
| **Date of CTP revision** | | 04 May 2016 |
| **EudraCT number** | | 2015-005049-29 |
| **BI Trial number** | | 1386.8 |
| **BI Investigational Product(s)** | | BI 147335 |
| **Title of protocol** | | Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects (double-blind, randomised, placebo-controlled within dose groups) |
| | | |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☒ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
| | | |
| **Section to be changed** | | 1. Synopsis and Flowchart<br>2. Section 1.2.5, Clinical experience in humans<br>3. Section 2, Rationale, objectives and benefit-risk assessment<br>4. Section 3.1, Overall trial design and plan<br>5. Section 3.3.2, Exclusion criteria<br>6. Section 3.3.4.1, Removal of individual subjects<br>7. Section 3.3.4.2. Discontinuation by the Sponsor<br>8. Section 4.1, Treatment<br>9. Section 5.2.2, Assessment of adverse events<br>10. Section 5.2.3, Assessment of safety laboratory parameters<br>11. Section 5.2.4.1, 12-lead resting ECG<br>12. Section 5.6.3, Methods of sample collection |

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| **Number of global amendment** | | 1 |
| | | 13. Section 7.3.4, Pharmacokinetic analysis<br>14. Section 8.4, Listedness and expedited reporting of adverse events<br>15. Section 10.1, Reconstitution instruction |
| **Description of change** | | The amended protocol includes major changes. Since most of the changes apply to several sections throughout the protocol, the changes may be described only once and not repeated for each section:<br><br>1. Synopsis, Flowchart<br>- Change of placebo (removal of quinine)<br>- Dose escalation steps modified to 10 mg, 15 mg and 20 mg, additional dose groups > 20 mg may be included taking into account predefined stopping criteria.<br>- Additional ECG recordings (including an ECG recording 15 minutes after dosing)<br>- 2 predose PD samples instead of only one sample<br>2. Section 1.2.5<br>- Correction of maximum individual $T_{max}$ to 1.1 h (instead of 1.3 h)<br>3. Section 2<br>- Deferred inclusion of subjects and implementation of more cohorts per dose group taking into account safety, tolerability and preliminary PK data<br>- Prespecified stopping criteria based on extrapolated PK data in the ongoing study ($C_{max}$ or $1/10^{th}$ AUC at NOAEL of 4 week rat study should not be exceeded)<br>4. Section 3.1<br>- Modified to comply with previous sections (Synopsis, Section 2)<br>5. Section 3.3.3.2<br>- Additional exclusion criterion GFR based on CKD-EPI > 90 ml/min<br>6. Section 3.3.4.1<br>- Additional stopping rules based on safety (such as eGFR calculated with the CKD-EPI formula < 80 ml/min; signs of rhabdomyolysis; threshold for |

| **Number of global amendment** | | 1 |
|---|---|---|
| | | thrombocytopenia, leukopenia, neutropenia)<br><br>7. Section 3.3.4.2<br>- Discontinuation criteria by the Sponsor modified to comply with previous sections<br><br>8. Section 4.1<br>- Description of treatment modified<br><br>9. Section 5.2.2<br>- Implementation of CTCAE grading<br><br>10. Section 5.2.3<br>- Additional renal safety marker (serum cystatine)<br><br>11. Section 5.2.3<br>- ECG schedule updated<br><br>12. Section 5.6.3<br>- Blood loss during the study (overall duration 6 to 7 weeks) will be ***510 mL*** *and thus in the range of a normal blood donation (500 mL)*<br><br>13. Section 7.3.4<br>- Modification of statistical section to further specify the interim PK assessments<br><br>14. Section 8.4<br>- Expedited reporting of SAEs and AEs is to FDA<br><br>15. Section 10.1<br>- Reconstitution instruction updated due to change of placebo (removal of quinine)<br><br>In connection with this amendment, minor inconsistencies such as discrepancies between text and flow chart or typing errors were corrected. |

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| **Number of global amendment** | | 1 |
| **Rationale for change** | | Based on the feedback by FDA, BfArM and Ethics Committee, the respective recommendations were included in a revised protocol. This applies for all major changes as summarized in 'Sections to be changed', in particular for the revised selection of doses, dose escalation procedures, the further deferred inclusion of subjects in the study, the withdrawal of quinidine as placebo, the implementation of additional stopping rules and the expedited reporting of (S)AEs. |

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| **Number of global amendment** | | 2 |
| **Date of CTP revision** | | 13 July 2016 |
| **EudraCT number** | | 2015-005049-29 |
| **BI Trial number** | | 1386.8 |
| **BI Investigational Product(s)** | | BI 147335 |
| **Title of protocol** | | Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects (double-blind, randomised, placebo-controlled within dose groups) |
| | | |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☐ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☒ |
| | | |
| **Section to be changed** | | 1. Abbreviations<br>2. Section 3.1, Overall trial design<br>3. Section 4.1.1, Identity of BI investigational product and comparator product<br>4. Section 4.1.5.1, Blinding<br>5. Section 5.2.3, Assessment of safety laboratory parameters<br>6. Section 5.5.2, Methods of sample collection<br>7. Section 6.2.1, Screening |
| **Description of change** | | 1. Abbreviations<br>- Added GFR<br>2. Section 3.1<br>- Correction of random numbers for replacement subjects<br>3. Section 4.1.1<br>- Powder for placebo solution deleted<br>4. Section 4.1.5.1<br>- Addition of CRA as unblinded sponsor |

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| **Number of global amendment** | | 2 |
| | | function<br>5. Section 5.2.3<br>- Minor modifications in the table section to be consistent with flow chart and text<br>6. Section 5.5.2<br>- In all PK sample tubes, replacement of the stabilizing agent semicarbazide by phenelzine<br>7. Section 6.2.1<br>- Pharmagonemic genotyping in all subjects as indicated in the flow chart |
| **Rationale for change** | | Pharmacokinetic sample handling was modified to consider most recent findings in which the stabilizing agent phenelzine was superior to semicarbazide. In context with these changes a few remaining inconsistencies were also corrected. |

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| **Number of global amendment** | | 3 |
| **Date of CTP revision** | | 05 OCT 2016 |
| **EudraCT number** | | 2015-005049-29 |
| **BI Trial number** | | 1386.8 |
| **BI Investigational Product(s)** | | BI 147335 |
| **Title of protocol** | | Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects (double-blind, randomised, placebo-controlled within dose groups) |
| | | |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☒ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
| | | |
| **Section to be changed** | | 1. Synopsis<br>2. Section 2, Rationale, objectives and benefit-risk assessment<br>3. Section 3.1, Overall trial design<br>4. Section 3.3, Selection of trial population<br>5. Section 5.5.2, Methods of sample collection<br>6. Section 7.3.1 and 7.3.2 Attainment of steady state |
| **Description of change** | | Changes apply to several sections throughout the protocol and are described only once and not repeated for each section:<br>1. Deletion of dose groups > 20 mg QD.<br>2. Increase of the individual AUC threshold, which must not be exceeded by subjects, from 1/10$^{th}$ to 1/2 of the NOAEL in the 4 week rat study.<br>3. Additional Stability samples for the 15 mg Dose Group will be taken to assess more data |

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| **Number of global amendment** | | 3 |
| | | of the stability of the analyte in whole blood.<br>4. Attainment of steady state analysis via MMRM model changes to secondary analysis and nonlinear mixed model analysis added as primary analysis. |
| **Rationale for change** | | The 10 mg dose group in this ongoing study 1386.8 has recently completed the 4 week treatment period. The evaluation is ongoing, preliminary data have become available. Overall, BI 1467355 was well tolerated. There were in particular no AEs considered to be dose limiting and no SAEs, all subjects completed the treatment period per protocol. There were no clinically relevant abnormalities with respect to safety laboratory, vital signs, or ECG. In particular there were no ECG findings suggesting adverse effects on the QT interval. Preliminary PK data obtained for the 10 mg dose level shows in all subjects an AUC exposure below Cmax and 1/10th of the AUC at NOAEL in the 1 month rats study, the initially defined exposure threshold not to be exceeded by subjects. Extrapolations based on the clinical PK data derived from the completed 10 mg dose group and the data obtained with the completed 2 week Phase I study suggest that with the next planned dose of 15 mg QD over 4 weeks some subjects may exceed the 1/10th AUC margin at the end of the 4 week treatment period. The estimated mean and the 95% prediction interval of Cmax extrapolation to 15 mg are still well below the Cmax at NOAEL. As steady state was not reached after 4 weeks of treatment with 10 mg BI 1467355 it is considered to be more appropriate to use a nonlinear fit for determination of the attainment of steady state. Additional data obtained with the 15 mg dose group are considered crucial to provide a safety margin regarding the assumed maximum efficacious dose of 10 mg QD in NASH patients. Since in the completed 10 mg dose group there were no safety signals precluding the continuation with the next higher dose it is considered to be justified to increase the initial exposure threshold from 1/10$^{th}$ AUC to ½ AUC at NOAEL obtained in the 4 week toxicology study in rats. It should |

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| **Number of global amendment** | | 3 |
| | | be highlighted that all remaining stopping rules (individual discontinuation criteria or stopping rules for the whole study) will remain unchanged. In addition the study is conducted under close clinical monitoring (including central ECG reading) to early identify adverse safety signals. In context with the changes required for Amendment 3 a few remaining inconsistencies were also corrected. |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c08854973** **Technical Version Number:4.0**

**Document Name:** clinical-trial-protocol-revision-03

**Title:** Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects (double-blind, randomised, placebo-controlled within dose groups)

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Trial Statistician | [redacted] | 06 Oct 2016 10:41 CEST |
| Author-Trial Clinical Monitor | [redacted] | 06 Oct 2016 10:51 CEST |
| Author-Clinical Pharmacokineticist | [redacted] | 06 Oct 2016 11:53 CEST |
| Approval-Therapeutic Area [redacted] | [redacted] | 06 Oct 2016 14:40 CEST |
| Approval-Team Member Medicine | [redacted] | 07 Oct 2016 08:29 CEST |
| Verification-Paper Signature Completion | [redacted] | 10 Oct 2016 07:10 CEST |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|