Clinical Trial Protocol

	Document Number: **228892_1076999_3.0**
EU Trial No. **Universal Trial No.**	2023-510464-12-00 U1111-1302-4229
BI Trial No.	1447-0010
BI Investigational Medicinal Product(s)	BI 1569912
Title	A double-micro-tracer human absorption, distribution, metabolism and excretion (hADME) and absolute bioavailability trial after a single oral dose of BI 1569912 (C-14) and a single, concomitant, intravenous micro-dose of BI 1569912 (C-13) in healthy male subjects (a phase I, open-label, non-randomised, single-dose, fixed-sequence trial)
Lay Title	A study in healthy men to test how BI 1569912 is processed in the body
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: +[redacted] Fax: +[redacted]
[redacted] **Investigator**	[redacted] Phone: +[redacted] E-Mail: [redacted]
Current Version, Date	Version 3.0, 13 Nov 2024
Original Protocol Date	31 May 2024

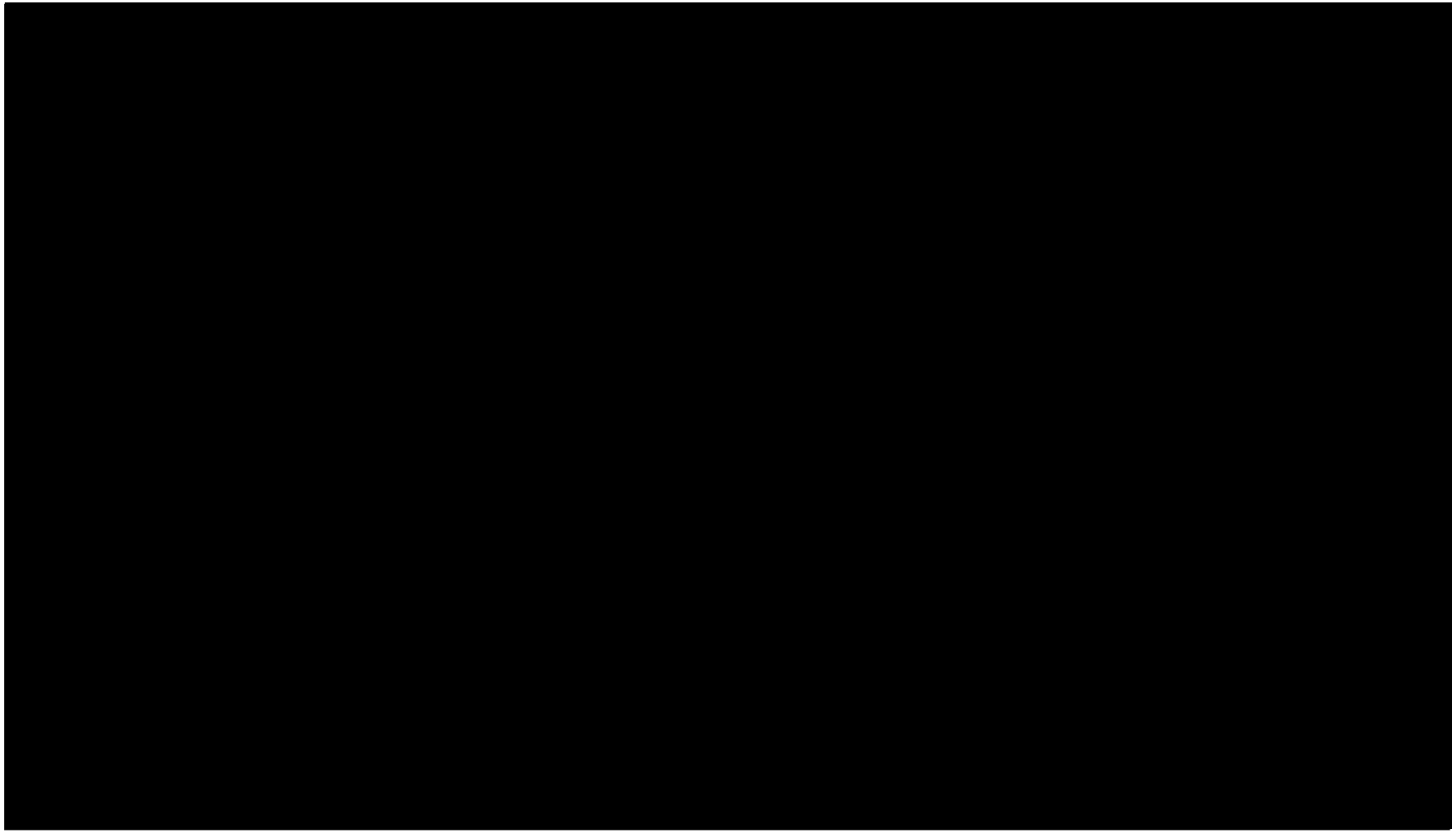
CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	31 May 2024
Revision date	13 Nov 2024
BI trial number	1447-0010
Title of trial	A double-micro-tracer human absorption, distribution, metabolism and excretion (hADME), and absolute bioavailability trial after a single oral dose of BI 1569912 (C-14) and a single, concomitant, intravenous micro-dose of BI 1569912 (C-13) in healthy male subjects (a phase I, open-label, non-randomised, single-dose, fixed-sequence trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	This combined mass balance and absolute bioavailability trial will inform the overall development program about: • The metabolism and excretion pathways, and absolute bioavailability of BI 1569912 which might necessitate specific DDI trials. • [redacted] • The necessity for conducting renal and/ or hepatic impairment trials. • Avoiding unnecessary exclusions of patients with varying renal and/ or hepatic function in safety and efficacy clinical trials which will support product approval.
Trial objectives	The main objectives are: • To assess the mass balance (total recovery of [^{14}C]-radioactivity) in urine and faeces after a single oral dose administration of BI 1569912 (C-14) (test treatment T) in healthy male subjects. • To investigate the absolute bioavailability of BI 1569912 using a single, concomitant intravenous micro-tracer administration of BI 1569912 (C-13) (reference treatment R). • To provide plasma, urine, and faecal samples for [redacted]

Trial endpoints	Primary endpoints will be: • $fe_{urine,0\text{-}tz}$ (fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point) of [^{14}C]-radioactivity. • $fe_{faeces,0\text{-}tz}$ (fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point) of [^{14}C]-radioactivity. • Sum of $fe_{urine,0\text{-}tz}$ and $fe_{faeces,0\text{-}tz}$ (total recovery of [^{14}C]-radioactivity). • $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity in plasma) of BI 1569912 and [^{13}C] BI 1569912 after a single oral administration of BI 1569912 (C-14) and a single concomitant intravenous administration of BI 1569912 (C-13). Secondary endpoints will be: • C_{max} (maximum measured concentration of the analyte in plasma) of BI 1569912 and [^{14}C]-radioactivity after a single oral administration of BI 1569912 (C-14). • C_{max} of [^{13}C] BI 1569912 after a single intravenous administration of BI 1569912 (C-13). • $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point in plasma) of BI 1569912 and [^{14}C]-radioactivity after a single oral administration of BI 1569912 (C-14). • $AUC_{0\text{-}tz}$ of [^{13}C] BI 1569912 after a single intravenous administration of BI 1569912 (C-13).
Trial design	Phase I, open-label, non-randomised, single-dose, fixed-sequence design
Number of subjects **total entered** **on each treatment**	 8 8
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 55 years (inclusive) body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product	BI 1569912 (C-14) oral [redacted] test treatment (T)
dose	[redacted] 1569912 (C-14) • [redacted] • [redacted] Containing a radioactive dose below 0.1 MBq
mode of administration	Oral [redacted] after an [redacted]
Reference product	BI 1569912 (C-13) intravenous [redacted] reference treatment (R)
dose	[redacted] BI 1569912 (C-13) • [redacted] • [redacted]
mode of admin.	Intravenous infusion [redacted] after the oral administration of [redacted] BI 1569912 (C-14)
Duration of treatment	Single dose for each treatment.
Statistical methods	Descriptive statistics will be calculated for all endpoints. Absolute bioavailability (F) will be estimated by the ratios of the geometric means (Test/Reference) for dose normalized $AUC_{0-\infty}$. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including the fixed effect for 'treatment' and 'subject' as a random effect. CIs will be calculated based on the residual error from the ANOVA.

FLOW CHART



[redacted]

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, standardized mental and neurological assessment, suicidality assessment, 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 procedure is to be performed and completed [redacted].
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. End-of-study (EoS; synonym for end of trial) examination to be performed [redacted] The EoS examination includes physical examination, standardized mental and neurological assessment, suicidality assessment, assessment of medication withdrawal, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.

5. Only drug and alcohol screening will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial but, specifically at the times points / intervals indicated in the Flow Chart above.
7. Urine collection intervals (for [^{14}C]-radioactivity [redacted] "┼" means end of last collection interval, start of following collection interval. For details on sample usage, refer to Section 5.3.2.4.
8. Stool collection (for [^{14}C]-radioactivity assessment and [redacted]. "┼" means end of last collection interval, start of following collection interval. For details on sample usage, refer to Section 5.3.2.1.
9. Subjects are to collect faeces at home within 24 h intervals before admission to in-house collection intervals. Home collection intervals: [redacted]. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces are collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
10. The planned times for admission, discharge, start and end of urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 h to the planned time.
11. Letters A and B describe different sets of safety laboratory examinations (refer to Table 5.2.3: 1).
12. Single 12-lead ECG for clinical evaluation by the investigator only. To be performed after subjects have rested for at least 5 min in a supine position. For details refer to Section 5.2.4.
13. After formal assessment and confirmation of the subject's fitness.
14. [redacted]; refer to Section 5.2.5.5 for details.
15. After discharge [redacted] the subject will continue with the EoS examination on the same day.
16. For details of standardized mental and neurological assessment, refer to Section 5.2.5.2.
17. For details of suicidality assessment (C-SSRS), refer to Section 5.2.5.3.
18. [redacted]
19. Vital signs to be measured after subjects have rested for at least 5 min in a supine position. For details of vital signs evaluation, refer to Section 5.2.2.
20. For details of local tolerability assessment, refer to Section 5.2.5.1.
21. For details of blood sampling for PK and for [redacted], refer respectively to Section 5.3.2.1 and 5.3.2.2.
22. At this time point no separate blood sample is taken for (BI 1569912, 14C, total). The back-up sample of (BI 1569912, 13C) is used for the analysis of [14C] BI 1569912.

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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
Ae feces 0-tz	Amount of analyte that is eliminated in urine from the time interval from 0 to the last quantifiable time point
Ae feces t1-t2	Amount of analyte that is eliminated in urine from the time interval t1 to t2
AESI	Adverse events of special interest
$Ae_{urine\ 0\text{-}tz}$	Amount of analyte that is eliminated in urine from the time interval from 0 to the last quantifiable time point
Aeurine t1-t2	Amount of analyte that is eliminated in urine from the time interval t1 to t2
ANOVA	Analysis of variance
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{0\text{-}24}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
$\%AUC_{tz\text{-}\infty}$	Percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation
$AUC_{t1\text{-}t2}$	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
[redacted]	
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
$CL_{R,\ t1\text{-}t2}$	Renal clearance of the analyte in plasma from the time point t_1 to t_2
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central Nervous System
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)

C-SSRS	Columbia Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EC_{50}	Half maximal effective concentration
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EFD	Embryo-foetal development
EoS	End of Study (synonym for End of Trial)
F	Absolute bioavailability factor
FAS	Full Analysis Set
FE	Food effect
fefaeces,0-tz	Fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
feurine,0-tz	Fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
feurine t1-t2	Fraction of administered drug excreted in urine from time point t1 to t2
FST	Forced swim test
GCP	Good Clinical Practice
GLP	Good laboratory practise
gMean	Geometric mean
hERG	Human ether-a-go-go related gene
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder

MDMA	Methylenedioxymethamphetamine
MEC	Minimal effective concentration
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
$MRT_{,in}$	Mean residence time of the analyte in the body, intravascular
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
NAM	Negative allosteric modulator
NMDA	N-methyl-D-aspartate
NOAEL	No observed adverse effect level
NR2B	NMDA receptor subunit 2B
OECD	Organisation for Economic Cooperation and Develeopment
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
[redacted]	
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

V_{ss}	Apparent volume of distribution at steady state after intravascular administration
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Major depressive disorder (MDD) is a common, severe, and frequently recurrent mental illness with an estimated global point prevalence of approximately 5% [R14-3147]. MDD poses a serious social and economic threat to modern societies, as it is a major cause of disability according to the Global Burden of Disease Study [R19-0778]. Despite numerous antidepressant treatment strategies, there is still significant unmet need in the treatment of MDD.

First-line antidepressants targeting the monoamine system alleviate symptoms in only 50% of patients after 12 weeks [R06-0086], and the overall cumulative remission rate with multiple treatment trials including drug switch, combination, and/ or augmentation is only 67% after up to 1 year of treatment [P06-11895]. Moreover, current treatments have a long onset of action, usually 3 to 4 weeks.

Ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor channel blocker, has demonstrated efficacy in multiple exploratory trials in patients with treatment-resistant depression (responder rate of approximately 50%), with a fast onset and an antidepressant effect of 1 week on average after a single infusion [R19-0553]. Meanwhile, the intranasal S-enantiomer esketamine received NDA approval by the FDA [R19-0829]. However, transient perceptual disturbances (dissociative reaction), sedation, blood pressure increase, and abuse potential (being a scheduled drug) require controlled distribution as well as cardiovascular and behavioral monitoring after drug application. Those unwanted effects may stem, at least in part, from ketamine's lack of selectivity, as ketamine blocks the ion channel across all NMDA subtypes [R19-0555].

Based on genetic mouse models, the NMDA receptor subunit 2B (NR2B) was identified as a key mediator of ketamine's efficacy [R19-0549]. In a small Phase II study with traxoprodil, an NR2B-specific negative allosteric modulator (NAM), the lower dose produced a rapid and robust antidepressant response without eliciting a dissociative reaction [R17-3810]. These data indicate that NR2B-selective NAMs (like traxoprodil) have a better therapeutic window compared with non-selective NMDA inhibitors (like ketamine).

1.2 DRUG PROFILE OF BI 1569912

1.2.1 Non-clinical pharmacology

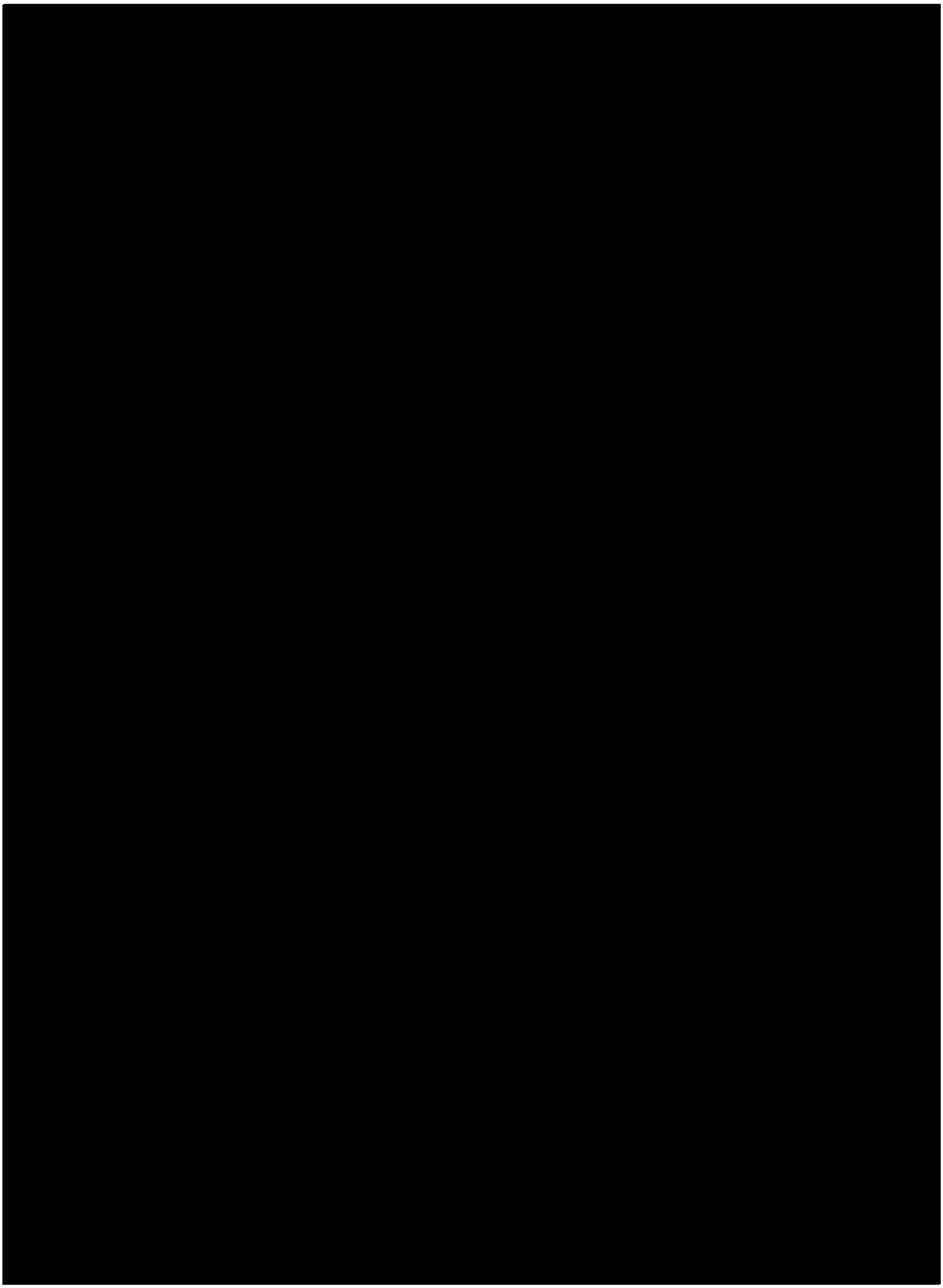
BI 1569912 is a potent negative allosteric modulator (NAM) of NR2B containing NMDA receptors with an EC50 of [redacted]

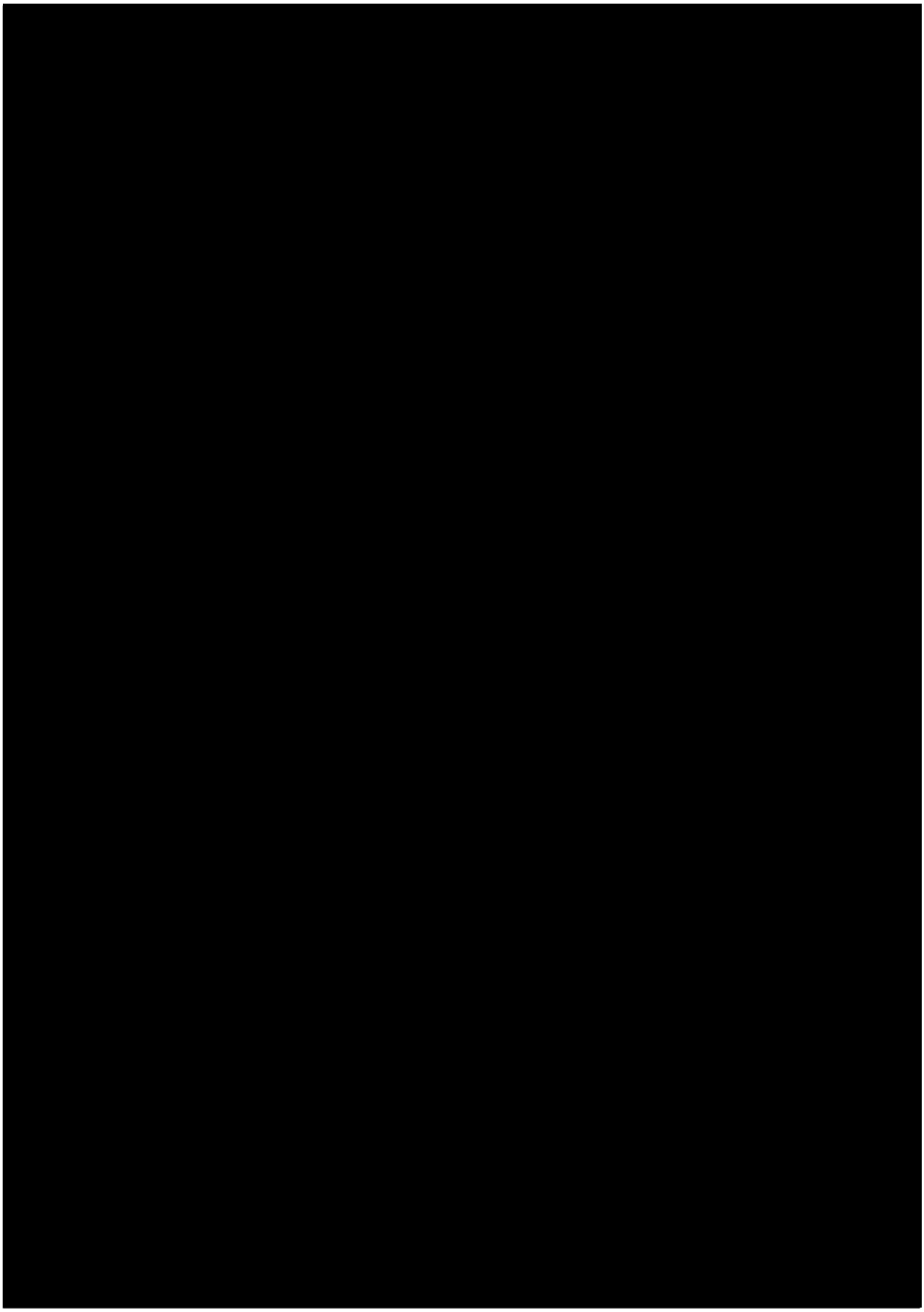
In the forced swim test (FST) in mice BI 1569912 demonstrated efficacy with a comparable effect size as the technical control ketamine [redacted] Repeated dosing over 3 days did not indicate any pharmacodynamics drug tolerance with respect to effects observed in the FST. [redacted]

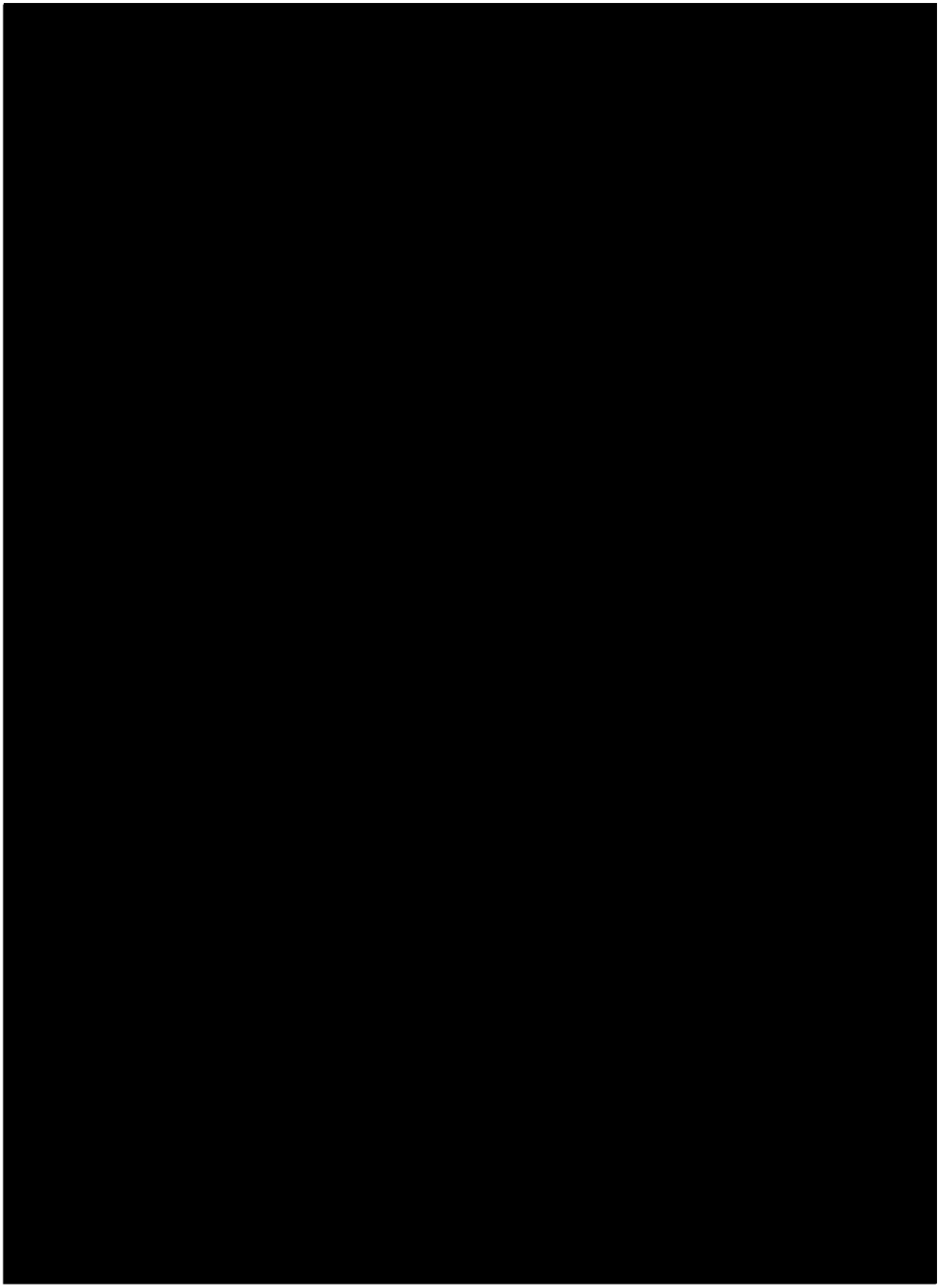
1.2.2 Safety pharmacology

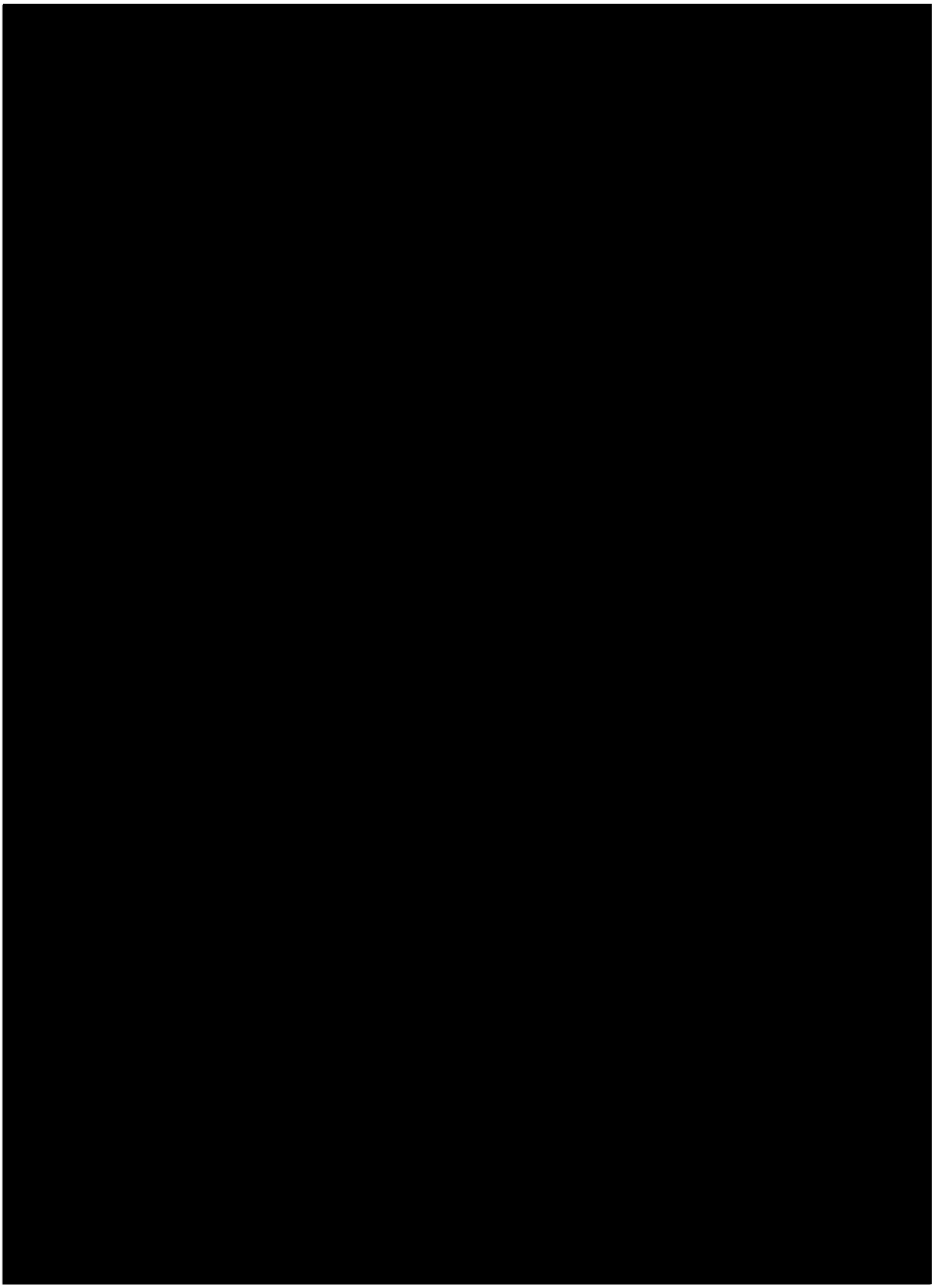
BI 1569912 was tested in a comprehensive set of safety pharmacology studies covering the ICH S7-defined core battery of tests.

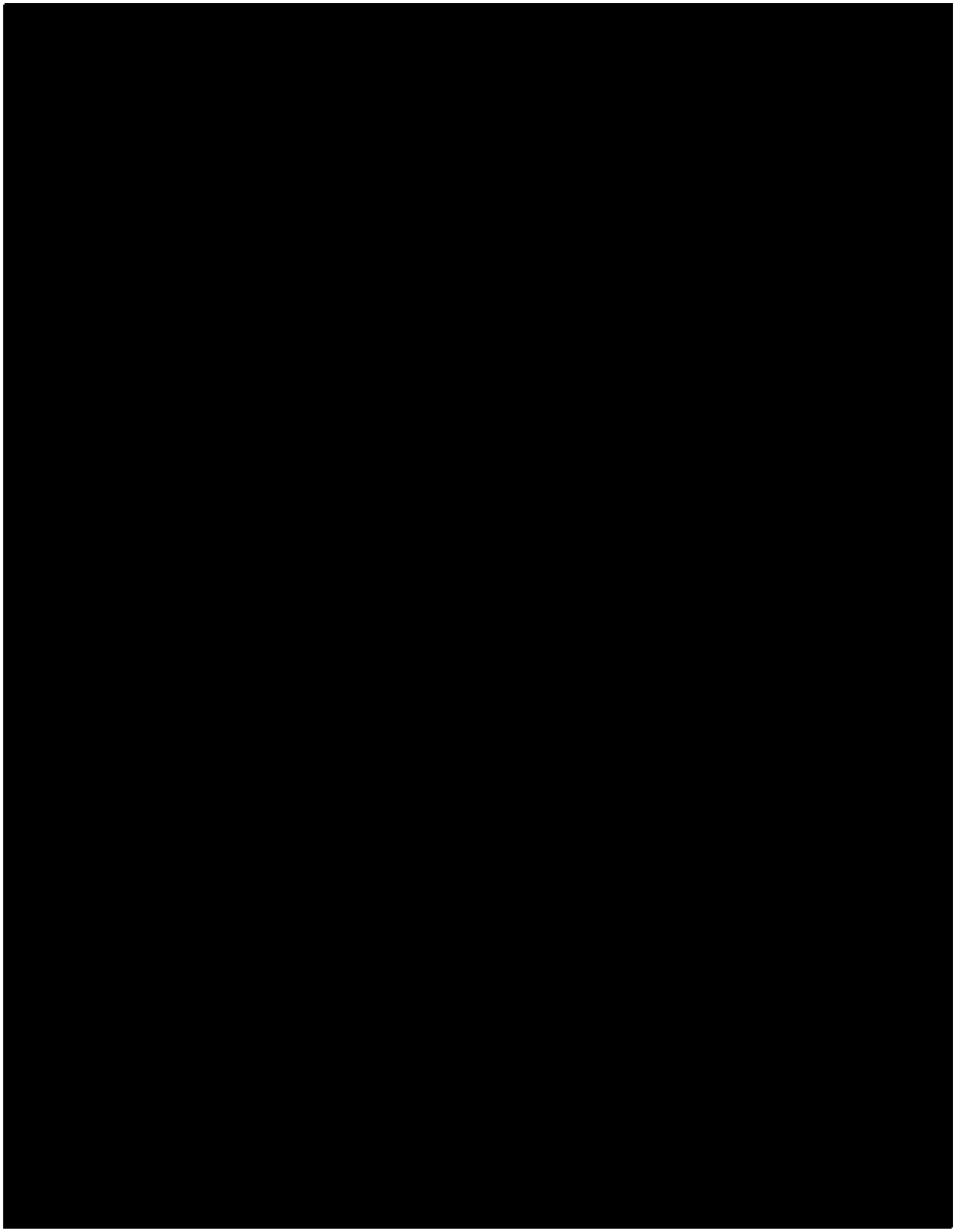
[redacted]

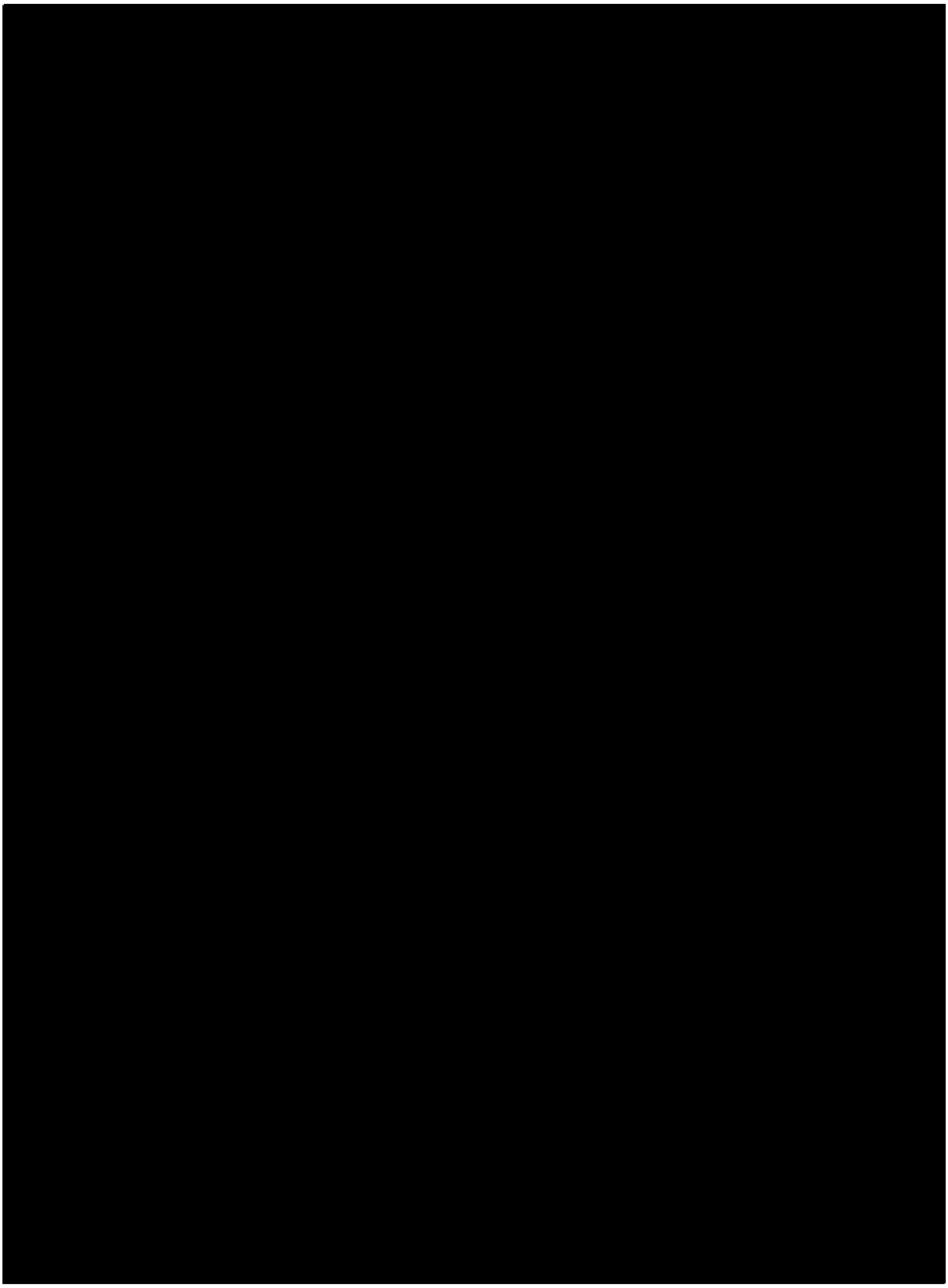












[redacted]

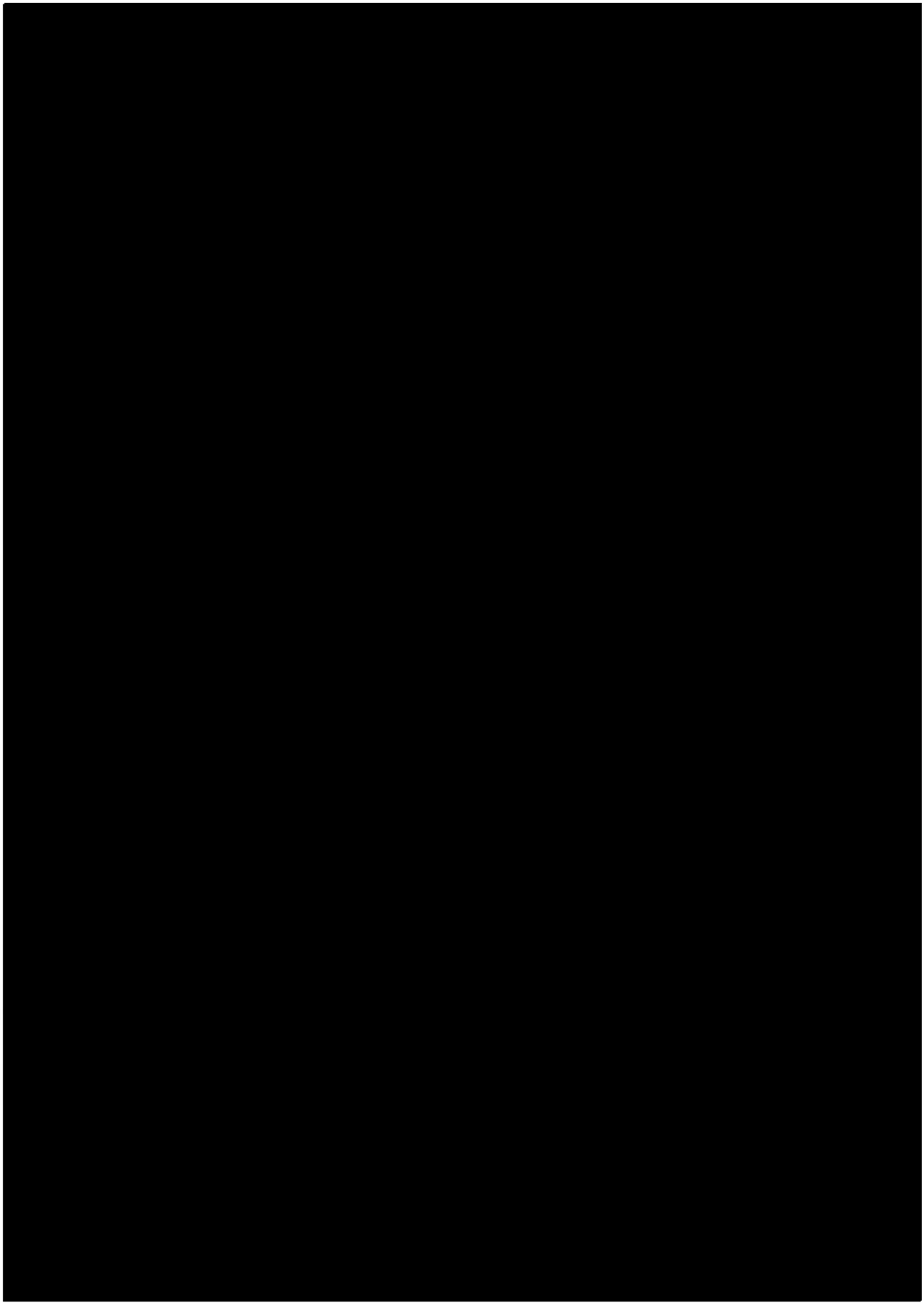
1.2.5 Clinical safety

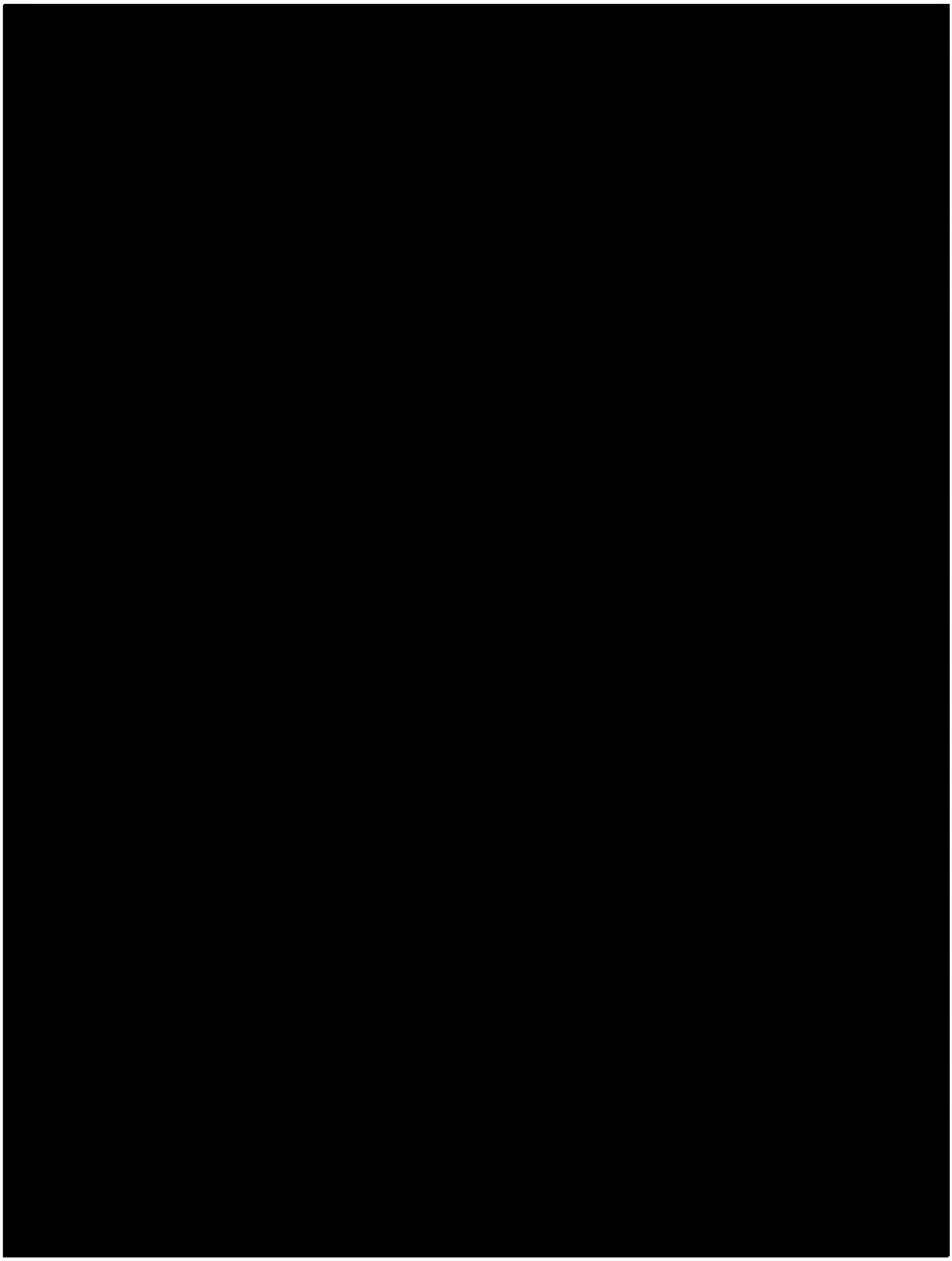
As of 15 May 2024, safety data were available from 2 completed [Trial 1447-0001 [SRD and BA/FE] and 1447-0004 [SRD and MRD in Japanese subjects]) [redacted] Also, safety data was available from 1 completed clinical trial in patients with MDD (1447-0003).

Trial 1447-0001 (SRD and BA/FE trial)

In the SRD part, 54 of 55 subjects (98.2%) completed the trial as planned; [redacted] Investigator-defined drug-related AEs were reported for 6 subjects (10.9%) overall and for 5 subjects (12.2%) receiving BI 1569912. Across observed AEs, there was no dose-dependent increase in frequency for any of these AEs. There were no AEs considered to be dose limiting and no SAEs [redacted]

[redacted]





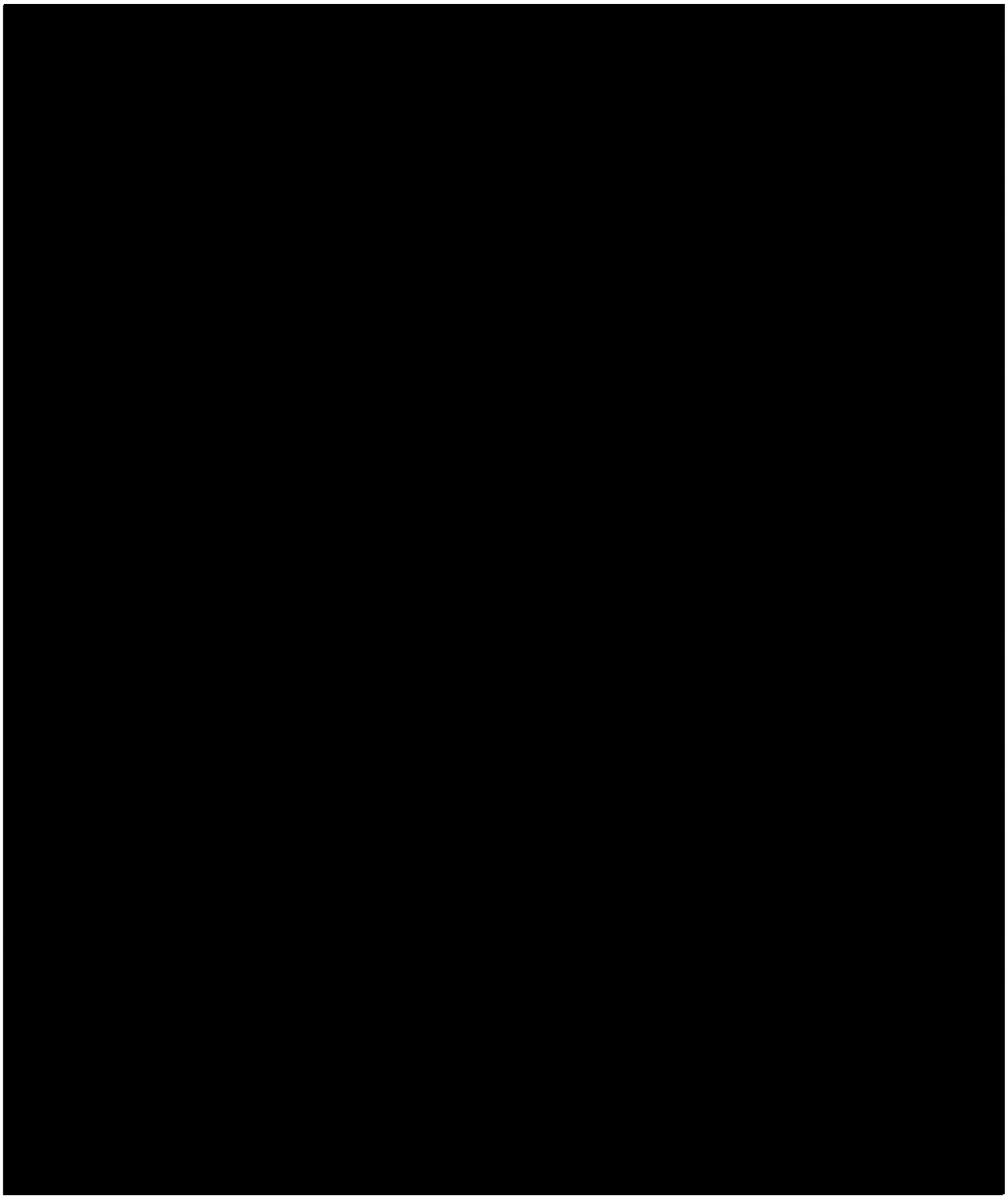
[redacted]

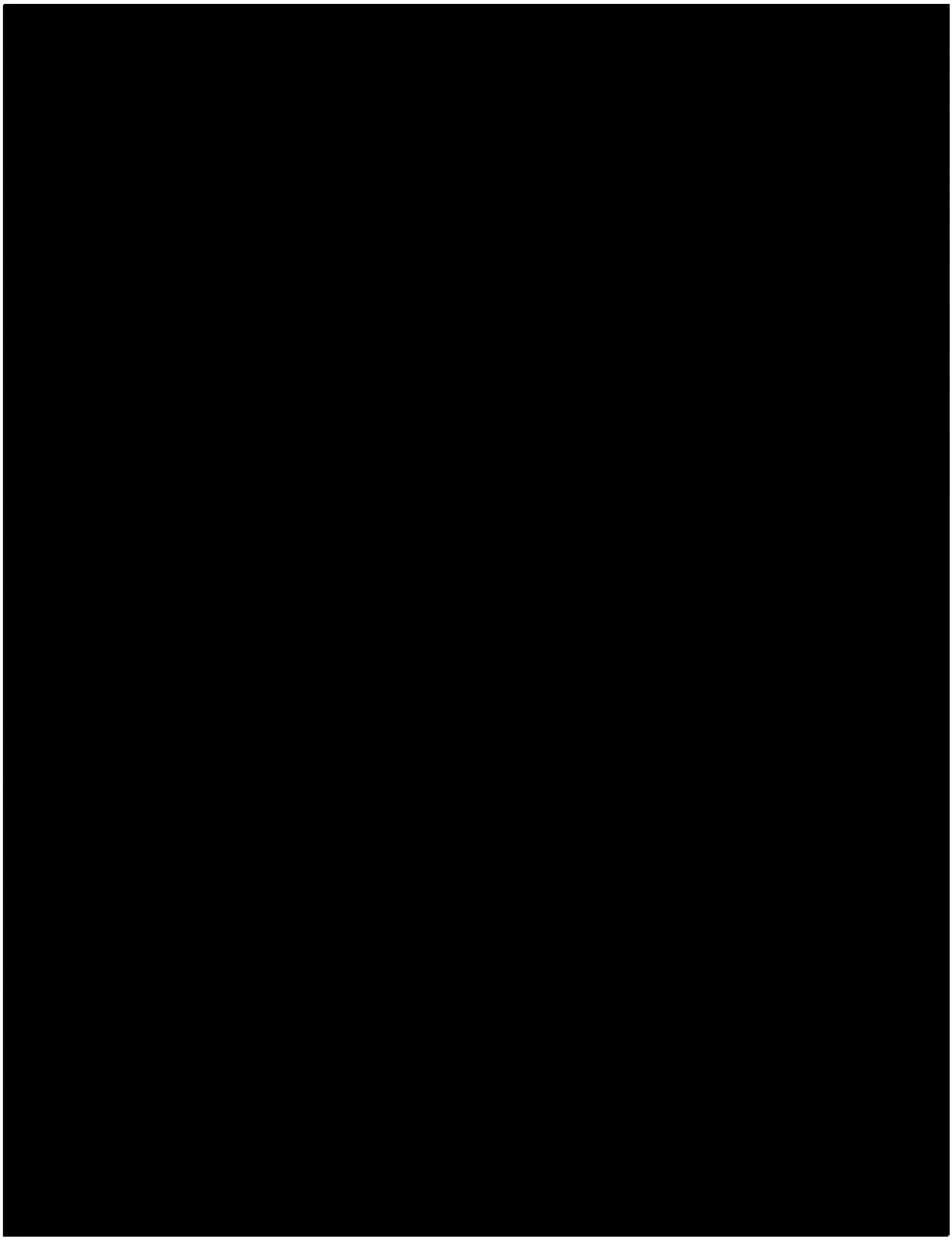
1.2.6 Clinical pharmacokinetics

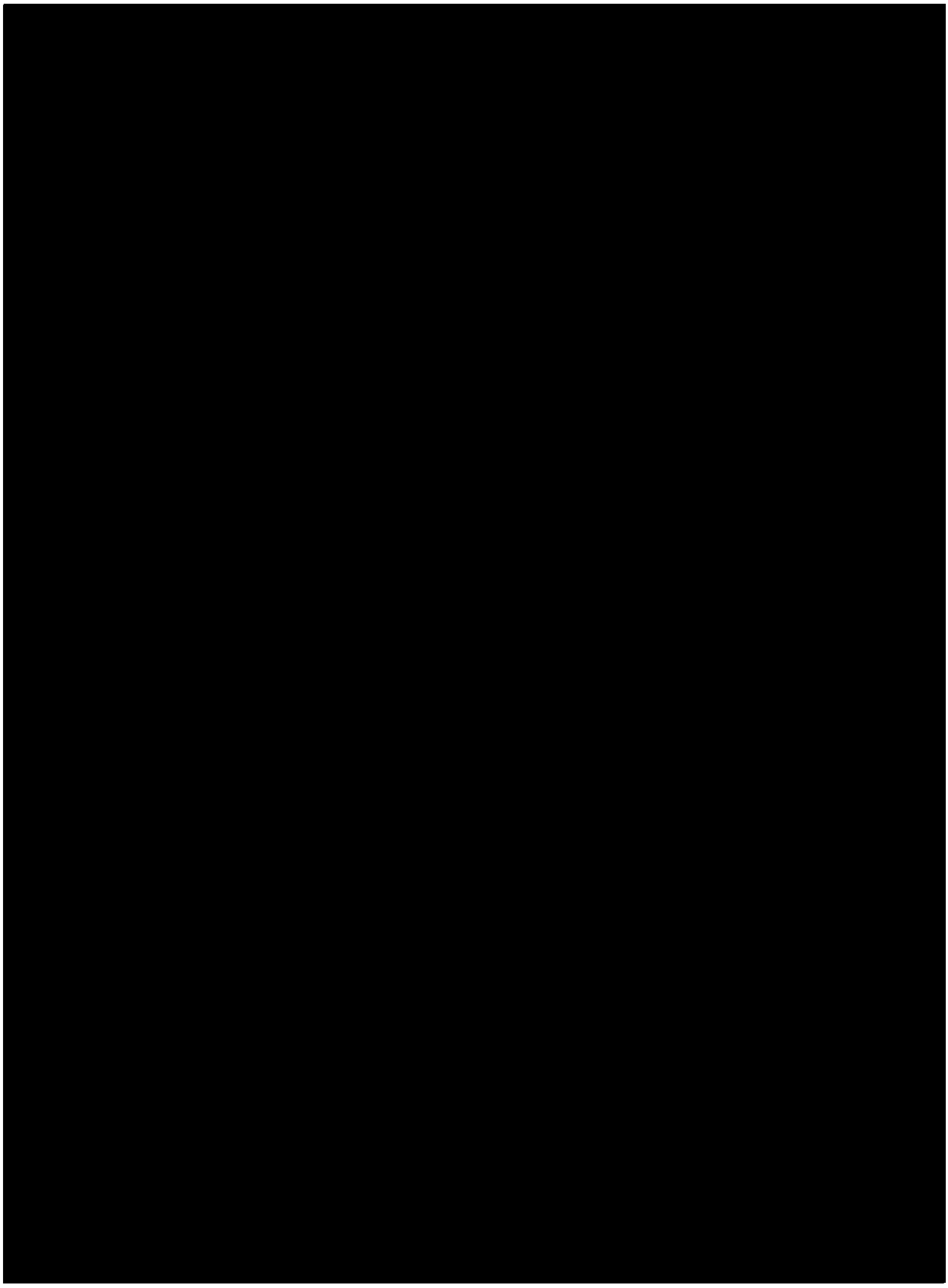
[redacted]

In Trial 1447-0001, after administration of a single oral dose of 0.25 mg to 30 mg as solution in the fasted state, BI 1569912 reached rapid maximum plasma concentrations within a median t_{max} of ~0.5 h. After reaching the maximum concentration, there was a fast decline with a parallel terminal phase for all dose groups with a short terminal half-life of ~4 h. A dose-proportional increase was observed for $AUC_{0-\infty}$ and C_{max}.

Urinary PK analysis revealed that the amount of BI 1569912 excreted in urine increased with increasing dose. The gMean fraction of dose excreted in urine was very low and ranged from 0.100% to 0.205%.







[redacted]

1.2.7 Residual Effect Period

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

This double micro-tracer trial is intended to examine the metabolism in humans and the mass-balance of excretion and plasma and urinary concentrations of BI 1569912 as well as the resulting PK parameters and [^{14}C]-radioactivity in blood, plasma, urine and faeces via a micro-tracer hADME approach combined with examination of the absolute bioavailability after a single concomitant intravenous micro-tracer administration of [^{13}C] BI 1569912 in healthy male volunteers.

The investigation of these processes, including the quantitative assessment of elimination pathways [redacted], is necessary for an in-depth understanding of the pharmacokinetics of BI 1569912 and further development of the compound. In addition, the quantitative determination of elimination pathways and [redacted] are required for application to regulatory authorities [R22-3641].

Additionally, this trial will inform the overall development program about:

- [redacted]
- The necessity for conducting renal and/ or hepatic impairment trials.
- Avoiding unnecessary exclusions of patients with varying renal and/ or hepatic function in safety and efficacy clinical trials which will support product approval.

1.3.1 Nomenclature

In this clinical trial protocol, the following nomenclature is used:

- [^{14}C]-radioactivity: Total Radioactivity measured in different matrix
- [C-14] BI 1569912: BI 1569912 compound labelled with ^{14}C (“hot” drug substance)
- BI 1569912: non-radioactive compound (“cold” drug substance)
- BI 1569912 (C-14) Final drug product, mixture of “hot” and “cold” drug substance
- [C-13] BI 1569912: BI 1569912 compound labelled with the stable isotope ^{13}C
- BI 1569912 (C-13) Final drug product containing pure [C-13] BI 1569912 drug substance [redacted]
- [^{13}C] BI 1569912: analyte (^{13}C labelled stable isotope) measured in plasma

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1569912.

1.4.2 Risks

BI 1569912 is a partial, reversible [redacted] negative allosteric modulator of subunit 2B (NR2B) containing N-methyl-D aspartate (NMDA) receptors which is a therapeutic concept for depression that has been well described [R17-3810]. Clinical information on compounds of the same pharmacological class (NR2B NAMs like traxoprodil and rislenemdaz) or a related pharmacological class (unselective NMDA inhibitors, like esketamine) are available. For NR2B-specific negative allosteric modulators, no serious safety concerns have been identified. [redacted]

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table 1.4.2: 1.

Table 1.4.2: 1 [redacted]

[redacted]

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1569912		
[redacted]		

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1569912		
[redacted]		

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1569912		
[redacted]		

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1569912		
Radiation burden	• The effective dose that each subject receives from one administration of [redacted] with approx. 0.1 MBq of 14C is expected to be below 0.1 mSv (Category I ICRP)	• The total effective dose of <0.1 mSv per subject is within the low-range or 'trivial' exposure limits proposed by ICRP. This level of exposure is considered relatively low and is commonly encountered in various situations, including medical diagnostics (such as X-rays and CT scans), natural background radiation, and certain occupational settings. • To minimize any risks resulting from exposure to ionizing radiation in this trial female subjects will be excluded from study participation as well as subjects with previously high exposure to radiation.
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

[redacted]

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are:

- To investigate basic pharmacokinetics of BI 1569912 and total radioactivity, including mass balance, excretion pathways and metabolism following oral administration of BI 1569912 (C-14) to healthy male subjects (test treatment, T).

- To investigate the absolute bioavailability of [redacted] BI 1569912 as single oral [redacted] dose, using a single, concomitant intravenous micro-tracer administration of BI 1569912 (C-13) (reference treatment, R)

2.1.2 Primary endpoints

hADME endpoints for[^{14}C]- radioactivity in urine and faeces:

Mass balance recovery for [14C]- radioactivity in urine and faeces after oral administration of BI 1569912 (C-14):

- $fe_{urine,0\text{-}tz}$ (fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point).

- $fe_{faeces,0\text{-}tz}$ (fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point).

- Sum of $fe_{urine,0\text{-}tz}$ and $fe_{faeces,0\text{-}tz}$ (total recovery of [^{14}C]-radioactivity).

Absolute BA endpoints for BI 1569912 and [^{13}C] BI 1569912 in plasma:

The following pharmacokinetic parameters will be determined for BI 1569912 and [^{13}C] BI 1569912 in plasma:

- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity in plasma) of BI 1569912 after a single oral administration of BI 1569912 (C-14).

- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity in plasma) of [^{13}C] BI 1569912 after a single intravenous infusion of BI 1569912 (C-13).

2.1.3 Secondary endpoints

hADME and Absolute BA endpoints for BI 1569912 in plasma:

- C_{max} (maximum measured concentration of the analyte in plasma) of BI 1569912 after a single oral administration of BI 1569912 (C-14).

- AUC_{0-tz} (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point in plasma) of BI 1569912 after a single oral administration of BI 1569912 (C-14).

hADME endpoints for[^{14}C]-radioactivity in plasma:

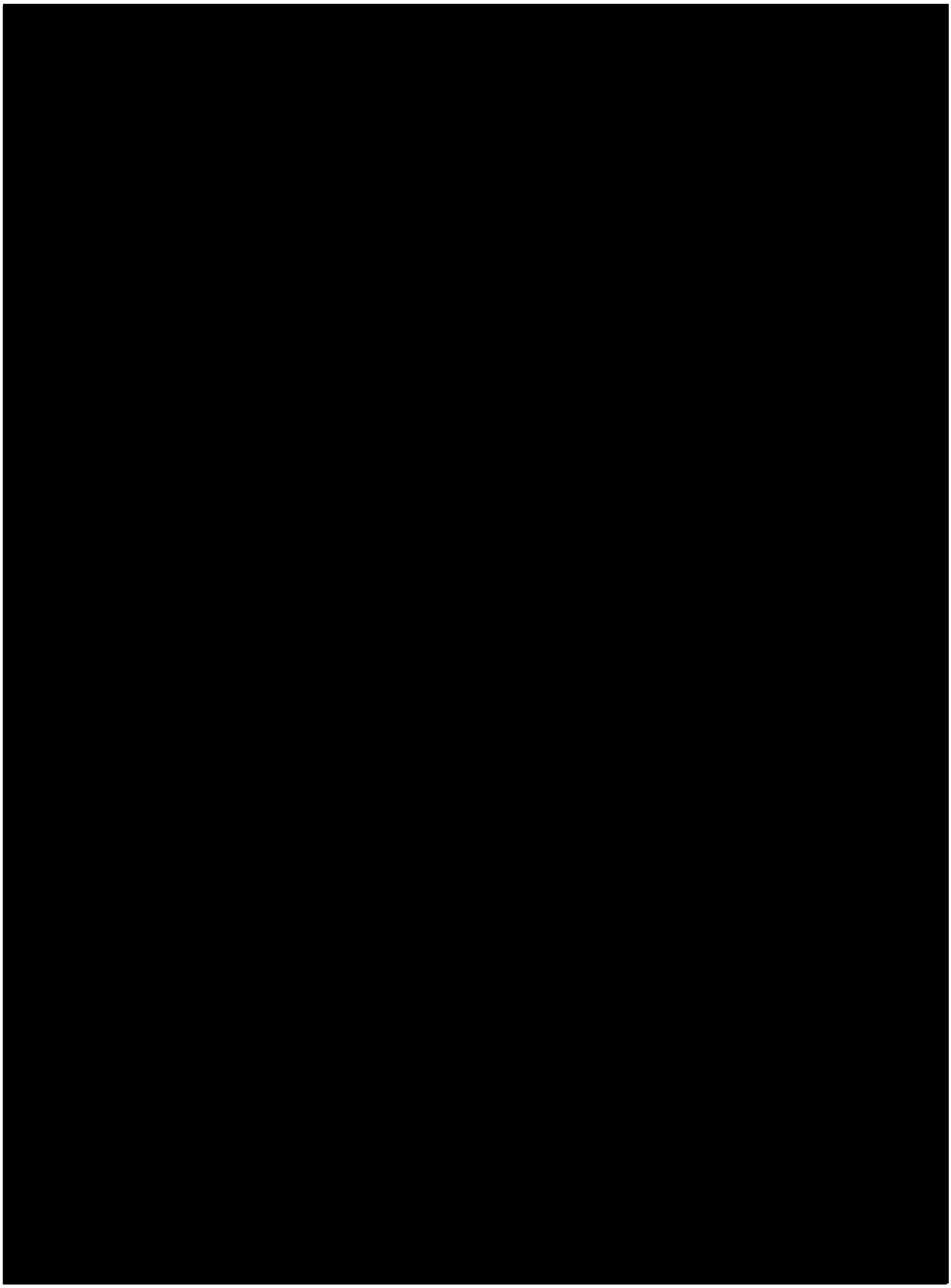
- C_{max} (maximum measured concentration of the analyte in plasma) of [^{14}C]-radioactivity after a single oral administration of BI 1569912 (C-14).

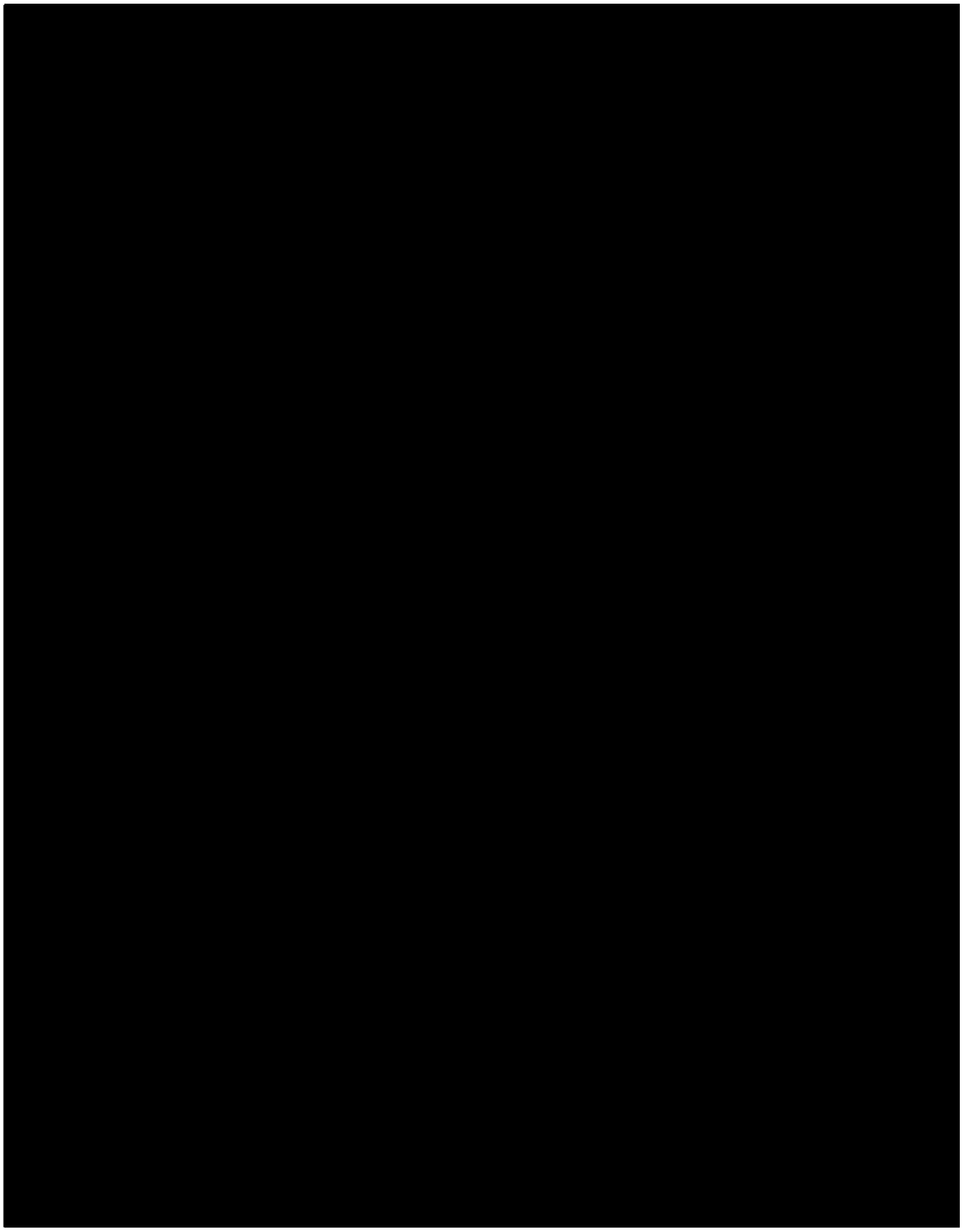
- AUC_{0-tz} (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point in plasma) of [^{14}C]-radioactivity after a single oral administration of BI 1569912 (C-14).

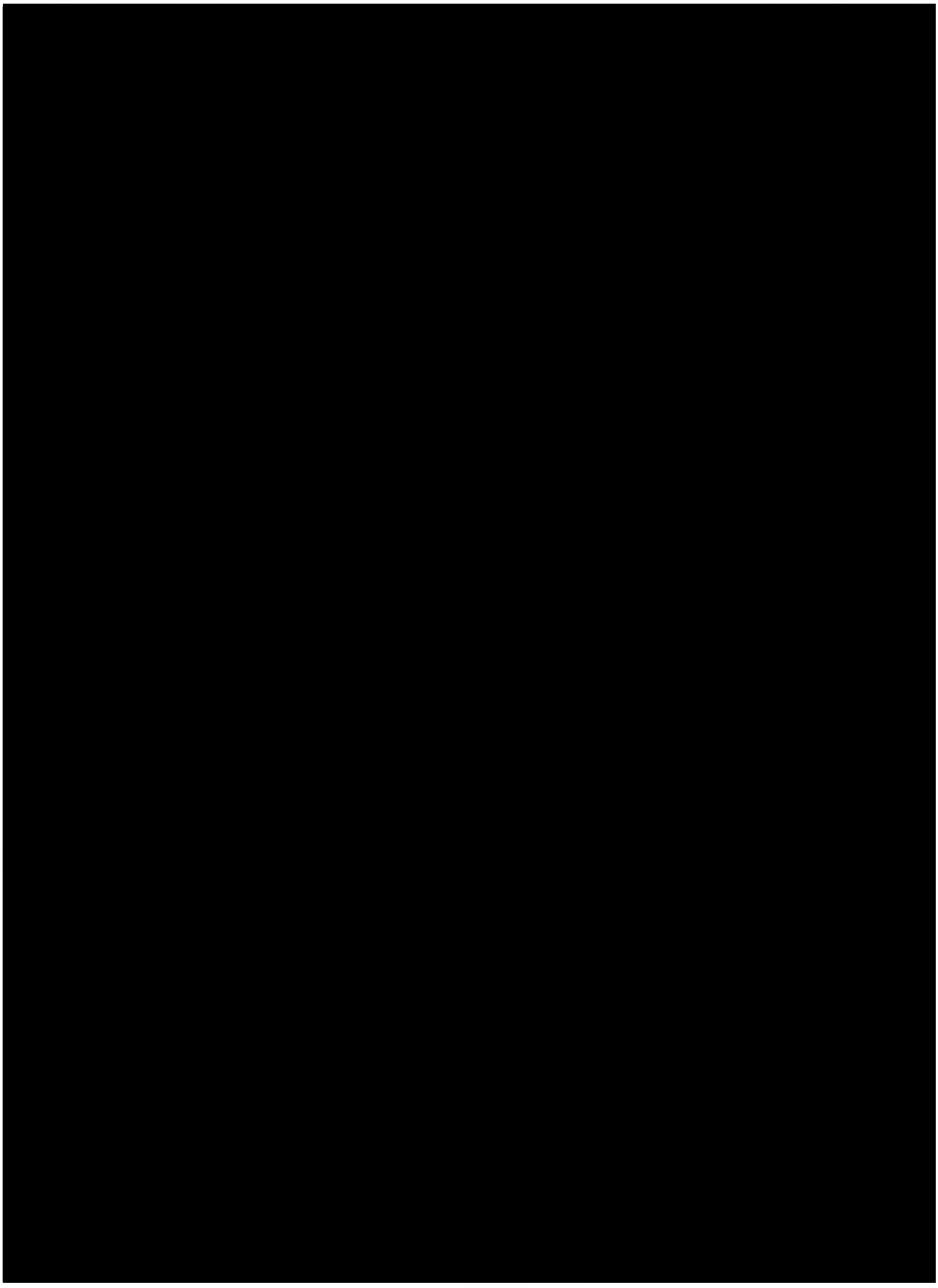
Absolute BA endpoints for[^{13}C] BI 1569912:

- C_{max} of [^{13}C] BI 1569912 after a single intravenous administration of BI 1569912 (C-13).

- AUC_{0-tz} of [^{13}C] BI 1569912 after a single intravenous administration of BI 1569912 (C-13).







[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 1569912 will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Suicidality assessment (C-SSRS)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, non-randomised, single-dose, fixed sequence design trial in healthy male subjects in order to investigate the basic pharmacokinetics of BI 1569912 and [14C]- radioactivity, including mass balance, excretion pathways, and metabolism following a single oral dose of [redacted] BI 1569912 (C-14) [test treatment, T], and the absolute bioavailability of BI 1569912 and [13C]- radioactivity after a single, concomitant intravenous micro-tracer administration of a single dose of [redacted] BI 1569912 (C-13) [reference treatment, R]. For details, refer to Section 4.1.

A total of 8 healthy male subjects is planned to participate in the trial. On Day 1, subjects will receive [redacted] of [^{14}C]-labelled BI 1569912 orally (T) followed by i.v. infusion of [redacted] [^{13}C]-labelled BI 1569912 [redacted]. The subjects will then stay in the study centre up to the morning of [redacted] for collection of samples of blood, urine, and faeces.

Subjects will be readmitted to the study centre for 24 h collection intervals of urine and faeces on [redacted]. Within 24 h before each of these in-house collection intervals, subjects are to collect faeces at home. This 24-h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval. Otherwise, it will be discarded. If a subject is unable to attend one of the once-weekly collection interval visits, they may be allowed to reschedule the visit if needed. After collection interval [redacted] no further collections are planned.

The [^{14}C]-radioactivity recovery results in excreta (urine and faeces) for individual subjects will be reported as a percentage of the administered dose.

For the final analysis, the total excreted [^{14}C]- radioactivity will be derived including an interpolation method to account for the time periods without samples taken, if applicable (see Section 7.2.2).

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

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

This double-micro-tracer trial is designed to investigate the absorption, distribution, metabolism, and excretion of BI 1569912 including determination of mass balance using a [^{14}C]- micro-tracer after a single oral administration (inclusion of a control group is not required for this investigation) and absolute bioavailability of BI 1569912 using a [^{13}C]-micro-tracer after a concomitant single i.v. administration. For absolute bioavailability trials, the cross-over design is preferred because of its efficiency: since each subject serves as his own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison [R94-1529]. Compared to the traditional cross-over design (i.e., two trial periods separated by a wash-out period), the chosen double-micro-tracer approach is considered more favourable, because both treatments are administered on the same day in a fixed sequence (i.e., [^{14}C]-labelled [redacted] of

BI 1569912 as oral dose and [^{13}C]-labelled [redacted] of BI 1569912 as i.v. dose), which also allows efficient investigation of the metabolism and the mass-balance of excretion in one study in the same subjects and in one trial period with overlapping intervals of PK sampling.

Eight healthy volunteers are included to ensure at least six evaluable subjects as requested by FDA guideline [R22-3641]. This accounts for subjects potentially vomiting within at least 2x t_{max}, for early drop-outs or for any other reason that subjects would not be evaluable.

For (C-14) treatment, the in-house sampling duration after drug administration is up to [redacted]

[redacted]

Randomisation is not applicable, because all subjects receive the same treatment. Blinding is not necessary, because the main and secondary endpoints refer to the drug's pharmacokinetics that are not influenced by the knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 8 healthy male subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site, or, if necessary, via external databases and advertisements.

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)

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

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
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 40 to 100 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance, in particular hepatic parameters (ALT, AST, total bilirubin) or renal parameters (creatinine) exceeding the ULN after repeated measurements
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or 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. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Current smoker or smoking within 30 days of planned administration of trial medication (including electronic cigarettes and shisha)
15. Alcohol abuse (consumption of more than 24 g per day)
16. Drug abuse or positive drug and/or alcohol test at screening or admission on Day -1
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial

18. Intention to perform excessive physical activities within 4 days prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. Any lifetime history of suicidal behaviour (i.e., actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
24. Any suicidal ideation of type 2 to 5 on the C-SSRS (i.e., active suicidal thought, active suicidal thought with method, active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent) in the past 12 months prior to screening
25. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) or to refrain from donating sperm from time point of the first administration of trial medication until 90 days after trial completion (see Section 4.2.2.3)
26. Participation in another ADME study with a radiation burden ≥0.1 mSv within 12 months prior to administration of study drug
27. Exposure to radiation for diagnostic reasons within 12 months prior to administration of study drug
28. Irregular defecation pattern (less than a mean of one bowel movement per 2 days)

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole (‘withdrawal of consent’) with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.7, the

discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and 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. The subject has relevant individual QT prolongations, i.e. a QTcF increase of greater than 60 ms from baseline and/or with absolute QT or QTcF greater than 500 ms, as confirmed by a repeat ECG recording
7. Suicidal ideation (type 2-5) or any suicidal behaviour based on C-SSRS questionnaires during the trial
8. In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.
9. If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued or temporarily halted immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if more than two subjects have drug-related severe non-serious adverse events, or if at least one drug-related serious adverse event is reported. In this case, the collection of pharmacokinetic samples and other scheduled activities should continue, if possible, without undue risk to already dosed volunteer(s).

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5 Replacement of subjects

In case more than 2 out of 8 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced, that is additional subjects may be included if considered necessary to reach the objectives of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. The total number of replacements may not exceed 2 (i.e., 1/3 of the total number of evaluable subjects required to complete the trial). A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 1569912 (C-14) treatment is administered as oral [redacted] The oral [redacted] contains a mixture of [^{14}C]- labelled BI 1569912 and non-radiolabelled BI 1569912 and is manufactured by [redacted] part of [redacted]

BI 1569912 (C-13) treatment is administered as [redacted] The [redacted] contains a pure [^{13}C]- labelled BI 1569912 and is manufactured by [redacted] part of [redacted]

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Name:	BI 1569912 (C-14) oral [redacted]
Substance:	unlabelled BI 1569912 mixed with [^{14}C]- labelled BI 1569912
Pharmaceutical formulation:	Oral [redacted]
Source:	[redacted]
Unit strength:	
Dose:	
Posology:	
Mode of administration:	Oral
Duration of use:	[redacted]

The characteristics of the reference product are given below:

Name:	BI 1569912 (C-13) [redacted]
Substance:	[^{13}C]- labelled BI 1569912
Pharmaceutical formulation:	[redacted]
Source:	
Unit strength:	
Dose:	
Posology:	
Mode of administration:	Intravenous (i.v.) infusion
Duration of use:	[redacted]

4.1.2 Selection of doses in the trial and dose modifications

For investigation of hADME and mass balance via treatment BI 1569912 (C-14), [redacted] of BI 1569912 was selected as the potential therapeutic dose in clinical drug development. The planned oral dose of [redacted] is associated with a radioactivity dose of approximately 0.1 MBq. This radioactive dose is considered to be necessary and sufficient to provide an adequate analytical sensitivity to enable [redacted]

For investigation of absolute bioavailability via treatment BI 1569912 (C-13), the planned dose of [redacted] of [^{13}C]-BI 1569912 is considered to be sufficient for PK measurements after intravenous administration.

4.1.3 Method of assigning subjects to treatment groups

All subjects receive the same treatments and same dose. There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment (namely, treatment T BI 1569912 (C-14) as [redacted] by treatment R BI 1569912 (C-13) as [redacted]).

Trial subject numbers will be assigned to trial subjects prior to first administration of trial medication in the morning of Day 1 of Visit 2.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable (for discussion of trial-associated risks and safety measures, see Section 1.4).

4.1.4 Drug assignment and administration of doses for each subject

This is a fixed-sequence study with an overlap of PK sampling intervals in time. All subjects will receive [redacted] Treatment R as i.v. infusion [redacted] the oral administration of treatment T in the single treatment period (therefore, no wash-out between treatments is applicable). The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

[redacted]

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 1569912 (C-14)	Oral [redacted]	[redacted]		
R (Reference)	BI 1569912 (C-13)	Intravenous [redacted]			

Administration of trial medications will be performed after subjects [redacted]

The investigator (or authorised designee) will administer BI 1569912 (C-14) as an oral dose [redacted] to subjects who are in a sitting or standing position followed by oral intake of [redacted]. The syringe will be weighed before and after drug administration to confirm the administered dose.

For the i.v. infusion of BI 1569912 (C-13) micro-tracer [redacted] an indwelling catheter is placed into an arm vein of the subject. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm. BI 1569912 (C-13) will be administered as continuous intravenous infusion [redacted] to subjects in semi-supine position under supervision of the investigating physician or an authorised designee. [redacted]

For all drugs administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

During the first 4 h after the first drug administration, subjects are advised not to lie down if possible (i.e. no declination of the upper body of more than 45 degrees from upright posture) except for medical examination or procedures or if necessary for any medical reasons (e.g., AEs).

Subjects will be kept under close medical surveillance until planned discharge from the trial site [redacted]

4.1.5 Blinding and procedures for unblinding

This non-randomised open-label Phase I trial will be handled in an open fashion throughout. The treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by [redacted]. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). The final clinical trial supply of the drug products consists of amber glass bottles containing oral [redacted] treatment BI 1569912 (C-14) and of vials containing the [redacted] for i.v. infusion ([redacted] for treatment BI 1569912 (C-13).

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

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

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 in accordance with the recommended (labelled) storage conditions. If 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 Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the manufacturing site when the following requirements are fulfilled:

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

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the 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 medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require 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 results of medical evaluations are acceptable.

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 trial 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 will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for starting from 10 h before until at least 4 h after drug intake.

From 1 h before the first drug intake until lunch, [redacted] and an additional [redacted] of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to [redacted].

On days of urine collection, subjects will be advised that total fluid intake should be at least

1500 mL but should not exceed 3500 mL.

Alcoholic beverages are not permitted starting 2 days before the first trial drug administration until after the last PK sample is collected.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 12 h before until 24 h after administration of the first trial medication.

Smoking is not allowed during trial participation.

Excessive physical activity (such as competitive sport) should be avoided from 4 days before the first administration of trial medication until the end of trial examination.

4.2.2.3 Contraception requirements

Subjects whose sexual partner is a WOCBP must be sexually abstinent or use male contraception (i.e. condom) starting from the first dosing with BI 1569912 and for at least 90 days afterwards.

Abstinence is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g., calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration requested, and withdrawal are not acceptable.

Unprotected sexual intercourse (i.e. without use of condom) of a male subject with a pregnant female partner and sperm donation is not allowed throughout the study and until 90 days after trial completion.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations and urinary and faecal excretion of trial medication 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. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), 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, a standardized mental and neurological assessment (see Section 5.2.5.2) and suicidality assessment (see Section 5.2.5.3). At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination, a standardized mental and neurological assessment and suicidality assessment.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the [redacted]. For retests, at the discretion of the investigator or designee, [redacted]

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

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

At the time points described in the Flow Chart, haematocrit measurements will be performed.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	Reticulocytes, absol.	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes	X	X
Automated partial WBC differential [%]	Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes	X	X
Automated WBC differential [absolute]	Neutrophil, Eosinophils, Basophils, Monocytes, Lymphocytes	X	X
Manual WBC differential (if automated WBC differential is abnormal) [%]	Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time reported as INR (International	X	X
	Normalization Ratio)	X	X
	Fibrinogen		
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
	Creatine Kinase [CK]		
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X
	Lactic Dehydrogenase	X	X
	Lipase	X	X
	Amylase (total)	X	X
		X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (serum)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	Albumin	X	X
	C-Reactive Protein (high sensitive)	X	X
	Uric Acid	X	--
	Cholesterol, total	X	--
	Triglyceride	X	--
Electrolytes	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
	Phosphate (as Inorganic)	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B
Urinalysis (Dipstick)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 and 3 (for time points refer to Flow Chart)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that 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 drug and alcohol screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and at admission to trial site on Day -1 of Visit 2.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Alcohol Amphetamine/MDA Barbiturates Benzodiazepine Cannabinoids Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Phencyclidine
Drug screening (serum)	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)

To encourage compliance with alcoholic restrictions, a urine alcohol test will be performed at screening (Visit 1), on Day -1 (Visit 2) at admission, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the safety laboratory of [redacted].

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

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the times provided in the Flow Chart.

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

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the trial.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings. Local findings assessed as clinically relevant by the investigator or designee must be recorded as AE.

5.2.5.2 Standardized mental and neurological assessment

At the time points specified in the Flow Chart, a neurological examination will be performed. The mental and neurological examination will include the following assessments:

- General level of arousal (vigilance)
- Attention and concentration
- Orientation
- Memory
- Eye movement
- Pupil size and pupil reactivity
- Deep tendon reflexes
- Assessment of muscle strength
- Gait
- Romberg test
- Tremor
- Point-to-point movements
- Sensitivity

Documentation, Assessment, and Reporting

Results will be documented directly in the source documents at the clinical trial site and assessed for clinical relevance by an investigator, deputy investigator or sub-investigator. Clinically relevant findings of the mental and neurological examination will be reported as adverse events (during the trial) or as baseline conditions (at screening). For details see Section 5.2.6.2). Case narratives may be written, if necessary.

5.2.5.3 Suicidality assessment

Based on the FDA guidance on prospective assessment of suicidality [R12-4395] suicidal ideation and behaviour (SIB) will be proactively evaluated as part of the drug development. This also refers to clinical trials in healthy volunteers with multiple dose administration of the IMP.

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behaviour and ideation [R08-1147].

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behaviour, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the ‘screening / baseline’ version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The lifetime history of suicidal ideation and behaviour will also be recorded. See Section 10.1 for the original English C-SSRS. For this trial, the paper version of the respective Dutch translation may be used.

After the screening visit, the 'since last visit' version is used for the suicidality assessment at the time points indicated in the Flow Chart.

The investigator is to review all reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If the report is confirmed, appropriate actions for the subject's safety have to be initiated.

There are following types of suicidal ideation and behaviour [R12-4395]:

Suicidal ideation

1. Passive
2. Active: nonspecific – no method, intent or plan
3. Active: method, but no intent or plan
4. Active: method and intent, but no plan
5. Active: method, intent, and plan

Suicidal behaviour

1. Completed suicide
2. Suicide attempt
3. Interrupted attempt
4. Aborted attempt
5. Preparatory actions toward imminent suicidal behaviours.

All results will be included in the database. For details regarding AE collection & reporting see Section 5.2.6.1.3 and 5.2.6.2. For further information, refer to Appendix 10.1.

[redacted]

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

SAE reporting in case of Suicidal Risk assessed by the C-SSRS as described in 5.2.5.3:

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

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

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

Please note, that adverse event reports, that are coded to terms that are associated with suicide (i.e. suicidal depression, suicidal ideation, suicidal threat) are on the "Always serious AE List" and therefore must be collected & reported as SAEs.

For 'Self-injurious behaviour, no suicidal behavior' standard AE/SAE collection & reporting rules are to be applied.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, OR
  - An elevation of AST or ALT and INR ≥1.5-fold ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
  - An elevation of AST or ALT ≥3-fold ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), OR
  - Aminotransferase (ALT, and/or AST) elevations ≥5-fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

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

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
    - 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 and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterized (e.g. as 'chronic' or 'stable'), or no further information can be obtained.

5.2.6.2.3 Pregnancy

Potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant (applicable from the time point of the first administration of trial medication until 90 days after trial completion). This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner: The investigator must report any drug exposure during pregnancy in a partner of the male trial participant (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood, urine and faeces samples will be collected at the time points / time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters. More details of sample processing can be found in the laboratory manual. Changes to conditions of sample processing described in this CTP may be implemented via non-substantial amendment.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for analysis of [14C]-radioactivity in plasma and whole blood and for analysis of BI 1569912 and [13C]-BI 1569912 in plasma

Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

For blood volumes see Appendix 10.4.

For a detailed description of PK sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

[redacted]

For a detailed description of PK sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.3 Sampling of blood for haematocrit for blood cell/plasma ratio

At the time points listed in the Flow Chart [redacted] a blood sample of approximately 3 mL will be drawn for measuring haematocrit, which is needed for determination of blood cell/plasma ratio of [^{14}C]-radioactivity (see Section 2.2.2.1).

For blood volumes see Appendix 10.4.

5.3.2.4 Urine sampling for analysis of [14C]-radioactivity [redacted]

All urine samples are planned to be used for determination of [^{14}C]-radioactivity. [redacted]

A blank urine sample will be collected before administration of trial medication (see Flow Chart) 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 polyethylene (PE) containers and stored at 4-8 °C during the sampling interval. Subjects will be instructed to empty their bladders before the first sampling interval and at the end of each sampling interval.

The exact start and end times of the urine collection intervals will be recorded in the CRF.

For a detailed description of sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.5 Sampling of faeces for analysis of [14C]-radioactivity [redacted]

A blank sample will be taken within approx. 48 hours prior to study drug administration. If several samples are available, the sample closest to drug administration will be used for analyses.

All faeces samples are planned to be used for determination of [^{14}C]-radioactivity. [redacted]

All stools will be collected continuously and quantitatively in portions as shown in the Flow Chart. After completion of an interval, stools from within the interval will be mixed and treated as one sample from that interval. The weight of the faeces and the exact times of faeces collection will be recorded in the CRF.

Subjects are to collect faeces at home within 24 h intervals before admission to in-house collection intervals. For home-collection intervals and in-house collection intervals see the Flow Chart. If faeces is collected during an in-house collection interval, this faeces sample will be used for analysis and the prior home-collection faeces sample will be discarded. If no faeces is collected during an in-house collection interval, the prior home collection faeces sample will be used.

For a detailed description of faeces labelling, storage and collection of faeces samples, refer to the laboratory manual.

5.3.2.6 Handling of vomit

If vomiting occurs within 4 hours after study drug administration, the vomit should be collected to calculate the weight and [^{14}C]-radioactivity levels.

Details of vomit sample preparation and processing, storage, labelling, and sample shipment are described in the laboratory manual.

5.3.2.7 Further investigations

After analysis of the trial, back-up and left-over samples (whole blood, plasma, urine, faeces) [redacted].

In addition, back-up and left-over samples (whole blood, plasma, urine, faeces), if not needed for their primary purpose anymore, may be used [redacted] or to address Health Authority questions regarding the results / methodology. However, only data related to BI 1569912 [redacted] will be generated by these additional investigations.

Trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

[redacted]

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 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 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 or i.v. administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

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 the end of trial examination are provided in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min.

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 blood sampling times and urine/faeces 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 the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment period

Each subject is expected to participate in one treatment period. The subjects will be admitted to the trial site on Day -1 (start of faeces collection at home is on Day -2), and kept under close medical surveillance until discharge from the trial site on [redacted] On the day of discharge, the subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness (fitness to be assessed by a physician).

Subjects are to return for once weekly 24 h in-house confinements with urine and faeces sampling. In the 24 h intervals directly before each in-house confinement, subjects are to collect faeces at home. For time intervals see the Flow Chart.

After collection interval [redacted] no further collections are planned.

For details on time points and procedures for collection of whole blood, plasma, urine, and faeces samples for PK analysis, [redacted], and mass balance assessments, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

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

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

To investigate human ADME, data will be reported with descriptive statistics only.

Absolute bioavailability (F) will be estimated by the ratios of the geometric means (Test/Reference) for dose normalized $AUC_{0-\infty}$. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including the fixed effect for 'treatment' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA.

It is not planned to test any statistical hypotheses in this trial.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

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

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification file. IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for BI 1569912 will be calculated according to the relevant BI internal procedures.

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

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.

Important protocol deviations 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

Whole blood, plasma, urine, and faeces 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).
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Whole blood, plasma, urine, and faeces concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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).

7.2.2 Primary endpoint analyses

hADME endpoints:

Primary endpoints will be analysed descriptively.

To avoid underestimation of the total recovery of [14C], the excretion during the nonsampling

phase of the study will be estimated using linear interpolation between the observed

24-h sampling periods before and after the non-sampling period for urine and faeces,

respectively.

Absolute BA endpoints:

The statistical model used for the analysis of dose normalized $AUC_{0-\infty}$ will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoint will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subject and treatment. The effect 'subject' will be considered as random, whereas the other effect 'treatment' will be considered as fixed. The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where

y_{km} = logarithm of response measured on subject m receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., n

τ_k = the k^{th} treatment effect, k = 1, 2,

e_{km} = the random error associated with the m^{th} subject who received treatment k.

where $s_m \sim N(0, \sigma_B^2)$ i.i.d., $e_{km} \sim N(0, \sigma_W^2)$ i.i.d. and s_m, e_{km} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for dose normalized $AUC_{0-\infty}$ (see Section 2.1) and the two-sided 90% confidence intervals (CIs) will be provided.

For dose normalized $AUC_{0-\infty}$, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs.

[redacted]

7.2.3 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.

[redacted]

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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 time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.7) will be assigned to the treatment period (BI 1569912). Events occurring after the REP but prior to end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and follow-up intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings. Additionally, differences from baseline will be evaluated.
Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

The assessment of the results of the [redacted], and standard mental and neurological assessments will be specified in the TSAP.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

This is a non-randomised trial, thus this section is not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

For this exploratory trial, no prospective calculations of statistical precision or power have been made. The planned sample size of 8 subjects is considered sufficient to get reliable results regarding the trial objectives. The sample size accounts for up to 2 dropouts or non-evaluable subjects in order to have at least 6 subjects who completed the trial as per protocol.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

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

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to 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 retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section 4.1.5 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

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

8.6 TRIAL MILESTONES

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

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

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted], The [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial 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 Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be manufactured by [redacted].

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

Analyses of [^{14}C]-radioactivity concentrations in whole blood and plasma will be performed at the [redacted]

Analyses of [^{14}C]-radioactivity concentrations in urine and faeces will be performed at [redacted]

Analyses of BI 1569912 and [^{13}C]-BI 1569912 concentrations in plasma will be performed at the [redacted]

[redacted] for plasma, urine, and faeces will be performed in the [redacted]

Radioprofiling [redacted] in plasma, urine, and faeces for the microtracer hADME arm with the [14C]-carbonyl label will be performed at [redacted]

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 and/or a contract research organisation appointed 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.

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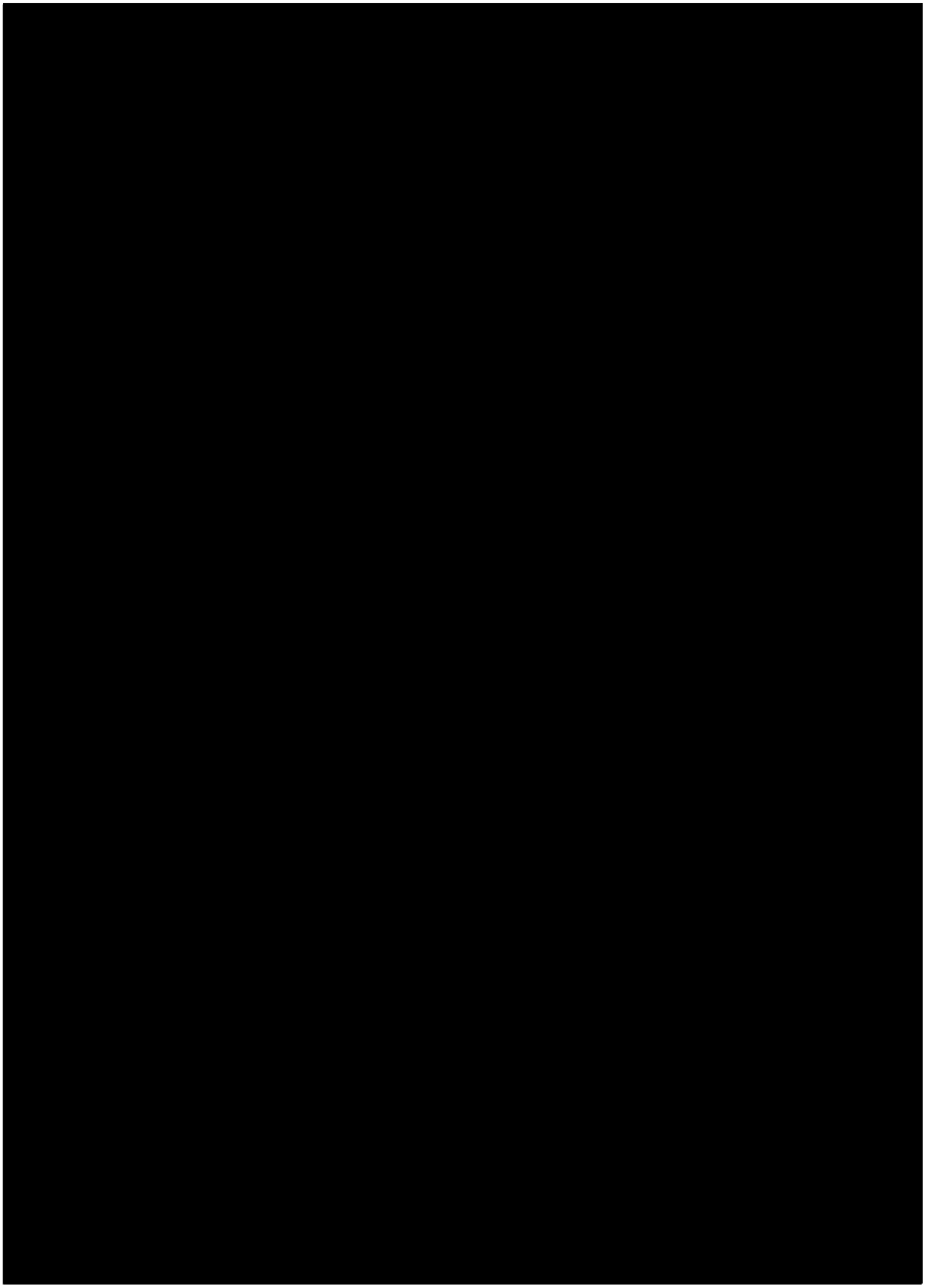


10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

10.1.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *and* [redacted] *Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *inquiries and training requirements contact* [redacted]

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AUS1_eng-USnn.doc

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past Months:**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* ____ *Type # (1-5)* ____ *Description of Ideation* Past X Months - *Most Severe Ideation:* ____ *Type # (1-5)* ____ *Description of Ideation*	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-7 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

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

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

 C-SSRS – Baseline/Screening (Version 1/14/09)

10.1.2 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *and* [redacted] *Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *inquiries and training requirements contact* [redacted]

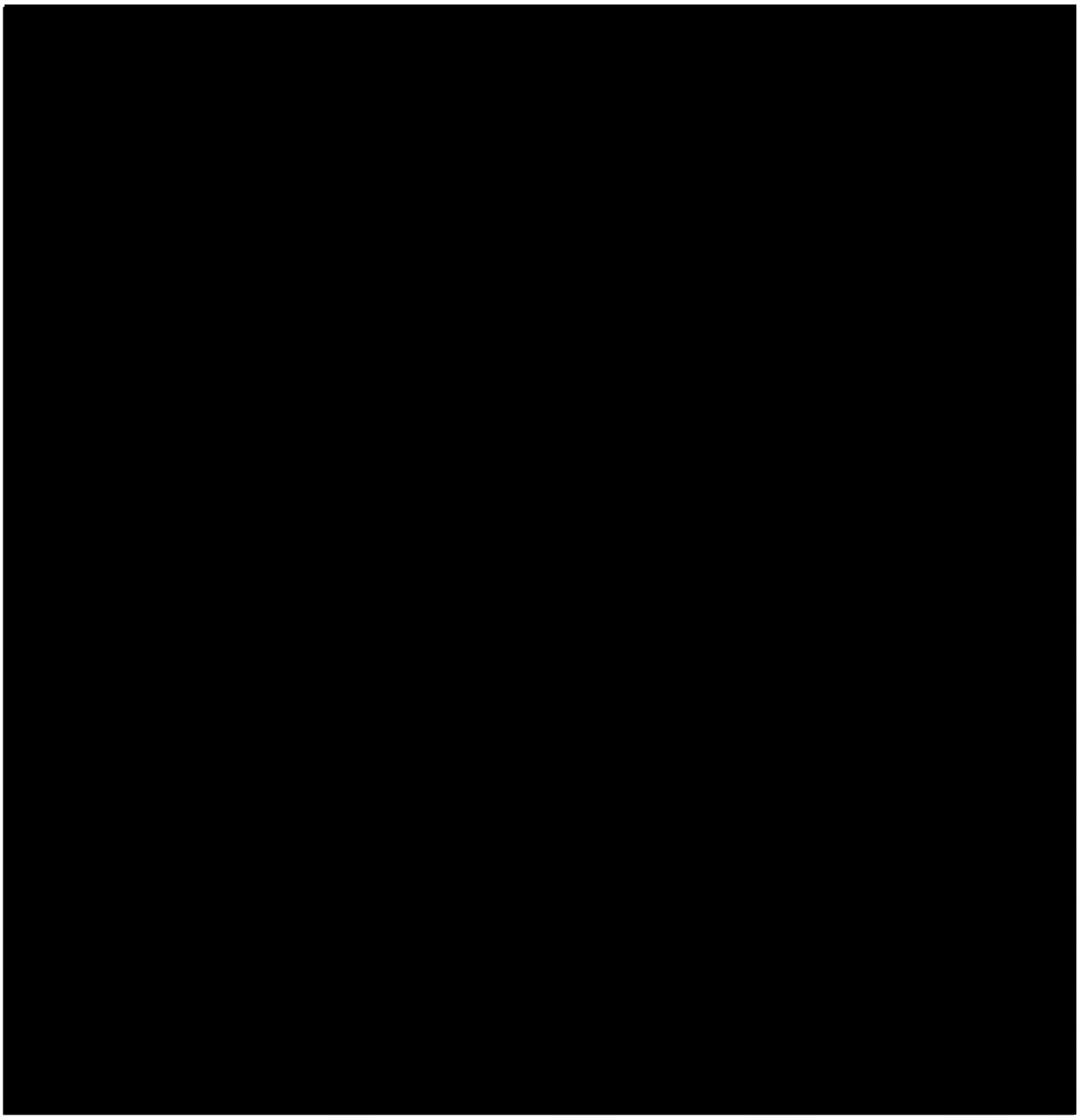
C-SSRS Since Last Visit - United States/English - Mapi:
C-SSRS-SinceLastVisit_AUS.1_eng-USen.doc

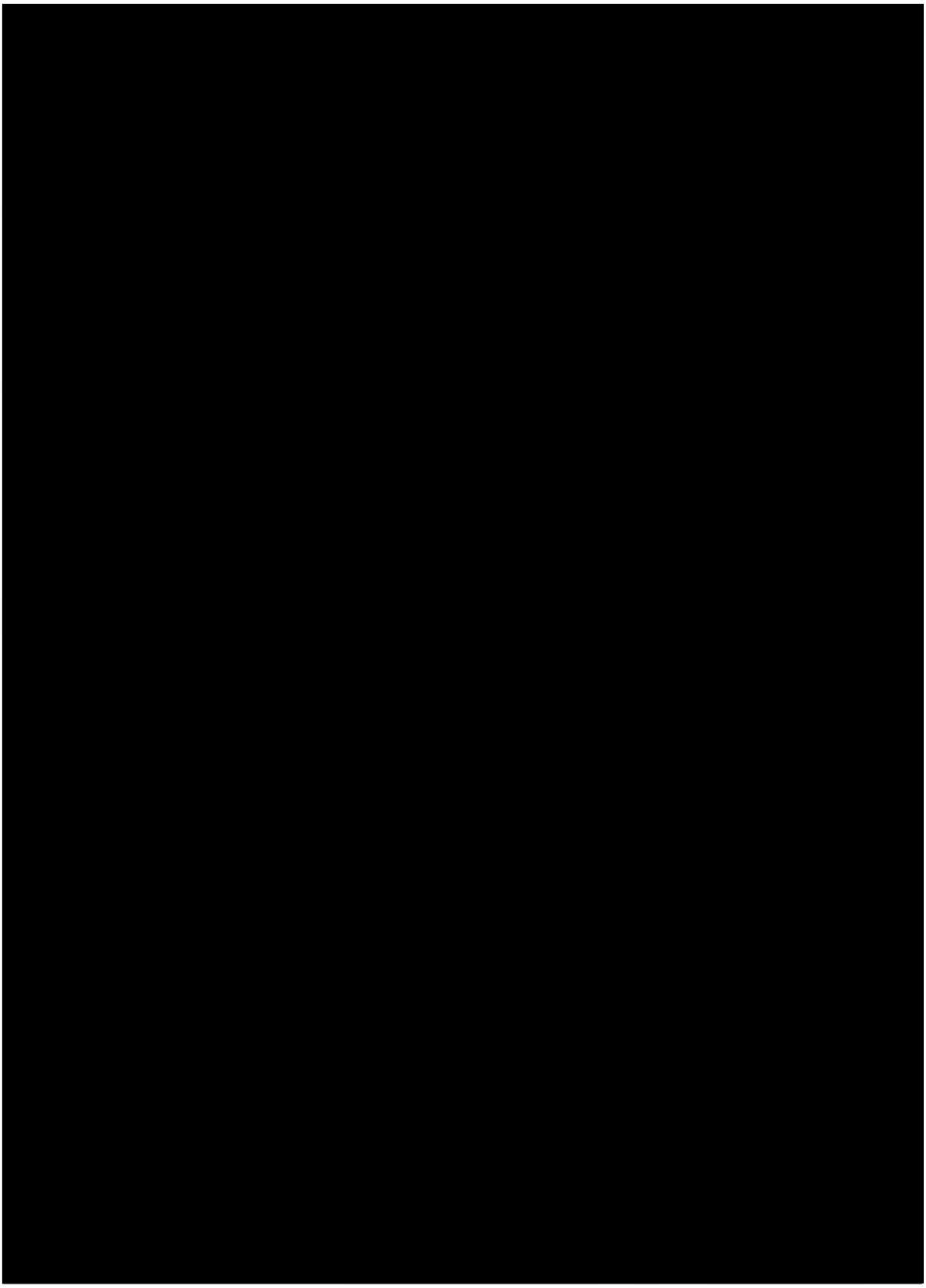
SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead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

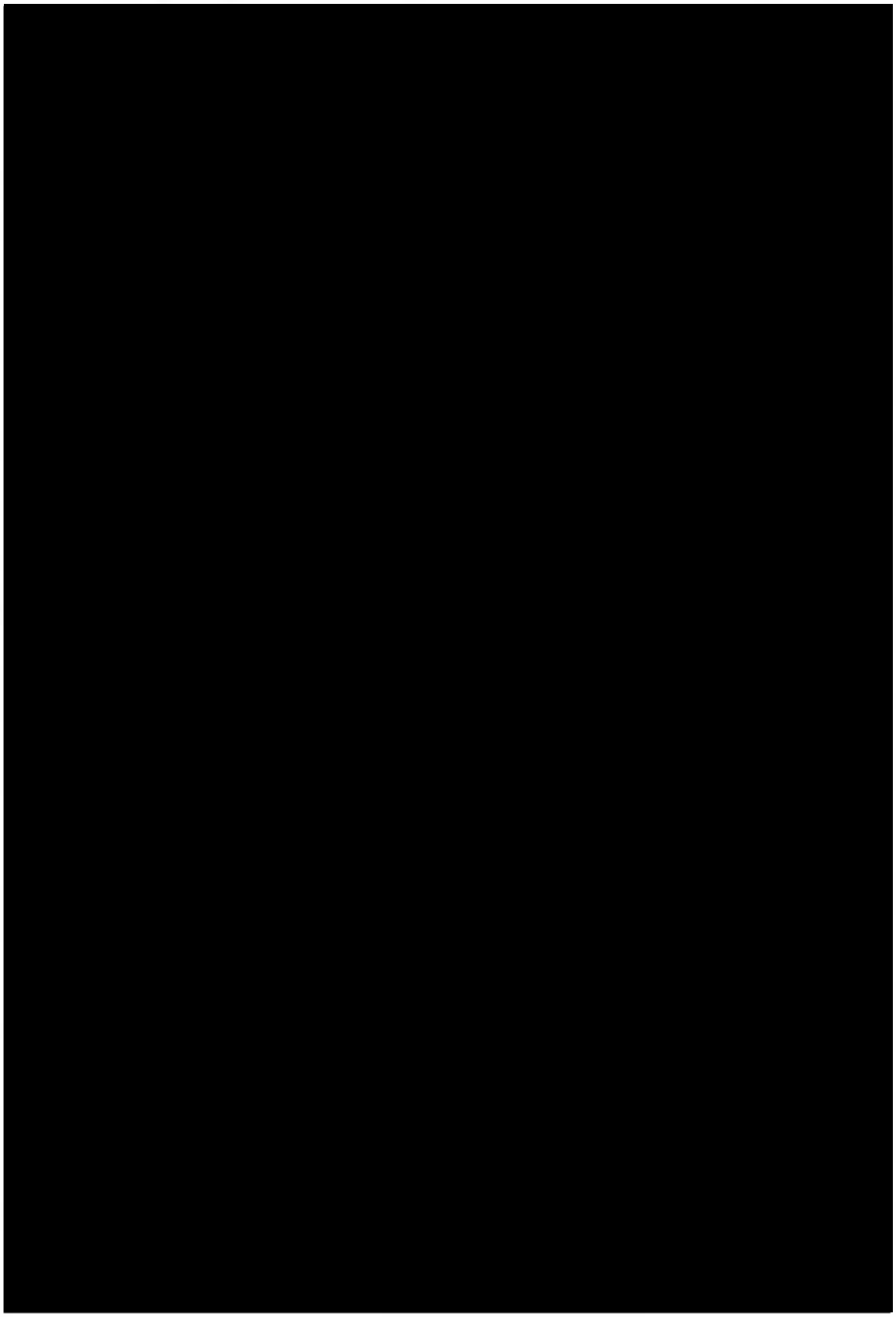
 C-SSRS—Since Last Visit (Version 1/14/08) Page 1 of 2

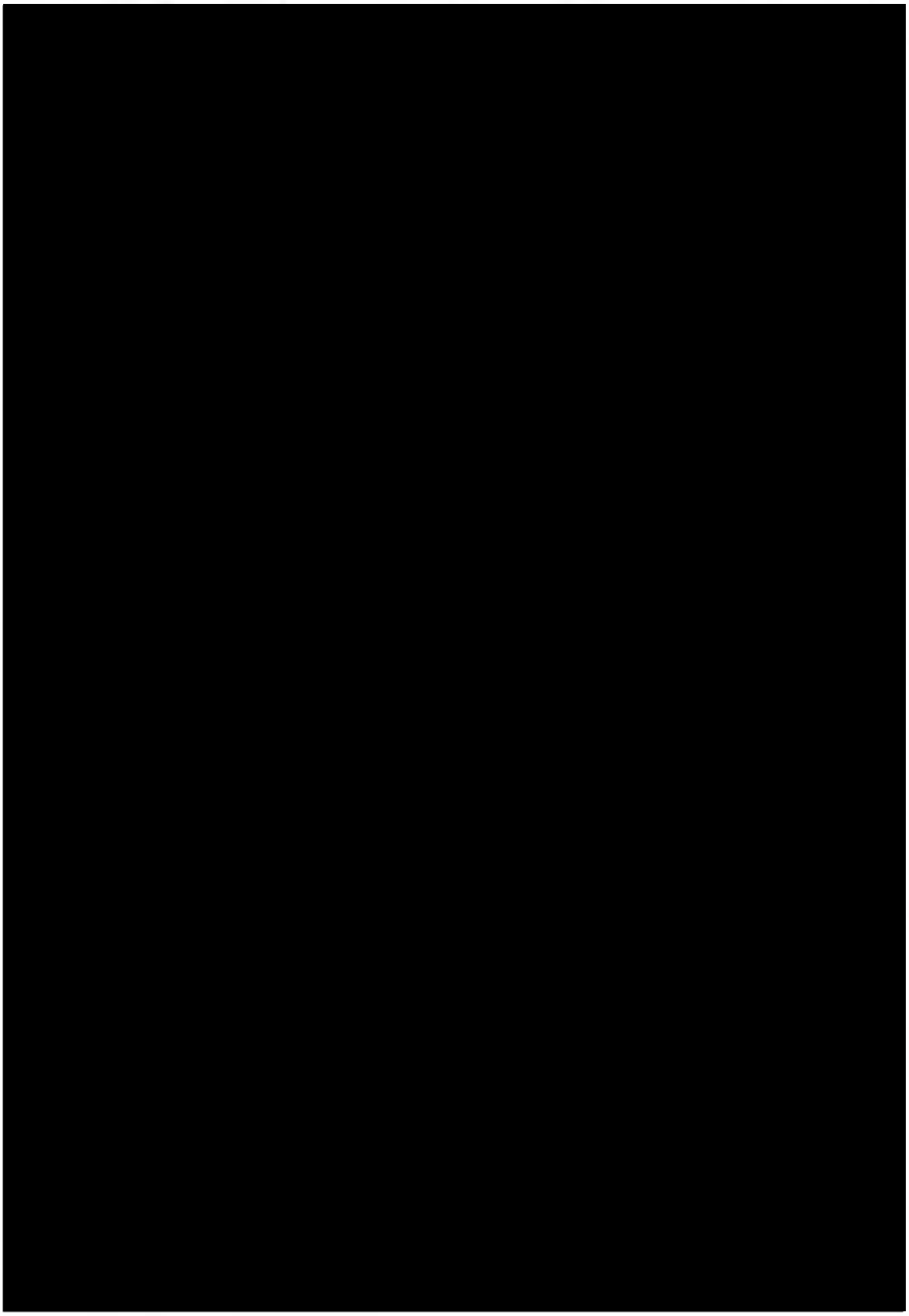
SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events, must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was at part thought of as method to kill oneself; intent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

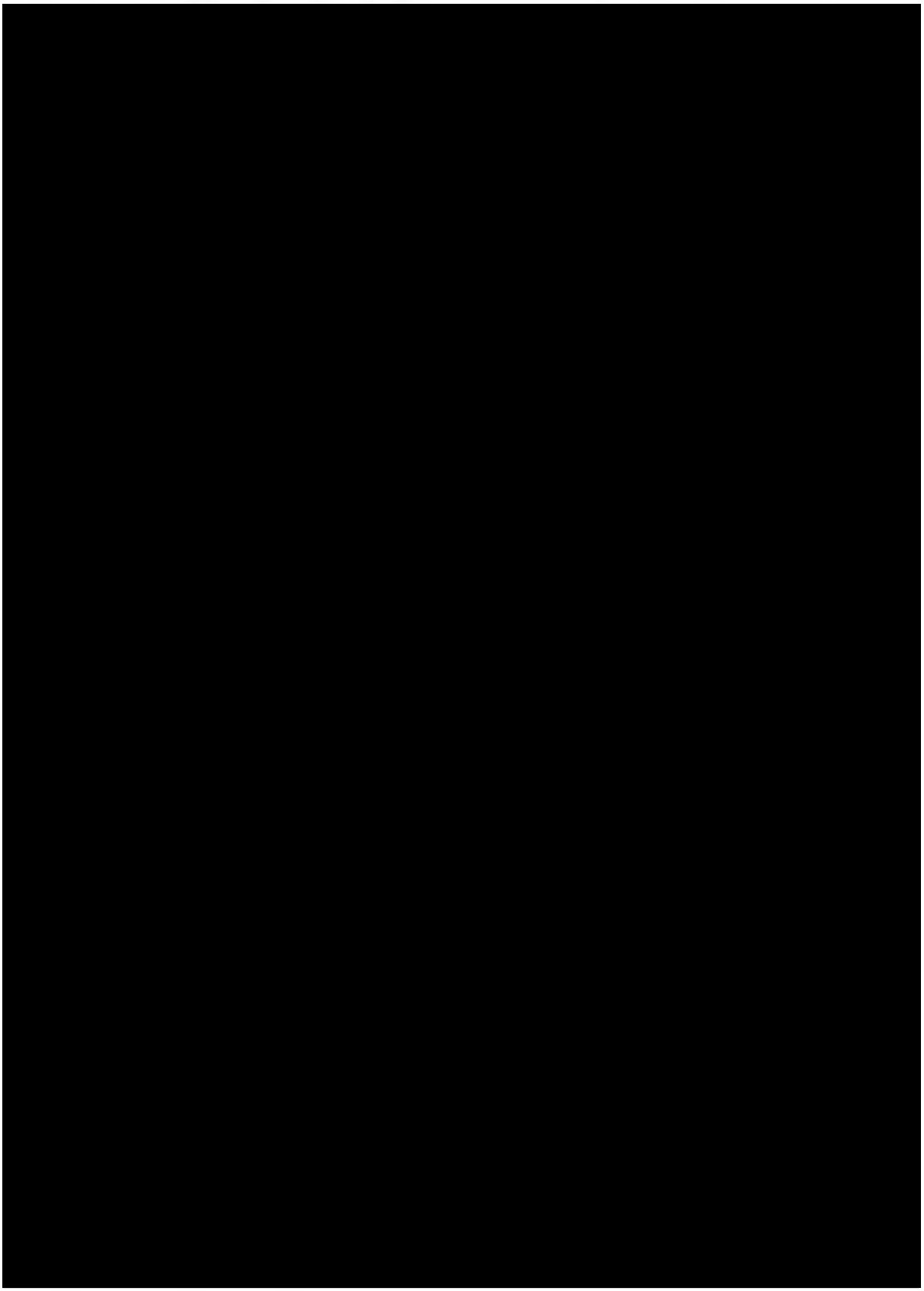
 C-SSRS – Since Last Visit (Version 1/14/09) Page 2 of 2

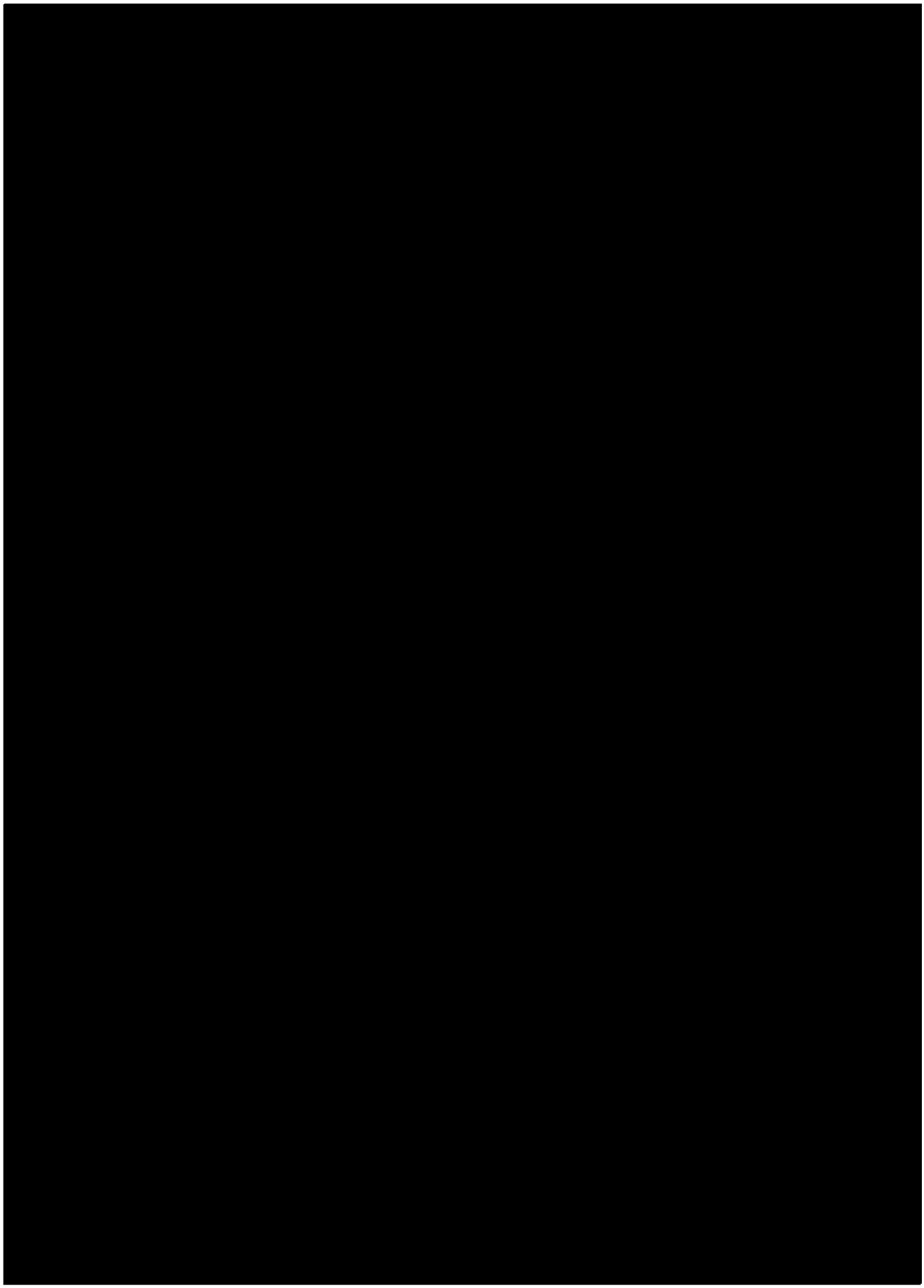












11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		30 Jul 2024
EUCT No.		2023-510464-12-00
BI Trial number		1447-0010
BI Investigational Medicinal Product(s)		BI 1569912
Title of protocol		A double-micro-tracer human absorption, distribution, metabolism and excretion (hADME), and absolute bioavailability trial after a single oral dose of BI 1569912 (C-14) and a single, concomitant, intravenous micro-dose of BI 1569912 (C-13) in healthy male subjects (a phase I, open-label, non-randomised, single-dose, fixed-sequence trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		FlowChart 3.3.3. Exclusion criteria 4.2.2.2. Restrictions on diet and life style [redacted] 8.7. Administrative structure of the trial
Description of change		FlowChart. Footnote 7 was clarified. 3.3.3. and 4.2.2.2. Current smokers and those who smoked within 30 days prior to drug intake were excluded from trial participation. Smoking was restricted during trial participation. 5.3.2.4. Urine sampling details were clarified. [redacted] 8.7. Details of analytical laboratories were clarified.
Rationale for change		3.3.3. and 4.2.2.2. Recommendation during IEC/CA review. FlowChart, 5.3.2.4., 5.3.3.3. and 8.7. Correction of typos and mistakes.

11.2 GLOBAL AMENDMENT 2

Date of amendment		13 Nov 2024
EUCT No.		2023-510464-12-00
BI Trial number		1447-0010
BI Investigational Medicinal Product(s)		BI 1569912
Title of protocol		A double-micro-tracer human absorption, distribution, metabolism and excretion (hADME), and absolute bioavailability trial after a single oral dose of BI 1569912 (C-14) and a single, concomitant, intravenous micro-dose of BI 1569912 (C-13) in healthy male subjects (a phase I, open-label, non-randomised, single-dose, fixed-sequence trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		FLOW CHART Appendix 10.4 BLOOD VOLUMES.
Description of change		Additional analysis of [14C] BI 1569912 out of the [13C] BI 1569912 plasma sample (including back-up sample) at time point 00:15 minutes.
Rationale for change		The trial aims to characterize the pharmacokinetic profile of total radioactivity. Knowing that the parent drug and its metabolites can have an early t_{max} at 15 minutes, analysis of early plasma sample (0:15 minutes after oral drug administration of BI 1569912 (C-14)) is required to fully characterize the pharmacokinetics of drug-related material.

Signature Page for VV-TMF-1076006 v3.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 14-Nov-2024 08:08:18 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Author Date of signature: 14-Nov-2024 08:16:19 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Author Date of signature: 14-Nov-2024 08:43:11 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Verification-Paper Signature Completion Date of signature: 16-Nov-2024 09:45:22 GMT+0000

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