Clinical Trial Protocol

	Document Number: **c43123112-01**
EU Trial No. **UT No.**	2023-510461-10-00 U1111-1303-9187
BI Trial No.	1447-0007
BI Investigational Medicinal Product	BI 1569912
Title	The effect of multiple doses of BI 1569912 on the single-dose pharmacokinetics of repaglinide, midazolam and bupropion following oral administration in healthy male and female subjects (an open-label, 2-period fixed-sequence trial)
Lay Title	A study in healthy men and women to test whether BI 1569912 influences the amount of repaglinide, midazolam and bupropion in the blood
Clinical Phase	I
Clinical Trial Leader	[redacted]
Principal Investigator	[redacted]
Current Version, Date	Version 1.0, 15 Feb 2024
Original Protocol Date	15 Feb 2024

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	15 Feb 2024
Revision date	Not applicable
BI trial number	1447-0007
Title of trial	The effect of multiple doses of BI 1569912 on the single-dose pharmacokinetics of repaglinide, midazolam and bupropion following oral administration in healthy male and female subjects (an open-label, 2-period fixed-sequence trial)
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	[redacted] It is therefore necessary to investigate the effect of BI 1569912 on the activity of CYP2C8, CYP3A4 and CYP2B6 by using *in vivo* probe drugs, repaglinide, midazolam and bupropion, recommended as sensitive substrates for the respective CYP enzymes.
Trial objectives	To investigate the [redacted] BI 1569912 on the pharmacokinetics of sensitive CYP2C8, CYP3A4 and CYP2B6 substrates
Trial endpoints	Primary endpoints: $AUC_{0-\infty}$ of repaglinide, midazolam and bupropion (specifically, S-bupropion and total bupropion) Secondary endpoints: AUC_{0-tz} and C_{max} of repaglinide, midazolam and bupropion (specifically, S-bupropion and total bupropion)
Trial design	Non-randomised, open-label, 2-period fixed-sequence design
Number of subjects **total entered** **on each treatment**	 18 (at least 5 of each sex) 18
Diagnosis	Not applicable
Main inclusion criteria	Healthy male and female subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product **dose** **mode of admin.**	BI 1569912 as [redacted] tablets [redacted] Oral with 240 mL of water in the morning after an overnight fast

Probe drug 1	Repaglinide as 0.5 mg tablet
dose	0.5 mg as single doses on Day 1 (Visit 2) and Day 1 (Visit 3)
mode of admin.	Oral with 240 mL of water in the morning after an overnight fast
Probe drug 2	Midazolam for injection 5 mg/5 ml used as oral solution
dose	2 mg as single doses (i.e. 1 x 2 ml) on Day 2 (Visit 2) and Day 2 (Visit 3)
mode of admin.	Oral with 240 mL of water in the morning after an overnight fast
Probe drug 3	Bupropion as 150 mg extended-release tablet
dose	150 mg bupropion hydrochloride as single doses on Day 3 (Visit 2) and Day 3 (Visit 3)
mode of admin.	Oral with 240 mL of water in the morning after an overnight fast
Duration of treatment	Single doses of repaglinide on Day 1 (Visit 2) and Day 1 (Visit 3) Single doses of midazolam on Day 2 (Visit 2) and Day 2 (Visit 3) Single doses of bupropion on Day 3 (Visit 2) and Day 3 (Visit 3) [redacted]
Statistical methods	For each probe drug (repaglinide, midazolam, bupropion), relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'subject' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to the repaglinide administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [15]	Bedside glucose monitoring [9]	PK blood Repaglinide [10]	PK blood Midazolam [10]	PK blood Bupropion & -metabolites [10]	[redacted]	Standardized mental and neurological assessment [16]	Suicidality assessment (C-SSRS) [11]	[redacted]	12-lead ECG [12]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	A						x	x		x	x	
1	2	-1	-12:00	20:00	Admission to trial site[14]	x[5]											x
		1	-02:00	06:00		x[2,18]	x[2]	x[2]							x[2]	x[2]	x[2]
			00:00	08:00	***Administration of repaglinide***												
			00:15	08:15				x									
			00:30	08:30			x	x									
			00:45	08:45				x									
			01:00	09:00			x	x									x
			01:30	09:30			x	x									
			02:00	10:00	240 mL fluid intake, cereal bars (mandatory)[3]		x	x									x
			03:00	11:00			x	x									
			04:00	12:00	240 mL fluid intake, lunch[3]		x	x									x
			06:00	14:00				x									
			07:00	15:00	Snack (voluntary)												
			08:00	16:00				x									
			10:00	18:00	Dinner[3]			x									
			12.00	20:00				x									x
		2	22:00	06:00					x[2]							x[2]	x[2]
			24:00	08:00	***Administration of midazolam***												
			24:15	08:15					x								
			24:30	08:30					x								
			24:45	08:45					x								
			25:00	09:00					x								x

Period	Visit	Day	Planned time (relative to the repaglinide administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [15]	Bedside glucose monitoring [9]	PK blood Repaglinide [10]	PK blood Midazolam [10]	PK blood Bupropion & -metabolites [10]	[redacted]	Standardized mental and neurological assessment [16]	Suicidality assessment (C-SSRS) [11]	[redacted]	12-lead ECG [12]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
			25:30	09:30					x								
			26:00	10:00	240 mL fluid intake				x								x
			27:00	11:00					x								
			28:00	12:00	240 mL fluid intake, lunch[3]				x								x
			30:00	14:00					x								
			31:00	15:00	Snack (voluntary)												
			32:00	16:00					x								
			34:00	18:00	Dinner[3]				x								
			36:00	20:00					x								x
		3	46:00	06:00						x[2]						x[2]	x[2]
			48:00	08:00	***Administration of bupropion***												
			49:00	09:00						x							
			50:00	10:00	240 mL fluid intake					x							x
			51:00	11:00						x							
			52:00	12:00	240 mL fluid intake, lunch[3]					x							x
			53:00	13:00						x							
			54:00	14:00						x							x
			55:00	15:00	Snack (voluntary)												
			56:00	16:00						x							
			58:00	18:00	Dinner[3]					x							
			60:00	20:00						x							x
		4	72:00	08:00	Breakfast (voluntary)[3], discharge from trial site					x						x[2]	x[2]
		5	96:00	08:00	Ambulatory visit					x							x
		6	120:00	08:00	Ambulatory visit					x							x
		7	144:00	08:00	Ambulatory visit					x							x
		8	168:00	08:00	Ambulatory visit	B[8]				x					x	x	x

Period	Visit	Day	Planned time (relative to the repaglinide administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [15]	Bedside glucose monitoring [9]	PK blood Repaglinde [10]	PK blood Midazolam [10]	PK blood Bupropion & -metabolites [10]	[redacted]	[redacted]	Standardized mental and neurological assessment [16]	Suicidality assessment (C-SSRS) [11]	[redacted]	12-lead ECG [12]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
[redacted]																		

Period	Visit	Day	Planned time (relative to the repaglinide administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [15]	Bedside glucose monitoring [9]	PK blood Repaglinde [10]	PK blood Midazolam [10]	PK blood Bupropion & -metabolites [10]	[redacted]	Standardized mental and neurological assessment [16]	Suicidality assessment (C-SSRS) [11]	[redacted]	12-lead ECG [12]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
[redacted]																	

Period	Visit	Day	Planned time (relative to the repaglinide administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [15]	Bedside glucose monitoring [9]	PK blood Repaglinde [10]	PK blood Midazolam [10]	PK blood Bupropion & -metabolites [10]	[redacted]	Standardized mental and neurological assessment [16]	Suicidality assessment (C-SSRS) [11]	[redacted]	12-lead ECG [12]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
[redacted]																	

Period	Visit	Day	Planned time (relative to the repaglinide administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [15]	Bedside glucose monitoring [9]	PK blood Repaglinde [10]	PK blood Midazolam [10]	PK blood Bupropion & -metabolites [10]	[redacted]	Standardized mental and neurological assessment [16]	Suicidality assessment (C-SSRS) [11]	[redacted]	12-lead ECG [12]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
[redacted]																	

Period	Visit	Day	Planned time (relative to the repaglinide administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [15]	Bedside glucose monitoring [9]	PK blood Repaglinde [10]	PK blood Midazolam [10]	PK blood Bupropion & -metabolites [10]	[redacted]	Standardized mental and neurological assessment [16]	Suicidality assessment (C-SSRS) [11]	[redacted]	12-lead ECG [12]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
[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 as well as pregnancy test in women), 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 within the 3 h prior to drug administration or discharge.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, standardized mental and neurological assessment, suicidality assessment, vital signs, ECG, safety laboratory, pregnancy test in women, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial but will be specifically asked for at the times indicated in the Flow Chart above.
7. to be taken within 10 min prior dosing
8. Safety laboratory at this time is to be taken and to be medically evaluated prior to first administration of BI 1569912 in Period 2.
9. For details of bedside glucose measurement, refer to Section 5.2.3.
10. For details of PK blood sampling, refer to Section 5.3.2.1.
11. For details of suicidality assessment (C-SSRS), refer to Section 5.2.5.1.
12. Single 12-lead ECG for clinical evaluation by the investigator only. For details refer to Section 5.2.4.
13. For details of vital signs evaluation, refer to Section 5.2.2.
14. At discretion of the investigator or designee, admission on the next morning no later than 2 h prior to first drug administration in each treatment period.
15. Letters A and B define different sets of safety laboratory examinations (for details refer to Section 5.2.3).
16. For details of standardized mental and neurological assessment, refer to Section 5.2.5.2.

17. For details of assessment of study medication withdrawal symptoms, refer to Section 5.2.5.3.
18. Only one sample for pharmacogenomic testing will be collected at this time (for details refer to Section 5.6.1).
19. For details of PK urine sampling, refer to Section 5.3.2.2. [redacted]

Note: No wash-out period is planned between Periods 1 and 2, i.e. Day -15 of Period 2 may be on the same calendar day as Day 8 of Period 1. However, up to 14 days between periods is allowed at discretion of the investigator or designee, e.g. for logistical reasons.

Note: On Days -13 to -3 and 4 to 8 of Period 2, meals will be provided by the trial site following local standards, [redacted]

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 h
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-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-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AWQ	Amphetamine withdrawal questionnaire
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CADDS	Clinician Administered Dissociative States Scale
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
COVID-19	SARS-CoV-2 induced disease
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
DDI	Drug drug interaction
DILI	Drug induced liver injury
EC_{50}	Half maximal effective concentration

ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EFD	Embryo-foetal development
EMA	European Medicines Agency
EoS	End of Study (synonym for End of Trial)
EudraCT	European Clinical Trials Database
FST	Forced swim test
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MEC	Minimal effective concentration
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MRD	Multiple-rising dose
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
NAM	NR2B-specific negative allosteric modulator
NMDA	Glutamate N-methyl-D-aspartate
NR2A	NMDA receptor subunit 2A
NR2B	NMDA receptor subunit 2B
OATP	Solute carrier organic anion transporter
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
$R_{Cmax, M/P}$	Ratio of metabolite C_{max} to parent C_{max}
$R_{AUC0-\infty, M/P}$	Ratio of metabolite $AUC_{0-\infty}$ to parent AUC
$R_{Cmax,T/R}$	Ratio of C_{max} value of the "test" treatment versus C_{max} value of the "reference" treatment
$R_{AUC,T/R}$	Ratio of the AUC value of the analyte of the "test" treatment versus AUC value of the "reference" treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SIB	Suicidal ideation and behaviour
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
T2DM	Type 2 diabetes mellitus
TMF	Trial master file
$t_{1/2}$	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_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).

[redacted]

1.2 DRUG PROFILE

1.2.1 BI 1569912

1.2.1.1 Non-clinical pharmacology

BI 1569912 is a potent negative allosteric modulator (NAM) of NR2B containing NMDA receptors with an EC50 of 16 nM [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]

1.2.1.2 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]

[redacted]

[redacted]

[redacted]

1.2.1.3 Toxicology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

[redacted] [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2.1.4 Non-clinical pharmacokinetics

[redacted]

[redacted]

[redacted]

1.2.1.5 Clinical safety

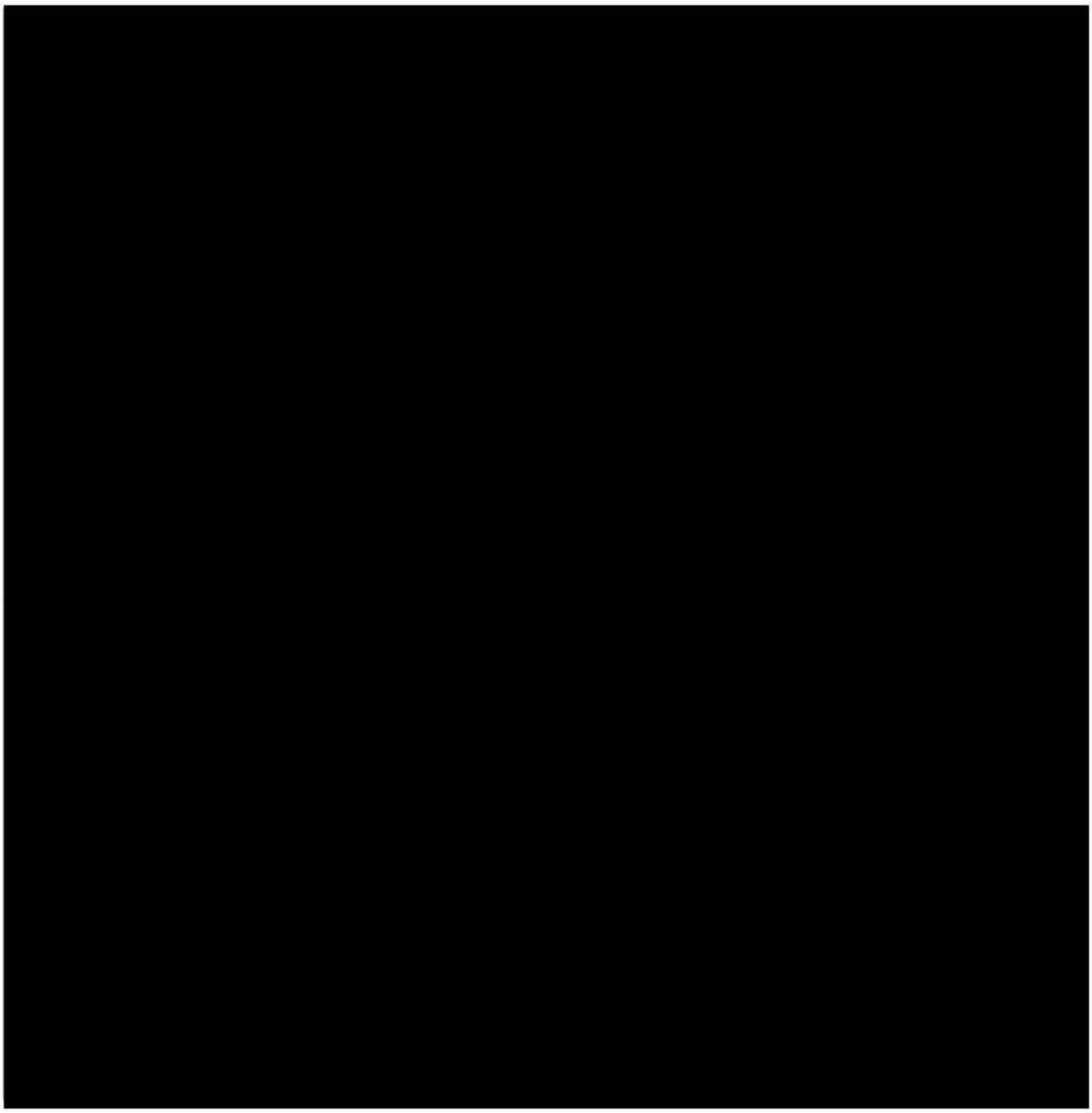
As of 01 February 2024, safety data were available from 1 completed [Trial 1447-0001 [SRD and BA/FE]) [redacted]

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]



[redacted]

In the ongoing MRD trial preliminary safety data was available from [redacted]

[redacted]

[redacted]

1.2.1.6 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%.

Table 1.2.1.6: 1 PK parameters (gMean (%gCV)) after single administrations of BI 1569912 as an oral solution in healthy volunteers in the SRD part of Trial 1447-0001

PK parameter	BI 1569912 solution						
	0.25 mg (N=6)	0.75 mg (N=6)	2 mg (N=6)	5 mg (N=6)	10 mg (N=6)	20 mg (N=6)	30 mg (N=5)
Plasma							
[redacted]							
$AUC_{0-\infty}$ [h·nmol/L]	32.9 (18.6)	85.1 (18.9)	252 (27.8)	539 (17.4)	1110 (13.8)	2540 (17.1)	2900 (16.9)
$AUC_{0-\infty,norm}$ [h·nmol/L/mg]	131 (18.6)	114 (18.9)	126 (27.8)	108 (17.4)	111 (13.8)	127 (17.1)	96.7 (16.9)
C_{max} [nmol/L]	11.9 (26.4)	33.1 (36.7)	105 (41.6)	228 (26.9)	361 (30.9)	1090 (32.1)	1100 (27.1)
$C_{max,norm}$ [nmol/L/mg]	47.4 (26.4)	44.1 (36.7)	52.5 (41.6)	45.6 (26.9)	36.1 (30.9)	54.5 (32.1)	36.6 (27.1)
$t_{1/2}$ [h]	4.12 (27.7)	3.65 (23.3)	3.67 (28.2)	4.47 (20.0)	4.30 (31.5)	4.03 (18.4)	3.72 (21.0)
t_{max} [h]#	0.500 (0.500 – 0.500)	0.625 (0.250 – 0.767)	0.500 (0.250 – 0.500)	0.500 (0.500 – 0.783)	0.500 (0.250 – 0.750)	0.375 (0.250 – 0.750)	0.500 (0.250 – 0.800)
CL/F [mL/min]	352 (18.6)	407 (18.9)	367 (27.8)	429 (17.4)	418 (13.8)	365 (17.1)	478 (16.9)
Vz/F [L]	126 (34.9)	129 (24.3)	116 (31.5)	166 (34.3)	155 (30.4)	127 (22.6)	154 (36.4)
Urine							
Ae_{0-48} [nmol]	-	-	11.4 (30.3)	18.4 (105)	38.6 (24.1)	88.1 (51.4)	83.3 (267)
fe_{0-48} [%]	-	-	0.205 (30.3)	0.133 (105)	0.139 (24.1)	0.159 (51.4)	0.100 (267)
$CL_{R,0-8}$ [mL/min]	-	-	-	-	0.657 (24.5)*	0.641 (45.7)	0.494 (286)

Median [min-max]
* n=5

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

1.2.2 Repaglinide

[redacted] of BI 1569912 on CYP2C8 will be investigated using the probe substrate repaglinide.

Repaglinide is indicated for therapy of T2DM alone or in combination with metformin. It is a short-acting stimulator of pancreatic insulin secretion. It causes depolarisation of pancreatic beta-cells which, in turn, enhances calcium influx, followed by insulin release.

After oral administration, repaglinide is rapidly absorbed with plasma t_{max} values within one hour and an absolute bioavailability of 63%. Volume of distribution is low (30 L), and plasma protein binding is high (>98%). Repaglinide is eliminated within 4-6 hours; plasma $t_{1/2}$ is around one hour. Elimination is principally via metabolisation, mainly by CYP2C8 and to a lesser extent by CYP3A4 [R14-3570]. The drug transporter OATP1B1 has been shown to contribute to hepatocellular uptake of repaglinide [P13-07476].

Repaglinide should be taken within 30 min before a meal. The recommended initial dose of repaglinide is 0.5 mg, the recommended maximal single dose is 4 mg, and the recommended maximal daily dose is 16 mg [R14-3570].

The most frequent side effect of repaglinide is hypoglycaemia.

Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend the use of repaglinide as *in vivo* probe drug for CYP2C8 in DDI trials (FDA draft guidance [P12-05791] and EMA guideline [P12-10638]).

In a clinical trial in 12 healthy volunteers, repaglinide (0.25 mg oral single dose) AUC and C_{max} were increased by 8.1- and 2.4-fold, respectively, by concomitant administration of the CYP2C8 and OATP1B1 inhibitor gemfibrozil, and $t_{1/2}$ was prolonged from 1.3 to 3.7 h. Concomitant administration of the CYP3A4 inhibitor itraconazole increased repaglinide AUC and C_{max} by 1.4- and 1.5-fold, respectively. Combined administration of both gemfibrozil and itraconazole increased repaglinide AUC and C_{max} by 19.4- and 2.8-fold, respectively, and prolonged $t_{1/2}$ to 6.1 h [R14-3624]. In another trial in 9 healthy volunteers, concomitant administration with the CYP2C8 inhibitor trimethoprim increased repaglinide AUC and C_{max} by 1.6- and 1.4-fold, respectively [R14-3625].

For a more detailed description of the repaglinide profile, please refer to the current summary of product characteristics (SmPC) [R24-0438].

1.2.3 Midazolam

[redacted] of BI 1569912 on activity of CYP3A4 will be investigated using the probe substrate midazolam.

Midazolam is a short acting benzodiazepine which is used for the treatment of insomnia and as sedative premedication before surgical or diagnostic procedures. It has a volume of distribution of 0.7 to 1.2 L/kg at steady state. Its elimination half-life in young healthy volunteers ranges from 1.5 to 2.5 hrs. The plasma clearance was determined to be 300 to 500 mL/min. Midazolam is almost completely eliminated by biotransformation to 1-hydroxymidazolam and this process is mediated by CYP3A enzymes [R23-4481].

In contrast to testosterone or erythromycin, which have also been proposed as probe drugs to monitor CYP3A activity, midazolam is metabolised specifically by CYP3A and does not serve as a substrate for other CYP450 isoenzymes or the drug transporter P-glycoprotein. Intravenous midazolam is a sensitive in vivo probe of hepatic CYP3A activity, whereas orally administered midazolam is metabolised by both, intestinal and hepatic CYP3A.

The therapeutic oral dose of midazolam is 7.5 mg - 15 mg, up to a maximum of 20 mg. In this trial, midazolam will be given as a single oral dose of 2 mg in both treatment periods. The PK of midazolam has been found to be dose proportional over a range of at least 0.001

µg to 3 mg [R17-3022]. The administration of an oral dose of 2 mg midazolam is without a major sedative effect [P10- 00100].

For a more detailed description of the midazolam profile, please refer to the current SmPC [R23-4481].

1.2.4 Bupropion

[redacted] of BI 1569912 on CYP2B6 will be investigated using the probe substrate bupropion.

Bupropion is used as antidepressant and smoking cessation aid. It acts as selective inhibitor of neuronal reuptake of noradrenalin and dopamine. The mechanism by which it helps in smoking cessation is unknown.

After oral administration of a 150 mg bupropion extended-release tablet (as used in this trial), t_{max} was observed at approximately 5 h. Bupropion is extensively metabolised with only 0.5% excreted unchanged in either faeces or urine. Hydroxybupropion, threohydrobupropion and erythrohydrobupropion are active metabolites. Only the formation of hydroxybupropion is catalysed via CYP2B6.

Based on a mouse anti-tetrabenazine model, hydroxybupropion is approximately 50% as active as bupropion, and threohydrobupropion and erythrohydrobupropion are approximately 20% as active as bupropion [P06-00643]. Plasma C_{max} and AUC of the main metabolite hydroxybupropion are approximately 3- and 14-fold higher than for bupropion, respectively. t_{max} of hydroxybupropion is reached approximately 7 h after administration of a single dose of bupropion [R24-0437].

Clinically, bupropion is used as a racemate, and disposition is stereoselective. CYP2B6 catalyzes hydroxylation of both enantiomers, R-bupropion and S-bupropion, to R,R-hydroxybupropion and S,S-hydroxybupropion, respectively [R14-3843]. The rate of S-bupropion hydroxylation has been reported to exceed R-bupropion hydroxylation by approximately 1.5- to 3-fold [R14-3843]. Interestingly, S,S-hydroxybupropion plasma concentration is formation-rate limited, whereas R,R-hydroxybupropion is elimination-rate limited [R14-3843]. Therefore, both plasma concentration of S,S-hydroxybupropion and the metabolite-to-parent ratio of S,S-hydroxybupropion to S-bupropion may be used as parameters for CYP2B6 activity in addition to plasma concentrations of bupropion or S-bupropion.

Mean plasma $t_{1/2}$ of bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion is approximately 20, 20, 37, and 33 h, respectively [R24-0437].

When used to help with smoking cessation, initial recommended dose is 150 mg q.d. followed by 150 mg b.i.d. starting on day 7. Maximal daily dose of bupropion is 300 mg. Recommended treatment duration is 7-9 weeks for smoking cessation or >6 months for treatment of depression.

The most frequent side effects of bupropion are psychiatric or neurologic reactions such as sleep disorders (especially when taken in the evening), agitation, anxiety, depression, concentration disorders, headache or dizziness, moreover hypersensitivity reactions such as urticaria, skin reactions such as exanthema, pruritus or increased sweating, or fever, or

gastrointestinal symptoms such as dry mouth, nausea, vomiting, or obstipation. Moreover, bupropion dose-dependently increases the risk of cerebral seizures (at doses of up to 450 mg bupropion hydrochloride the frequency of cerebral seizure is reported as 0.1%).

Use of bupropion is contraindicated in patients with cerebral seizure, bulimia, anorexia, or a bipolar mood disorder in the medical history.

Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend the use of bupropion as in vivo probe drug for CYP2B6 in DDI trials [P12-05791, P15-06991]. The EMA guideline specifically recommends the investigation of S-bupropion (hydroxylation) as in vivo marker for CYP2B6 activity.

For a more detailed description of the bupropion profile, please refer to the current SmPC [R24-0437].

1.2.5 Residual Effect Periods

The Residual Effect Period (REP) [redacted]

The REP of repaglinide, midazolam and bupropion is 6 h, 12 h and 5 days, respectively.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Drug-drug interactions (DDI) are complex and have proven to be a major challenge for health care providers. One of the questions that must be addressed before new drugs can be safely administered is whether there is a drug interaction with other medications taken by the patient for the treatment of co-morbidities. Therefore, the interaction potential of a new compound is regularly evaluated during clinical drug development.

[redacted]. Results of this DDI trial will provide for a general signal of potentially important DDI upon which further exploration can be based.

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 to 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 including BI 1569912, repaglinide, midazolam and bupropion. An overview of trial-related risks is given in Table 1.4.2: 1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1569912		
[redacted]	• [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
<u>Investigational Medicinal Product</u>: BI 1569912		
[redacted]	• [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]	[redacted]	[redacted]
[redacted]	[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]	[redacted]	[redacted]
[redacted]	[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
Probe drug 1: Repaglinide		
Hypoglycaemia	• The most frequent side effect of repaglinide is hypoglycaemia.	• The investigated dose of repaglinide of 0.5 mg is the lowest clinical dose and limited to 2 single intakes. • After each administration of repaglinide, the subjects will consume 2 cereal bars at 2 h post-dose (mandatory). • Subjects are frequently asked for AEs after repaglinide dosing, and at pre-defined time-points, blood glucose bedside tests are performed. • During the first 4 h after administration of repaglinide, subjects will be confined to bed in sitting or half-sitting position unless lower or supine positioning is required for trial-related measurements. • In case of relevant hypoglycemia, oral glucose tablets will be administered (see Section 4.2.1) and further repaglinide treatment should be avoided.
Probe drug 2: Midazolam		
CNS-related effects	• In line with its target indication the therapeutic use of midazolam will cause sedative effects.	• The investigated dose of midazolam is 2 mg which is lower than the oral adult therapeutic dose (7.5 - 15 mg, maximum dose up to 20 mg). • Subjects are under close monitoring at the site. • Prior discharge the subject will be assessed by the investigator including its ability to drive and operate machines. If required, the inhouse period will be extended until the subject has completely recovered.

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
<u>Probe drug 3</u>: Bupropion		
CNS-related effects incl. cerebral seizures	• The most frequent side effects of bupropion are psychiatric and neurologic reactions as sleep disorders (especially when taken in the evening), agitation, anxiety, depression, concentration disorders, headache or dizziness. • Bupropion dose-dependently increases the risk of cerebral seizures (at doses of up to 300 mg bupropion hydrochloride the frequency of cerebral seizure is reported as 0.1%).	• In the current trial, the dose of bupropion hydrochloride is limited to two single doses of 150 mg. • Subjects with history of cerebral seizure, bulimia, anorexia, or a bipolar mood disorder will be excluded from study participation. • Administration of other drugs that are known to decrease the cerebral seizure threshold (such as tramadol, theophylline, systemically acting glucocorticoids, fluoroquinolones, or sedating antihistaminic drugs) should be avoided, if possible, during the trial.
<u>Trial procedures</u>		
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]

[redacted]

The probe drugs (repaglinide, midazolam and bupropion) are used at low or sub- therapeutic single doses in the current trial. [redacted]

The most frequent side effect of repaglinide is hypoglycemia. Repaglinide may be given to healthy subjects at fasted state, before a breakfast, or with sugar-containing drinks (e.g., apple juice or glucose-water solution). However, intake of carbohydrate-containing solution may relevantly slow gastric emptying and could therefore affect repaglinide oral absorption. Therefore, in the current trial repaglinide will be administered at fasted state without a concomitant intake of carbohydrates. In order to prevent hypoglycemic episodes, the risk

mitigation strategy applied including carbohydrate-containing cereal bars at 2 h post-dose and bedside blood glucose monitoring (see Table 1.4.2: 1).

Taking into account specific safety measures, including a mental and neurological monitoring, and resulting from this, the possibility to stop the application of treatment at any point in time, a participation in this clinical trial does not represent an undue risk to healthy subjects.

[redacted]

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate [redacted] of multiple oral doses of [redacted] BI 1569912 [redacted] on the pharmacokinetics of a single oral dose of repaglinide, midazolam and bupropion (i.e. sensitive CYP2C8, CYP3A4 and CYP2B6 substrates).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for repaglinide, midazolam and bupropion (specifically, S-bupropion and total bupropion) when administered without BI 1569912 and co-administered at BI 1569912 steady-state:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined for repaglinide, midazolam and bupropion (specifically, S-bupropion and total bupropion) when administered without BI 1569912 and co-administered at BI 1569912 steady-state:

- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives are the evaluation and comparison of additional pharmacokinetic parameters between the treatments and assessment of safety and tolerability.

2.2.2 Further endpoints

2.2.2.1 Further pharmacokinetic endpoints

[redacted]

[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)
- Standardized mental and neurological assessment

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a non-randomised, open-label, two-period trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R) using the fixed sequence R-T. An overview of both treatments is given below, for details refer to Section 4.1.

Reference Treatment (R):

- 0.5 mg repaglinide given orally alone on Day 1 of Visit 2, single dose in the morning
- 2 mg midazolam given orally alone on Day 2 of Visit 2, single dose in the morning
- 150 mg bupropion given orally alone on Day 3 of Visit 2, single dose in the morning

Test Treatment (T)

- [redacted]
- 0.5 mg repaglinide given orally alone on Day 1 of Visit 3, single dose in the morning
- 2 mg midazolam given orally alone on Day 2 of Visit 3, single dose in the morning
- 150 mg bupropion given orally alone on Day 3 of Visit 3, single dose in the morning

Probe treatments (repaglinide, midazolam and bupropion) will be given under fasting conditions. There will be no washout period, [redacted] However, up to 14 days between treatment periods is allowed at discretion of the investigator or designee, e.g. for logistical reasons. As per the Flow Chart, there will be at least an interval of 21 days between the two single-dose administrations of the CYP2C8 probe, repaglinide (Day 1 of Visits 2 and 3), as well as the two single-dose administrations of the CYP3A4 probe, midazolam (Day 2 of Visits 2 and 3), and the two single-dose administrations of the CYP2B6 probe, bupropion (Day 3 of Visit 2 and 3). In Period 2, [redacted]

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

For this one-sided DDI-trial (investigates the effect of the [redacted] BI 1569912 on [redacted]epaglinide, midazolam, and bupropion), the fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects, because the trial duration is short enough so that nonspecific time-effects are not expected.

According to the FDA guideline on drug-drug interactions [P12-05791] it may take 2 weeks (or more) of daily drug administration to achieve the maximum level of induction in a specific pathway.

[redacted]

For the [redacted] probe drugs (repaglinide, midazolam and bupropion), single doses are sufficient.

In this pharmacokinetic drug-drug interaction trial, the open-label treatment is acceptable, because the primary and secondary trial endpoints are derived from measurement of plasma concentrations of the analytes. These endpoints are not expected to be affected by knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 18 healthy male and female subjects (at least 5 of each sex) will enter the trial. They will be recruited from the volunteers' pool of the trial site.

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 or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, standardized mental and neurological assessment, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests without clinically significant abnormalities
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

5. Either male subjects or female subjects who meet the following criteria requiring highly effective contraception from at least 30 days before the first administration of trial medication until 30 days after trial completion:

   - Use of adequate contraception, i.e. use of condom (male subjects or male partners of female subjects) plus any of the following methods (female subjects or female partners of male subjects): intrauterine device, hormonal contraception (e.g. implants, injectables, combined oral or vaginal contraceptives), , surgically sterilised (including bilateral tubal occlusion/ligation, hysterectomy, bilateral oophorectomy) or postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 40 U/L is confirmatory)
   - Sexually abstinent (considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)
   - Vasectomised male subjects or male partners of female subjects (vasectomy at least 1 year prior to enrolment) in combination with a barrier method (i.e. use of condom) and provided that the partner is the sole sexual partner of the trial participant

   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 30 days after trial completion. Female subjects should not participate in egg donation from the first trial medication administration, for the duration of the study and for at least 30 days after trial completion.

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 50 to 90 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, bulimia or anorexia, or bipolar mood disorder), 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 first planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation) or that are known to decrease the threshold for cerebral seizure (such as tramadol, theophylline, systemically acting glucocorticoids, fluoroquinolones, or sedating antihistaminic drugs)
13. Intake of an investigational drug in another clinical trial within 60 days of first planned administration of trial medication in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 24 g per day for males or 12 g per day for females)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of first planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the first administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms for males or 470 ms for females) or any other relevant ECG finding (such as a marked prolongation of PQ interval greater than 240 ms) at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. 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
24. Any lifetime history of suicidal behaviour (i.e., actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
25. 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 randomization

26. History or presence of epilepsy, history of more than one febrile seizure in childhood or a family history of seizures/ convulsions
27. History of clinically relevant head injury or trauma (e.g., associated with loss of consciousness)
28. During COVID-19 pandemic: laboratory test or any symptom indicative of an ongoing SARS-CoV-2 infection
29. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of 30 days before the first administration of trial medication until 30 days after trial completion
30. For female subjects: Lactation, pregnancy, or plans to become pregnant during the trial or within 30 days after trial completion
31. For female subjects: Positive pregnancy test

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 1.2.5), 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 pregnancy, 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. An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial
7. 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
8. Suicidal ideation (type 2-5) or any suicidal behaviour based on C-SSRS questionnaires during the trial
9. Case of relevant hypoglycemia revealed during bedside blood glucose monitoring on Day 1 of Visits 2 or 3 which required oral glucose administration

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

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

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

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 4 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 objective 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. A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Test product – Investigational drug BI 1569912

Substance:	BI 1569912
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	[redacted]
Mode of administration:	Oral
Duration of use:	[redacted]

Probe drug 1 – CYP2C8 probe

Name:	NovoNorm®
Substance:	Repaglinide
Pharmaceutical formulation:	Tablet
Source:	Novo Nordisk A/S, Denmark
Unit strength:	0.5 mg
Posology:	1 – 0 – 0
Mode of administration:	Oral
Duration of use:	Single doses on Days 1 of Visit 2 and 3, in the morning

Probe drug 2 – CYP3A4 probe

Name:	Midazolam Accord® 1 mg/ml
Substance:	Midazolam
Pharmaceutical formulation:	Solution for injection (to be used as oral solution)
Source:	Accord Healthcare B.V., Netherlands
Unit strength:	5 mg/5 mL
Posology:	2 ml – 0 – 0
Route of administration:	Oral
Duration of use:	Single doses on Day 2 of Visit 2 and 3, in the morning

Probe drug 3 – CYP2B6 probe

Name:	Wellbutrin XR®
Substance:	Bupropion hydrochloride
Pharmaceutical formulation:	Extended-release tablet
Source:	GlaxoSmithKline Pharmaceuticals s.a./n.v., Belgium
Unit strength:	150 mg
Posology:	1 – 0 – 0
Mode of administration:	Oral
Duration of use:	Single doses on Days 3 of Visit 2 and 3, in the morning

4.1.2 Selection of doses in the trial and dose modifications

BI 1569912:

[redacted] is the therapeutic dose that is used in clinical drug development.

Repaglinide:

The clinically recommended dose for adults is 0.5 mg to 4 mg, the maximum daily dose is 16 mg. 0.5 mg is the lowest clinical dose, which is 8-fold lower than the highest recommended dose and 32-fold lower than the maximum daily dose.

Midazolam:

The clinically recommended dose for adults is 7.5 mg to 15 mg. For safety reasons a dose of 2 mg has been selected for this trial. [redacted]

Bupropion:

150 mg is a standard clinical dose, which is 3-fold lower than the maximum daily dose (450 mg).

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a trial subject number by first-come-first-serve principle prior to first administration of trial medication (repaglinide, a probe drug) in the morning of Day 1 of Visit 2. The trial medications will be administered in the order specified in the Flow Chart.

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 2-period fixed-sequence trial. All subjects will receive BI 1569912 and the probe drugs in the fixed treatment sequence (R-T). The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R (Reference)	Repaglinide	Tablet	0.5 mg	1 tablet on Day 1 Visit 2	0.5 mg
	Midazolam	Oral solution	5 mg/5 mL	2 mL on Day 2 Visit 2	2 mg
	Bupropion	Extended-release tablet	150 mg	1 tablet on Day 3 Visit 2	150 mg
T (Test)	BI 1569912	Tablet	[redacted]	[redacted]	[redacted]
	Repaglinide	Tablet	0.5 mg	1 tablet on Day 1 Visit 3	0.5 mg
	Midazolam	Oral solution	5 mg/5 mL	2 mL on Day 2 Visit 3	2 mg
	Bupropion	Extended-release tablet	150 mg	1 tablet on Day 3 Visit 3	150 mg

On Days 1, 2 and 3 of Visit 2 and Visit 3, and also Days -14 and -1 of Visit 3, administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. *On Days -13 to -2 and 4 to 7 of Visit 3*, [redacted] *On all days for all drug administrations*, the investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting/standing position, and 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.

Subjects will be kept under close medical surveillance until 24 h after bupropion administration in Period 1 (Visit 2) [redacted]

On Days 2 and 3 of Visit 2 and Visit 3, during the first 4 h after the probe drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture), except for medical reasons or for recording of 12-lead ECG and vital signs measurements. *On Day 1 of Visits 2 and 3*, during the first 4 h after administration of repaglinide, subjects will be confined to bed in sitting or half-sitting position (i.e. no declination of the upper body of more than approximately 45 degrees from upright posture) unless lower or supine positioning is required for trial-related measurements.

There will be no washout period between treatment periods and Day -15 of Period 2 can be directly Day 8 of Period 1. However, up to 14 days is allowed between end of Period 1 and start of Period 2, e.g. for logistical reasons, at discretion of the investigator or designee.

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

BI 1569912

The investigational medicinal product BI 1569912 will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

- The label will be prepared according to regulation (EU) No 536/2014, Annex 6, omitting certain particulars with the following justification:
- The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.
- The visit number is not relevant for the label because the product will remain at the clinical site.
- The investigator name was omitted from the label because it is included on the Trial Identification Card (TIC), which will be issued to each trial participant.

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

The probe drugs

Repaglinide, midazolam and bupropion will be obtained by the clinical trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

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 CT 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 sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee

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

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 all unused or partially used drug supplies have been returned by the clinical trial subject and 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

In case of clinical signs of hypoglycemia or blood glucose concentrations below 45 mg/dL (<2.5 mmol/L) in the glucose bedside test, oral glucose will be administered in a stepwise manner in defined amounts of about 10 g carbohydrates (e.g., two glucose tablets "Dextro Energy classic").

There are no other 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.

In particular, any known inhibitors/inducers of CYP2C8, CYP3A4 and CYP2B6 should be avoided during the entire trial, [redacted]

Also, bupropion increases the risk for cerebral seizure. Therefore, administration of other drugs that are known to decrease the cerebral seizure threshold (such as tramadol, theophylline, systemically acting glucocorticoids, fluorochinolones, or sedating antihistaminic drugs) should be avoided, if possible, during the trial.

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 on Days 1, 2 and 3 of Visit 2 and 3, and Days -14, -2 and -1 of Visit 3 at the times indicated in the Flow Chart. On trial Days -13 to -3 and 4 to 8 of Period 2 meals will be provided by the trial site following local standards.

For probe drug administrations (Days 1, 2 and 3 of Visit 2 and 3), no food is allowed starting from 10 h before until at least 4 h after repaglinide, midazolam and bupropion intake, with exception of 2 cereal bars 2 h after repaglinide administration. *On repaglinide PK profile days (Day 1 of Visit 2 and 3)*, each subject will be served 2 cereal bars which are to be mandatory consumed at approximately 2 h after repaglinide administration (e.g., “Nature valley crunchy oat and honey bars”, per bar 98 kcal, 13.5 carbohydrates, thereof 5.65 sugar).

[redacted]

For probe drug administrations on Days 1, 2 and 3 of Visit 2, from 1 h before the probe drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL 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 3000 mL.

[redacted]

On Days -13 to -3 and 4 to 7 of Visit 3, fluid intake is not restricted.

Poppy-seeds containing foods should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug screen.

Alcoholic beverages are not permitted starting 2 days before the first trial drug administration until discharge from the trial site in each treatment period.

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 of each trial period is collected.

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

Smoking is not allowed during in-house confinement.

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

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

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 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 results 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, a physical examination, a standardized mental and neurological assessment (see Section 5.2.5.2) and suicidality assessment (see Section 5.2.5.1). At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, 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 (e.g. Dinamap Pro 100, GE Medical Systems, Freiburg, Germany or equivalent) 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 samples will be collected by the trial site at the times indicated in the Flow Chart [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 will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

PCR or Antigen Rapid test for SARS-CoV-2 may be performed at Screening (including Day -3) or at any other time at the discretion of the investigator or designee.

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
	Reticulocytes/Erythrocyte	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
	Fibrinogen	X	X
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]	X	X
	Creatine Kinase Isoenzyme MB	X	X
	Lactic Dehydrogenase	X	X
	Lipase	X	X
	Amylase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
	Follicle Stimulating Hormone (only females)	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	Albumin	X	X
	C-Reactive Protein (Quant)	X	X
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
	Phosphate (as Phosphorus, Inorganic)	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B
Urinalysis (Stix)	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	All results will be reported to the eSource system	X	X

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined on Day 8 of Visit 2 and Days -7, -1 and 8 of Visit 3 and at Visit 4 (end of trial examination)

Glucose bedside test

A glucose bedside test out of capillary blood will be performed for safety reasons at pre-defined time points on Day 1 of Visits 2 and 3 (see Flow Chart). For quantification of blood glucose, one drop (approximately 50 µL) of blood taken from a fingertip will be sufficient. The results will not be reported in the CTR.

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 pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to admission at each treatment period, and as part of the end of trial examination. Drug screening will be performed at screening and prior to each admission to the trial site.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates 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)
Pregnancy test (serum/urine)[1]	Beta human chorionic gonadotropin (beta-HCG)

[1] pregnancy tests in serum only at screening and EOT and in urine at each other time point as per Flow Chart

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 5107410 or 55106810, Dräger Safety, Belgium or equivalent) will be performed prior to each treatment period, 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 [redacted], with the exception of drug screening and urine pregnancy tests. These tests will be performed at the trial site using Triage TOX Drug screen test and Alere, beta-HCG urine test, respectively, or comparable test systems.

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 (e.g. Mortara Device, Mortara Instruments, Inc., USA or equivalent) 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 at the site in the eSource system. 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)..

All 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 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 life time 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 reported to the database. For details regarding AE reporting see Section 5.2.6.1.3 and 5.2.6.2. For further information, refer to Appendix 10.1.

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 eSource system 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). Case narratives may be written, if necessary.

[redacted]

[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 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:

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

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

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

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 reported as SAEs.

For 'Self-injurious behaviour, no suicidal behaviour' standard AE/SAE 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
  - 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 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

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and 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. If there is an SAE and/or AESI associated with the pregnancy, an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis of BI 1569912 [redacted] repaglinide (and its metabolites), midazolam (and its metabolites), bupropion (and its metabolites)

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

[redacted]

[redacted]

At a minimum, the sample tube labels should list BI trial number, analyte, barcode, subject number, visit, aliquot number and planned sampling time.

After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.2.2 Urine sampling for pharmacokinetic analysis of BI 1569912 [redacted]

The details of urine sampling and probe preparation will be provided in the Laboratory Manual prior to the Site Initiation Visit.

After analysis, the urine samples may be used for further methodological investigations (e.g. for stability testing, assessment [redacted]) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its [redacted] will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of repaglinide, midazolam, bupropion and BI 1569912 [redacted] plasma concentrations

[redacted]

5.3.3.2 Analytical determination of BI 1569912 [redacted] urine concentrations

The details of analytical method will be provided in the Laboratory Manual prior to the Site Initiation Visit.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

[redacted]

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 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 or discharge as per the Flow Chart are to be performed and completed within a 3 h-period prior to it.

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 on the days of stationary stay and ± 3 h for ambulatory visits assessments with the exception of urine samples for urine safety laboratory tests which can be obtained in the morning of the given day.

[redacted]

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 or puncture of fingertip for capillary blood collection 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, 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, and pregnancy test in women), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days 1 to 8 in Period 1 and Days -15 to 9 in Period 2). There will be no washout period between treatment periods and

[redacted] However, up to 14 days is allowed between end of Period 1 and start of Period 2, e.g. for logistical reasons.

On Day -1 of Period 1 and Day -15 of Period 2, trial participants will be admitted to the trial site. At discretion of the investigator or designee, admission on day of the first drug intake in each treatment period no later than 2 h in advance is also possible. The subjects will be kept under close medical surveillance until 24 h after bupropion administration in Period 1 (Visit 2) [redacted]. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, subjects will be treated in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

Samples for pharmacogenomic testing will be collected from all randomized subjects, these samples will be analysed in case of observed PK variability (for details, see Section 5.6).

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 (including pregnancy test in women), 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

The relative bioavailability of each probe (repaglinide, midazolam, and bupropion) given [redacted] without BI 1569912 compared with repaglinide, midazolam, and bupropion given [redacted] administration of BI 1569912 will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

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 the drugs repaglinide, midazolam, bupropion, and BI 1569912 will be calculated according to the relevant BI internal procedures.

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatments (Median t_{max} is to be determined excluding the subjects experiencing emesis)
- A predose concentration of either drug is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma/urine 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

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints 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 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 each pairwise comparison) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For the primary endpoint, the difference between the expected mean for log response of the test treatment – log response of the reference treatment 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 for each endpoint.

Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoints but with all sources of variation ('subject', 'treatment') considered as fixed effects.

In addition to the model based approach all parameters will be calculated and analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

7.2.4 Further endpoint analyses

7.2.4.1 Pharmacokinetic analyses

Attainment of steady state

[redacted]

Further PK endpoints will be analysed descriptively if applicable.

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 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 1.2.5) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or 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 database lock 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), and other significant AEs (according to ICH E3) will be listed separately.

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

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values 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.

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

Relevant ECG findings will be reported as AEs.

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

The trial will not be randomised, thus this section is not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 18 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

[redacted]

For various assumptions around the gCV of 35%, Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.5: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2-period fixed sequence trial (N=12, 18).

N	gCV [%]	Precision upper CL** / relative BA estimate	90% CI [%] of respective ratio*		
			50	75	100
12	20	1.21	(41.18; 60.72)	(61.76; 91.07)	(82.35; 121.43)
12	25	1.27	(39.28; 63.65)	(58.91; 95.48)	(78.55; 127.31)
12	30	1.33	(37.49; 66.68)	(56.24; 100.02)	(74.99; 133.36)
12	35	1.4	(35.83; 69.78)	(53.74; 104.67)	(71.65; 139.56)
12	40	1.46	(34.27; 72.95)	(51.40; 109.43)	(68.54; 145.90)

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.
**Confidence interval limit

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 4.2.2.

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 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.

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 his 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. 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.

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 International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.

The trial will be conducted at [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 provided by the [redacted]

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

Analyses of repaglinide, midazolam, bupropion and its metabolites and BI 1569912 [redacted] concentrations in plasma and urine will be performed [redacted]

Analyses of pharmacogenomic biomarkers will only be performed in case of observed PK variability [redacted]

The digitally recorded 12-lead ECGs will be evaluated locally by the investigator or designee and stored in the eSource system at the trial site.

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P06-00643 Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. Clin Ther 2005;2711:1685-1695.

P06-11895 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163 11:1905-1917.

P10-00100 Turpault S, Brian W, Horn R van, Santoni A, Poitiers F, Donazzolo Y, Boulenc X. Pharmacokinetic assessment of a five-probe cocktail for CYPs 1A2, 2C9, 2C19, 2D6 and 3A. Br J Clin Pharmacol 2009;686:928-935.

P12-10638 European Medicines Agency (EMA). Committee for Human Medicinal Products (CHMP): guideline on the investigation of drug interactions: final (21 June 2012, CPMP/EWP/560/95/Rev. 1). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/0 7/WC500129606.pdf (access date: 14 September 2012); 2012.

P12-05791 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: drug interaction studies - study design, data analysis, implications for dosing, and labelling recommendations (draft guidance, February 2012 (this guidance document is being distributed for comment purposes only)). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guida nces/ucm292362.pdf (access date: 14 May 2012) ; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2012.

P13-07476 Kalliokoski A, Neuvonen PJ, Niemi M. SLCO1B1 polymorphism and oral antidiabetic drugs. Basic Clin Pharmacol Toxicol 2010;1074: 775-781.

P15-06991 European Medicines Agency (EMA). Committee for Human Medicinal Products (CHMP): guideline on the investigation of drug interactions (21 June 2012, CPMP/EWP/560/95/rev. 1 corr. 2). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/0 7/WC500129606.pdf (access date: 8 July 2015) ; London: European Medicines Agency (EMA); 2012.

P19-01288 Ministry of Health, Labour and Welfare. Guideline on drug interaction for drug development and appropriate provision of information. Website: mhlw.go.jp/hourei/doc/tsuchi/T190212I0040.pdf (access date: 12 February 2019); Ministry of Health, Labour and Welfare 2019.

P21-11010 Guideline on the investigation of drug interactions (21 June 2012, CPM P/EWP/560/95/rev. 1 corr. 2). Website:ema.europa.eu/en/investigationdrug-interactions#current-effective-version---under-revision-section (access date: 22 November 2021); 2012.

R03-2269 Guidance for industry: food-effect bioavailability and fed bioequivalence studies. In: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2002:1-9.

R06-0086 Trivedi MH, Rush AJ, Wisniewski SR, et al., STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163(1):28-40.

R08-1147 Posner K. State of the science: measurement of suicidal adverse events and the Columbia Suicide Severity Rating Scale. 47th NCDEU Ann Mtg, Boca Raton, 11 - 14 Jun 2007. 2007:15

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R12-4395 Guidance for industry: suicidal ideation and behavior: prospective assessment of occurrence in clinical trials (draft guidance, August 2012). http://www.fda.gov/downloads/Drugs/Guidanc eRegulatoryInformation/Guidances/UCM22 5130.pdf (access date: 5 October 2012); 2012.

R14-3147 Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med (Lond) 2013;43(3):471-481.

R14-3570 NovoNorm® 0,5 mg Tabletten (Fachinformation Novo Nordisk, 04/2012).

R14-3624 Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia 2003;463:347-351.

R14-3625 Niemi M, Kajosaari LI, Neuvonen M, Backman JT, Neuvonen PJ. The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. Br J Clin Pharmacol 2004;574: 441-447.

R14-3843 Kharasch ED, Mitchell D, Coles R. Stereoselective bupropion hydroxylation as an in vivo phenotypic probe for cytochrome P4502B6 (CYP2B6) activity. J Clin Pharmacol 2008;484:464-474.

R17-1266 Bolon B, Garman RH, Pardo ID, et al. STP position paper: recommended practices for sampling and processing the nervous system (brain, spinal cord, nerve, and eye) during nonclinical general toxicity studies. Toxicol Pathol 2013;41(7):1028-1048.

R17-3022 Halama B, Hohmann N, Burhenne J, Weiss J, Mikus G, Haefeli WE, et al. A nanogram dose of the CYP3A probe substrate midazolam to evaluate drug interactions. Clin Pharmacol Ther 2013;936:564-571.

R17-3810 Preskorn SH, Baker B, Kolluri S, et al. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP 101,606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol 2008;28(6):631-637.

R19-0549 Miller OH, Yang L, Wang CC, et al. GluN2B-containing NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine. eLife 2014;3:e03581.

R19-0553 Caddy C, Giaroli G, White TP, et al. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. Ther Adv Psychopharmacol 2014;4(2):75-99.

R19-0555 Hedegaard MK, Hansen KB, Andersen KT, et al. Molecular pharmacology of human NMDA receptors. Neurochem Int 2012;61(4):601-609.

R19-0778 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990 - 2016: a systematic analysis for the Global Burden of Disease study 2016. Lancet 2017;390(10100):1211-1259.

R19-0829 Paterson B, Fraser H, Wang C, et al. A randomized, double-blind, placebo-controlled, sequential parallel study of CERC-301 in the adjunctive treatment of subjects with severe depression and recent active suicidal ideation despite antidepressant treatment. NNDC 2015, Ann Conf of the National Network of Depression Centers (NNDC), Ann Arbor, 5-6 Nov 2015 (Poster) 2015

R20-0052 Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress 1998;111:125-136.

R20-0261 Guidance for industry: in vitro drug interaction studies – cytochrome P450 enzyme- and transporter-mediated drug interactions (January 2020, clinical pharmacology). Website: fda.gov/media/134582/download (access date: 28 January 2020); Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2020.

R23-0306 Brann DW, Mahesh VB. Endogenous Excitatory Amino Acid Involvement in the Preovulatory and Steroid-Induced Surge of Gonadotropins in the Female Rat. Endocrinology 1991;128 (3);1541-1547.

R23-4481 SmPC Midazolam accord healthcare 1 mg/ml, oplossing voor injectie of infusie (Accord Healthcare, 08/2021)

R24-0437 SmPC Wellbutrin 150 mg tabletten met gereguleerde afgifte (GlaxoSmithKline Pharmaceuticals s.a./n.v. 09/2023)

R24-0438 SmPC Repaglinide NovoNorm 0,5 mg tabletten (Novo Nordisk A/S, 23 Jul 2008

R97-2207 Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 1989. 244:1360-1362.

9.2 UNPUBLISHED REFERENCES

[redacted]

[redacted]

[redacted]

c36232730 Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 1569912 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design) with an additional relative bioavailability/food effect part (open label, randomised, three-way crossover design). 1447-0001. 30 May 2022.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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 John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

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

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AUS.1_eng-USori.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) 2-5 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—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) Page 2 of 2

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 John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

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

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AUS.1_eng-USori.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
____

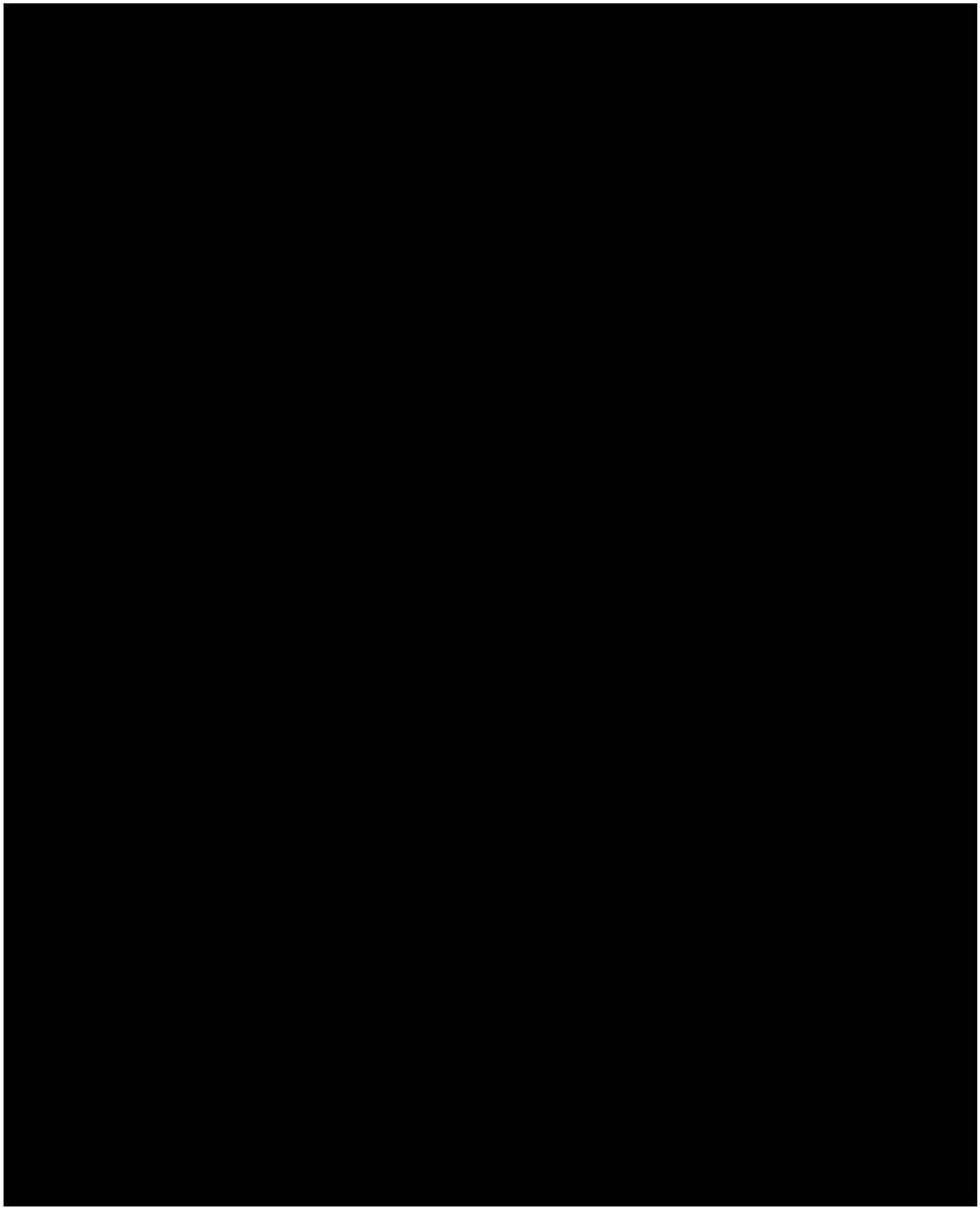
 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

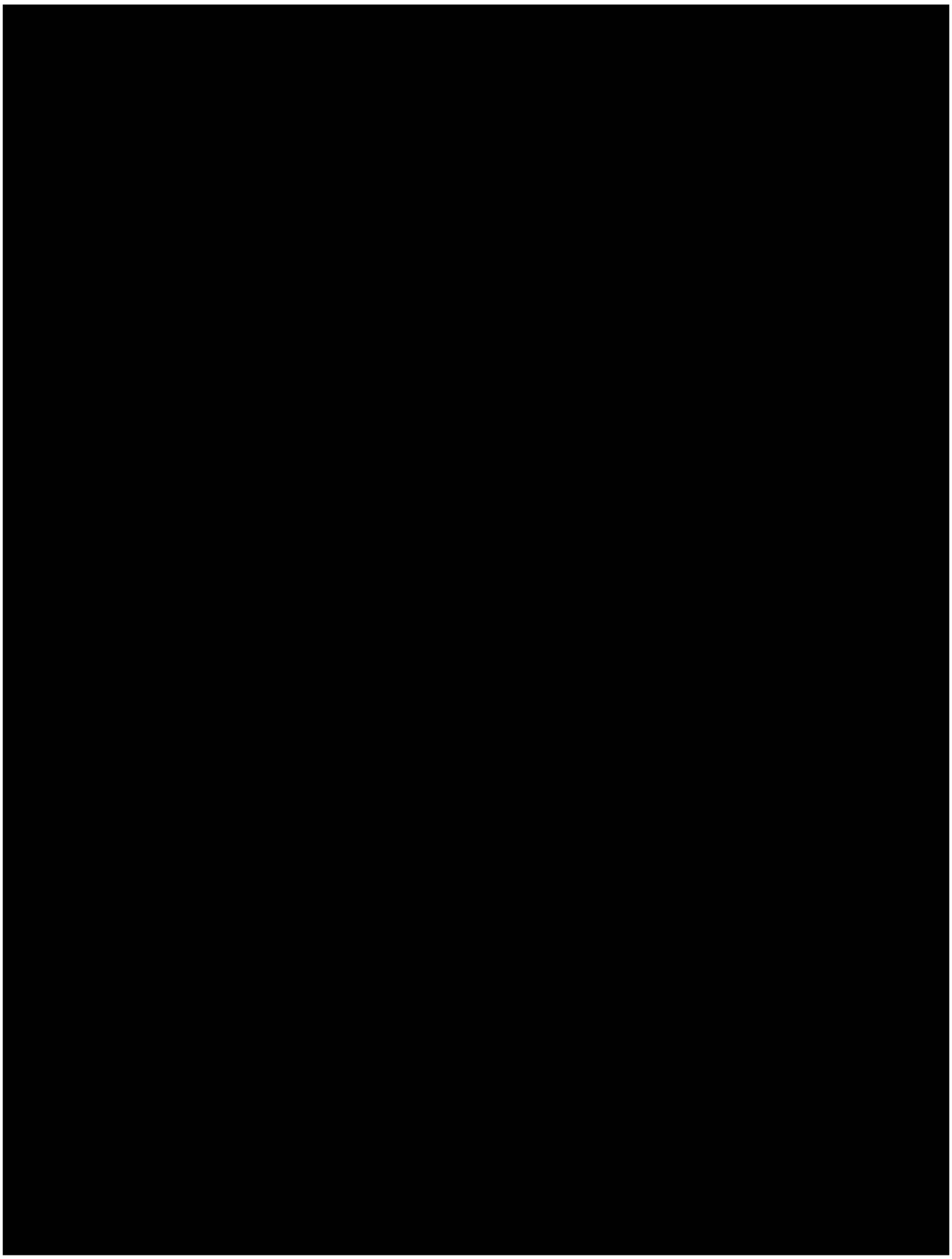
SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent 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 _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**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* _____

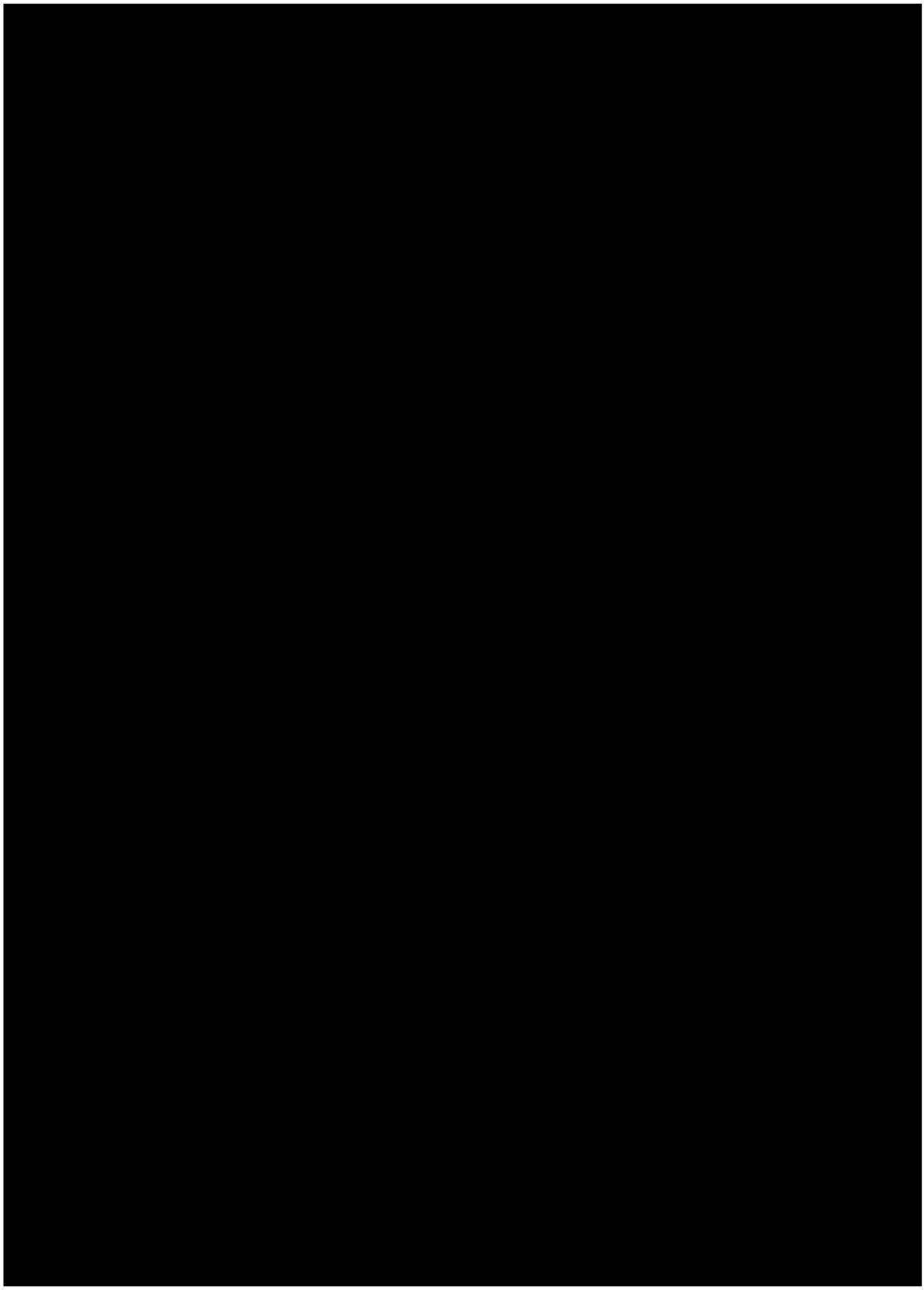
 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

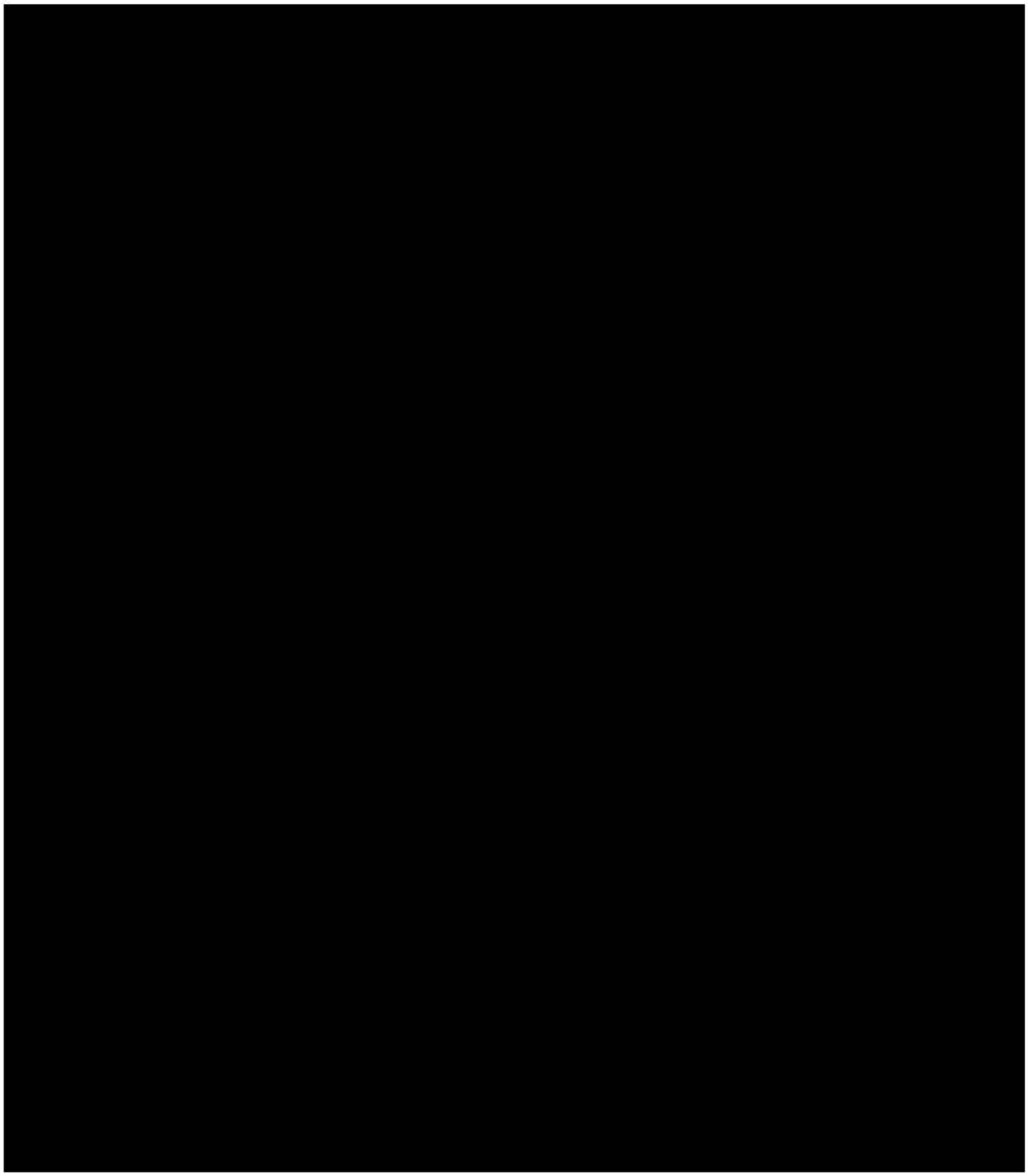
[redacted]

[redacted]









11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.