Clinical Trial Protocol

	Document Number:	**c33487150-03**
BI Trial No.	1447-0004	
BI Investigational Medicinal Product	BI 1569912	
Title	Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design)	
Lay Title	A study in healthy Japanese men to test how different doses of BI 1569912 are taken up by the body and how well they are tolerated	
Clinical Trial Leader	[redacted] Telephone: [redacted] Fax: [redacted]	
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol / Revised Protocol (based on global amendment 2)	
Version and Date	Version: 3.0	Date: 06 Sep 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	19 Apr 2021
Revision date	06 Sep 2023
BI trial number	1447-0004
Title of trial	Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	Safety, tolerability and pharmacokinetics of BI 1569912 will be assessed in healthy male Japanese subjects receiving single rising doses (SRD) and multiple doses (MD) in order to provide the basis for a clinical development of BI 1569912 in the indication for Major Depressive Disorder (MDD) in Japan. In addition, safety, tolerability and pharmacokinetics of BI 1569912 will be assessed in healthy male Japanese subjects receiving single oral dose in the morning and evening and to assess safety to evaluate if an evening dosing regimen which may attenuate sedative or visual adverse effects would be beneficial for patients in phase 2 trials.
Trial objectives	To investigate safety, tolerability and pharmacokinetics following single rising doses and multiple doses of BI 1569912 as well as a single oral dose of BI 1569912 after oral administration in the morning versus oral administration in the evening
Trial endpoints	**Primary endpoint:** **SRD and MD part:** the percentage [%] of subjects with drug-related AEs **Evening PK part:** AUC_{0-tz}, C_{max} of BI 1569912 **Secondary endpoints:** **SRD part:** $AUC_{0-\infty}$, C_{max} of BI 1569912 **MD part:** After the first dose: AUC_{0-24}, C_{max} of BI 1569912 After the last dose: $AUC_{\tau,ss}$, $C_{max,ss}$ of BI 1569912 **Evening PK part:** the percentage [%] of subjects with drug-related AEs per treatment group. $AUC_{0-\infty}$ of BI 1569912 Further PK parameters of interest will be calculated as appropriate.

Trial design	SRD part, MD part: Single-blind, randomised within dose groups, placebo-controlled parallel-group design Evening PK part: Randomised, two-sequence, open-label, two period, two-way cross over design
Number of subjects **total entered** **each treatment**	Total 56 SRD part: 32* 8 per dose group (6 on BI 1569912 and 2 on placebo) MD part: 12* 12 subjects (9 on BI 1569912 and 3 on placebo) Evening PK part: 12 12 subjects (12 on BI 1569912) * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g., preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 44, but is not to exceed 60.
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male Japanese subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive)
Test product **dose** **mode of admin.**	BI 1569912 as Tablets (strength 2.5 mg and 5 mg) SRD part: 2.5 mg, 5 mg, 10 mg and 20 mg MD part: 20 mg q.d. Evening PK part: 5 mg SRD part, MD part*:* Oral with 240 mL of water after an overnight fast of at least 10 h Evening PK part: Oral with 240 mL of water after an overnight fast of at least 10 h for morning administration. Oral with 240 mL of water after a fast period of at least 5 h for evening administration.
Comparator product **dose** **mode of admin.**	Matching placebo Not applicable Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	Single rising dose (SRD) group: Single dose Multiple dose (MD) group: Once daily, multiple doses over 14 days [redacted]

Statistical methods	Descriptive statistics will be calculated for all endpoints. Evening PK part: The effect of evening dosing will be estimated by ratios of 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-test 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 sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA.

FLOW CHART 1

SRD part

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} [10]	[redacted]	Safety EEG[10]	Medical Examination	C-SSRS	CADSS [10]	12-lead ECG[10]	Continuous ECG monitoring	Vital signs (BP, PR, RR, T)[10]	Questioning for AEs and concomitant therapy [6, 10]
1	-28 to -3			Screening (SCR)[1]	A			x[13]	x	x	x	x		x	
2	-2	-38:00	19:00	Admission to trial site	B[5]										
		-35:30	21:30	Snack (voluntary)											
	-1	-25:00	08:00									x		x	x
		-24:00	09:00						x						
	1	-1:00	08:00	Allocation to treatment[2,7]		x[2, 11]						x[2, 9]			
		-0:45	08:15						x[2]				x[2]		
		0:00	09:00	Drug administration									▲		x
		0:15	09:15			x						x[17]		x	▲[12]
		0:30	09:30			x						x[17]		x	
		0:45	09:45			x						x[17]		x	
		1:00	10:00			x		x[14]				x[17]		x	
		1:15	10:15			x						x[17]			
		1:30	10:30			x					x[14]	x[17]		x	
		2:00	11:00	240 mL fluid intake		x						x[17]		x	
		2:30	11:30			x						x[17]			
		3:00	12:00			x		x				x[17]		x	
		4:00	13:00	240 mL fluid intake, thereafter lunch[3]	B	x					x	x[17]	▼	x	
		6:00	15:00			x						x[17]		x	
		8:00	17:00	Snack (voluntary)[3]		x		x				x[17]		x	
		10:00	19:00	Dinner[3]		x						x[17]			
		12:00	21:00			x						x[17]		x	
	2	24:00	09:00		B	x		x	x			x[17]		x	
		36:00	21:00			x						x[17]		x	
	3	48:00	09:00			x		x				x[17]		x	
	4	72:00	9:00	Breakfast (voluntary) Discharge from trial site	B[15]	x			x	x		x[17]		x	▼
3	4 to 14			End of trial (EOT) examination[4,16]	A				x			x		x	x[12]

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of 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; procedures are to be performed and completed within the 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last.
4. EOT examination includes medical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.

5. Urine drug screening and alcohol breath test 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.

[redacted]

9. At baseline (i.e. prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
10. In case of multiple assessments at the same timepoint, the following order/priority applies: 12-lead ECG, Vital Signs, PK_{blood}, safety EEG, CADSS, Questioning for AEs and concomitant therapy
11. Includes one blood sample for genotyping of genes involved in absorption, distribution, metabolism and elimination or related to safety (see Section 5.6.1). This sample will be taken preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent remains valid.
12. Dissociative symptoms are reported as AEs and should be quantified with CADSS.
13. The EEG performed at the Screening Visit is to identify and exclude subjects with an unknown susceptibility for epileptiform abnormalities and/or seizures. Therefore, Screening EEG will include spontaneous EEG activity in resting condition as well as provocation maneuvers (intermittent photic stimulation and hyperventilation). All EEGs will be reviewed by neurologists experienced in EEG reading.
14. This measurement should be performed at around t_{max}. Actual timepoint may be refined based on new data available.
15. If EOT is performed on Day 4, laboratory A instead of B will be performed.
16. If EOT is performed on Day 4, no need to conduct duplicated procedure.
17. The ECG recording has to be performed in triplicate at this time.

FLOW CHART 2

MD part

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} [9,13]	Safety EEG[13]	Medical Examination	C-SSRS	CADSS[13]	12-lead ECG[13]	Vital signs (BP, PR, RR, T)[13]	Questioning for AEs and concomitant therapy[6, 13]
1	-28 to -3			Screening (SCR)[1]	A		x[1, 11]	x	x	x	x	x	
2	-2	-38:00	19:00	***Admission to trial site***	B[5]								
		-35:30	21:30	Snack (voluntary)									
	-1	-25:00	08:00								x	x	x
		-24:00	09:00					x	x				
	1	-1:00	08:00	Allocation to treatment[2]		x[2, 7]					x[2,10]	x[2]	x[2]
		-0:45	08:15					x[2]					
		-0:30	08:30				x						
		0:00	**09:00**	**First drug administration**									
		0:15	09:15			x					x[8]		
		0:30	09:30			x					x[8]		
		0:45	09:45			x					x[8]		
		1:00	10:00			x	x[12]			x[12]	x[8]	x	x
		1:15	10:15			x					x[8]		
		1:30	10:30			x					x[8]		
		2:00	11:00	240 mL fluid intake		x					x[8]	x	x
		2:30	11:30			x					x[8]		
		3:00	12:00			x	x				x[8]		
		4:00	13:00	240 mL fluid intake, thereafter lunch[3]		x				x	x[8]	x	x
		6:00	15:00			x					x[8]		
		8:00	17:00	Snack (voluntary)[3]		x	x				x[8]	x	x
		10:00	19:00	Dinner[3]		x					x[8]		
		12:00	21:00			x					x[8]	x	x
	2	23:00	08:00		B	x					x[8]	x	x
		24:00	09:00	Drug administration									
		25:00	10:00				x[12]			x[12]	x	x	x
		27:00	12:00				x						
		32:00	17:00				x						
	3	47:00	08:00			x					x[8]	x	x
		48:00	09:00	Drug administration				x					
		49:00	10:00				x[12]			x[12]	x	x	x
		51:00	12:00				x						
		56:00	17:00				x						
	4	71:00	08:00			x					x[8]	x	x
		72:00	09:00	Drug administration									
		74:00	11:00								x		
	5	95:00	08:00			x							
		96:00	09:00	Drug administration									
		97:00	10:00				x[13]					x	x
		98:00	11:00								x		
	6	119:00	08:00			x						x	x
		120:00	09:00	Drug administration				x					
		122:00	11:00								x		
	7	143:00	08:00			x						x	x
		144:00	09:00	Drug administration									
		146:00	11:00								x		

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [9,13]	Safety EEG[13]	Medical Examination	C-SSRS	CADSS[13]	12-lead ECG[13]	Vital signs (BP, PR, RR, T)[13]	Questioning for AEs and concomitant therapy [6,13]
	8	167:00	08:00		B	x					x		
		168:00	09:00	Drug administration									
		169:00	10:00				x[12]			x[12]		x	x
		170:00	11:00								x		
	9	191:00	08:00			x						x	x
		192:00	09:00	Drug administration				x	x				
		194:00	11:00								x		
	10	215:00	08:00			x						x	x
		216:00	09:00	Drug administration									
		218:00	11:00								x		
	11	239:00	08:00			x							
		240:00	09:00	Drug administration									
		241:00	10:00				x[12]					x	x
		242:00	11:00								x		
	12	263:00	08:00			x						x	x
		264:00	09:00	Drug administration				x					
		266:00	11:00								x		
	13	287:00	08:00			x						x	x
		288:00	09:00	Drug administration				x					
		290:00	11:00								x		
	14	311:00	08:00		B	x		x			x[8]	x	x
		312:00	09:00	**Last drug administration**									
		312:15	09:15			x					x[8]		
		312:30	09:30			x					x[8]		
		312:45	09:45			x					x[8]		
		313:00	10:00			x	x[12]			x[12]	x[8]	x	x
		313:15	10:15			x					x[8]		
		313:30	10:30			x					x[8]		
		314:00	11:00	240 mL fluid intake		x					x[8]	x	x
		314:30	11:30			x					x[8]		
		315:00	12:00			x					x[8]		
		316:00	13:00	240 mL fluid intake, thereafter lunch[3]		x					x[8]	x	x
		318:00	15:00			x					x[8]		
		320:00	17:00	Snack (voluntary)[3]		x					x[8]	x	x
		322:00	19:00	Dinner[3]		x					x[8]		
		324:00	21:00			x					x[8]	x	x
	15	335:00	08:00		B	x	x				x[8]	x	x
	16	359:00	08:00			x		x			x[8]	x	x
	17	383:00	08:00	Breakfast (voluntary), ***Discharge from trial site***	B	x		x	x		x[8]	x	x
3	17 to 27			End of trial (EOT) examination[4]	A		x[14]	x	x		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/ exclusion criteria.
2. The time is approximate; the procedures are to be performed and completed within the 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.

3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EOT examination includes medical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Urine drug screening and alcohol breath test 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. Includes one blood sample for genotyping of genes involved in absorption, distribution, metabolism and elimination or related to safety (see Section 5.6.1). This sample will be taken preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent remains valid.
8. The ECG recording has to be performed in triplicate at this time
9. Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK data) including addition of samples and visits as long as the total blood volume removed does not exceed 400 mL per subject.
10. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
11. The EEG performed at the Screening Visit is to identify and exclude subjects with an unknown susceptibility for epileptiform abnormalities and/or seizures. Therefore, Screening EEG will include spontaneous EEG activity in resting condition as well as provocation maneuvers (intermittent photic stimulation and hyperventilation). All EEGs will be reviewed by neurologists experienced in EEG reading.
12. This measurement should be performed at around t_{max}. Actual timepoint may be refined based on new data available.
13. In case of multiple assessments at the same timepoint, the following order/priority applies: 12-lead ECG, Vital Signs, PK_{blood}, safety EEG, CADSS, Questioning for AEs and concomitant therapy
14. Conducted only in case positive result observed at Day 15.
15. If EOT is performed on Day 17, no need to conduct duplicated procedure.

FLOW CHART 3

Evening PK part I (Morning to Evening)

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood [8]	Safety EEG [8]	Medical Examination	C-SSRS	CADSS [8]	12-lead ECG [8]	Vital signs (BP, PR, RR, T)[8]	Questioning for AEs and concomitant therapy [6, 8]
1	-28 to -2	-	-	Screening (SCR)[1]	A		x[10]	x	x	x	x	x	
2	-1	-24:00	09:00	***Admission to trial site***	B[5]								x
		-23:00	10:00	Allocation of treatment									
	1	-1:00	08:00			x[2,14]					x[2, 7]	x[2]	
		0:00	09:00	Drug administration									x
		0:15	09:15			x							▲[9]
		0:30	09:30			x							|
		0:45	09:45			x							|
		1:00	10:00			x	x						|
		1:30	10:30			x				x			|
		2:00	11:00	240 mL fluid intake		x							|
		3:00	12:00			x							|
		4:00	13:00	240 mL fluid intake, thereafter lunch[3]	B	x					x[11]	x	|
		6:00	15:00			x							|
		8:00	17:00			x					x[11]	x	|
		10:00	19:00	Dinner[3]		x							|
		12:00	21:00			x					x[11]	x	|
	2	24:00	09:00		B	x	x	x			x[11]	x	|
		36:00	21:00			x					x[11]	x	|
	3	48:00	09:00	Discharge from trial site	B			x			x[11]	x	▼
	4 to 7	-	-	Wash-out period									
2a	1	-13:00	09:00	***Admission to trial site***	B[5]			x					▲[9]
		-5:00	17:00	Light meal[12]									|
		-1:00	21:00			x[2]					x[2,7]	x[2]	|
		0:00	22:00	Drug administration									|
		0:15	22:15			x							|
		0:30	22:30			x							|
		0:45	22:45			x							|
		1:00	23:00			x	x						|
		1:30	23:30			x				x			|
	2	2:00	0:00	240 mL fluid intake[13] (optional)		x							|
		3:00	1:00			x							|
		4:00	2:00	240 mL fluid intake[13] (optional)	B	x					x[11]	x	|
		6:00	4:00			x							|
		8:00	6:00			x							|
		10:00	8:00	Breakfast[3]		x							|
		12:00	10:00			x		x			x[11]	x	|
		24:00	22:00		B	x	x				x[11]	x	|
	3	36:00	10:00			x		x			x[11]	x	|
		48:00	22:00		B						x[11]	x	▼
3	12 to 13	-	-	End of trial (EOT) examination[4] / Discharge from trial site	A			x	x		x	x	x[9]

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of 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; procedures are to be performed and completed within the 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last.
4. EOT examination includes medical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Urine drug screening and alcohol breath test 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. At baseline (i.e. prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
8. In case of multiple assessments at the same timepoint, the following order/priority applies: 12-lead ECG, Vital Signs, PK_{blood}, Safety EEG, CADSS, Questioning for AEs and concomitant therapy
9. Dissociative symptoms are reported as AEs and should be quantified with CADSS.
10. The EEG performed at the Screening Visit is to identify and exclude subjects with an unknown susceptibility for epileptiform abnormalities and/or seizures. Therefore, Screening EEG will include spontaneous EEG activity in resting condition as well as provocation maneuvers (intermittent photic stimulation and hyperventilation). All EEGs will be reviewed by neurologists experienced in EEG reading.
11. The ECG recording has to be performed in triplicate at this time.
12. Light meal has to be consumed within one hour.
13. Water will only be provided in case the subject is awake.

[redacted]

FLOW CHART 4

Evening PK part II (Evening to Morning)

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood [8]	Safety EEG [8]	Medical Examination	C-SSRS	CADSS [8]	12-lead ECG [8]	Vital signs (BP, PR, RR, T)[8]	Questioning for AEs and concomitant therapy [6, 8]
1	-28 to -2	-	-	Screening (SCR)[1]	A		x[10]	x	x	x	x	x	
2	-1	-37:00	09:00	***Admission to trial site***	B[5]								x
		-36:00	10:00	Allocation of treatment									
		-24:00	22:00										
	1	-5:00	17:00	Light meal[12]									
		-1:00	21:00			x[2,14]					x[2, 7]	x[2]	
		0:00	22:00	Drug administration									x
		0:15	22:15			x							▲[9]
		0:30	22:30			x							|
		0:45	22:45			x							|
		1:00	23:00			x	x						|
		1:30	23:30			x				x			|
	2	2:00	0:00	240 mL fluid intake[13] (optional)		x							|
		3:00	1:00			x							|
		4:00	2:00	240 mL fluid intake[13] (optional)	B	x					x[11]	x	|
		6:00	4:00			x							|
		8:00	6:00			x							|
		10:00	8:00	Breakfast[3]		x							|
		12:00	10:00			x					x[11]	x	|
		24:00	22:00		B	x	x	x			x[11]	x	|
	3	36:00	10:00			x					x[11]	x	|
		48:00	22:00		B						x[11]	x	|
	4	60:00	10:00	Discharge from trial site	B			x			x[11]	x	▼
	5 to 7	-	-	Wash-out period									
2a	-1	-23:00	10:00	***Admission to trial site***	B[5]			x					x
	1	-1:00	08:00			x[2]					x[2,7]	x[2]	▲[9]
		0:00	09:00	Drug administration									|
		0:15	9:15			x							|
		0:30	9:30			x							|
		0:45	9:45			x							|
		1:00	10:00			x	x						|
		1:30	10:30			x				x			|
		2:00	11:00	240 mL fluid intake		x							|
		3:00	12:00			x							|
		4:00	13:00	240 mL fluid intake, thereafter lunch[3]	B	x					x[11]	x	|
		6:00	15:00			x							|
		8:00	17:00			x					x[11]	x	|
		10:00	19:00	Dinner[3]		x							|
		12:00	21:00			x					x[11]	x	|
	2	24:00	9:00	Breakfast[3]	B	x	x				x[11]	x	|
		36:00	21:00			x					x[11]	x	|
	3	48:00	9:00	Breakfast[3]	B						x[11]	x	▼
3	12 to13	-	-	End of trial (EOT) examination[4] / Discharge from trial site	A			x	x		x	x	x[9]

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of 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; procedures are to be performed and completed within the 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last.
4. EOT examination includes medical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Urine drug screening and alcohol breath test 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. At baseline (i.e. prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
8. In case of multiple assessments at the same timepoint, the following order/priority applies: 12-lead ECG, Vital Signs, PK_{blood}, Safety EEG, CADSS, Questioning for AEs and concomitant therapy
9. Dissociative symptoms are reported as AEs and should be quantified with CADSS.
10. The EEG performed at the Screening Visit is to identify and exclude subjects with an unknown susceptibility for epileptiform abnormalities and/or seizures. Therefore, Screening EEG will include spontaneous EEG activity in resting condition as well as provocation maneuvers (intermittent photic stimulation and hyperventilation). All EEGs will be reviewed by neurologists experienced in EEG reading.
11. The ECG recording has to be performed in triplicate at this time.
12. Light meal has to be consumed within 1 hour.
13. Water will only be provided in case the subject is awake.

[redacted]

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
[redacted]	[redacted]
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24h}	Area under the plasma concentration-time curve from time zero to 24 h
[redacted]	[redacted]
$AUC_{\tau,ss}$	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
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CADSS	Clinician Administered Dissociative States Scale
CI	Confidence interval
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRA	Clinical Research Associate
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
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
[redacted]	[redacted]
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EOT	End of trial
FDA	Food and Drug Administration
FE	Food effect
[redacted]	[redacted]
FIH	First in Human
FST	Forced swim test
fU	fraction unbound
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GLP	Good laboratory practice
gMean	Geometric mean
hAGP	human α1-acid glycoprotein
[redacted]	[redacted]
HR	Heart rate
HSA	Human serum albumin
hERG	human ether-a-go-go related gene
IB	Investigator's brochure
IC_{50}	50% Inhibition Concentration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MD	Multiple dose
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder

MDMA	Methylenedioxymethamphetamine
MEC	Minimal effective concentration
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
NAM	Negative allosteric modulator
NDA	New drug application
NMDA	N-methyl-D-aspartate
NOAEL	No Observed Adverse Effect Level
NR2B	Negative allosteric modulator of subunit 2B
PCR	Polymerase Chain Reaction
[redacted]	[redacted]
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF)
R	Treatment Reference
REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
T	Temperature, Treatment T
TMF	Trial master file
[redacted]	[redacted]
[redacted]	[redacted]
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
[redacted]	[redacted]

[redacted]	[redacted]
XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

BI 1569912 is a negative allosteric modulator of the subunit 2B (NR2B), contained in N-methyl-D-aspartate (NMDA) receptors, to be developed for major depressive disorder (MDD).

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]. 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.

The role of glutamate in depression became apparent after it was reported that tricyclic antidepressants blocked the cation (sodium and calcium) channel associated with the NMDA glutamate receptor [R19-0681] and that functional antagonists of the NMDA receptor had antidepressant-like behavioural effects in animals. These effects were confirmed by a trial in humans in which single intravenous infusion of ketamine, an unspecific NMDA receptor antagonist used for anaesthesia, alleviated depressive symptoms in patients with depression within hours after administration of sub-anaesthetic doses, peaking some days later [R19-0772].

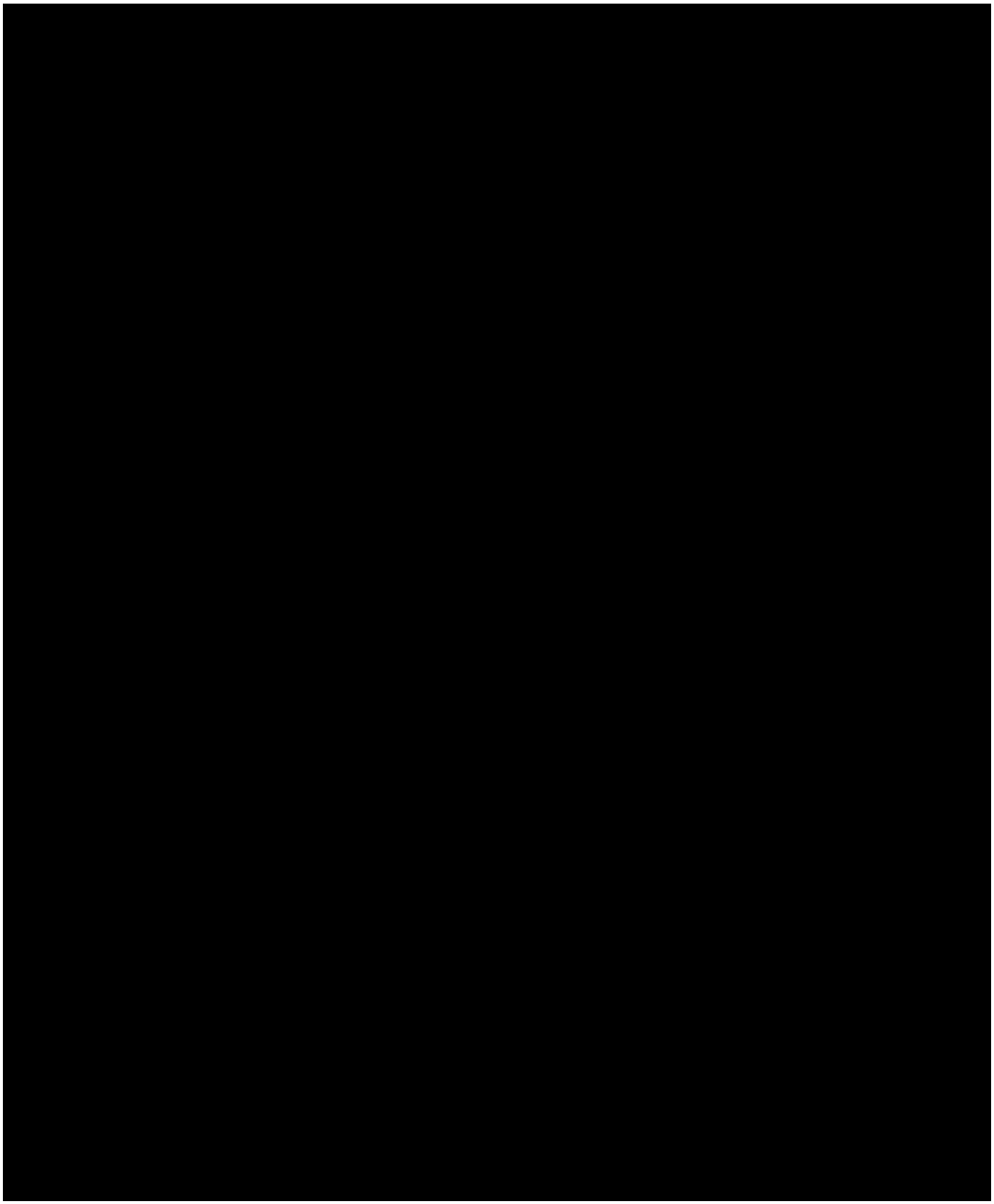
Since then, ketamine has demonstrated efficacy in multiple exploratory trials in patients with treatment-resistant depression. The responder rate in these trials was approximately 50%, the onset was fast and the average antidepressant effect lasted for 1 week after a single infusion [R19-0553]. Meanwhile, the intranasal S-enantiomer esketamine received NDA approval by the FDA [R19-0829].

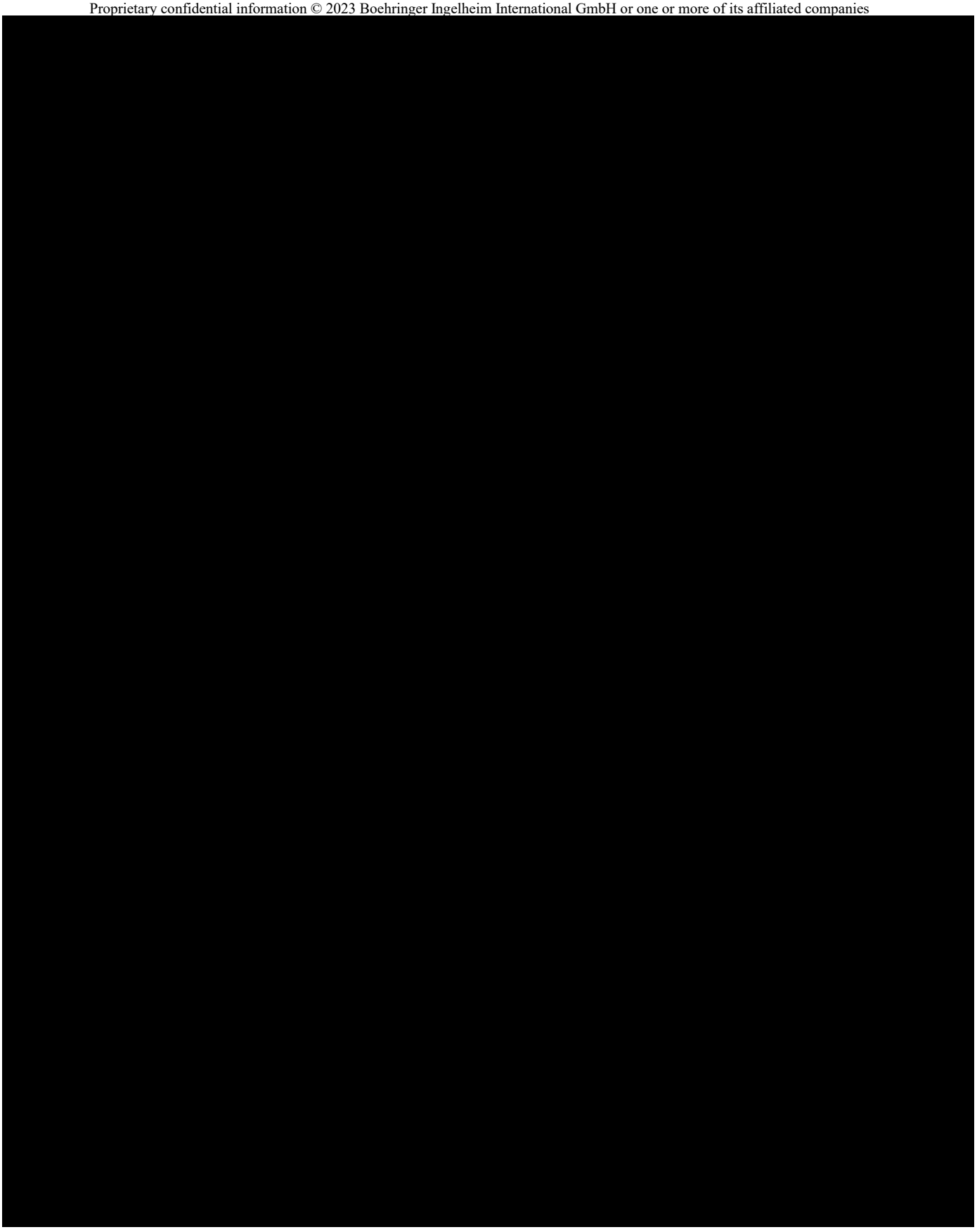
However, transient perceptual disturbances (dissociative reaction), sedation, blood pressure increases, and an abuse potential (being a scheduled drug) require controlled distribution as well as cardiovascular and behavioural monitoring after drug application. Those unwanted effects may, at least in part, derive from ketamine's lack of selectivity, as ketamine blocks the cation channel across all NMDA subtypes [R19-0555].

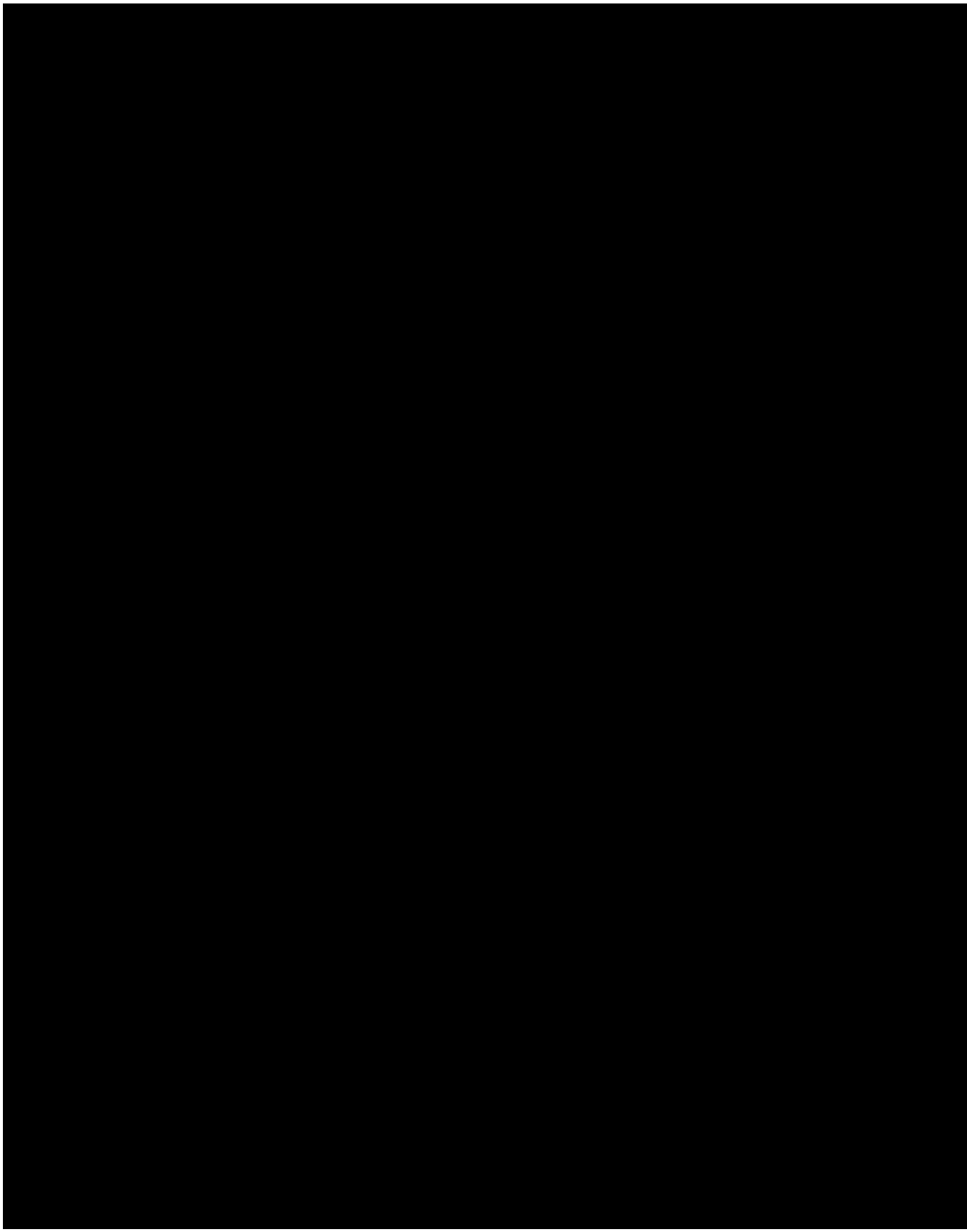
Based on genetic mouse models, the NR2B subunit was identified as a key mediator of ketamine efficacy [R19-0549]. In a small Phase II study with traxoprodil, an NR2B-specific negative allosteric modulator (NAM), a rapid and robust antidepressant response without eliciting a dissociative reaction was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

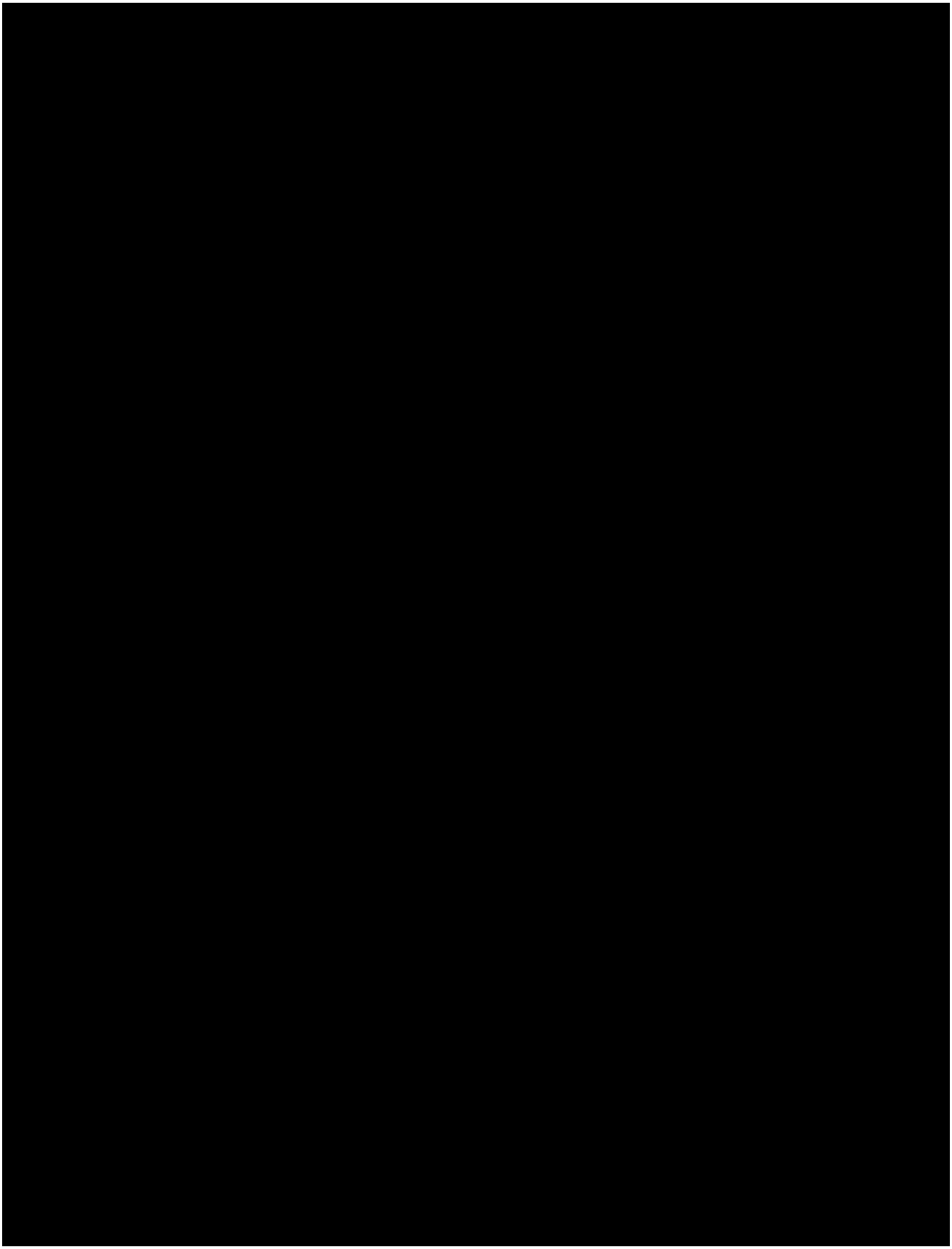
For further information, see current Investigator's Brochure (IB) [c29289852].

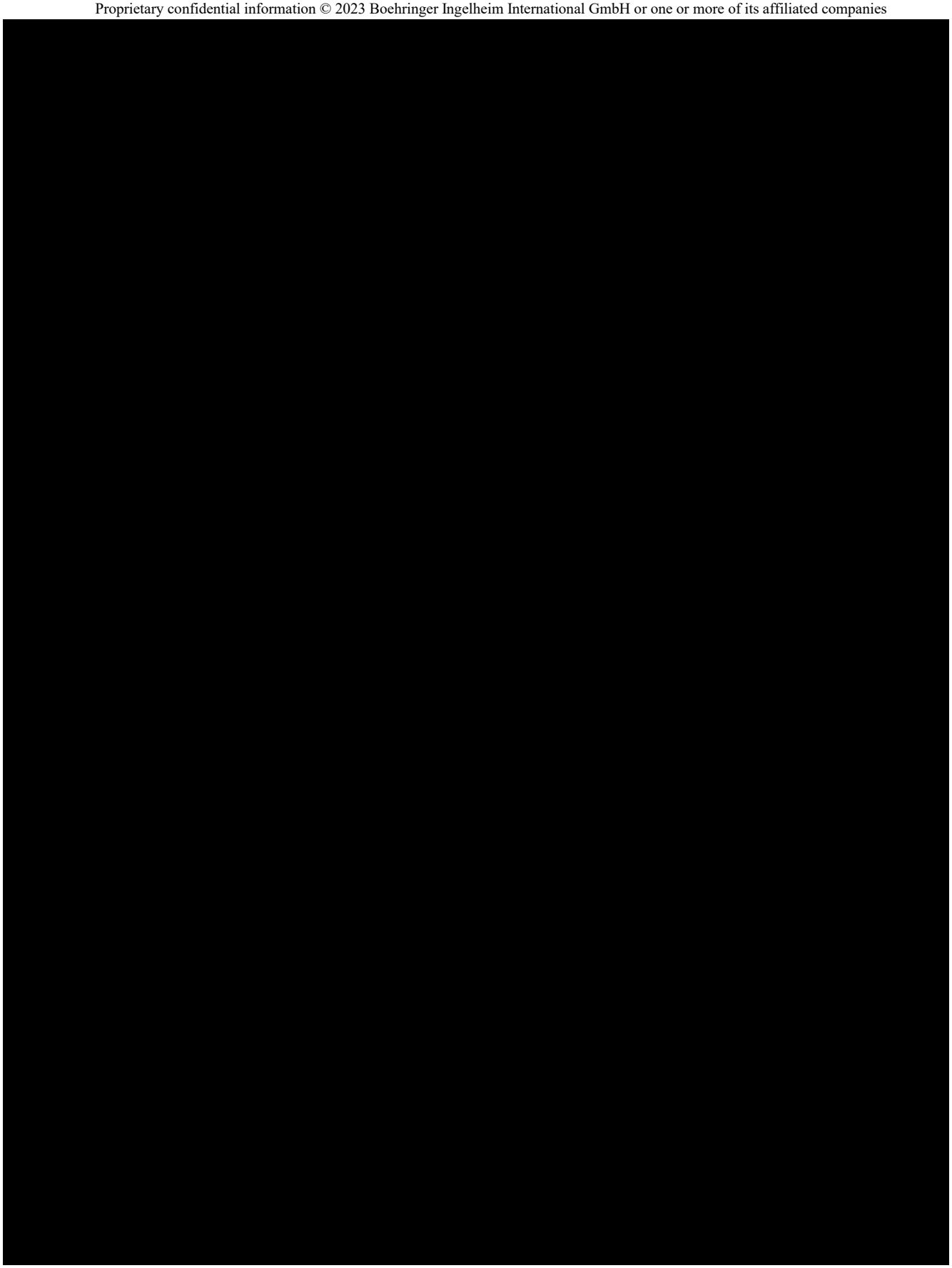
1.2 DRUG PROFILE











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1.2.5 Clinical experience in humans

To date, clinical experience with BI 1569912 is limited to single-dosing in a SRD study in healthy male subjects (1447-0001). This trial evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of BI 1569912. The trial consisted of a SRD part and a subsequent relative bioavailability/food effect (BA/FE) part. At the time of this amendment, the multiple rising dose study (1447-0002) is ongoing and the SRD part of 1447-0004 is completed.

In the SRD part of Trial 1447-0001, 54 of 55 subjects (98.2%) completed the trial as planned; 1 subject in the placebo group discontinued for trial-unrelated reasons. Adverse events were reported in 7 subjects on treatment (6 on BI 1569912 and 1 on placebo); all AEs reported on BI 1569912 were of mild intensity. 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.

In the BA/FE part of Trial 1447-0001, 13 subjects were treated in 3 treatment periods (oral solution fasted/tablet fasted/tablet fed). Five subjects (38.5%) prematurely discontinued the trial: 4 subjects due to termination of the trial and 1 subject for personal reasons. No AEs were reported for the 13 subjects treated in the BA/FE part [c36232730].

Apart from occasional ‘non-epileptiform’ abnormalities without any clinical relevance, there were no relevant changes over time and no relevant differences between the treatment groups

(including placebo) in Trial 1447-0001. Especially, no indication for epileptiform signals under trial medication was seen at any time point or dose.

In the ongoing MRD trial (1447-0002) safety data was available from the 2.5, 5 mg and 10 mg dose groups (9 subjects on BI 1569912 and 3 on placebo for each dose). One subject (11.1%) from two BI 1569912 dose group withdrew from the trial and 1 subject (11.1%) from the placebo group did not complete the treatment period for other reasons. Adverse events were reported in 11 subjects on treatment (10 on BI 1569912 and 1 on placebo), in which 3 subjects (16.7%) on BI 1569912 and 1 subject (11.1%) on placebo were defined as drug-related by the investigator. No AE was reported for more than 1 subject in any single treatment group. There were no AEs of severe intensity or that led to discontinuation of the trial drug, and none were SAEs.

In addition, single doses of BI 1569912 from 2.5 mg up to 20 mg have been investigated in 32 healthy Japanese men in this trial (1447-0004) and no adverse event was reported.

Additional Safety Assessments
There were no clinically relevant changes of vital signs or lab values at all dose levels. Explorative analysis of dissociative symptoms as assessed by the CADSS showed equal results between subjects across all dose groups and compared to placebo without any abnormalities in the score at any dose level.

The suicidality assessment based on C-SSRS did not reveal an individual subject who developed suicidal ideation by end of the study period.

ECGs recorded from Day 1 pre-dose until Day 4/72 h post-dose were analyzed. No clinical relevant results were observed, including no dose dependent trend of a possible QTcF prolongation.

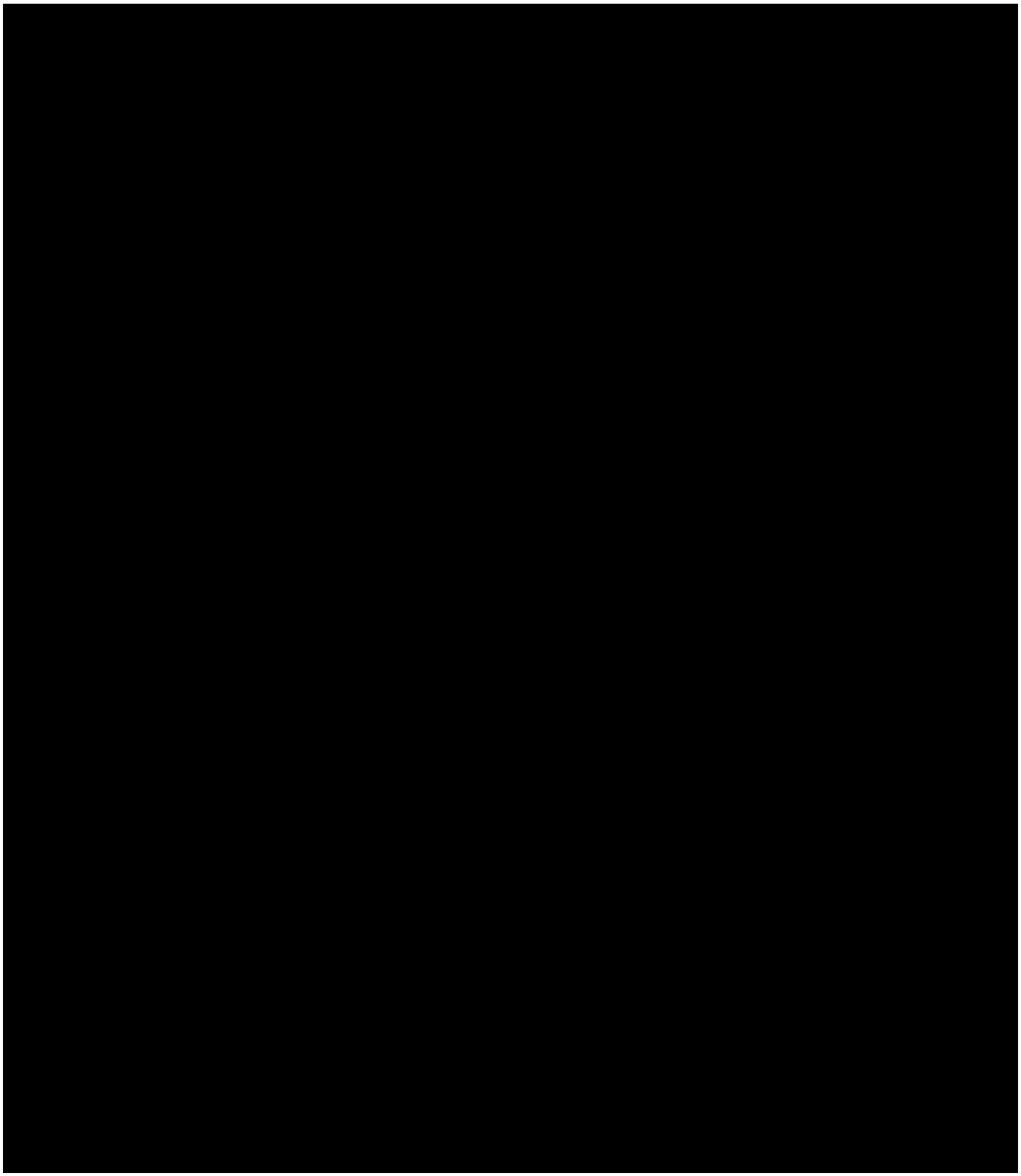
Based on the prespecified criteria of the trial protocol, EEG recordings did not reveal a subject with a positive test after dosing, i.e. no signs of an altered cerebral excitability.

From compounds of the same pharmacological class (NR2B NAM), there is also clinical information available.
In a phase II study with traxoprodil, dose-dependent dissociative symptoms were reported. Dissociative symptoms were transient and resolved completely within hours. Other side effects were mild and included abnormal feeling, dry mouth, somnolence and an increase in blood pressure [R17-3810].
In phase II studies with rislenemdaz, another NR2B NAM, dizziness, headache, diarrhoea, dry mouth, somnolence, paraesthesia and blood pressure increase were reported. Rislenemdaz, however, did not lead to dissociative symptoms [R19-0986]. Overall, no serious safety concerns have been identified so far for NR2B-specific NAMs.

[redacted]

[redacted]

[redacted]



[redacted]

1.2.6 Residual Effect Period

The Residual Effect Period (REP) of BI 1569912 in humans [redacted] This is the period after the last dose with measurable drug levels and/ or pharmacodynamic effects still likely to be present. [redacted]

1.2.7 Drug product

For a more detailed description of the BI 1569912 profile, see current IB [c29289852].

BI 1569912 tablets have been developed in 3 dosage strengths: 0.5 mg (approx. 5.5 mm round), 2.5 mg (approx. 10 mm round) and 5 mg (approx. 17.8x8.6 mm oval). In addition to the drug substance, the tablets contain the following standard pharmaceutical excipients in common amounts: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate.

The clinical trial supplies will be provided in polypropylene bottles with screw-cap closures.

The tablets should be stored in the containers provided and handled according to the labelled storage instructions and shelf life.

For further information, see Section 4.1 and current IB [c29289852].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The objective of this trial is to investigate the safety, tolerability and pharmacokinetics of BI 1569912 in healthy male Japanese subjects. The chosen population of healthy male subjects receiving single rising oral doses is considered adequate to provide the basis for the clinical development program of BI 1569912 in Japan. This trial will also provide pharmacokinetic information in healthy volunteers at steady state exposure.

The evening PK part is designed to investigate and compare the pharmacokinetics of BI 1569912 after a single dose administration in the morning vs. in the evening. These data will help to evaluate if an evening dosing regimen which may attenuate adverse effects would be appropriate for patients in phase II trial.

The first in human phase I trial (1447-0001) is ongoing in Europe and it explores safety, tolerability, pharmacokinetics and pharmacodynamics in healthy male Caucasian subjects after single oral doses of BI 1569912 solution. Currently, 48 subjects received trial medication in 6 dose groups with the dose ranging from 0.25 mg to 20 mg. In each dose group, 6 subjects received BI 1569912 and 2 subjects received placebo. All treated subjects received a single dose of trial medication as planned and completed the trial according to the CTP except for 1 subject in the 2 mg dose arm who discontinued the trial for trial-unrelated reasons. At all dose levels, the single dose of BI 1569912 was well tolerated by healthy male subjects.

The dose range selected for this trial is expected to cover the potential therapeutic dose range in the further clinical development program of BI 1569912. In the current trial, no dose level will be included which was not already tested in the FIH trial and was not shown to be safe and well tolerated at the time of start of treatment.

1.3.1 Justification for starting dose

The starting dose is 2.5 mg. This dose level was shown to be safe and well tolerated in 1447-0001 and is 8 fold lower of the maximum tested dose of the FIH study up to now (Trial 1447-0001). Predicted human therapeutic dose is 2 mg from non-clinical studies.

1.3.2 Maximum dose

The maximum dose of this trial is 20 mg and this dose will not be exceeded in this trial. The maximum dose of 20 mg was selected to cover the range of expected exposure in the subsequent global phase II trial, as the therapeutic effects and corresponding dose in humans are currently unknown and for the arguments given per section below.

[redacted]

Exposures, higher than the predicted human therapeutic dose, are typically explored in the well-controlled clinical environment of phase I trial, if supported by the currently available safety data, in order to provide a sufficient safety margin for potential subsequent trials, e.g.

- To cover exposures eventually reached in trials with multiple dosing and accumulation
- To cover exposures eventually reached in trials in patients with impaired excretion function, such as renal / hepatic impairment, where substantial increases in exposure may be seen
- To cover exposures eventually reached in subsequent drug-drug interaction trials
- To derive a safe supra-therapeutic dose for a thorough QT (tQT) trial or to achieve high enough exposures to waive a tQT trial

[redacted]

1.3.3 Justification for dose escalation scheme

For all dose groups, dose escalation will be 2-fold compared to the preceding dose level as usual safeguarding and the previous use in the 1447-0001.

1.4 BENEFIT - RISK ASSESSMENT

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 for symptomatic treatment of patients with MDD.

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

Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising and, in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

The total volume of blood withdrawn per subject during the entire study will not exceed the volume of a normal blood donation (400 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

Drug-related risks and safety measures

Factors of risk may derive from particular knowledge or the lack thereof, regarding (1) the mode of action, (2) the nature of the target, (3) the relevance of animal models, (4) findings in non-clinical safety studies and or (5) risks resulting from clinical trial experience. Further aspects will be (6) risks resulting from trial medication auxiliaries, and (7) drug induced liver injury, and (8) COVID-19, resulting in (9) measures of risk minimization (including safety precautions and stopping rules – see Section 1.4.7)

1.4.1 Mode of action

BI 1569912 is a negative allosteric modulator (NAM) 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.

1.4.2 Nature of the target

BI 1569912 is a partial, reversible and time-dependent negative allosteric modulator of the human NR2B-subunit contained in NMDA receptors (highly permeable to Ca++ influx but also allows K+ efflux). As such, BI 1569912 is not considered to be a high risk compound.

[redacted]

1.4.4 Findings in non-clinical safety studies

[redacted]

1.4.5 Findings in clinical trial studies

See section 1.2.5.

1.4.6 Risks resulting from trial medication auxiliaries

Tablets contain lactose.

1.4.7 Drug induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety (see Section 5.2.6.1.4).

1.4.8 Measures of risk minimization (including safety precautions and stopping rules)

The following precautionary measures will be taken in this study in order to minimize the risk for healthy subjects:

General Risk Minimization Measures:

- Careful selection of study subjects according to in- and exclusion criteria (see Section 3.3.2 and Section 3.3.3).
- Careful starting dose selection (see Section 1.3.1).
- Extensive standard safety laboratory measurements will be performed before and after drug administration (see Flow Chart and Section 5.2.3).
- A thorough ECG and heart rate monitoring will be performed, including continuous ECG measurements, over 4 hours post dose to cover the anticipated period of highest drug exposure, and additional repeated triplicate 12-lead ECGs (see Flow Charts). Prior to each dose escalation, a documented safety review about the past dosing group will be performed by the Principal Investigator (or deputy, Sub-investigator) and the Clinical Trial Leader (CT Leader) (or deputy, associate CT leader) (see Section 3.1).
- Ensure that the general measures implemented by the government to control the spread of COVID-19 in the Japanese population are adhered to. COVID-19 infection testing such as PCR test will be conducted before hospitalization.

BI 1569912 Specific Risk Minimization Measures:

- If one dose level is safe and shows acceptable tolerability, and if no stopping criteria are met, the next higher dose may be given, keeping a minimum dosing time interval of 7 days between the first subjects of sequential dose-groups.
- Subjects will be confined to the study site until end of trial, and will be discharged only after a formal assessment and confirmation of health by an investigator or qualified designee. During in-house confinement, subjects will be under medical observation and thoroughly monitored for any adverse events.
- Subjects will be evaluated with electrophysiological and functional assessments to identify any possible adverse event. Specifically, any signs of pro-convulsive activity of the brain will be assessed by repeated EEG measurements in each dose group. Close neurological/ psychiatric evaluation using a standardized clinical assessment for the detection of neurological symptoms, the Columbia-Suicide Severity Rating Scale for the assessment of suicidality, and the CADSS for the assessment of suspected dissociative symptoms. The occurrence of anticipated dissociative symptoms will be reduced by quiet ambient conditions during and after drug administration.
- The preliminary determination of the REP is up [redacted]
- MD part will start after confirming the safety data of corresponding dose level from the 1447-0002, and preliminary PK data up to dose group 4, 10 mg in this trial.
- [redacted]

1.4.9 Overall assessment and conclusion

Based on the well-characterized mode of action, nature of target, pre-clinical data with a comprehensive non-clinical safety package of BI 1569912, the preliminary clinical data from the on-going FIH study with good safety and tolerability, as well as the implemented safety measures described above, a participation in this single dose regimen does not represent an undue risk to healthy subjects. Considering the medical need for a better MDD treatment and taking into account the potential advantage of a highly selective NR2B negative allosteric modulator, the expected benefit of this trial is likely to outweigh the potential risks and justifies the exposure of healthy subjects to BI 1569912.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

In SRD and MD part, the main objectives of this trial are to investigate safety and tolerability of BI 1569912 in healthy male Japanese subjects following oral administration of single rising doses and multiple doses per day over 14 days.

Secondary objectives are the exploration of pharmacokinetics (PK) of BI 1569912 after single and multiple oral dosing.

In evening night PK part, the main objectives of this trial are to investigate and compare single dose pharmacokinetics of BI 1569912 after administration of 5 mg in the morning and after administration in the evening.

The secondary objective is to assess safety and tolerability of BI 1569912.

2.1.2 Primary endpoint

SRD and MD part

The primary endpoint for assessment of safety and tolerability of BI 1569912 is the percentage of subjects with drug-related adverse events.

Evening PK part

The following pharmacokinetic parameters will be determined if feasible :

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameters will be determined if feasible:

SRD part

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

MD part

After the first dose:

- $AUC_{0\text{-}24}$ (area under the concentration-time curve of the analyte in plasma from 0 to 24 h)
- C_{max} (maximum measured concentration of the analyte in plasma)

After the last dose:

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

Evening PK part

- The percentage of subjects with drug-related adverse events.
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives are the exploration of the pharmacokinetics including dose proportionality, and linearity.

2.2.2 Further endpoints

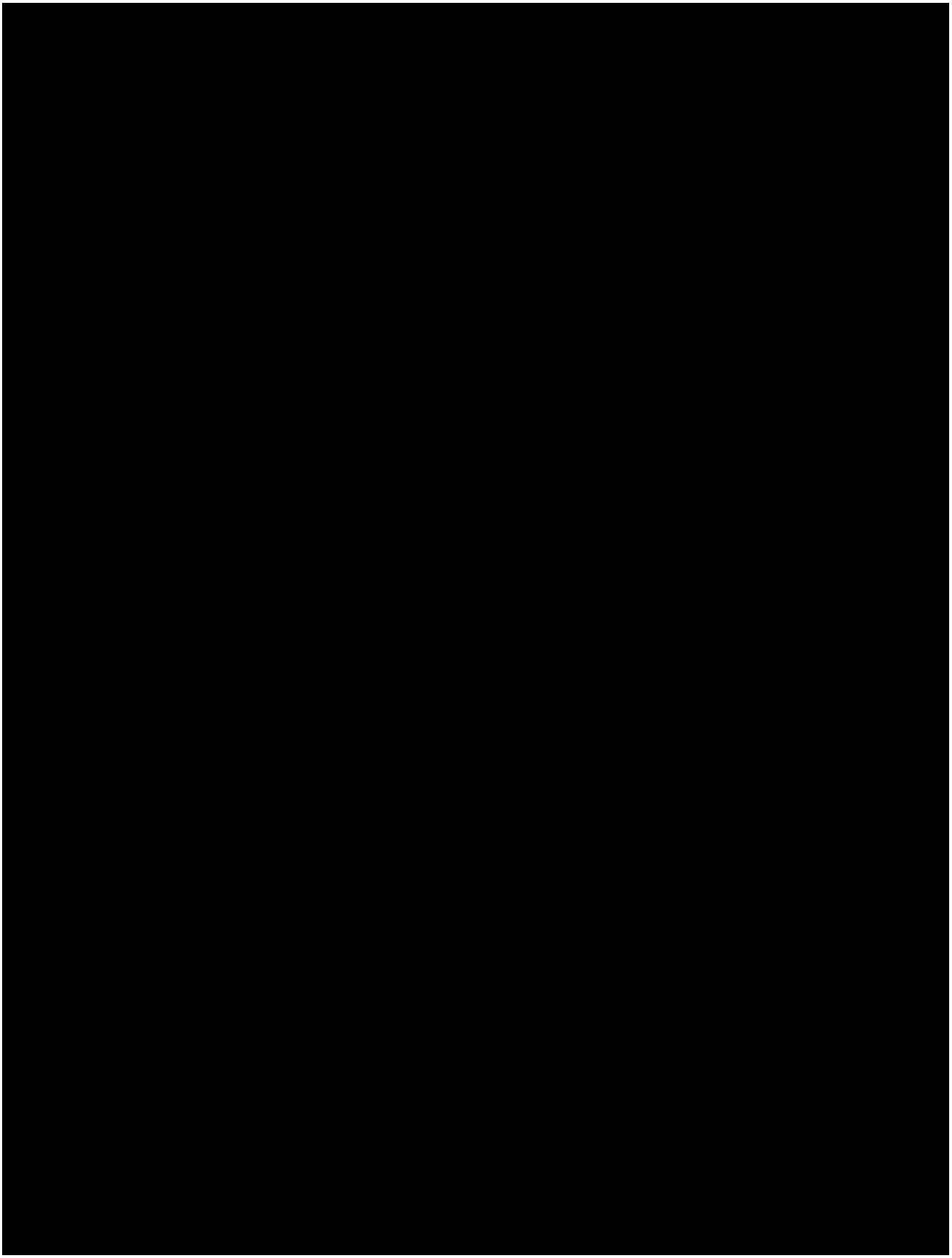
2.2.2.1 Further endpoints of interest

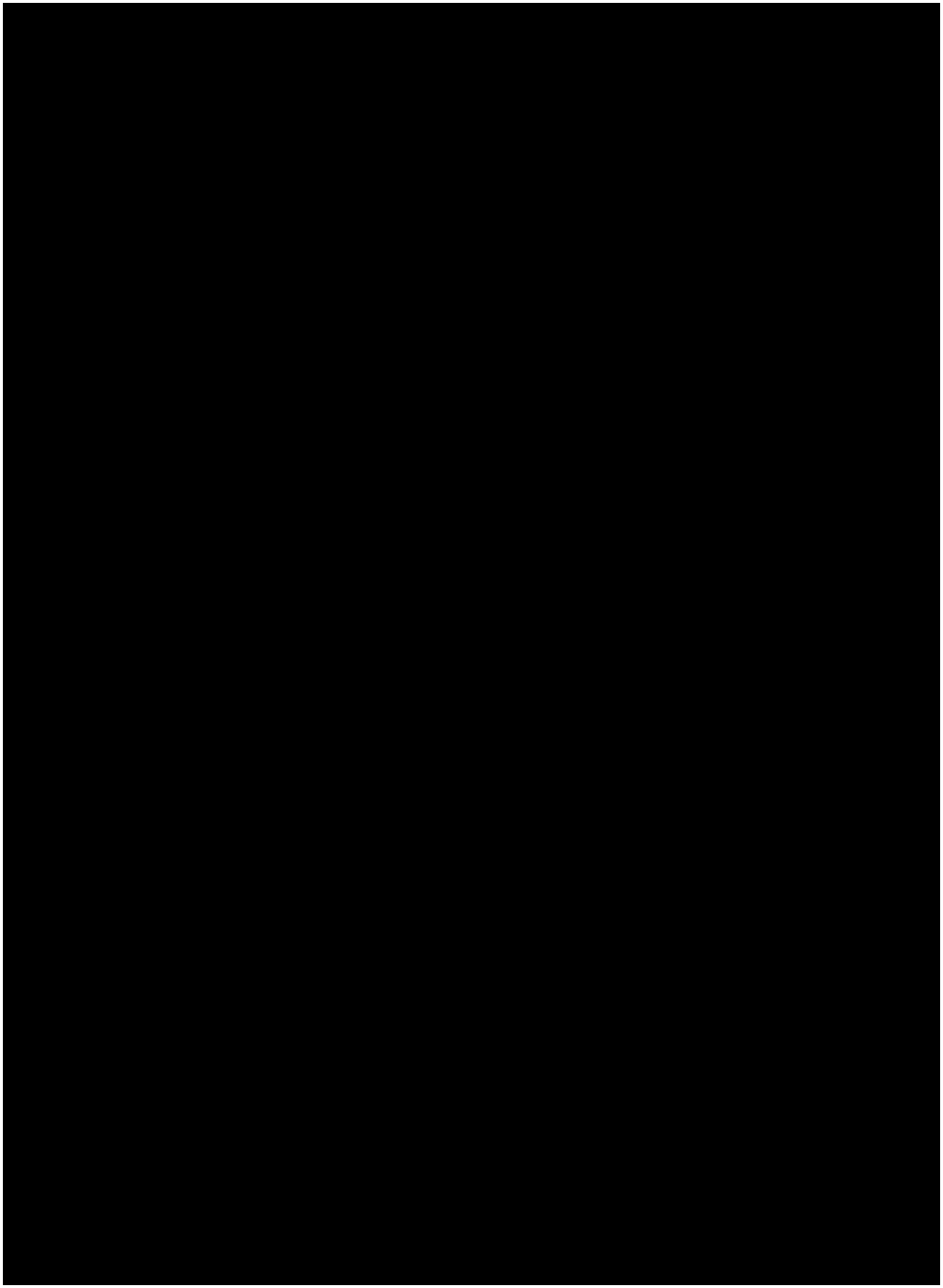
- AEs (including clinically relevant findings from the medical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring (SRD-Part, only)
- Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)

2.2.2.2 Further BI 1569912 specific endpoints of safety and tolerability

- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Standardized medical assessment
- Assessment of dissociative symptoms (e.g. CADSS)
- Electroencephalogram (EEG)

[redacted]





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single rising dose and multiple dose trial is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups in SRD and MD part.

In the single dose part, it is planned to include a total of 32 healthy male subjects. The subjects will be assigned to 4 groups consisting of 8 subjects per group; the groups will be dosed sequentially. Within each dose group, 6 subjects will receive BI 1569912 and 2 will receive placebo.

It is planned to include 12 healthy male subjects in the MD part of the trial. Within this group, 9 subjects will receive BI 1569912 and 3 will receive placebo.

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

Table 3.1: 1 Dose groups

Part	SRD				MRD		Evening PK
Dose Group	1	2	3	4	5*	6**	7
Dose (mg)	2.5	5	10	20	10	20	5
Number of subjects	8	8	8	8	12	12	12
Subjects receiving placebo	2	2	2	2	3	3	0
Subjects receiving active drug	6	6	6	6	9	9	12

** CTP Amendment No.1: In the multiple dose part, original planned 10 mg dose group (dose group 5) will be omitted. For technical reasons dose group 5 was not reassigned.*
*** In case of further dose modification is required in MRD study (1447-0002) or planned highest dose is changed in global phase II study, 20 mg in the MD part is adjusted accordingly in this trial. However, the maximum dose will not exceed 20 mg.*

Applicable as of CTP Amendment No. 1

In the multiple dose part, originally planned 10 mg dose group (Dose Group 5) will be omitted. Instead, an additional dose group of 20 mg (Dose Group 6) is added.
Evening PK part is designed as a randomised, two-sequence, open-label, two period, two-way cross over trial. Within this part, it is planned to include 12 healthy male subjects and all subjects will receive BI 1569912.

Dose escalation and safety review
The groups will be dosed consecutively in ascending order of the doses, and a time interval of at least 7 days will be maintained between the last drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose

group. The decision to treat the next dose group will be based upon safety and tolerability of all the preceding dose groups. The next dose group will only be treated if, in the opinion of the Principal Investigator (or authorised deputy, sub investigator), CT Leader, no safety concerns have arisen in the preceding dose groups, i.e. no dose-limiting events occurred, and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1).
A documented safety review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator, or an authorised deputy, Sub Investigator, or the sponsor of the trial, e.g. in case of any unforeseen adverse events. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy, Sub Investigator), the CT Leader.

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern, and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1).

At minimum, data from 2/3 of subjects on active drug need to be available for escalation to a higher dose. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least 48 h post dosing, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG and continuous ECG monitoring in the current and preceding dose groups up to at least 48 h post dosing
- Vital signs in the current and preceding dose groups up to at least 48 h post dosing
- Clinical laboratory tests in the current and preceding dose groups up to at least 24 h post dosing
- EEG reports up to at least 24 h post dosing
- Check of criteria for stopping subject treatment as per Section 3.3.4.1
- Preliminary pharmacokinetic data of at least 4 subjects on active treatment in Dose Group 3 for up to at least 24 h post dosing as per Section 7.4 (Only for Dose Group 4)
- In addition to preliminary pharmacokinetic data of at least 4 subjects on active treatment in Dose Group 4 for up to at least 24 h post dosing, MD data of 20 mg from 1447-0002 (Only for Dose Group 6)

The decision to escalate the dose will be made jointly by the Principal Investigator, or an authorised deputy, Sub Investigator, CT Leader after in-depth analysis of all available safety data, especially serious adverse event (SAE)s, AEs, and out-of-range laboratory results that are considered clinically significant by the investigator. Dose escalation will only be permitted if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy, Sub Investigator), CT Leader.

Safety Reviews can be conducted face-to-face or by video/telephone conference. The CT Leader is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy, Sub Investigator), CT Leader, and will be filed in the investigator site file (ISF) and TMF.

Additional subjects may be entered to allow additional testing on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 44, but will not exceed 60 subjects. CTP will be amended if additional subject entry has decided.
An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

For single rising dose and multiple dose trials, the sequential rising dose design described in Section 3.1 is viewed favourably under the provision not to expose the subjects to undue risks, since the main trial objective is to investigate safety and tolerability of BI 1569912.

Single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, subjects and investigators will be aware of the dose of the drug administered. The disadvantage of this trial design is a possible observer bias with regard to the dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in single rising dose and multiple dose trials involving healthy subjects to include a placebo group to control for safety and tolerability of the trial medication to reduce the observer expectation effect.

Multiple doses will be tested at 20 mg to assess the safety, tolerability and PK in Japanese healthy male subjects after multiple dose administration before the participation of global phase II trial, which helps to estimate the PK and safety of Japanese population after multiple doses in phase II trials.

SRD part; Each dose group consists of 8 subjects, with 6 on active treatment and 2 on placebo. For data analysis purposes, the placebo control group will include all subjects that were treated with placebo, regardless of the groups they were treated. Six subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

MD part; Group consists of 12 subjects, with 9 on active treatment and 3 on placebo. Nine subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

Evening PK part; for the comparison of pharmacokinetics after administration in the morning and in the evening, the cross-over design is preferred due to its efficiency: since each subject serves as his own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes inter-subject variability from the comparison between treatments (cf. R94-1529).

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of BI 1569912.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 44 healthy males in SRD and MD part and 12 healthy males in Evening PK part will enter the study. The actual number of subjects entered may exceed the total of 44 if additional intermediate doses are tested in SRD and MD part (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time.

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 study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a medical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Japanese ethnicity, according to the following criteria: born in Japan, have lived outside of Japan <10 years, and have parents and grandparents who are Japanese
3. Age of 18 to 45 years (inclusive)
4. BMI of 18.5 to 25.0 kg/m^2 (inclusive)
5. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
6. Subjects who agree to minimize the risk of making their partner pregnant by fulfilling any of the following criteria starting from the first administration of trial medication until 90 days after last administration of trial medication

   - Use of adequate contraception, any of the following methods plus condom: intrauterine device, combined oral contraceptives that started at least 2 months prior to the first drug administration.

   - Vasectomized (vasectomy at least 1 year prior to enrolment)

- Surgical sterilization (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subject's female partner

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 40 to 90 mmHg, or pulse rate outside the range of 40 to 99 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections (Subjects who were positives to Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibodies, HIV-1 and HIV-2 antigen and/or antibody and Syphilis test)
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 3 months (4 months for new active ingredients) of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking or nicotine contained products on specified trial days
15. Alcohol abuse including sign or symptoms (consumption of more than 30 g per day for males)
16. Drug abuse including sign or symptoms or positive drug screening

17. Blood donation of more than 400 mL within 12 weeks or 200 mL within 30 days or plasma donation within 2 weeks prior to administration or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. History of disease that affects the present situation

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

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 year prior to randomisation
26. History or presence of epilepsy, history of more than one febrile seizure in childhood or a family history of seizures/ convulsions
27. Epileptiform abnormalities in EEG at Screening
28. History of clinically relevant head injury or trauma (e.g., associated with loss of consciousness)

In addition, the following SARS-CoV-2/COVID-19-specific exclusion criteria apply:

29. A positive infection test for SARS-CoV-2/COVID-19 on the day of hospitalization and/ or any clinical symptom suggestive for this disease.
30. SARS-CoV-2 vaccination within 28 days prior to randomisation.

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.

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

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

At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.6), 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 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
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, 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 adverse events [AEs], or diseases)
5. 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
6. 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

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.

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:

1. Failure to meet expected enrolment goals overall
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk assessment. Dose escalation will be terminated if more than 50% of the subjects at one dose level show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
3. Violation of GCP, or the CTP impairing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product

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

If some subjects do not complete the trial, the CT Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. For SRD and MD part, a replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces. For Evening PK part, a replacement subject will be assigned a unique trial subject number, and will be assigned to the same sequence as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products have been manufactured by BI Pharma GmbH & Co. KG.

See also Section 1.2.7 and current IB [c29289852].

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 1569912
Pharmaceutical formulation:	Tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	2.5 mg, 5 mg
Posology:	1-0-0 (DG 1 and 2); 2-0-0 (DG 3 and 5); 4-0-0 (DG 4 and 6); 1-0-0 and 0-0-1 (DG 7), for provisional DGs (See Table 4.1.4: 1)
Route of administration:	oral
Duration of use:	SRD part; Single dose MD part; 14 days q.d. dosing [redacted]

The characteristics of the reference product (placebo) are given below:

Substance:	Placebo
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable
Posology:	1-0-0 (DG 1 and 2); 2-0-0 (DG 3 ~~and 5~~); 4-0-0 (DG 4 and 6), for provisional DGs (See Table 4.1.4: 1)
Route of administration:	oral
Duration of use:	SRD part; Single dose MD part; 14 days q.d. dosing Evening PK part; Not applicable

4.1.2 Selection of doses in the trial and dose modification

The doses in the trial were selected on the bases of the data obtained from the ongoing FIH SRD trial and the planned MRD trial to allow ethnic comparison in PK and safety.

The doses selected for this trial should cover the estimated human therapeutic dose range and potentially supra-therapeutic doses that will be tested in phase II studies. Hence in this study, single rising doses of 2.5 mg, 5 mg, 10 mg and a dose at or close to 20 mg will be investigated in Japanese subjects to cover potential therapeutic dose ranges and to provide a safety margin for future development (see Section 1.2). This number of doses will also allow for evaluation of dose proportionality and ethnic similarity of pharmacokinetics of BI 1569912 between Caucasian and Japanese subjects. So far, dose levels up to 20 mg oral solution were well tolerated in FIH SRD trial 1447-0001.

10 mg was selected to be tested in multiple dose part. It is in the range of potential phase II doses, and is one dose level below to the highest dose in Japanese which will be tested in SRD part. At the time of start of multiple dose part in this study, safety and PK data from MRD trial 1447-0002 will be available up to 10 mg. Trial 1447-0002 is planning to investigate multiple dose up to 20 mg. Once safety and PK data of 20 mg multiple dosing are confirmed, additional multiple dose part will be added to this study, if necessary. CTP will be amended if additional entry has decided.

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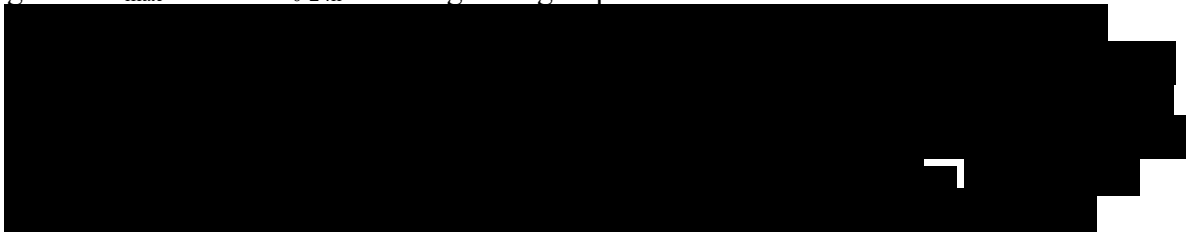
20 mg was selected instead of 10 mg as the dose to be tested in the MD part. Based on the data obtained from 1447-0001 and 1447-0002 in healthy non-Japanese adults and the SRD part of this study, 20 mg q.d. is planned to be the potential highest dose in the global phase II . Safety was confirmed after single oral administration up to 20 mg in this study and single oral administrations of up to 30 mg in 1447-0001. The exposure in Japanese is slightly higher, however such difference is considered mainly attributable to difference in body weight. In the MRD study (1447-0002) conducted in Caucasian healthy adults, the cumulative exposure after multiple doses of 2.5, 5 and 10 mg was minimal. The safety and PK data for doses up to 20 mg q.d. from 1447-0002 will be confirmed before the MD part of this study. Hence, it is appropriate to evaluate the safety and PK of Japanese at the dose of 20 mg q.d., which is the highest dose planned for the global phase II study. Such data can support Japanese subjects to participate in phase II trials more safely.

gMean C_{max} and AUC_{0-24h} of 20 mg dose group was 1310 nmol/L and 2780 nmol·h/L in this



In case of further dose modification is required in MRD study (1447-0002) or planned highest dose is changed in global phase II study, 20 mg in the MD part is adjusted accordingly in this trial. However, the maximum dose will not exceed 20 mg (Section 1.3.2).

5 mg was selected as the dose to be tested in the evening PK part. Based on the data from 1447-0001 and animal experiments, 5 mg BI 1569912 is considered as the clinically relevant dose at present (expected to show efficacy). Indeed, 5 mg BI 1569912 has been tested in 1447-0001 (SRD part and Bioavailability/Food effect part), 1447-0002 (MRD), and has been tested in 1447-0003 (Proof-of-clinical principle in patients), and is planned to be included in the 1447-0005 (Proof-of-clinical concept) trial. Thus, 5 mg was selected to investigate and compare single dose PK of BI 1569912 after administration in the morning and in the evening.

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates.

SRD and MD part:

The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects are allocated to a dose group, the following subjects will be allocated to one of the other dose groups. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. Because the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Numbers of the randomisation list will be allocated to subjects with 'first come first served' principle. Subjects are then assigned to treatment according to the randomisation list.

Evening PK part:

The randomisation scheme will be provided to the trial site in advance. On Day -1 (Visit 2), subjects will be allocated to treatment sequences prior to the first administration of trial medication on Day 1. For this purpose, numbers of the randomisation scheme will be allocated to the subjects. Subjects are then assigned to a treatment sequence according to the randomisation scheme. Once a subject number has been assigned, it cannot be reassigned to any other subject.

To minimize the complexity of the trial procedures, the following randomisation process will be implemented for Evening PK part and a record of each step will be appropriately documented at the site.

1. On Day -1 (Visit 2), all 12 subjects will be randomly allocated to either of the treatment sequence (morning-evening (R-T) or evening-morning (T-R)) with 'first come first served' principle.
2. The treatment sequences (R-T or T-R) will be re-ordered with morning-evening part first. Subject numbers will be allocated based on the re-ordered treatment sequences on Day 1. Thus, the subject numbers will be in ascending order in each treatment sequence.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of tablets for placebo corresponds to the number of tablets of the corresponding dose level.

Table 4.1.4: 1 BI 1569912 and placebo treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Number of tablets per administration	Total daily dose
1	BI 1569912	Tablet	2.5 mg	1 tablet single dose	2.5 mg
2	BI 1569912	Tablet	5 mg	1 tablet single dose	5 mg
3	BI 1569912	Tablet	5 mg	2 tablets single dose	10 mg
4	BI 1569912	Tablet	5 mg	4 tablets single dose	20 mg
5*	BI 1569912	Tablet	5 mg	2 tablets q.d. for 14 days	10 mg
6**	BI 1569912	Tablet	5 mg	4 tablets single dose	20 mg
7	BI 1569912	Tablet	5 mg	1 tablet single dose	5 mg
1-6	Placebo	Tablet	--	identical to active treatment	--

* CTP Amendment No.1: In the multiple dose part, original planned 10 mg dose group (dose group 5) will be omitted. For technical reasons dose group 5 was not reassigned.
** In case of further dose modification is required in MRD study (1447-0002) or planned highest dose is changed in global phase II study, 20 mg in the MD part is adjusted accordingly in this trial. However, the maximum dose will not exceed 20 mg.

SRD part and MD part:

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. 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. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, 1 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. To ensure a dosing interval of 24 h, the administration of trial medication should take place at the same time every day.

During the first 4 h after drug administration, the subjects are not allowed to lie down, i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination, or to sleep (Only for Day 1 and 14).

Subjects will be kept under close medical surveillance until 48 h after first administration of BI 1569912.

Evening PK part:

The medication will be administered on Day 1 of Visit 2 and Visit 2a as a single oral dose together with about 240 mL of water to a subject in the sitting/standing position under supervision of the investigating physician or an authorised designee. Administration will be

performed either in the morning (treatment reference (R)) or in the evening (treatment test (T)) according to the randomisation scheme.

Subjects will be kept under close medical surveillance until at least 24 h following drug administration. For treatment R, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) during the first 2 h after drug administration. For treatment T, subjects are requested to go to bed, lie down (i.e. no declination of the upper body of less than 45 degrees from upright posture except for medical examination) and try to sleep. For restrictions with regard to diet see Section 4.2.2.2.

[redacted]

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

SRD and MD part are designed single-blind. The treatments administered (active or placebo) will be blinded to subjects, but will be known to the investigators (outcome assessors). Only the current dose level will be known to the subjects due to the rising dose design.

A single–blind design is considered acceptable because the potential bias in this type of study seems to be low and according to study procedures it is assured that the investigator's knowledge of the next treatment does not influence the decision to enter a subject.

Evening PK part will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

All trial data will be handled open label. This means that trial functions of the sponsor are unblinded (including CT leader, clinical trial manager (CT Manager), data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated personnel of the trial site).

Access to the randomisation schedule will be controlled and documented in the TMF.

4.1.5.2 Unblinding and breaking the code

As this trial will be conducted single blind, subjects' treatment assignments will be known to investigators. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area 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 CT Manager (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 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 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 medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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 adequately documenting 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 trial medication will be returned to the sponsor. Receipt, usage, and return of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

SRD and MD part:

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after the first and last drug intake on Day 1 and 14 (MD part only). On Days 2 to 13 (MD part only), food is not allowed for at least 2 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served on Day 1 and 14 (MD part only) at 2 h and 4 h post-dose (mandatory for all subjects).

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

Evening PK part:

No food is allowed for at least 4 hours after drug intake in treatment R and prior to the breakfast, i.e. 10 hours after drug administration, served the next morning in treatment T. From 1h before drug intake until lunch for treatment R and until 4 hours for treatment T, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose. For subjects in treatment T, the additional water at 2 h and 4 h after drug administration will only be served in case the subject is awake.

Treatment T, subjects are requested to go to bed immediately after drug administration.

SRD, MD and Evening PK parts:

Alcoholic beverages, 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 study period is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, 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 while admitted to the trial site.

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 study.

4.3 TREATMENT COMPLIANCE

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

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

5.2 ASSESSMENT OF SAFETY

5.2.1 Medical examination

At screening, the medical examination will include demographics, height and body weight, body temperature, smoking and 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, and a physical and neurological examination (please see also Section 5.2.4.1). Medical examination during Visit 2 and Visit 2a will include an examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and neurological examination. At the EOT examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical/ neurological examination including determination of weight.

5.2.2 Vital signs

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

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow chart after the subjects have fasted for at least 10 h (Except SRD part Day 1 post 4 h, Evening PK Visit 2a Day 2 and 3; post 4h, 24h, and 48h in Part I and Visit 2 Day 2 and 3; post 4h, 24h, and 48h in Part II). For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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

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	Neutrophils, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (*if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator*)	Neut. Poly (segs)/ Leukocytes; Neutrophils Bands/ Leukocytes; Eosinophils/ Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/ Leukocytes		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
	Fibrinogen	X	X
Enzymes	AST [Aspartate transaminase]/ GOT, SGOT	X	X
	ALT [Alanine transaminase]/ GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
	Creatine Kinase [CK]	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated and clinically relevant in the opinion of the investigator]	X	X
	Lactic Dehydrogenase	X	X
	Lipase	X	X
	Amylase		
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	Albumin	X	X
	Albumin (Protein Electrophoresis)	X	--
	Alpha-1-Globulin (Protein Electrophoresis)	X	--
	Alpha-2-Globulin (Protein Electrophoresis)	X	--
	Beta-Globulin (Protein Electrophoresis)	X	--
	Gamma-Globulin (Protein Electrophoresis)	X	--
	C-Reactive Protein (Quant)	X	X
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X
	Urea (BUN)		
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 (microscopic examination *if erythrocytes, leukocytes, nitrite or protein are abnormal in urine*)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	X	X

A: parameters to be determined at Visit 1 (screening examination) and Visit 3 (EOT examination)

B: parameters to be determined at Visit 2/2a (for time points refer to Flow Chart)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. It is planned to perform these tests at screening only. Drug screening will be performed at screening or prior to administration.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA
	Barbiturates
	Benzodiazepine
	Cannabis
	Cocaine
	Methamphetamines/MDMA/XTC
	Opiates
	Phencyclidine
	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative)
	Hepatitis B surface antibody (qualitative)
	Hepatitis B core antibody (qualitative)
	Hepatitis C antibodies (qualitative)
	HIV-1 and HIV-2 antibody (qualitative)
	Syphilis test (RPR, TP antibody method)
Infectious test (saliva)	SARS CoV2

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed prior to each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at local laboratory of the trial site or/and at a CRO designated by the sponsor. Laboratory data will be transmitted electronically from the site to BI.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

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

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

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart.

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

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

Storing

All ECGs will be stored as paper and electrically.

Data transfer

For time points specified in the Flow Chart, ECGs will be transferred electronically to the central ECG lab for evaluation and/or storage except for ECGs from screening and EOT visits which will not be transferred. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included in the statistical analysis of interval lengths.

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

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

Evaluation

a) Central ECG lab
Central ECG lab evaluation will be performed post-study for the first of three replicate ECGs at every timepoint. Where 3 triplicate ECGs are recorded, only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated.

This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details).

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

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

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

b) Trial site

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcF values generated by the computerised ECG system or their manual corrections by the investigators will be used.
In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

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

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

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording using the for at least 15 min before drug administration (for baseline assessment) and for 4 h following drug administration). This continuous ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous ECG monitoring.

ECG data from continuous ECG recording will not be transferred to the clinical trial database. Abnormal findings during continuous ECG recording will be recorded as AEs if judged clinically relevant by the Investigator.

5.2.5 Other safety parameters

5.2.5.1 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)
- Orientation
- 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 in source data 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.

For further information, see Appendix 10.1.

5.2.5.2 Suicidality assessment

At the time points, specified in the Flow Chart, potential suicidality or suicidal ideations will be assessed using the ‘Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a semi-structured interview which was developed to assess both suicidal behaviour and suicidal ideation in order to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials. Two versions of the C-SSRS will

be used in this study: the 'Baseline/ Screening' version and the 'Since-last-visit' version. The 'Baseline/ Screening' questionnaire will be used at the Screening visit, and the 'Since-last-visit' questionnaire will be used at EOT, before discharge from the trial site. 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 5 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 questions related to suicidal behaviour and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed. The investigator has to directly evaluate the scale and write a report considering plausibility and clinical relevance of results. Doubtful outcomes may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behaviour or suicidal ideation type 2, 3, 4 or 5 after start of trial, the investigator is to immediately interview the patient during the clinic visit. If the investigator did not administer the C-SSRS leading to the positive report, he/she has to consult a psychiatrist, if considered necessary. If the positive report is confirmed, appropriate actions for the patient's safety have to be initiated.

For each report of suicidal ideation type 1, 2 or 3 after start of the trial, the investigator has to decide, based on his/her clinical judgment, whether it represents an AE as defined in the protocol, and, if it is considered to be an AE, reported it accordingly.

All C-SSRS reports of suicidal ideation type 4 to 5 and all reports of suicidal behavior must be reported as SAEs by the investigator and appropriate actions must be taken.

5.2.5.3 Assessment of dissociative symptoms

Dissociative symptoms will be assessed via the 'Clinician Administered Dissociative States Scale' (CADSS) at time points indicated in the Flow Chart. The CADSS is a clinician administered measure of perceptual, behavioural and attentional alterations during active dissociative experiences. The scale contains 23 subjective items, each rated from 0 (not at all) to 4 (extremely). This scale provides a validated assessment of dissociative states sensitive to change over time and amenable to repeated measures [R20-0052]. This instrument, for the purpose of the study, has a here-and-now (current) lookback timeframe.

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

5.2.5.4 Electroencephalography

Encephalography (EEG) is an electrophysiological, non-invasive method for the recording of electrical activity arising from the human brain cortex with electrodes placed on the scalp. Preferably, EEG recordings are carried out with the subject sitting in a half-reclined position. For further details about EEG data capture, please also refer to the EEG user manual.

Recording

EEGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. The repeat EEGs are assigned to the respective scheduled time point.

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

The screening EEG is a standard EEG recording of approximately 20 min in total, including provocation procedures (photic stimulation and hyperventilation).

For all further EEGs during the course of the study, at time points indicated in the Flow Chart, each EEG sample will last 10 min in total and will be performed without photic stimulation and hyperventilation. Two sequences will be included: (1) a ***resting EEG*** with eyes closed for at least 5 min; (2) a vigilance controlled EEG with ***eyes open*** for about 5 min. Time spans of EEG samples after drug administration should approximately match time spans at baseline to allow for comparability of the occurrence of abnormal EEG signals. Safety EEG recordings may also be used for analysis of quantitative EEG parameters.

For further details, please refer to the EEG user manual.

Storing

All EEGs will be stored electronically.

Data Transfer

EEGs will be transferred electronically to the central EEG lab for evaluation.

In case of repeat EEGs due to quality reasons, only the repeated EEG recordings will be transferred to the central EEG lab, whereas the initially recorded EEGs will be discarded.

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

Evaluation

All EEGs will be independently evaluated by two readers at central EEG lab who evaluate recordings according to the same standards.

Both readers will provide their results in a report within 48 hours. Should these readers be in disagreement with each other, an adjudicator will make a final decision which will be reflected in the final report.

In case of an abnormal EEG result, a third reader with expertise in epilepsy and with full access to the source data can be consulted for advice. The Principal Investigator and the Clinical Trial Leader will then discuss the clinical relevance and the relatedness to the study drug of this finding.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of safety during the study, the reports will be reviewed by the investigator.

Abnormal findings will be reported as baseline conditions (at screening) or AEs (during the trial), if judged clinically relevant by the investigator.

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

5.2.6 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 or not considered related to the medicinal product.

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based 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

The following events will be handled as ‘deemed serious for any other reason’. An AE which possibly leads to disability will be reported as an SAE.

5.2.6.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.5.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure 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 the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

Once the male subject has been enrolled in the clinical trial and has taken trial medication, and, if a partner of the male trial participant becomes pregnant, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner was obtained.

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and clock times of drug administration and pharmacokinetic sampling will be recorded in the CRFs.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per subject does not exceed 400 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1569912 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

EDTA-anticoagulated blood samples will be centrifuged for approximately 10 minutes at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.6 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 75 min with interim storage of blood samples and aliquots in ice water or on ice. The time at which each aliquot was placed in the freezer will be documented. Until

transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately 20 °C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first one. At the analytical laboratory, plasma samples will be stored at approximately -20 °C or below until analysis.

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

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

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

[redacted]

[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 and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials.

Since, in pre-clinical studies, seizures/ convulsions were detected in dogs at higher exposure levels, a routine EEG is included in order to detect suspect EEG signals as early as possible. The pharmacokinetic parameters and measurements outlined in Section 5.4 are generally used assessments of drug exposure. [redacted]

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.

Acceptable deviation from the scheduled time on Day- 1 for ECG, EEG and vital signs will be ±1 h, Medical exam and questionnaires will be within Day -1.

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

The acceptable deviation from the scheduled time for vital signs, ECG, and blood laboratory tests will be ± 5 minutes for the first 4 h (-10 min for triplicate ECG), ±10 minutes thereafter up to 24 h after trial drug administration and ± 30 minutes thereafter. The acceptable deviation for urine laboratory tests will be ± 1 h for the first 4 h, -3 h thereafter.

The acceptable deviation from the scheduled time for safety EEG will be -10 to +20 minutes.

The acceptable deviation from the scheduled time for CADSS will be ± 45 minutes.

The tolerance for drug administration will be ± 1 min on Days 1 and 14 (MD part only) and ± 10 min on all other treatment days.

If several activities are scheduled at the same time point in the Flow Chart, PK sample collection has priority, i.e. that venepuncture will be performed at the exact time point and only exceptionally the order of assessments will be changed. For planned individual plasma concentration sampling times and [redacted] collection intervals, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

SRD part: Each subject will receive one dose of trial medication (BI 1569912 or placebo) at Visit 2.

MD part: Each subject will receive a multiple daily dose of BI 1569912 or placebo for 14 days from Day 1 onwards.

[redacted]

Trial medication will be taken orally by each subject under direct supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

In SRD and MD part, study participants will be admitted to the trial site in the evening of Day -2 and kept under close medical surveillance for at least 48 h following the first /last drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.

In Evening PK part, subjects will be admitted to the trial site in the morning on Day -1 of Visit 2 and kept under close medical surveillance for at least 24 h following drug administration. On Day 3 (treatment R) or Day 4 (treatment T) of Visit 2, subjects will be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. After the wash-out period, subjects will be admitted to the trial site again in the morning on Day -1 of Visit 2a (treatment R) and Day 1 of Visit 2a (treatment T) and kept under close medical surveillance for at least 24 h following the 2nd drug administration.

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

The safety measurements performed during the treatment period are specified in Section 5.3 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and medical examination during the follow-up period, see Sections 5.2.1 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EOT Visit.

If a subject discontinues from the trial, the subject will be followed until the investigator or sub-investigator is convinced of the subject's safety. If follow-up is not possible or comes to an end, follow-up should be formally completed after discussion with the sponsor. If a subject

stops attending trial assessments, the investigator should assess the subject's status as comprehensively as possible, and the well-being of the subject should be monitored. However, if the subject withdraws from the trial, it is the subject's choice whether or not to participate in further assessments; he cannot be compelled.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

SRD Part:

The main objectives of this trial will be assessed by calculating descriptive statistics for safety.

Secondary objectives will be assessed by calculating descriptive statistics for PK endpoints, which will be compared between the treatment groups. Further analyses of these endpoints comprise the power model for assessment of dose proportionality.

MD Part:

The main objectives of this trial will be assessed by calculating descriptive statistics for safety.

Secondary objectives of this trial will be assessed by calculating descriptive statistics for PK endpoints.

Evening PK Part:

The main objective will be assessed by using an analysis of variance (ANOVA) model.

Secondary objectives of this trial will be assessed by calculating descriptive statistics for safety.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the study; i.e., confidence intervals are considered as interval estimates for effects.

Regarding evening PK part of the trial, the evening dosing effect of BI 1569912 (treatment T) compared to BI 1569912 given in the morning (treatment R) will be estimated by the ratios of the geometric means (T/R). Additionally, the two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomised and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one secondary PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he 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.
- Pharmacokinetic parameter evening analysis set (PKS-E): This set includes all subjects in the treated set (TS) who provide at least one primary or secondary PK endpoint value that was not excluded due to a protocol deviation relevant to the statistical 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-E, even if he contributes only one PK parameter value for one period to the statistical assessment. This analysis set only includes subjects from Dose Group 7 and is the base for the evaluation of evening dose administration (evening PK). Descriptive and model-based analyses of PK parameters will be based on the PKS-E.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification document, based on the critical data as defined in the Integrated Quality and Risk Management Plan. iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

Pharmacokinetics

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

Plasma and [redacted] 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.

Relevant 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 [redacted] concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

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

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

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

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards.

SRD and MD part:

The analysis will be based on the treated set (TS) and will be descriptive in nature.

Evening PK part:

The analysis will be based on the PK evening analysis set (PKS-E).

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: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}, \text{ where}$$

y_{ijkm} = logarithm of response measured on subject m in sequence i receiving treatment k in period j,
μ = the overall mean,
ζ_i = the i^{th} sequence effect, i = 1, 2
s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., 12
π_j = the j^{th} period effect, j = 1, 2
τ_k = the k^{th} treatment effect, k = 1, 2
e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.
where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratio of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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

[redacted]

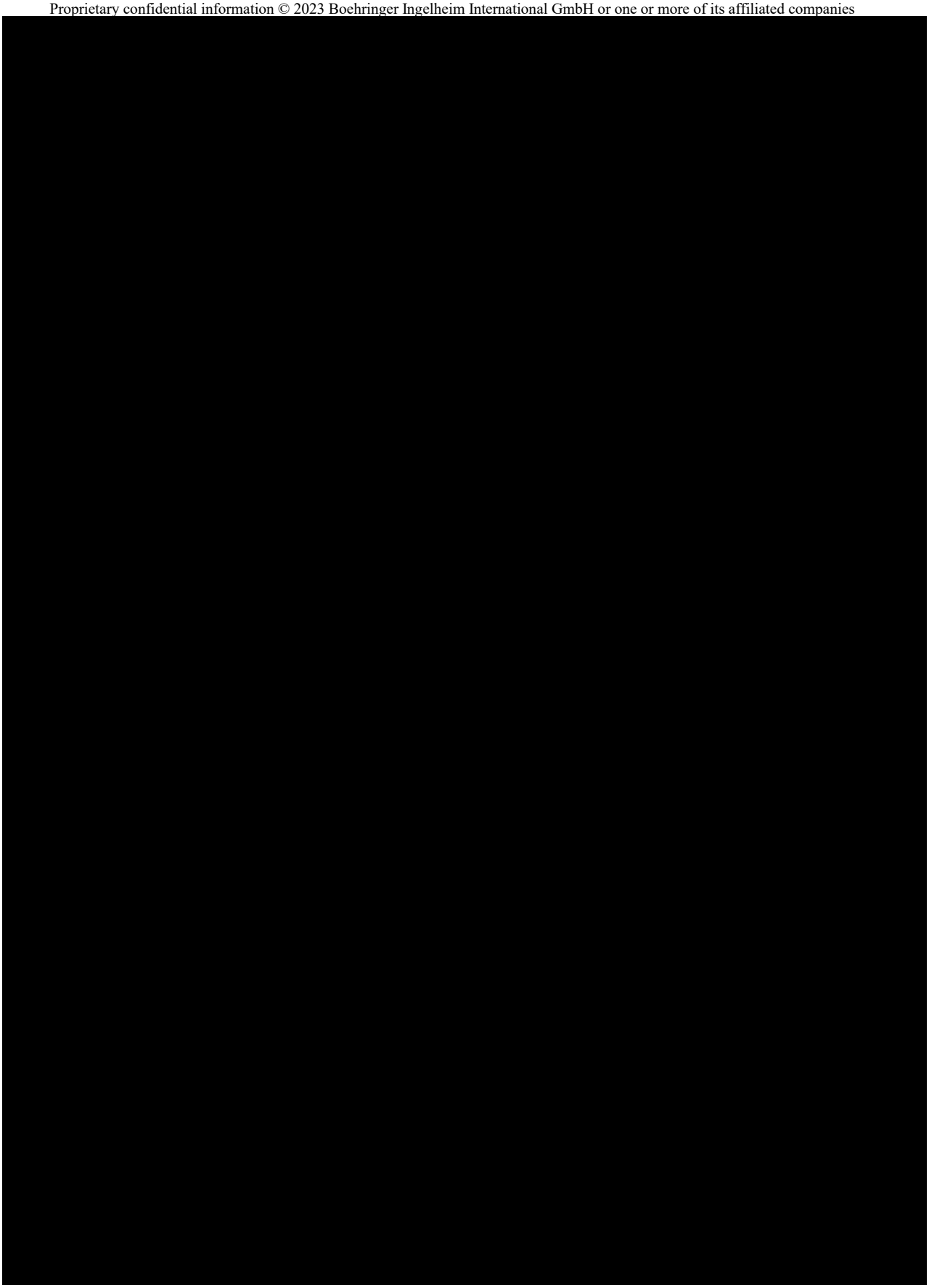
7.3.2 Secondary endpoint analyses

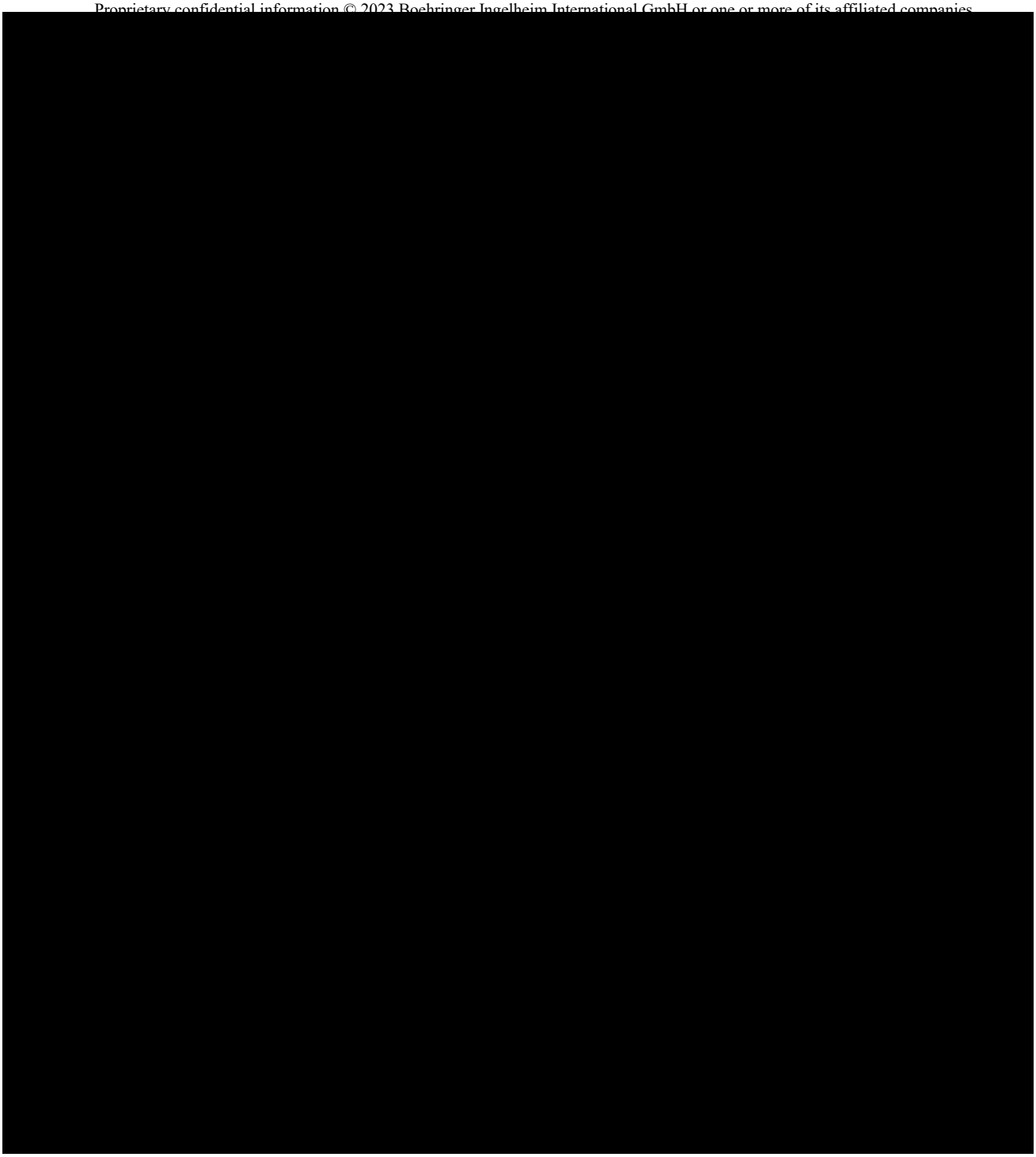
The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.

[redacted]

Evening PK part (evening dosing effect):

The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant SOP of the Sponsor and will be assessed statistically using the same methods as described for the primary endpoints.





7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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

Treatments will be compared in a descriptive way. The placebo group in the safety evaluation of the SRD part will consist of all subjects treated with placebo in the SRD part, regardless of the dose group in which they were treated. Within the SRD part and within the MD part the test treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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

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

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

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

Laboratory data will be compared to their reference ranges. Values outside the reference range 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 ECG variables QT, HR, QTcF, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints. These endpoints and their analyses will be described in the TSAP.

7.4 INTERIM ANALYSES

No formal interim analysis is planned.

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 1569912), provided as individual values and geometric means, will be performed for all dose level after dose group 3 (10 mg).

In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The preliminary analysis will provide individual and mean concentration-time profiles and summary statistics of individual values without subject identification information. The preliminary results will be distributed to the investigator and the trial team.

Depending on the results of available preliminary PK/PD analyses and the tolerability and safety of the compound, changes to the dosing schedule (e.g., additional intermediate doses), and additional PK/PD preliminary analysis may be performed if requested by the CT Leader, the investigator, or Trial Clinical Pharmacokineticist. Preliminary PK/PD results will not be reported in the CTR.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant Corporate Procedure.

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

7.6 RANDOMISATION

SRD Part:
Subjects will be randomised within each dose group in a 3:1 ratio (test treatment to placebo).

MD Part:
Subjects will be randomised in a 3:1 ratio (test treatment to placebo). If an additional dose group will be added subjects will be randomised within each dose group in a 3:1 ratio (test treatment to placebo).

Evening PK part:
The subjects will be randomly allocated to the 2 treatment sequences (R-T or T-R) in a 1:1 ratio. The block size will be documented in the CTR.

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

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

7.7 DETERMINATION OF SAMPLE SIZE

SRD and MD part: It is planned to include a total of 44 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) in single-rising dose studies, and 12 subjects per dose group (9 on active treatment, and 3 on placebo) in multiple dose studies are commonly used of the present types and is in general considered as sufficient for the exploratory evaluation of safety and pharmacokinetics.

Evening PK part: It is planned to enter a total of 12 subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trail. 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 through the ratio of upper to lower confidence interval limit. Note that the precision is independent of the actual ratio of geometric means.

Intra-subject variability was assumed to be gCV=21.7%. Table 7.7: 1 provides an overview on the achievable precision for estimating the ratio of geometric mean (test/reference) when comparing the morning and evening dosing for this gCV. For illustrative purposes, the expected 90% confidence intervals with 95% coverage probability are displayed for different values of geometric means ratios T/R.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for gCV=21.7% in a two-way crossover trial (N=12)

gCV [%]	Precision (upper CI limit/point estimate)	Ratio[1] [%]	90% CI [%]
21.7	1.208	80	(66.21, 96.67)
	1.208	100	(82.76, 120.84)
	1.208	125	(103.45, 151.05)

1. Ratio of the geometric means (test/reference) for a PK endpoint defined by $\exp(\mu_T)/\exp(\mu_R)$

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 (R11-5230) using R Version 3.6.1.

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 56, but will not exceed 60 subjects entered.

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, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles.

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. 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 archiving of the CTR.

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 responsible Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The investigator or delegate must give a full explanation to trial subjects based on the subject information form. A language understandable to the subject should be chosen and technical terms and expressions avoided, if possible.

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

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. 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.

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

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

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

- Subject identification: sex, 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 (e.g. EEG), with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Questionnaire, Assessment form answered by subjects (e.g. CADSS and C-SSRS)
- 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 must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

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

8.6 TRIAL MILESTONES

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

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

Early termination of the trial is defined as the premature termination of the trial for 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.

When the trial is completed, the investigator should inform the head of the trial site in writing of the completion of the trial, and the head of the trial site should promptly inform the IRB and sponsor in writing of the completion.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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.

BI has appointed a 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 CT Manager, CRA 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.

Analyses of BI 1569912 concentrations in plasma will be performed at the [redacted] or a suitable CRO.

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

The digitally recorded EEGs will be sent to a specialised contract research organisation [redacted] for evaluation.

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

Data management and statistical evaluation will be done by BI or a contract research organisation appointed by BI, according to BI SOPs.

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

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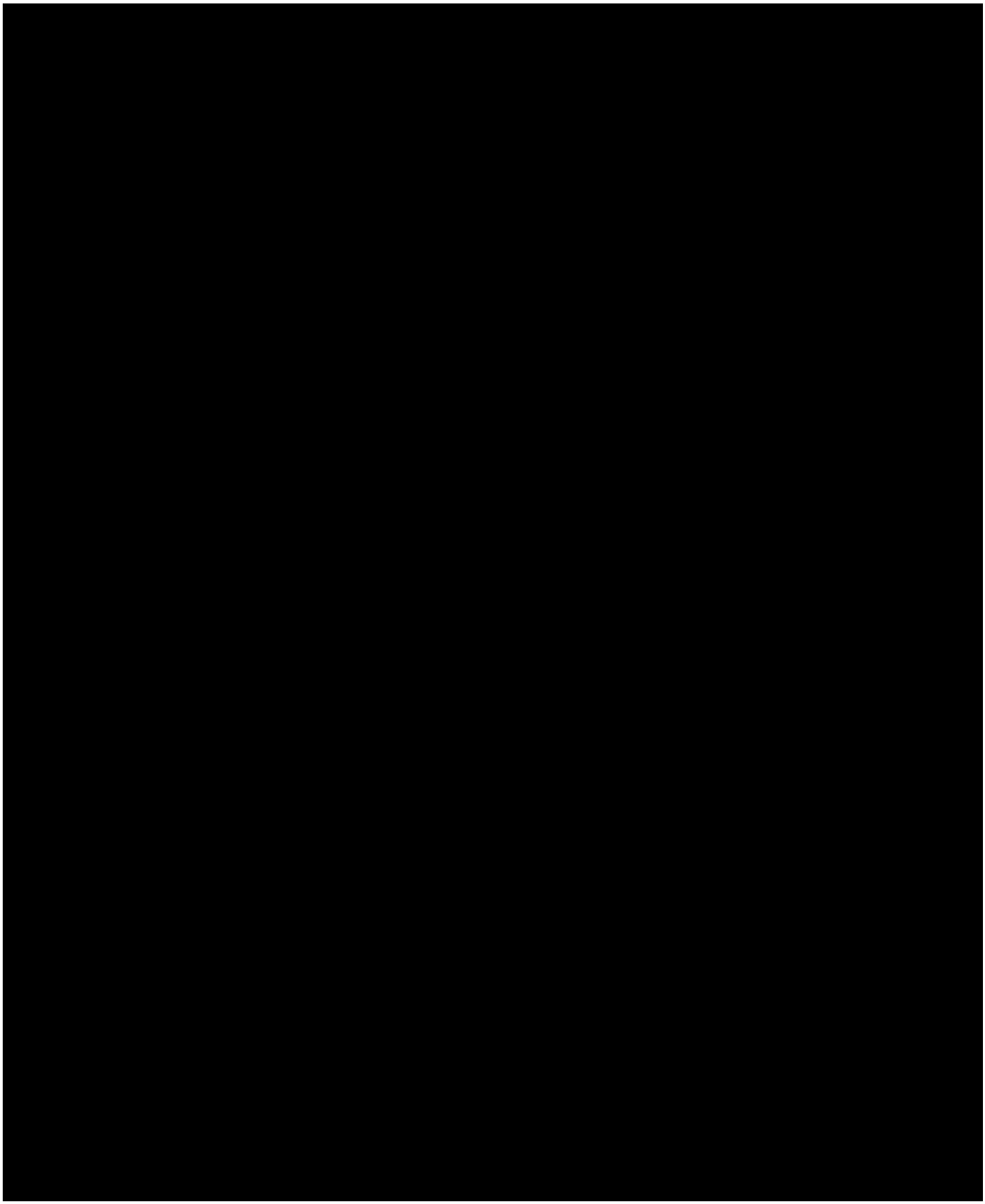


10. APPENDICES

10.1 STANDARDIZED NEUROLOGICAL ASSESSMENT FORM

STANDARDIZED NEUROLOGICAL ASSESSMENT FORM

SID: <SID>		RND:		
Last name: <Lastname>		First name: <Firstname>		
Planned time: *(corresponds to flow chart)*	☐ SCR ☐ Day -1 ☐ Day 2(24 h post-dose)	☐ EOT ☐ Day 1(pre-dose) ☐ Day 4(72h post-dose)	☐ Other: ☐ Day 1(4h post-dose)	
Date: *(DD-MMM-YYYY)*		Actual time: *(hh:mm / Start of examination)*		

No.	**Test range** (Minimum set of tests / assessments) ncs: not clinically significant: Description in the comment box cs: clinically significant: Description must be documented in the comment box and additionally as **AE** or **Baseline Condition**	Normal	Abnorm. ncs	Abnorm. cs
1.	**General level of arousal** *(Attention, wakefulness, mood)* (Explicit ["How do you feel?"] and implicit [behaviour, eye contact, speech, comprehension, posture] assessment)			
2.	**Orientation** (Orientation to time, place, situation and person)			
3.	**Eye movement** (Gaze straight ahead [crossed eyes? Symmetrical deviation? Eyelid fissure symmetrical?], 6 cardinal positions of gaze [palsy? saccades?])			
4.	**Pupil size and pupil reactivity** (Direct and consensual response to light, pupil size: comparison of both sides)			
5.	**Gait** (Walking in a straight line: gait, posture, arm swing present, motion symmetry; dyskinesia? tendency to fall?)			
6.	**Assessment of muscle strength** *(muscle strength; pareses?)* (Elbow flexion against resistance, standing on the balls of the foot on one leg)			
7.	**Romberg test** *(test for gait ataxia including arm extension test)* (Swaying? tendency to fall? Arm extension test [20-30 sec. Holding the position with eyes closed, hands supine])			
8.	**Tremor** (Postural tremor, resting tremor, intention tremor; please document increased physiological tremor)			
9.	**Reflexes** *(autonomic and polysynaptic reflexes)* (Biceps brachii reflex, quadriceps reflex, plantar skin reflex)			
10.	**Sensitivity** (Sensitivity to touch [upper arm, lower arm, thigh, lower leg, insole and sole of the foot] sharp/blunt, cold/warm)			
11.	**Point-to-point movements** (Finger-nose test, heel-knee-shin test)			
	Comment box ("ad X" + comment; incl. normal version, if applicable) ☐ no comment ☐ See back for further explanations			
	Examiner: *Name* *Signature*			

10.2 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

10.2.1 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)

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

10.2.2 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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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

10.3 CLINICIAN ADMINISTERED DISSOCIATIVE STATES SCALE (CADSS)

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name_____ ID_____ Date_____
Subjective Items:

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4. Do you feel as if you are looking at things from outside of your body?
   - 0= Not at all.
   - 1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
   - 2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
   - 3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
   - 4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.
5. Do you feel as if you are watching the situation as an observer or a spectator?
   - 0= Not at all.
   - 1= Mild, I feel slightly detached from what is going on, but I am basically here.
   - 2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
   - 3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in

this room.

4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
   - 0= Not at all.
   - 1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
   - 2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
   - 3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
   - 4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.
7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
   - 0= Not at all.
   - 1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
   - 2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
   - 3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
   - 4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.
8. Do people seem motionless, dead, or mechanical?
   - 0= Not at all.
   - 1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
   - 2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
   - 3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
   - 4= Extreme, it's as if everyone were frozen or completely like machines.
9. Do objects look different than you would expect?
   - 0= Not at all.
   - 1= Mild, things seem slightly different than normal, although it is barely perceptible.
   - 2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
   - 3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
   - 4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.
10. Do colors seem to be diminished in intensity?
    - 0= Not at all.
    - 1= Mild, things seem slightly paler than usual if I think about it.
    - 2= Moderate, colors are somewhat diminished, but still recognizable.
    - 3= Severe, colors are extremely pale, in no way as vivid as they usually are.

4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    0= Not at all.
    1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.
12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
    0= Not at all.
    1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
    2= Moderate, it seems as if this interview has gone on for at least two hours.
    3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
    4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.
13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
    0= Not at all.
    1= Mild, things are happening slightly faster than normal.
    2= Moderate, things seem to be happening at least twice as fast as normal.
    3= Severe, things seem to be happening at least 10 times faster than normal.
    4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.
14. Have there been things which have happened during this interview [assessment] that now you can't account for?
    0= Not at all.
    1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
    2= Moderate, at least once there were things which happened which now I can't account for.
    3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
    4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.
15. Have you spaced out, or in some other way lost track of what was going on during this experience?
    0= Not at all.
    1= Mild, I have had some episodes of losing track of what is going on, but I have

followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a

person, or if I am many people.

4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
    - 0= Not at all.
    - 1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
    - 2= Moderate, I feel like I have different parts which don't quite fit together.
    - 3= Severe, there are two or more sides to myself which have unique characteristics.
    - 4= Extreme, I have two or more parts to myself with unique personality characteristics.
22. Do you have gaps in your memory?
    - 0= Not at all.
    - 1= Mild, there are some recent things which I cannot remember.
    - 2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
    - 3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
    - 4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.
23. Do you feel like you have more than one identity?
    - 0= Not at all.
    - 1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
    - 2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
    - 3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
    - 4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		15 Jun 2023
BI Trial number		1447-0004
BI Investigational Medicinal Product(s)		BI 1569912
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomized within dose groups, placebo-controlled, parallel-group design) and comparison of pharmacokinetics of a single oral dose of BI 1569912 after oral administration in the morning versus oral administration in the evening in healthy male Japanese subjects (randomised, two-sequence, open-label, two period, two-way cross over) (Evening PK Part)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title Page – Title Clinical Trial Protocol Synopsis – Title of trial
Description of change		From: Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomized within dose groups, placebo-controlled, parallel-group design) To: Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomized within dose groups, placebo-controlled, parallel-group design) and comparison of pharmacokinetics of after single oral administration of BI 1569912 in the morning versus evening in healthy male Japanese subjects (randomised, two-sequence, open-label,

		two period, two-way cross over) (Evening PK Part)
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Title Page – Lay Title
Description of change		From: A study in healthy Japanese men to test how well different doses of BI 1569912 are tolerated To: A study in healthy Japanese men to test how different doses of BI 1569912 are taken up by the body and how well they are tolerated
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Title Page – Clinical Trial Leader
Description of change		From: [redacted] Telephone: [redacted] Fax: [redacted] To: [redacted] Telephone: [redacted] Fax: [redacted]
Rationale for change		Change of person in charge and department name
Section to be changed		Clinical Trial Protocol Synopsis – Trial rationale
Description of change		From: Safety, tolerability and pharmacokinetics of BI 1569912 will be assessed in healthy male Japanese subjects receiving single rising doses (SRD) and multiple doses (MD) in order to provide the basis for a clinical development of BI 1569912 in the indication for Major Depressive Disorder (MDD) in Japan. To:

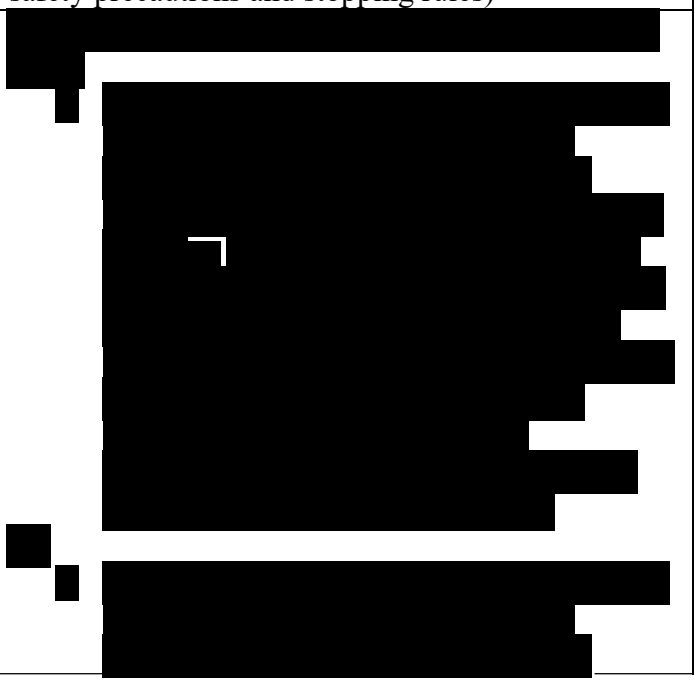
		Safety, tolerability and pharmacokinetics of BI 1569912 will be assessed in healthy male Japanese subjects receiving single rising doses (SRD) and multiple doses (MD) in order to provide the basis for a clinical development of BI 1569912 in the indication for Major Depressive Disorder (MDD) in Japan. In addition, safety, tolerability and pharmacokinetics of BI 1569912 will be assessed in healthy male Japanese subjects receiving single oral dose in the morning and evening and to assess safety to evaluate if an evening dosing regimen which may attenuate sedative or visual adverse effects would be beneficial for patients in phase 2 trials.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Trial objectives
Description of change		From: To investigate safety, tolerability and pharmacokinetics following single rising doses and multiple doses of BI 1569912 To: To investigate safety, tolerability and pharmacokinetics following single rising doses and multiple doses of BI 1569912 as well as a single oral dose of BI 1569912 after oral administration in the morning versus oral administration in the evening
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Trial endpoints
Description of change		From: **Primary endpoint:** the percentage [%] of subjects with drug-related AEs per treatment group Secondary endpoints: **SRD part:** $AUC_{0-\infty}$, C_{max} of BI 1569912 **MD part:** $AUC_{\tau,ss}$, $C_{max,ss}$ of BI 1569912 Further PK parameters of interest will be calculated as appropriate. To: **Primary endpoint:**

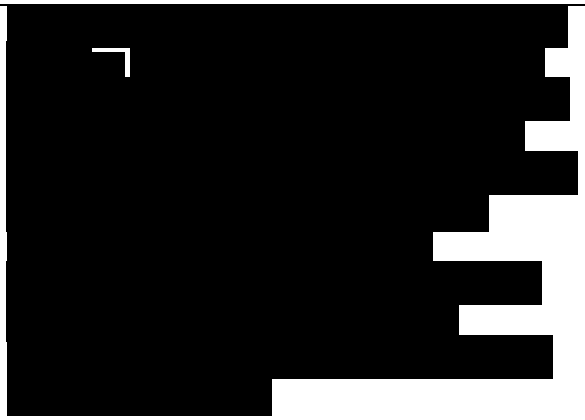
		SRD and MD part: the percentage [%] of subjects with drug-related AEs per treatment group **Evening PK part:** AUC_{0-tz}, C_{max} of BI 1569912 **Secondary endpoints:** **SRD part:** $AUC_{0-\infty}$, C_{max} of BI 1569912 **MD part:** $AUC_{\tau,ss}$, $C_{max,ss}$ of BI 1569912 **Evening PK part:** the percentage [%] of subjects with drug-related AEs per treatment group. $AUC_{0-\infty}$ of BI 1569912 Further PK parameters of interest will be calculated as appropriate.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Trial design
Description of change		From: Single-blind, randomised within dose groups, placebo-controlled parallel-group design To: SRD part, MD part: Single-blind, randomised within dose groups, placebo-controlled parallel-group design Evening PK part: Randomised, two-sequence, open-label, two period, two-way cross over design
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Number of subjects
Description of change		From: Total 44 To: Total 56
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Number of subjects total entered each treatment
Description of change		From: (…) MD part: 12* 12 per dose group (9 on BI 1569912 and 3 on placebo) (…)

		To: (…) MD part: 12* 12 subjects (9 on BI 1569912 and 3 on placebo) Evening PK part: 12 12 subjects (12 on BI 1569912) (…)
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Main criteria for inclusion
Description of change		From: Healthy male Japanese subjects, age of 20 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive) To: Healthy male Japanese subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive)
Rationale for change		Updated to align with the Japanese regulations
Section to be changed		Clinical Trial Protocol Synopsis – Test product dose
Description of change		From: 2.5 mg, 5 mg, 10 mg and 20 mg q.d. To: SRD part: 2.5 mg, 5 mg, 10 mg and 20 mg MD part: 20 mg q.d. Evening PK part: 5 mg
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Test product mode of admin.
Description of change		From: Oral with 240 mL of water after an overnight fast of at least 10 h To: SRD part, MD part*:* Oral with 240 mL of water after an overnight fast of at least 10 h Evening PK part: Oral with 240 mL of water after an overnight fast of at least 10 h for morning administration. Oral with 240 mL of water after a

		fast period of at least 5 h for evening administration.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Duration of treatment
Description of change		From: Single rising dose (SRD) group: Single dose Multiple dose (MD) group: Once daily, multiple doses over 14 days To: Single rising dose (SRD) group: Single dose Multiple dose (MD) group: Once daily, multiple doses over 14 days [redacted]
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Clinical Trial Protocol Synopsis – Statistical methods
Description of change		From: Descriptive statistics will be calculated for all endpoints. To: Descriptive statistics will be calculated for all endpoints. Evening PK part: The effect of evening dosing will be estimated by ratios of 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-test 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 sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA.
Rationale for change		Updated due to the addition of Evening PK cohort

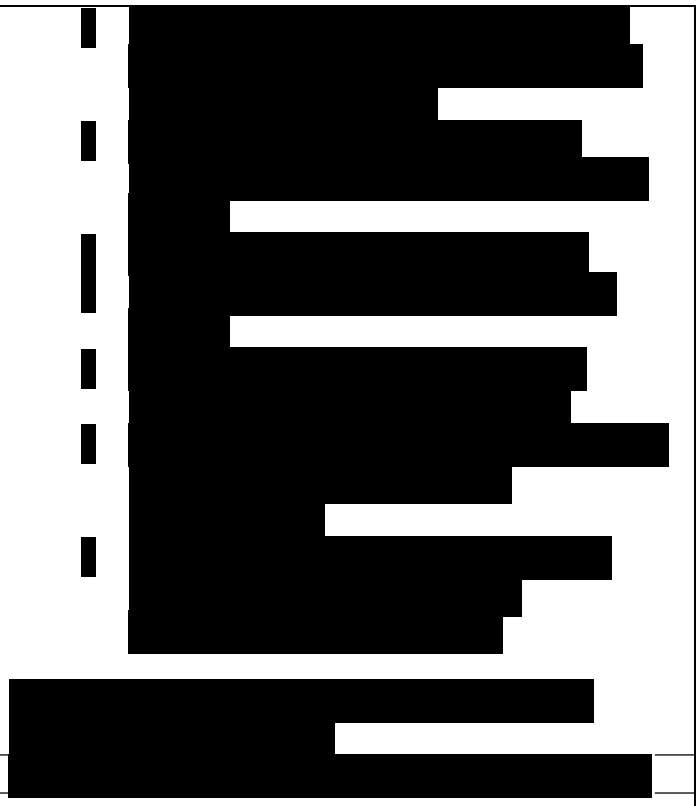
Section to be changed		Flow Chart 1 – SRD part
Description of change		Approximate clock time of actual day at Day 2 of Visit From:19:00 Change to: 21:00
Rationale for change		To correct a typo in the previous version
Section to be changed		Flow Chart 1 – SRD part
Description of change		Annotation No.9 From: At baseline (i.e. Day -1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes. Changed to: At baseline (i.e. prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
Rationale for change		Typo in the previous version
Section to be changed		Flow Chart 2 – MD part
Description of change		PK blood was removed from Planned Time of 98:00 h at Visit 2 Day 5 Planned Time of 346:00 h at Visit 2 Day 15 was removed
Rationale for change		Typo in the previous version
Section to be changed		Flow Chart 3 and 4
Description of change		Entire section added
Rationale for change		Added due to the addition of Evening PK cohort
Section to be changed		Abbreviations
Description of change		The following abbreviations were added: ANOVA: Analysis of variance CI: Confidence interval
Rationale for change		Added due to the addition of Evening PK cohort
Section to be changed		1.2.5 Clinical experiences in humans
Description of change		Entire section was updated
Rationale for change		Updated to reflect the current data from the preceding trials

Section to be changed		1.3 – Rationale for performing the trial
Description of change		From: (…) The first in human phase I trial (…) To: (…) <u>The evening PK part is designed to investigate and compare the pharmacokinetics of BI 1569912 after a single dose administration in the morning vs. in the evening. These data will help to evaluate if an evening dosing regimen which may attenuate adverse effects would be appropriate for patients in phase II trial.</u> The first in human phase I trial (…)
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		1.4.8 Benefit-Risk Assessment in context of COVID-19 pandemic for subjects participating in clinical trials investigating BI 1569912.
Description of change		Entire section was deleted and section 1.4.9 and 1.4.10 were changed to 1.4.8 and 1.4.9 respectively
Rationale for change		To remove unnecessary measures as COVID 19 situation has become stable in Japan
Section to be changed		1.4.9 Measures of risk minimization (including safety precautions and stopping rules)
Description of change		

		 Section number was changed to 1.4.8 due to the deletion of 1.4.8 Benefit-Risk Assessment in context of COVID-19 pandemic for subjects participating in clinical trials investigating BI 1569912.
Rationale for change		Updated due to the modification made to MD part
Section to be changed		2.1.1 Main Objectives
Description of change		From: The main objectives of this trial are to investigate safety and tolerability of BI 1566912 in healthy male Japanese subjects following oral administration of single rising doses and multiple doses per day over 14 days. Secondary objectives are the exploration of pharmacokinetics (PK) of BI 1566912 after single and multiple oral dosing. To: In SRD and MD part, the main objectives of this trial are to investigate safety and tolerability of BI 1569912 in healthy male Japanese subjects following oral administration of single rising doses and multiple doses per day over 14 days. Secondary objectives are the exploration of pharmacokinetics (PK) of BI 1569912 after single and multiple oral dosing. In evening night PK part, the main objectives of this trial are to investigate and compare single dose pharmacokinetics of BI 1569912 after

		administration of 5 mg in the morning and after administration in the evening. The secondary objective is to assess safety and tolerability of BI 1569912.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		Section 2.1.2 Primary endpoint
Description of change		From: The primary endpoint for assessment of safety and tolerability of BI 1566912 is the percentage of subjects with drug-related adverse events. To: SRD and MD part The primary endpoint for assessment of safety and tolerability of BI 1569912 is the percentage of subjects with drug-related adverse events. Evening PK part The following pharmacokinetic parameters will be determined if feasible : • 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)
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		2.1.3 Secondary endpoint
Description of change		From: (…) MD part After the first dose: • AUC_{0-24} (area under the concentration-time curve of the analyte in plasma from 0 to 24 h) • C_{max} (maximum measured concentration of the analyte in plasma) After the last dose: • $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma over the dosing interval τ at steady state)

		• $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state) To: (…) MD part After the first dose: • AUC_{0-24} (area under the concentration-time curve of the analyte in plasma from 0 to 24 h) • C_{max} (maximum measured concentration of the analyte in plasma) After the last dose: • $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma over the dosing interval τ at steady state) • $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state) <u>Evening PK part</u> • <u>The percentage of subjects with drug-related adverse events.</u> • <u>$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)</u>
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		[redacted]
Description of change		[redacted]

		
Rationale for change		
Section to be changed		3.1 Overall trial design and plan
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		3.2 Discussion of trial design, including the choice of control group
Description of change		From: (…) Multiple dose will be tested at 10 mg to assess the safety, tolerability and PK in Japanese healthy male subjects after multiple dose administration before the participation of global phase II trial, which helps to estimate the PK and safety of Japanese population after multiple doses in phase II trials. (…) MD part; Group consists of 12 subjects, with 9 on active treatment and 3 on placebo. Nine subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics. To: (…)

		Multiple doses will be tested at 20 mg to assess the safety, tolerability and PK in Japanese healthy male subjects after multiple dose administration before the participation of global phase II trial, which helps to estimate the PK and safety of Japanese population after multiple doses in phase II trials. (…) MD part; Group consists of 12 subjects, with 9 on active treatment and 3 on placebo. Nine subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics. Evening PK part; for the comparison of pharmacokinetics after administration in the morning and in the evening, the cross-over design is preferred due to its efficiency: since each subject serves as his own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes inter-subject variability from the comparison between treatments (cf. R94-1529). The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of BI 1569912.
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		3.3 Selection of trial population
Description of change		From: It is planned that 44 healthy male will enter the study. The actual number of subjects entered may exceed the total of 44 if additional intermediate doses are tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site. (…) To: It is planned that 44 healthy males in SRD and MD part and 12 healthy males in Evening PK part will enter the study. The actual number of subjects entered may exceed the total of 44 if additional intermediate doses are tested in SRD and MD part

		(see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		3.3.2 Inclusion criteria
Description of change		From: (…) 3.Age of 20 to 45 years (inclusive) (…) To: (…) 3.Age of 18 to 45 years (inclusive) (…)
Rationale for change		To align with the Japanese regulations
Section to be changed		3.3.5 Replacement of subjects
Description of change		From: If some subjects do not complete the trial, the CT 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, and will be assigned to the same treatment as the subject he replaces. To: If some subjects do not complete the trial, the CT Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. For SRD and MD part, a replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces. For Evening PK part, a replacement subject will be assigned a unique trial subject number, and will be assigned to the same sequence as the subject he replaces.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		4.1.1 Identify of the investigational medicinal products
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part

Section to be changed		4.1.2 Selection of doses in the trial and dose modification
Description of change		The following paragraph was added at the end of this section: Applicable as of CTP Amendment No. 1 20 mg was selected instead of 10 mg as the dose to be tested in the MD part. Based on the data obtained from 1447-0001 and 1447-0002 in healthy non-Japanese adults and the SRD part of this study, 20 mg q.d. is planned to be the potential highest dose in the global phase II . Safety was confirmed after single oral administration up to 20 mg in this study and single oral administrations of up to 30 mg in 1447-0001. The exposure in Japanese is slightly higher, however such difference is considered mainly attributable to difference in body weight. In the MRD study (1447-0002) conducted in Caucasian healthy adults, the cumulative exposure after multiple doses of 2.5, 5 and 10 mg was minimal (~10%). The safety and PK data for doses up to 20 mg qd from 1447-0002 will be confirmed before the MD part of this study. Hence, it is appropriate to evaluate the safety and PK of Japanese at the dose of 20 mg q.d., which is the highest dose planned for the global phase II study. such data can support Japanese subjects to participate in phase II trials more safely. gMean Cmax and AUC0-24h of 20 mg dose group [redacted] In case of further dose modification is required in MRD study (1447-0002) or planned highest dose is changed in global phase II study, 20 mg in the MD part is adjusted accordingly in this trial. However, the maximum dose will not exceed 20 mg (Section 1.3.2).

Rationale for change		Updated due to the modification of MD part
Section to be changed		4.1.3 Method of assigning subjects to treatment groups
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		4.1.4 Drug assignment and administration of doses for each subject
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		4.1.5.1 Blinding
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		4.1.8 Drug accountability
Description of change		From: All unused trial medication will be disposed of locally by the trial site upon written authorisation of the CT Leader. Receipt, usage, and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies. To: All unused trial medication will be returned to the sponsor. Receipt, usage, and return of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.
Rationale for change		To correct a typo in the previous version
Section to be changed		4.2.2 Restrictions on diet and life style
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		5.2.1 Medical examination
Description of change		From: At screening, the medical examination will include demographics, height and body weight, body

		temperature, smoking and 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, and a physical and neurological examination (please see also Section 5.2.4.1). Medical examination during Visit 2 will include an examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and neurological examination. At the EOT examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical/ neurological examination including determination of weight. To: At screening, the medical examination will include demographics, height and body weight, body temperature, smoking and 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, and a physical and neurological examination (please see also Section 5.2.4.1). Medical examination during Visit 2 and Visit 2a will include an examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and neurological examination. At the EOT examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical/ neurological examination including determination of weight.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		The following sentence was deleted: For details on SARS-CoV-2/ COVID-19 specific tests at screening and Day -2, refer to Appendix 10.4.
Rationale for change		To remove unnecessary measures as COVID 19 situation has become stable in Japan
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Table 5.2.3:1 Annotation B

		From: B: parameters to be determined at Visit 2 (for time points refer to Flow Chart) To: B: parameters to be determined at Visit 2/2a (for time points refer to Flow Chart)
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		5.2.5 Assessment of adverse events
Description of change		The following sentence was deleted: For the documentation of adverse events, related to SARS-CoV-2/COVID-19, refer to Appendix 10.4.
Rationale for change		To remove unnecessary measures as COVID 19 situation has become stable in Japan
Section to be changed		5.6.1.1 Methods and timing of sample collection
Description of change		From: One blood sample of at most 3 mL will be taken from an arm vein at Visit 2 for both parts – SRD and MD (see Flow Chart). If not feasible at Visit 2, the sample may also be drawn at any later visit. Directly after blood collection, gently invert the tube at least 8 times and then store the blood sample at a temperature of approximately -20°C or below. Once frozen, thawing of the samples should be avoided. To: One blood sample of at most 3 mL will be taken from an arm vein at Visit 2 for all parts – SRD, MD and evening PK part (see Flow Chart). If not feasible at Visit 2, the sample may also be drawn at any later visit. Directly after blood collection, gently invert the tube at least 8 times and then store the blood sample at a temperature of approximately -20°C or below. Once frozen, thawing of the samples should be avoided.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		6.2.1
Description of change		The following sentence was deleted: For details on SARS-CoV-2/ COVID-19 specific measures, refer to Appendix 10.4.
Rationale for change		To remove unnecessary measures as COVID 19 situation has become stable in Japan

Section to be changed		6.2.2 Treatment period
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		7.1 Statistical design – model
Description of change		The following sentence was added at the end of this section: *Evening PK-Part:* The main objective will be assessed by using an analysis of variance (ANOVA) model. Secondary objectives of this trial will be assessed by calculating descriptive statistics for safety.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		7.2 Null and alternative hypotheses
Description of change		The following sentence was added at the end of this section: Regarding evening PK part of the trial the evening dosing effect of BI 1569912 (treatment T) compared to BI 1569912 given in the morning (treatment R) will be estimated by the ratios of the geometric means (T/R). Additionally, the two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		7.3 Planned analyses
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		7.3.1 Primary endpoint analyses
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		7.3.2 Secondary endpoint analyses

Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		7.3.4 Safety analyses
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		7.6 Randomisation
Description of change		From: (…) MD-Part: Subjects will be randomised in a 3:1 ratio (test treatment to placebo). If an additional dose group will be added subjects will be randomized within each dose group in a 3:1 ratio (test treatment to placebo). The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable. (…) To: (…) MD-Part: Subjects will be randomised in a 3:1 ratio (test treatment to placebo). If an additional dose group will be added subjects will be randomized within each dose group in a 3:1 ratio (test treatment to placebo). <u>Evening PK part:</u> <u>The subjects will be randomly allocated to the 2 treatment sequences (T-R or R-T) in a 1:1 ratio.</u> <u>The block size will be documented in the CTR.</u> The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system that uses a pseudo-random number

		generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable. (…)
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		7.7 Determination of sample size
Description of change		Entire section was updated
Rationale for change		Updated due to the addition of Evening PK cohort and modification of MD part
Section to be changed		9.2 Unpublished references
Description of change		From: [redacted] Investigator's brochure BI 1569912 in major depressive disorder (MDD). 3 Feb 2020. [redacted] To: [redacted] [redacted] Safety, tolerability, pharmacokinetics and [redacted] [redacted]

		[redacted] (…)
Rationale for change		Addition of a new reference
Section to be changed		10.4 SARS COV-2 / Covid 19 related measures
Description of change		Entire section deleted
Rationale for change		To remove unnecessary measures as COVID 19 situation has become stable in Japan

11.2 GLOBAL AMENDMENT 2

Date of amendment		06 Sep 2023
BI Trial number		1447-0004
BI Investigational Medicinal Product(s)		BI 1569912
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title Page – Title Clinical Trial Protocol Synopsis – Title of trial
Description of change		Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design) ~~and comparison of pharmacokinetics of after single oral administration of BI 1569912 in the morning versus evening in healthy male Japanese subjects (randomised, two-sequence, open-label, two period, two-way cross over) (Evening PK Part)~~
Rationale for change		Updated to protect commercially confidential information at this early development stage
Section to be changed		Clinical Trial Protocol Synopsis – Trial endpoints

Description of change		**Primary endpoint:** **SRD and MD part:** the percentage [%] of subjects with drug-related AEs ~~per treatment group~~ **Secondary endpoints:** **SRD part:** $AUC_{0-\infty}$,, C_{max} of BI 1569912 **MD part:** ~~$AUC_{\tau,ss}$, $C_{max,ss}$ of BI 1569912~~ After the first dose: AUC_{0-24}, C_{max} of BI 1569912 After the last dose: $AUC_{\tau,ss}$, $C_{max,ss}$ of BI 1569912
Rationale for change		Updated to be consistent with the description in Section 2.1.2 and 2.1.3
Section to be changed		Flow Chart 2 – MD part
Description of change		The timing of PK sample, Safety laboratory, Medical Examination, C-SSRS, 12-lead ECG, Vital signs, Questioning for AEs and concomitant therapy during Visit 2 Day 15 to Day 17 were updated.
Rationale for change		Correction and clarification
Section to be changed		Flow Chart 3 – Evening PK part I (Morning to Evening)
Description of change		Day of Visit 2a at Planned Time of 48:00 From: 4 Change to: 3 Safety laboratory Annotation #5 was added to Safety laboratory assessment on Visit 2a Day 1 at Planned Time of -13:00 C-SSRS assessment From: C-SSRS is required at Screening and Planned Time 36:00 on Visit 2 Day 2 Change to: C-SSRS is required at Screening and End of Trial on Visit 3 Vital sign (BP, PR, RR, T) Annotation #2 was added to Vital sign on Visit 2 Day 1 at Planned Time of -1:00 and Visit 2a Day 1 at Planned Time of -1:00

Rationale for change		Correction and clarification
Section to be changed		Flow Chart 4 – Evening PK part II (Evening to Morning)
Description of change		Safety laboratory Annotation #5 was added to Safety laboratory assessment on Visit 2a Day -1 at Planned Time of -23:00 C-SSRS assessment From: C-SSRS is required at Screening and Planned Time 60:00 on Visit 2 Day 4 Change to: C-SSRS is required at Screening and End of Trial on Visit 3 Vital sign Annotation #2 was added to Vital sign on Visit 2 Day 1 at Planned Time of -1:00 and Visit 2a Day 1 at Planned Time of -1:00 Questioning for AEs and concomitant therapy From: Questioning for AEs and concomitant therapy are not required from Planned Time -1:00 of Day 1 to Planned Time 48:00 of Day 3 on Visit 2a Change to: Questioning for AEs and concomitant therapy are required from Planned Time -1:00 of Day 1 to Planned Time 48:00 of Day 3 on Visit2a
Rationale for change		Correction and clarification
Section to be changed		1.2.3.2 Repeated dose toxicity
Description of change		[redacted]
Rationale for change		Correction and clarification
Section to be changed		1.2.5 Clinical experience in humans
Description of change		In the BA/FE part of Trial 1447-0001, 13 subjects were treated in 3 treatment periods (oral solution fasted/tablet fasted/tablet fed). Five subjects (38.5%) prematurely discontinued the trial:

		4 subjects due to termination of the trial and 1 subject for personal reasons. No AEs were reported for the 13 subjects treated in the BA/FE part [c36232730].
Rationale for change		Typo correction
Section to be changed		1.4.7 Drug induced liver injury
Description of change		Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety (see Section 5.2.6~~5~~.1.4).
Rationale for change		Updated based on the changes made to Section 5.2
Section to be changed		3.1 Overall trial design and plan
Description of change		**Applicable as of CTP Amendment No. 1** In the multiple dose part, originally planned 10 mg dose group (Dose Group 5) will be omitted. Instead, an additional dose group of 20 mg (Dose~~s~~ Group 6) is added. Evening PK part is designed as a randomised, two-sequence, open-label, two period, two-way cross over trial. Within this part, it is planned to include 12 healthy male subjects and all subjects will receive BI 1569912.
Rationale for change		Typo correction
Section to be changed		3.3.3 Exclusion criteria
Description of change		A positive infection test for SARS-CoV-2/COVID-19 on the day of hospitalization ~~Day -2~~ and/ or any clinical symptom suggestive for this disease.
Rationale for change		Updated due to the addition of Evening PK cohort
Section to be changed		4.1.2 Selection of doses in the trial and dose modification
Description of change		The following paragraph was added at the end of this section: 5 mg was selected as the dose to be tested in the evening PK part. Based on the data from 1447-0001 and animal experiments, 5 mg BI 1569912 is

		considered as the clinically relevant dose at present (expected to show efficacy). Indeed, 5 mg BI 1569912 has been tested in 1447-0001 (SRD part and Bioavailability/Food effect part), 1447-0002 (MRD), and has been tested in 1447-0003 (Proof-of-clinical principle in patients), and is planned to be included in the 1447-0005 (Proof-of-clinical concept) trial. Thus, 5 mg was selected to investigate and compare single dose PK of BI 1569912 after administration in the morning and in the evening.
Rationale for change		Added a rationale for dose selection in Evening PK cohort
Section to be changed		4.1.3 Method of assigning subjects to treatment groups
Description of change		Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. <u>SRD and MD part:</u> The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects are allocated to a dose group, the following subjects will be allocated to one of the other dose groups. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. Because the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected. ~~SRD and MD part:~~ Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Numbers of the randomi~~z~~<u>s</u>ation list will be allocated to subjects with 'first come first served' principle. Subjects are then assigned to treatment according to the randomisation list. Evening PK part: The randomisation scheme will be provided to the trial site in advance. ~~According to the planned sample size, 2 cohorts are planned. Prior to the start of the trial, subjects willing to participate will be recruited to cohorts according to their temporal~~

		~~availability. In the morning of~~ On Day -1 (Visit 2), subjects will be allocated to treatment sequences prior to the first administration of trial medication on Day 1. For this purpose, numbers of the randomisation scheme will be allocated to the subjects. Subjects are then assigned to a treatment sequence according to the randomisation scheme. Once a subject number has been assigned, it cannot be reassigned to any other subject. To minimize the complexity of the trial procedures, the following randomisation process will be implemented for Evening PK part and a record of each step will be appropriately documented at the site. 1. On Day -1 (Visit 2), all 12 subjects will be randomly allocated to either of the treatment sequence (morning-evening (R-T) or evening-morning (T-R)) with 'first come first served' principle. 2. The treatment sequences (R-T or T-R) will be re-ordered with morning-evening part first. Subject numbers will be allocated based on the re-ordered treatment sequences on Day 1. Thus, the subject numbers will be in ascending order in each treatment sequence. The randomisation procedure is described in Section 7.6.
Rationale for change		Correction and clarification
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		For the assessment of laboratory parameters, blood and [redacted] samples will be collected by the trial site at the times indicated in the Flow chart after the subjects have fasted for at least 10 h (Except SRD part Day 1 post 4 h, Evening PK Visit 2a Day 2 and 3; post 4h, 24h, and 48 in Part I and Visit 2 Day 2 and 3; post 4h, 24h, and 48h in Part II).
Rationale for change		Correction and clarification
Section to be changed		5.2.4 Electrocardiogram
Description of change		Section number for Electrocardiogram was updated from "5.2.3.1" to "5.2.4". Section title "5.2.4.1 12-lead resting ECG" added.

		Subsequent section numbers after 5.2.4 within Section 5.2 were updated.
Rationale for change		Correction and clarification
Section to be changed		5.2.6.1.4 Adverse events of special interest
Description of change		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~~5~~.2.2.
Rationale for change		Updated based on the changes made to Section 5.2
Section to be changed		5.2.6.2.1 AE collection
Description of change		The only exceptions to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
Rationale for change		Typo correction
Section to be changed		6.2.2 Treatment Period
Description of change		In Evening PK part, subjects will be admitted to the trial site in the morning on~~of~~ D~~d~~ay -1 of Visit 2 and kept under close medical surveillance for at least 24 h following drug administration. On D~~d~~ay 3 of Visit 2 (treatment R) or D~~d~~ay 4 of Visit 2 (treatment T), subjects will be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. After the wash-out period, subjects will be admitted to the trial site again in the morning on~~of~~ D~~d~~ay -1 of Visit 2a (treatment R) and D~~d~~ay 1 of Visit 2a (treatment T) and kept under close medical surveillance for at least 24 h following the 2nd drug administration.
Rationale for change		Clarification
Section to be changed		7.3 Planned analyses

Description of change		Pharmacokinetic parameter evening analysis set (PKS-E): This set includes all subjects in the treated set (TS) who provide at least one primary or secondary PK endpoint value that was not excluded due to a protocol deviation relevant to the statistical 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-E, even if he contributes only one PK parameter value for one period to the statistical assessment. This analysis set only includes subjects from D~~d~~ose G~~g~~roup 7 and is the base for the evaluation of evening dose administration (evening PK). Descriptive and model-based analyses of PK parameters will be based on the PKS-E.
Rationale for change		Typo correction
Section to be changed		7.3.4 Safety analyses
Description of change		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~~5~~.1) and other significant AEs (according to ICH E3) will be listed separately.
Rationale for change		Updated based on the changes made to Section 5.2
Section to be changed		7.6 Randomisation
Description of change		Evening PK part: The subjects will be randomly allocated to the 2 treatment sequences (~~T-R or~~ R-T or T-R) in a 1:1 ratio. The block size will be documented in the CTR.
Rationale for change		Correction and clarification
Section to be changed		Entire Section
Description of change		Unified to use "Randomise" across this protocol instead of "Randomize"
Rationale for change		Correction

APPROVAL / SIGNATURE PAGE

Document Number: c33487150 **Technical Version Number:3.0**

Document Name: clinical-study-protocol-version-3

Title: Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	07 Sep 2023 07:40 CEST
Approval-Clinical Program Leaders	[redacted]	07 Sep 2023 10:57 CEST
Author-Trial Statistician	[redacted]	10 Sep 2023 21:22 CEST
Verification-Paper Signature Completion	[redacted]	11 Sep 2023 00:12 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**