Clinical Trial Protocol

	Document Number:	**c26985010-03**
BI Trial No.	1289-0057	
BI Investigational Medicinal Products	BI 409306, BI 425809	
Title	A randomized, placebo controlled, double-blind, double-dummy three-way cross over trial to investigate the effect of BI 409306, BI 425809 and lamotrigine on ketamine-induced cognitive deficits in healthy male subjects	
Lay Title	A study in healthy men to test whether BI 409306, BI 425809 or lamotrigine can reverse the memory problems caused by ketamine	
Clinical Phase	I	
Clinical Trial Lead	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigators	1. [redacted] Phone/Fax: [redacted] 2. [redacted] Phone/Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 12 November 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	30 January 2020
Revision date	12 November 2021
BI trial number	1289-0057
Title of trial	A randomized, placebo controlled, double-blind, double-dummy three-way cross over trial to investigate the effect of BI 409306, BI 425809 and lamotrigine on ketamine-induced cognitive deficits in healthy male volunteers
Principal Investigators	1. [redacted] 2.
Trial sites	1. [redacted] 2.
Clinical phase	I
Trial rationale	To investigate the effect of BI 409306 (a PDE 9 inhibitor in clinical development) and BI 425809 (a GlyT1 inhibitor in clinical development) on ketamine-induced cognitive deficits. Lamotrigine that has been reported to attenuate ketamine-induced cognitive deficits will be used as a technical control.
Trial objective	To investigate if and to what extent BI 409306, BI 425809 and lamotrigine attenuate ketamine induced cognitive deficits
Trial design	Randomized, placebo controlled, double-blind, double-dummy, three-way cross over trial
Trial endpoints	*Primary endpoint:* • PAL Total Errors Adjusted (PALTEA28) on ketamine *Secondary endpoints:* • SWM Between Errors (SWMBE468) on ketamine • RVP A' Prime (RVPA) on ketamine
Number of subjects **total entered** **each treatment**	 N = 36 N = 36 (placebo; R) N = 24 (each active treatment; T1, T2 and T3)

Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, Age of 18 to 55 years (inclusive), Body mass index (BMI) of 18.5 to 32 kg/m^2 (inclusive), CYP2C19 non-poor metabolizers, Normative performance within 2 SD (compared against an age matched sample) on CANTAB PALTEA28 at screening V1 and V2 (pre-ketamine), Ketamine-responders (defined as ≥ 10 errors change on CANTAB PALTEA28 from baseline (pre-ketamine) to ketamine challenge (on ketamine) at screening V2
Test product 1	Lamotrigine, [redacted] 100 mg tablets
Dose	300 mg
Mode of admin.	Oral with 240 mL of water after a light snack
Test product 2	BI 409306, [redacted] tablets
Dose	[redacted]
Mode of admin.	Oral with 240 mL of water after a light snack
Test product 3	BI 425809, [redacted] tablets
Dose	[redacted]
Mode of admin.	Oral with 240 mL of water after a light breakfast
Reference product 1	Matching placebo to lamotrigine
Dose	NA
Mode of admin.	Oral with 240 mL of water after a light snack
Reference product 2	Matching placebo to [redacted] BI 409306 tablets
Dose	NA
Mode of admin.	Oral with 240 mL of water after a light snack
Reference product 3	Matching placebo to [redacted] BI 425809 tablets
Dose	NA
Mode of admin.	Oral with 240 mL of water after a light breakfast
Challenge agent	Ketamine hydrochloride, [redacted], 500 mg/10 ml
Dose	0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% (or 0.00073 mg/kg/min) every 15 min)
Mode of admin.	Intravenous 1-minute bolus followed by an intravenous infusion over 89 minutes

Duration of treatment	*Screening:* • SCR KET: Intravenous ketamine infusion (administered as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 minutes (reduced by 10% every 15 min))* *4 Treatments**:* **Lamotrigine Treatment (T1)** = Ketamine + 300 mg Lamotrigine + Placebo to BI 409306 + Placebo to BI 425809: • Day 1 of Period 1 or 2 or 3 o Single dose of 300 mg lamotrigine, 2h prior to ketamine infusion o Single dose of placebo to [redacted] BI 409306, 2h prior to ketamine infusion o Single dose of placebo to [redacted] BI 425809, 5h prior to ketamine infusion o Intravenous ketamine infusion (administered as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min))* **BI 409306 [redacted] Treatment (T2)** = Ketamine + Placebo to Lamotrigine + [redacted] BI 409306 + Placebo to BI 425809: • Day 1 of Period 1 or 2 or 3 o Single dose of placebo to lamotrigine, 2h prior to ketamine infusion o Single dose of [redacted] BI 409306, 2h prior to ketamine infusion o Single dose of placebo to [redacted] BI 425809, 5h prior to ketamine infusion o Intravenous ketamine infusion (administered as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min))* **BI 425809 [redacted] Treatment (T3)** = Ketamine + Placebo to Lamotrigine + Placebo to BI 409306 + [redacted] BI 425809: • Day 1 of Period 1 or 2 or 3 o Single dose of placebo to lamotrigine, 2h prior to ketamine infusion o Single dose of placebo to [redacted] BI 409306, 2h prior to ketamine infusion o Single dose of [redacted] BI 425809, 5h prior to ketamine infusion o Intravenous ketamine infusion (administered as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min))* **Placebo Treatment (R)** = Ketamine + Placebo to Lamotrigine + Placebo to BI 409306 + Placebo to BI 425809: • Day 1 of Period 1 or 2 or 3 o Single dose of placebo to lamotrigine, 2h prior to ketamine infusion o Single dose of placebo to [redacted] BI 409306, 2h prior to ketamine infusion o Single dose of placebo to [redacted] BI 425809, 5h prior to ketamine infusion o Intravenous ketamine infusion (administered as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min))* * *infusion can be prolonged for a maximum of 15 min, i.e. to 105 min in total, in case of delays from the planned time of the assessments on ketamine, or terminated earlier if the planned assessments on ketamine are completed or any test drops out*

	*** each subject will receive R treatment and 2 of 3 randomly allocated T1 or T2 or T3; each treatment period is separated by a washout of at least 11 days between study drug administrations*
Statistical methods	The differences between Lamotrigine and Placebo as well as BI 409306 and Placebo, and BI 425809 and Placebo will be evaluated for the primary endpoint based on a linear mixed effects model. The statistical model will include fixed effects for treatment, sequence, period and baseline values (pre and on ketamine at Visit 2), whereas "subject within sequence" will be included as a random effect. Formal hypotheses tests will not be performed, instead the adjusted mean differences and their 95% confidence intervals will be shown. Descriptive statistics will be calculated for all endpoints.

FLOW CHART A (SUMMARY)

Period	Visit	Day	Planned time (relative to Drug administration (1) [h:min]	Approximate clock time of actual day [hh:min]	Event and comment	Safety laboratory[26]	Targeted physical examination[29]	DSST, MOAA/S, CADSS, SFST[30]	C-SSRS[31]	CANTAB (RVP, SWM, PAL)[8,19]	[redacted]	12-lead ECG[32]	Continuous ECG monitoring[32]	Vital signs (BP, PR, SaO_2)[24]	AEs and concomitant therapy[33]
Screening[6]	1	-28 to -9			**Screening Examination**[1]	x[1]		x[1]	x[1,31]	x[1]		x[1]		x[1]	
	2	-22 to -3	-12:00	20:00[5]	Admission to trial site[9] for **Screening Ketamine Challenge**[2]	x[7]									x
		-21 to -2	-2:00	06:00[2]			x[2]					x[2]		x[2]	x[2]
			-0:30	07:30	Light breakfast[10]										
			0:00[8]	***08:00***	240 mL fluid intake										
			2:55	10:55	Light snack (clear liquid)[10]										
			3:00	***11:00***	240 mL fluid intake										
			3:25	11:25	[redacted]										
			3:36	11:36	[redacted]										
			4:20	12:20	*CANTAB*[19], [redacted]					⊢					
			4:55	12:55						⊢		x		x[14]	x
			5:00	***13:00***	***Start of ketamine infusion***[11]								⊢	⊢[25]	
			5:06	13:06	*CANTAB*[19], [redacted]					⊢			|	|	x
			5:26	13:26						⊢			|	|	
			5:40	13:40	[redacted]					⊢			|	|	x
			6:00	14:00									|	|	
			6:20	14:20	[redacted]								|	|	x
			6:30	***14:30***	***Stop of ketamine infusion***[12]								|	|	
			7:00	15:00								x	|	|	x
			7:30	15:30	Confirmation of recovery[13], 240 mL fluid intake, thenafter lunch								⊢	⊢	x
			10:00	18:00										x	x
			11:00	19:00	Dinner										
		-20 to -1	24:00	08:00	Breakfast (voluntary)[15], discharge from trial site[16]		x	x	x			x		x	x
1/2/3	3/4/5	-1	-12:00	20:00[5]	Admission to trial site[9]	x[7]									x
		1	-2:00	06:00[3]	Allocation to treatment[3] (visit 3 only)		x[3]		x[3]			x[3]		x[3]	x[3]
			-0:30	07:30	Light breakfast[10]										
			0:00	***08:00***	***Drug administration (1)***[17], 240 mL fluid intake										
			0:30	08:30											
			1:00	09:00										x	x
			2:00	10:00											

Period	Visit	Day	Planned time (relative to Drug administration (1)) [h:min]	Approximate clock time of actual day [hh:min]	Event and comment	Safety laboratory[26]	Targeted physical examination[29]	DSST, MOAA/S, CADSS, SFST[30]	C-SSRS[31]	CANTAB (RVP, SWM, PAL)[8,19]	[redacted]	[redacted]	[redacted]	[redacted]	12-lead ECG[32]	Continuous ECG monitoring[32]	Vital signs (BP, PR, SaO_2)[24]	AEs and concomitant therapy[33]
			2:55	10:55	Light snack (clear liquid)[10]													
1/2/3 (3 identical periods with a washout of at least 11 days)	3/4/5	1	***3:00***	***11:00***	***Drug administration (2)***[18], 240 mL fluid intake						[redacted]							
			3:25	11:25	[redacted]													
			3:36	11:36														
			4:00	12:00													x	x
			4:20	12:20	*CANTAB*[19], [redacted]					⊢								
			4:30	12:30						⊢								
			4:55	12:55						⊢					x		x[14]	x
			5:00	***13:00***	***Start of ketamine infusion***[11]											⊢	⊢[25]	
			5:06	13:06	*CANTAB*[19], [redacted]					⊢						|	|	x
			5:26	13:26						⊢						|	|	
			5:40	13:40	[redacted]					⊢						|	|	x
			6:00	14:00												|	|	
			6:20	14:20	[redacted]											|	|	x
			6:30	***14:30***	***Stop of ketamine infusion***[12]											|	|	
			7:00	15:00											x	|	|	x
			7:30	15:30	Confirmation of recovery[13], 240 mL fluid intake, thenafter lunch											⊢	⊢	x
			8:00	16:00														
			9:00	17:00														
			10:00	18:00											x		x	x
			11:00	19:00	Dinner													
		2	24:00	08:00	Breakfast (voluntary)[15]	x											x	x
			27:00	11:00	Discharge from trial site[16]		x	x	x						x		x	x
		4			Follow-Up Phone call													x
		6			Follow-Up Phone call													x
		9			Follow-Up Phone call													x
EoT	6	12 to 19			End of trial (EoT) examination[4]	x	x		x						x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. For details of **screening procedures** at ***Screening Examination (V1)***, refer to Flow Chart B.
2. The time is approximate; the procedure is to be performed and completed before light breakfast, within 2 h prior to planned time 0:00. For details of **screening procedures** at ***Screening Ketamine Challenge (V2)***, refer to Flow Chart C.
3. The time is approximate; the procedure is to be performed and completed before light breakfast, within 2 h prior to *Drug administration (1)*. For details of **procedures** at each ***Treatment Day (V3, V4, V5)***, refer to Flow Chart D.
4. *End of Trial (EoT) Examination* includes physical examination (incl. targeted examination), visual acuity test, C-SSRS, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. For details, refer to Section 6.2.3.

5. The time is approximate; admission is to be performed no later than 10 h prior to planned time 0:00. At discretion of the investigator or designee, admission on the next morning no later than 2 h prior to planned time 0:00 is possible.
6. *Screening period* consists of *Screening Examination (V1)* and (if applicable) *Screening Ketamine Challenge (V2)*. Only subjects who have already passed all applicable eligibility criteria at *Screening Examination* (incl. confirmation on CYP2C19 status, except not yet determined response to ketamine) will be invited to *Screening Ketamine Challenge* that has to be scheduled on a different day. For details regarding *screening period*, refer to Section 6.2.1.
7. Only urine drug screening and alcohol breath test will be done at this time.
8. **CANTAB tests**, [redacted] at *Screening Ketamine Challenge* have to occur time-matched to these assessments in each *treatment period*. Therefore, planned time 0:00 at *Screening Ketamine Challenge (V2)* should equal planned time 0:00 relative to *Drug administration (1)* on *Day 1 (V3, V4 and V5)*. *Before ketamine infusion,* the planned time for these tests should be adhered as closely as possible. *During ketamine infusion,* time intervals between these tests should be minimized, i.e. if any test completed earlier or dropped out, the next test should start straight away. The assessments will occur in environmentally controlled rooms, only one subject per room is allowed.
9. SARS-CoV-2 PCR test will be performed within 72 h prior to admission to trial site. For details, refer to Appendix 10.7.
10. For details of light breakfast and light snack composition, refer to Section 4.1.4.
11. If ketamine infusion is interrupted for a technical reason, the reason to be eliminated as soon as possible, before start of a new test, after the ongoing test has been completed (if applicable). An interruption of maximum of 15 min for technical reasons is allowed. For details, refer to Section 4.1.2.
12. Ketamine infusion can be prolonged for a maximum of 15 min, i.e. to 105 min in total, in case delays from the planned time occur for CANTAB tests, [redacted]; or terminated earlier, if the above assessments on ketamine are completed (or any test drops out) [redacted]
13. Confirmation of recovery from ketamine must be confirmed via criteria of recovery from ketamine after a minimum of 60 min of recovery follow up. For details, refer to Section 5.2.5.6.
14. Vital signs at 5 min prior to start of ketamine infusion include recording of respiratory rate and effort, and will serve as baseline for confirmation of recovery from ketamine. For details, refer to Section 5.2.5.6
15. If several actions are indicated at the same time point, the intake of meal will be the last action.
16. Discharge after assessment of fitness by the investigator or designee.
17. **Drug administration (1) at planned time 0:00:** BI 425809 or Placebo to BI 425809. For details, refer to Section 4.1.4.
18. **Drug administration (2) at planned time 3:00:** BI 409306 + Placebo to Lamotrigine, or Lamotrigine + Placebo to BI 409306, or Placebo to BI 409306 + Placebo to Lamotrigine. For details, refer to Section 4.1.4.
19. The selected tests from the **CANTAB test battery** will be done with a 4 min break in between each test in the following sequence: **Rapid Visual Information Processing (RVP)**, **Spatial Working Memory (SWM)**, **Paired Associates Learning (PAL)**. For details, refer to Section 5.4.1.

[redacted]

24. For details of vital signs evaluation, refer to Section 5.2.2, Flow Chart C and Flow Chart D.
25. From start of ketamine infusion until confirmation of recovery from ketamine, oxygen saturation (SaO_2) will be monitored continuously. For other details of vital signs recording, refer to Flow Chart C and Flow Chart D.
26. For details of safety laboratory evaluation, refer to Section 5.2.3.

[redacted]

29. Targeted physical examination includes skin inspection for signs of rash, check for lymphadenopathy and neurological examination (mental status, motor examination, reflexes, sensory, gait and cranial nerves).
30. For details of DSST, MOAA/S, CADSS and SFST, refer to Section 5.2.5.5 and Appendices 10.3, 10.4, 10.5 and 10.6.
31. C-SSRS will be administered at Screening Examination (V1) using the 'screening/baseline' version. After Screening Examination, the assessment 'since last visit' will be performed at each time point as per the Flow Chart above. For details, refer to Section 5.2.6.1.7 and Appendix 10.2.
32. For details of 12-lead ECG and Continuous ECG monitoring, refer to Section 5.2.4.

33. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.

FLOW CHART B (SCREENING EXAMINATION)

Day -28 to -9 (Visit 1)

Planned time [h:min]	Approximate clock time [hh:min]	Event(s)	Comment(s)
		Informed Consent	Subject must be informed and written informed consent obtained prior to starting any screening procedures
		Demographics	
		Medical History	
		Smoking and Alcohol History	
		Concomitant Medications	
		Questioning for COVID-19	
		Body Temperature	
		Body Height and Weight	
		Physical Examination	
		Vital Signs	BP and PR incl. orthostatic testing, SaO_2
		DSST, MOAA/S, CADSS, SFST	
		C-SSRS 'screening/baseline'	
		Review Inclusion Exclusion Criteria	*If subject remains eligible based on above assessments, proceed with additional testing indicated below.*
		Visual Acuity Test	For details, refer to Section 5.2.5.4.
		12-lead ECG	
		CANTAB RVP	
		CANTAB SWM	
		CANTAB PAL	*In the end of PAL, eligibility results will be displayed*
		[redacted]	
		Review Inclusion Exclusion Criteria	*If subject remains eligible based on above assessments, proceed with additional testing indicated below.*
		Drug and Tobacco Screening (urine)	
		Safety Laboratory (blood, urine)	Hematology, Biochemistry, Hormones, Coagulation, Urinalysis, Infectious Serology
		SARS CoV-2 PCR Test (nasal swab sample)	
		PGx sampling for CYP2C19 (blood)	For details, refer to Section 5.6.1.
		Review Inclusion Exclusion Criteria *(after results of Safety Laboratory, SARS CoV-2 PCR test and confirmation of CYP2C19 status are available)*	*If subject remains eligible based on above assessments, invite to Screening Ketamine Challenge (V2) that will be scheduled on a different day.*

FLOW CHART C (SCREENING KETAMINE CHALLENGE)

Day -21 to -2 (Visit 2)

Planned time* [h:min]	Approximate clock time [hh:min]	Event(s)	Comment(s)
-12:00[1]	20:00[1]	**Admission to trial site**[2] Questioning for AEs and concomitant therapy Questioning for COVID-19 Body Temperature Drug Screening (urine) Alcohol Breath Test	[1] The time is approximate; admission is to be performed no later than 10 h prior to planned time 0:00. At discretion of the investigator or designee, admission on the next morning no later than 2 h prior to planned time 0:00 is possible. [2] SARS-CoV-2 PCR test will be performed shortly (within 72 h) prior to admission
-2:00[1]	06:00[1]	Questioning for AEs and concomitant therapyC-SSRS 'since last visit' Targeted Physical Examination[2] Vital Signs (BP, PR, SaO_2) 12-lead ECG [redacted]	[1] the time is approximate; the procedures are to be performed and completed before light breakfast, within 2 h prior to PT 0:00 [2] incl. skin inspection for signs of rash, check for lymphadenopathy and neurological examination
-0:30	07:30	Light breakfast	
0:00	08:00	240 mL fluid intake	
2:55	10:55	Light snack (clear liquid)	
3:00	11:00	240 mL fluid intake	
3:25	11:25	[redacted]	
	11:35	1 min break	
3:36	11:36	[redacted]	
	11:49	1 min break	
	11:50	[redacted]	
	11:55	[redacted]	
	12:00	1 min break	
	12:01	[redacted]	
	12:12	1 min break	
	12:13	[redacted]	
	12:19	1 min break	
4:20	12:20	**CANTAB RVP**	
	12:27	[redacted]	
	12:31	**CANTAB SWM**	
	12:37	[redacted]	
	12:41	**CANTAB PAL** **Review In-/ Exclusion Criteria**	*in the end of PAL, eligibility results will be displayed*
	12:53	2 min break	
4:55	12:55	Questioning for AEs Vital Signs (BP, PR, SaO_2 +Resp.Rate/Effort) 12-lead ECG	instructing study subjects before ketamine infusion; [redacted]
4:59	12:59	[redacted]	[redacted]
5:00[1]	13:00[1]	*Start of ketamine infusion*[1] Start of continuous ECG and SaO_2 monitoring	[1] if ketamine infusion is interrupted for a technical reason, the reason to be eliminated as soon as possible, before start of a new test, after the ongoing test has been completed (if applicable)
	13:03	[redacted] Questioning for AEs[1]	[redacted] right before CANTAB RVP

		Vital Signs (BP, PR, SaO_2)[1]	
5:06	13:06	**CANTAB RVP**	
	13:13	[redacted] Vital Signs (BP, PR, SaO_2)[1]	[redacted] right before CANTAB SWM
	13:17	**CANTAB SWM**	
	13:23	[redacted] Vital Signs (BP, PR, SaO_2)[1] PK blood (ketamine)[1]	[redacted] right before CANTAB PAL
	13:27	**CANTAB PAL** **Review In-/ Exclusion Criteria**	*in the end of PAL, eligibility results will be displayed*
	13:39	Questioning for AEs Vital Signs (BP, PR, SaO_2)	
5:40	13:40	[redacted]	
	13:53	Vital Signs (BP, PR, SaO_2)	
	13:54	[redacted]	
	13:57	[redacted]	
	14:00	Vital Signs (BP, PR, SaO_2) [redacted]	
	14:01	[redacted]	
	14:12	Vital Signs (BP, PR, SaO_2)	
	14:13	[redacted]	
	14:19	Questioning for AEs	
6:20	14:20	[redacted]	
6:30[1]	14:30[1]	Vital signs (BP, PR, SaO_2) [redacted] *Stop of ketamine infusion*[1] Stop of continuous ECG and SaO_2 monitoring	[1] can be prolonged for a maximum of 15 min, in case delays from PT occur for CANTAB, [redacted] or terminated earlier, if the above tests are completed (or any test drops out)
6:45	14:45	Vital Signs (BP, PR, SaO_2)	
7:00	15:00	Questioning for AEs Vital Signs (BP, PR, SaO_2) 12-lead ECG	
7:15	15:15	Vital Signs (BP, PR, SaO_2)	
7:30[1]	15:30[1]	Questioning for AEs Vital Signs (BP, PR, SaO_2) *Confirmation of recovery from ketamine*[2,3] 240 mL fluid intake	[1] a minimum of 60 min of recovery follow up [2] as per Criteria of recovery from ketamine [3] lunch will be served after confirmation of recovery
10:00	18:00	Questioning for AEs Vital Signs (BP, PR)	dinner will be served in the evening
24:00[1]	08:00[1]	Questioning for AEs Vital Signs (BP, PR) 12-lead ECG C-SSRS 'since last visit' DSST, MOAA/S, CADSS, SFST Targeted Physical Examination[2] **Discharge from trial site**[3,4]	[1] Day -20 to -1 at V2. The time is approximate; the procedures to be performed and completed ± 2 h. [2] incl. skin inspection for signs of rash, check for lymphadenopathy and neurological examination [3] after confirmation of fitness by the investigator [4] breakfast will be served before discharge

***** planned time 0:00 at *Screening Ketamine Challenge (V2)* should equal planned time 0:00 relative to *Drug administration (1)* on *Day 1 (V3, V4 and V5)*.

FLOW CHART D (TREATMENT KETAMINE CHALLENGE)

Day 1 of each Treatment Period (Visits 3, 4 and 5)

Planned time* [h:min]	Approximate clock time [hh:min]	Event(s)	Comment(s)
-12:00[1]	20:00[1]	**Admission to trial site**[1,2] Questioning for AEs and concomitant therapy Questioning for COVID-19 Body Temperature Drug Screening (urine) Alcohol Breath Test	[1] Day -1 at V3, V4 and V5. The time is approximate; admission is to be performed no later than 10 h prior to first study drug administration. At discretion of the investigator or designee, admission in the morning of Day 1 no later than 2 h prior to planned time 0:00 is possible. [2] SARS-CoV-2 PCR test will be performed shortly (within 72 h) prior to admission
-2:00[1]	06:00[1]	**Allocation to treatment (only at V3)** Questioning for AEs C-SSRS 'since last visit' Targeted Physical Examination[2] Vital Signs (BP, PR, SaO_2) 12-lead ECG [redacted]	[1] the time is approximate; the procedures are to be performed and completed before light breakfast, within 2 h prior to first study drug administration [2] incl. skin inspection for signs of rash, check for lymphadenopathy and neurological examination
-0:30	07:30	Light breakfast	
0:00	08:00	**Drug administration (1)**[1] 240 mL fluid intake	[1] **BI 425809** or **Placebo to BI 425809**
1:00	09:00	Questioning for AEs Vital Signs (BP, PR) P[redacted]	
2:00	10:00	[redacted]	
2:55	10:55	Light snack (clear liquid)	
3:00	11:00	[redacted] **Drug administration (2)**[1] 240 mL fluid intake	[1] **BI 409306 + Placebo to Lamotrigine**, or **Lamotrigine + Placebo to BI 409306**, or **Placebo to BI 409306 + Placebo to Lamotrigine**
3:25	11:25	[redacted]	
	11:35	1 min break	
3:36	11:36	[redacted]	
	11:49	1 min break	
	11:50	[redacted]	
	[redacted]	[redacted]	
	12:00	Questioning for AEs Vital Signs (BP, PR) [redacted]	
	12:01	[redacted]	
	12:12	1 min break	
	12:13	[redacted]	
	12:19	1 min break	
4:20	12:20	**CANTAB RVP**	
	12:27	[redacted]	[redacted]
	12:31	**CANTAB SWM**	
	12:37	[redacted]	

	12:41	**CANTAB PAL**	
	12:53	2 min break	
4:55	12:55	Questioning for AEs Vital Signs (BP, PR, SaO_2 +Resp.Rate/Effort) 12-lead ECG [redacted]	instructing study subjects before ketamine infusion; [redacted]
4:59	12:59	[redacted]	[redacted]
5:00[1]	13:00[1]	*Start of ketamine infusion*[1] Start of continuous ECG and SaO_2 monitoring	[1] if ketamine infusion is interrupted for a technical reason, the reason to be eliminated as soon as possible, before start of a new test, after the ongoing test has been completed (if applicable)
	13:03	[redacted] Questioning for AEs[1] Vital Signs (BP, PR, SaO_2)[1]	[1] [redacted], right before CANTAB RVP
5:06	13:06	**CANTAB RVP**	
	13:13	[redacted] Vital Signs (BP, PR, SaO_2)[1]	[redacted], right before CANTAB SWM
	13:17	**CANTAB SWM**	
	13:23	[redacted] Vital Signs (BP, PR, SaO_2)[1] [redacted]	[redacted], right before CANTAB PAL
	13:27	**CANTAB PAL**	
	13:39	Questioning for AEs Vital Signs (BP, PR, SaO_2)	
5:40	13:40	[redacted]	
	13:53	Vital Signs (BP, PR, SaO_2)	
	13:54	[redacted]	
	13:57	[redacted]	
	14:00	Vital Signs (BP, PR, SaO_2) [redacted]	
	14:01	[redacted]	
	14:12	Vital Signs (BP, PR, SaO_2)	
	14:13	[redacted]	
	14:19	Questioning for AEs Vital Signs (BP, PR, SaO_2)	
6:20	14:20	[redacted]	
6:30[1]	14:30[1]	Vital signs (BP, PR, SaO_2) [redacted] *Stop of ketamine infusion*[1] Stop of continuous ECG and SaO_2 monitoring	[1] can be prolonged for a maximum of 15 min, in case delays from PT occur for CANTAB, [redacted] or terminated earlier, if the above tests are completed (or any test drops out)
6:45	14:45	Vital Signs (BP, PR, SaO_2)	
7:00	15:00	Questioning for AEs Vital Signs (BP, PR, SaO_2) 12-lead ECG [redacted]	
7:15	15:15	Vital Signs (BP, PR, SaO_2)	
7:30[1]	15:30[1]	Questioning for AEs Vital Signs (BP, PR, SaO_2) *Confirmation of recovery from ketamine*[2,3] 240 mL fluid intake	[1] a minimum of 60 min of recovery follow up [2] as per criteria of recovery from ketamine [3] lunch will be served after confirmation of recovery
8:00	16:00	[redacted]	
9:00	17:00	[redacted]	

10:00	18:00	Questioning for AEs Vital Signs (BP, PR) 12-lead ECG	dinner will be served in the evening
24:00[1]	08:00[1]	Questioning for AEs Vital Signs 12-lead ECG Safety Laboratory (blood, urine)[2,3]	[1] Day 2 at V3, V4 and V5. The time is approximate; the procedures to be performed and completed ± 2 h. [2] Hematology, Biochemistry, Coagulation, Urinalysis [3] breakfast will be served after blood sampling
27:00[1]	11:00[1]	Questioning for AEs Vital Signs C-SSRS 'since last visit' DSST, MOAA/S, CADSS, SFST Targeted Physical Examination[2] **Discharge from trial site**[3]	[1] time is approximate; the procedures to be performed and completed within 2 h prior to discharge [2] incl. skin inspection for signs of rash, check for lymphadenopathy and neurological examination [3] after confirmation of fitness by the investigator, and at least 24h after the last study drug administration

***** planned time relative to *Drug administration (1)* on *Day 1 (V3, V4 and V5)*.

TABLE OF CONTENTS

[redacted]

[redacted]

ABBREVIATIONS

AD	Alzheimer disease
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
APS	Attenuated Psychosis Syndrome
[redacted]	[redacted]
AST	Aspartate transaminase
[redacted]	[redacted]
[redacted]	[redacted]
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CADSS	Clinician Administered Dissociative States Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CIAS	Cognitive impairment in schizophrenia
[redacted]	[redacted]
[redacted]	[redacted]
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
C-SSRS	Columbia Suicidal Severity Rating scale
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DDI	Drug drug interaction
DILI	Drug induced liver injury
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSST	Digit Symbol Substitution Test
[redacted]	[redacted]
ECG	Electrocardiography

eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
[redacted]	[redacted]
EoT	End of trial
ERP	Event-Related Potential
ET	Eye tracking
FEP	First episode of psychosis
FU	Follow-up
GCP	Good Clinical Practice
GlyT1	Glycine transporter 1
HLH	Hemophagocytic Lymphohistiocytosis
HR	Heart rate
HV	Hyperventilation
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
ISF	Investigator site file
i.v.	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LTP	Long term potentiation
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Mismatch-Negativity
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
PAL	Paired Associates Learning
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PDE9	Phosphodiesterase-9
P-gp	P-glycoprotein
[redacted]	[redacted]
PM	Poor metaboliser

PR	Pulse rate
qd	Quaque die, once daily
[redacted]	[redacted]
qPCR	Quantitative polymerase chain reaction
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
R_{max}	Maximum rate of urinary excretion
RVP	Rapid Visual Information Processing
SAE	Serious adverse event
SaO_2	Oxygen saturation
SCR	Screening
SD	Standard deviation
SFST	Standardized Field Sobriety Test
SOA	Stimulus onset asynchrony
SOP	Standard operating procedure
SPL	Sound pressure level
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
SWM	Spatial Working Memory
T	Test product or treatment
TMF	Trial master file
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TSAP	Trial statistical analysis plan
WHO	World Health Organization
XTC	Ecstasy

1. INTRODUCTION

BI 409306 is a [redacted] that is being developed for relapse prevention in patients [redacted]), and for the prevention of [redacted]) in subjects with [redacted].

BI 425809 is a [redacted] under development for treatment of [redacted] in adult patients [redacted] also referred to as [redacted]

1.1 MEDICAL BACKGROUND

[redacted] is a chronic, severe, and disabling brain disorder affecting both men and women. For the majority of patients, the [redacted] and [redacted] symptoms of [redacted] preceded [redacted] by many months and years. In the course of the [redacted], most patients experience multiple relapses, which are characterized by [redacted] has been shown to be a major determinant of poor functional outcome [R14-3766]. The c[redacted] i[redacted] seen in [redacted] tend to be severe, leading to functional disability for life, and there is no pharmacological treatment of [redacted]. Existing treatment options for [redacted]) are primarily efficacious in treating [redacted] and have limited, if any, efficacy for the prevention o[redacted] [redacted] No pharmacologic therapies have been approved to delay or prevent a first [redacted], and none are indicated for the symptomatic treatment of the [redacted] seen in patients [redacted]

[redacted] is characterized by abnormalitie [redacted] [R13-4521]. These abnormalities are hypothesized to lead to [redacted] activation triggers a cascade of intracellular, [redacted] through elevation of [redacted] and [redacted] and manifestation of [redacted] [R10-5092], [R10-5102].

[redacted] with the highest affinity of [redacted] and is highly [redacted]. Therefore, it is likely to be a significant determinant of intracellular [redacted]. In addition, increasing evidence suggests that [redacted] may play a key role in [redacted] individuals with [redacted] [R15-3327], [R15-1457].

[redacted] may be a proximal cause of [redacted] seen in those who [redacted] presumably via [redacted] [R15-1457]. Consequently, [redacted] should restore [redacted] and thus [redacted] and translate into [redacted] via strengthening of [redacted]. Moreover, based on mode-of-action and on preclinical

data in a [redacted] model, [redacted] also represents a rational approach for improvement and potentially normalization of those [redacted] leading to the [redacted] even [redacted] [c01694347][n00270327].

[redacted] properties of BI 409306 have been demonstrated in [redacted] and signal of clinical [redacted] Treatment with BI 409306 is expected to [redacted] in subjects [redacted] and to reduce the [redacted].

[redacted] aims at improving [redacted] in patients with [redacted] thereby leading to improvement of [redacted]

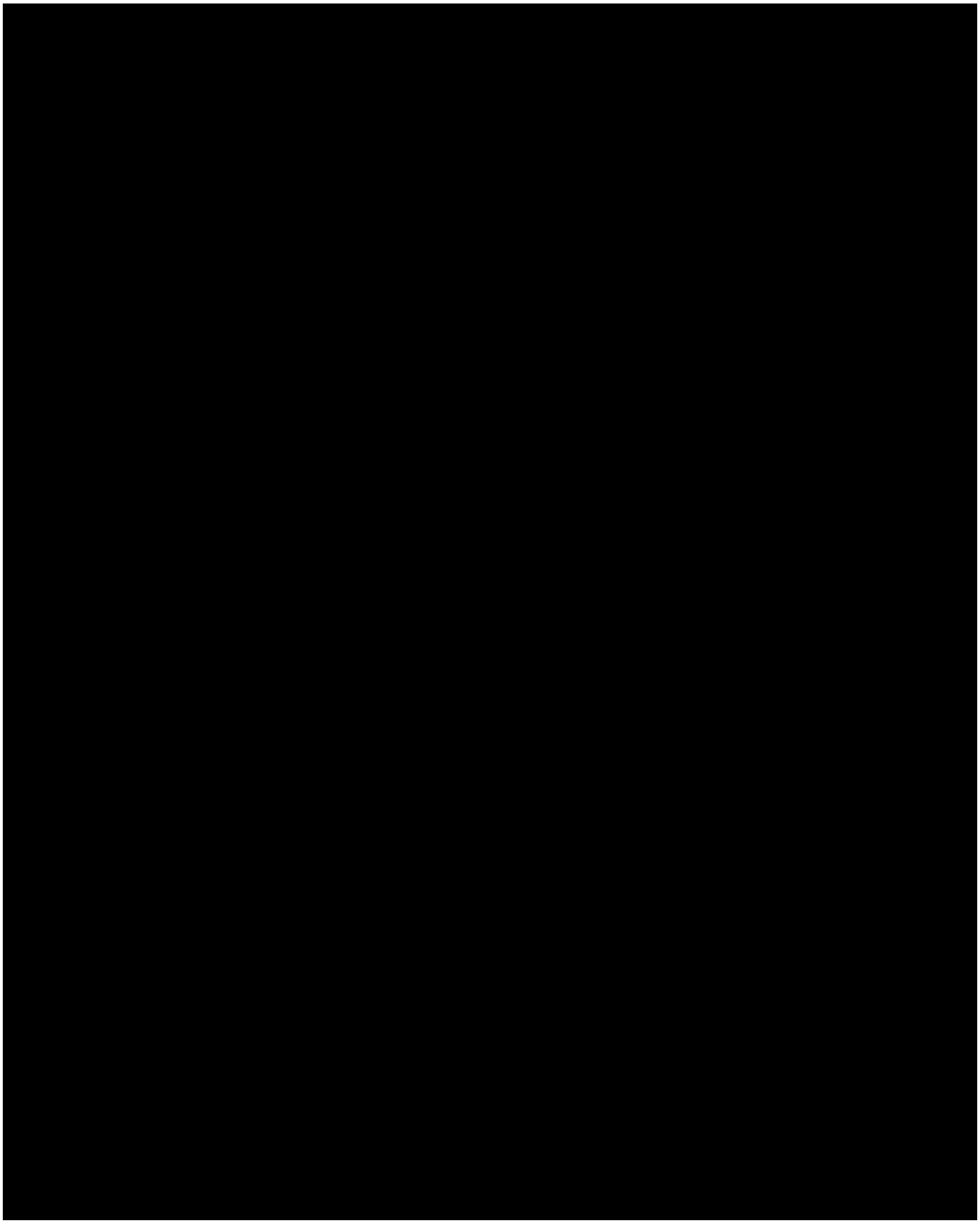
Results from preclinical studies with BI 425809 demonstrated [redacted]. Currently in Phase [redacted], treatment with BI 425809 resulted in [redacted] in patients [redacted]

1.2 DRUG PROFILE

[redacted]

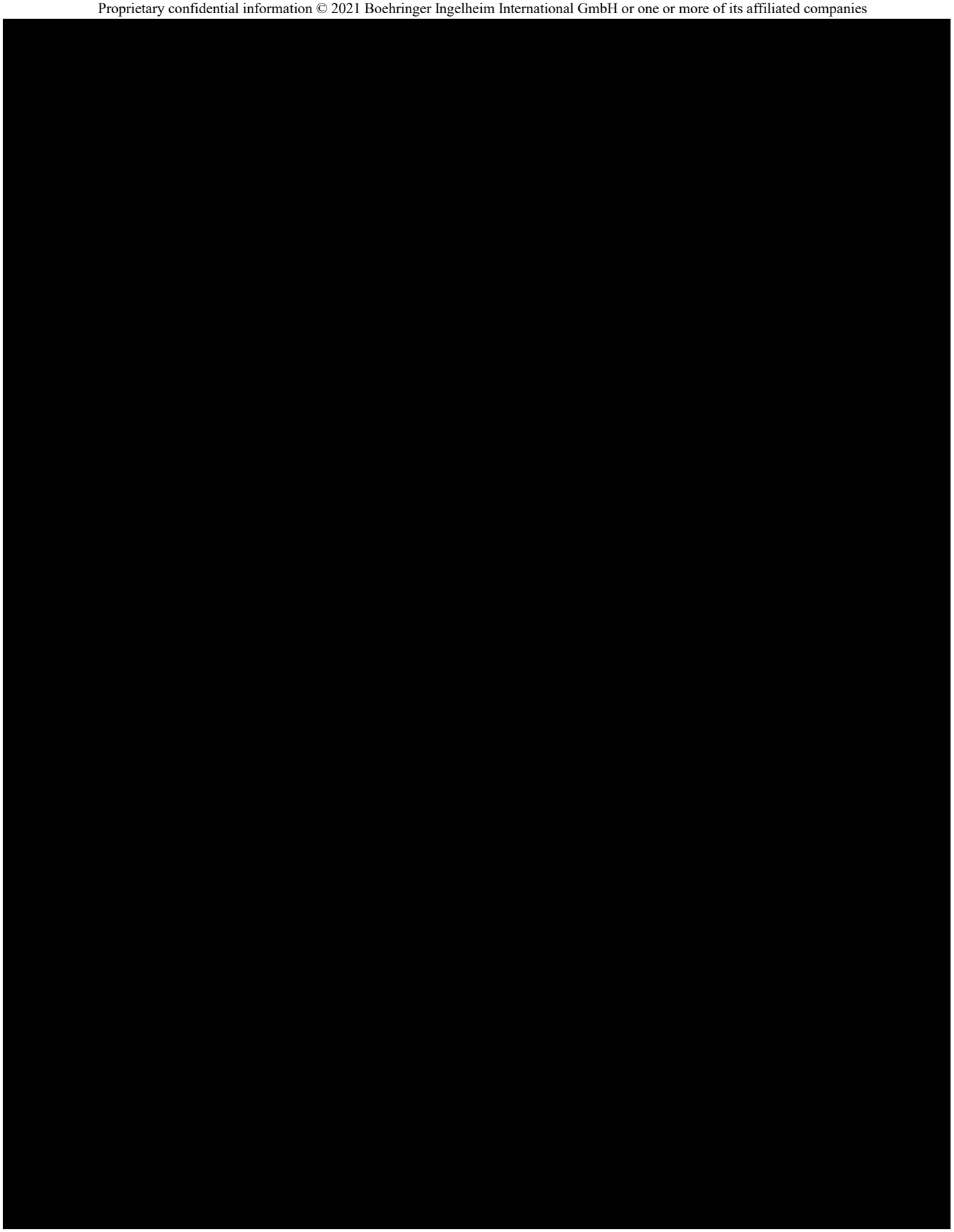
[redacted]

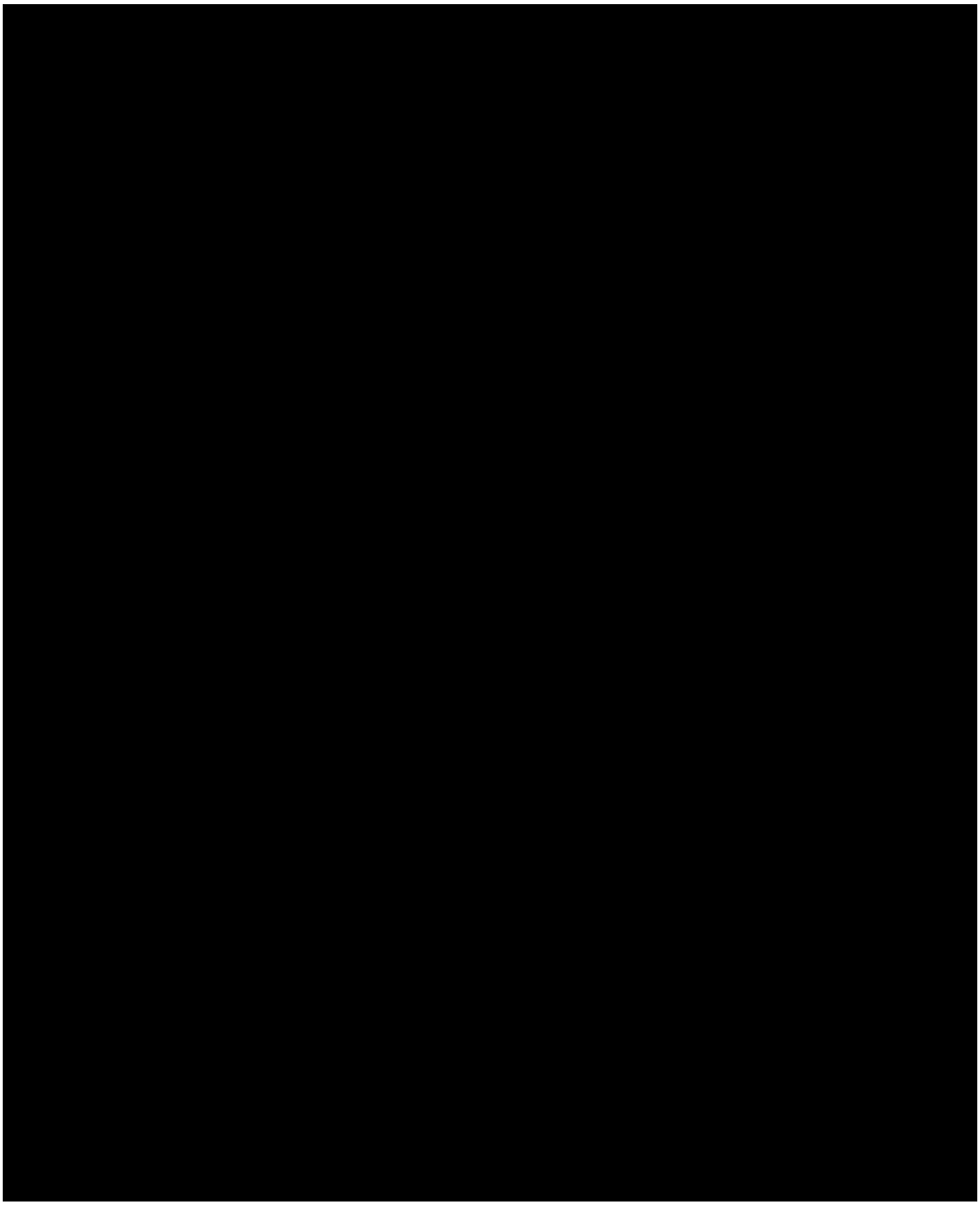
[redacted]

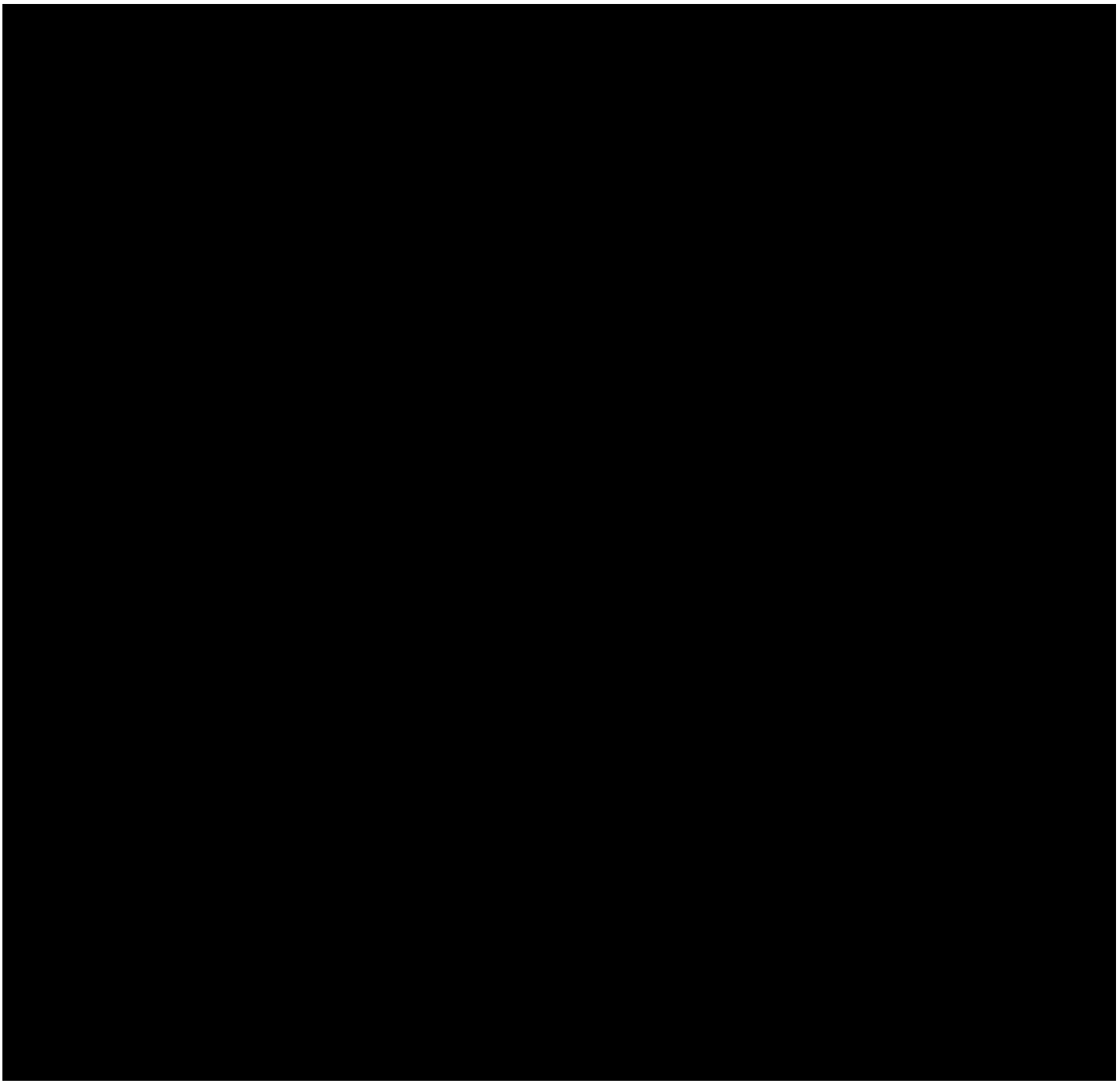


[redacted]

[redacted]







1.2.3 Lamotrigine

Lamotrigine is approved for epilepsy and bipolar disorders [R19-0416] and was first brought into clinical practice in Europe in 1990 [R19-0502]. The exact mechanism by which lamotrigine exerts its anticonvulsant action as well as its therapeutic action in bipolar disorders have not been elucidated yet.

One proposed mechanism of its anticonvulsant action involves a use- and voltage-dependent blockade of neuronal sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits these sodium channels, thereby stabilizing neuronal membranes and

consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate). However, its relevance to humans remains to be established [R20-0058].

For lamotrigine's psychotropic effects in bipolar disorders, anti-glutamatergic and neuroprotective actions are considered to be important candidate mechanisms [R19-0413].

To increase tolerability lamotrigine is up-titrated up to the usual therapeutic dose of 300 – 500 mg/day [R19-0414].

1.2.3.1 Clinical pharmacokinetics

After oral administration lamotrigine is rapidly and completely absorbed with negligible first-pass metabolism (absolute bioavailability is 98%, no food effect). Peak plasma concentrations occur within 1.4 to 4.8 hours following drug administration. Lamotrigine is marketed in different formulations, namely as a chewable/dispersible and as a compressed tablet. However, in terms of rate and extent of absorption the lamotrigine chewable/dispersible tablets were found to be equivalent, whether they were administered dispersed in water, chewed and swallowed, or swallowed as whole, and they were also equivalent to the lamotrigine compressed tablets [R19-0416]. Lamotrigine exhibits linear kinetics in healthy volunteers over a dose range of 50 – 400 mg. In vitro data show that lamotrigine is not highly bound to plasma proteins (approx. 55% bound in human plasma). Clinically significant interactions with other drugs through competition for protein binding sites are unlikely. In accordance with this, no change in protein binding was observed for combinations of lamotrigine and phenytoin, phenobarbital, valproate or carbamazepine [R19-0416].

Lamotrigine is metabolized predominantly by glucuronic acid conjugation via Uridine 5′-diphospho-glucuronyl transferases (UGT). Its major metabolite is an inactive 2-N-glucuronide conjugate. Drugs that induce or inhibit glucuronidation may therefore affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGT may also enhance the metabolism of lamotrigine. For example, rifampicin, phenytoin, and phenobarbital reduce lamotrigine concentration by approx. 40% due to induction of lamotrigine glucuronidation. After oral administration of ^{14}C-lamotrigine to healthy volunteers, 94% (10% unchanged) was recovered in the urine and 2% was recovered in the faeces.

In healthy volunteers, following single doses of lamotrigine from 50 to 400 mg, elimination half-life ($t_{1/2}$) averages 33 hours. The $t_{1/2}$ decreased by an average of 26% (mean steady state $t_{1/2}$ of 26.4 hours) following repeated dosing in healthy volunteers. In patients taking further anti-epileptic drugs (AED) half-life varied depending on concomitant AEDs. [R19-4225]

Some estrogen-containing oral contraceptives (e.g. levonorgestrel, ethinylestradiol) have been shown to decrease serum concentrations of lamotrigine. The effect of lamotrigine on these oral contraceptives had no clinical significance.

Lamotrigine is an inhibitor of renal tubular secretion via organic cationic transporter 2 (OCT2) proteins which may result in increased plasma levels of certain drugs that are substantially excreted via this route. Co-administration of lamotrigine with OCT2 substrates with a narrow therapeutic index (e.g., dofetilide) is therefore not recommended.

1.2.3.2 Clinical experience in humans

Clinical experience of 300 mg lamotrigine in healthy volunteers

Single doses of 300 mg lamotrigine have previously been administered to healthy volunteers without any reported safety concern.

- 180 healthy male and female volunteers aged 18 - 55 years received a single dose of 300 mg lamotrigine XR (single 300 mg XR tablet or 100 mg XR + 200 mg XR tablet) in an open-label, randomized bioequivalence and food effect study [R19-0420], [R19-0415]. All doses of lamotrigine XR were well tolerated in the fasted and fed states and there were no clinically significant safety findings. The most frequent AE were headache (~13%) fatigue, nasopharyngitis, flatulence, nausea, dizziness, erythema and sleep disorder. There was one serious adverse event (SAE) of multiple injuries, which was unrelated to study drug [R19-0420].

- In another study LAM105377, 60 healthy male and female subjects, aged 18 - 55 years were exposed to 4 single doses of 300 mg lamotrigine to investigate the bioavailability of three, prototype, 300 mg enteric coated, modified release tablet formulations of lamotrigine compared to a reference formulation. Reported AEs were headache (most frequent), nausea and hot flush (only in one formulation). Further, petechiae and erythematous rash were each reported by one subject, but both of these AEs were of a mild intensity and neither was considered by the investigator to be related to study drug. There were no SAEs, deaths, or withdrawals due to AEs in study LAM105377 [R19-0415].

- SCA104648 was a placebo-controlled repeat-dose/multi-dose study to evaluate the effect of lamotrigine at doses up to 400 mg/day on QT/QTc interval. Adverse events in this study were consistent with those seen in earlier clinical pharmacology studies with lamotrigine (headache, dizziness, nausea) [R19-0415].

- In a ketamine challenge trial done by Anand at al, healthy subjects were exposed to a single dose of 300 mg lamotrigine/placebo followed by an infusion of low-dose ketamine or placebo. In this trial, no rash has been observed after lamotrigine administration. One subject dropped out due to the AE nausea; however, it is not reported if this was considered related to lamotrigine or ketamine [R19-0417].

- In two MRI trials investigating the effect of lamotrigine on ketamine induced MRI responses 37 subjects in total were exposed to a single dose of 300 mg lamotrigine. [R19-1361], [R19-1360]

Safety profile in patients

In clinical trials in patients suffering from epilepsy the most common adverse reactions (incidence ≥ 5%) in adults were dizziness, headache, ataxia, coordination abnormalities, accidental injury, tremor, dyspepsia, nausea, vomiting, anxiety, insomnia, nystagmus, diplopia, blurred vision, somnolence, lymphadenopathy, sinusitis, rhinitis, pharyngitis, infection, pain, weight decrease, asthenia, chest pain, dysmenorrhea, pruritus and rash.

Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related.

Approximately 10% of the adult patients diagnosed with epilepsy and treated with lamotrigine as monotherapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%). The overall adverse reaction profile for lamotrigine was similar between female and male patients and was independent of age.

In clinical trials with adult patients (18 - 82 years) diagnosed with bipolar disorder the most common adverse reactions (incidence ≥ 5%) seen in association with the use of lamotrigine as monotherapy (100 to 400 mg/day) over 18 months were nausea, constipation, vomiting, abdominal pain, insomnia, somnolence, xerostomia, back pain, fatigue, rash, rhinitis, pharyngitis, exacerbation of cough, and xerostomia.

Adverse reactions that occurred with a frequency of <5% and >1% of patients treated with lamotrigine were nervous system disorders (amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia) as well as fever, neck pain, migraine, flatulence, weight gain, oedema, arthralgia, myalgia and urinary frequency.

In addition, looking at all patients (n = 6694) treated with lamotrigine in clinical trials confusion, paraesthesia, and amblyopia were frequently (occurring in at least 1/100 patients) reported. All other adverse drug reactions occurred infrequently (occurring in 1/100 to 1/1,000 patients) or rarely (occurring in less than 1/1,000 patients).

Lamotrigine is contraindicated in patients who have demonstrated hypersensitivity (e.g. rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) to the drug or its ingredients.

The following serious adverse reactions are described for lamotrigine [R19-0414], [R20-0058].

- Serious Skin Rashes

  In clinical trials, serious rash (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema) associated with hospitalization and discontinuation of lamotrigine treatment occurred in 0.08% - 0.3% of adult patients. There were no rash-related deaths reported in adult clinical trials, however, in worldwide post marketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported. However, their numbers are too few to permit a precise estimate of the rate.

Apart from age (higher risk in paediatric population) there are no further risk factors identified to predict the risk of occurrence or the severity of rash caused by lamotrigine. There are suggestions that the risk of rash may also be increased by

(1) co-administration of lamotrigine with valproate,
(2) exceeding the recommended initial dose of lamotrigine, or
(3) exceeding the recommended dose escalation for lamotrigine.

However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by lamotrigine have occurred within 2 to 8 weeks of treatment initiation; but isolated cases have also occurred after prolonged treatment (e.g. 6 months).

Lamotrigine can also cause benign rashes but as it is not possible to predict which rashes will turn out to be serious or life threatening, lamotrigine has to be stopped at the first sign of rash (refer to Section 3.3.4.1).

- Hemophagocytic Lymphohistiocytosis (HLH)

  HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation, e.g. fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin, and liver function and coagulation abnormalities. It is associated with high mortality rates if not recognized early and treated. In cases of HLH associated with lamotrigine, symptoms have been reported to occur within 8 to 24 days after initiation of treatment. Therefore, subjects that develop early manifestations of pathologic immune activation should be evaluated immediately, considering a diagnosis of HLH. These subjects must not be exposed to lamotrigine again (see stopping rules).

- Multiorgan Hypersensitivity Reactions and Organ Failure (= drug reaction with eosinophilia and systemic symptoms (DRESS))

  DRESS typically presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. Isolated liver failure without rash or involvement of other organs has also been reported

  In clinical trials, fatalities associated with acute multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients suffering from epilepsy who received lamotrigine. Rare fatalities from multiorgan failure have also been reported in post marketing use.

  It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately and not be reexposed to lamotrigine (refer to Section 3.3.4.1).

- Blood Dyscrasias

  Cases of blood dyscrasias, including neutropenia, leukopenia, anemia, pancytopenia, thrombocytopenia, and, rarely, aplastic anemia and pure red cell aplasia have been reported, that may or may not be associated with DRESS.

- Suicidal Behavior and Ideation

  It is known that AEDs, including lamotrigine, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed (up to 24 weeks).

- Aseptic Meningitis

  Postmarketing experience showed an increased risk of developing aseptic meningitis in patients treated with lamotrigine. The onset of symptoms varied from 1 day up to 1.5 months after start of treatment and mostly resolved after discontinuation of lamotrigine. However, in case of re-exposure symptoms returned quickly (within 30 min – 1 day after re-start of treatment) and often were more severe.
  Some patients also presented with signs and symptoms of involvement of other organs (predominantly hepatic and renal involvement), which may suggest that in these cases the aseptic meningitis observed was part of a hypersensitivity reaction.

- Withdrawal Seizures, Status Epilepticus, Sudden Unexplained Death in Epilepsy

  Overdoses up to 15 g of lamotrigine have been reported, some of which have been fatal. Subjects presented with ataxia, nystagmus, seizures (including tonic-clonic seizures), decreased level of consciousness, coma, and intraventricular conduction delay. For treatment of overdose, refer to Section 4.2.

For a more detailed description of lamotrigine profile, including a list of infrequent and rare adverse reactions, refer to the Lamotrigine ([redacted]) Drug Label Information [R20-0058].

1.2.4 Ketamine

Ketamine acts as an non-competitive NMDA-receptor (NMDAR) antagonist. It is a phencyclidine (PCP) derivative that binds to the allosteric PCP binding site within the pore of the NMDAR ion channel [R19-0419]. Since 1970, Ketamine (ketamine hydrochloride) has been in clinical use as rapid acting iv-anaesthetic and has FDA approval

- As the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation,

- For the induction of anaesthesia prior to the administration of other general anaesthetic agents and

- To supplement low-potency agents such as nitrous oxide [R19-0414], [R19-0419].

The onset of its anaesthetic action is rapid; an intravenous dose of 2 mg/kg of body weight usually produces surgical anaesthesia within 30 seconds after injection, with the anaesthetic effect lasting five to ten minutes [R19-0414]. Average steady state plasma concentrations of 2200 ng/ml are needed to induce anaesthesia and awakening from ketamine-induced anaesthesia occurs at plasma concentrations ranging from 640 to 1100 ng/ml [R19-0419].

Apart from its well-known anaesthetic effect, ketamine also possesses analgesic, anti-inflammatory and antidepressant effects. Intravenous ketamine is used in sub-anaesthetic doses, as low as [redacted], as an analgesic, e.g. to reduce chronic and acute postoperative pain or after acute trauma. When administered intravenously, ketamine's analgesic effects are associated with plasma concentrations ranging between 70 and 160 ng/ml, i.e. below anaesthetic concentrations [R19-0419].

In addition, sub-anaesthetic doses of ketamine have an antidepressant action as shown in clinical trials with patients suffering from treatment-refractory major depression, or bipolar depression [R19-0418], [P19-01142]. The most commonly used sub-anaesthetic antidepressant dose of ketamine (0.5 mg/kg; 40-minute infusion) results in a maximal plasma concentration (C_{max}) of 185 ng/ml [R19-0419].

1.2.4.1 Use of ketamine as a challenge agent

Of special interest for this trial is the observation, that single sub-anaesthetic doses of ketamine produce schizophrenia-like symptoms, including memory deficits, in healthy volunteers [R97-3753], [R19-1363]. This observation is in accordance with the hypothesis of an underlying dysfunction in NMDAR-mediated glutamatergic neurotransmission in the pathology of schizophrenia [R19-0484]. NMDAR inhibitors are used in animal and human models of schizophrenia [R13-0697], [R19-0485].

The Ketamine model of schizophrenia in healthy volunteers was first fully verified by Krystal et al [R13-0697], [R97-3753].

Focussing on the effects of the ketamine model on cognition, cognitive dysfunction associated with the activity of frontal and temporo-hippocampal parts of the brain is impaired in healthy volunteers. This ketamine-induced cognitive dysfunction is similar to findings in schizophrenia, and includes worsening of verbal fluency tests, interpretation of proverbs, working and semantic memory, Stroop test and Wisconsin Card Sorting Test [R13-0697]. In the trial done by Krystal et al, vigilance, verbal fluency, and delayed recall were impaired during/immediately following a 40-minute i.v. infusion of 0.5 mg/kg ketamine (resulting in plasma C_{max} estimated to be 100–250 ng/ml) and recovered shortly after termination of the infusion [R19-0419]. NMDAR are necessary for long-term potentiation (LTP) and thereby for learning and memory. Their dysfunction in schizophrenic or Alzheimer patients as well as their inhibition in the ketamine model in healthy volunteers are in accordance with the observed learning and memory deficits in these subjects.

There is significant heterogeneity how "sub-anaesthetic" is translated into an infusion dose/regimen in trials using ketamine as challenge as well as in ketamine trials investigating its antidepressant and/or analgesic effect [P19-11590]. For example, in one clinical trial evaluating intravenous ketamine for cancer-related pain, a low-dose, 24-hour infusion of 1 mg/kg was used; in another pain trial, a low-dose ketamine infusion of 0.6 mg/kg over 4 hours was administered [P19-11590].

In this trial, the ketamine infusion will be performed as an initial 0.26 mg/kg bolus over 1 min followed by a 89 min continuous infusion of 0.65 mg/kg (or 0.0073 mg/kg/min) as it demonstrated to achieve the systemic exposure at which cognitive effects were observed. In turn, these effects were attenuated by a single dose of 300 mg of lamotrigine administered 2 hours prior to ketamine infusion [R19-0417]. After a bolus ketamine infusion, the maintenance dose will be reduced by 10% (or 0.00073 mg/kg/min) every 15 min to hold concentrations constant [R19-4226], [R15-3321].

Perry et al reviewed the mental/psychiatric safety and tolerability of the ketamine challenge in healthy volunteers [R19-1358]. Safety data of fifteen ketamine challenge studies with healthy volunteers, plus one study with abstinent alcohol-abusing subjects were analysed, accounting to a total of 450 subjects receiving at least 1 ketamine infusion and 833 ketamine infusions being administered. The frequency of mental/psychiatric adverse events was low (< 2% of subjects) and AEs resolved spontaneously. Further, during long-term follow up (1wk – 6 months after last ketamine infusion) no evidence of ketamine abuse by subjects following study participation and no evidence of subsequent psychiatric problems related to ketamine exposure was found [R19-1358].

Published data on adverse events related to sub-anaesthetic doses of ketamine in a ketamine challenge is limited; but more data are available about the use of sub-anaesthetic ketamine in depression or pain treatment.

In a systematic review of safety and tolerability of ketamine used for treatment of depression, the most common side effects were headache, dizziness, dissociation, elevated blood pressure, and blurred vision. The most common psychiatric side-effects was anxiety. Most adverse effects occurred immediately/during intravenous ketamine infusion and resolved shortly after the administration [R19-0673]. In clinical trials with sub-anaesthetic ketamine for chronic pain no serious adverse reactions observed are and most of the adverse events were transient and could be treated by lowering the rate of infusion or stopping it [consensus paper ketamine in chronic pain]. However, it was also pointed out, that ketamine is associated with significant adverse events; mainly neuropsychiatric (incl. sedation, vivid dreams or nightmares, hallucinations, out-of-body experiences, headache, dizziness, fatigue, changes in mood, altered vision and hearing, light-headedness, paresthesia, changes in taste, dysarthria, euphoria, and inebriation), gastrointestinal, cardiovascular (incl. tachycardia, arrhythmias, and hypertension), and respiratory (incl. hypoventilation or hyperventilation, oxygen desaturation, and hypoxia). These adverse effects vary depending on the dose and subject.

1.2.4.2 Clinical pharmacokinetics

Ketamine is a racemic mixture consisting of (S)- and (R)-ketamine. As an anaesthetic for humans, (S)-ketamine is reported to be twice as potent as the racemic mixture and approximately three times more potent than (R)-ketamine. The pure S-ketamine stereoisomer is also marketed (e.g. Ketanest). In this trial, the racemic form will be used as it appears to cause more pronounced cognitive impairment as equianalgesic doses of the stereo-isomere [R19-1359].

Ketamine is administered to humans via multiple routes, including i.v., i.m., oral, intranasal, epidural and intrarectal. However, the most common route of administration is via i.v. infusion. Following i.v. administration, the ketamine concentration has an initial alpha phase lasting about 45 minutes (half-life of 10 to 15 minutes) that corresponds clinically to the anaesthetic effect of the drug. The anaesthetic action is terminated by a combination of redistribution from the CNS to slower equilibrating peripheral tissues and by hepatic biotransformation to its less active metabolite norketamine. The later half-life of ketamine (beta phase) is 2.5 hours [R19-0414]. Oral administration is less preferable as due to its extensive first-pass hepatic metabolism the oral bioavailability of ketamine (16%–29%, with peak concentration levels of the drug occurring within 20–120 minutes) is limited [R19-0419]. Ketamine undergoes extensive metabolism starting with demethylation to norketamine primarily by CYP2B6 and CYP3A4. CYP3A4 demethylates the (S)-ketamine enantiomer more rapidly than the (R)-ketamine enantiomer, whereas CYP2B6 demethylates both enantiomers of ketamine with near equal efficiency. Norketamine is further metabolized to the hydroxynorketamines (HNKs) and dehydronorketamine (DHNK). In addition to this major metabolic pathway further minor pathways exist [R19-0419].

Following an i.v. sub-anaesthetic (antidepressant) dose of ketamine (0.5 mg/kg administered over a 40-minute infusion) plasma levels of ketamine were below detectable levels within 1 day; however, circulating levels of DHNK and HNK were observed for up to 3 days [R19-0419]. In adult humans, racemic ketamine has a high volume of distribution (Vd = 3-5 l/kg), a fast systemic clearance (26.3 +/- 3.5 ml/kg) and a short elimination half-life (2–4 h). Compared to the racemic mixture, the elimination half-life of (S)-ketamine is slightly longer (5 h) and its systemic clearance is faster (14.8 +/- 1.7 ml/kg). A possible explanation for this observation may be an inhibition of (S)-ketamine's clearance by the (R)-ketamine.

Elimination of ketamine is primarily via the kidneys, with low levels excreted as ketamine (2%), norketamine (2%), and DHNK (16%) whereas the majority of the drug (~80%) is excreted as hydroxyketamine (HK) and HNK.

1.2.4.3 Clinical safety

Ketamine is known to affect the cardiovascular and respiratory system. Commonly (≥1/100 to <1/10) an increase in blood pressure, heart rate and respiratory rate is observed. However, although to a lesser rate (uncommon (≥1/1,000 to <1/100) an apparently opposite effect, namely bradycardia, arrhythmias and hypotension, as well as respiratory depression and laryngospasm and in rare cases (≥1/10,000 to <1/1,000) obstructive airway disorders and apnoea can occur.

Central nervous system and psychiatric disorders are also reported, ranging from common (hallucination, abnormal dreams, nightmare, confusion, agitation, abnormal behavior, nystagmus, hypertonia, tonic clonic movements), over uncommon (anxiety) to rare ones (delirium, flashback, dysphoria, insomnia, disorientation). If Ketamine is used as a general anaesthetic, an emergence delirium may occur (often consisting of dissociative or floating sensations) that some patients experience as unpleasant [R20-2543].

In addition, common adverse reactions are skin disorders (erythema, rash morbilliform), nausea and vomiting, and diplopia.

Anorexia, injection site pain and injection site rash are classified as uncommon and anaphylactic reactions, salivary hypersecretion, cystitis and haemorrhagic cystitis are rarely observed. After prolonged use (> 3 days or chronic use) abnormal liver function tests and Drug-induced liver injury has been reported, but the frequency cannot be estimated from the available data. In addition, single cases of increased intraocular pressure are known.

Ketamine has a wide safety margin; reported overdoses of Ketamine (up to 10 times that usually required) have been followed by prolonged but complete recovery [R20-2543].

For a more detailed description of ketamine profile, refer to the Ketamine hydrochloride ([redacted]) Drug Label Information [R20-2543].

1.2.5 Residual Effect Period

The Residual Effect Period (REP) of [redacted], for lamotrigine 10 days, and for ketamine 24 hours. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

This exploratory trial is designed to investigate if there is a [redacted] effect of BI 409306 and BI 425809 in an [redacted]. In this pharmacological model in healthy volunteers (as described in Section 1.2.3.1), infusion of the [redacted] [R13-0697], [P19-01512].

[redacted] affects various [redacted] and [redacted] specific disruption [redacted] [R19-4239], [R19-4224]. In preclinical models, an effect on [redacted] was also seen. Moreover, effects of [redacted] on [redacted] was observed in human subjects [R20-0059], [R20-0060]. Similarly, [redacted] induces effects in [redacted] R19-3170], [R19-3171]. Pre-treatment with drugs that reduce or counteract the effects of [redacted] should therefore result in a measurable improvement in the mentioned [redacted] and thereby in the respective [redacted]

BI 409306 is a [redacted] in clinical development. As [redacted] its [redacted] should restore [redacted] due to [redacted] to physiological levels and give rise [redacted] manifestation of [redacted] [R10-5110], [P10-10289], [R10-5097].

BI 425809 is a [redacted] in clinical development that is targeting [redacted] with [redacted] Inhibition of [redacted] leads to [redacted] of [redacted] a physiological [redacted] showing efficacy in [redacted] are available as well as indirect evidence of BI 425809's pharmacodynamic efficiency in humans ([redacted] treatment with BI 425809 resulted in improved [redacted] in patients with [redacted]

Considering the mode of action of BI 409306 and BI 425809 as well as ketamine, BI 409306 and BI 425809 are expected to [redacted]

Lamotrigine, a drug with a known positive effect on [redacted] -0417].

1.4 BENEFIT - RISK ASSESSMENT

For details on the specific benefit/risk assessment of participation of healthy subjects in this clinical study in context of the COVID-19 pandemic, refer to Appendix 10.7.

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance to investigate the effect of BI 409306 and BI 425809 on [redacted] Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication and ketamine.

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 (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

Drug-related risks and safety measures

Risks related to BI 409306 administration

Based on the results from completed trials in healthy volunteers, main adverse events are [redacted]

[redacted] see Section 1.2.1). [redacted] (also refer to Section 1.2).

Thus, for this trial the assumed therapeutic dose of [redacted] (single dose) was selected that was shown to be safe and well tolerated in healthy volunteers.

Risks related to BI 425809 administration

Based on the results from completed Phase I/II trials, the main dose-limiting AEs observed so far, were [redacted]

Risks related to lamotrigine administration

The selected dose of 300 mg of lamotrigine is a dose commonly used in the setting of such a ketamine challenge trial (Section 1.2.2) with no published safety concerns, including rash, so far. However, for patients treated with lamotrigine further serious adverse reactions, including serious rashes, have been reported, therefore specific safety measures will be implemented (see further below).

Risks related to ketamine administration

Ketamine is a broadly used drug and has a long history of clinical use. The dose administered in this trial is sub-anaesthetic and has been used safely as a challenge agent for cognitive effects before, alone as well as in combination with lamotrigine [R19-1361], [R19-1360], [R19-0417]. BI 409603 and ketamine, as well as BI 425809 and ketamine, have not been administered together so far. However, considering their modes of action, ketamine causing

NMDA-receptor hypofunction and BI 409306 and BI 425809 attenuating NMDA receptor hypofunction you would rather expect an attenuation of ketamine induced psychotomimetic effects.

To minimize the risk for subjects the following safety measures will apply:

- Careful selection of eligible subjects (ref Section 3.3.2 and 3.3.3)
- Investigators will pay special attention to
    - The skin of subjects to detect any early sign of rash and check for lymphadenopathy (targeted physical examination as indicated in the Flow Chart)
    - Any signs of mood change in the subjects
    - Any symptoms of pathologic immune activation, e.g. fever, lymphadenopathy. In this case, the subject should be evaluated immediately, considering a diagnosis of HLH or DRESS
    - Any signs of meningitis (e.g. stiff-back)
- Subjects will be instructed prior to lamotrigine treatment
    - To observe their own skin carefully and report any changes
    - That a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that, the subject should report any such occurrence to a trial staff immediately.
- Any new rash will be evaluated by a licensed medical practitioner qualified to evaluate dermatological abnormalities. If the rash is then deemed of clinical significance or of indeterminate significance, the subject will be referred to a dermatologist
- In case a subject develops rash/signs of pathologic immune activation after drug administration he will not be dosed again (ref Section 3.3.4.1)
- Resuscitative equipment should be ready for use
- The subject will be informed before the first ketamine infusion that he may experience psychotomimetic symptoms and that he can request to stop the infusion at any time
- The initial intravenous ketamine bolus has to be administered over a period of 60 seconds as more rapid administration may result in respiratory depression or apnoea and enhanced pressor response
- Close monitoring of blood pressure, pulse rate and oxygen saturation during and after ketamine infusion

- Continuous ECG monitoring during and after ketamine infusion until confirmation of recovery from ketamine

- Recovery from the ketamine administration will be followed up for at least 60 min after stop of infusion, until confirmation of recovery from ketamine as per criteria of recovery from ketamine, and must be documented. (see Section 5.2.5.6).

[redacted]

- Visual acuity test will be performed at the Screening Examination and the End of Trial Examination, and also in case visual disturbances develop. Subjects with ophthalmologic disorders will be excluded from the study.

- Regular safety laboratory examinations, including haematology to monitor for blood dyscrasias

- Only healthy subjects with no co-medication will be enrolled.

- In case AEs occur that require treatment, anti-epileptic drugs (AEDs) are not allowed

- Prior to discharge the subjects will be assessed by an investigator for their fitness, including a DSST, MOAA/S, CADSS and a SFST, and suicidality including C-SSRS. Their in-house refinement can be extended anytime if deemed necessary by the medical judgment of the investigator

- Subjects will be informed that driving an automobile, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more after ketamine infusion

Drug-induced liver disease

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 also Section 5.2.6.1.4, adverse events of special interest.

Summary

Considering the good safety profile of BI 409306 and BI 425809 observed so far, the published tolerability data of the ketamine challenge model with and without lamotrigine and the implemented safety measures, the overall potential risk for participating subjects is considered to be low. Successful investigation of a pro-cognitive effects of BI 409306 and 425809 would provide further evidence of their potential for clinical development.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate if and to what extent BI 409306, BI 425809 and lamotrigine attenuate [redacted]

2.1.2 Primary endpoint

The primary endpoint of the study is

- PAL Total Errors Adjusted (PALTEA28) on ketamine

2.1.3 Secondary endpoints

The secondary endpoints of the study are

- SWM Between Errors (SWMBE468) on ketamine
- RVP A' Prime (RVPA) on ketamine

[redacted]

[redacted]

2.2.2.3 Safety and tolerability

Safety and tolerability of BI 409306, BI 425809, lamotrigine and ketamine will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination incl. targeted examination, visual acuity test, vital signs; as well as clinically relevant abnormal results in C-SSRS and safety tests (DSST, MOAA/S, CADSS and SFST))
- Safety laboratory tests (only abnormal findings will be reported as AEs)
- 12-lead ECG and continuous ECG monitoring (only abnormal findings will be reported as AEs)
- Vital signs (BP, PR, SaO_2)
- Suicidality assessment (C-SSRS)

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomized, placebo controlled, double-blind, double-dummy, three-way cross over trial in healthy male subjects in order to investigate if and to what extent BI 409306, BI 425809 and lamotrigine attenuate ketamine [redacted]

In total, 36 healthy male subjects are planned to participate in this study. The subjects will be randomly allocated to one of the 18 3-period sequences including placebo in one of the periods and 2 out of the 3 active treatments in the remaining periods, namely T1–T2–R, T1–R–T2, T1–T3–R, T1–R–T3, T2–T1–R, T2–R–T1, T2–T3–R, T2–R–T3, T3–R–T1, T3–T1–R, T3–T2–R, T3–R–T2, R–T1–T2, R–T2–T1, R–T1–T3, R–T3–T1, R–T2–T3, R–T3–T2. For details, see below and refer to Section 4.1.

The treatments will be:

- **Lamotrigine Treatment (T1):** one single dose of 300 mg of lamotrigine and one single dose of placebo to BI 409306 (2h prior to ketamine infusion), and one single dose of placebo to BI 425809 (5h prior to ketamine infusion), administered to subjects orally after a light snack/ breakfast, followed by intravenous ketamine infusion (a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 minutes (reduced by 10% every 15 min))
- **BI 409306 [redacted] (T2):** one single dose of [redacted] of BI 409306 and one single dose of placebo to lamotrigine (2h prior to ketamine infusion), and one single dose of placebo to BI 425809 (5h prior to ketamine infusion), administered to subjects orally after a light snack/ breakfast, followed by intravenous ketamine infusion (a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 minutes (reduced by 10% every 15 min))
- **BI 425809 [redacted] (T3):** one single dose of placebo to BI 409306 and one single dose of placebo to lamotrigine (2h prior to ketamine infusion), and one single dose of [redacted] of BI 425809 (5h prior to ketamine infusion), administered to subjects orally after a light snack/ breakfast followed by intravenous ketamine infusion (a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 minutes (reduced by 10% every 15 min))
- **Placebo Treatment (R):** one single dose of placebo to lamotrigine and one single dose of placebo to BI 409306 and one single dose of placebo to BI 425809 administered to subjects orally after a light snack/ breakfast, followed by intravenous ketamine infusion (a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 minutes (reduced by 10% every 15 min))

There will be a washout period of at least 11 days between the treatments.

As part of the screening procedure, subjects will be challenged with intravenous ketamine infusion (a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073

mg/kg/min over 89 minutes (reduced by 10% every 15 min)). The subjects who achieved < 10 errors change on CANTAB PALTEA28 on ketamine vs. pre-ketamine infusion will not be included in the study.

Prior to ketamine challenge at screening, all subjects will be genotyped for CYP2C19 status (if CYP2C19 status isn't known at screening). Only CYP2C19 non-poor metabolizers will be eligible for the ketamine challenge at screening. For details, refer to Section 5.6.1.

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

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

For this trial, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [R94-1529]. However, more than 3 periods are deemed not feasible due to the burden for the subjects. In addition, an increased dropout rate has to be expected with an increased duration of the study period. For these reasons, a 3-period incomplete block crossover design will be applied maintaining most of the benefits of the complete crossover design as each subject still serves as his own control with regard to the comparison to placebo while limiting subjects' burden and duration of study period.

The anticipated effects on CANTAB tests on ketamine of the lamotrigine treatment (T1) will serve as a benchmark to conclude about effects on CANTAB tests on ketamine of the BI 409306 treatment (T2) and the BI 425809 treatment (T3). The use of placebo treatment (R) will allow estimating the impact of individual factors on the cognitive effects of the ketamine challenge.

Double-blind, double dummy conditions will be maintained throughout the study. The trial medication will be dispensed by unblinded pharmacists from the bulk bottles to the individual subjects' dispensing bottles (see Section 4.1.4).Because lamotrigine and placebo could be distinguished due to an imprint on lamotrigine tablets (see Section 4.1.1), the study drug will be administered by unblinded nurses. The subjects will be kept blinded regarding lamotrigine or placebo treatment via using a blinding eye mask in each treatment period during the study drug administration (see Section 4.1.4).

3.3 SELECTION OF TRIAL POPULATION

It is planned that 36 healthy male subjects will enter the study. They will be recruited from the trial site's participant database and other means, such as advertisement pre-approved by the Institutional Review Board.

Only CYP2C19 non-poor metabolisers will be included in the trial in order to minimize potential impact on the study endpoints due to the known higher exposure of BI 409306 in CYP2C19 poor metabolisers, and minimize the safety risks related to this as well (see Section 1.2.1.4 and the current version of the IB [c01694347]). CYP2C19 status must be

known prior to the ketamine challenge at screening in order to avoid exposure of non-eligible subjects to ketamine.

[redacted] subjects performing within the normative range on CANTAB PALTEA28 at screening will be put forward for evaluation of ketamine response. Subjects will identify as normative if they perform within 2 SD of an age matched normative sample at Visit 1 and Visit 2 prior to ketamine infusion. The CANTAB software will use detailed normative data and compare each recruited participant against it. At the end of each screening session, a report will be available for download that will indicate whether the subject is eligible to proceed to ketamine challenge.

Only subjects who demonstrated response to ketamine at the selected dose/regimen at the screening ketamine challenge (Visit 2) will be included in the trial in order to increase study sensitivity. Response to ketamine is defined as a change of ≥ 10 errors on CANTAB PALTEA28 from baseline (pre-ketamine) to ketamine challenge (on ketamine). A change of 10 or more errors on PALTEA28 is equivalent to a 1 (between subjects) SD change in performance. This threshold for change will allow sufficient variability for evaluating attenuation of ketamine-induced cognitive deficits between the study treatment arms.

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 physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 32 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Male subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception, e.g. use of condom (male subjects) *plus* any of the following methods (female partners): intrauterine device, hormonal contraception (e.g. implants, injectables, combined oral or vaginal contraceptives) that started at least 2 months prior to first drug administration, or barrier method (e.g. diaphragm with spermicide)
   - Sexually abstinent
   - Vasectomised (vasectomy at least 1 year prior to enrolment)

- Surgically sterilised female partner (including hysterectomy, bilateral tubal occlusion or bilateral oophorectomy)
- Postmenopausal female partner, defined as at least 1 year of spontaneous amenorrhea

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 ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 100 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm evaluated as clinically significant by Investigators
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. History of diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication, the challenge agent 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 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Current smoker or ex-smoker who quit smoking less than 30 days prior to screening
14. Inability to refrain from smoking
15. Alcohol abuse (consumption of more than 24 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within 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) 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

The following trial-specific exclusion criteria apply:

23. CYP2C19 poor metabolizers (CYP2C19 status must be known prior to the ketamine challenge at screening (Visit 2))
24. At the screening examination (Visit 1) or the screening ketamine challenge (Visit 2) prior to ketamine infusion, demonstrated results outside of the normative range (± 2 SD or percentile equivalent) per age group on CANTAB PALTEA28
25. At the ketamine challenge at screening (Visit 2), demonstrated no response to ketamine, defined as a change of < 10 errors on CANTAB PALTEA28 from baseline (pre-ketamine) to ketamine challenge (on ketamine)

[redacted]

27. Subjects with any condition that would preclude administration of lamotrigine and ketamine (i.e. contraindicated as per [R20-0058] and [R20-2543])
28. Any lifetime history of suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
29. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (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)
30. Subjects with ophthalmological disorders, which may result in photophobia, chromatopsia, visual brightness or other visual disturbances, with exception of myopia and hyperopia

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

31. A positive PCR test for SARS-CoV-2 and/ or any clinical symptom suggestive for COVID-19 at screening examination (Visit 1) and each time within 72 h prior to admission to trial site at screening ketamine challenge (Visit 2) and treatment period 1 (Visit 3)

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 (BI 425809 or BI 409306 or lamotrigine or placebo) or ketamine, 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 1.2.4), 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 surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
6. The subject has rash or other signs or symptoms of hypersensitivity or pathologic immune activation (e.g., fever, lymphadenopathy)
7. The subject exhibits hypoxemia (i.e. SaO_2 <90%) during and up to 30 min after the ketamine infusion
8. During the ketamine infusion, the subjects experiences psychotomimetic symptoms which are intolerable, and requests to stop the infusion
9. The subject exhibits serious suicidality, in the clinical judgment of the investigator or according to the following criteria:
   - any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
   - any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)
10. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of

sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial

11. The subject experiences a serious adverse reaction which is considered at least possibly related to the IMP administration
12. The subject experiences COVID-19 virus infection as confirmed by PCR test for SARS-CoV-2 and/or other applicable criteria (e.g. CT of lungs)

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

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3. If treatment is discontinued due to SARS-CoV-2/ COVID-19, refer to Appendix 10.7.3.2 for details of other related measures.

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 overall or at a particular trial site at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported
3. Violation of GCP, or the CTP, or the contract with BI 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

In case some subjects do not complete the trial, the Clinical Trial Lead together with 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.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products BI 409306 and matching placebo, BI 425809 and matching placebo, and placebo to lamotrigine have been manufactured by BI Pharma GmbH & Co. KG. Placebo to lamotrigine was originally produced as placebo matching BI 425809, but because of comparable tablets' characteristics will be used to match lamotrigine in this clinical study.

Lamotrigine tablets, USP 100mg produced by [redacted] & Ketamine HCl Injection, USP 500 mg/10 mL produced by [redacted] will be sourced from a local pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	**Lamotrigine**
Pharmaceutical formulation:	tablet*
Source:	[redacted]
Unit strength:	100 mg
Posology:	3-0-0 on Day 1 of Treatment T1, 2h prior to ketamine infusion
Route of administration:	oral
Duration of use:	Single dose in Treatment T1

Substance:	**BI 409306**
Pharmaceutical formulation:	film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	1-0-0 on Day 1 of Treatment T2, 2h prior to ketamine infusion
Route of administration:	oral
Duration of use:	Single dose in Treatment T2

Substance:	**BI 425809**
Pharmaceutical formulation:	film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Route of administration:	oral
Posology:	1-0-0 on Day 1 of Treatment T3, 5h prior to ketamine infusion
Route of administration:	oral
Duration of use:	Single dose in Treatment T3

The characteristics of the reference product are given below:

Substance:	**Placebo to lamotrigine**
Pharmaceutical formulation:	film-coated tablet*
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	3-0-0 on Day 1 of Treatment T2, 2h prior to ketamine infusion 3-0-0 on Day 1 of Treatment T3, 2h prior to ketamine infusion 3-0-0 on Day 1 of Treatment R, 2h prior to ketamine infusion
Route of administration:	oral
Duration of use:	Single dose in treatments T2, T3 & R

Substance:	**Placebo to [redacted] BI 409306 tablet**
Pharmaceutical formulation:	film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	1-0-0 on Day 1 of Treatment T1, 2h prior to ketamine infusion 1-0-0 on Day 1 of Treatment T3, 2h prior to ketamine infusion 1-0-0 on Day 1 of Treatment R, 2h prior to ketamine infusion
Route of administration:	oral
Duration of use:	Single dose in Treatments T1, T3 & R

Substance:	**Placebo to [redacted] BI 425809 tablet**
Pharmaceutical formulation:	film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	1-0-0 on Day 1 of Treatment T1, 5h prior to ketamine infusion 1-0-0 on Day 1 of Treatment T2, 5h prior to ketamine infusion 1-0-0 on Day 1 of Treatment R, 5h prior to ketamine infusion
Route of administration:	oral
Duration of use:	Single dose in Treatments T1, T2 & R

The characteristics of the challenge agent are given below:

Substance:	**Ketamine hydrochloride**
Pharmaceutical formulation:	injection solution
Source:	[redacted] (or equivalent) ,

Unit strength:	500 mg/10 mL (administered as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% (or 0.00073 mg/kg/min) every 15 min)
Posology:	X**-0-0 at SCR Visit 2 X**-0-0 on Day 1 of Treatment T1 X**-0-0 on Day 1 of Treatment T2 X**-0-0 on Day 1 of Treatment T3 X**-0-0 on Day 1 of Treatment R
Route of administration:	i.v.
Duration of use:	90 min infusion***, consisting of a bolus over 1 minute, followed by continuous infusion over 89 minutes at SCR KET, and in treatments T1, T2, T3 & R

** tablets of lamotrigine have imprint "ZC 80" on one side whereas matching placebo do not have it. To ensure double-blind conditions, an eye blinding mask will be used by subjects each time during the study drug administration, and unblinded staff will be involved in dispensing and administration of the study drug.*

*** ketamine to be administered intravenously 5h after administration of BI 425809 or placebo and 2h after administration of BI 409306 or lamotrigine or placebo.*

**** infusion can be prolonged for a maximum of 15 min, i.e. to 105 min in total, in case of delays from the planned time of the assessments on ketamine, or terminated earlier if the planned assessments on ketamine are completed or any test drops out.*

4.1.2 Selection of doses in the trial and dose modifications

BI 409306:

The dose of [redacted] was selected in order to measure the effect of the anticipated therapeutic dose of BI 409306. It is the highest dose tested in the ongoing Phase 2 study. So far, single doses of BI 409306 up to [redacted] were administered to healthy volunteers in multiple studies with no safety concern (see Section 1.2.1.3).

BI 425809:

The dose of [redacted] was selected because it provides comparable plasma concentrations after a single dose, i.e. [redacted] to the steady state exposures at multiple doses of 10 mg of BI 425809 (the assumed therapeutic dose), i.e. [redacted]. So far, single doses of BI 425809 up to [redacted] were administered to healthy volunteers in Phase I studies without safety concerns (see Section 1.2.2.3).

Lamotrigine:

The dose of 300 mg of lamotrigine selected for this trial is one of the standard clinical doses. In case of multiple doses administration, up-titration is recommended to increase tolerability. [R19-0414]. In this study, a single dose of 300 mg of lamotrigine will be administered as it has demonstrated to attenuate ketamine induced cognitive deficits with no safety concern

[R19-0417]. So far, single doses of 300 mg lamotrigine have previously been administered to healthy volunteers in multiple studies without any reported safety concern (see Section 1.2.2.2).

Ketamine:

A single sub-anaesthetic dose of ketamine produces schizophrenia-like symptoms, including memory deficits, in healthy volunteers [R97-3753], [R19-1363]. In this trial, ketamine infusion will be performed intravenously as an initial 0.26 mg/kg bolus over 1 min followed by a 89 min continuous infusion of 0.65 mg/kg (or 0.0073 mg/kg/min) as per Anand et al. This demonstrated to be sufficient to achieve the systemic exposure at which ketamine induced cognitive deficits, and which in turn were attenuated by a single dose of 300 mg of lamotrigine [R19-0417].

The total duration of ketamine infusion will be 90 min based on the planned duration of the required evaluations on ketamine as per the Flow Chart. Previous research has demonstrated that ketamine blood levels slowly increase during a constant ketamine infusion [R19-4226]. Thus, after an initial bolus infusion of ketamine, maintenance dose will be reduced by 10% (or 0.00073 mg/kg/min) every 15 minutes to keep ketamine levels fairly constant as per Umbricht et al [R15-3321]. Ketamine infusion can be prolonged for a maximum of 15 min, i.e. to 105 min in total, in case delays from the planned time occur for CANTAB tests, [redacted] Ketamine infusion is to be terminated earlier, if the above assessments on ketamine are completed (or any test drops out) [redacted]

If ketamine infusion is interrupted for a technical reason (e.g. occlusion of i.v. catheter), the reason to be eliminated as soon as possible, before start of a new test. If an interruption occurred during the ongoing test, the reason should be eliminated after the test has been completed (if it can distract the subject and thereby influence the outcome). An interruption of maximum of 15 min for technical reasons is allowed.

If ketamine infusion is interrupted due to safety reasons (e.g. the subject exhibits hypoxemia or experiences psychotomimetic symptoms, which are intolerable, and requests to stop the infusion), the subject will discontinue trial treatment (see Section 3.3.4.1).

BI 425809 or placebo will be administered 5 hours prior to ketamine infusion [redacted]

BI 409306 or lamotrigine or placebo will be administered 2 hours prior to ketamine infusion based on the anticipated t_{max} of lamotrigine in plasma and BI 409306 in CSF. BI 409306 [redacted]). There is no data about t_{max} of lamotrigine in CSF in human, the design of Anand et al using mean t_{max} in plasma will be followed.

4.1.3 Method of assigning subjects to treatment groups

The randomisation list will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 3). For this purpose, numbers of the randomisation list will be allocated to the subjects by the method 'first come first served'. Subjects are then assigned to a treatment sequence according to the randomisation list. Access to the randomisation lists are restricted to unblinded pharmacists and pharmacy staff members at the investigators' sites.

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

The randomisation procedure is described in Section 7.4.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a 3-way crossover study with 4 treatment arms (see Table 4.1.4: 1).

At screening, all subjects will undergo a ketamine challenge receiving ketamine infusion as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min). Only those subjects who demonstrated response to ketamine, as well as confirmed their eligibility in accordance to the other inclusion and exclusion criteria indicated in Sections 3.3.2 and 3.3.3, will be included in the study, and will receive 3 treatments: each subject will be randomly allocated to one of the 18 3-period sequences including placebo in one of the periods and 2 out of the 3 active treatments (T1, T2 and T3) in the remaining periods.

Administration of *BI 425809 or placebo* will be performed 5 h prior to ketamine infusion, after subjects had a light breakfast (e.g. a muffin with a glass of juice), which will be served 30 min before the drug administration.

Administration of *lamotrigine or BI 409306 or placebo* will be performed 2 h prior to ketamine infusion, after subjects had a light snack (clear liquid) (e.g. one or two cups of gelatin or a popsicle), which will be served approximately 5 min before the drug administration.

Before administration, the study drug will be dispensed into the individual subjects' dispensing bottles by the unblinded pharmacists. The unblinded nurses will administer the trial medication as oral doses each time together with about 240 mL of water to subjects who are in a sitting position. During administration of *lamotrigine or BI 409306 or placebo* in each treatment period, subjects will wear an eye blinding mask. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one unblinded authorised employee of the trial site should witness the administration of trial medication, and its dispensing.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T1 (Test 1)	Lamotrigine	Tablet	100 mg	3 tablets once 2h prior to ketamine infusion	300 mg
Lamotrigine Treatment	Placebo to [redacted] BI 409306	Tablet	N/A	1 tablet once 2h prior to ketamine infusion	N/A
	Placebo to [redacted] BI 425809	Tablet	N/A	1 tablet once 5h prior to ketamine infusion	N/A
	Ketamine	Solution for intravenous injection	500 mg/10 ml	bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min)	
T2 (Test 2) BI 409306 Treatment	Placebo to [redacted] BI 425809 (= placebo to lamotrigine)	Tablet	N/A	3 tablets once 2h prior to ketamine infusion	N/A
	BI 409306	Tablet	[redacted]	1 tablet once 2h prior to ketamine infusion	[redacted]
	Placebo to [redacted] BI 425809	Tablet	N/A	1 tablet once 5h prior to ketamine infusion	N/A
	Ketamine	Solution for intravenous injection	500 mg/10 ml	bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min)	
T3 (Test 3) BI 425809 Treatment	Placebo to [redacted] BI 425809 (= placebo to lamotrigine)	Tablet	N/A	3 tablets once 2h prior to ketamine infusion	N/A
	Placebo to [redacted] BI 409306	Tablet	N/A	1 tablet once 2h prior to ketamine infusion	N/A
	BI 425809	Tablet	[redacted]	1 tablet once 5h prior to ketamine infusion	[redacted]
	Ketamine	Solution for intravenous injection	500 mg/10 ml	bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min)	
R (Reference) Placebo Treatment	Placebo to [redacted] BI 425809 (= placebo to lamotrigine)	Tablet	N/A	3 tablets once 2h prior to ketamine infusion	N/A
	Placebo to [redacted] BI 409306	Tablet	N/A	1 tablet once 2h prior to ketamine infusion	N/A
	Placebo to [redacted] BI 425809	Tablet	N/A	1 tablet once 5h prior to ketamine infusion	N/A
	Ketamine	Solution for intravenous injection	500 mg/10 ml	bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min)	

5 h after administration of *BI 425809 or placebo* and 2 hours after administration of *lamotrigine or BI 409306 or placebo*, ketamine infusion will start. Ketamine will be provided in vials containing 500 mg of ketamine hydrochloride in 10 ml solution for intravenous injection. Immediately prior to use, 10 ml of the solution from the vial will be aseptically transferred to 240 mL of Sodium Chloride (0.9%) Injection, USP (Normal Saline) and mixed well. The resultant solution will contain 2 mg of ketamine per ml. Ketamine infusion will be performed as a bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 min (reduced by 10% every 15 min). Infusion systems, e.g. B.Braun Vista Basic Infusion Pump or comparable, should be used for the i.v. administration of ketamine.

After ketamine infusion, recovery must be confirmed via criteria of recovery from ketamine as compared to pre-ketamine infusion. Recovery follow up can be terminated after a minimum of 60 minutes when all applicable criteria are met (see Section 5.2.5.6).

Subjects will be kept under close medical surveillance until 24 h after the last study drug administration (i.e. *lamotrigine or BI 409306 or placebo*) in each treatment period, and overnight after ketamine infusion at screening. During ketamine infusion, vital signs including oxygen saturation will be measured frequently as per the Flow Chart.

The treatments will be separated by a wash-out phase of at least 11 days.

4.1.5 Blinding and procedures for unblinding

The trial is designed double-blind. Neither subject nor investigator will be aware of the trial treatments. The investigator will be supplied with a set of sealed envelopes containing the medication codes. The envelopes will be kept unopened at the study site until the end of data collection or, in an emergency requiring the investigator to know a subject's treatment allocation, opened with appropriate documentation. At the trial close-out visit, all envelopes will be collected.

At the investigators' sites, access to the randomisation schedule is restricted to unblinded pharmacists and pharmacy staff members for drug dispensing. Access to the randomisation codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

Persons directly involved in the conduct of the trial will be blinded to trial treatments. Because lamotrigine and placebo could be distinguished due to an imprint on lamotrigine tablets (see Section 4.1.1), the study drug will be administered by the unblinded nurses. In case of occasional unblinding of investigators, the risk of an observer bias regarding the study endpoints is considered minimal. The subjects' blinding status will be ensured via wearing a blinding eye mask during drug administration (see Section 4.1.4).

[redacted]

Regarding the sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical trial lead, data manager,

statistician, pharmacovigilance, bioanalyst, pharmacokineticist, pharmacokinetic analyst as well as dedicated CRO personnel). The objective of the trial is not expected to be affected.

4.1.6 Packaging, labelling, and re-supply

4.1.6.1 BI 409306, BI 425809, placebo to BI 409306, placebo to 425809, placebo to Lamotrigine

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.

No re-supply is planned.

4.1.6.2 Lamotrigine, Ketamine

The marketed products will be used for the study. Transport and storage are under the responsibility of the investigators and must comply with the pertinent information[R20-2543], [R20-0058].

Documentation on the commercial drug products, containing at least the following information, must be available on-site in the ISF:

- Clinical trial number
- Investigator name
- Trade name of drug product
- Substance International non-proprietary name (INN)
- Holder of marketing authorization
- Dosage form
- Quantity
- Unit strength
- Batch/lot number
- Use-by date
- Point of purchase
- Date of receipt
- Recipient (name and function)

In addition, documentation of drug purchase, including identification of drug products and quantity, must be available at the clinical site and filed 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 local clinical monitor (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor 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
- Availability of FDA Form 1572

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 that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator’s possession.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

No specific rescue medication is foreseen for BI 409306 and BI 425809, and 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.

In case of ketamine overdose, respiratory depression can occur requiring supportive ventilation. Each time after start of ketamine infusion until confirmation of recovery from ketamine, oxygen saturation (SaO_2) will be monitored continuously, and if SaO_2 is <90%, a prompt medical evaluation is to be done. Mechanical support of respiration that will maintain adequate blood oxygen saturation and carbon dioxide elimination is preferred to administration of analeptics.

- In case of clinically significant changes in blood pressure and pulse rate during the ketamine infusion, the infusion has to be stopped immediately. Treatment, e.g. with α_2-agonists (e.g. Clonidine) or β-blockers may be initiated in case of sustained and severe hypertension and tachycardia [P19-11590].

- If the subject experiences distressing psychomimetic symptoms, the ketamine infusion has to be stopped and further treatment with benzodiazepines, such as midazolam or diazepam may be indicated [P19-11590].

- If the subject experiences distressing psychomimetic symptoms, the ketamine infusion has to be stopped and further treatment with benzodiazepines, such as midazolam or diazepam may be indicated [P19-11590].

- In the rare event of ketamine-induced seizures, treatment should be started with benzodiazepines followed by barbiturates or propofol if persistent [P19-11590].

Following a suspected lamotrigine overdose, hospitalization and general supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. Induction of emesis should be considered. It is uncertain whether haemodialysis is an effective means of removing lamotrigine from the blood.

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.

- Paracetamol and diclofenac must be avoided as symptomatic therapy of AEs due to its potential liver toxicity. Ibuprofen may be used if needed.

- Anti-epileptic drugs (AEDs) are not allowed due to their potential impact on the PK characteristics of lamotrigine.

- Carbamazepine, extracts from Gingko, artemisinin, enzalutamide, efavirenz, lopinavir, ritonavir, tipranavir, rifampicin are not allowed due to CYP2C19 induction potential.

- Allicin, indomethacin, fluvoxamine, fluoxetine, ticlopidine, moclobemide, etravirine, ketoconazole (non-topical), voriconazole (non-topical), fluconazole (non-topical), esomeprazole, lansoprazole, pantoprazole, or omeprazole are not allowed due CYP2C19 inhibition potential.

- Ciprofloxacin, enoxacin, cinafloxacin, zafirlukast, oltipraz, mexiletine, phenylpropanolamine, methoxalen, hormonal oral contraceptives and hormonal replacement therapy are not allowed due to potential for CYP1A2 inhibition.

- The use of moderate and strong CYP3A4 inhibitors and inducers is not permitted.

- CYP3A4 sensitive drugs with narrow therapeutic range are not permitted during the trial period.

- Use of N-methyl-D-aspartate (NMDA)-antagonists (except ketamine administration as indicated in the Flow Chart) such as amantadine, or dextromethorphan

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No other food is allowed during the stationary stay.

On all treatment days (Day 1 of Visit 3, 4 and 5), the trial medication will be administered after a light breakfast at least 5 h prior to ketamine infusion *(BI 425809 or placebo)* and a light snack at least 2 h prior to ketamine infusion *(lamotrigine or BI 409306 or placebo)* (see Flow Chart). Meals will be served in order to avoid prolonged fasting and related to it inconveniences and common AEs (e.g. headache, fatigue). After stop of ketamine infusion, food intake is allowed after confirmation of recovery from ketamine, after a minimum of 60 minutes of recovery follow up. From 1 h before intake of BI 425809 or placebo until confirmation of recovery from ketamine, fluid intake is restricted to 240 mL of water with each study drug administration and an additional 240 mL of water at confirmation of recovery from ketamine (mandatory for all subjects).

At the screening ketamine challenge (Day -21 to -2 of Visit 2), subjects are supposed to adhere to same restrictions and follow same schedule of trial procedures as on all treatments days, so that response to ketamine at screening could be demonstrated in same conditions, that would be applied on treatment days. Thus, subjects will be instructed to admit to the trial site after an overnight fast of at least 10 h (mandatory for all subjects). A light breakfast and a light snack will be served at least 5 h and 2 h prior to ketamine infusion accordingly. Fluids will be limited to 240 mL of water at 5 h and 2 h before ketamine infusion and at confirmation of recovery from ketamine (mandatory for all subjects).

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 [redacted]

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

Smoking is not allowed starting from 30 days prior to screening until end-of-trial examination.

Excessive physical activity (such as competitive or high performance 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 unblinded site staff. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination, incl. targeted examination

At the screening examination (Visit 1), the medical examination will include demographics, height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, visual acuity test, C-SSRS assessment, safety testing (DSST, MOAA/S, CADSS and SFST), review of vital signs (BP and PR incl. orthostatic testing, SaO_2), 12-lead ECG, [redacted] laboratory tests, and a physical examination.

At the screening ketamine challenge (Visit 2) and during the treatment periods (Visits 3, 4 and 5), vital signs (BP, PR, SaO_2), 12-lead ECG, continuous ECG monitoring, laboratory tests, and a physical examination with a targeted examination (skin inspection for signs of rash, check for lymphadenopathy and neurological examination (mental status, motor examination, reflexes, sensory, gait and cranial nerves)) will be performed at the time points indicated in the Flow Chart. *Each time at discharge from trial site*, the subjects will be assessed by an investigator for their fitness including C-SSRS assessment, safety testing (DSST, MOAA/S, CADSS and SFST), review of vital signs (BP, PR, SaO_2), 12-lead ECG, laboratory tests, a physical examination with a targeted examination as described above.

At the end of trial examination (Visit 6), the medical examination will include review of vital signs (BP, PR, SaO_2), 12-lead ECG, laboratory tests, C-SSRS assessment, visual acuity test, a physical examination with a targeted examination as described above and determination of weight.

In context of pandemic, evaluation of subjects for COVID-19 will be performed ***at each visit***, including temperature assessment, questionnaire and medical assessment, and PCR test for SARS-CoV-2. For details, refer to Appendix 10.7.

Results of the physical examinations incl. targeted examinations and evaluation of subjects for COVID-19 will be kept in source data only, but not collected in the CRF. Only clinically relevant abnormal findings will be reported as AEs.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (e.g. Dinamap Pro 100, [redacted] or comparable) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position when possible.

Pulse oximetry is a non-invasive method for monitoring O_2 saturation (SaO_2). A blood-oxygen monitor displays the percentage of blood that is loaded with oxygen and used to

detect abnormalities in ventilation. SaO_2 will be measured by a pulse oximeter (e.g. [redacted] TruSat, [redacted] or comparable).

All recordings should be made using the same type of blood pressure and oxygen saturation recording instrument on the same arm, if possible.

At the screening examination (Visit 1), orthostatic tests will be performed. Subjects should have spent at least 5 min in the supine position before blood pressure and pulse rate will be measured the first time. Further 2 measurements will be performed immediately after standing up and after 3 min in a standing position.

At the screening ketamine challenge (Visit 2) and on treatment days (Visits 3, 4 and 5):

- *Before ketamine infusion* and *after confirmation of recovery from ketamine,* vital signs (BP, PR, SaO_2) to be measured at the time points indicated in the Flow Chart C and Flow Chart D. Vital signs 5 min prior to start of ketamine infusion (incl. recording of respiratory rate and effort this time) will serve as baseline for confirmation of recovery from ketamine.
- *During ketamine infusion*, vital signs (BP, PR, SaO_2) to be measured and recorded in the breaks between the tests at the time points indicated in the Flow Chart C and Flow Chart D. Oxygen saturation (SaO2) will be monitored continuously from start of ketamine infusion until confirmation of recovery from ketamine (see below). If SaO_2 is <90%, a prompt medical evaluation is to be done.
- *After stop of the ketamine infusion*, vital signs to be measured every 15 minutes for at least 60 min *until confirmation of recovery from ketamine*. Recovery must be confirmed via criteria of recovery from ketamine as compared to pre-ketamine infusion. Vital signs 5 min prior to start of ketamine infusion (incl. recording of respiratory rate and effort this time) will serve as baseline. Recovery follow up can be terminated after a minimum of 60 minutes when all applicable recovery criteria are met (see Section 5.2.5.6).

Blood pressure and pulse rate values will be collected in the CRF. Oxygen saturation, respiratory rate and effort assessments will be kept in source data only, but not collected in the CRF. Only clinically relevant abnormal findings will be reported as AEs.

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. 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.

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

The safety laboratory tests' results will not be entered in the CRF/database and will not be reported in the CTR. Only clinically relevant abnormal findings will be reported as AEs.

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.

The eGFR based on the CDK-EPI creatinine equation [R13-3447] will be calculated at screening:

$$eGFR\ (males) = 141 \times \min(S_{Cr}/0.9, 1)^{-0.411} \times \max(S_{Cr}/0.9, 1)^{-1.209} \times 0.993^{Age} \times 1.159\ [if\ Black]$$

With

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2
S_{Cr} (standardized serum creatinine) = mg/dL
min = indicates the minimum of S_{Cr}/κ or 1
max = indicates the maximum of S_{Cr}/κ or 1
age = years

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Haematology	Haematocrit	X	X	X	X
	Haemoglobin	X	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X	X
	Reticulocytes, absol.	X	X	X	X
	White Blood Cells/Leucocytes	X	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X	X
	Alkaline Phosphatase	X	X	X	X
	Gamma-Glutamyl Transferase	X	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X	X
	Creatine Kinase [CK]	X	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X	X
	Lactic Dehydrogenase	X	X	X	X
	Lipase	X	X	X	X
	Amylase	X	X	X	X
Coagulation	Activated Partial Thromboplastin Time	X	X	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	X	X
	Fibrinogen	X	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--	--
	Free T3 - Triiodothyronine	X	--	--	--
	Free T4 – Thyroxine	X	--	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Substrates	Glucose (Plasma)	X	X	X	X
	Hemoglobin A1C	X	--	--	--
	Creatinine	X	X	X	X
	eGFR	X	--	--	--
	Bilirubin, Total	X	X	X	X
	Bilirubin, Direct	X	X	X	X
	Protein, Total	X	X	X	X
	Albumin	X	X	X	X
	C-Reactive Protein (Quant)	X	X	X	X
	Uric Acid	X	X	X	X
	Cholesterol, total	X	--	--	X
	Triglyceride	X	--	--	X
Electrolytes	Sodium	X	X	X	X
	Potassium	X	X	X	X
	Calcium	X	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X	X
	Urine Protein (qual)	X	X	X	X
	Urine Glucose (qual)	X	X	X	X
	Urine Ketone (qual)	X	X	X	X
	Urobilinogen (qual)	X	X	X	X
	Urine Bilirubin (qual)	X	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X	X
	Urine pH	X	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 3, 4 and 5; on Day 1, prior to drug administration
C: parameters to be determined at Visit 3, 4 and 5; on Day 2, prior to discharge
D: parameters to be determined at Visit 6 (end of trial examination)

The tests listed in Table 5.2.3:2 are exclusionary laboratory tests that may be repeated as required. It is planned to perform tobacco screening and infectious serology at screening examination (V1) only. Drug screening will be performed at screening examination and each time at admission to trial site. COVID-19 screening will be performed at screening examination and each time shortly (within 72 hours) prior to admission to trial site (see Flow Chart).

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Tobacco screening (urine)	Cotinine
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies and RNA (qualitative) HIV-1 and HIV-2 antibody (qualitative)
COVID-19[1]	SARS CoV-2 PCR test from a nasal swab sample

[1] evaluation will be performed at screening examination (V1) and shortly (within 72 hours) prior to each admission to trial site (V2, V3, V4 and V5).

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

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the local laboratory of the trial sites (see Section 8.7), with the exception of drug screening tests. These tests will be performed at the trial site using e.g. [redacted] respectively, or comparable test systems.

5.2.4 Electrocardiography

5.2.4.1 12-lead ECG

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g. CardioSoft EKG System, [redacted] or comparable) at the times provided in the Flow Chart.

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

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

All ECGs will be stored electronically. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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

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

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording using e.g. CARESCAPE Monitor B450 ( ) or comparable from start of ketamine infusion until confirmation of recovery from ketamine. 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.

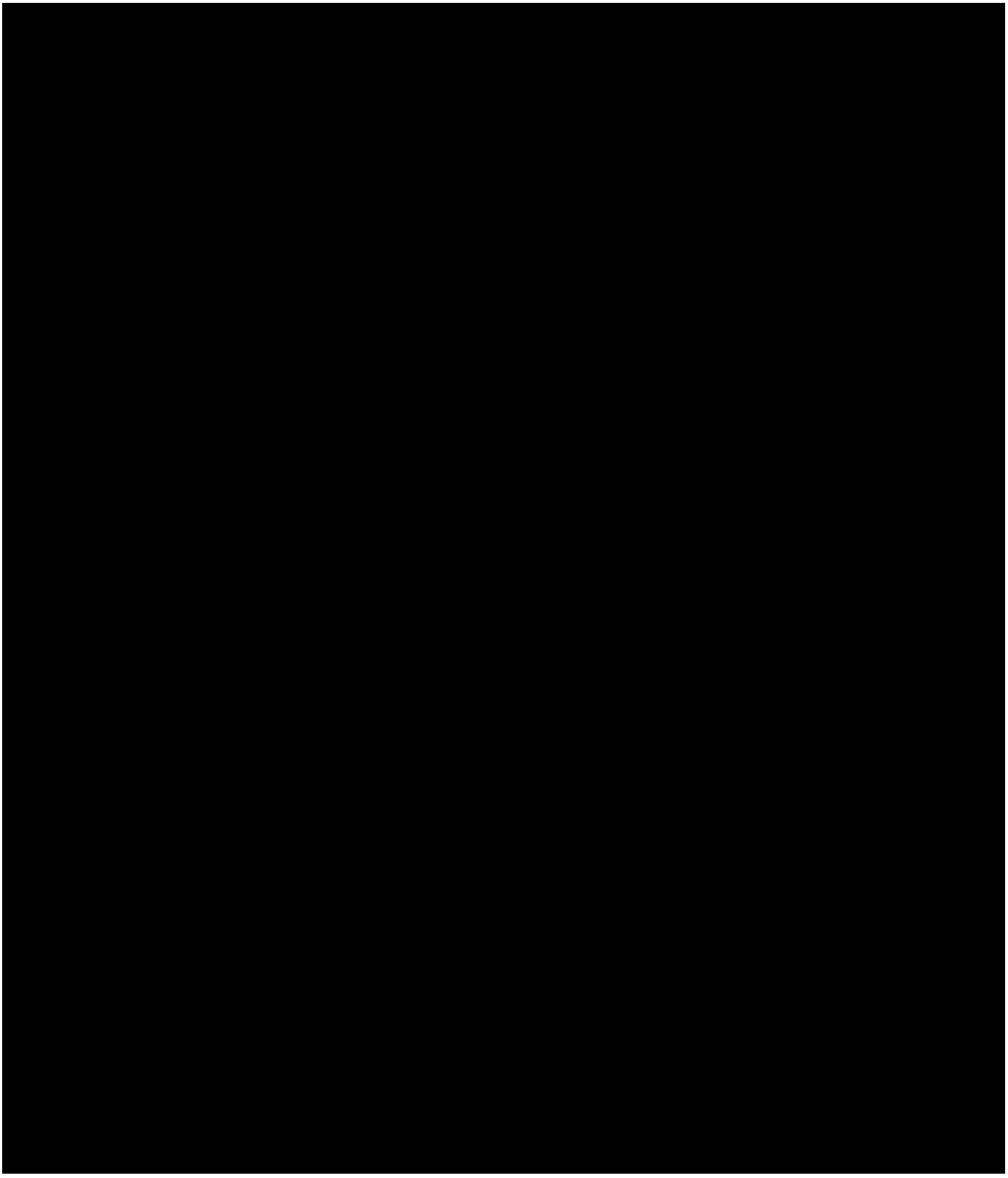
5.2.5 Other safety parameters

5.2.5.2 Suicidality monitoring

Based on the FDA guidance on prospective assessment of suicidality [R12-4395] suicidal ideation and behavior should be assessed as part of the evaluation of any drug being developed for a psychiatric condition.

Suicidality assessment to further evaluate the psychological status of the subject will be performed at the times indicated in the Flow Chart using the Columbia Suicidal Severity Rating scale (C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both, behavior and ideation. The C-SSRS was designed to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials.

The original English version is shown in Appendix 10.2.



5.2.5.4 Visual acuity test (near visual acuity)

Near vision cards (e.g. Jaeger Eye Chart) will be used to measure visual acuity at the screening examination and the end-of-trial examination, and also in case visual disturbances develop during the course of study. The smallest line that a subject can read at a distance of 35 cm will be recorded. If the subject uses glasses or contact lenses, then the test should be performed using them. Tests results will be reviewed by investigator or his/her designee for correctness and deteriorations. Any deterioration occurring during the study will be documented as an AE and an additional ophthalmologic examination should be considered.

5.2.5.5 Safety tests (DSST, MOAA/S, CADSS and SFST)

At the screening examination and each time prior to discharge from trial site, the subjects will be assessed by an investigator for their fitness, including a DSST, MOAA/S, CADSS and SFST. Based on the outcome of these tests and the medical judgment of the investigator, their in-house refinement can be extended anytime if deemed necessary.

Results of the safety tests will be kept in source data only, but not collected in the CRF. Only clinically relevant abnormal results will be reported as AEs.

5.2.5.5.1 Digit Symbol Substitution Test (DSST)

The DSST [R20-0105] is a psychometric test assessing the integrity of several [redacted] domains, including executive function, processing speed, attention, spatial perception, and visual scanning. It has been shown to be a valid and sensitive instrument to evaluate [redacted] and changes in [redacted] [R20-0054]. The DSST is a paper-and-pen timed (2-minutes) test where the subject is required to copy into spaces below rows of numbers the symbols that are matched to each number according to a key located on the top of the page. The DSST is scored based on both the number of correct answers and the speed at which they were determined. The DSST is arguably the most commonly used [redacted] due to its brevity, high discriminant validity, and sensitivity to change [R20-0055]. The DSST is being administered in this trial to ensure the subject has the [redacted] before being discharged from the unit.

The original English version is shown in Appendix 10.3.

5.2.5.5.2 Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

The MOAA/S [R20-0053] will be used in the current study to measure treatment-emergent sedation. The MOAA/S is a widely used clinician-administered measure of alertness/sedation for clinical trials. The MOAA/S measures the alertness/sedation spectrum on a 6-point scale (0 to 5) based on verbal cues using a here-and-now timeframe [R20-0057].

The original English version is shown in Appendix 10.4.

5.2.5.5.3 Clinician Administered Dissociative States Scale (CADSS)

The CADSS [R20-0052] is a 28-item clinician-administered measure of perceptual, behavioral, and attentional alterations occurring during active dissociative experiences

composed of 23 subjective self-reported and 5 objective observer-reported ratings, each scored from 0 (not at all) to 4 (extremely). The CADSS provides a validated assessment of dissociative states sensitive to change over time and amenable to repeated measures [R20-0052]. The CADSS is a clinician-administered instrument which for the purposes of the current study has a here-and-now (current) lookback timeframe.

The original English version is shown in Appendix 10.5.

5.2.5.5.4 Standardized Field Sobriety Test (SFST)

The Standardized Field Sobriety Test (SFST) is a battery of three tests administered and evaluated in a standardized manner to obtain validated indicators of impairment, e.g. in persons who have used narcotics [R19-1364], [R19-1365]. These tests were developed based on research sponsored by the National Highway Traffic Safety Administration (NHTSA).

The description of SFST is provided in Appendix 10.6.

5.2.5.6 Criteria of recovery from ketamine

Each time after ketamine infusion, recovery must be confirmed via criteria of recovery from ketamine (see below) as compared to pre-ketamine infusion. Vital signs at 5 min prior to start of ketamine infusion (incl. recording of respiratory rate and effort this time) will serve as a baseline for confirmation of recovery. Recovery follow up can be terminated after a minimum of 60 min. The physician responsible for the administration of ketamine or another qualified care provider must remain available until all applicable recovery criteria are met.

Criteria of recovery from ketamine:

a) Patient is able to freely move their extremities
b) Respiratory rate and effort are at baseline
c) Blood pressure is within 20% of baseline
d) Patient is fully awake
e) Oxygen saturation is greater than 94% on room air
f) Patient has minimal or no nausea and no emesis for at least 20 minutes

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, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered 'Always Serious'

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

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

5.2.6.1.7 Suicidality assessment

Suicidality assessment to further evaluate the psychological status of the subject will be performed at the time points indicated in the Flow Chart using the Columbia Suicidal Severity Rating scale (C-SSRS).

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

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

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the 'screening/baseline' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time

prior to the screening or baseline visit. The life time history of suicidal ideation and behavior will also be recorded.

After the baseline visit the assessment 'since last visit' will be performed at each clinic or phone visit ('since last visit' version). The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator. For 'Self-injurious behavior, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied.

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

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 exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication or ketamine.

In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

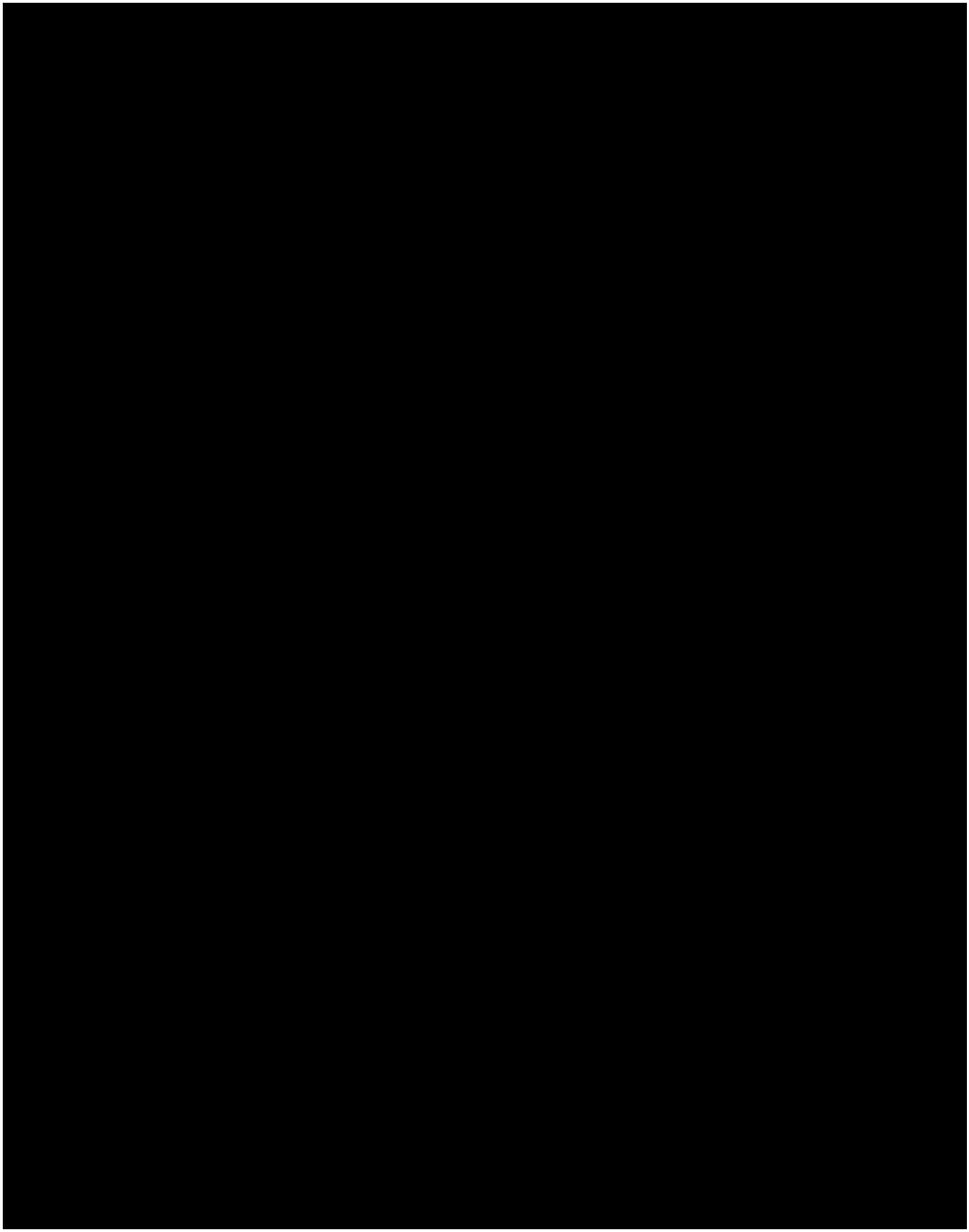
5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process 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 send the BI SAE form.

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

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 sufficiently assessed as 'chronic' or 'stable', or no further information can be obtained.



[redacted]

[redacted]

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKERS

5.4.1 Cambridge Neuropsychological Test Automated Battery (CANTAB)

Attenuation of [redacted] will be evaluated on the CANTAB test battery. The [redacted] assessed in this battery include: Paired Associates Learning task (PAL; visuospatial episodic memory), Spatial Working Memory (SWM; working memory), and Rapid Visual Information Processing (RVP; sustained attention).

The CANTAB tests will be performed in the same order, i.e. RVP, SWM, PAL, with a 4 min break between tests, pre-ketamine and during ketamine infusion, following administration of BI 409306 (T2) or BI 425809 (T3) or lamotrigine (T1, positive control) or placebo (R). The anticipated effects on the CANTAB tests on ketamine of the lamotrigine treatment (T1) will serve as a benchmark to conclude about effects on the CANTAB tests on ketamine of the BI 409306 (T2) or BI 425809 (T3) treatment. The use of placebo treatment (R) will allow estimating the impact of individual factors on the cognitive effects of the ketamine challenge.

The full list of outcome measures to be analysed from the CANTAB test battery is included in Table 5.4.1: 1 below.

The CANTAB tests (RVP, SWM, PAL) can be completed in approx. 35 minutes.

Table 5.4.1: 1 CANTAB tests, domains and outcome measures

CANTAB test	Domain	Outcome measurements
Paired Associates Learning (PAL)	Episodic memory & new learning	KEY: Total Errors Adjusted (PALTEA28) [redacted]
Spatial Working Memory (SWM)	Executive function & working memory	KEY: Between Errors (SWMBE468) [redacted]
Rapid Visual Information Processing (RVP)	Sustained attention/vigilance	KEY: A Prime (RVPA)

5.4.1.1 Paired Associates Learning (PAL)

PAL assesses visual memory and new learning. [redacted]

Description: Boxes are displayed on the screen and open in turn to reveal a number of patterns. Participants are instructed to try to remember the location in which each pattern was shown. After all the boxes have been opened, each pattern is then shown in the center of the screen in a randomised order, and the participant touches the box in which the pattern was located. If an error is made, all the patterns are re-presented to remind the participant of their locations. As the test progresses so the stages become more difficult as the number of patterns to be remembered increases. For participants who fail to complete all levels, an adjusted total is calculated that allows for errors predicted in the stages that were not attempted.

Key Outcome Measure: Total Errors Adjusted (PALTEA28). The number of errors committed by the subject plus an adjustment for the estimated number of errors they would have made on any stages that were not reached. Calculated across all assessed two, four, six and eight box trials.

5.4.1.2 Spatial Working Memory (SWM)

SWM assesses the ability of the participant to retain spatial information and manipulate it in working memory. It is a self-ordered task that also gives a measure of strategy (an aspect of executive function). [redacted]

Description: A number of coloured boxes are presented on the screen, and the computer hides a token in these boxes one at a time. The participant is instructed to touch the boxes in turn to search for the token that has been hidden. When a token is found it should be placed in a home area on the right side of the screen. The participant then searches for more tokens

until the same number of tokens as the number of coloured boxes has been found. The key task instruction is that the computer will never hide a token in the same coloured box twice in the same problem. As the test progresses, so it becomes more difficult.

Key Outcome Measure: Between Errors (SWMBE468). The number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials.

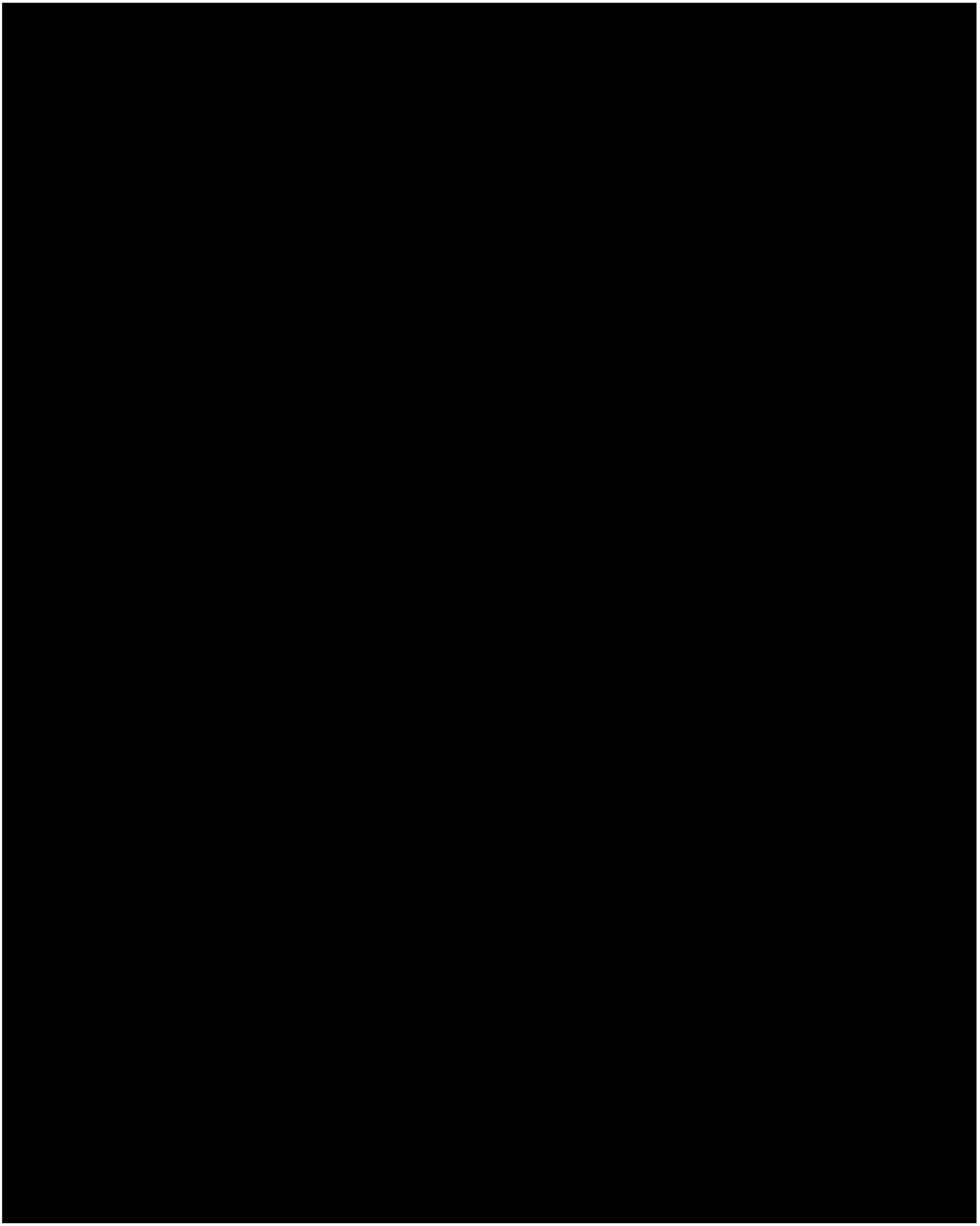
5.4.1.3 Rapid Visual Information Processing (RVP)

RVP is a sensitive measure of sustained attention, outputting measures of response accuracy, target sensitivity and reaction times. [redacted]

Description: During the RVP task, single digits appear in a pseudo-random order at a rate of 100 digits per minute in a box in the centre of the screen. Subjects must detect a series of 3-digit target sequences (e.g. 3-5-7; 2-4-6; 4-6-8) and respond by touching the button at the bottom of the screen when they see the final number of the sequence. Nine target sequences appear every minute.

Key Outcome Measure: A' Prime (RVPA). The signal detection measure of a subject's sensitivity to the target sequence (string of three numbers), regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, this metric is a measure of how good the subject is at detecting target sequences.

[redacted]



[redacted]

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, C-SSRS, safety tests, 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 and intravenously administered drugs, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Sections 5.4 and 5.6 are of exploratory nature only. The C-SSRS is a validated tool to monitor for suicidality and recommended by the FDA [R12-4395]. The visual acuity test is commonly used to screen for visual disturbances and can be extended to a full ophthalmologic examination if needed. DSST, MOAA/S, CADSS and SFST are commonly used for assessment and confirmation of subjects' fitness after administration of ketamine before discharge from the clinic. Recovery from ketamine will be evaluated as per criteria common in clinical practice.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' planned time 0:00 on Day -21 to -2 of Visit 2 are to be performed and completed within a 2 h period prior to planned time 0:00.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 of Visit 3, 4 and 5 are to be performed and completed within a 2 h period prior to the trial drug administration.

The acceptable deviation from the scheduled time **for C-SSRS assessments, targeted physical examination, safety tests (DSST, MOAA/S, CADSS and SFST) and laboratory tests** will be ± 2 h for all days.

On treatment days (Day 1 of Visit 3, 4 and 5) and at the Screening Ketamine Challenge (Day -21 to -2 of Visit 2), the planned times for **CANTAB tests, E** [redacted] as per the Flow Chart should be adhered as closely as possible *before ketamine infusion*, whereas *during ketamine infusion* time intervals between these tests should be minimized, i.e. if any test is completed earlier or dropped out, the next test should start straight away. Overall, deviations ± 15 min from the planned times for these tests are acceptable.

CANTAB tests, [redacted] at the Screening Ketamine Challenge (Visit 2) have to occur time-matched to these assessments in each treatment period (Visit 3, 4 and 5). Therefore, planned time 0:00 on Day -21 to -2, the Screening Ketamine Challenge, should equal planned time 0:00 relative to drug administration on Day 1 of Period 1, 2 and 3.

Before start of ketamine infusion and *after confirmation of recovery from ketamine,* the acceptable deviation from the scheduled time for **vital signs, ECG and Questioning for AEs and concomitant therapy** will be ± 15 min. *During ketamine infusion until confirmation of recovery from ketamine*, the planned times for vital signs, ECG assessments and Questioning for AEs and concomitant therapy as per the Flow Chart C and Flow Chart D should be adhered as closely as possible.

Ketamine infusion can be prolonged for a maximum of 15 min, i.e. to 105 min in total, in case delays from the planned time occur for CANTAB tests, [redacted] Ketamine infusion is to be terminated earlier, if the above assessments on ketamine are completed (or any test drops out) [redacted] Evaluation as per **criteria of recovery from ketamine** must be not earlier than 60 min after stop of ketamine infusion.

If several actions are indicated in the Flow Chart at the same time point, the intake of meals will be the last action, and 12-lead ECG recordings have to be done first. Furthermore, if

several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

[redacted]

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.

The screening period consists of the Screening Examination (Visit 1) and (if applicable) the Screening Ketamine Challenge (Visit 2). Only subjects who have already passed all eligibility criteria, incl. confirmation on CYP2C19 status, except not yet determined response to ketamine, will be invited to the Screening Ketamine Challenge, that has to be scheduled on a different day after the screening examination.

At the Screening Examination, genotyping for CYP2C19 will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 3.3.3 and 5.6.1).

At the Screening Examination, subjects who are not able to tolerate procedures of [redacted] or demonstrate abnormal results will be excluded from further screening activities (see Section 5.2.5.3).

At the Screening Examination (Visit 1) and the Screening Ketamine Challenge (Visit 2) prior to ketamine infusion, subjects will be tested on CANTAB RVP, SWM and PAL. Each subject will be compared to an age matched sample of normative individuals from Cambridge Cognition's CANTAB normative database (to be made for PALTEA28 only). Subjects will be excluded if they perform at any visit outside of the normative range (± 2 SD or percentile equivalent) for their age level on the PAL outcome measure PAL Total Errors Adjusted (PALTEA28). An indication of whether the subject should be excluded from further screening procedures due to absence of normative performance will be provide through the CANTAB software as a downloadable report and will be available after completion of the CANTAB assessments.

For the Screening Ketamine Challenge eligible subjects will come to the clinic in the morning of the test day, where they will participate in two assessment-sessions:

- Screening Baseline (= SCR BL)

  CANTAB tests, [redacted] will be done without any treatment, i.e. with no ketamine infusion

- Screening Ketamine (= SCR KET)

  CANTAB tests, [redacted] will be done during ketamine infusion

SCR BL will be done first followed by SCR KET, as indicated in the Flow Chart. Only subjects that show [redacted] will be allowed to enter the trial. [redacted]. A change of 10 or more errors on PALTEA28 is equivalent to a 1 SD (between subjects) change in performance. This will allow ample variability to evaluate attenuation of k[redacted] between treatment arms. An indication of whether a participant should be screened out due to absence of [redacted] will be provided through the CANTAB software as a downloadable report and will be available following completion of the CANTAB assessments.

The assessments of SCR KET will also be used as baseline for the assessments performed on the test days of the treatment periods, i.e. under treatments T1, T2, T3 and R. Therefore, it is of upmost importance that SCR KET assessments will be performed time-matched, i.e. exactly at the same time of the day, to the later assessments under treatments T1, T2, T3 and R.

Recovery from ketamine must be confirmed via criteria of recovery from ketamine. Recovery follow up can be terminated after a minimum of 60 minutes when all applicable recovery criteria are met (see Section 5.2.5.6).

During and after assessments subjects are kept under close medical surveillance for at least 5 h after stop of the ketamine infusion. The subjects will then be allowed to leave the trial site after successful completion of the discharge assessments (incl. C-SSRS; DSST, MOAA/S, CADSS, SFST), formal assessment and confirmation of their fitness. Discharge will be postponed if subjects fail to pass C-SSRS, DSST, MOAA/S, CADSS and/or SFST or any time if deemed necessary by the investigator (for details refer to Sections 5.2.5.2 and 5.2.5.5).

For information regarding laboratory tests (including drug and virus screening), ECG, [redacted] C-SSRS, vital signs, safety tests (DSST, MOAA/S, CADSS, SFST), visual acuity test and physical examination incl. targeted examination, refer to Section 5.2.

For details on the trial procedures related to SARS-CoV-2/ COVID-19 in context of pandemic during screening period, refer to Appendix 10.7.3.1.

6.2.2 Treatment periods

Each subject is expected to participate in 3 treatment periods (Days 1, 2, 4, 6 and 8 in each period). At least 11 days will separate drug administrations in all treatment periods.

In the evening of Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following study drug administration. The subjects will then be allowed to leave the trial site after successful completion of the discharge assessments (incl. C-SSRS; DSST, MOAA/S, CADSS, SFST) and formal assessment and confirmation of their fitness. These in-house period can be

extended any time in case considered necessary by the investigator or if the subject failed to pass the discharge assessments (for details refer to Section 5.2.5.2 and 5.2.5.5). On Days 4, 6 and 8 subjects will be contacted via phone and questioned about their well-being.

[redacted]

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on 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.

For details on the trial procedures related to SARS-CoV-2/ COVID-19 in context of pandemic during treatment periods, refer to Appendix 10.7.3.2.

6.2.3 Follow-up period and trial completion

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is a randomised, placebo-controlled, double-blind, double-dummy, three-way cross-over trial applying an incomplete block design, including a washout of at least 11 days between the treatments (Section 3.1).

The main objective of this trial is to investigate the pharmacodynamic effects of single doses of BI 409306 (T2) and BI 425809 (T3) on [redacted] compared to placebo (R) on the basis of the pharmacodynamic endpoints listed in Section 2.1.2. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of linear mixed effects models.

The primary and secondary PD endpoints will be compared between BI 409306 and placebo as well as BI 425809 and placebo. The Lamotrigene (T1) treatment period acts as a positive control group. It is not planned to compare PD effects between Lamotrigine, BI 425809 and BI 409306. The primary and secondary PD endpoints will be compared between Lamotrigine and placebo to investigate the sensitivity of the design.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing is performed and hence no null and alternative hypotheses are defined. A justification of the sample size is provided in Section 7.5.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Statistical analyses will be based on the following analysis sets:

- Treated set (TS):
  The treated set includes all subjects who were randomized and treated with at least one dose of study drug or ketamine. The treated set will be used for safety analyses.
- Pharmacodynamic set (PDS):
  PD analyses will be based on the PDS which is defined as all randomised patients who performed the post ketamine tests in at least one period. More details on the definition of the PDS and any potential updates will be provided in the TSAP.

All individual data will be listed.

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (IPD) categories will be suggested in the IQRMP and specified in more detail in the TSAP, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

7.2.2 Primary endpoint analyses

A linear mixed effects model will be used for the analysis of the primary endpoint. This model will include effects for sequence, subject within sequence, period, baseline values (obtained at screening visit 2 prior to and on ketamine) and treatment. The effect 'subject within sequence' will be considered as random, whereas the other effects will be considered as fixed. All three periods (if available) will be included in the analysis.

7.2.3 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be assessed statistically using the same methods as described for the primary endpoint.

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 11 days after the last dose of randomised trial medication, will be assigned to the on-treatment period for evaluation.

The safety analysis will be done by ‘treatment at onset’.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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

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

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

It is not planned to impute missing values.

7.4 RANDOMISATION

Subjects will be randomised in blocks to one of the 18 treatment sequences in a 1:1:…:1:1 ratio. Approximately equal numbers of subjects will be randomised to each sequence. 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.

7.5 DETERMINATION OF SAMPLE SIZE

This is an exploratory trial and the sample size is not based on any formal sample size estimation. Based on available literature, a sample size of 36 subjects, i.e. 24 within subject comparisons, is considered sufficient to detect relevant effects (BI 409306 versus placebo, BI 425809 versus placebo and Lamotrigine versus placebo).

The figures in the subsequent table are based on the following assumptions:

- Normative data in healthy subjects show a SD of about 12

- high retest reliability of the test results in small within patient differences (with low variability) in case the drug is not working. The table below shows as examples SDs of 3, 6 and 8.

- with increasing effect size variability of within patient differences is in increasing

Table 7.5: 1 Probabilities to observe certain differences between periods for given drug effects and standard deviations for a sample size of 24 within subject comparison.
Δ is the underlying true treatment difference and $\widehat{\Delta}$ the observed treatment difference.

Δ (Plc – BI)	SD(Δ)	Prob($\widehat{\Delta}$<=0)	Prob($\widehat{\Delta}$>=1)	Prob($\widehat{\Delta}$>=2)	Prob($\widehat{\Delta}$>=3)
0	3	50%	5%	<0.1%	
0	6	50%	21%	5%	<1%
0	8	50%	27%	11%	3%
4	6	<0.1%	99%	95%	79%
4	8	0.7%	97%	89%	73%
4	12	5%	89%	80%	66%
6	8	<0.1%	>99%	99%	97%

Based on this considerations it is unlikely to observe a difference to placebo of 2 or more errors with 24 within subject comparisons in case of no effect. The probability to observe a difference of 2 or more errors assuming a standard deviation of 3 is less than 0.1% and with an assumed SD of 8 about 11%. On the other hand, it is unlikely to observe a difference of less than 2 errors in case about 30%-50% of the [redacted] are restored resulting in a difference of presumably 4 to 6 errors or even more. In case of a true difference of 4 errors and an assumed SD of 12 the probability to observe a difference of at least 2 errors is still 80%.So, even if the variability is higher and multiple testing is considered the sample size of 36 subjects should suffice to detect a difference of about 30%-50% of the ketamine induced deficit.

So far no experience exist with the trial design in this setting and sequence or period effects cannot be excluded a priori. Therefore the sample size of 36 subjects, i.e. 2 per sequence and at least 8 per period is deemed the minimum to investigate whether such effects potentially exist.

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

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

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 webpage: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to 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 respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

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.

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 Investigators. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- ensure appropriate training and information of local clinical trial managers (CTM), Clinical Research Associates, and investigators of participating trial sites

BI 409306 and matching placebo, BI 425809 and matching placebo, and matching placebo to lamotrigine will be provided by the [redacted]. Lamotrigine and ketamine will be supplied by the pharmacies at the above mentioned investigators' sites.

Safety laboratory tests will be performed by the local laboratories of the trial sites.

[redacted]
at [redacted].

The genotyping of CYP2C19 will be performed at a contract analytical laboratory (details will be available prior to start of screening in the study).

[redacted].

[redacted].

[redacted].

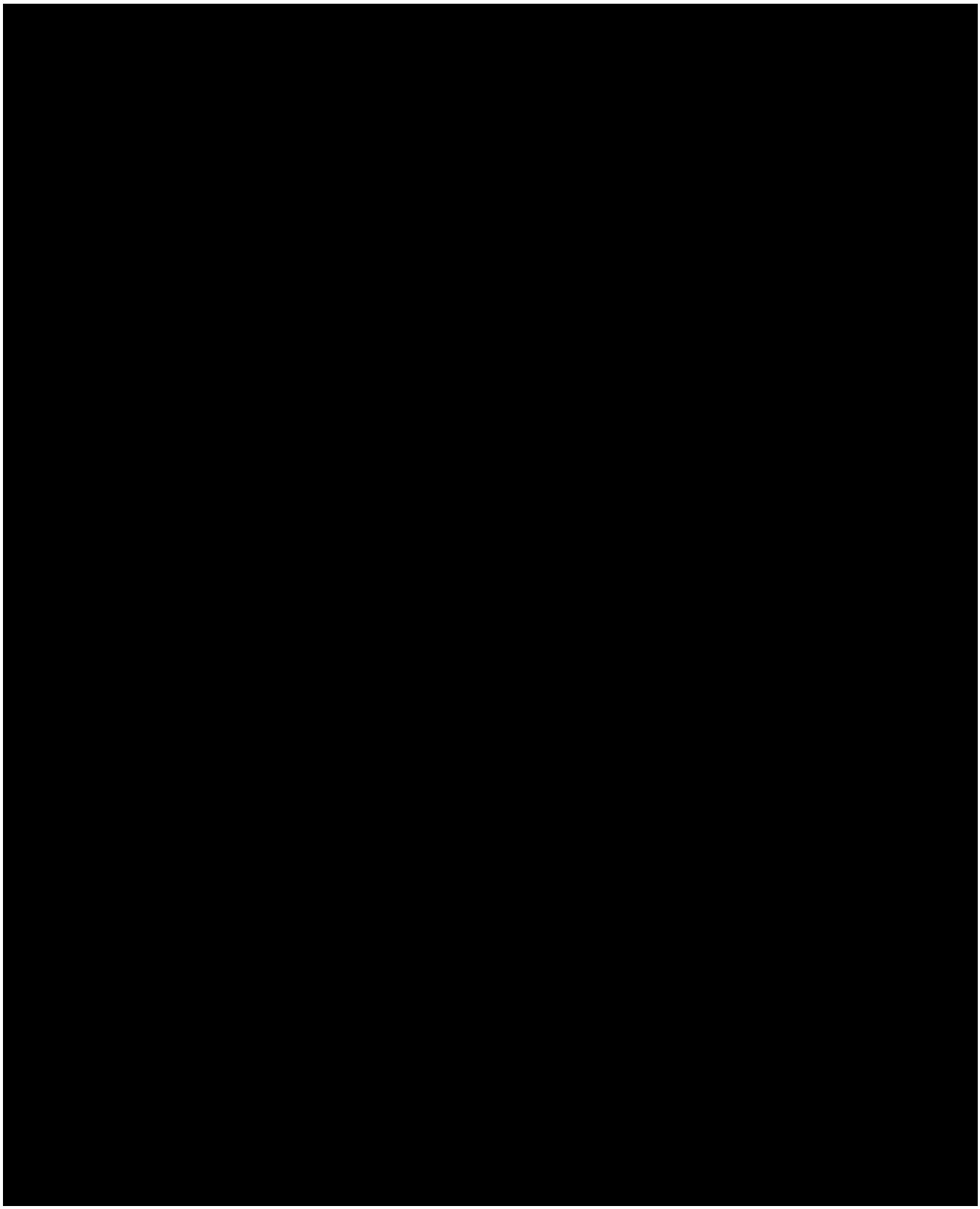
On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

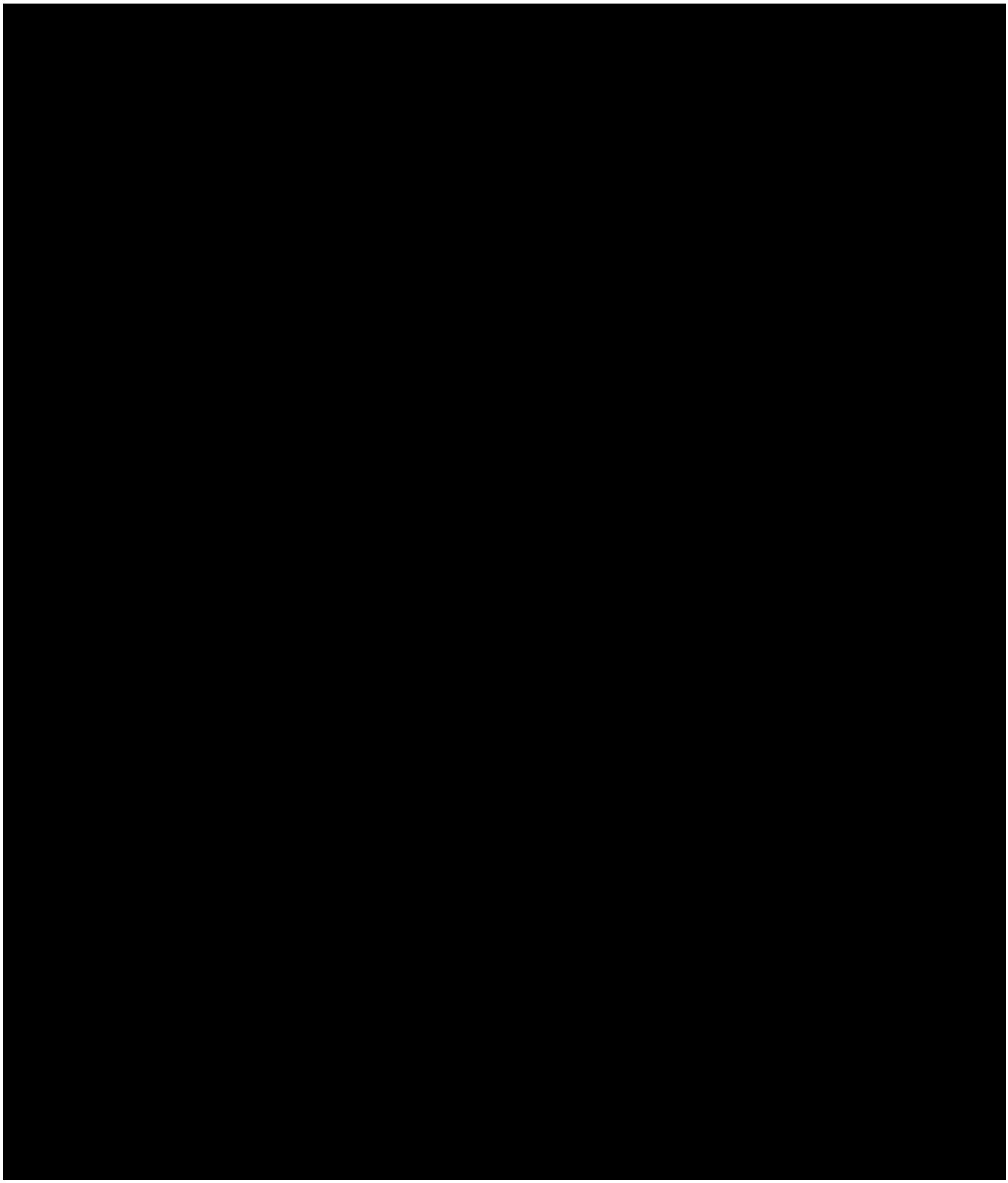
Data management and statistical evaluation will be done by BI according to BI SOPs.

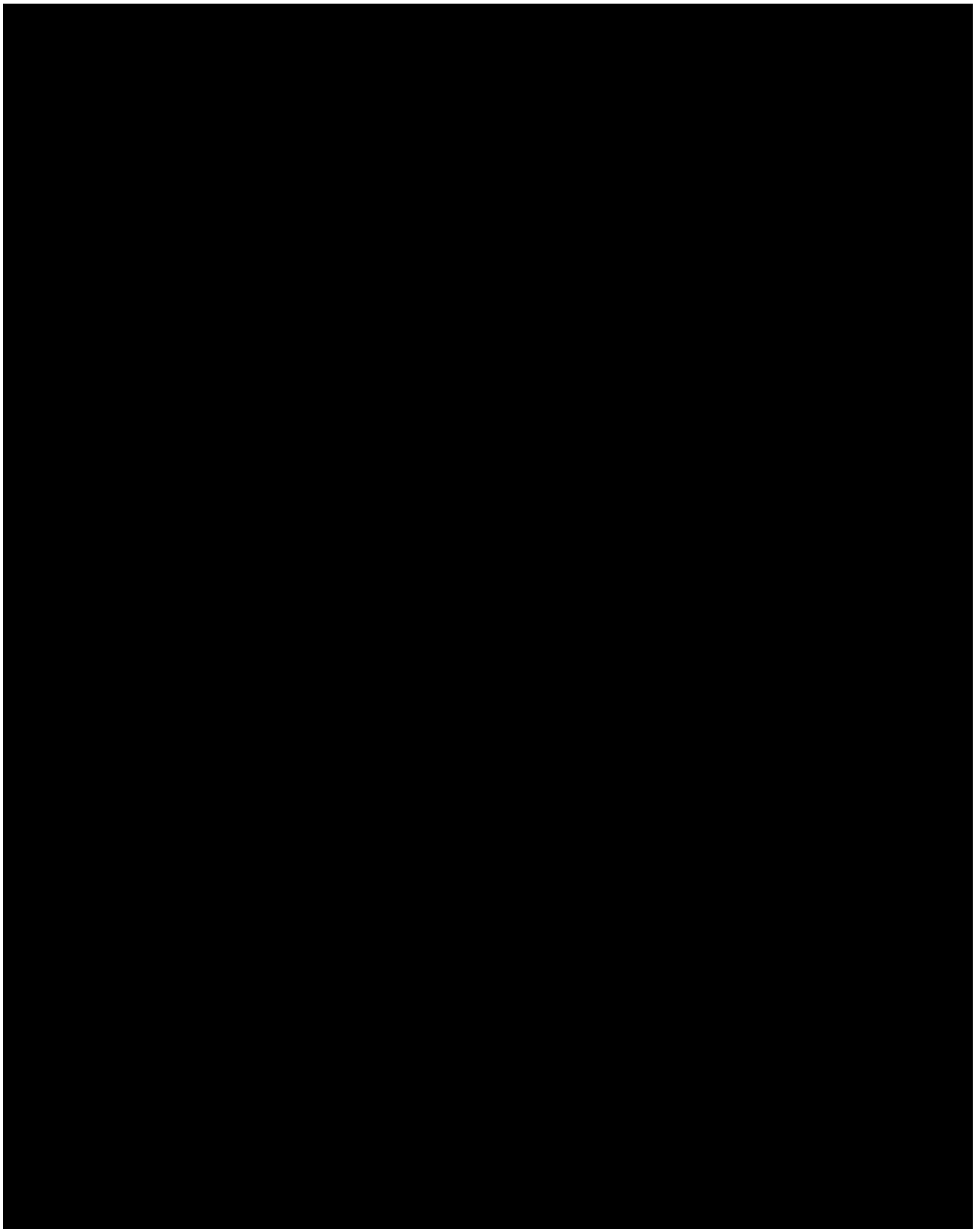
Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

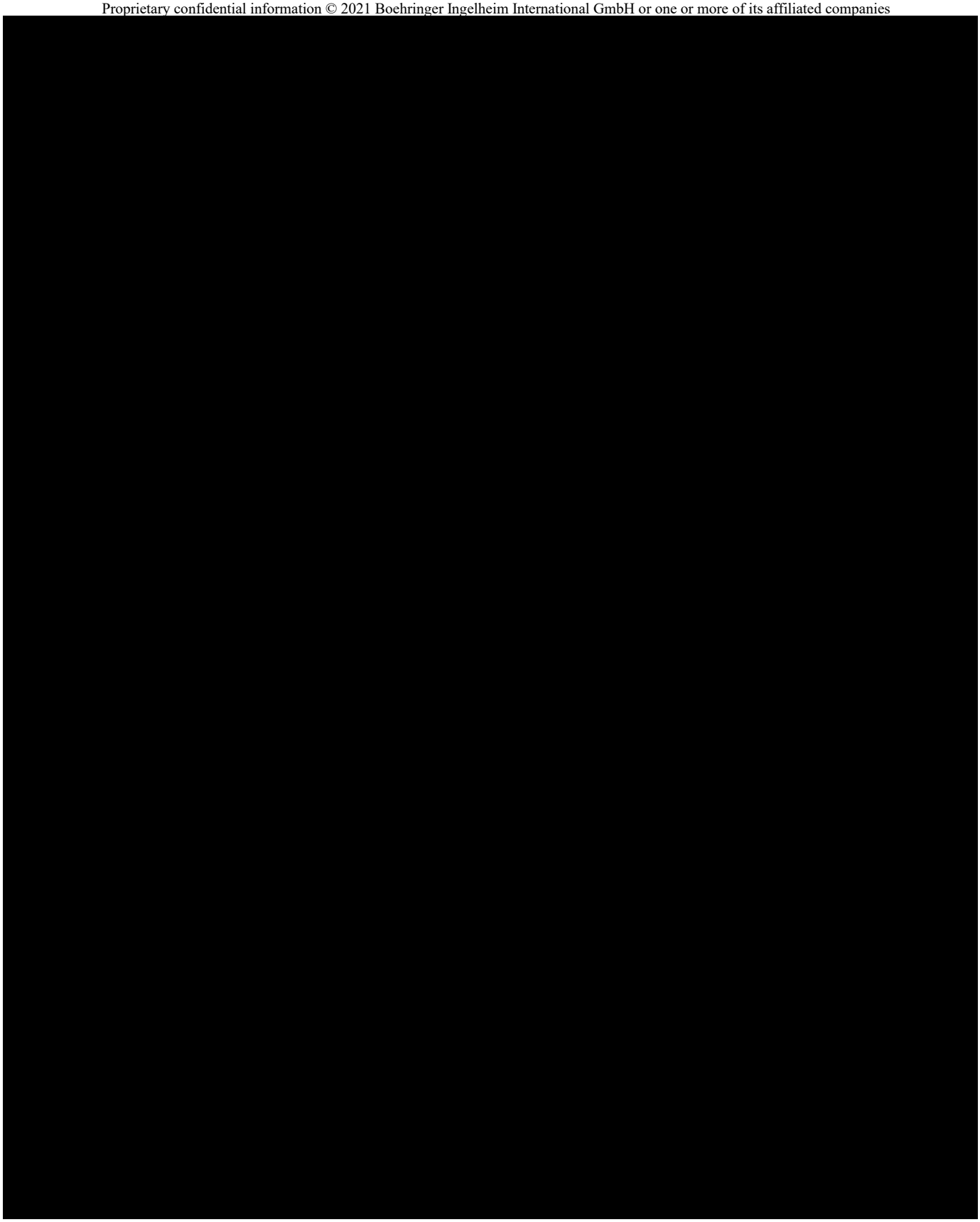
9. REFERENCES

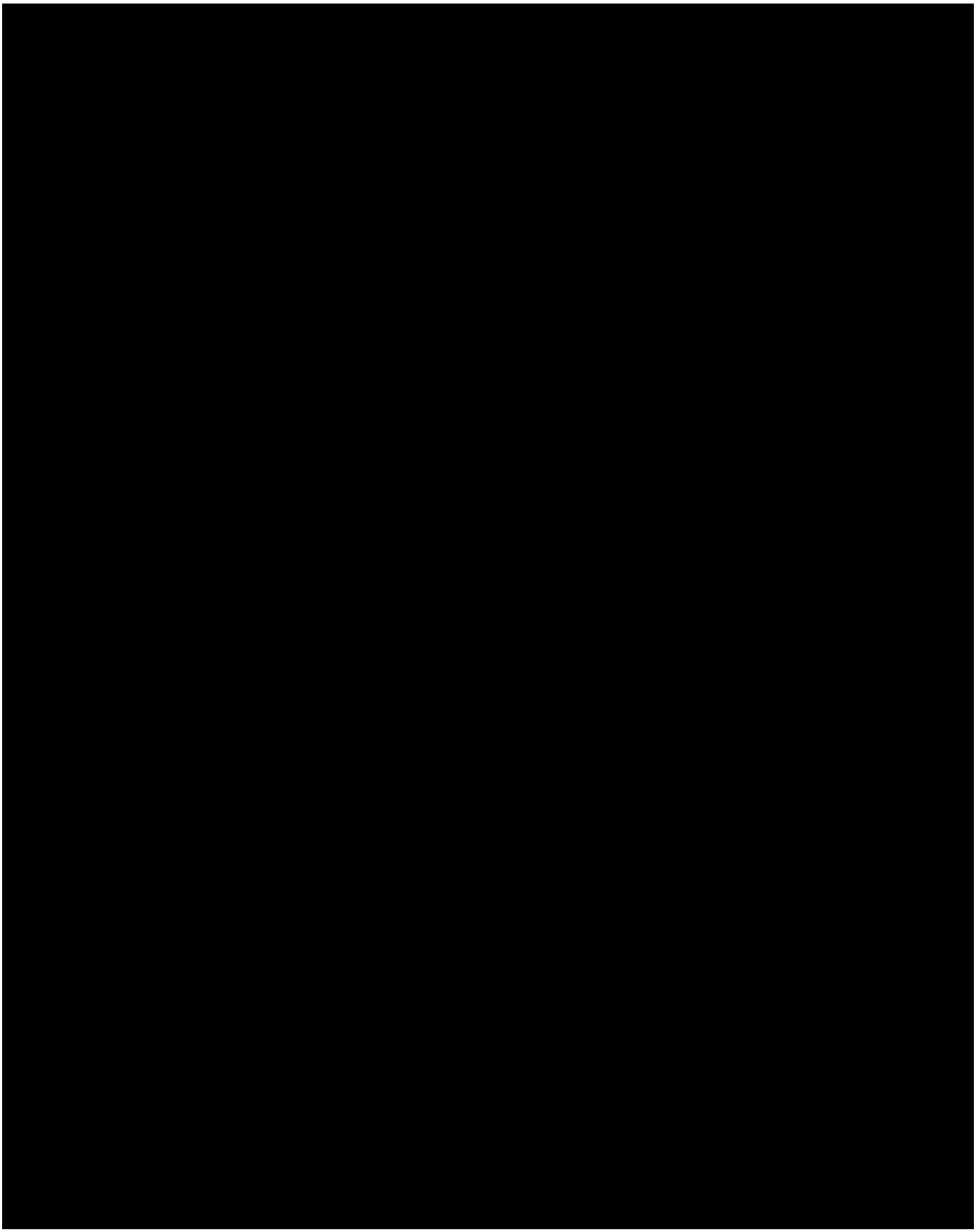
9.1 PUBLISHED REFERENCES

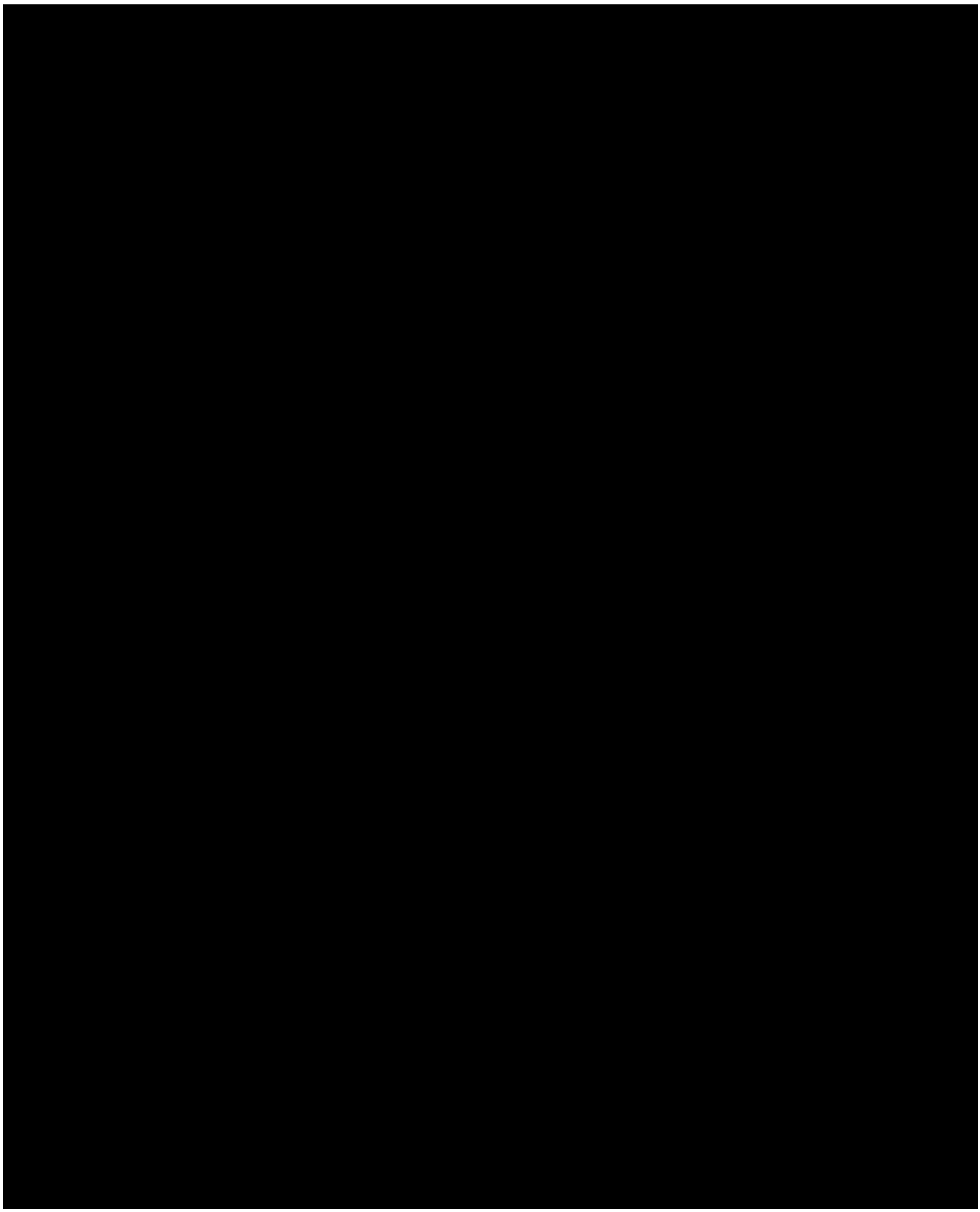




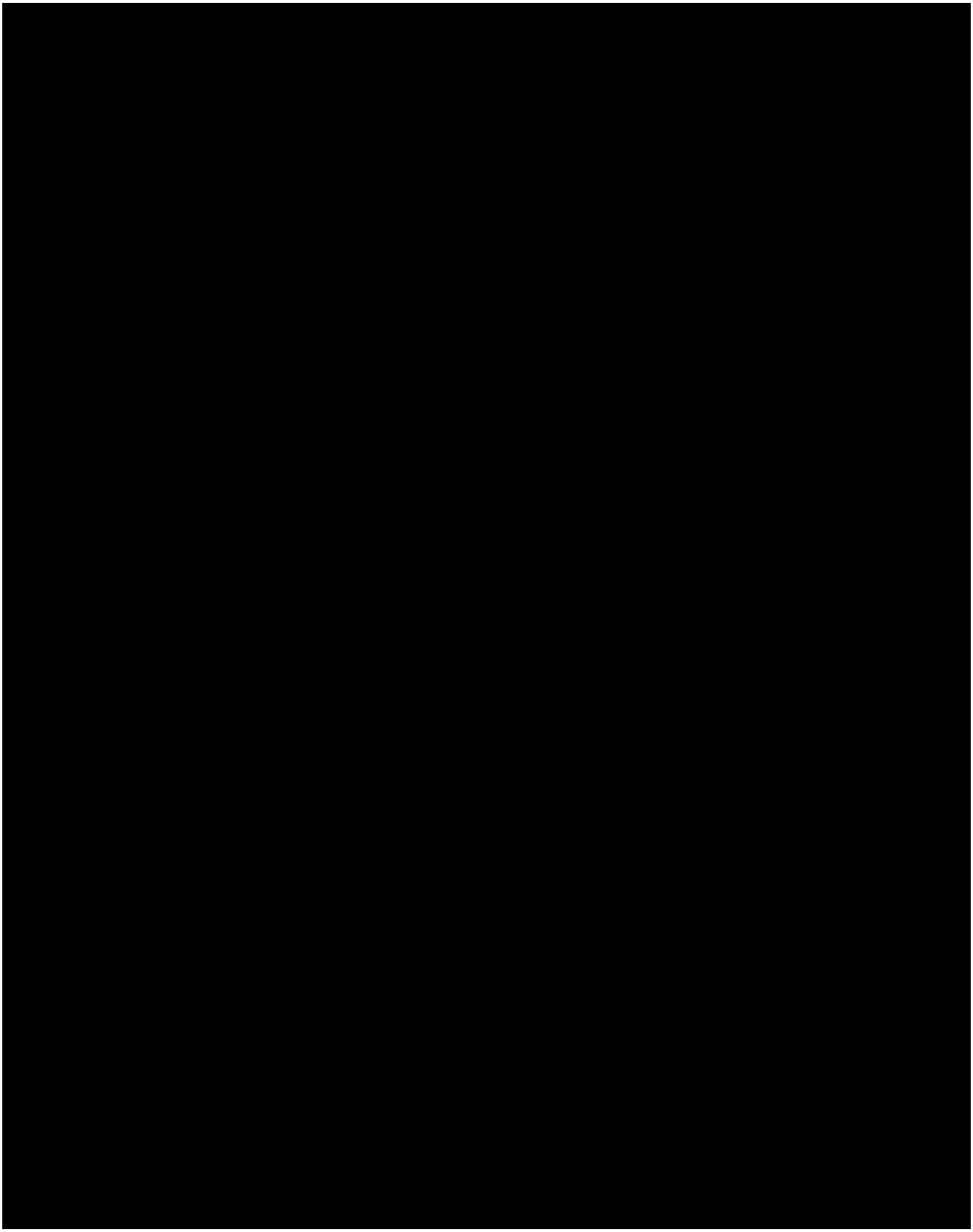








10. APPENDICES



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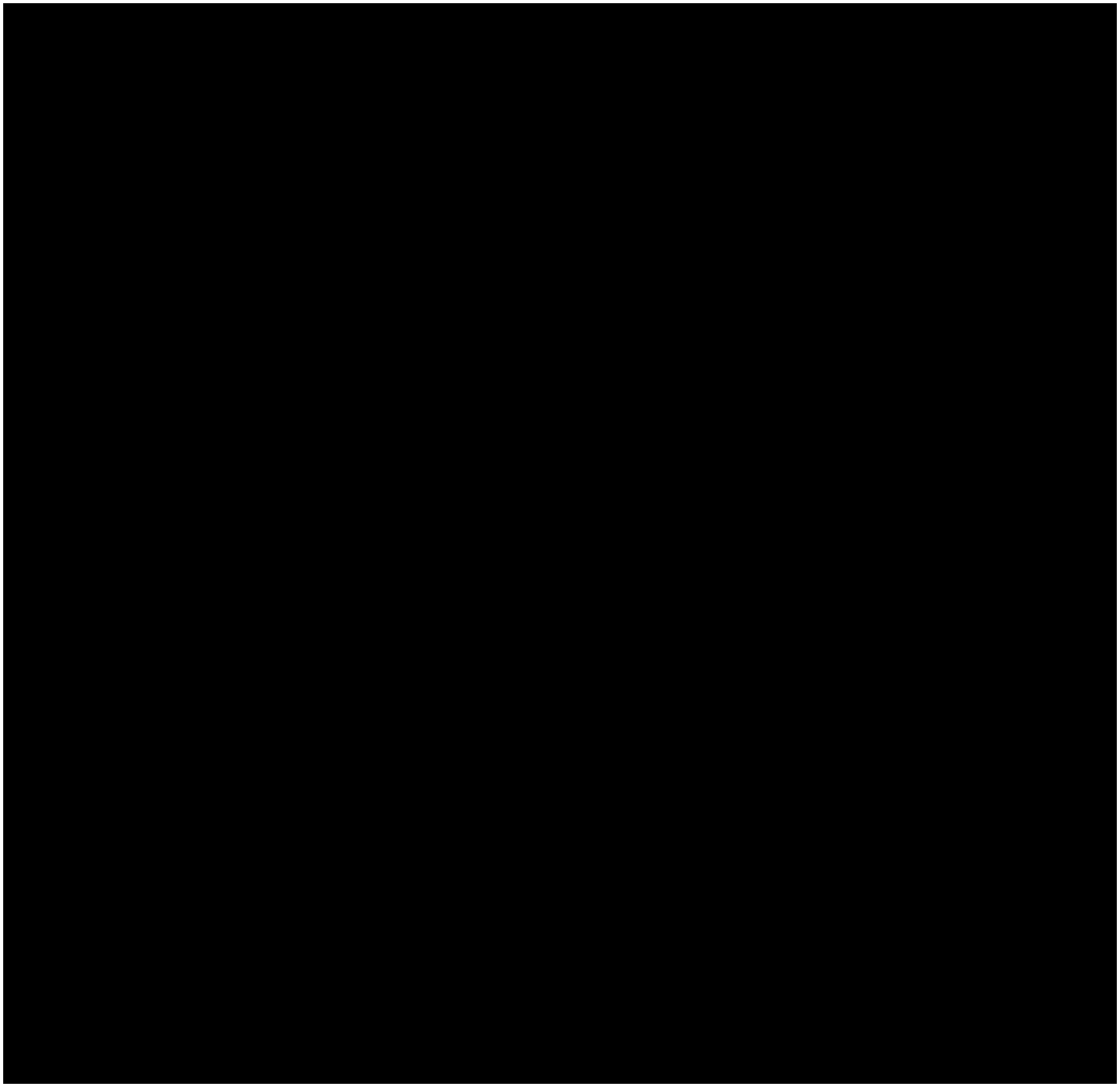

10.2 COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032.* ([redacted] *Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *and* [redacted] *Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032.* ([redacted] *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 [redacted]*, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_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 DIGIT SYMBOL SUBSTITUTION TEST (DSST)

Study: Boehringer Ingelheim 1289-0057 Date: ___ ___ / ___ ___ / ___ ___ ___ ___
Day Month Year

Visit Number: _____ Time of Assessment (24 Hour Clock): ___ ___ : ___ ___

Subject Number: ___ - ___ ___ ___ - ___ ___ ___ - ___ ___ ___

Coding

1	2	3	4	5	6	7	8	9
⌟	)	∧	–	‖	⊢	(	⌝	⊣

Demo Sample

6	8	3	9	5	4	1	7	2	1	4	8	2	7	6	9	3	5

8	3	1	9	2	5	6	4	3	7	2	9	8	1	4	7	6	5

9	1	2	4	7	2	5	6	9	5	8	6	4	3	1	7	8	3

1	3	9	6	3	9	7	5	1	4	2	8	7	2	8	5	6	4

7	6	4	1	3	2	8	1	7	9	2	5	3	4	8	6	5	9

8	1	9	5	1	4	2	6	9	8	7	3	5	6	4	7	2	3

3	6	8	9	1	8	4	7	5	2	9	6	7	1	5	2	3	4

6	4	1	9	5	7	3	6	8	3	2	7	5	8	4	2	9	1

Clinician Signature: _____

Date: _____ Boehringer Ingelheim 1289-0057 – DSST – Page 1 of 1

10.4 MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)

Study: Boehringer Ingelheim 1289-0057 Date: ____ ____/____ ____ ____/____ ____ ____ ____
Day Month Year

Visit Number: _____ Time of Assessment (24 Hour Clock): ____ ____ : ____ ____

Subject Number: ____-____ ____ ____-____ ____ ____-____ ____ ____

Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

Chernik, DA, Gillings, D, Laine, H, *et al*. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990; **10**:244– 51.

Please check the most appropriate level of responsiveness

Responsiveness	Score
☐ Responds readily to name spoken in normal tone	5 (Alert)
☐ Lethargic response to name spoken in normal tone	4
☐ Responds only after name is called loudly and/or repeatedly	3
☐ Responds only after mild prodding or shaking	2
☐ Responds only after painful trapezius squeeze	1
☐ Does not respond to painful trapezius squeeze	0

Clinician Signature: _____

Date: _____ Boehringer Ingelheim 1289-0057- MOAA/S - Page 1 of 1

10.5 CLINICIAN ADMINISTERED DISSOCIATIVE STATES SCALE (CADSS)

Study: Boehringer Ingelheim 1289-0057 Date: ____ ____ / ____ ____ ____ / ____ ____ ____ ____
Day Month Year

Visit Number: _____ Time of Assessment (24 Hour Clock): ____ ____ : ____ ____

Subject Number: ____ - ____ ____ ____ - ____ ____ ____ - ____ ____ ____

The Clinician Administered Dissociative States Scale (CADSS)

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

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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.

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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

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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

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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.

Clinician Signature: _____

Date: _____ Boehringer Ingelheim 1289-0057- CADSS - Page 5 of 5

10.6 STANDARDIZED FIELD SOBRIETY TEST (SFST)

The Standardized Field Sobriety Test (SFST) is a battery of three tests administered and evaluated in a standardized manner to obtain validated indicators of impairment, e.g. in persons who have used narcotics [R19-1364], [R19-1365]. These tests were developed based on research sponsored by the National Highway Traffic Safety Administration (NHTSA).

The three tests of the SFST are:

1. Horizontal gaze nystagmus (HGN):

   Hereby the investigator asks the subject to follow a torch light, moved horizontally about 25-30 cm in front of the subject`s eyes, only with his eyes, i.e. without moving the head. Occurrence of a nystagmus is considered an abnormal finding.

2. Walk-and-turn (WAT):

   In this test, the subject is directed to take nine steps, heel-to-toe, along a straight line, then turn on one foot and return in the same manner in the opposite.

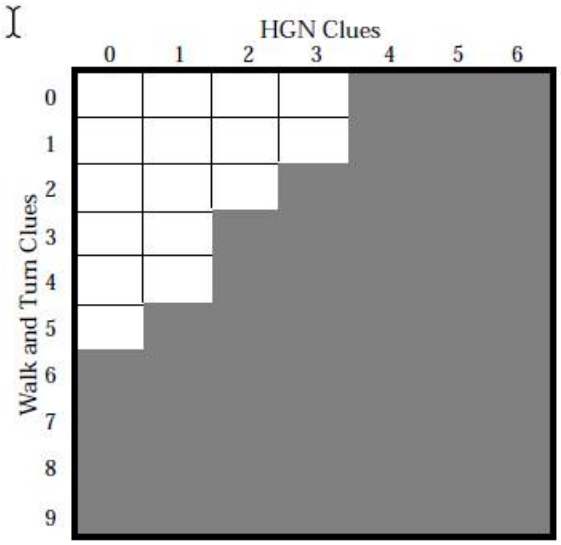
   The following signs are considered abnormal: the subject
   - cannot keep balance while listening to the instructions
   - begins before the instructions are finished
   - stops while walking to regain balance
   - does not touch heel-to-toe
   - steps off the line
   - uses arms to balance
   - makes an improper turn
   - takes an incorrect number of steps

3. One-leg stand (OLS):

   The subject is instructed to stand with one foot approx. 10 cm off the ground and count aloud by thousands (one thousand-one, one thousand-two, etc.) until told to put the foot down (after 30 seconds).

   Abnormal findings are:
   - swaying while balancing
   - using arms to balance
   - hopping to maintain balance
   - putting the foot down

The SFST findings are assessed using the following table:



If the subject's score is within the shaded area the subject may not be discharged until the result of control test lies within the white area.

10.7 SARS-COV-2/ COVID-19 RELATED BENEFIT-RISK ASSESSMENT AND RISK MITIGATION MEASURES

10.7.1 Introduction

Due to the COVID-19 pandemic early 2020, it was assessed (based on current knowledge) if treatment with BI 409306 and BI 425809, as well as lamotrigine and ketamine, may pose a higher risk associated with SARS-CoV-2 infection. The general risk of SARS-CoV-2/ COVID-19 in context of the trial population's underlying disease and common co-morbidities was assessed as well. In addition, risk mitigation measures were implemented to protect study participants and personal involved in clinical trials. This document summarizes the benefit-risk assessment and the measures in context of COVID-19 pandemic.

10.7.2 Benefit-Risk Assessment in Context of COVID-19 Pandemic

Risks in context of the trial medication

No additional risks related to administration of BI 409306 and BI 425809 have been identified. For details, refer to Benefit-Risk Assessments in context of COVID-19 pandemic for patients participating in clinical trials investigating BI 409306 [c32968037] and BI 425809 [c32354247].

The exact mechanism of action of lamotrigine have not been elucidated yet. Presumably, lamotrigine inhibits neuronal sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate). Ketamine is a non-competitive NMDA-receptor (NMDAR) antagonist. These effects are not expected to increase the risk of acquiring or progression of SARS-CoV-2/ COVID-19. So far, there is no evidence in the literature of increased risk of infection or severe illness upon treatment with lamotrigine or ketamine.

Considerations around drug-drug-interactions are not included in this benefit-risk assessment – for those it should be referred to the Investigator's Brochures of BI 409306 and BI 425809, Drug Label Information of lamotrigine ([redacted]) and ketamine ([redacted]), and the most recent label of the respective medication(s) used for treatment of COVID-19.

Risks in context of the trial population:

The study is planned in male healthy volunteers 18 to 55 years of age (inclusive). This population does not have co-morbid medical conditions that predispose to a higher risk of severe COVID-19. While it is understood that in general, older age is associated with more severe disease, mortality was highest amongst the oldest individuals (i.e. age ≥ 65) [R20-1319], who are not represented in this study population.

Procedure-related risks:

During COVID-19 pandemic, participation in this clinical study will increase the risk of SARS-CoV-2/ COVID-19 virus infection due to traveling to the trial site, overnight stays at the trial site and completing the protocol-defined procedures at the trial site during

ambulatory visits and overnight stays. Therefore, this study will only be conducted after the COVID-19 situation has been managed and in accordance with the local public health precautions.

The risk mitigation plan has been set up at both trial sites that detail specific precautionary measures (e.g. hygiene rules, wearing of face masks and physical distance), screening for SARS-CoV-2, and discontinuation of trial treatment of subjects with confirmed SARS-CoV-2/ COVID-19 virus infection.

Summary:

The overall benefit-risk assessment of participation in this clinical study for healthy subjects remains unchanged, i.e. low as indicated in Section 1.4, after consideration of COVID-19 risks and implementation of mitigation strategies. Thus, this trial can be conducted after the COVID-19 situation has been managed and in accordance with the local public health precautions.

The investigators will take the totality of information related to each single subject and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each subject's (continued) participation in the planned trial. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the subject.

10.7.3 Risk Mitigation Measures in Context of COVID-19 Pandemic

10.7.3.1 Screening Period

Subjects with positive PCR test from nasal swab for SARS-CoV-2 and/ or any clinical symptom suggestive for COVID-19 virus infection at *screening examination (V1)* and each time within 72 hours prior to admission to trial site at *screening ketamine challenge (V2)* and *treatment period 1 (V3, if subjects leave the site premises after V2)* will be not eligible for this study.

The following measures will be performed:

(1) Study participants will be informed about, and asked to agree to SARS-CoV-2/ COVID-19 specific requirements with their diagnostic, therapeutic, and legal implications

(2) Evaluation of subjects for SARS-CoV-2/ COVID-19 will be performed at *screening examination (V1)* and each time not later than 72 hours prior to admission to trial site at *screening ketamine challenge (V2)* and *treatment period 1 (V3)*, including

- Temperature assessment
- Questionnaire and medical assessment
- PCR test for SARS-CoV-2 from a nasal swab sample

10.7.3.2 Treatment Periods

Evaluation of subjects will be performed each time not later than 72 h prior to admission to trial site in *treatment periods 2 and 3 (V4 and V5)*, incl. temperature assessment, questionnaire and medical assessment, and PCR test for SARS-CoV-2 from a nasal swab sample.

In case COVID-19 is suspected in a subject during trial participation, a SARS-CoV-2 PCR test and other applicable diagnostic measures (if required, e.g. CT of lungs) will be initiated without delay.

- If COVID-19 virus infection is confirmed, the measures will include isolation, sponsor/ authority notification, contact tracing and other as appropriate. Subjects who discontinue treatment should undergo the EoTrial Visit, but only after recovery from COVID-19 is confirmed incl. negative SARS-CoV-2 viral testing in accordance to the local public health precautions.

- If COVID-19 virus infection is not confirmed by SARS CoV-2 PCR test and other applicable criteria, the treatment may be not discontinued, but the next treatment (if applicable) will be conservatively postponed for at least 10 days have passed since symptoms first appeared and at least 72 hours have passed since last fever without the use of fever-reducing medications and symptoms (e.g., cough, shortness of breath) have resolved. Ultimately, clinical judgement and suspicion of SARS-CoV-2 infection determine whether to discontinue the subject for trial treatment.

The Risk Mitigation and Response Plans fully describing the site-specific measures related to SARS-CoV-2/ COVID-19 (e.g. hygiene rules, wearing of face masks and physical distance) will be filed in the ISF.

10.7.4 Assessment of Adverse Events related to COVID-19

For any AE related to SARS-CoV-2/ COVID-19, please note the BI standard processes should be followed, meaning:

(1) If a SARS-CoV-2/ COVID-19 virus infection is associated with clinical symptoms (AEs):

- Report as a non-serious AE, if the serious criteria are not met
- Report as a SAE, if serious criteria are met – e.g., hospitalization, serious for medical reasons, or AE term describing the clinical symptoms is on the “always serious list”. The mere fact that someone is infected with the SARS-CoV-2/ COVID-19 should not lead to a judgement of seriousness

(2) If a SARS-CoV-2/ COVID-19 virus infection is not associated with clinical symptoms, meaning there is just a positive SARS-CoV-2 PCR test:

- Report as a (non-serious) AE, as a positive test means a subject has an infection

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		25 Aug 2020
EudraCT number **EU number**		n.a.
BI Trial number		1289-0057
BI Investigational Medicinal Products		BI 409306, BI 425809
Title of protocol		A study in healthy men to test whether BI 409306, BI 425809 or lamotrigine can reverse the memory problems caused by ketamine
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 Clinical Trial Protocol Synopsis Flow Charts A-D Sections 1-9 Appendices 10.1, 10.3-10.7
Description of change		1. BI 425809 (T3) treatment arm has been added. Drug profile and B/R assessment related to BI 425809 have been described. 2. The number of total entered subjects has been increased to 36. 3. Randomisation of subjects will be conducted applying incomplete block design: each subject will receive R treatment and 2 of 3 randomly allocated T1 or T2 or T3. 4. Washout period between treatments has been increased to 11 days [redacted]. 5. Flow Charts B, C and D detailing procedures at screening examination, screening ketamine challenge and treatment days have been added; Flow Chart A (Summary) has been updated. 6. [redacted] will be implemented during the breaks between the CANTAB tests (pre-ketamine and during ketamine infusion) and in the start of ketamine infusion.

		[redacted] 8. Light breakfast and light snack (clear liquid) will be served not later than 5h and 2h accordingly before the start of ketamine infusion. 9. SARS-CoV-2 virus PCR tests are being implemented at screening examination and shortly before each admission to the study site. 10. Exclusion and Discontinuation of trial treatment criteria specific to SARS-CoV-2/ COVID-19 have been added. 11. B/R assessment and risk mitigation measures in context of COVID-19 pandemic have been summarized in Appendix 10.7.
Rationale for change		1-5. Due to progress in clinical development, BI 425809 has been included as additional treatment (T3) in the study, which required further update of the study design. [redacted]. 8. Because of increased total duration of procedures at screening ketamine challenge and treatment days, meals will be served in order to avoid prolonged fasting and related to it common AEs. 9-11. Due to the COVID-19 pandemic, and given infected individuals may be clinically asymptomatic, the study design has been adapted to safeguard the subject's safety, and exclude infected volunteers from study participation.

11.2 GLOBAL AMENDMENT 2

Date of amendment		12 Nov 2021
EudraCT number **EU number**		n.a.
BI Trial number		1289-0057
BI Investigational Medicinal Products		BI 409306, BI 425809
Title of protocol		A study in healthy men to test whether BI 409306, BI 425809 or lamotrigine can reverse the memory problems caused by ketamine

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		1. Clinical Trial Protocol Synopsis 2. Flow Charts C-D 3. Section 3.3.3 4. Section 5.6.1.1
Description of change		1. Number of subjects in each treatment has been clarified. Criteria of normative performance on CANTAB PAL test have been clarified. 2. In Screening V2, admission of subjects is allowed in the evening before the screening ketamine challenge. In V2-V5, admission in the morning of ketamine challenge is also possible at discretion of the Investigator or designee. 3. Exclusion criteria have been clarified. 4. Methods of pharmacogenomics sample collection have been adapted to include requirements of the sites' local laboratories, as well as the central lab
Rationale for change		Changes are based on the need to facilitate and operationally adapt the procedures of Screening Visit 2 by including an overnight stay prior to screening ketamine challenge. With this amendment minor inconsistencies in the study protocol have been corrected and other protocol clarifications have been provided.

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-03

Title: A randomized, placebo controlled, double-blind, double-dummy three-way cross over trial to investigate the effect of BI 409306, BI 425809 and lamotrigine on ketamine-induced cognitive deficits in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	16 Nov 2021 12:46 CET
Verification-Paper Signature Completion		18 Nov 2021 09:32 CET
Approval-Team Member Medicine		18 Nov 2021 20:27 CET
Approval-Biostatistics		19 Nov 2021 13:00 CET

(Continued) Signatures (obtained electronically)

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