Clinical Trial Protocol

	Document Number:	**c26441810-03**
EudraCT No.	2019-000468-36	
BI Trial No.	1346-0039	
BI Investigational Medicinal Product	BI 425809	
Title	A study to investigate the effects of memantine on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (non-randomized, single-arm, open-label, three-period, one fixed sequence cross-over study)	
Lay Title	A study in healthy men and women to test which effects memantine and BI 425809 have on each other	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: + Fax: +	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 19 July 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	19 March 2019
Revision date	19 July 2019
BI trial number	1346-0039
Title of trial	A study to investigate the effects of memantine on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (non-randomized, single-arm, open-label, three-period, one fixed sequence cross-over study)
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	Memantine is a common medication used in patients diagnosed with Alzheimer's Disease (AD). Since BI 425809 is developed as a symptomatic treatment for AD it is very likely that it may be used on top of memantine in clinical practice. Therefore, it is crucial to investigate if there are any relevant pharmacokinetic interactions between BI 425809 and memantine when administered together before their concomitant use could be allowed in Phase 3 trials and later in clinical practice.
Trial objectives	To investigate the effect of steady state exposure of memantine on the steady-state pharmacokinetics of BI 425809 and vice versa in healthy subjects
Trial design	Non-randomized, single arm, open-label, three-period, one fixed sequence cross-over design
Trial endpoints:	Primary endpoints: • $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 425809 in blood • $AUC_{\tau,ss}$ and $C_{max,ss}$ of memantine in blood
Number of subjects **total entered**	N = 16
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male/female subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Trial product 1 **dose** **mode of admin.**	BI 425809, film coated tablet 25 mg Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 2 **dose** **mode of admin.**	Memantine film-coated tablets 5 mg, 10 mg, 15 mg, 20 mg Oral administration with 240 mL of water. Memantine dosing follows an up-titration regime from 5 mg to 20 mg for tolerability reasons

Duration of treatment	***Period 1 = Visit 2:*** *Treatment R1 (Reference 1 = BI 425809 alone)* Trial product 1: Days 1-10: multiple doses of 25 mg BI 425809 q.d. Period 1 and 2 will be separated by a wash-out phase of at least 7 days between last treatment administration in Period 1 and first treatment administration in Period 2. ***Period 2 = Visit 3:*** *Up-Titiration to R2 followed by Treatment R2 (Reference 2 = Memantine alone)* Trial product 2: Up-titration regimen to Treatment R2, i.e. Days 1-7: multiple doses of 5 mg memantine q.d. Days 8-14: multiple doses of 10 mg memantine q.d. Days 15-21: multiple doses of 15 mg memantine q.d Days 22-28: multiple doses of 20 mg memantine q.d Trial product 2: Treatment R2, i.e. Days 29-35: multiple doses of 20 mg memantine q.d ***Period 3 = Visit 4:*** *Treatment T (Test = BI 425809 + Memantine)* Trial product 1: Days 1-10 multiple doses of 25 mg BI 425809 q.d. Trial product 2: Days 1-10 multiple doses of 20 mg memantine q.d. Period 3 follow directly of period 2, i.e. the last day of period 2, is the calendar day before the first day of period 3.
Statistical methods	The effects of BI 425809 on the pharmacokinetics of memantine (T to R1) and the effects of memantine on the pharmacokinetics of BI 425809 (T to R2) will be evaluated based on the ratio (test to reference treatment) of the point estimates of the geometric means (gMeans) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for ‘subject’ and ‘treatment’. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Safety assessments	PK BI 425809 blood	PK memantine blood	PK urine memantine	C-SSRS	Vital signs (BP, PR) & 12-lead ECG	Questioning for AEs and concomitant therapy[6]
SCR	1	-21 to -1			Screening (SCR)[1]	x	x[12,17]				x	x	
1[18]	2	-1	-14:00	18 :00	Admission to trial site	x[5]	x[12,17]				x		x
		1	-2:00	06:00	Allocation to subject numbers[2]	x[2]		x[2]	x[2]			x[2]	x[2]
			0:00	08:00	Administration of 25 mg BI 425809								
			0:30	08:30				x					
			1:00	9:00				x					
			2:00	10:00	240 mL fluid intake			x					
			3:00	11:00				x					
			3:30	11:30				x					
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]			x				x	x
			4:30	12:30				x					
			5:00	13:00				x					
			6:00	14:00				x					
			7:00	15:00				x					
			8:00	16:00	Snack (voluntary)			x					
			10:00	18:00				x					
			11:00	19:00	Dinner[3]							x	x
			12:00	20:00				x					
		2	24:00	08:00	Administration of 25 mg BI 425809	x		x[8]					x
			25:00	09:00	Breakfast (voluntary), discharge from trial site							x	x
		3	48:00	08:00	Ambulatory visit, Administration of 25 mg BI 425809								x
		4	72:00	08:00	Ambulatory visit, Administration of 25 mg BI 425809								x
		5	96:00	08:00	Ambulatory visit, Administration of 25 mg BI 425809	x							x
		6	120:00	08:00	Ambulatory visit, Administration of 25 mg BI 425809								x
		7	144:00	08:00	Ambulatory visit, Administration of 25 mg BI 425809								x
		8	168:00	08:00	Ambulatory visit, Administration of 25 mg BI 425809								x

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Safety assessments	PK BI 425809 blood	PK memantine blood	PK urine memantine	C-SSRS	Vital signs (BP, PR) & 12-lead ECG	Questioning for AEs and concomitant therapy [6]
		9	192:00	08:00	Ambulatory visit, Administration of 25 mg BI 425809	x							x
			202:00	18:00	Admission to trial site	x[5]	x[12]				x		x
		10	216:00	08:00	Administration of 25 mg BI 425809			x[8]				x[2]	x[2]
			216:30	08:30				x					
			217:00	09:00				x					x
			218:00	10:00	240 mL fluid intake			x					x
			219:00	11:00				x					x
			219:30	11:30				x					
			220:00	12:00	240 mL fluid intake, thereafter lunch[3]			x				x	x
			220:30	12:30				x					
			221:00	13:00				x					
			222:00	14:00				x					x
			223:00	15:00				x					
			224:00	16:00	Snack (voluntary)[3]			x					x
			226:00	18:00				x					x
			227:00	19:00	Dinner								
			228:00	20:00				x				x	x
		11	240:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x	x[12]	x			x	x	x
2[18]	3[7]	1	-2:00	06:00	Admission to trial site	x[2,5]	x[2,12]		x[2]	x	x[2]	x[2]	x[2]
			0:00	08:00	Administration of 5 mg Memantine					[13]			
			0:30	08:30					x				
			1:00	09:00					x				x
			2:00	10:00	240 mL fluid intake				x				x
			3:00	11:00					x				x
			3:30	11:30					x				
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]				x			x	x
			4:30	12:30					x				
			5:00	13:00					x				
			6:00	14:00					x				x
			7:00	15:00					x				
			8:00	16:00	Snack (voluntary)[3]				x			x	x
			10:00	18:00					x				x
			11:00	19:00	Dinner								
			12:00	20:00					x			x	x
		2	24:00	08:00	Administration of 5 mg Memantine				x[8]			x[2]	x[2]
			25:00	09:00	Breakfast (voluntary)[3], discharge from trial site		x[12]				x	x	x
		3 -7	48:00[15]	08:00	Ambulatory visit, Administration of 5 mg Memantine	x[2,10]						x[2,9]	x[2,9]

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Safety assessments	PK BI 425809 blood	PK memantine blood	PK urine memantine	C-SSRS	Vital signs (BP, PR) & 12-lead ECG	Questioning for AEs and concomitant therapy [6]
		8 -14	168:00[15]	08:00	Ambulatory visit, Administration of 10 mg Memantine	x[2,10]	x[12,16]		x[8,16]			x[2,9]	x[2,9]
		15-21	336:00[15]	08:00	Ambulatory visit, Administration of 15 mg Memantine	x[2,10]	x[12,16]		x[8,16]			x[2,9]	x[2,9]
		22-33	504:00[15]	08:00	Ambulatory visit, Administration of 20 mg Memantine	x[2,14]	x[12,16]		x[8,11]			x[2,9]	x[2,9]
		34	792:00	08:00	Ambulatory visit, Administration of 20 mg Memantine				x[8]			x	x
			802:00	18:00	Admission to trial site	x[5]	x[12]				x		x
		35	816:00	08:00	Administration of 20 mg Memantine	x[2]			x[8]	[13]		x[2]	x[2]
			816:30	08:30					x				
			817:00	09:00					x				x
			818:00	10:00	240 mL fluid intake				x				x
			819:00	11:00					x				x
			819:30	11:30					x				
			820:00	12:00	240 mL fluid intake, thereafter lunch[3]				x				x
			820:30	12:30					x				
			821:00	13:00					x				
			822:00	14:00					x				x
			823:00	15:00					x				
			824:00	16:00	Snack (voluntary)[3]				x				x
			826:00	18:00					x				x
			827:00	19:00	Dinner								
			828:00	20:00					x			x	x
3	4[7]	1	0:00	08:00	Administration of 25 mg BI 425809 and 20 mg Memantine	x		x[8]	x[8]			x[2]	x[2]
			1:00	09:00	Snack (voluntary)[3]								
			2:00	10:00									
			4:00	12:00	lunch[3]							x	x
			6:00	14:00									
			8:00	16:00	Snack (voluntary)[3]							x	x
			10:00	18:00									
			11:00	19:00	Dinner								
			12:00	20:00								x	x
		2	24:00	08:00	Administration of 25 mg BI 425809 and 20 mg Memantine							x[2]	x
		3	48:00	08:00	Administration of 25 mg BI 425809 and 20 mg Memantine							x[2]	x[2]
			49:00	09:00	Breakfast (voluntary)[3], discharge from trial site		x[12]				x	x	x

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Safety assessments	PK BI 425809 blood	PK memantine blood	PK urine memantine	C-SSRS	Vital signs (BP, PR) & 12-lead ECG	Questioning for AEs and concomitant therapy [6]
		4	72:00	08:00	Ambulatory Visit: Administration of 25 mg BI 425809 and 20 mg Memantine	x						x[2]	x[2]
		5	96:00	08:00	Ambulatory Visit: Administration of 25 mg BI 425809 and 20 mg Memantine			x[8]	x[8]			x[2]	x[2]
		6	120:00	08:00	Ambulatory Visit: Administration of 25 mg BI 425809 and 20 mg Memantine			x[8]	x[8]			x[2]	x[2]
		7	144:00	08:00	Ambulatory Visit: Administration of 25 mg BI 425809 and 20 mg Memantine								x[2]
		8	168:00	08:00	Ambulatory Visit: Administration of 25 mg BI 425809 and 20 mg Memantine								x[2]
		9	192:00	08:00	Ambulatory Visit: Administration of 25 mg BI 425809 and 20 mg Memantine			x[8]	x[8]			x[2]	x[2]
			202:00	18:00	Admission to trial site	x[5]	x[12]				x		x
		10	216:00	08:00	Administration of 25 mg BI 425809 and 20 mg Memantine	x[2]		x[8]	x[8]	[13]		x[2]	x[2]
			216:30	08:30				x	x				
			217:00	09:00				x	x				x
			218:00	10:00	240 mL fluid intake			x	x				x
			219:00	11:00				x	x				x
			219:30	11:30				x	x				
			220:00	12:00	240 mL fluid intake, thereafter lunch[3]			x	x				x
			220:30	12:30				x	x				
			221:00	13:00				x	x				
			222:00	14:00				x	x				x
			223:00	15:00				x	x				
			224:00	16:00	Snack (voluntary)[3]			x	x				x
			226:00	18:00				x	x				x
			227:00	19:00	Dinner								
			228:00	20:00				x	x				x
		11	240:00	08:00	Breakfast (voluntary)[3], discharge from trial site		x[12]	x	x		x	x	x
		18			Phone call								x
FU	5	32 -37			End of trial (EoTrial) examination[4]	x	x[12,17]				x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, visual tests, C-SSRS assessment, ECG, safety laboratory (including drug screening and alcohol breath test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. End of trial examination includes physical examination including neurological assessment, vital signs, visual tests, C-SSRS assessment, ECG, safety laboratory, recording of AEs and concomitant therapies,.
5. Only urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. There will be no further wash-out period between visit 3 and 4, i.e. Day 1 of Visit 4 the following calendar day of Day 35 visit 3
8. The sample is to be taken within 10 min prior to next dosing
9. During the up-titration phase to steady state vital signs, ECG and AE/CT questioning is performed on each day prior to memantine medication
10. During the up-titration phase to steady state safety lab is taken at the last day of each memantine dose level
11. Only on day 22 and 33
12. Neurological assessment for details refer to Section 5.2.1
13. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals as indicated above. For technical reasons the planned stop time of the urine sample obtained starting visit 3, 828:00, will be 840:00.
14. Only on day 28
15. The column “planned time” only includes start time of the first day of the respective interval of days
16. To be done on the first day of each dose level
17. Visual tests, for details refer to Section 5.2.3
18. Period 1 and 2 will be separated by a wash-out phase of at least 7 days between last treatment administration in Period 1 and first treatment administration in Period 2

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
C-SSRS	Columbia Suicide Severity Rating Scale
CA	Competent authority
CI	Confidence interval
CIAS	Cognitive impairment associated with schizophrenia
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRA	Clinical Research Associates
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	Contract Research Organisation
CTL	Clinical Trial Leader
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture

EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
GlyT1	Glycine transporter 1
gMean	Geometric mean
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IPD	Important protocol deviations
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
NMDAR	NMDA receptor
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
q.d.	quaque die (once a day)
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
RTA	Renal tubular acidosis
SAE	Serious adverse event
SCR	Screening

SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
XTC	Ecstasy

1. INTRODUCTION

BI 425809 is a glycine transporter 1 (GlyT1) inhibitor that is being developed for symptomatic treatment of Alzheimer's Disease (AD) and cognitive impairment associated with schizophrenia (CIAS).

1.1 MEDICAL BACKGROUND

Schizophrenia and AD are chronic, severe, and disabling brain disorders affecting both men and women. Both disorders are characterized by abnormalities in glutamatergic pathways related to N-methyl-D-aspartate (NMDA) receptor hypofunction in cortical and hippocampal brain areas. These abnormalities are hypothesized to lead to negative symptoms and cognitive impairment in schizophrenia and cognitive impairment in AD. Inhibition of GlyT1 aims at improving NMDA receptor hypoactivation in patients with schizophrenia and AD by increasing the concentration of the NMDA receptor co-activator glycine in the synaptic cleft, thereby leading to improvement of negative and cognitive symptoms in patients with schizophrenia (as add-on therapy to antipsychotics) as well as to cognitive improvement in AD patients (as add-on therapy to acetylcholinesterase inhibitors).

BI 425809 is a potent and selective inhibitor of GlyT1 and does not show species selectivity regarding inhibition of human, rat and pig GlyT1. In vivo proof-of-mechanism (i.e. target engagement in brain) is demonstrated by a dose dependent increase of glycine in rat cerebrospinal fluid. Results from pre-clinical studies with BI 425809 have demonstrated pro-cognitive properties in relevant animal models of learning and memory impairment. Therefore it is expected that treatment with BI 425809 has the potential to improve cognitive functioning in patients with AD and CIAS.

BI 425809 has been administered to healthy volunteers in so far 8 Phase 1 trials, one Phase 1 trial in healthy volunteers and 2 Phase 2 trials in patients are currently ongoing. In addition, BI 425809 is not a first in class compound. Other GLYT1 inhibitors (e.g. Bitopertin and sarcosine) have been tested in clinical trials before (R13-4447, R13-4508).

1.2 DRUG PROFILE

1.2.1 BI 425809

1.2.1.1 Non-clinical pharmacokinetics

Elimination of BI 425809 in preclinical species and humans primarily occurs through oxidation. CYP3A is predicted to contribute to >90% of the hepatic metabolism of BI 425809 which is consistent with a 6-fold increase in BI 425809 $AUC_{0-\infty}$ with co-administration of itraconazole, a specific CYP3A inhibitor [c03355329].

however, once daily, oral administration of BI 425809 (25 mg) resulted in mild induction of CYP3A-mediated elimination of the sensitive CYP3A substrate, midazolam, in humans [c08949593].

In vitro inhibition of P-gp by BI 425809 did not translate into a clinically relevant exposure change of digoxin (a selective P-gp substrate) in humans [c08949593].

1.2.1.2 Non-clinical safety pharmacology and toxicology

A comprehensive package of safety pharmacology, genetic toxicology, embryo-foetal development and general toxicology studies have been conducted that support repeated administration of BI 425809 to adult human subjects for up to 13 weeks duration, including women of child-bearing potential with a medically acceptable method of contraception. As preclinical studies to assess pre- and post-natal development have not been performed yet BI 425809 may not be administered to women who are, or who may be, breastfeeding.

In summary, there were no effects on blood pressure, heart rate, or electroretinogram in safety pharmacology studies. Adverse findings were mainly on-target effects or secondary to CNS depressant effects on the central nervous system (CNS) at doses higher than the anticipated maximum therapeutic dose of 25 mg BI 425809. Haematology changes including a decrease in haemoglobin and red blood cells and associated histopathology changes like splenic extramedullary haematopoiesis were mild and occurred in rats at human equivalent doses higher than planned for clinical studies.

Two major human metabolites of BI 425809, BI 758790 and BI 761036 have been identified and their toxicity evaluated with no evidence of pharmacological activity, genotoxicity, feto-toxicity or teratogenicity, or adverse effects in repeat-dose toxicity in studies in animals up to 15 weeks duration.

For a more detailed description of the BI 425809 profile, please refer to the current Investigator's Brochure (IB) [c02155957].

1.2.1.3 Clinical experience in humans

At the time of preparation of this clinical trial protocol, BI 425809 has been investigated in eight Phase 1 trials. Two Phase 2 trials (1346-0009 and 1346-0023) and one Phase 1 trial (1346-0015) are ongoing.

More than 245 healthy subjects have received one or more doses of BI 425809 (single doses of 0.5 mg to 150 mg and multiple doses of 5 mg to 75 mg bid (150 mg/day)), including 18 subjects aged 65 years or older (for details please refer to IB, Table 6.1:1 [c02155957]). Altogether, BI 425809 was generally well tolerated in young and elderly healthy male and female volunteers. No deaths or serious adverse events (SAEs) and no AEs of special interest (AESI) were reported. Across all BI 425809 treatment groups, there were 3 subjects with severe, but self-limiting AEs. Overall, drug-related AEs have been seen more frequently in the subjects treated with BI 425809 (33.5% vs 26.9% on placebo). Across all BI 425809 treatment groups, 3 subjects discontinued treatment due to an AE (2x nausea and vomiting, 1x procedural headache), all subjects recovered (for details please refer to IB, Table 6.3.1.1:3 [c02155957]).

The most frequent AEs for BI 425809 were nervous system disorders (25.3%), with headache being the most common (18.0%). These AEs appear to be dose-related, with a tendency for greater frequency at higher doses and can be clinically monitored.
In addition, transient visual disturbances (at doses ≥ 25 mg BI 425809 qd, mainly blurred vision) and somnolence (drowsiness) were observed. These effects are mostly mild to moderate and transient.

In general, there were no clinically relevant findings in the clinical laboratory evaluation, 12-lead ECG, vital signs. No suicidal ideation or behaviour was observed. No notable decrease in haemoglobin or haematocrit was noted in the BI 425809 treatment groups compared with placebo.

For a more detailed list of observed AEs and safety measures please refer to the current Investigator's Brochure, section 6 [c02155957].

1.2.1.4 Clinical pharmacokinetics

After administration of BI 425809 tablets, maximum plasma concentrations of BI 425809 occurred around 3 to 5 h after dosing. The terminal half-life was independent of the administered dose and ranged from 37 to 59h. Exposure increased in the tested dose range of 5 to 75 mg but with a trend to a less than dose proportional behaviour for doses of 50 mg and above. Food increased drug exposure (fed/fast ratio for C_{max}: 142%, for AUC_{0-tz}: 126%).

Steady state was reached after 6 days of BI 425809 dosing with accumulation ratios for C_{max} ranging from 1.96 to 2.63 and for AUC from 2.31 to 3.21. No exposure difference between

young and elderly healthy subjects was observed. Furthermore, pharmacokinetics in Japanese and Chinese subjects were comparable with Caucasians.

As BI 425809 is a substrate of CYP3A4, co-administration of weak, moderate and strong CYP3A4 inhibitors and inducers is not permitted.

Due to a mild induction potential for CYP3A4 [c08949593], BI 425809 should be administered with caution in presence of sensitive substrates of these enzymes, and sensitive CYP3A4 substrates with a narrow therapeutic index are not permitted. BI 425809 had no relevant effect on CYP2C9, CYP2C19, and P-gp substrates.

In plasma from young and elderly healthy volunteers administered single or multiple oral doses of BI 425809 (10, 25 and 50 mg) (trials 1346.1 and 1346.2), four oxidative metabolites, M526, M528, BI 758790, and M544 and two metabolites resulting from hydrolysis of the amide bond, BI 761036 and M312 (IN00079211), were identified. BI 761036 was with 54% the main contributor to plasma drug-related exposure, BI 758790 occurs at plasma exposures similar to parent, each made up around 20% of total drug-related exposure.

For a more detailed description of the BI 425809 profile please refer to the current Investigator's Brochure [c02155957].

1.2.2 Memantine

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia [R18-3740, R18-3739].

1.2.2.1 Drug product

Film-coated tablet in dose strengths of 5, 10, 15, and 20 mg are commercially available. For the therapy of patients, the recommended maximum daily dose is 20 mg per day. To reduce the risk of undesirable effects, the maintenance dose shall be achieved by upward titration of 5 mg per week over the first 3 weeks [R18-3740, R18-3739].

1.2.2.2 Clinical experience in humans

- In a clinical trial, potential drug-drug interactions were investigated between memantine and dextromethorphan in healthy male volunteers. The trial was conducted in an open-label, randomized, parallel-group design [P13-15942].
  In one group (N=23), subjects were administered memantine in an up-titration scheme from 5 mg to 20 mg (10 mg bid) to steady state, similar to the dosing regimen in the planned trial 1346-0039. Therefore, the safety profile from this group is described in more detail: The adverse events observed after the up-titration phase under during memantine monotherapy (10 mg bid for 11 days) included headache, somnolence,

decreased appetite, and dry mouth. All AEs were mild to moderate, no severe AEs, no deaths or serious adverse events were reported. Clinically significant increased ALT values ranged from 50 to 156 U/L.
One subject was withdrawn from the trial during the upitration phase due to adverse events. The subject experienced nine central nervous system (CNS) and gastrointestinal AEs after 10 days of memantine monotherapy (i.e. 2 days after starting with 5 mg bid);These AEs included lightheadedness, dizziness, insomnia, constipation, abdominal pain,nausea, and loose stools, as well as emotional lability.

- A double-blind, fixed-dose study in 78 patients with moderate to severe AD assessed the safety and tolerability of a memantine 20 mg once-daily regimen compared with a 10 mg dose taken twice daily. Further, a 1-step once-daily dose titration schedule was compared with the standard 3-step up-titration schedule. Safety analysis suggest that once-daily dosing of memantine is as well tolerated as twice-daily dosing and that the standard 3-step up-titration schema may be better tolerated than a 1-step up-titration regimen. These results are in alignment with the current dosing recommendation provided by the SmPC [R18-3740, R18-3739] and are reflected in the design of this trial.

According to the current summary of product characteristics (SmPC) [R18-3740, R18-3739] common side effects of memantine are somnolence, dizziness, headache, balance disorders, dyspnea, constipation, hypertension, elevated liver function tests, and drug hypersensitivity.

Uncommon side effects of memantine include fungal infection, confusion, hallucinations (mainly observed in patients with severe Alzheimer´s disease), abnormal gait, venous thrombosis/thromboembolism, vomiting, fatigue and cardiac failure.

Seizures are described as very rare side effects.

From post-marketing experience there were reports of psychotic reactions, pancreatitis, and hepatitis in the context of memantine use. The frequency of these events is not known. Further In post-marketing experience depression, suicidal ideation and suicide have been reported in patients treated with Memantine. However, Alzheimer's disease has been associated with these events, too.

Memantine has minor or moderate influence on the ability to drive and use machines such that subjects should be warned to take special care.

Overdose

Relative large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination, and gait disturbance) and/or gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2000 mg memantine with effects on the central nervous system (coma for 10 days, and later diplopia and agitation). The patient received symptomatic treatment and plasmapheresis. The patient recovered without permanent sequelae.
In another case of a large overdose, the patient also survived and recovered. The patient had received 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness.
In the event of overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate.
In case of signs and symptoms of general central nervous system (CNS) overstimulation, careful symptomatic clinical treatment should be considered [R18-3740, R18-3739]

1.2.2.3 Clinical pharmacokinetics

After oral administration in humans, memantine is completely absorbed with an absolute bioavailability of approximately 100%. There is no indication that food influences the absorption of memantine. T_{max} is between 3 and 8 hours and memantine has demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg in healthy volunteers [R18-3740, R18-3739].

Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 µmol/L) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean cerebrospinal fluid (CSF)/serum ratio of 0.52 was calculated. The volume of distribution is around 10 l/kg. About 45% of memantine is bound to plasma-proteins.
In humans, about 80% of the circulating memantine-related material is present as the parent compound. Main human metabolites are N-3,5-dimethyl-gludantan, the isomeric mixture of 4- and 6-hydroxy-memantine, and 1-nitroso-3,5-dimethyl-adamantane. None of these metabolites exhibit NMDA-antagonistic activity. No cytochrome P450-catalysed metabolism has been detected *in vitro* and memantine did not inhibit CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A, Flavin-containing monooxygenase, epoxide hydrolase or sulphation *in vitro*. [R18-3740, R18-3739]

Unchanged memantine is mainly excreted renally with a terminal $t_{½}$ of 60 to 100 hours. Tubular secretion as well as tubular reabsorption are involved in its renal elimination. In vitro data suggest a potential role of MATE1 and OCT2 for renal secretion of memantine [R17-3276, R15-0935] and also indicate that both, MATE1 and to an even higher extent OCT2, are inhibited by memantine, albeit with reported IC_{50} values that exceed unbound plasma concentrations expected during therapy [R17-3276]. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of up to 7 to 9. Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet. Therefore, concomitant use of drugs that have an alkalizing effect on the urinary pH, e.g. massive ingestion of alkalising gastric buffers, or that compete at / inhibit the transporters of the renal cation transporter system (OCT2, MATE1) may theoretically lead to

memantine accumulation [P17-09169, R17-3276]. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min), daily dose of memantine should be 10 mg per day that may be increased to 20 mg/day if well tolerated. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be reduced to 10 mg per day.

For a more detailed description of the memantine profile please refer to the current SmPC [R18-3740, R18-3739]

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of BI 425809 and of Memantine 21 days. 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

Memantine is a common medication used in patients diagnosed with Alzheimer's Disease (AD). Since BI 425809 is developed as a symptomatic treatment for AD it is very likely that it may be used on top of memantine in clinical practice. Therefore, it is crucial to investigate if there are any interactions between BI 425809 and memantine when administered together before their concomitant use could be allowed in Phase 3 trials and later in clinical practice.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 425809. The assessment of the drug-drug-interaction potential of BI 425809 will contribute to a safe clinical use of this GlyT1 inhibitor in patients with AD who often have to use multiple co-medications Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

Procedure-related risks

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

The total volume of blood withdrawn per subject during the entire study will not exceed the volume of a normal blood donation (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 425809 administration

In this trial, a dose of 25 mg BI 425809 q.d. will be administered over two periods of 10 days each, once alone and once in combination with memantine. Multiple oral doses of 25 mg BI 425809 have already been administered in trial 1346.2 (12 days) and 1346.3 (14 days) and are considered safe and well tolerated (for details please refer to Section 1.2.1.3). Further, two Phase II trials, one in patients with Alzheimer's disease (1346.23) and one in patients with CIAS (1346.9), are currently ongoing in which patients receive up to 25 mg BI 425809 qd in an ambulatory setting over a period of 12 weeks with no safety issues reported so far.

Based on its mechanism of action, its preclinical profile and the data obtained from ongoing and completed Phase I/II studies so far, there is no indication that BI 425809 should be regarded as a high risk compound.

The main dose-limiting AEs observed so far, were expected based on its mode of action. These adverse CNS symptoms, including dizziness, headache, and visual effects showed a trend towards dose dependency and were monitorable and reversible after treatment discontinuation. The reported adverse events were mostly of mild to moderate intensity and did not jeopardize the subject's wellbeing. Adequate safety monitoring including neurological examinations, vital signs/ECG, visual tests, safety laboratory, suicidality assessment and adverse events monitoring has been implemented. Though the trial is designed in parts in an ambulatory fashion, if the investigator has any clinical concern the safety of the subject will be paramount and the inpatient stay will be extended or initiated.

Risks related to memantine administration

Memantine can cause a variety of side effects that can range from mild to severe and serious (see Section 1.2.2). Many of these have been reported from clinical trials in patients with AD, i.e. in patients with considerable comorbidities.
Data from clinical trials with memantine administration in healthy volunteers indicate good tolerability in general. Dizziness, headache, somnolence, decreased appetite were observed adverse events and increased ALT values were seen in the safety lab. These AEs were mild to moderate, they are monitorable and will be reflected in the safety measures.

Risks related to the combined administration of BI 425809 and Memantine

Based on available data (see Section 1.2), a clinically relevant pharmacokinetic or pharmacodynamic interaction between memantine and BI 425809 is considered unlikely based on the following considerations:

Pharmacokinetic interaction:

Memantine selectively inhibits CYP2B6 activity at clinically relevant concentrations, whereas inhibition of other CYPs during memantine therapy is unlikely, i.e. it is not expected to affect BI 425809 metabolism that is mostly CYP3A4 mediated (see Section 1.2.1.1) [P04-11747]. In vitro memantine also inhibits OCT2 and to a lesser extent MATE. BI 425809 is not a substrate of OCT2, regarding MATE there are no in vitro data available. However, as the gMean fractional renal excretion of BI 425809 is low (around 5% over all dose groups), the impact of a potential interaction via MATE inhibition should be minor (see Section 1.2.1.1).

For memantine, no cytochrome P450-catalysed metabolism has been detected in vitro. An interaction based on the mild induction potential of BI 425809 on CYP3A4 is therefore considered unlikely. The renal transporters OCT2 and MATE1 may be involved in the tubular secretion of memantine [R17-3276]. In in vitro studies, BI 425809 did not inhibit the organic cation transporter OCT2 and was found to only inhibit MATE1 and MATE2K transporters with IC_{50} values between 30 and 100 uM [n00241265, n00263124]. Based on exposures associated with the current highest dose of BI 425809 (25 mg qd) and DDI prediction approaches outlined in regulatory guidelines [P14-08681, P12-05791], clinically-relevant inhibition of memantine renal secretion is considered unlikely. No trend towards an alkalization of urine by BI 425809 has been observed after multiple doses of BI 425809 (CTR 1346.2, Listing 1.1 [c02958024]).

Pharmacodynamic interaction:

Both drugs, BI 425809 and memantine, are targeting the NMDA receptor (NMDAR). However, the mode of action of both drugs is different.

Memantine is a moderate-affinity uncompetitive NMDAR antagonist. The NMDAR is a voltage-sensitive, glutamate-gated ion channel that, after activation, allows entry of calcium into the neuron. One hypothesis is that chronic overactivity at the NMDAR, allows excessive calcium influx and may via subsequnt synaptic or dendritic damage, necrosis or apoptosis, play a role in the progression of AD, especially at later stages of the disease (moderate-to-severe). At rest, the NMDAR channel is blocked by a magnesium ion. Memantine binds at, or near, the magnesium-binding site and thereby blocks calcium entry into the cell at times of partial neuronal depolarization, but allows entry during full neuronal depolarization. This allows normal physiologic signal transmission during times of learning or recall, along with inhibiting pathologic, tonic overactivation [P18-12042, R18-3925].

BI 425809 inhibits GlyT1 leading to increased glycine concentrations in the synaptic cleft. Glycine is a physiological co-activator of the NMDAR. The physiological NMDAR function is critical for learning and memory and cognitive performance. It has been shown that mice with point mutations in the NMDAR glycine binding site display greatly reduced NMDAR function and show severe deficits in learning and memory performance. These deficits can be rescued by administration of the NMDA receptor glycine site agonist D-serine [R18-3925].

BI 425809 is hypothesized to reduce NMDAR hypofunction in regard to disturbed physiological signal transmission required for learning and memory. On the other hand memantine is thought to inhibit the overactivation of the NMDAR in late stage Alzheimer's disease patients, while at the same time it does not affect at therapeutic exposure levels (approximately 50% occupancy of the NMDAR) the physiological signal transmission needed for cognitive function.
Therefore, in conclusion, a pharmacodynamic interaction of BI 425809 and mementine by counteracting the effects of the other drug is not expected.

Drug-induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.8.1.4, adverse events of special interest.

Safety measures:

- A thorough screening examination will ensure that only suitable healthy subjects will enter the study, for example subjects with
  - with high liver enzymes or history of or current liver disease
  - GFR < 80 ml/min
  - medical conditions or nutrition habits that may cause urine alkalization

  will be excluded from study participation.
- Close monitoring of
  - Adverse events
  - Safety lab (special focus on hepatic parameters, eGFR)
  - ECG and Vital signs (focus on blood pressure)
  - C-SSRS
- Prohibition to use drugs that may cause urine alkalization (Section 4.2.2)
- Drugs, medical conditions or nutrition habits that may cause urine alkalization are not allowed
- As memantine may impact the ability to operate vehicles and/or machines, subjects are not allowed to drive a vehicle or operate machines during Visit 3 and 4
- Close medical surveillance for at least 25 hours post-dose on the day of first administration of BI 425809 and memantine, respectively, and for up to 49 hours post-dose after combined administration of BI 425809 and memantine

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

To investigate the effect of steady state exposures of memantine on the steady-state pharmacokinetics of BI 425809 and vice versa in healthy subjects.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 425809 and for memantine:

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

- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)

2.1.3 Secondary endpoint

Not applicable.

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 425809 will be assessed based on:

- Adverse events (including clinically relevant findings from the physical and neurological examination)
- Safety laboratory tests
- 12-lead ECG (only abnormal findings will be reported as AE)
- Visual tests (only abnormal findings will be reported as AE)
- Vital signs (blood pressure, pulse rate)
- Suicidality assessment (C-SSRS)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed in healthy male and female subjects and is designed non-randomized, single-arm, open-label, three-period, one fixed sequence cross-over to investigate the effects of steady state exposures of memantine on steady state pharmacokinetics of BI 425809 and vice versa.

Considering the well-known safety profiles of the selected dose of BI 425809 and memantine, the unlikelihood of increased drug exposures due to a pharmacokinetic memantine-BI 425809 interaction and the already implemented safety measures (ref Section 1.4) treatment of all 16 subjects in one cohort in this trial is not considered to be an undue risk for enrolled subjects. However, treatment in cohorts for logistical reasons is possible. In this case, the cohorts should be of about the same size, e.g. two cohorts of 8 subjects, and be treated not too wide apart in terms of time for better comparability and reducing any possible factors influencing the readout.
An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

Open-label design
This trial is conducted open-label. Blinding is not possible because the treatments are distinguishable. The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analytes provided by a bioanalytical laboratory which is blinded to treatment allocation.

Fixed sequence design
A fixed sequence design was selected due to the long half-life of both, memantine and BI 425809. The fixed-sequence design enables intra-individual comparisons and is not expected to lead to systematic errors in the estimation of the treatment effects, because the trial duration is short enough so that nonspecific time-effects are not expected.

Dosing durations are long enough to achieve steady-state drug exposures of both drugs reliably and to exclude any transient effects.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male or female subjects will enter the study. They will be recruited from the volunteer's pool of the trial site.

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

3.3.1 Main diagnosis for trial entry

The 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 or female 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 50 years (inclusive)
3. BMI of 18.5 to 29.9 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, or female subjects who meet any of the following criteria from the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception that does not contain hormones, i.e. non-hormonal intrauterine device *plus* condom
   - Sexually abstinent
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)

7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 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. Smoker
14. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
15. Drug abuse or positive drug screening
16. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
17. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
18. Inability to comply with the dietary regimen of the trial site
19. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
20. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
21. 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

Female subjects will not be allowed to participate, if any of the following apply:

22. Positive pregnancy test, pregnancy, or plans to become pregnant within 30 days after study completion
23. Lactation

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

24. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
25. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought without method, intent or plan; active suicidal thought with method but without intent or plan; active suicidal thought with method and

intent but without specific plan; or active suicidal thought with method, intent and plan)

26. eGFR (CKD-EPI equation) < 80ml/min at screening
27. Liver tests (ALT, AST, GGT, AP), total bilirubin and creatinine outside the normal range at the screening examination
28. History of relevant liver diseases such as disturbance of liver function, jaundice, drug induced liver injury, Dubin-Johnson syndrome, Rotor syndrome, or liver tumors
29. Any presence or history of a condition linked with significantly elevated urine pH, including but not limited to renal tubular acidosis (RTA), severe infections of the urinary tract with Proteus bacteria.
30. Concomitant use of hormonal replacement therapy or hormonal contraceptives
31. Vegetarian diet or the purpose to switch from carnivore to vegetarian diet is not allowed during this trial due to potential urine alkalization.
32. History of macular degeneration or any abnormal finding in visual tests (Amsler grid test, colour discrimination test) at screening

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.3), 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.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.8.2.4.

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 pregnancy, surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN OR 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 exhibits serious suicidality, in the clinical judgment of the investigator or according to the following criteria:
   - any suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
   - 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)

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall 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 more than 2 subjects discontinue the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products have been manufactured by BI Pharma GmbH & Co. KG (BI 425809) and by (Memantine).

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the trial products are given below:

Trial product 1:

Substance:	BI 425809
Pharmaceutical formulation:	Film coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	25 mg
Posology:	1-0-0
Route of administration:	Oral
Duration of use:	Period 1 = Visit 2 Days 1-10: multiple doses of 25 mg BI 425809 q.d. Period 3 = Visit 4 Days 1-10: multiple doses of 25 mg BI 425809 q.d.

Trial product 2:

Name:	*Memantine (Startpackung and 20 mg Filmtabletten)*
Substance:	Memantine
Pharmaceutical formulation:	Film coated tablet
Source:	
Unit strength:	*Memantine Startpackung* 5 mg, 10 mg, 15 mg, 20 mg *Memantine 20 mg Filmtabletten* 20 mg
Posology:	1-0-0
Route of administration:	Oral
Duration of use:	*Memantine Startpackung* Visit 3 = Period 2 Days 1-28: During up-titration, 5 mg, 10 mg, 15 mg, 20 mg tablets will all be used as multiple doses over 7 days

Memantine *20 mg Filmtabletten*

Days 29-35: Multiple doses of 20 mg tablets q.d.

Visit 4 = Period 3

Days 1-10: Multiple doses of 20 mg tablets q.d.

4.1.2 Selection of doses in the trial

The memantine dose selected for this trial is the standard clinical dose [R18-3740, R18-3739] and the chosen up-titration scheme is recommended to improve tolerability. The dose selected for BI 425809 is the highest dose to be tested in the ongoing Phase 2 and presumably in the following Phase 3 trials.

4.1.3 Method of assigning subjects to treatment groups

This is an open-label, three-period, fixed-sequence trial. All subjects will receive the same treatment sequence. Reference and test treatments will be administered in the sequence specified in the Flow Chart. Once a subject number has been assigned, it cannot be reassigned to any other subject. All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required.

The following procedure regarding reserve subjects applies:

Reserve subjects will attend the Screening Visit and follow all trial procedures up to treatment allocation on Day 1, but will not be dosed unless they replace a subject who does not fulfil the requirements of the trial before administration of the IMP, i.e. they will remain at the trial site until all intended subjects have been allocated to treatment. They will be informed that they will be reserve subjects.

4.1.4 Drug assignment and administration of doses for each subject

This trial is an open-label, three-period, one fixed sequence study. All subjects will receive the three treatments

The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R1 (Reference 1)	BI 425809	Tablet	25 mg	1 tablet (Day 1-10/Visit 2) q.d.	250 mg
Up-titration to R2	Memantine	Tablet	5 mg	1 tablet (Days 1-7/Visit 3) q.d.	35 mg
	Memantine	Tablet	10 mg	1 tablet (Days 8-14/Visit 3) q.d.	70 mg
	Memantine	Tablet	15 mg	1 tablet (Days 15-21/Visit 3) q.d.	105 mg
	Memantine	Tablet	20 mg	1 tablet (Days 22-28/Visit 3) q.d.	140 mg
R2 (Reference 2)	Memantine	Tablet	20 mg	1 tablet (Days 29-35/Visit 3) q.d.	140 mg
T (Test)	BI 425809	Tablet	25 mg	1 tablet (Day 1-10/Visit 4) q.d.	250 mg
	Memantine	Tablet	20 mg	1 tablet (Days 1-10/Visit 4) q.d.	200 mg

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until at least 25 h after administration of BI 425809 alone and memantine alone on Day 1, Visit 2, and Day 1 Visit 3, respectively. Following the first combined administration of memantine and BI 425809 on Day 1 Visit 4, subjects will stay in the unit until at least 49 hours after administration.

The in-house surveillance period can be extended anytime if deemed necessary based on the medical judgement of the investigator.

During the first 4 h after drug administration on PK profile days (Day 1 and 10, Visit 2; Day 1 and 35, Visit 3 and Day 10, Visit 4), subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

4.1.5 Blinding and procedures for unblinding

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

Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

4.1.6 Packaging, labelling, and re-supply

BI 425809 tablets 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. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

For ***memantine***, the commercially available product will be supplied by a public pharmacy. Transport and storage are under the responsibility of the investigator and must comply with the pertinent information in the SmPC of the drug product used in the clinical trial [R18-3740, R18-3739].

Documentation on the commercial drug product, 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 product and quantity, must be available at the clinical site and filed in the ISF.

Also, if required according to the SmPC of the drug product, documentation of temperature monitoring during shipment/transport must be available at the clinical site and filed in the ISF (e.g. for commercial drug products required to be stored cooled or frozen).

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

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, as applicable. 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 locally by the trial site upon written authorisation of the clinical trial leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

No specific rescue medication is foreseen for BI 425809. 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 (for restrictions please refer to Section 4.2.2.1). 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 a memantine overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate [R18-3740, R18-3739].

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed including hormonal contraceptives or ovary hormone replacement. However, in case there are AEs needing treatment special care is to be taken that the following concomitant medications should be avoided:

- Use of N-methyl-D-aspartate(NMDA)-antagonists such as amantadine, ketamine or dextromethorphan
- Active substances such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine
- The use of weak, moderate or strong CYP3A4 inhibitors and inducers is not permitted. CYP3A4 sensitive drugs with narrow therapeutic range are not permitted during the trial period.
- Gastric buffers (such as sodium hydrogencarbonat) or other drugs which might result in urine alkalinization are not allowed in this trial. Urine alkalinization is known to reduce memantine elimination.
- Paracetamol and diclofenac must be avoided as symptomatic therapy of AEs due to its potential liver toxicity.

All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at standard times if not indicated otherwise in the Flow Chart.

On all dosing days, the trial medication will be administered after an overnight fast of at least 10 h prior. Fluid intake is not allowed from 1 h pre-dose until drug administration.

On PK profile days (Day 1 and 10, Visit 2; Day 1 and 35, Visit 3 and Day 10, Visit 4) subjects will remain fasted until 4 hours after administration. Their fluid intake is restricted to the water administered with the drug and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects) from 1 hour before drug intake until 4 hours post dose. From lunch until 24 h post-dose, subjects are advised that total fluid intake should be in the range of 2000 - 3000 mL.

On all other dosing days subjects have to remain fasted for 1 h after drug administration.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the first administration of trial medication until after the last PK sample of each study period is collected.

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

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

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

A switch from carnivore to vegetarian diet is not allowed during this trial due to potential urine alkalinisation.

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures). Hormonal contraception is not allowed.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At the screening visit, the medical examination will include documentation of subject information and informed consent, demographics including height and body weight, smoking and alcohol history (alcohol history will only be documented in the source documents),, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, visual tests, C-SSRS assessment, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination (including a neurological examination consisting of Romberg and Unterberger test, assessment of gait, further tests as needed). At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, C-SSRS assessment, visual tests and a physical examination with a neurological assessment (i.e. Romberg and Unterberger test, assessment of gait, further tests as needed). During the treatment period neurological examination (i.e. Romberg and Unterberger test, assessment of gait, further tests as needed) will be performed at the time points indicated in the Flow Chart. In addition, neurological examinations are to be performed at any times CNS adverse events are reported. The occurrence of headache, however, does not require the performance of neurological assessments (except upon discretion of the investigator). The reason for this is that headaches are in most cases unspecific symptoms without clear causative CNS involvement that occur frequently in clinical trials in healthy volunteers.

Only abnormal findings of the physical and neurological examination will be reported as AEs.
Results of neurological examinations will be kept in source data only, but not collected in the CRF.

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) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.3 Visual tests

Visual tests will be performed at any time point indicated in the Flow Chart and any time the subject reports visual adverse events or if it is deemed necessary by the investigator or designee.

All test results will be documented in the source documents and entered into the eCRF. Any abnormal findings detected in this test during the screening examination will lead to the exclusion of the subject. Any deterioration occurring during the study will be documented as an AE and an additional ophthalmologic examination should be considered.

5.2.3.1 Color discrimination test

Color vision will be tested using the Ishihara test for color deficiency.

The test consists of a number of colored plates, called Ishihara plates, each of which contains a circle of dots appearing randomized in color and size. Within the pattern are dots which form a number visible to those with normal color vision and invisible, or difficult to see, for those with a color vision deficiency.

Two plates will be randomly selected for each time point as well as a plate with a positive (the plate number must be recognized by all subjects) and a negative control (the plate number should not be recognized by any subject).

Subjects will be instructed to recognize and report the numbers seen on the plates. Test results will be reviewed by investigator or his/her designee for correctness.

5.2.3.2 Visual acuity test (near visual acuity)

Near vision cards (e.g. Jaeger Eye Chart) will be used to measure visual acuity. The smallest line that a subject can read at a distance of 35 centimeter will be recorded.

If the subject uses glasses, then the test should be performed using them.

Tests results will be reviewed by investigator or his/her designee for correctness and deteriorations from the baseline will be documented as an AE (narratives will be written).

5.2.3.3 Amsler grid test

The Amsler grid is a grid of horizontal and vertical lines used to monitor a person's central visual field. It is a diagnostic tool that aids in the detection of visual disturbances caused by changes in the retina, particularly the macula (e.g. macular degeneration, epiretinal membrane), as well as the optic nerve and the visual pathway to the brain.

If the subject uses glasses, then the test should be performed using them. Subjects should hold the Grid at a normal reading distance about 35 cm away from the face using only one eye (another eye closed) and look at the dot in the center of the grid. If any of the lines in the grid look distorted, blurry, or missing, this will be documented in the source documents as AE (narratives will be written).

5.2.4 Suicidality monitoring

Based on the FDA guidance on prospective assessment of suicidality [R12-4395] suicidal ideation and behaviour should be assessed as part of the evaluation of any drug being

developed for a psychiatric condition. This recommendation also refers to clinical trials in healthy volunteers with multiple dose administration of the IMP.

The C-SSRS will be used as a monitoring tool as depression, suicidal ideation and suicide has been observed in Alzheimer patients treated with Memantine [R18-3740, R18-3739]. Further, with multiple doses of BI 425809, suicidal thoughts and behaviour will also be assessed by C-SSRS [R08-1147]. For details see Section 5.2.8.1.7. The original Columbia Suicidal Severity Rating scale is shown in Appendix 10.1.
C-SSRS will be performed at the times indicated in the Flow Chart.

5.2.5 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 5.2.5: 1 and 5.2.5: 2. Reference ranges will be provided in the ISF, Section 10.

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

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

$$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if Black}]$$

With

- eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2
- S_{Cr} (standardized serum creatinine) = mg/dL
- κ = 0.7 (females) or 0.9 (males)
- α = -0.329 (females) or -0.411 (males)
- min = indicates the minimum of S_{Cr}/κ or 1
- max = indicates the maximum of S_{Cr}/κ or 1
- age = years

Table 5.2.5: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil; Eosinophils; Basophils; Monocytes; Lymphocytes	X	X	X
Manual differential WBC *(*if automatic differential WBC is abnormal and seen as clinically relevant by the investigator)*	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.	X*	X*	X*
Coagulation	Activated Partial Thromboplastin Time	X	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	X
	Fibrinogen	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	AP [Alkaline Phosphatase]	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
	Lactic Dehydrogenase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	Free T3 - Triiodothyronine	X	--	--
	Free T4 – Thyroxine	X	--	--
	Estradiol (* if needed for confirmation of postmenopausal state)	X*	--	--
	FSH (* if needed for confirmation of postmenopausal state)	X*	--	--
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	eGFR	X	--	--
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	Albumin	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	X	X
	Cholesterol, total	X	--	X
	Triglyceride	X	--	X

Table 5.2.5: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Chloride	X	X	X
	Calcium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	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)	X*	X*	X*
Pregnancy test (urine) *(*to be done as indicated by footnote 5 in the Flow Chart)*	Beta human chorionic gonadotropin (beta-HCG)	X	X*	X

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined during Visit 2, Visit 3 and Visit 4 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 5 (end of trial examination)

The tests listed in Table 5.2.5: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to each admission to the unit.

Table 5.2.5: 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
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g.) will be performed at screening and at each admission to the trial site as indicated in the Flow Chart, 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 5.2.5: 1 and 5.2.5: 2 will be performed at , with the exception of drug screening and pregnancy tests. These tests will be performed at the trial site using and , respectively, or comparable test systems.

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

5.2.6 Electrocardiogram

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

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

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

All ECGs will be stored electronically on the). 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). Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.7 Other safety parameters

Not applicable.

5.2.8 Assessment of adverse events

5.2.8.1 Definitions of adverse events

5.2.8.1.1 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.

5.2.8.1.2 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

5.2.8.1.3 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 5.2.8.2, 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.

5.2.8.1.4 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 5.2.8.2.2.

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.

5.2.8.1.5 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

5.2.8.1.6 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

5.2.8.1.7 Suicidal risk assessed by the 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 behaviour must be reported as separate SAEs by the investigator. For 'Self-injurious behaviour, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied.

For each negative report (suicidal ideation type 1, 2 or 3) after 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.

5.2.8.2 Adverse event collection and reporting

5.2.8.2.1 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. 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.

5.2.8.2.2 AE reporting to the sponsor and timelines

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

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

5.2.8.2.3 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.

5.2.8.2.4 Pregnancy

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

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

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

5.3.2.1 Blood sampling for pharmacokinetic analysis of BI 425809

For quantification of BI 425809 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and

stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples and aliquots on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

5.3.2.2 Blood sampling for pharmacokinetic analysis of memantine

For quantification of memantine plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a Li-Hep (Lithium-Heparin)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. The Li-Hep-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and 4 to 8 °C. Two plasma aliquots containing at least 0.5 mL will be obtained and stored in polypropylene tubes. Within a maximum time of 2 hours after sampling at room temperature, the samples should be stored in a freezer. Plasma samples will be stored frozen in an upright position at about –20°C or below until shipment on dry ice to the analytical laboratory. At the analytical laboratory, the plasma samples will be stored at about –20°C or below until analysis.

5.3.2.3 Urine sampling for pharmacokinetic analysis of memantine

A blank urine sample will be collected before administration of trial medication (within 2 h before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 2 L polyethylene (PE) containers and stored at room temperature. Subjects are told to empty their bladders at the end of each sampling interval. In order to facilitate urine sampling, subjects will be advised to drink at least 100 mL water before the end of each urine sampling interval.

Due to the known adsorption of the drug (its metabolites) to the container wall, 10 mL of 10% Tween 20 solution will be added to each 2 L PE collection container prior to the start of urine sampling. The weight of the empty container will be determined, thereafter 10 mL of 10% Tween 20 will be added, and the weight of the container at the end of each sampling interval will be determined.

The urine weight/volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done, i.e. 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in PP tubes for bioanalytical measurements. If more than one collection container is used in a sampling interval, the contents of all containers have to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device made of

PE, PP, Teflon, or glass). Generally, the collection container should be shaken upon addition of every urine fraction to ensure proper distribution of Tween and urine.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned collection time.

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

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

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of BI 425809 and memantine plasma concentration

BI 425809 and memantine concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

5.3.3.2 Analytical determination of memantine urine concentration

The memantine concentration PK urine study samples will be determined by validated liquid chromatography tandem mass spectrometry assays (LC-MS/MS) at a contracted laboratory with given authorization by BI. All details of the analytical method will be available prior to the start of sample analysis.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

5.4 ASSESSMENT OF BIOMARKER

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 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 parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard

laboratory values, and ECG parameters that might occur because of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The C-SSRS is a validated tool to monitor for suicidality and recommended by the FDA [R12-4395]. The visual tests (Ishiara plates, Amsler grid test, and visual acuity test) are tests commonly used to assess and monitor the visual sense and have been implemented in previous clinical trials with BI 425809 [c02820512, c02958024].

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration, i.e. marked as "pre-dose" (footnote 2 in the Flow Chart) 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 vital signs, C-SSRS, ECG, and laboratory tests will be ± 30 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, visual tests, C-SSRS 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.

For planned blood sampling times and urine collection intervals, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, visual tests, C-SSRS assessment and physical and neurological examination, refer to Sections 5.2.3 to 5.2.8.

6.2.2 Treatment periods

Each subject is expected to participate in 3 treatment periods (Visit 2 - 4).

In the evening of Day -1, and Day 9, Visit 2 study participants will be admitted to the trial site and kept under close medical surveillance until at least 24 h after drug administration on Day 1 and Day 10, respectively.

During Visit 3, subjects will be admitted to the trial site on Day 1 in the morning and remain in-house up to 25 h after the first memantine administration on Day 1, Visit 3. In the evening of Day 34, Visit 3, subjects will again be admitted and stay under close medical surveillance until at least 49 h after the first combined administration of BI 425809 and memantine on

Day 1, Visit 4. They will be readmitted to the trial site in the evening of Day 9, Visit 4 and discharged not earlier than 24 h after the last drug administration of this trial.

At each discharge subjects will be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, subjects will be treated in an ambulatory fashion.

The in-house surveillance period can be extended anytime if deemed necessary based on the medical judgement of the investigator.

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

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

On day 18 of Visit 4 (= Period 3) subjects will be contacted by phone and questioned about their well-being.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.2 to 5.2.8.
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

7.1 STATISTICAL DESIGN – MODEL

The main objectives of this trial are to investigate the relative bioavailability of

- 25 mg of BI 425809 in Steady State when given alone (Reference 1, R1) compared with co-administration of 25 mg of BI 425809 and 20 mg of memantine both in Steady State (Test, T),

and the relative bioavailability of

- 20 mg of memantine in Steady State when given alone (Reference 2, R2) compared with co-administration of 25 mg of BI 425809 and 20 mg of memantine both in Steady State (Test, T),

following oral administration on the basis of the primary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics.

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 425809 administered alone compared with co-administration with memantine and the relative bioavailability of memantine administered alone compared with co-administration with BI 425809 will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of study drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary and was not excluded due to a protocol deviations relevant to the evaluation of PK or due

to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 425809 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol violations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- The subject experiences emesis at any time during the labelled dosing interval
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

7.3.1 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. The model used will include effects accounting for the following sources of variation: subjects and treatment. The effect 'subjects' will be considered as random, whereas the effect 'treatment' will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean,

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

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

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

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

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

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

Further exploratory analyses

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

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

7.3.2 Secondary endpoint analyses

Not applicable.

7.3.4 Safety analyses

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

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used.

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

Measurements (such as vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.8.1), and other significant AEs (according to ICH E3) will be listed separately.

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

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

Suicidality monitoring will be assessed by the C-SSRS questionnaire (Section 5.2.4). Results will be documented by means of an overall question ("Based on the C-SSRS, has the subject expressed any current suicide ideation or current/past suicide behaviour?" - yes/no). In case this overall question is answered with "yes", the full questionnaire will be included in the clinical trial report. Findings will be reported as AE, the completed forms will be stored at the site.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant Corporate Procedure (001-MCS-36-472). PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.6 RANDOMISATION

No randomization is necessary (cf. Section 4.1.3).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for BI 425809 in the DDI study with itraconazole [c03355329] was roughly 11% for C_{max} and 24% for AUC. An intra-individual variability of 7.7% was observed for memantine [R19-0656].

For various assumptions around the gCV of 24%, Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a one fixed sequence design trial

Drug	gCV [%]	Sample Size	Precision**	Ratio [%]*	Lower CL [%]	Upper CL [%]
BI 425809	22.0	12	1.238	100	80.80	123.76
		14	1.210		82.63	121.03
		16	1.190		84.03	119.00
		18	1.174		85.16	117.42
	24.0	12	1.261	100	79.29	126.12
		14	1.231		81.24	123.09
		16	1.208		82.75	120.85
		18	1.191		83.96	119.10
	26.0	12	1.285	100	77.82	128.50
		14	1.252		79.89	125.17
		16	1.227		81.49	122.71
		18	1.208		82.78	120.80
Memantine	7.7	12	1.078	100	92.74	107.83
		14	1.070		93.47	106.98
		16	1.063		94.03	106.34
		18	1.058		94.48	105.84

* Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.
** Defined as ratio of upper CL and relative BA estimate.

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 3.5.1.

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 web page: trials.boehringer-ingelheim.com. As a general rule, no trial results should be published prior to archiving of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or 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. As treatment assignments will be known to investigators, rules about emergency code breaks are not applicable (see Section 4.1.5). 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 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.

The EC/competent authority will be notified about the trial milestones according to the laws of the member state.
A final report of the clinical trial data will be written only after all subjects have completed the trial, so that all data can be incorporated and considered in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
BI has appointed a Clinical trial leader (CTL), 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, Clinical Research Associates (CRA), and investigators of participating trial sites

BI 425809 will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany. Marketed memantine will be sourced locally by the clinical trial site from public pharmacy.
Safety laboratory tests will be performed by the local laboratory of the trial site

Analyses of BI 425809 in plasma and memantine concentrations in plasma and urine will be performed at the

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

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P04-11747 Micuda S, Mundlova L, Anzenbacherova E, Anzenbacher P, Chladek J, Fuksa L, Martinkova J. Inhibitory effects of memantine on human cytochrome P450 activities: prediction of in vivo drug interactions. Eur J Clin Pharmacol 2004. 60(8):583-589.

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

P13-15942 Pope LE, Schoedel KA, Bartlett C, Sellers EM A study of potential pharmacokinetic and pharmacodynamic interactions between dextromethorphan/quinidine and memantine in healthy volunteers. Clin Drug Invest 32 (8), e1 - e15 (2012).

P14-08681 European Medicines Agency (EMA). Committee for Human Medicinal Products (CHMP): guideline on the investigation of drug interactions, final (21 June 2012, CPMP/EWP/560/95/Rev. 1 Corr.) (this guideline replaces guideline CPMP/EWP/560/95). http://www.ema.europa.eu/docs/en _GB/document_library/Scientific_guideline/2012/0 7/WC500129606.pdf (access date: 4 June 2014) ; London: European Medicines Agency (EMA); 2012.

P17-09169 Caraci F, Sultana J, Drago F, Spina E Clinically relevant drug interactions with anti-Alzheimer's drugs.CNS Neurol Disord Drug Targets 16 (4), 501 - 513 (2017).

P18-12042 Schmitt F, Ryan M, Cooper G. A brief review of the pharmacologic and therapeutic aspects of memantine in Alzheimer's disease. Expert Opin Drug Metab Toxicol 2007;3(1):135-141.

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

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

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

R13-3447 Levey AS, de Jong P, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt K. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney International (2011) 80, 17–28.

R13-4447 Lane HY, Chang YC, Liu Y, Chiu CC, Tsai GE. Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study. Arch Gen Psychiatry 2005;62:1196-1204.

R13-4508 Martin-Facklam M, Patat A, Hofmann C, Boetsch C, Banken L, Biedinger U, Boutouyrie-Dumont B. Safety, tolerability and pharmacokinetics of bitopertin (RG1678), a novel glycine reuptake inhibitor after multiple doses in healthy volunteers. 3rd Biennial Conf of the Schizophrenia International Research Society (SIRS), Florence, 14 - 18 Apr 2012 (Poster). 2012.

R15-0935 Busch AE, Karbach U, Miska D, Gorboulev V, Akhoundova A, Volk C, Arndt P, Ulzheimer JC, Sonders MS, Baumann C, Waldegger S, Lang F, Koepsell H. Human neurons express the polyspecific cation transporter hOCT2, which translocates monoamine neurotransmitters, amantadine, and memantine. Mol Pharmacol 1998;54(2):342-352.

R17-3276 Mueller F, Weitz D, Derdau V, Sandvoss M, Mertsch K, Koenig J, et al. Contribution of MATE1 to renal secretion of the NMDA receptor antagonist memantine. Mol Pharm 2017;14(9):2991-2998.

R18-0242 Guidance for industry: in vitro metabolism- and transporter-mediated drug-drug interaction studies (draft guidance, this guidance document is being distributed for comment purposes only) (October 2017, clinical pharmacology). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guid ances/UCM581965.pdf (access date: 19 January 2018) ; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2017.

R18-3739 Memantine 20 mg, verschreibungspflichtig (Fachinformation, Stand der Information: 07/2017). 2017.

R18-3740 Memantine Startpackung verschreibungspflichtig (Fachinformation, Stand der Information: 07/2017). 2017.

R18-3925 Moskal JR, Burch R, Burgdorf JS, Kroes RA, Stanton PK, Disterhoft JF, et al. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. Expert Opin Invest Drugs 2014;23(2):243-254.

R19-0656 Chladek J, Zaludek B, Sova P, Franc A, Sispera L, Martinkova J, et al. Steady-state bioequivalence studies of two memantine tablet and oral solution formulations in healthy volunteers. J Appl Biomed 2008;6:39-45.

10. APPENDICES

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

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

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	___	___

Version 1/14/09

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

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	____

Version 1/14/09

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* _____

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		27 May 2019
EudraCT number **EU number**		2019-000468-36
BI Trial number		1346-0039
BI Investigational Medicinal Product(s)		BI 425809
Title of protocol		A study to investigate the effects of memantine on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (non-randomized, single-arm, open-label, three-period, one fixed sequence cross-over study)

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. Flow Chart 2. Section 3.1 3. Section 5.2.8.1.7 4. Appendix 1.1
Description of change		1. a) Errors in the planned times and time points of the C-SSRS assessments were corrected. b) By mistake, 3 memantine PK samples on day 10, period 3, visit 4 at 219:30, 220:30 and 221:00 were not entered in the Flow Chart of the CTP 1.0. This was corrected. 2. The size of possible cohorts was added and the risk assessment of this design was further specified. 3./4.The Screening version of the C-SSRS was replaced by the Screening/Baseline version of the C-SSRS as this is the correct version to be used.
Rationale for change		Based on EC feedback section 3.1 was revised as recommended. 3 PK samples of memantine were added that were by mistake not included in the original CTP. This correction was needed to align the sampling scheme for memantine in order to guarantee comparability of

		profiles following administration of memantine alone and in combination with BI 425809. In addition, some errors/typos were corrected.

11.2 GLOBAL AMENDMENT 2

Date of amendment		19 July 2019
EudraCT number **EU number**		2019-000468-36
BI Trial number		1346-0039
BI Investigational Medicinal Product(s)		BI 425809
Title of protocol		A study to investigate the effects of memantine on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (non-randomized, single-arm, open-label, three-period, one fixed sequence cross-over study)
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. Title page 2. Flow chart 3. Table 5.2.5: 1 4. Section 5.2.3
Description of change		1. Clinical Trial Leader was changed to new contact details were provided. 2. In the listing of SCR procedures under footnote 1, visual tests and C-SSRS were missing. Footnote 8 was missing for the PK sample on Day 2, Visit 2. These were corrected. 3. A reference to the pregnancy test, indicating that tests are to be done as per footnote 5 in the Flow Chart, was missing. This was corrected. 4. For visual tests, a reference to any time point as per the Flow Chart was added instead of SCR and EOT.
Rationale for change		1. The study has been handovered to 2./3. Addition of the missing data. 4. Correction of errors/typos.

APPROVAL / SIGNATURE PAGE

Document Number: c26441810 **Technical Version Number:3.0**

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

Title: A study to investigate the effects of memantine on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (non-randomized, single-arm, open-label, three-period, one fixed sequence cross-over study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		19 Jul 2019 10:30 CEST
Author-Clinical Trial Leader		19 Jul 2019 10:32 CEST
Author-Trial Statistician		22 Jul 2019 09:49 CEST
Approval-Therapeutic Area		23 Jul 2019 11:26 CEST
Verification-Paper Signature Completion		25 Jul 2019 11:26 CEST
Approval-Team Member Medicine		25 Jul 2019 16:34 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed